The effect of vitamin D and physical activity on knee osteoarthritis symptoms in older obese adults: a mixed methods study

Rebecca Joanne Brown

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Newcastle University

Institute of Cellular Medicine

Human Nutrition Research Centre

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Abstract

Background: There is an inverse relationship between Vitamin D concentrations and KOA but the effects of Vitamin D supplementation on KOA symptoms are poorly understood. Physical activity (PA) is recommended for KOA yet evidence on how to sustain increased PA is limited. Online PA interventions offer advantages including personalisation and scalability. This pilot study explored the acceptability and feasibility of vitamin D and PA interventions within an older obese KOA population.

Methods: Patients meeting our inclusion criteria (age 50-70y, BMI 30-40kg/m^2, diagnosed symptomatic KOA ACR criteria) were recruited (March-April/September–December 2015) from eight GP surgeries. Eligible individuals attended a study visit where blood samples, questionnaires, knee assessments and PA accelerometry (3-5 day accelerometry) were taken. Screening was performed for the 3-month pilot intervention study (25(OH)D 25-50nmol/L OR <60min/week moderate activity) and eligible participants were given either daily Vitamin D supplements (2000IU [50µg]) or access to an online PA programme. Assessments were repeated 6 and 12 weeks later and a qualitative interview to explore participants views on acceptability of the study performed immediately after the 12 week visit.

Results: Eight GP surgeries identified 791 participants of whom 45 (5.7%) were eligible and attended the study visit. Pilot intervention study screening yielded 17 (2.1%) participants; nine were allocated to each intervention group. The average compliance to the vitamin D intervention was 99% compliance (defined as % tablets taken) and 67% compliance with the PA interventions (defined as use of website beyond registration visit). The PA intervention resulted in a mean decrease of 107 minutes (95% CI: -259.8, 45.0) daily sedentary time and mean increase of 4.4 minutes (95% CI -3.0, 11.8) daily moderate activity time. The Vitamin D intervention led to a mean increase in plasma 25(OH)D concentration of 51nmol/L (SD: ±23.1). Feedback from interviews suggested recruitment and interventions were acceptable and suggestion for improvements on study materials were made.

Conclusion: Recruitment from GP surgeries and delivery of a Vitamin D and online-based PA intervention is feasible. Most participants were compliant to study procedures and data suggest improved PA and vitamin D status after the respective interventions. Further studies are needed to further pilot test improvements and test the effectiveness of the interventions.

Dedication

I would like to dedicate this PhD to everyone who provided their unwavering support and kindness over the past 3 years. Firstly to my parents, Steven and Carol, without whom I would never have gone to university. To my sister, Amanda, for every stress busting fat Friday. To my nephew and niece, Ethyn and Belle, with the hope it will inspire them to achieve whatever they desire. To all of the friends, new and old, who have made every day a pleasure and adventure.

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"You have brains in your head,
You have feet in your shoes,
You can steer yourself any direction you choose.
You're on your own,
And you know what you know.
And you are the one who'll decide where to go."

Dr Seuss

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Presentations and Awards

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- Brown R, O'Brien N, Avery L, Cuthbertson D, Birrell F, Mathers J. "Vitamin D and Physical Activity for Osteoarthritic Pain, Cross-section and Pilot study:

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- Brown R, O'Brien N, Cuthbertson D, Birrell F, Mathers J. "Impact of Physical Activity (PA) and Vitamin D supplementation on osteoarthritic knee pain in older obese adults: a cross section study and RCT" *Liverpool University Rheumatology regional meeting2015.*University Hospital Aintree, Liverpool
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- Brown R, O'Brien N, Avery L, Cuthbertson D, Birrell F, Mathers J. "Vitamin D and Online Activity Programme for Knee Osteoarthritis symptoms: a recruitment review" *In: Human Nutrition Research Centre (HNRC) Seminar Series 2017;* Newcastle University

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- **Best Academic Poster – 1st Prize:** "Vitamin D and physical activity programmes for osteoarthritic pain, cross-sectional and pilot Study: Recruitment review" *In: Human Nutrition Research Annual Research Day 2016.* Newcastle University
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- **Best Academic Poster – 3rd Prize: "**Vitamin D and Physical Activity interventions for older obese adults with osteoarthritic knee pain: a pilot study" *In: Institute of Cellular Medicine (ICM) Student Poster Evening 2017;* Newcastle University

List of Abbreviations

1,25(OH)D	1,25 Hydroxyvitamin D
25(OH)D	25 Hydroxyvitamin D
ACR	American College of Rheumatology
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Chief Investigator
CIMA	Centre for Integrated research into Musculoskeletal
Ageing	
CRN	Clinical Research Network
GCP	Good Clinical Practice
GP	General Practitioner
HACs	Human Articular Chondrocytes
IL	Interleukin
IOM	Institute of Medicine
IRAS	Integrated Research Application System
KOA	Knee Osteoarthritis
LA	Leah Avery
MCS	Mental Component Score
MMPs	Matrix Metalloproteinases
MRC	Medical Research Council
MSK	Musculoskeletal
NECS	North East Commissioning Group
NO	Nicki O'Brien
NIHR	National Institute for Health Research
NHS	National Health Service
NO	Nitric Oxide
NTGH	North Tyneside General Hospital
OA	Osteoarthritis
PA	Physical Activity

PCT	Primary Care Trust
PCS	Physical Component Score
PGE2	ProtagladinE2
PhD	Doctor of Philosophy
POW	People with Osteoarthritis Walking programme
QoL	Quality of Life
R&D	Research and Development
RB	Rebecca Brown
RCT	Randomised Control Trial
REC	Research Ethics Committee
SF-36	Short Form – 36
SI Units	Standard International Units
TNFα	Tumour Necrosis Factor α
TUG	Timed Up and Go
UHA	University Hospital Aintree
UK	United Kingdom
VAS	Visual Analogue Scale
VDR	Vitamin D Receptor
VDRE	Vitamin D response Elements
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster universities Arthritis

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Chapter 1. Introduction

1.1 Osteoarthritis

Osteoarthritis (OA) is the most common type of arthritis[1], incidence of which increases substantially with age [2]. It commonly occurs in the knee, hip, and hand joints and is usually associated with pain, stiffness and decreased mobility leading to significant functional impairment [3].

The pathophysiology of OA is complex and poorly understood, being multifactorial and involving a range of individual systemic biochemical and local biomechanical factors. Indeed it is still disputed whether OA is a single or multiple disorders [2].

Understanding of OA including the very definition of OA, has evolved substantially in recent decades. In this section I aim to summarise the most recent research regarding the pathophysiology, risk factors and burden of Knee OA (KOA).

1.1.1 Classification and Diagnosis

Because of a lack of a 'diagnostic' test for KOA, defining and diagnosing KOA using non-invasive methods can be difficult. Therefore we must rely on readily available methods such as x-ray, laboratory and clinical examination findings in order to diagnose KOA in practice. [4]

There have been many guidelines published to aid the diagnosis of OA for healthcare and research purposes. Below I have outlined some of the most common guidelines used for the diagnosis of KOA.

Classification for subsets of osteoarthritis	
I. Idiopathic	**II. Secondary**
A. Localised	A. Post-traumatic
1. Hands: e.g. Heberden's and Bouchard's nodes (nodal), erosive interphalangeal arthritis (non-nodal), scapho-metacarpel, scaphotrapezial.	B. Congenital or developmental diseases
2. Feet :e.g., hallux valgus, hallux rigidus, contracted toes (hammer/cockup toes), talonavicular	1. Localised: a) Hip diseases, e.g. Legg-Calve-Perthes, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum, b) Mechanical and local factors, e.g. obesity (?), unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis
3. Knee a) Medial compartment, b) Lateral compartment, c) Patellofemoral compartment (e.g. chondromalacia)	2. Generalised: a) Bone dysplasias, e.g. epiphyseal dysplasias, spondulo-apophyseal dysplasia, b) Metabolic disease, e.g. hemochromatosis, ochronosis, Gauchers disease, hemoglobinopathy, Ehler-Danlos disease
4. Hip: a) Eccentric (superior), b) Concentric (axial, medial), c) Diffuse (coxac senilis)	C. Calcium deposition disease
5. Spine (particularly cervical and lumbar): a) Apophyseal, b) Intervertebral (disk), c) Spodylosis (osteophytes), d) Ligamentous (hyperostosis [Forestier's disease, or DISH])	1. Calcium pyrophosphate deposisition disease 2. Apatite arthropathy 3. Destructive arthropathy (shoulder, knee)
6. Other single sites: e.g. shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular	D. Other bone and joint disorders
B. Generalised: Includes 3 or more areas listed above (Kellgren-Moore)	e.g. avascular nercrosis, rheumatoid arthritis, gouty arthritis, spetic arthritis, Pagets disease, osteopetrosis, osteochondritis
	E. Other Diseases
1. Small (peripheral) and spine 2. Large (central) and spine 3. Mixed (peripheral and central) and spine	1. Endocrine diseases: e.g. diabeties mellitus, acromegaly, hypothyroidism, hyperparathyroidism 2. Neuropathic arthropathy (Charcot joints) 3. Miscellaneous e.g. frostbite, Kashin-Beck disease, Caisson disease

Table 1.1: American Rheumatology Association Diagnostic and Therapeutic Criteria Committee subcommittee on OA classification criteria for OA. This is split into 2 main sections: Primary (Idiopathic) and Secondary OA. Taken from Table 1 [4].

1.1.1.1 Classification of OA

Broadly, OA can be Primary /Idiopathic (in which there is no obvious underlying cause) or Secondary (as a direct result of trauma, repetitive joint motion or another underlying disease) [4] (Table 1.1). Treatment of OA will vary according to the cause, which I will discuss further in Section 1.5.

1.1.1.2 Diagnosis of KOA

a) Kellgren and Lawrence Score

Commonly, x-rays are used in the diagnosis and grading of KOA. The most widely accepted x-ray based system for grading KOA changes is the Kellgren & Lawrence (K&L) score [5], developed in 1957, which has been recommended by the WHO since 1961 [4]. The K&L system aims to identify evidence of KOA and to define the severity of KOA. It also provides a tool to track changes in the osteoarthritic joint over time. The score is formed by looking for specific features of the joint, the presence of which indicate the presence of OA. These features are:

(1) Osteophytes (bony outgrowths on the margin of the joint)

(2) Cartilage/joint space narrowing

(3) Subchondral bone sclerosis

(4) Cyst formation

(5) Abnormal bone shape [6]

Depending on the amount and severity of the changes seen, a score will be assigned from Grade 0 (no evidence of OA) to Grade 4 (evidence of severe OA) [7].

Although the K&L scoring system provides an objective method of assessing KOA presence and severity, it has several limitations. Firstly, assigning a grade to an x-ray image can be quite a subjective process and can vary between interpreters. Secondly, the score does not take into account the fact that a large proportion of people may have mild to severe radiological joint changes and no symptoms of OA. Therefore, those identified as having KOA using the K&L system may not be those in need of any medical assistance.

b) *American College of Rheumatology (ACR) Criteria*

ACR Criteria for Idiopathic KOA		
Clinical and Laboratory	Clinical and Radiographic	Clinical
Knee Pain **AND >5 OF THE FOLLOWING:** - Age >50 years - <30 mins morning stiffness - Crepitus on active motion - Bony tenderness - Bony enlargement - No palpable joint warmth - ESR <40mm/hr - RF <1:40 - SF OA	Knee Pain **AND >1 OF THE FOLLOWING:** - Age - <30min morning stiffness - Crepitus on active motion - Osteophytes	Knee Pain **AND >3 OF THE FOLLOWING:** - Age ->30mins morning stiffness - Crepitus on active motion - Bony tenderness - Bony Enlargement - No palpable joint warmth
92% sensitivity, 75% specificity	91% sensitivity, 86% specificity	95% sensitivity, 69% specificity

Table 1.2: A summary of the Clinical, Laboratory and Radiographic ACR criteria.ESR: Erythrocyte Sedimentation Rate, RF: Rheumatoid Factor, SF OA: Synovial fluid signs of OA (clear viscous or white blood cell count <2000mm3). Adapted from [4].

The American College of Rheumatology (ACR) developed specific criteria for the diagnosis of KOA in 1986 (see Table 1.2) with the aim of clarifying the definition of KOA and providing a standard for defining KOA. After assessing 28 historical, 16 physical examination, 3 laboratory test, 10 synovial fluid and 28 radiographic features, 3 sets of classification criteria were developed: Clinical Examination and Laboratory Tests (e.g. for use in GP surgeries), Clinical Examination, Laboratory and Radiographic Tests (e.g. useful in clinical trials or where radiographs are available) and Clinical exam (e.g. population survey). The criteria aim to identify people with OA from other rheumatic conditions with a certain degree of sensitivity and specificity, which varies between the different classifications criteria developed. [4] However, a 2006 review of the use of ACR in identifying KOA cases in the general population found only 41% sensitivity (compared with the 89% originally reported) in their KOA sample for the ACR Clinical Criteria. These authors concluded that use of the ACR clinical criteria resulted in a high level of 'false negative' results and that the criteria may be sensitive to advanced disease only, therefore alternative means need to be employed for the identification of mild-moderate KOA [8].

c) National Institute for Health and Care Excellence (NICE) Guidelines

In the UK, NICE (who provide evidence-based guidelines and information on health conditions for use in healthcare practice [9]) have produced evidence-based guidelines on the identification and treatment of OA. Diagnosis of OA is based on 3 criteria:

- Age: >45yrs
- Activity related joint pain
- Morning stiffness in the joint <30mins

It was concluded that radiological evidence of OA was not needed for diagnosis as x-ray changes were not consistently linked with symptoms of OA. Therefore, a diagnosis of OA is to be made without further investigation if the above criteria are met. However, if an alternate diagnosis is possible it is recommended that further procedures e.g. imaging, are carried out to eliminate these alternate diagnoses [10].

1.2 Prevalence and Incidence of OA

1.2.1 Worldwide

OA is common worldwide but there are relatively few large population based studies which makes estimating worldwide incidence and prevalence of OA difficult. Other factors, which make estimating OA prevalence and incidence difficult, are discussed further in section 1.2.3.

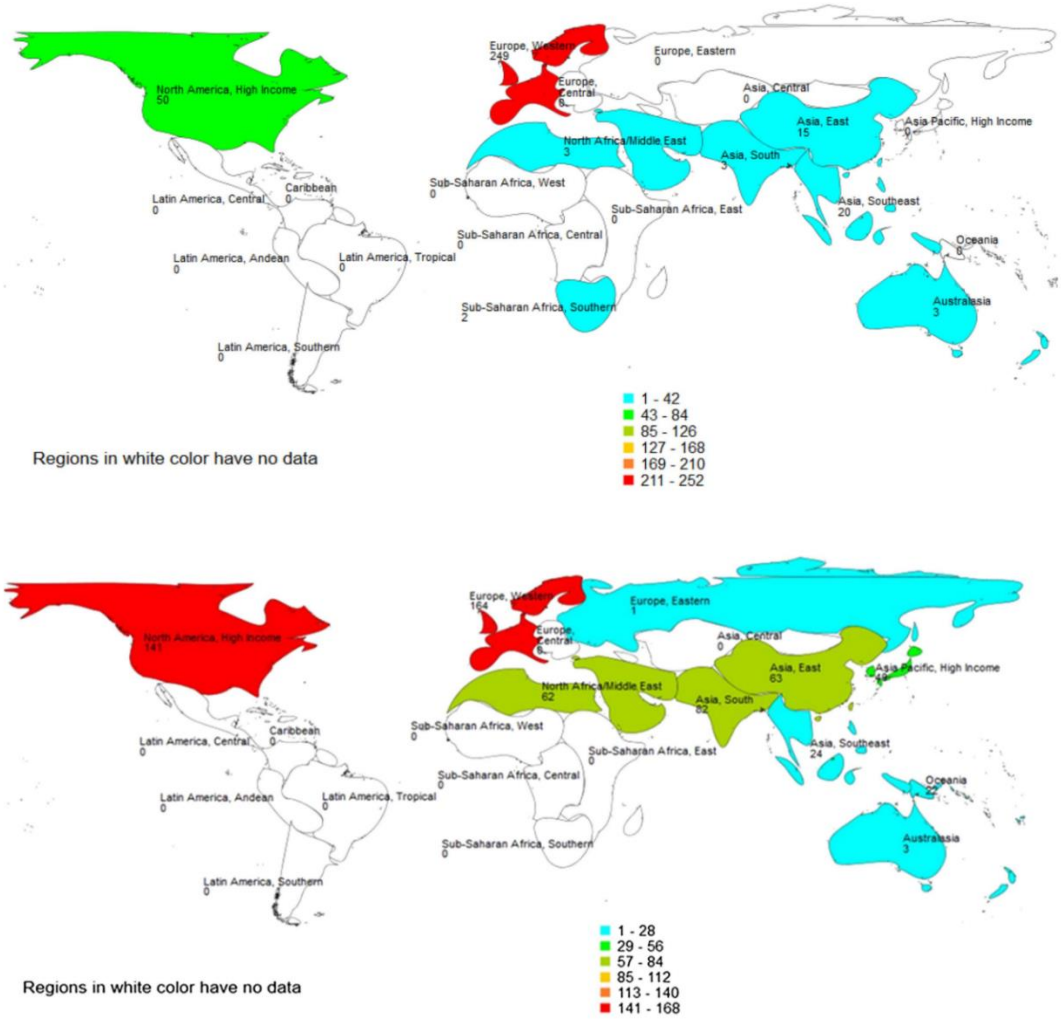


Figure 1.1: Global burden of disease 2010 data on the total amount of available data (n= of studies) by geographical location for KOA prevalence estimates (top) and hip OA prevalence estimates (bottom). Taken from Figure 1 &2 [1, 11]

The largest available epidemiological study of OA prevalence is the 2010 Global Burden of disease study which systematically reviewed and compiled data on the prevalence of symptomatic, radiologically confirmed (K&L Grade 2-4) hip OA (HOA) and KOA. In this data compilation, Back OA was excluded on the basis it would be included in estimates of back and neck pain. Prevalence estimates were derived from 102 published studies with most studies originating from Western Europe and North America (see Figure 1.1). Prevalence of KOA in 2010 was estimated at 3.8% globally, with a higher prevalence in females (mean 4.8%) than in males (mean 2.8%), with prevalence peaking at 50years (see Figure 1.2). HOA was less common than KOA, with a worldwide prevalence estimate of 0.85%, with, again, higher prevalence in females (mean 0.98%) than in males (mean 0.7%). Prevalence increased steadily with age (see Figure 1.2) with no peaking [11]

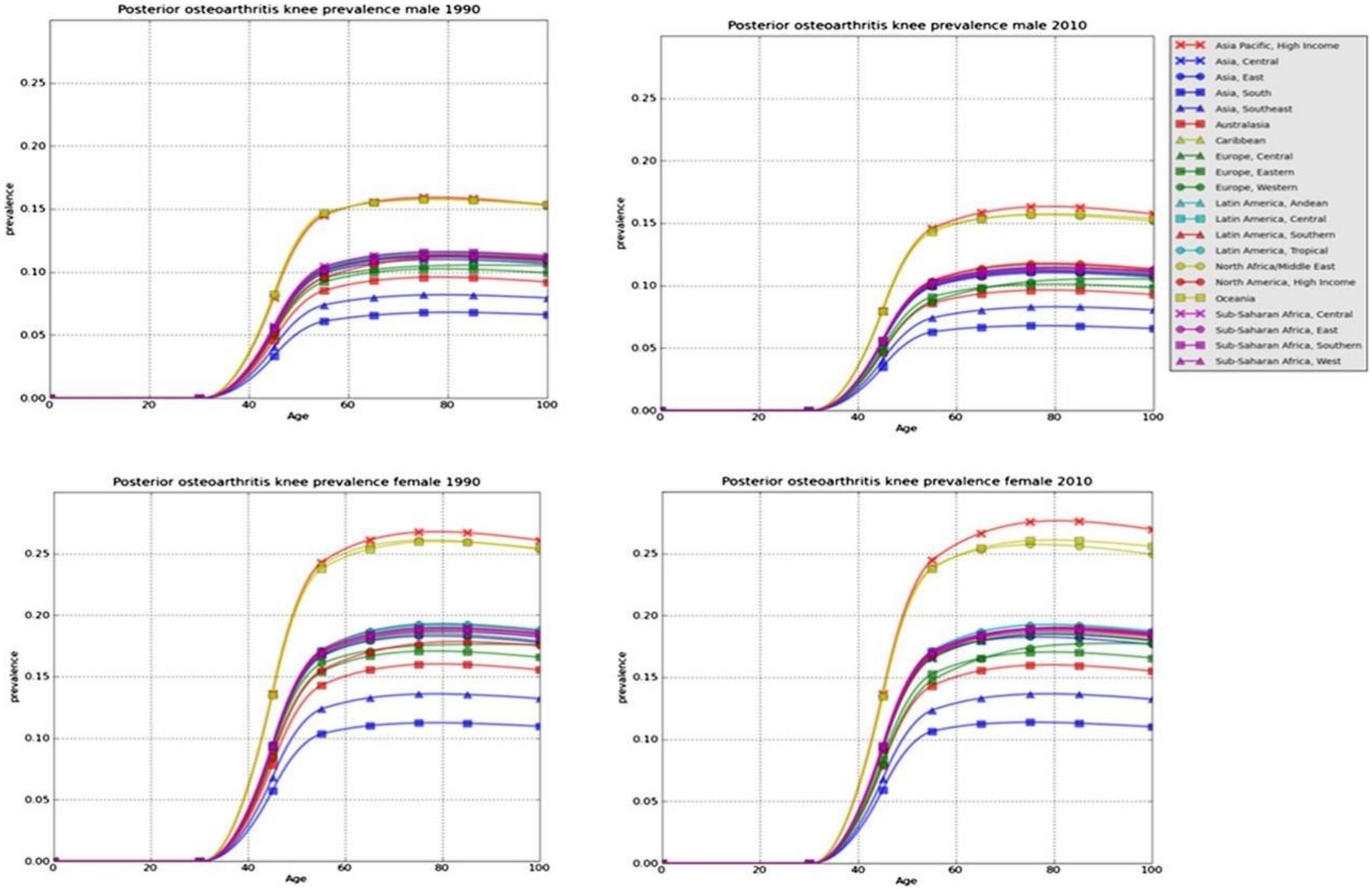


Figure 1.2: Prevalence (y-axis) of radiographic symptomatic KOA in males (top left) and females (bottom left) and radiological symptomatic HOA in males (top right) and females (bottom right) by age (x-axis) and country (individual's lines).Taken from Figure 3 and 4 [11]

Estimates of prevalence of OA will vary according to the definition of OA used (symptomatic or radiographic criteria), the joint affected and geographical location. In the large American cohort study, The Framingham Study, prevalence of radiological and symptomatic OA at several different sites (hand, hip and knee) was estimated. For HOA, age standardised prevalence of radiographic OA (defined as K&L grade >2) was 19.6% which was almost 5 times higher than age-standardised prevalence for symptomatic OA (defined as radiographic OA plus hip pain) which was 4.2%. [12] Similarly, for KOA, prevalence of radiological KOA (K&L grade >2) at 15.7% was more than 50% higher than the prevalence of symptomatic KOA (pain experienced on most days >1month) estimated to be 9.5%. Prevalence increased with age and was generally higher in women than in men (see Table 1.3).[13]

Prevalence of radiographic and symptomatic KOA in subjects of The Framingham Study		
Age (years)	% radiographic KOA	% symptomatic KOA
<70	27.4	7
70-79	34.1	11
>80	43.7	11.2
All women	34.4	11.4
All Men	30.9	6.8

Table 1.3: The prevalence of radiographic and symptomatic KOA in the Framingham Cohort (n=1805). Adapted from Table 3 and table 5 [13]

Age standardised prevalence of radiographic Hand OA (K&L grade >2) was 44.2% in women and 37.7% in men, which, again, were several times higher than the age standardised prevalence of symptomatic Hand OA (radiographic OA plus pain/stiffness) which was 14.4% and 6.9% in women and in men respectively [14]. Compared with data on OA prevalence, there are few reports on incidence rates of OA. However, an American cohort study using data from a large community health centre estimated incidence rates of 100, 88 and 240/100,000 person years for hand, hip and knee OA respectively [15].

1.2.2 UK

According to estimates by Arthritis Research UK (ARUK), 8.75 million people in UK have sought treatment for OA which equates to a third of people aged >45years. In the UK,

4.11, 2.46, 1.77 and 1.56 million people were estimated to have OA of the knee, hip, foot/ankle and hand/wrist respectively [16]. According to data from ARUK, this equates to 10.92% and 18.25% of the total UK population having hip and knee OA respectively [17]. KOA is the most common form of OA in the UK, contributing to half of all consultations regarding OA. [16]

Prevalence of OA differs by gender, BMI and physical activity level. Prevalence of KOA is higher in Females (19.7%, n=2,332,130) than in males (16.55%, n=1,775,721) in the UK.

OA prevalence also increases with increasing age and BMI (see Table 1.4 and Table 1.5) [17].

	Prevalence in the UK population	
Age	Hip OA	Knee OA
45-64	10.93	18.6
65-75	11.44	19.21
>75	10.27	15.79

Table 1.4: The association of age on UK prevalence rates (% of total UK population) of KOA and HOA. Adapted from [17]

	Prevalence in the UK population	
BMI	Hip OA	Knee OA
Underweight (<18.5)	8.38	12.5
Normal (18.5-25)	8.34	12.41
Overweight (25-30)	11.17	17.95
Obese (>30)	14.45	27.61

Table 1.5: The association of BMI on UK prevalence rates (% of total UK population) of KOA and HOA. Adapted from [17]

1.2.3 Problems with Estimating OA prevalence and Incidence

The Global Burden of Disease study 2010 pointed out many limitations to estimating OA prevalence and incidence.

Firstly, as most of the data regarding OA prevalence is concentrated within North America and Western Europe, it is unclear if estimates based on this are representative of worldwide prevalence. The authors recommended that future research should focus on population studies in areas of missing data (see Figure 1.1), such as South America, Africa and parts of Asia, so that global estimates are more accurate and representative.

Secondly, estimates of prevalence and incidence can vary depending on the definition of OA used, with studies using estimates based on radiographic evidence being generally higher than estimates based on symptomatic OA definitions. This presents a problem with the comparability of studies which use different definitions of OA. [11]

1.2.4 Disease Burden

As the global population ages and prevalence of obesity increases, it is important to consider the burden of OA, as this is set to become a major problem in the future [11]. The WHO scientific group on Rheumatic disease estimated that 10% of the global 65+ population have clinical problems attributable to OA [18] and due to a global ageing population and increasing obesity rates this is expected to rise to 140% of current OA prevalence by 2025 [19].

The burden caused by OA can be viewed from different perspectives, including implications for quality of life for the individual sufferers and direct and indirect cost to society.

1.2.4.1 Burden to the Individual

KOA often results in pain and severe disability and affects everyday life because it limits ability to perform activities of daily living (ADLs) such as walking, climbing stairs and squatting. These symptoms and related limitations often lead to more far reaching impacts on the patients' lives including social interaction, mental functioning and sleep quality. In consideration of this Health-Related Quality of Life (HRQoL) is often measured in studies of OA populations. HRQoL comprises 5 dimensions; physical, psychological, social and cognitive functioning and well-being [19]. Previous studies have consistently found lower HRQoL scores (indicating worse outcomes) in KOA populations compared to the general population which inversely correlates with pain and radiographic KOA severity [20, 21]. As knee pain is the strongest correlate regarding HRQoL in KOA patient, treatments which aim to improve quality of life in this clinical population need to be effective in reducing pain [19].

1.2.4.2 Burden to Society

The GBD 2010 study identified KOA as the 11th largest determinant of global disability (rising from 15th place in 1990) and estimated that it contributed to 2.2% (17.1 million) of the global years lived with disability [11].

In an analysis of DALYs (disability adjusted life years - a combination of years of life lost due to premature mortality and years lived with disability) for 291 diseases worldwide, MSK disorders accounted for 6.8% of total DALYs with 10% of this being due to OA. This equates to 249 DALYs per 100,000 people according to 2010 estimates. [22]

Apart from the physical restrictions associated with OA, there are also social and mental impacts e.g. limitations on social interaction, mental functioning and quality of sleep [19]. Lower Health Related Quality of Life (HRQoL) has also been reported in those with KOA which inversely correlates with joint pain and disease severity [19].

a) Direct Costs

Direct costs involve those directly related to the treatment of OA. Estimates of direct costs are variable depending on the geographical location and study population. Costs of treating people in the USA and Canada are approximately double those who do not have OA, at a cost of $3952/year in Canada and $5294-5704/year per person with OA in the USA [23].The direct costs of OA in Italy (as a result of hospitalisation, diagnosis and treatment) was estimated at €934/year, with 25% of that cost attributable to hospitalisation, despite the low numbers of patients hospitalised in the sample. Therapy was the smallest component of costs equivalent to €144/patient/year [24].

There is no published research data relating to direct costs of OA in the UK. However, a 2008 costing report published by NICE found that, in 2005-2006, 167,000 and 1.4 million OA patients were prescribed topical and ORAL NSAIDs respectively, at a cost of £8.5 million and £25 million respectively. In addition, £25 million was spent on arthroscopic debridement procedures, which are limited for use only in patients with mechanical problems due to their OA. It was estimated that £852 million was spent on hip and knee replacements in 2010, far outstripping the cost of other OA treatments [25].

b) Indirect Costs

Indirect costs refer to costs incurred not as a result of medical cost for OA, but due to loss in wages, productivity and increased costs such as childcare and home care needed as a result of OA. An analysis of costs related to OA concluded OA populations incurred several additional indirect costs compared to non-OA populations including; 3 additional days of medical care per year, increased costs associated with home care, childcare and home remodelling and loss of jobs and earnings [23].

The indirect cost of OA in the UK is significant, with an estimated 32 and 30.6 million working days lost in 2002 and 2013 respectively due to musculoskeletal problems. Financial costs due to loss of work was also substantial, with £2.41 million paid in Disability Living Allowance (DLA) to those with arthritis, more than for heart disease, stroke and cancer combined. [25]

A summary of the direct and indirect costs of OA in various countries was compiled by Chen 2012 [25], and is summarised in Table 1.6.

Author	Year of Study	Country	Cost type studied	Individual cost per annum (2010 £) per OA patient	Population cost per annum (2010 £)
McClean *et al.*	1993	USA	Direct cost	£1,526	US $548 million
Lanes *et al.*	1994	USA	Direct cost	£496	N/A
Buckwater *et al.*	2000	USA	Indirect cost	N/A	£2-8 billion
Kotlartz *et al.*	2005	USA	Indirect cost	£355	£7.25 billion
Maetzel *et al.*	2000	Canada	Direct cost Indirect cost	£3162 £1407	N/A
Gupta *et al.*	2002	Canada	Direct cost Indirect cost	£1768 £9986	N/A
Loza *et al.*	2003	Spain	Direct cost Indirect cost	£1292 £209	£4.04 billion £654 million
Le Pen *et al.*	2003	France	Direct cost	£316	£1.58 billion
Leardini *et al.*	2001	Italy	Direct cost Indirect cost	£981 £1299	N/A
Woo *et al.*	2001	Hong Kong	Direct cost Indirect cost	£6561 £620	£323 million (combined)
Xie *et al.*	2005	Singapore	Indirect cost	£ 610-£730	N/A

Table 1.6: Annual direct and indirect costs of OA (per patient and total population) in 7 different countries. Taken from Figure 2 [25]

1.3 Pathophysiology of KOA

The pathogenesis of KOA is complex and current research is concentrating on the role of all joint tissues in the pathology of KOA. Broadly speaking OA can be considered an imbalance between the breakdown and repair of all the joint tissues, leading to a variety of pathological changes, including:

- Hyaline cartilage loss
- Subchondral bone remodelling
- Capsular stretching
- Quadriceps muscle weakness
- Synovitis
- Ligament Laxity
- Development of bone marrow legions
- Bone misalignment [26]

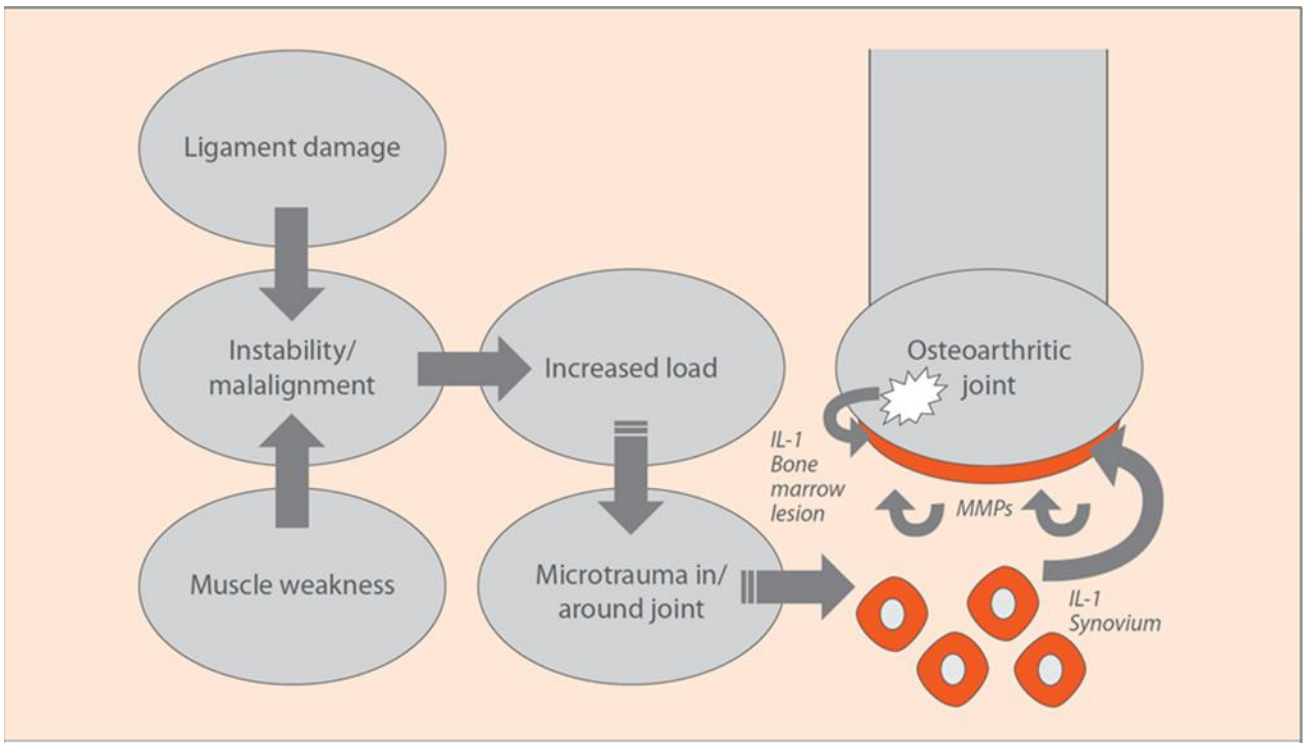


Figure 1.3: Model of OA of the biomechanical and inflammatory factors which cause structural damage in OA. Taken from Figure 1 [27].

Whilst many attempts have been made to compile a model of OA pathogenesis, these have been hampered by the complexity and changing ideas of what is involved in the pathogenesis of OA. However in a report by ARUK (2011), a model summarising the more recent evidence regarding OA pathogenesis was proposed (see Figure 1.3). This model highlights a shift from the 'wear and tear' hypothesis (which states that wear accumulated over a lifetime leads to the development of OA) to 'tear, flare and repair' where 'tear' represents some factor causing damage to the joint (e.g. overuse or obesity), 'flare' representing inflammatory processes which take place in OA, and 'repair', the processes the joint undergoes to repair the damage. In the case of OA, this last 'repair' step may be suboptimal, leading to chronic damage or 'tears' which accumulate and result in OA. [28]

It is thought OA is initiated when individual risk factors result in the changes in the joint which are illustrated in Figure 1.3. The exact risk factors (which I have explained in more detail in section 1.4) which drive the development of OA vary between individuals.

According to the 'wear, tear and repair' theory, the process of KOA pathogenesis can be split into several main steps:

1. Biomechanical factors ('Wear and Tear'):

Biomechanical factors may contribute to Instability in the joint, which increases loading in the joint beyond its normal capacity. This can then lead to micro trauma or injury to the joints tissues. Such biomechanical factors may be the result of acute injury, 'tear', (such as ligament rupture or fracture of the bone's articular surface) or more chronic in nature, 'wear', (e.g. mild developmental abnormalities, occupation related or repetitive activity, heavy loading on the joints, bone misalignment and obesity). The trauma or 'tears' which occur due to the above biomechanical factors are thought to contribute to the subsequent inflammatory effect in the joint seen in OA. [27]

2. Joint Inflammation and Biochemical Mediators ('Flare'):

Historically, OA was considered a purely mechanical disease [29] but more recent studies have highlighted the important role of chronic inflammation in the pathogenesis and progression of OA [30-32]. It has been proposed that the inflammatory molecules produced as a response to biomechanical factors (and other potential systemic inflammatory drivers, e.g. metabolic syndrome, obesity and ageing) may tip the homeostasis of the joint tissues to net degradation.

There are 2 main sites of inflammation in the OA joint: synovium and subchondral bone. Synovitis is now considered one of the hallmarks of KOA (discussed in more detail below) and bone marrow lesions in the subchondral bone are common. [27, 29, 33]. Inflammatory cytokines and chemokines are thought to be produced by these tissues (mainly by the synovial cell and chondrocytes) locally, and can be measured in the synovial fluid of OA patients. Commonly these inflammatory molecules include; IL1, TNFα and MMPs (see the section 1.3.1 below for more detail about the inflammatory process in the joint tissues) and are thought to upregulate the production of enzymes e.g. aggrecanases and proteinases which degrade the cartilage. [33]

3. Bone Response ('Repair'):

There are two main ways in which the bone responds to the above biomechanical and inflammatory insults; the formation of bone marrow oedema and cysts and the formation of osteophytes (see section 1.3.1 below for more detail about these bone responses). Both of these responses seem to be attempts to remodel and repair damaged bone tissue. In particular, bone marrow oedema correlates with joint pain in OA and with the progression of bone and cartilage lesions [27, 34].

1.3.1 The role of individual joint tissues in the pathogenesis of OA

Considerable research has focused on identifying the involvement of the different joint tissues in the pathogenesis of OA. Whilst it is important to consider the process as a whole each tissue in the joint may respond differently to the OA development process, which eventually leads to disease.

Below I have summarised the current evidence regarding the pathogenesis of OA in the various joint tissues.

1.3.1.1 Cartilage

Changes to the joint cartilage are the most characteristic pathological changes associated with OA. Cartilage is an avascular tissue composed of collagens, proteoglycans and chondrocytes, which maintain the extracellular matrix (ECM). During OA, the equilibrium between the breakdown and synthesis of the ECM by chondrocytes is disrupted, resulting in a net breakdown of cartilage tissue.

Chondrocytes can respond to biomechanical influences (e.g. joint injury, instability and stress) and inflammatory molecules (e.g. cytokines and growth hormones), by prompting the release of degradative enzymes leading to the breakdown of the cartilage. I have summarised below two of the processes, inflammation and mechanical loading, which may lead to the expression of these degradative enzymes.

MMPs (e.g.MMP-1, MMP-8, MMP-13, MMP-2, and MMP-9) and aggrecanases (ADAMTS-4, ADAMTS-5) are dysregulated in OA and degrade collagen and proteoglycans in the cartilage ECM. [35]

a) Inflammation

Pro-inflammatory molecules, such as cytokines and chemokines, are produced by a number of joint cells in OA, including primarily, the synovial cells and chondrocytes. Chondrocytes then respond to these cytokines by producing proteinases and prostaglandins. These cytokines can promote the release of further pro-inflammatory cytokines, (e.g. IL-1 can induce the release of many pro-inflammatory cytokines) and so amplify the effect. Adipokines (pro-inflammatory cytokines released from white adipose tissue) have also been implicated in this process and may partly explain the link found between obesity and OA progression. This is discussed in more detail in section 1.4.2.1.

b) Mechanical Loading

Abnormal mechanical loading on the joint has been established as a risk factor for OA, particularly KOA. This process may be mediated though the chondrocytes which, in response to mechanical loading, increase expression of inflammatory molecules and proteases. This is a result of the activation of chondrocyte receptors, which usually activate in response to ECM components, but which are also activated by mechanical stimulation. [35, 36]

1.3.1.2 Bone

The role of the subchondral bone in the normal functioning of the joint is important, firstly in supporting the specific shape of the cartilage (important for smooth joint articulation) and for absorbing shock/stress applied to the joint.

In OA, it is thought that repeated damage, or micro trauma, to the bone (brought about by biomechanical stresses) stimulates bone remodelling (where damaged bone is broken down by osteoclasts and replaced with new bone by osteoblasts). However, in OA, bone remodelling is increased and bone remodelling is high, resulting in abnormal growth and structural changes to the bone in response to damages [37]. It was originally thought that OA pathogenesis started with an increase in subchondral bone stiffness, which had subsequent impacts on the articular cartilage and a detrimental effect on the ability of the bone and cartilage to adapt to mechanical stresses [38]. However, it has been subsequently found that in early OA subchondral

bone density is decreased and existing bone hypomineralised, resulting in bone that is more easily deformed under mechanical pressure. The result of these bone changes is the increased loading on, and damage to, the cartilage. [34, 39]

The abnormal bone growth, characteristic of OA subchondral bone, can take several forms and include: thickening of the subchondral plate, formation of osteophytes and formation of bone marrow lesions (BMLs) [37]. BMLs appear to be localized to areas of increased bone remodelling in the trabecular bone, which are sclerotic and hypomineralised, possibly the result of bone damage [40]. The presence and quantity of BMLs strongly correlate with knee pain, KOA progression and cartilage loss [41-43]. Osteophytes are bony outgrowths found at the edge of the joint. Osteocytes develop when periosteal cells (cells of the periosteum, a connective tissue which surrounds the bone) proliferate and differentiate into chondrocytes. These chondrocytes are then ossified and form the bony outgrowth which is the osteocyte. They are found in areas where joint loading occurs and are thought to contribute to the stability of the joint [34].

1.3.1.3 Synovium

The presence of synovitis (inflammation of the synovial membrane which surrounds the joint) is now recognised as common and characteristic at all disease stages of OA, although to a lesser degree than that seen in RA.

Several changes occur in the synovium during OA, including:

- Thickening (hyperplasia) of the lining layer of the synovium
- Increased vascularity
- Infiltration of the synovium with inflammatory cells (mainly lymphocytes and monocytes)
- Fibrosis of the synovium (seen in late stage OA)

a) Synovial Changes in Early OA

Studies in participant's with early stage OA showed histological evidence of synovium lining proliferation, macrophage infiltration and increased vascularity [44]. Synovitis is fairly common and was present in 55% of participant's with early OA [45].

b) Synovial Changes in Late OA

The main difference in the synovium of those with late stage OA is the type of inflammatory cell which infiltrates the synovium. Instead of macrophages, there are more lymphocytes, a characteristic which is more similar to RA [45].

Synovitis has an important role in cartilage degradation and in the pathophysiology of OA. The immune cell infiltrates and cytokines released by these immune and synovial fibroblast cells contribute to the destruction of the cartilage by stimulating the release of proteases which degrade the cartilage ECM (see Fig 1.4 below). The change in permeability of the normally semi-permeable synovial membrane during OA, also allows essential large molecules (lubrican and hyaluronic acid) to escape from the joint, resulting in a lack of joint lubrication.

Synovitis is correlated with OA symptoms, predominantly pain and loss of function as well as rapid cartilage destruction [46, 47].

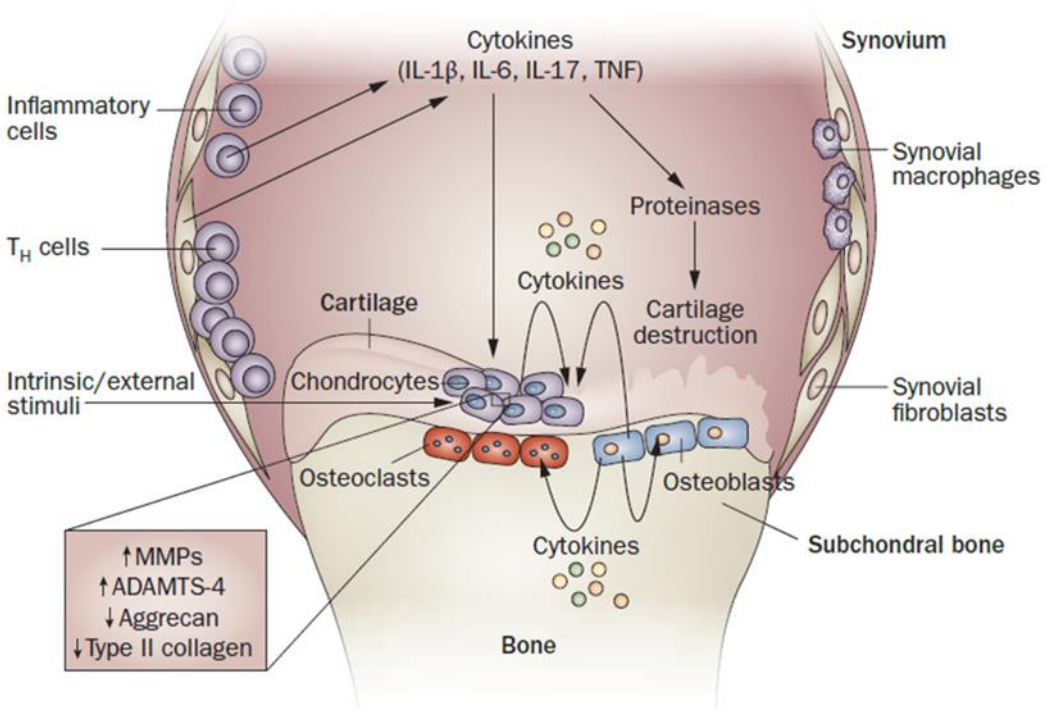


Figure 1.4: The sources and effect of pro-inflammatory cytokines in the pathogenesis of OA. Pro-inflammatory cytokines are secreted by inflammatory cells which have infiltrated the synovium and the synovial fibroblasts. Cytokines stimulate the release of proteinases which result in destruction of the cartilage. Taken from Figure 1 [48].

1.4 Risk Factors for OA

Many potential risk factors for OA have been identified which may contribute to the development and progression of OA. These risk factors can be classified into systemic (those affecting the whole body) and local (those acting on the joint) factors. They can also be split into modifiable (factors which can be changed) and non-modifiable (factors which cannot be changed) risk factors (see Table 1.7)[2]. Classifying and identifying risk factors are important firstly for identifying the groups at high risk of OA, and secondly in the case of modifiable factors, as a basis for the development of interventions which may slow the progression of OA. Below I have summarised the main risk factors identified in the development and progression of OA.

Summary of KOA risk factors		
	Systemic Factors	**Local Factors**
Non-Modifiable	Age Gender Ethnicity Genetics	
Modifiable	Obesity Nutrition Bone Density Smoking Hormonal Staus	Obesity Abnormal Joint loading Joint alignment Occupational activities High impact/intensity sports Past joint injury/surgery Muscle (quadriceps) weakness

Table 1.7: Risk factors for OA development and progression, classified by locality in the body (systemic or local) and ability to change (modifiable and non-modifiable)

1.4.1 Non-Modifiable Risk Factors

1.4.1.1 Age

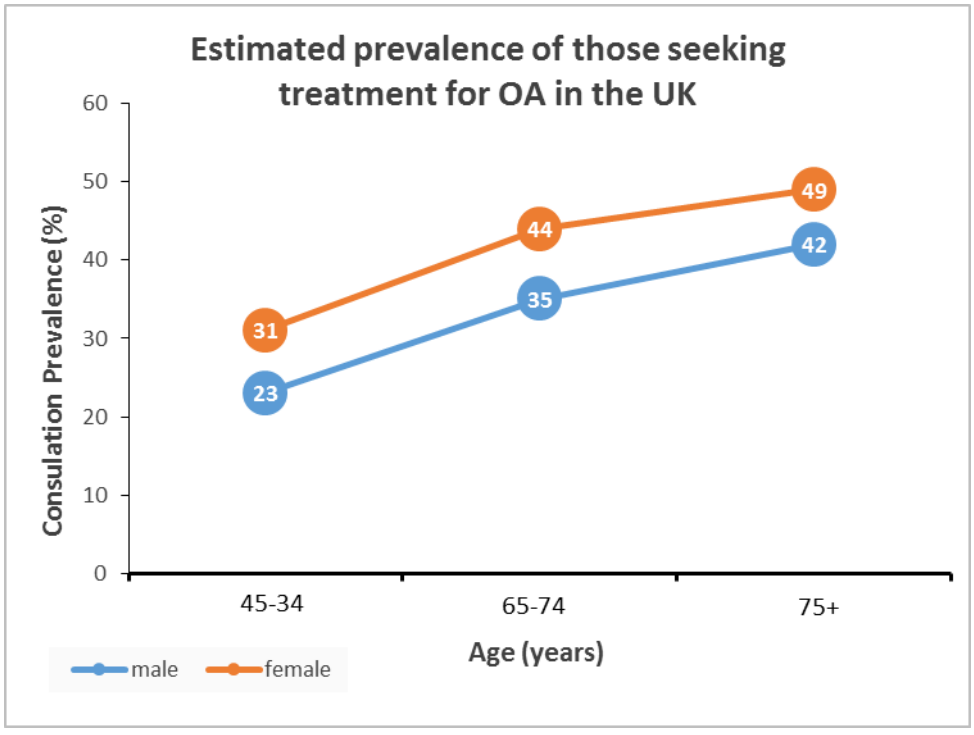


Figure 1.5: Estimated prevalence of those seeking treatment (estimated by number of GP consultations) for OA in the UK in 2015 by age and gender. Adapted from Figure 2 [49]

OA is classically considered an 'age related disease' and has been consistently identified as a significant risk factor for the onset of KOA [50, 51]. The relationship between age and KOA is nonlinear, with a step increase in KOA incidence occurring from 50-75 years and then slower increases in incidence after this [51].

Estimates by ARUK on people seeking treatment for KOA, affecting 33% >45 year olds and 49% women and 42% men >75years in the UK (see Figure 1.5).

Although the incidence of OA increases with age, OA is not an inevitable consequence of age. On this basis, it has been hypothesised that ageing causes changes to the MSK system which increases susceptibility to development of OA when exposed to other OA risk factors [50]. In Table 1.8 below I have summarised some of the changes that occur in the MSK system with increasing age and indicated how these changes may affect the development of OA.

Age-related changes to the MSK system	Effect on the development of OA
As cells age, they can adopt a 'senescent secretory phenotype' (characterised by the secretion of cytokines and Matrix Metalloproteinases [MMPs]). This phenotype is very similar to the changes seen in chondrocytes during OA (increased production of cytokines and MMPs). It is possible that induction of this senescent secretory phenotype in chondrocytes with age may increase likelihood of OA related changes	Increased production of cytokines and MMPs by chondrocytes stimulates the release of proteinases by chondrocytes. This leads to degradation of collagen and aggrecans in cartilage (important in maintaining the structure of the cartilage). This may result in the characteristic cartilage degradation seen in OA.
Older chondrocytes have a reduced response to growth factors (IGF-1, BMP-7, TGF-β), which normally stimulate the production of anabolic enzymes. A reduced response of chondrocytes to growth factors has also been observed in OA.	Reduced production of anabolic enzymes results in decreased production of the ECM components of the cartilage. This potentially 'tips the balance' in the cartilage to net destruction of the cartilage tissue.
Changes to the cartilage matrix proteins can occur over time with increased production of Advanced Glycation End-products (AGEs) occurring with increasing age. AGEs spontaneously form as a result of glycation of proteins. The turnover of proteins in the joint is very low (especially type 2 collagen which has a half-life of 100 years), providing opportunities for AGE accumulation specifically in cartilage.	AGE formation in collagen causes 'cross-links' to be formed which can change the biomechanical properties of the cartilage, making it more stiff and brittle and increasing the risk of injury/damaged to the cartilage under normal loading.

ROS (Reactive Oxygen species) production increases in ageing tissue, including in the cartilage. Because of the slow turnover of cells and matrix components in the cartilage, any ROS produced may accumulate, causing DNA damage in the chondrocytes which has several effects. Firstly, ROS may induce a senescent cell phenotype and therefore reduce cartilage ECM production. Secondly, cytokines released during OA, can induce ROS production in chondrocytes which can further induce the production of MMPs	ROS may tip the balance of cartilage homeostasis to degradation by 2 methods. Firstly decreasing anabolism of new ECM component by inducing a senescent phenotype in chondrocytes. Secondly by inducing the production of MMPs which actively cleave ECM components.

Table 1.8: Summary of the changes in the MSK system with increasing age and their potential impact on the development of OA. [50, 52, 53]

1.4.1.2 Gender

The incidence and prevalence of OA are higher in women than in men from the age of 50, particularly in the hand, foot and knee [2]. A 2010 meta-analysis of 8 studies has reported a pooled OR of 1.84 (95% CI 1.32–2.55) in favour of females having KOA. [54] The effect has been demonstrated to be independent of differences in body composition as a 10 year follow up study showing obesity (defined as a BMI >30kg/m2) was significantly associated with KOA incidence at 10 years (OR: 2.77, 95% CI: 1.35, 5.71). According to this analysis there were no statistically significant interaction effect between gender and BMI, with the multivariate adjusted (adjusted for age, gender, work type and leisure time activities) association between obesity and KOA at 10 years demonstration a OR: 2.81 (95% CI: 1.32, 5.96). [55]

It is unclear why this gender difference exists but it has been suggested that risk factors may differ between genders. The increase in OA incidence, particularly after the menopause in women, suggests hormonal status may be involved. However the mechanism through which female hormones such as oestrogen may affect OA incidence and progression is unclear and the available evidence is contradictory. [2] Cohort studies suggest that oestrogen may be protective in the development of OA [56-58], whereas other studies suggest exposure to oestrogen may lead to increased bone mass, which increases the risk of OA [59].

1.4.1.3 Ethnicity

Prevalence of OA amongst different ethnicities differs, with comparisons between white and African American people the most extensively researched [2]. For example, the Johnson County Osteoarthritis Project (American population study (n=3018)) measured the prevalence of knee symptoms, radiographic and symptomatic KOA and found a non-significant trend for higher prevalence of knee symptoms, radiographic and symptomatic KOA and a significantly higher prevalence of severe (K&L grade 3-4) radiographic KOA in African Americans compared with Caucasians. [60]

The reasons for the ethnic differences in OA are unclear and are likely multifactorial, involving lifestyle, socioeconomic and genetic factors [2].

1.4.1.4 Genetics

There is strong evidence for genetic involvement in OA risk and heredity may explain 65% risk in hand and hip OA, and 40% of the risk for KOA [61]. However the genetics of OA are complex and it is likely the result of polygenic inheritance rather than by inheritance of a single gene [62]. Many genome wide association studies (GWAS) [63-66] and candidate gene studies have been conducted in KOA populations, however so far these studies have yielded inconsistent results, with only one OA candidate gene, growth differentiation factor 5 (GDF5), consistently reported as being associated with KOA [67-69].

A 2014 meta-analysis reviewed the results of nine GWAS of >24,000 single nucleotide polymorphisms (SNPs) in 199 previously identified OA candidate genes in 5636 KOA patients and 4349 HOA patients. The results of the meta-analysis concluded that of the 199 candidate genes tested, no genes were significantly associated with KOA and two genes, COL11A1 and VEGF (in men only), will significantly associated with HOA. [70]

1.4.2 Modifiable Risk Factors

1.4.2.1 Obesity

Obesity is a significant risk factor for incidence and progression of KOA. How obesity mediates this greater risk can be attributed to its biomechanical and biochemical effects:

a) *Biomechanical effects of obesity in KOA*

i) Overloading

Overloading of the knee because of the increased weight in obesity may cause joint damage and instability, exacerbating progression of KOA. In support of this idea, it has been shown that for every kg increase in body weight, there is 2-3kg increase in the overall force across the knee [2]. This excessive mechanical force on joint tissues can lead to:

- Changes in cartilage composition and structure leading to cartilage breakdown [2]
- Bone marrow lesions [71]

ii) Mechanoreceptor Activation

Chondrocytes, osteoblasts and synoviocytes possess mechanoreceptors, and it is hypothesised that increased load as a result of obesity can activate these mechanoreceptors, leading to a signalling cascade which induces the expression of cytokines, MMPs and prostaglandins, thus adding to the effects of inflammation seen in KOA and accelerating the breakdown of the cartilage [72]

b) Biochemical effects of obesity in KOA

Obesity is also a strong risk factor for OA in non-load bearing joints e.g. hand joints [73], suggesting that there is a systemic mechanism through which obesity mediates KOA. The following theories are proposed to explain how this may occur:

i) Adipokines

Adipokines (e.g. leptin, adiponectin and resistin), cytokines produced by adipose tissue, which are elevated in osteoarthritic joint tissues, have been proposed as candidates in mediating the systemic effects of obesity in OA pathogenesis [74]. The role played by adipokines in OA is not yet clear but it is thought they cause damage directly to joint tissue and indirectly through control of inflammatory pathways [75].Summarised below is current evidence on the adipokines thought to be key in OA:

ii) Leptin

Leptin concentrations increase with increasing adiposity [76] and, in the obese, are higher not only in the blood but also in osteoarthritic cartilage and subchondral bone [74]. Leptin has many pro-inflammatory, catabolic effects in OA, e.g.

- Inducing release of collagen from cartilage resulting in cartilage degradation
- Up-regulating MMP1, MMP-9 and MMP-13 expression in chondrocytes
- Up-regulation of pro-inflammatory cytokines e.g. IL-1b
- Increasing expression of aggrecanases ADAMT-4 and 5 [72, 74, 75]

iii) Adiponectin

The role of adiponectin in OA is contradictory. Adiponectin concentrations have been observed to be 100-fold higher in the synovial fluid of OA joints compared with corresponding concentrations in serum. Some evidence suggests that adiponectin may have a protective effect in OA by down- regulating MMP-13 and pro-inflammatory cytokine expression [75] and by increasing expression of the MMP inhibitor TIMP-2. However, some studies suggest a pro-inflammatory effect of adiponectin by stimulating vascular endothelial growth factor (VEGF) and MMP production [71].

iv) Resistin

Resistin stimulates production of pro-inflammatory cytokines (e.g. TNFα, IL-1b, IL-6)[74], which may be key in the pathogenesis of inflammation seen in OA [48]. In mouse cartilage extracts, resistin stimulated proteoglycan degradation and, in human explants, inhibited its synthesis, resulting in cartilage matrix breakdown [77].

c) Metabolic Factors

Obesity may induce other systemic metabolic effects which affect OA pathogenesis such as disordered glucose and lipid metabolism, which result in increased pro-inflammatory cytokine production. However few studies have focused on the effect of these metabolic factors in the obese with KOA [75].

1.4.2.2 Nutrition

In addition to nutrition's importance as a determinant of obesity, the role of individual nutrients in influencing OA risk have been investigated. The results of these nutrient trials are conflicting and unclear after being reviewed systematically, as can be seen in Table 1.9 below.

Nutrient Investigated	Concluded effect on KOA
Glucosamine	Results of systematic reviews regarding the effect of glucosamine on KOA outcomes are variable but generally report small improvements in KOA outcomes in response to glucosamine supplementation. A 2010 systematic review of 10 trials concluded no clinically significant reductions in KOA pain (measured by 10mm VAS) [78]. A 2015 systematic review of 31 studies concluded significant improvements in WOMAC Pain and Functions scores SMD: −0.75 (95% CI: −1.18, −0.32), −4.78 (95% CI: −5.96, −3.59) with glucosamine supplementation [79]. However, NICE have concluded that clinicians do not offer the use of glucosamine for treatment of OA [10].
Chondroitin	Results of systematic reviews of the effect of chondroitin on KOA generally show an effect of chondroitin on KOA pain. A 2007 systematic review of 22 trials of chondroitin in OA showed a large effect size of -0.75 (95% CI: -0.99, -0.50) of chondroitin vs placebo for pain outcomes (difference of 1.6/10cm pain scale). However there was a high level of heterogeneity between studies identified (I^2 of 92%, p=0.001). Analysis of difference in change between chondroitin and placebo in JSN (mean difference: 0.23mm) revealed a small effect size of 0.18 SD units (0.23 mm, 95% CI: 0.09, 0.37) in favour of chondroitin. [80] In a 2015 systematic review, it was concluded that chondroitin supplementation was associated with

	significant reductions in pain (mean -0.45cm/10cm) and JSN (standardised mean difference [chondroitin vs placebo] of 0.29, 95% CI 0.04-0.50) compared with placebo treatment [81]. However NICE have concluded in their 2014 report that chondroitin should not be recommended for treatment of OA [10].
MSM (Methylsulfonylmethane)	Moderate amounts of evidence exist for the effect of MSM on KOA over 3 months [82]. Of the two RCTs published, one showed a significant decrease in pain index score (p=<0.001) with 1500mg/d MSM and the other reported a significant improvement in WOMAC pain and physical function compared to placebo with 3g/d of MSM [83, 84].
DMSO (dimethyl sulfoxide)	Evidence for the efficacy of DMSO on KOA is unclear [82]. Of the four RCTs published all were short term (3-4 weeks) and used 'suboptimal' doses of DMSO. The results of these studies were contradictory, with one showing a significant difference in VAS pain between DMSO and placebo (p=0.015) and another showing no difference between DMSO and placebo in WOMAC Pain (p value NR) [85, 86].
Vitamin D	Several observational studies have identified an inverse relationship between 25OHD concentrations and KOA outcomes [87-89], although evidence from supplementation studies are currently limited [90-92]. A 2013 systematic review concluded [93] there was strong evidence for an negative association between 25(OH)D and cartilage loss and moderate evidence for a negative association between 25(OH)D and radiographic KOA. However there was limited evidence for an association between 25(OH)D and symptomatic KOA, with the authors identifying only two cross-sectional studies).

Unsaponifiables (ASUs): Avocado/Soybean lipids	There is some evidence that supplementation with 300mg ASUs/day over 3 months reduces NSAID intake (p=<0.01) [94, 95]. However a long-term study (2 years) of 300mg ASU/day showed no change in Joint Space Narrowing or KOA symptoms compared to placebo [96].

Table 1.9: A summary of the current evidence of the effect of individual nutrients on KOA outcomes. References provided within table.

The authors highlighted that most of the studies regarding individual nutrients and KOA suffered from poor design and contradictory evidence. They also observed that many of the studies used unphysiological levels of the chosen nutrient in their trials, calling into question the relevance of such results and safety of using them in practice [97].

The role of Vitamin D in OA is currently under investigation in light of several cross-sectional studies demonstrating correlations between serum 25(OH)D concentration (the accepted biomarker of vitamin D status) and progression of KOA, with those with low 25(OH)D status suffering from more severe disease [98]. However, further interventional studies are required to establish the direction of the relationship between KOA and vitamin D, and whether this could be a viable treatment option for sufferers.

1.4.2.3 Occupation

Occupations involving repetitive movement or weight bearing on specific joints increase the risk of OA in that joint; for example, occupations involving kneeling, bending or squatting along with load bearing increase risk of HOA and KOA. This is thought to be because forces in the knee increase in the squatting or bending position, and carrying a heavy load from this position further increases load on the joint, which may contribute to KOA risk. [2]

In a French cross-sectional study [99] of 1394 patients diagnosed with hand, knee or hip OA, links with longest held occupation were investigated. This study had a higher than average (when compared with the French population) proportion of female cleaners (6x higher than expected) in the OA study sample. They also found those

working in construction, mechanics and the clothing sector had a high prevalence of hand OA (48%) and reported a high degree of subsequent extreme disability (42.8% compared with 25% in those with hand OA in different employment, p=0.04). The French researchers concluded that these occupations should be considered high risk populations for OA, and that the contribution of repetitive joint movement and heavy loading bearing are important contributors to the development of OA [99].

1.4.2.4 Joint injury and Surgery

Risk of OA is significantly increased by the incidence of acute joint injuries, such as joint dislocation, ligament and meniscal tears and ruptures, which are thought to increase the instability of the joint, and which have been seen to precede the onset of OA [2].

The importance of earlier joint injury in the later development of OA was investigated in a prospective study with a 36 year follow up of 141 people who reported joint injuries to the hip, knee or both. This showed that injury to the joint substantially increased the risk of later development of OA in that joint (with a relative risk of 5.17 and 3.5 for the development of KOA and HOA respectively) [100].

1.4.2.5 Muscle Weakness

Quadriceps muscle weakness is commonly found in those with KOA, and can lead to pain and disability. However, it is unclear whether this weakness is a result of disuse due to the disease, or is a contributing factor in the development of the disease. A 2010 cross-sectional study of quadriceps strength in women with no (K&L score <1), mild (K&L score 2) and moderate-severe KOA (K&L grade 3-4) found that the quadriceps of women with mild KOA was 18% weaker than those without KOA, and no significant difference in weakness with the moderate-severe KOA group. The authors inferred that quadriceps weakness is a feature of KOA which is present from the beginning of disease and that addressing this with early intervention with quadriceps strengthening exercises may be beneficial in preventing the onset of symptoms and in maintaining knee function [101]. This is supported by evidence from quadriceps strengthening exercise interventional studies, showing improvements in reported pain and function in those with KOA [102, 103].

1.5 Treatment of Osteoarthritis

As there is no cure for OA; treatment of OA centres on the control of symptoms, primarily pain and function, and improvement of quality of life. The treatment received will vary between individuals depending on the risk factors presented in that individual, e.g. weight management options may be suggested for overweight and obese patients [104].

Treatments for OA can be split into three different groups; lifestyle (e.g. weight management, exercise and education), pharmacological (e.g. painkillers and intra-articular injections) and surgical (e.g. arthroscopy and joint replacement).

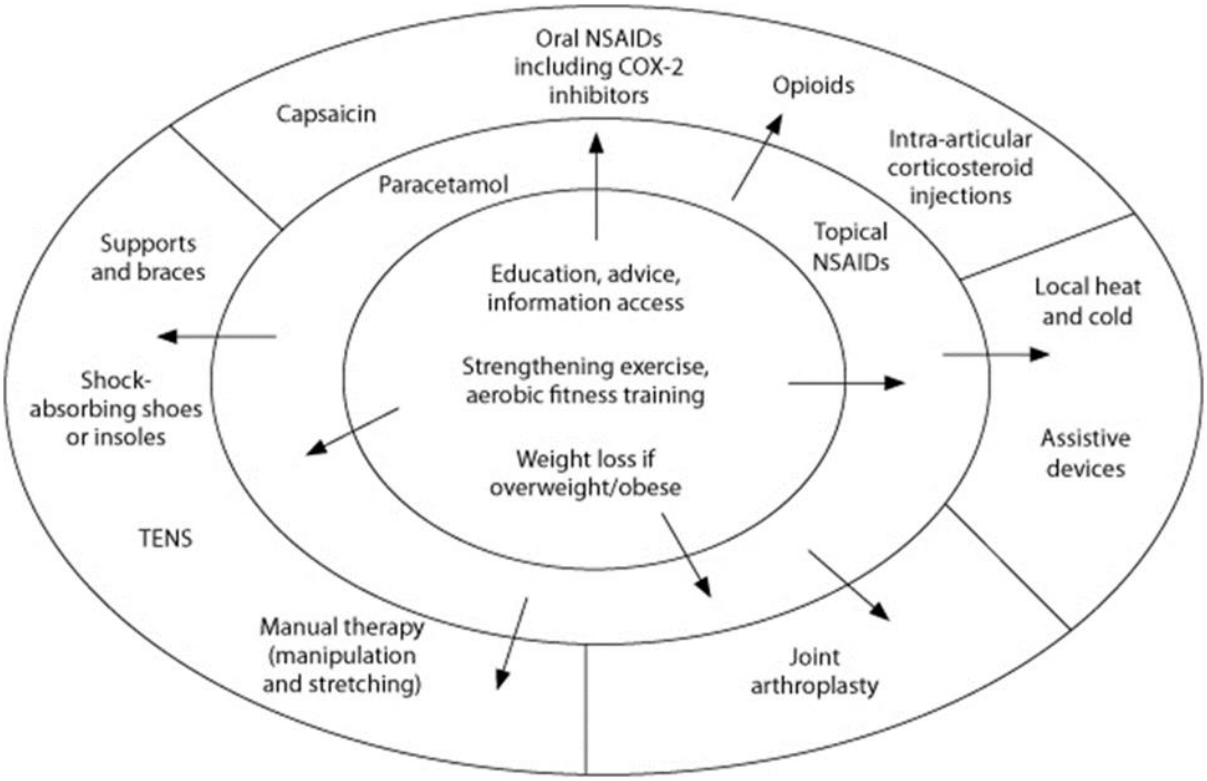


Figure 1.6: Summary of the treatments recommended by NICE Guidelines. All treatment starts with the central or 'core' treatments and progress outwards into pharmacological treatments (middle ring) and finally to the outer ring treatments, which generally more expensive and higher risk for the patient [105]

The NICE guidance for treatment of OA patients in the UK is also split into core lifestyle treatments, progressing to pharmacological treatment and finally to more expensive and risky interventions for those who are unresponsive to the previous treatments (see Figure 1.6).

NICE recommend a holistic approach (see Figure 1.7) to treatment in OA by assessing the impact of the person's condition on many different aspects of their life, including on function, quality of life, occupation, relationships, mood and leisure. Treatments are then offered based on the issues which are expressed [10].

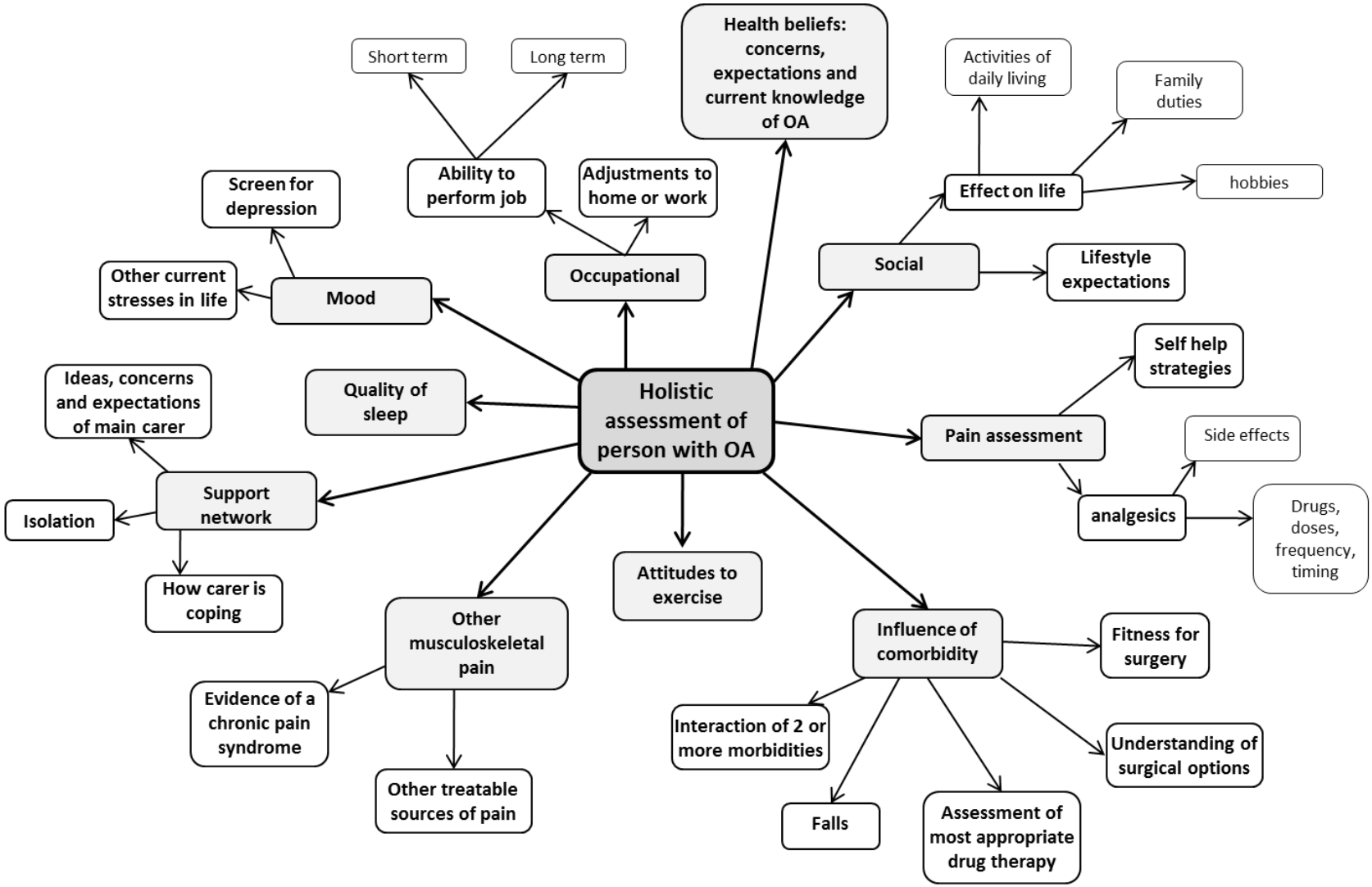


Figure 1.7: Holistic approach to assessing patients with OA for treatment as recommended by NICE. The holistic approach focuses on assessing the major areas of health and quality of life which may be effected by OA (as a core treatment in OA).Taken from [10].

1.5.1 Core Treatments

According to NICE Guidelines, all patients with OA will be offered at least these core treatments as part of their treatment plan. They are often prescribed in conjunction with other treatments e.g. painkillers or thermotherapy to achieve relief from symptoms. The importance of these treatments is stressed regularly and the Guidelines emphasise that they should not be offered just once at the beginning of treatment but reviewed regularly with the patient [10].

1.5.1.1 Patient Education and self-management

This involves providing patients with verbal or written materials explaining what OA is and the options available for treatment. A strategy for self-management e.g. weight loss (where applicable) and exercise particularly and use of thermotherapy (application of hot or cold to the joint), should also be discussed [10].

1.5.1.2 Exercise

Exercise is recommended to all OA patients, regardless of the joint affected, age or severity of disease. This includes two types of activity: aerobic and muscle strengthening activity.

Muscle strengthening exercises are particularly useful in KOA, where quadriceps weakness is commonly seen and correlates with pain. Strengthening the muscles can increase the stability of the joints and improve pain [26]. A systematic review of PA interventions in KOA found an effect size (calculated as the difference in mean pain/disability score between intervention and control groups) change of 0.32 in interventions of home-based quadriceps muscle strengthening exercises for improving pain (95% CI 0.23, 0.42) and disability (95% CI 0.23, 0.41) [103].

Low impact aerobic exercises are also effective in reducing pain. Progressive, low impact exercise e.g. swimming is recommended to avoid pain. [26] In the same systematic review described above, aerobic walking exercises improved pain by an effect size of 0.52 (95% CI 0.34, 0.70) and disability by an effect size of 0.46 (95% CI 0.25, 0.67) [103].

The problem presented with recommending exercise interventions for OA is not their efficacy but how to deliver interventions in a way which will improve engagement with the patient. There is currently no consensus on how this can be achieved and this is a current topic of investigation [10].

1.5.1.3 Weight Loss

Weight loss interventions in overweight and obese patients with KOA are recommended. Such interventions include:

- Lifestyle interventions (improved diet, increased physical activity)

- Pharmacological diet aids (e.g. orlistat)

- Bariatric surgery (in those with BMI >35) [106]

Because obesity is an important risk factor for the progression of OA (see section 1.4.2.1), maintenance of a healthy weight is important in OA. A systematic review and meta-analysis of the effect of weight loss in obese patients with KOA showed a pooled effect size of 0.2 (95% CI 0 to 0.39) on knee pain and an effect size of 0.32 (95% CI 0.04 to 0.42) on self-reported disability in favour of weight loss. The authors calculated that patients would need to lose 7.5% (0.6%/week) body weight to achieve a moderate clinical improvement in symptoms [107].

1.5.2 Secondary Treatments

1.5.2.1 Topical and Oral Analgesics

Paracetamol is offered as the first analgesic drug (along with topical NSAIDs) due to its safety and low cost. However, if pain relief by paracetamol is inadequate, treatment will proceed to NSAIDs[104, 108].

NSAIDs can be prescribed in place of, or alongside, paracetamol use to combat joint pain and inflammation. It is recommended that NSAIDs are started at the lowest effective dose for symptom relief and co-prescribed with Proton Pump Inhibitor Drugs (PPIs), e.g. omeprazole, to mitigate gastrointestinal side effects. Gastrointestinal effects of the use of NSAIDs include gastric bleeding, and liver and renal toxicity [10, 104].

1.5.3 Tertiary Treatment

1.5.3.1 Aids and Devices

People with suspected biomechanical problems of joint instability should be offered bracing, joint supports and insoles according to NICE guidance [10]. The aim of the use of these devices is to alter and lessen loading on the joint. Additionally, aids such as walking sticks can be useful for patients who have difficulty with activities of daily living and can be used to reduce load on the joint while walking [26, 108].

1.5.3.2 Invasive and surgical treatments

Invasive and surgical treatments are the last line of treatments to be considered for OA after conservative management methods have been exhausted [108]. The criteria for surgical intervention can vary, however NICE recommend referral for those with severe and persistent (after treatment with non-surgical options) symptoms which affect the patient's quality of life [10].

Intra-articular injections of corticosteroid are recommended for relief of severe pain in OA. However, NICE does not recommend injections of Hyaluronic Acid due to inconsistent evidence and uncertainty (as a result of publication bias of reporting of positive results) on their efficacy [10]. They are however approved for use by the FDA in the USA [26].

Finally, there is joint replacement surgery, which is considered for patients with have symptoms which have a significant impact on their quality of life and who are unresponsive to all other treatment options. Joint replacement surgery involves the removal of the joint and replacement with a prosthetic joint, usually made of metal or ceramic. Joint replacement surgery is highly successful and can eliminate symptoms in those with end-stage OA. Due to the longevity of the prosthetic joint, patients with a life expectancy >20years after replacement may be considered for surgery at a later date or require revision surgery. Therefore, considerable discussion about the procedure (including risks and benefits of surgery and recovery and rehabilitation) will occur before referral for surgery [10, 26, 104].

As mentioned above, treatments for OA are often used in combination but there are no specific guidelines on how to use these treatments effectively in combination. NICE

have therefore highlighted the importance of research into the effect and benefits of different combinations of treatments to identify the most effective and cost effective treatment combinations for use in practice [10].

1.6 Vitamin D

Vitamin D is a steroid hormone which is the ligand of the Vitamin D Receptor (VDR), a transcription factor which recognizes cognate vitamin D response elements (VDREs) in DNA and so regulates the expression of several hundred genes [109]. I will discuss in this section the sources, actions and factors influencing vitamin D.

1.7 Vitamin D Metabolism

1.7.1 Sources

There are two different types of Vitamin D: D2 (Ergocalciferol) and D3 (Cholecalciferol)[110]. D2 is derived from plant sources (from the UVB irradiation of ergosterol in plants, e.g. Fungi). D3 is derived from the UVB irradiation of the skin in animals and can be ingested from animal products (e.g. oily fish, eggs, meat) or synthesised from exposure of the skin to sunlight [111]. The majority of Vitamin D in humans comes from cutaneous synthesis, with dietary sources becoming more important as UVB exposure decreases [110].

The steps in Vitamin D metabolism from intake to production of the active Vitamin D metabolite (1, 25(OH)D) are described below.

1.7.1.1 Cutaneous Synthesis

The main source of Vitamin D is synthesis in the skin. The process of D_3 production by cutaneous synthesis can be seen in Figure 1.8andis briefly as follows. Firstly UVB radiation (wavelength 280-315nm) penetrates the skin triggering the conversion of 7-dehydrocholestrol (7-DHC) in the dermis (35%) and epidermis (65%) to pre-vitamin D. Pre-vitamin D is thermodynamically unstable and so is converted into Vitamin D (a more stable metabolite) via an uncatalysed thermal isomerization reaction in the epidermal and dermal cells over the following 3 days [110, 112]. Finally Vitamin D3 is then translocated and diffuses into the dermal capillary bed for transportation to the general circulation. Little is known about the mechanisms of this process, although it is

thought that the movement of Vitamin D into the bloodstream may be prompted by its attraction to the DBP in the circulation [113].

Excessive exposure to UVB does not result in Vitamin D intoxication due to a variety of negative feedback mechanisms (pictured in Figure 1.8), including:

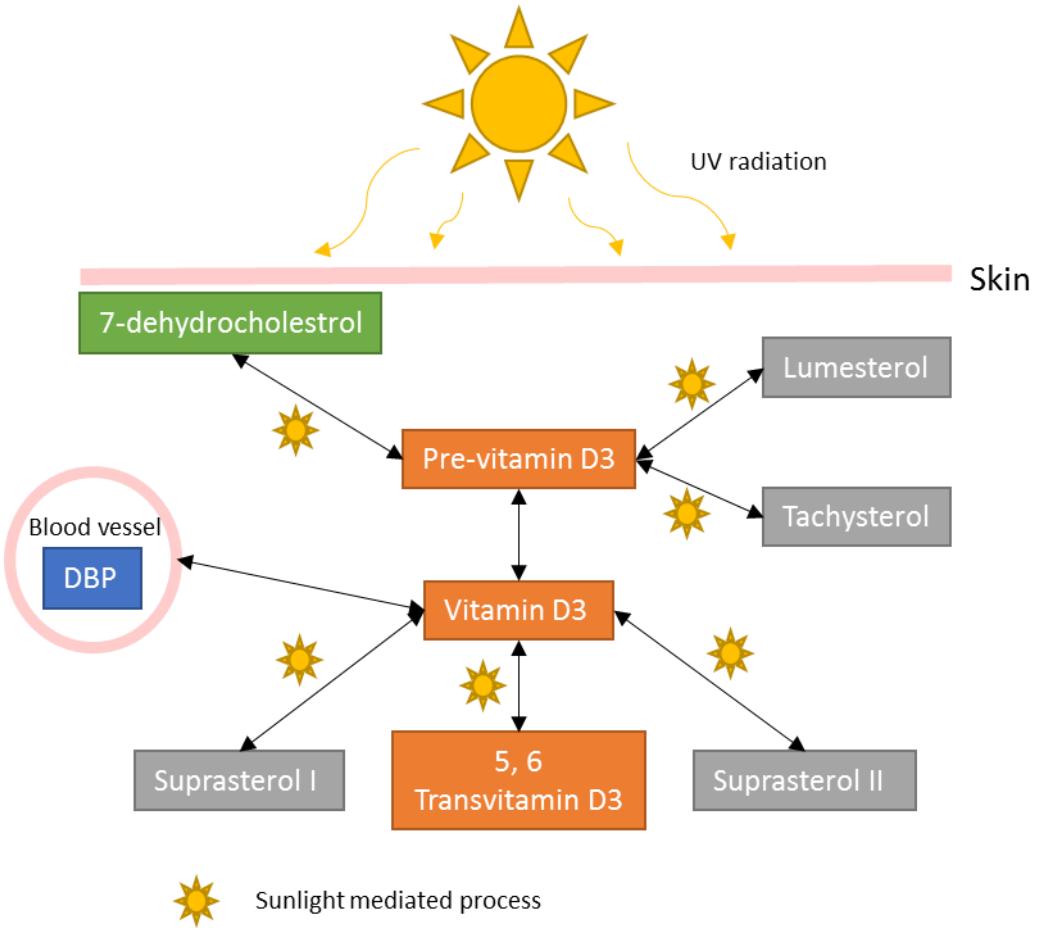


Figure 1.8: Diagram summarising the metabolic pathway for the production of Vitamin D by endogenous synthesis. Adapted from Figure 4 [113].

1. Only 12-15% of 7-DHC in the skin is converted to pre-vitamin D (which reaches its peak concentration a few hours after exposure), limiting the amount of pre-vitamin D produced[110, 112].
2. Prolonged UVB exposure triggers the conversion of pre-vitamin D into the biologically inactive metabolites e.g. lumisterol and tachysterol. The amounts of these Vitamin D photoisomers increase with time exposed to sunlight, e.g. after 1hr and 8hrs exposure, 30% and 60%, respectively 7-DHC is converted to lumisterol [113].
3. Once converted to Vitamin D, prolonged UVB exposure can also trigger a reversible isomerization conversion of Vitamin D in the skin to the

photoproducts suprasterol 1, suprasterol 2 and 5,6 pre-vitamin D3. This prevents the build-up of toxic concentrations of vitamin D and also means that when Vitamin D concentrations fall, these photoproducts can be converted back to Vitamin D for use in the body. [110, 112]

1.7.1.2 Dietary Absorption

Vitamin D obtained from diet becomes particularly important when UVB exposure is low and can contribute significantly to Vitamin D intake. As a fat soluble vitamin, vitamin D from food sources is absorbed in the small intestine with dietary fat. The latter is essential for effective vitamin D absorption, and a lack of dietary fat, or the presence of malabsorption disorders which inhibit fat absorption, can significantly reduce the body's ability to absorb Vitamin D. In the enterocyte, Vitamin D along with lipids (e.g. cholesterol, triglycerides and lipoproteins) are packed together into chylomicrons which then travel via the lymph system into the general circulation. Chylomicrons are hydrolysed in tissues (e.g. adipose and skeletal muscle) which express lipoprotein lipase, releasing the vitamin D [110, 112].

1.7.2 Conversion to 250HD

1.7.2.1 Vitamin D in the Circulation

After vitamin D has been ingested or synthesized by the body, it is transported in the blood plasma, bound mostly by vitamin D binding protein (VDBP)[114]. VDBP carries most Vitamin D metabolites in the circulation, binding around 88% 25(OH) D with high affinity and 85% of 1,25(OH)D, with 0.4% metabolites 'free' or unbound and the remaining metabolites bound to other serum proteins such as albumin [115] (see Figure 1.8).

Vitamin D does not remain in the plasma for long (half-life 4-6 hours) as it is either taken up by the adipose tissue for storage or transported to the liver for metabolism [109, 110, 116].

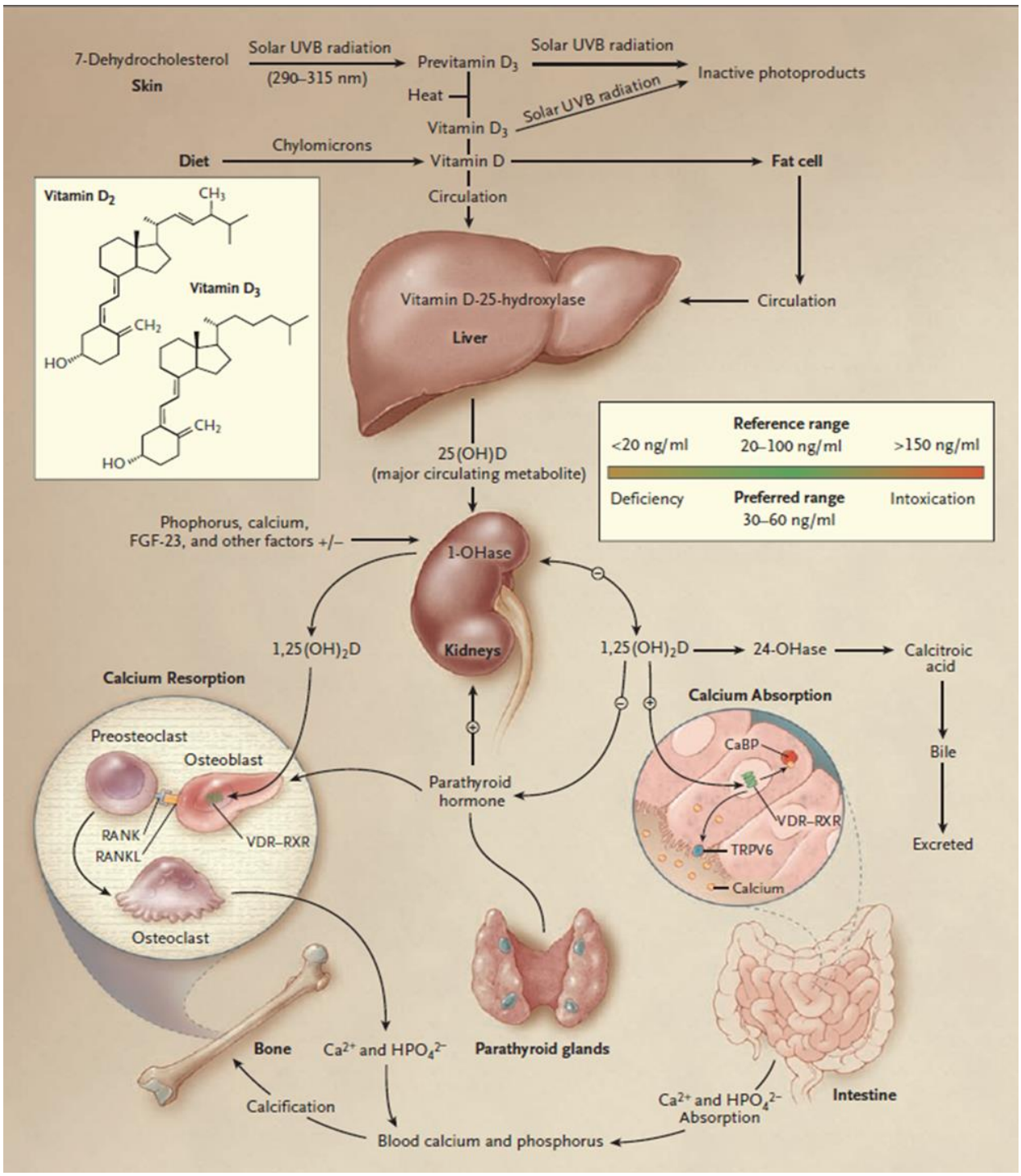


Figure 1.9: Metabolism pathway and classical actions of Vitamin D in calcium homeostasis. . Vitamin D is absorbed and transported to the general circulation. Vitamin D is stored in adipose tissue or converted to 25(OH)D by 25-hydroxylase in the liver. 25(OH)D circulates in the bloodstream until low serum calcium concentrations are signalled by increased release of PTH stimulating the conversion of 25(OH)D to 1,25(OH)D in the Kidney. 1,25(OH)D stimulates calcium resorption from the intestine (by increasing the expression calcium transporters), kidney (by stimulating uptake of calcium from the distal renal tubule) and bone (By stimulating osteoblasts to produce RANKL, which enables the maturation of osteoclasts, which break down the bone matrix to release calcium). Serum calcium concentrations increase, PTH secretion decreases and 1,25(OH)D production by the kidney decreases. Taken from Figure 1 [117].

1.7.2.2 Hepatic Metabolism of Vitamin D

Vitamin D is metabolised by two major hydroxylation reactions, the first of which takes place in the liver where it is converted to 25(OH)D by 25-hydroxylases (see Figure 1.9).

The 25(OH)D is transported back into the bloodstream until required for conversion to 1, 25(OH)D [110, 112] (see Figure 1.9).

1.7.2.3 Conversion to 1,25(OH)D

The tightly regulated process of the conversion of 25(OH)D to 1,25(OH)D occurs mostly in the renal proximal kidneys, although other tissues including bone, skin (keratinocytes), placenta, breast, colon, prostate, endothelial cells, pancreatic islets and parathyroid glands are able to carry out this reaction in small amounts for paracrine and autocrine purposes. I will describe 1,25(OH)D hydroxylation in the context of the kidneys and its role in calcium and phosphate homeostasis [110].

1.7.2.4 25(OH)D transport to the Kidneys

When calcium or phosphate concentrations are low, the VDBP bound 25(OH)D from the general circulation is transported into the kidney by receptor mediated endocytosis, in the following process:

1. VDBP bound 25(OH)D binds directly to Megalin in the renal proximal tubules.
2. Cubilin isolates the 25(OH)D-Megalin complex on the renal cell surface.
3. Megalin internalises the VDBP-25(OH)D and releases the complex within the cell.
4. Megalin and Cubilin are recycled back to the cell surface [110].

1.7.3 25(OH)D conversion to 1,25(OH)D

Once inside the cells of the proximal renal tubule of the kidney, the second hydroxylation reaction occurs, converting 25(OH)D (an inactive Vitamin D metabolite) into 1, 25(OH)D (the active Vitamin D metabolite) by 1a-hydroxylases, particularly CYP27B1 (a mitochondrial enzyme). 1, 25(OH)D then mediates many Vitamin D actions on e.g. renal, bone and intestinal cells [110]. This second hydroxylation is a tightly regulated process and when calcium and phosphate concentrations rise to the normal

range, 1,25(OH)D conversion ceases. The Vitamin D endocrine system and actions are described further Figure 1.9and in section 1.9.3.

1.7.3.1 Breakdown and Excretion

As the metabolism of Vitamin D is such a tightly regulated pathway, there are many stages of the pathway where Vitamin D metabolites may be inactivated, stored or broken down and excreted. These include:

- When calcium levels are sufficient, instead of undergoing 1a-hydrosylation to 1,25(OH)D, 25(OH)D is hydroxylated by 24-hydroxylases (CYP24). This results in an inactive water soluble molecule (mainly calcitriol acid).
- 1,25(OH)D can also modulate its own destruction by inducing the production of CYP24 in Vitamin D target tissues.
- These inactive water soluble Vitamin D metabolites are then excreted via the bile in faeces, with very little excreted in urine [110, 112].

1.8 Biomarkers of Vitamin D status

There are many Vitamin D metabolites in the body which could potentially be used as biomarkers of vitamin D status. However, plasma total 25(OH)D concentration is usually used for this purpose and is currently the best biomarker of Vitamin D status for the following reasons:

- It combines dietary intake and cutaneously synthesised Vitamin D as both are converted into 25(OH)D. Therefore it reflects the total amount of Vitamin D taken into the body from all sources.
- 25(OH)D can be considered the storage metabolite for Vitamin D in the body since this is the major form in which it circulates in the bloodstream and is stored in adipose tissue. 25(OH)D is a widely used biomarker for Vitamin D status in multiple countries, and therefore allows studies to be comparable [110].
- Most other Vitamin D metabolites have very short half-lives and so are of limited practical use in assessing Vitamin D status. However, 25(OH)D has a longer half-life of 21-30 days.

- Since 1,25(OH)D concentration is tightly regulated and is determined mainly by calcium and phosphate concentrations (and not specifically vitamin D stores), it can be a poor measure of Vitamin D status [118].

However, there are several limitations in using 25(OH)D as a biomarker of Vitamin D status:

- As 25(OH)D is a storage metabolite with no active function (unlike 1,25(OH)D, the 'active' Vitamin D metabolite, which can interact with the VDRE), it is therefore debatable whether 25(OH)D can be extrapolated in the case of Vitamin D effect. Therefore, studies linking 25(OH)D, rather than 1,25OHD status, to disease and clinical outcomes may be flawed.
- The concentration of 25(OH)D in plasma can be affected by many difficult to control and quantify factors, such as UVB exposure, (reviewed in section 1.10.5), which have the potential to introduce variation between individual study subjects during Vitamin D supplementation studies, potentially 'confounding' any results.
- There are no internationally agreed 25(OH)D concentration cut-off points for defining deficiency, insufficiency and sufficiency which means that results between countries may not be comparable [110].
- The concentration of 25(OH)D obtained from a blood sample can vary according to the type of assay used, the laboratory used and the quality assurance system employed. The 'gold' standard for 25OHD measurement, providing the most specific and sensitive results, is liquid chromatography tandem mass spectrometry (LC-MS/MS). However, due to the high equipment costs, LC-MS/MS is not widely used for clinical 25(OH)D measurements. Immunoassays are more often used for clinical diagnosis which can be more variable in their reliability and accuracy. Streamlining and standardisation of 25(OH)D measurement methods however could improve the reliability of such assays for the measurement of 25(OH)D [119].

1.9 Vitamin D Actions

Vitamin D can act via both regulation of DNA transcription (genomic action) or through the activation of signalling pathways (non-genomic actions). Both are mediated by the interaction of 1, 25(OH)D with the VDR.

The VDR is a steroid hormone receptor of the thyroid/Vitamin D/retinoic acid subfamily. VDR has 2 main binding domains: a C domain (DNA Binding domain) and an E domain (ligand binding domain – for which 1,25(OH)D has a high affinity) [110, 120].

The genomic and non-genomic actions of Vitamin D are outlined below.

1.9.1 Genomic Actions

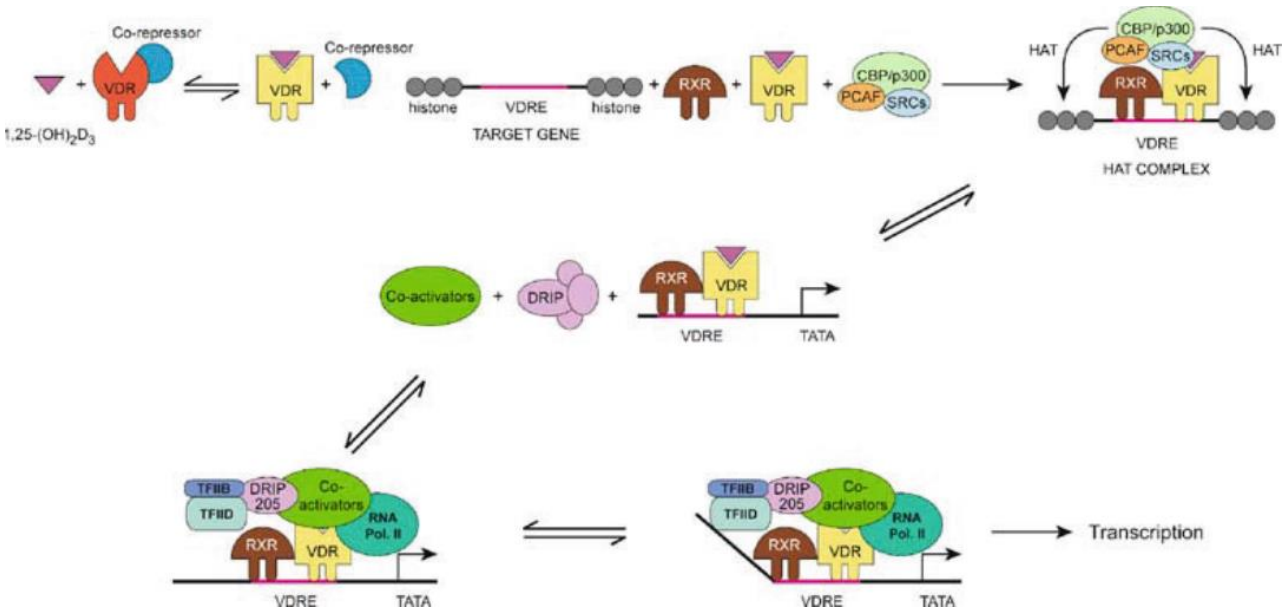


Figure 1.10: Diagramatic representation of the proposed genomic mechanism of action for Vitamin D. Taken from Fig 4 [120]

- 1, 25(OH)D binds to the VDR of a target cell.
- The ligand activated VDR then forms a heterodimer complex with retinoid X receptor in the cell nucleus. This step is essential for effective binding of the VDR to DNA.
- The VDR-RXR complex then binds to VDRE (Vitamin D response elements). VDREs are sequences in DNA (usually 2 hexametric repeats of AGGTCA sequences separated by 3 nucleotides) that found in the promotor regions of genes that are regulated by Vitamin D. The VDR binds to the 3'end and RXR binds to the 5'end of the promotor region.

- A protein complex then forms on the VDRE with the attached VDR which acts to loosen the chromatin structure of the DNA.
- A second protein complex then forms on the VDRE which initiated gene transcription or repression (see Figure 1.10)[120].

1.9.2 Non-Genomic Action

The non-genomic vitamin D-dependent responses within cells are thought to be carried out through interaction of the ligand activated VDR with cavolae that are small lipid raft pits involved in pathway signalling and endocytosis [121]) on the plasma membrane of target cells.

The effects of 'rapid response pathways' can occur within 1-45mins compared with genomic responses which can take several hours [122].

VDR-cavolae may induce a signalling cascade resulting in the recruitment of the secondary messengers MAPK (mitogen-activated protein kinase) and cAMP (cyclic adenosine monophosphate) to affect calcium channels within the cell [110]. These pathways may also influence genomic actions of vitamin D by 'cross talk' (see Figure 1.11) [122].

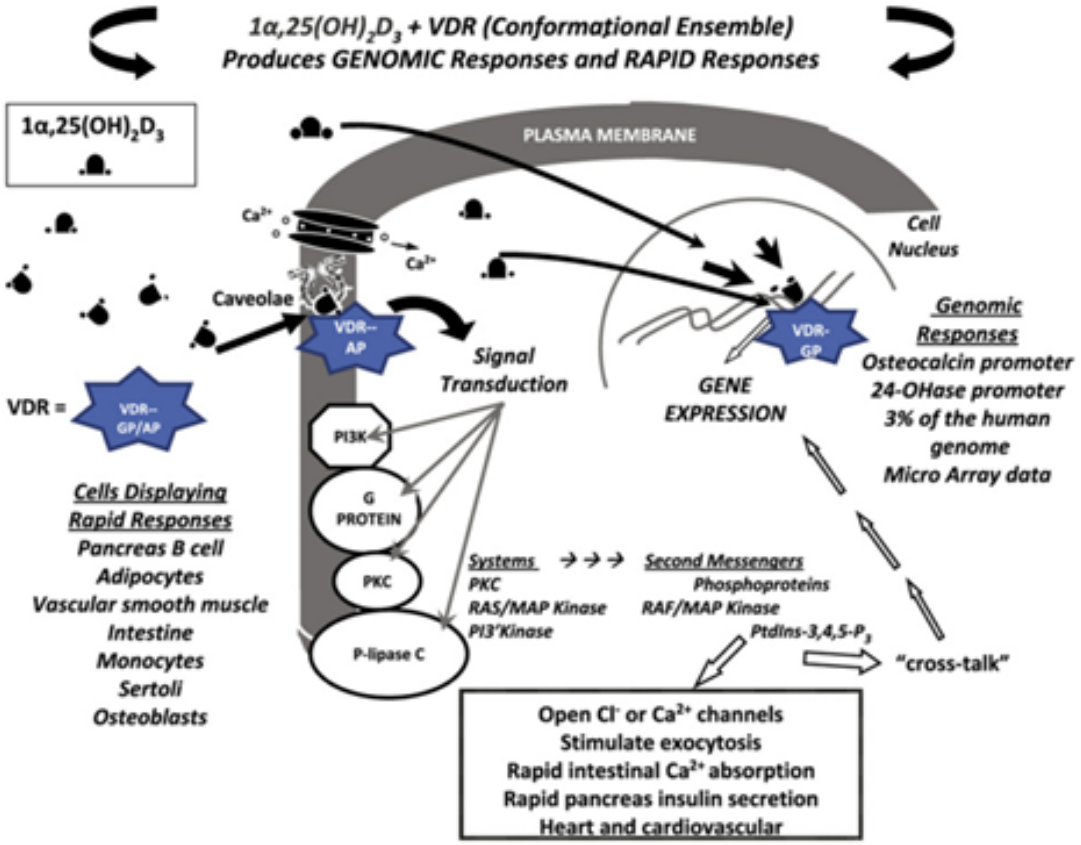


Figure 1.11: Proposed mechanism of action for non-genomic vitamin D actions or 'fast response pathways'. Firstly free 1,25(OH)D binds to VDRs located in the cavolae of cell membranes. This triggers a signalling transduction pathway, of which the secondary messengers stimulate the opening of calcium ion channels on the cell surface and rapid calcium uptake. These secondary messengers are also able to interact with the genomic actions of Vitamin D (gene expression). Taken from Figure 4 [122].

1.9.3 Physiological Actions

1.9.3.1 Classical Actions

The main action of Vitamin D is in ensuring homeostasis of calcium and phosphate concentrations in the body (see Figure 1.12). This is important for the mineralisation of the bone (ensuring a strong skeleton) and for avoiding hypocalcaemic tetany [120].
The main steps of this Vitamin D mediated homeostatic loop are summarized below:

- It is important that serum calcium concentration is kept between 1-2.5nmol/L.
- Decreases in circulating calcium concentration are sensed by calcium sensing cells (C-cells) in the parathyroid gland.
- This induces the release of parathyroid hormone (PTH) into the general circulation [110].

- PTH stimulates the kidney to convert 25(OH)D to 1,25(OH)D by increasing 1a-hydroxylase activity. 1,25(OH)D has 3 main actions in increasing calcium levels:[120]
    1. Intestinal Calcium Absorption:
        a. 1,25(OH)D interacts with the VDR and initiates the expression of epithelial calcium channels and calbindin 9k (calcium binding proteins).
        b. The expression of these proteins leads to active uptake of calcium from the intestinal lumen (from dietary sources) into the general circulation[110].
        c. Absorption is greatest in the duodenum and jejunum of the small intestine[112].
    2. Kidney Calcium reabsorption:
        a. 1,25(OH)D and PTH stimulate reabsorption of calcium in the renal distal tubule.
        b. This ensures that calcium is retained and not excreted in the urine [112].
    3. Bone resorption:
        a. 1,25(OH) D interacts with the VDR in osteoblasts and stimulates the expression of RANKL (NFκB ligand).
        b. RANKL induces the maturation and activation of osteoclasts.
        c. Osteoclasts resorb bone (osteoclastigenesis), releasing calcium stored within the bone matrix [110, 112].
- As a result of the above actions, serum calcium concentrations rise. This is sensed by the calcium sensing cells of the thyroid gland and PTH secretion reduces.
- When serum calcium concentrations become too high, the C-cells of the thyroid gland secrete the protein calcitonin which blocks the bone resorption described above and therefore lowers serum calcium concentrations [110, 112].

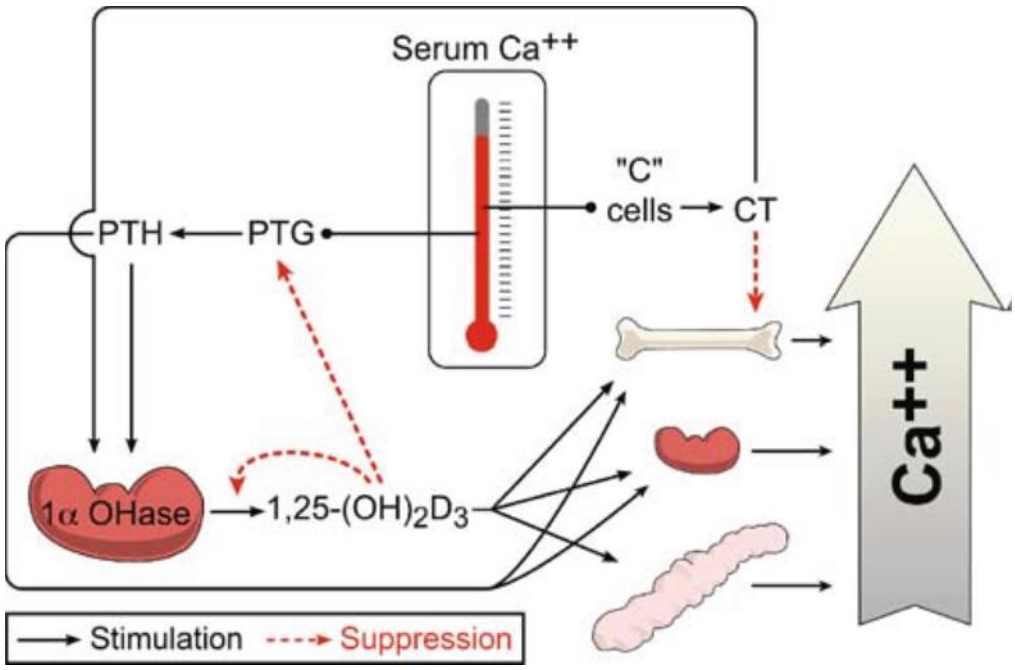


Figure 1.12: The stimulatory and suppressive effects of hormones (1,25(OH)D and PTH) on Calcium homeostasis. Low calcium concentrations are sensed by C-cells in the parathyroid gland (PTG) which responds by secreting parathyroid hormone (PTH). PTH stimulates the kidney to convert 25(OH)D to 1,25(OH)D which exerts its action on the bones, kidney and intestines to increase calcium resorption. Serum Calcium concentrations increase, which is sensed by the PTG and responds by decreasing PTH secretion (feedback mechanism).Taken from figure 1 [120].

1.9.3.2 Non-Classical Actions

VDRs also occur in multiple cells unrelated to calcium and phosphorus homeostasis including**,** pancreatic, immune, epithelial, skin, colonic and placental cells [120]. Through these VDRs, 1, 25(OH)D regulates the expression of over 200 target genes, including genes involved in cell proliferation and differentiation, apoptosis and angiogenesis [117]. This suggests that Vitamin D may have roles in regulating the function of multiple cells and tissues, and inadequate vitamin D status may contribute to the aetiology of several diseases. Potential non-classical actions of vitamin D, summarised in Figure 1.13, include roles in immunity.

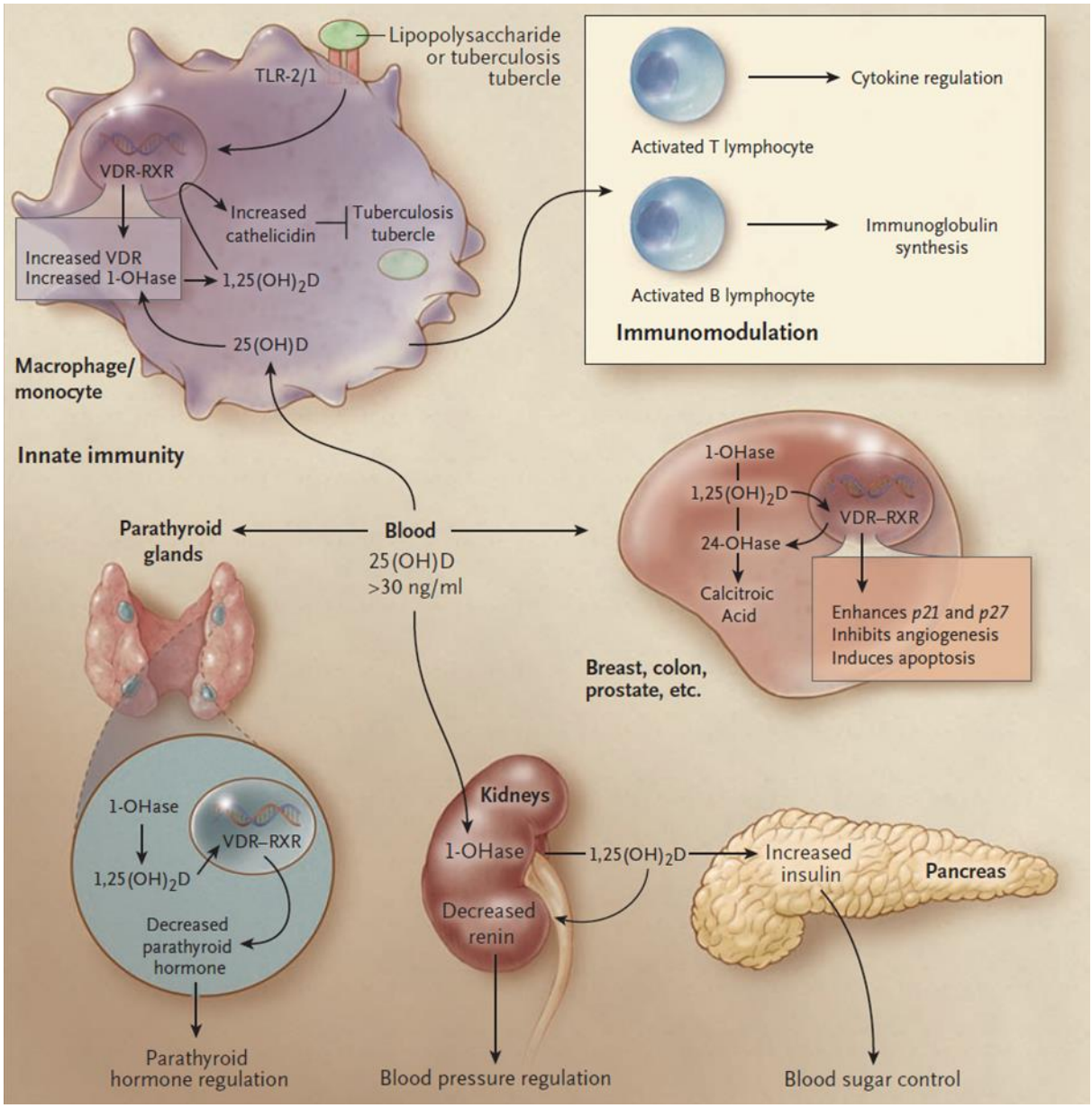


Figure 1.13: Diagram summarising the potential non-skeletal mechanisms of 1, 25(OH)D. Taken from Figure 2 [117].

a) *Immunity*

Macrophages: When stimulated by infection (e.g. mycobacterium tuberculosis) or LPS (lipopolysaccharide), VDRs are expressed on macrophages and 25OHD from the general circulation is converted to 1,25(OH)D. Activation of the VDR leads to the expression of cathelicidin (peptide used to destroy infectious agents). When circulating concentrations of 25(OH)D are<50nmol/L, macrophages cannot initiate this innate immune reaction, leaving the individual more susceptible to the infection [117].

Lymphocytes: 1,25(OH)D produced by macrophages may act on locally activated T and B lymphocytes to regulate the expression and secretion of cytokines and immunoglobulins, therefore having an immunomodulatory effect [123].

1.10 Vitamin D Deficiency

1.10.1 Defining Vitamin D Deficiency

Historically, Vitamin D deficiency was diagnosed from the clinical presentation of rickets - a childhood condition caused by the impaired mineralisation and ossification of the bone, often resulting in skeletal deformities [124]. However, 250HD is now used as a biomarker of vitamin D status [125, 126].

Defining Vitamin D deficiency is difficult because there is currently a lack of consensus about what serum 25(OH)D concentrations define deficiency, insufficiency and sufficiency. Examples of the cut-offs for 25(OH)D concentration used by different authorities are summarised in Table 1.10 below.

	Serum 250HD (nmol/L) Vitamin D Status Definitions		
	SACN (UK) 2016	**IOM (USA) 2011**	**Heaney and Holick 2011**
Deficiency	<25	<30	<50
Insufficiency	25-50	30-50	50-75
Sufficiency	>50	>50	>75

Table 1.10: The definitions of Vitamin D Deficiency, Insufficiency and Sufficiency based on serum 250HD concentrations (nmol/L). SACN= Scientific Advisory Committee on Nutrition, IOM = Institute of Medicine. [110, 112, 126].

Most definitions of Vitamin D status are based the concentrations at which 25(OH)D affect calcium, bone and muscle metabolism. Vitamin D deficiency is usually defined as the level of 25(OH)D below which skeletal disease (osteomalacia in adults and rickets in children) is most likely to occur [125]. This is defined by the Department of Health in the UK as the level at which 97.5% of the UK population would need to protect against osteomalacia and rickets.

Vitamin D insufficiency and sufficiency cut offs can be more variable than estimates of deficiency, with cut off levels of insufficiency and sufficiency ranging from 25-75nmol 25(OH)D and >50nmol-125nmol respectively [127].

1.10.2 Prevalence of vitamin D inadequacy

1.10.2.1 Vitamin D status Worldwide

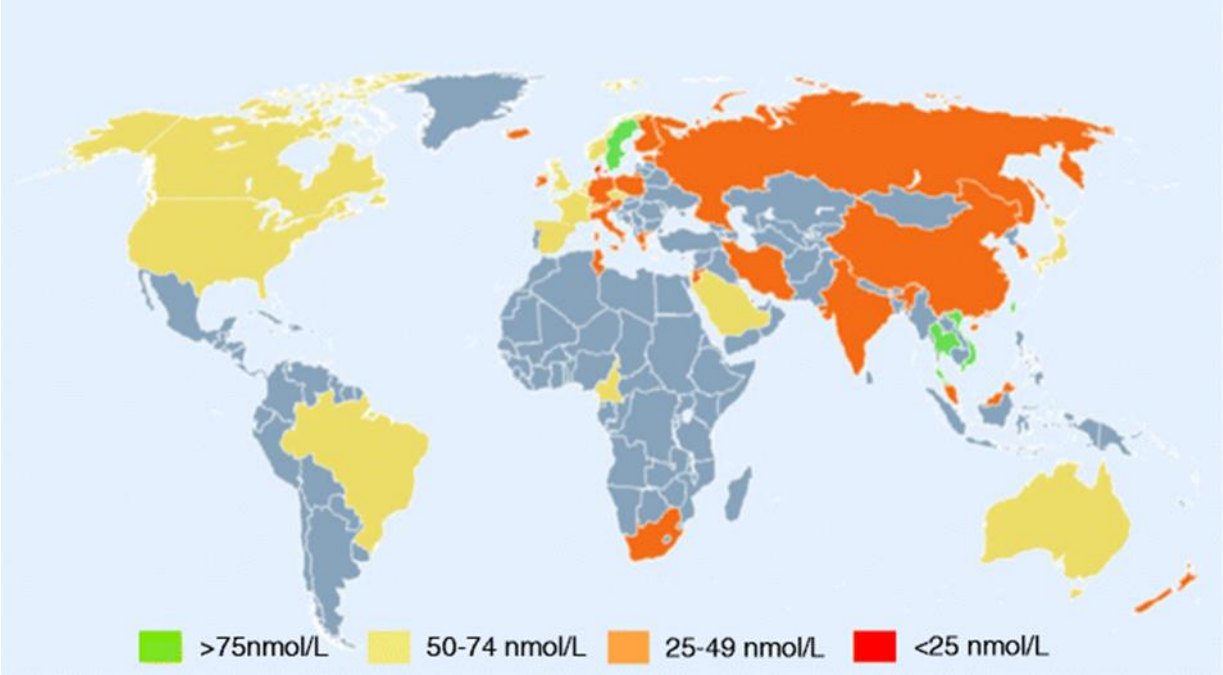


Figure 1.14: Map of global Vitamin D status (serum 25OHD [nmol/L]) in adults (18+yrs). Mean 25OHD Values calculated from winter measurements. Taken from Fig. 2 [128].

Low Vitamin D concentrations are of global concern. A systematic review of 200 studies summarising the mean serum 25(OH)D in 46 countries concluded that Vitamin D inadequacy (defined as <50nmol/L 25(OH)D) was widespread across much of Asia and that the vast majority of countries were below the 'optimum' Vitamin D concentration of 75nmol/L 25(OH)D as depicted in Figure 1.14 [128].

1.10.2.2 Vitamin D status in the UK

There have been concerns in recent years that Vitamin D deficiency is becoming more common in Western countries including the UK. From the 1960s in the UK and elsewhere in Europe, rickets has begun to emerge in the general population, and over the last 15 years there have been reports of cases of rickets across the UK [127]. For example, between 2002 and 2008, there were 160 cases of Vitamin D deficiency related rickets reported in a children's hospital in Scotland.

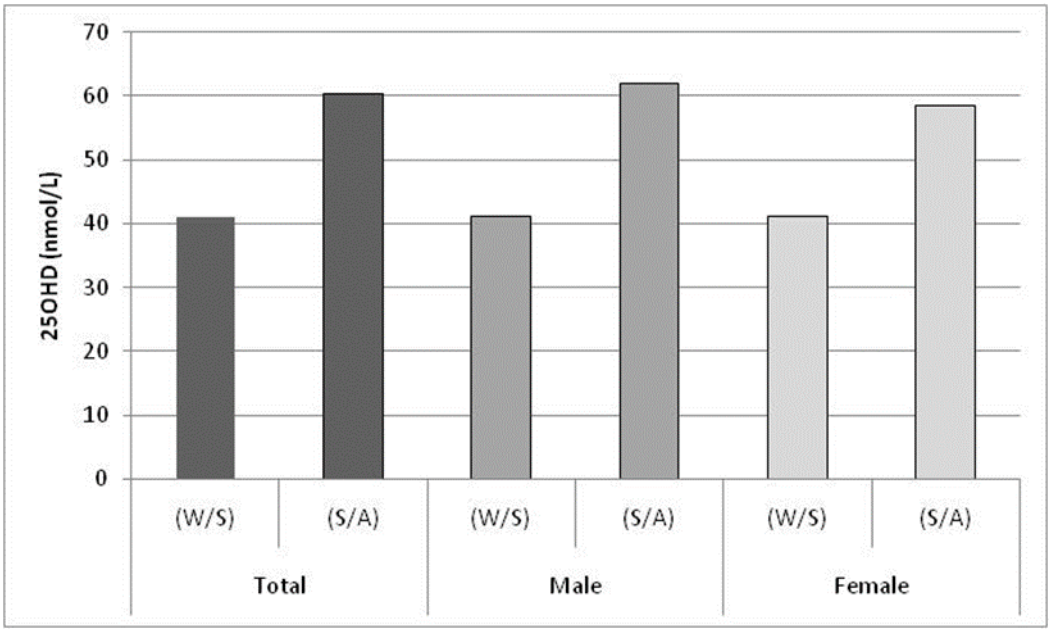


Figure 1.15: Graph depicting the serum 25(OH)D concentrations of 45 year olds from the UK by gender and season. (W/S= Winter/Spring, S/A=Summer/Autumn).Adapted from Table 2 [129].

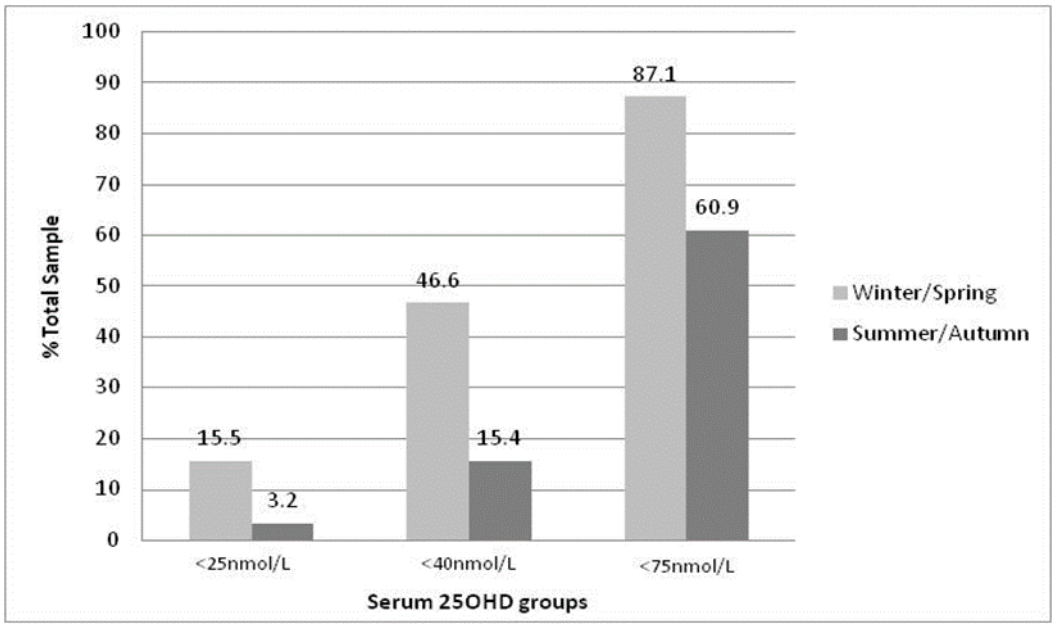


Figure 1.16: Graph depicting the % of the total study sample with 25(OH)D concentrations below 3 different vitamin D sufficiency cut offs (25nmol <25nmol/L, <40nmol/L and <75nmol/L), grouped by season. . Adapted from Table 2 [129].

In a cross-sectional study published by Hypponen (2007), 7437 white British 45 year olds completed dietary and lifestyle questionnaires on factors affecting 25(OH)D levels, and gave blood samples for 25(OH)D measurement. Average Winter/Spring serum 25(OH)D concentrations were 41.1nmol/L and average Summer/Autumn serum 25(OH)D levels were 60.3nmol/L. This suggested that, on average for half of the year, the British population is Vitamin D insufficient (<50nmol/L) (see Figure 1.15 and Figure 1.16). The authors concluded that Vitamin D deficiency was not just a problem

restricted to 'at-risk' groups in the UK, but that it is a widespread problem amongst the general British population, which may have important implications for bone health [129].

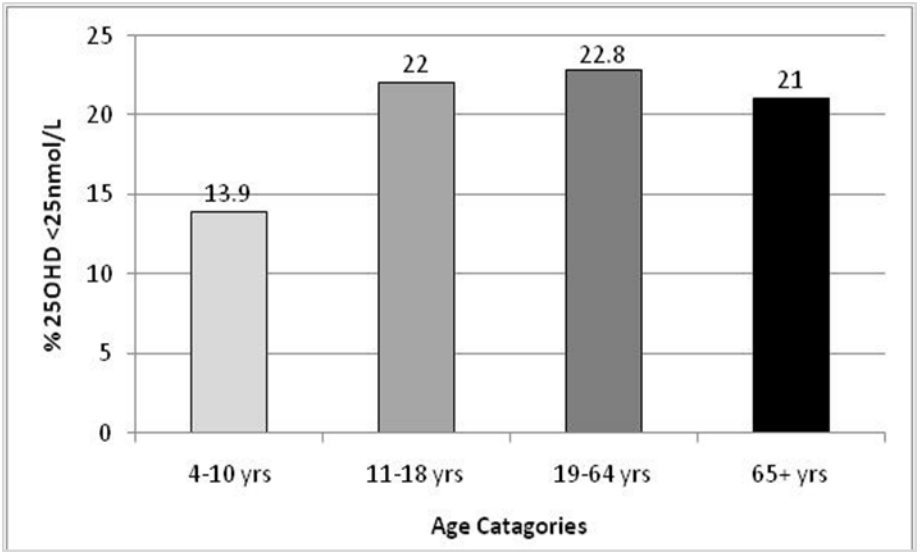


Figure 1.17: Bar chart depicting the % NDNS sample with 25(OH)D<25nmol/L, grouped by age category. (Children: 4-10years, Adolescents: 11-18yrs, Adults: 19-64 and Older adults: >65yrs).Adapted from Table 6.3 [130].

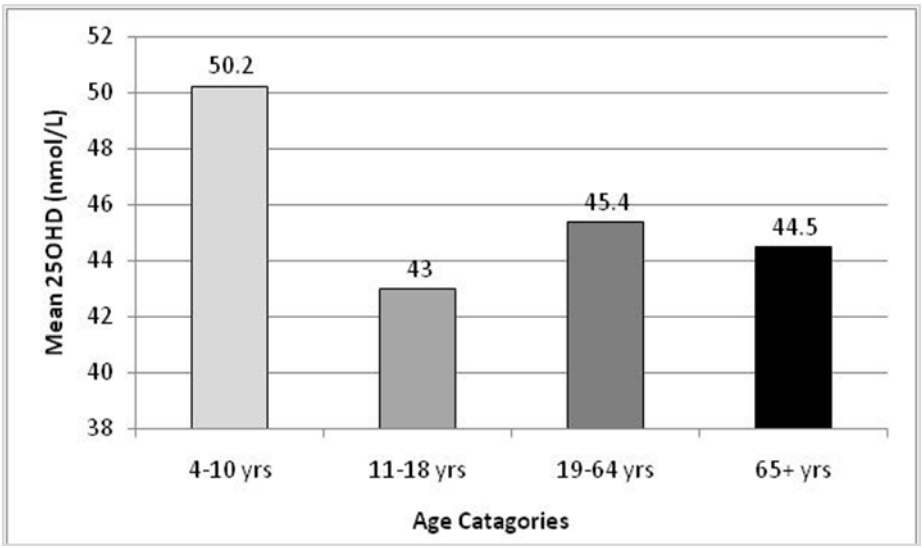


Figure 1.18: Bar chart of mean serum 25(OH)D concentration of NDNS sample by age category.(Children: 4-10years, Adolescents: 11-18yrs, Adults: 19-64 and Older adults: >65yrs).Adapted from Table 6.3 [130].

The National Dietary Nutritional Survey conducted by Public Health England and the Food Standards Agency, also measured 25(OH)D concentrations amongst UK participant's in a rolling programme in 2007/2008 and 2011/2012. From serum 25(OH)D measurements made throughout the year, average serum 25(OH)D concentrations were 43nmol/L in adults (19-64yrs) and 44.5nmol/L in older adults (65+yrs). Mean serum 25(OH)D concentrations and % <25nmol/L were lowest in

adolescents and older adults at 43nmol/L and 22%, and44.5nmol/L and 21% respectively (see Figure 1.18 and Figure 1.17). This information demonstrated that both adolescents and older adults are both 'at-risk' groups for Vitamin D deficiency in Britain [130]

1.10.3 Seasonal Variation

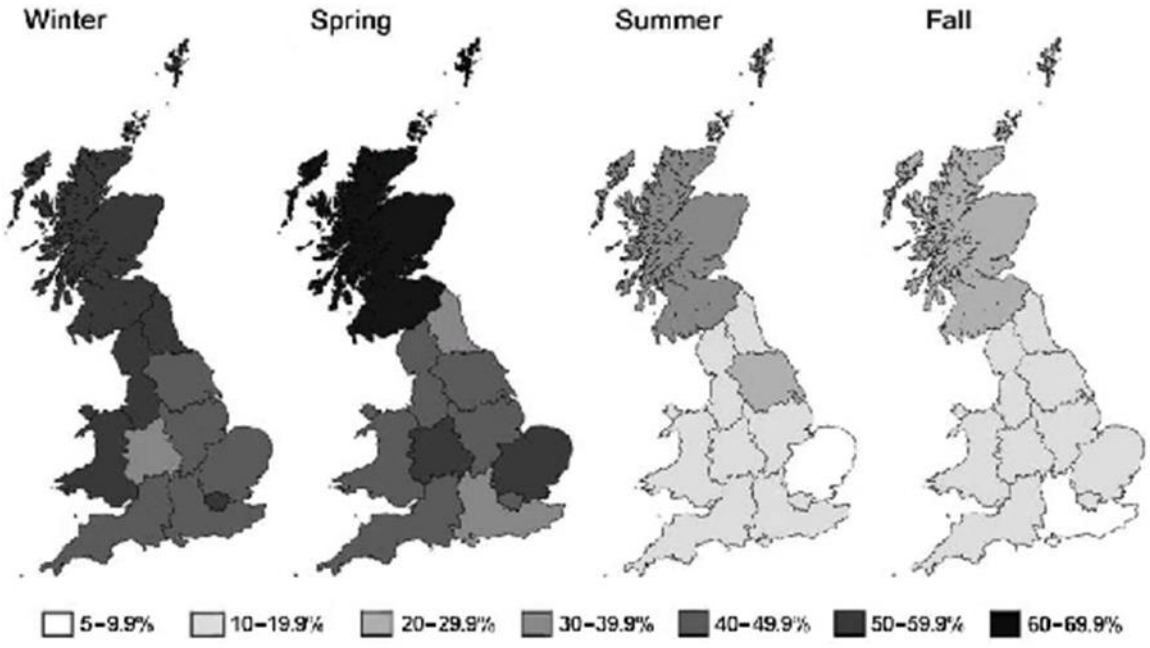


Figure 1.19:% of UK population with of 25(OH)D deficiency (<25nmol/L) by season. Winter (December-February), spring (March-May), summer (June-August) and fall (September – November). Taken from Figure 3 [129].

As can be seen in Figure 1.19, there are clear seasonal variations in Vitamin D deficiency in the UK due to the lack of available of appropriate UV light for cutaneous Vitamin D production in the UK between October and April [110]. As described in section 1.10.2.2 above, Hypponen assessed 25(OH)D levels in 7437 British adults and found mean 25(OH)D levels varied from 41.1 (95% CI: 40.4, 41.8) in December – May to 60.3 (95%CI 59.5, 61.0) in June-September, peaking in September and at their lowest point in January-April [129]. This data was also reflected in the NDNS 2007/2008 and 2011/2012rolling programmes which showed a peak in 25(OH)D deficiency in the UK in January – March and lowest levels of 25(OH)D deficiency July-September [130] (see Figure 1.20).

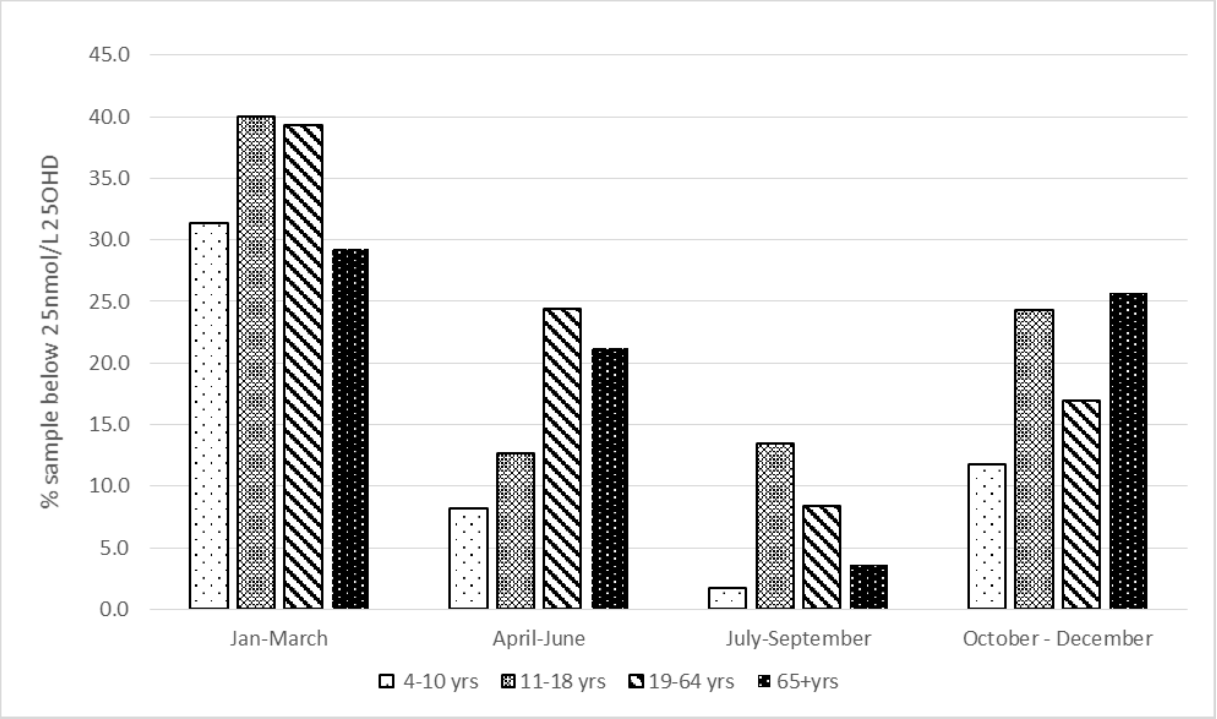


Figure 1.20: Bar chart of the % of NDNS sample classed as Vitamin D deficient (<25nmol/L) from serum 25OHD measurement by month of sample collection and age group(Children: 4-10yrs, Adolescents: 11-18yrs, Adults: 18-64yrs and Older adults: >65yrs) [130].Adapted from Table 6.3.1. NDNS [130].

1.10.4 Vitamin D deficiency: at-risk groups

NICE is now emphasising the importance of ensuring that vitamin D adequacy in vulnerable groups is addressed in their recent guidelines 'Vitamin D: Increasing supplement use in at risk groups'. This guideline focuses on increasing the awareness of the importance of vitamin D and access to vitamin D supplements in at risk groups. Supplementation of 100% RNI/day is recommended in this guidance: 340IU (8.5µg)/day for infants, 280IU (7µg)/day for children (<5yrs) and 400IU (10µg)/day for adults [131].

According to NICE Guidance, those considered 'at risk' groups for Vitamin D deficiency are:

- Pregnant and Breastfeeding women
- Infants and Children (<5 years)
- Older Adults (>65 years)
- People with low/no exposure to sunlight, e.g. those who cover their skin for cultural reasons or housebound individuals

- People with darker skin, e.g. individuals of African, African-Caribbean and South Asian descent[131].

In a 2014 review of Vitamin D status in Europe, Spiro *et al.* also identified additional at risk groups amongst the European population:

- Migrant populations/Asylum seekers
- Adolescents (particularly females)[127]

Data from the NDNS (National Dietary Nutritional Survey) in England (2008-2012) also demonstrated that there was a high prevalence of Vitamin D deficiency amongst adolescents (11-18 yrs) and adults (19-64 yrs), with 40% and 39.3% of these groups, respectively, showing vitamin D deficiency (<25 nmol/L) during winter (Jan-March)[130].

Data from earlier (2000-2001) NDNS reports demonstrate more differentiation between the adults groups and support the idea that younger adults are at higher risk of Vitamin D deficiency, compared with other adult groups (Figure 1.21) [132].

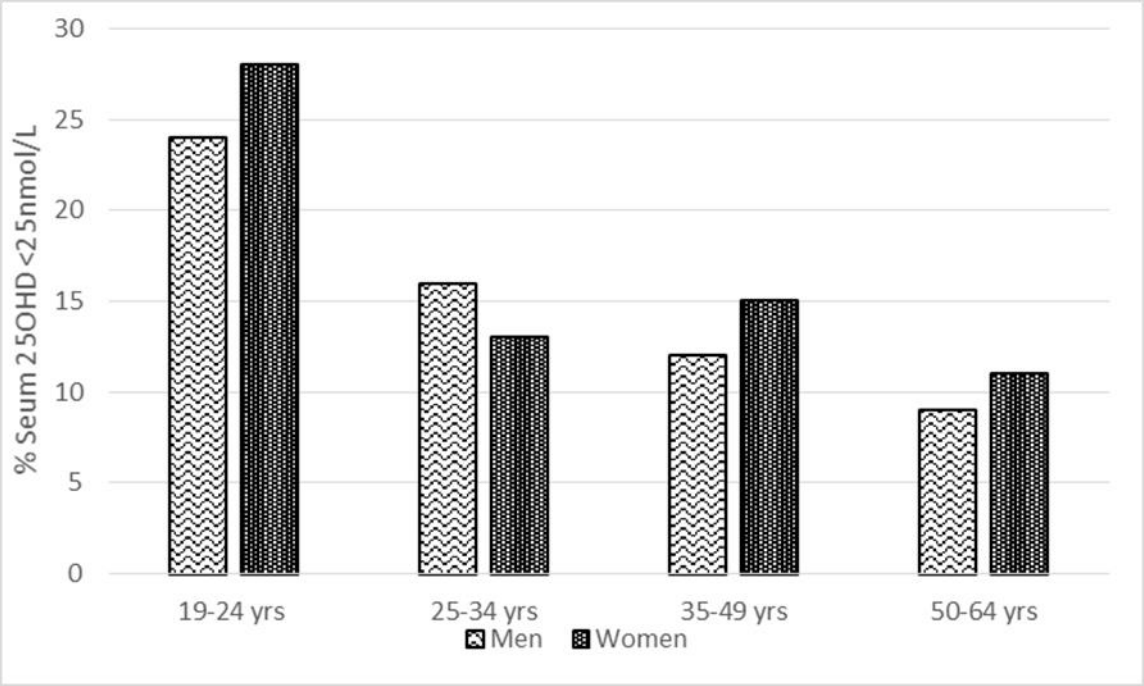


Figure 1.21: % NDNS sample with serum 25(OH)D<25nmol/L in 4 adult age groups (19-64yrs) by gender. Adapted from Table 4.33 [132].

1.10.5 Summary of Factors affecting Vitamin D status

Several environmental, dietary and individual factors influence each individual's 25(OH)D concentration (see Table 1.11), and negatively affect 25(OH)D production resulting in increased risk of 25(OH)D deficiency. Age and obesity are discussed in detail in sections 1.10.5.1 and 1.10.5.2.

Factor affecting Vitamin D intake		Explanation
Environmental Factors	UVB availability: Latitude, Season and Time of Day.	UVB radiation between the wavelengths of 280-315nm are required to trigger dermal synthesis of Vitamin D in humans. However, the amount of UVB reaching the earth's surface depends heavily upon latitude, season, and time of day due to the variation in the angle the radiation takes through the earth's atmosphere (specifically the ozone layer). The smaller the angle (e.g. at noon/summer/low latitudes), the more direct the path UVB radiation takes to the earth's

		surface and the more UVB reaches the surfaces [110]. The above means that in the UK, UVB exposure is effective for dermal Vitamin D production in the late spring, summer and early autumn (April-October) between 10:00-15:00 [133].
	Weather and pollution	Cloud cover and pollution can filter and block sunlight of the required wavelength to make vitamin D, thereby reducing the amount of vitamin D that can be made by individuals [133]. Additionally, weather and pollution may influence individual's choices on skin exposure and outdoor activities, which may further limit exposure to UVB [110].
	Time spent outdoors	As exposure to UVB radiation is essential to dermal Vitamin D production, individuals who are institutionalised or housebound are at high risk of vitamin D deficiency due to a lack of UVB exposure [133].
	Clothing choices	Clothing can be effective in blocking sunlight exposure and therefore dermal synthesis of Vitamin D. Those who cover most of their body e.g. including face, head and arms may increase risk of Vitamin D deficiency [133]. For example, a study of 100 young females from Istanbul measured serum 25(OH)D in those who adopted Muslim dress (covering whole body except face and hands) and those who did not. Mean serum 25(OH)D was 21.1 (±6.7) and 29.7 (±3.1) and % vitamin D

		deficiency (defined as <50nmol/l) was 55% and 20% respectively.
	Sunscreen use	Sunscreens which block UVA and UVB wavelength radiation from penetrating the skin could limit the amount of Vitamin D produced by the skin. However, in a real world setting, due to variation in application, it is likely that Vitamin D production is possible even with sunscreen use [110, 112].
Dietary Factors	Intake from Natural sources	There are few naturally Vitamin D rich foods. The richest dietary sources of Vitamin D are Salmon (100-1000IU [2.5-25µg]/100g), Cod Liver oil (400-1000IU [10-25µg]/1tsp), Sardines (300IU [7.5µg]/100g), Mackerel (250IU [6.25µg]/100g), Tuna (230IU [6.25µg]/102g), Shitake Mushrooms (100-1600IU [2.5-40 µg]/100g) and Egg Yolk (20IU [0.5µg]/yolk) [117]. Intake from dietary sources becomes particularly important when UVB exposure is low, and can contribute significantly to Vitamin D status along with supplementation and fortification [133]. E.g. Scandinavian countries receive limited UVB exposure, however, due to high oily fish consumption and food fortification policy, population 25OHD concentrations are relatively high compared with the rest of Europe [127]. In the UK, Vitamin D intake from food sources (excluding supplements) is generally low, with

		the average adult (18-64yrs) consuming 3.6µg/day (27% daily RNI) [130].
	Supplements	Vitamin D supplement use and promotion vary between countries. In the UK, supplements are readily available and are recommended to specific 'at-risk' groups for Vitamin D deficiency, including; children <3years, pregnant/lactating women, adults >65years, ethnic minorities and those with restricted sunlight exposure [131]. Supplementation is also prescribed to those who are diagnosed as 25(OH)D deficient (<25nmol/L) (10,000IU [250µg]/day for 8-12 weeks) [134].
	Food Fortification	Fortification of foods as a mechanism of increasing nutrient levels at a population level is particularly important in countries where intake of that nutrient may be low; however, Vitamin D fortification policies vary between countries. In Europe there is mandatory fortification of margarine (in 2013 in the UK this mandatory fortification was removed but fortification of many margarines continues on a voluntary basis [110]) and in the UK specifically mandatory fortification of infant formulae. There is also voluntary fortification of breakfast cereals and some milk products (e.g. yogurts). [127] Vitamin D fortified foods contribute significantly to the mean dietary vitamin D intake in the UK, with fat spreads, cereal products and milk products contributing 19%,

		13% and 5% of the average adult (18-64) dietary vitamin D intake/day respectively [130]. However, there are disadvantages to fortification, e.g. fortification of a single food item means that non-consumers of that item will not increase their intake. Also, high consumers of that food item may be at increased risk of toxicity. This has led to suggestions that fortification of many different foods with low concentrations of Vitamin D may be a better option [127].
Individual factors	Skin pigmentation	Observational studies have shown that those with darker skin pigmentation have lower serum 25(OH)D concentrations. A meta-analysis of studies assessing 25(OH)D concentrations in healthy free living populations found that Caucasians (n=96 studies) had an average 25(OH)D concentration of 68.0 (±3.2) compared with 47 (±4.0) nmol/l in non-Caucasians (n=55 studies). This is a mean difference of 21.2 (±5.1) (p=0.01) [135]. Reasons for this difference in 25(OH)D concentrations with skin pigmentation include differences in sun behaviours (e.g. sun avoidance or clothing coverage) and genetic differences. In addition, higher concentrations of melanin (the pigment giving skin its brown/black colour) in the skin may absorb more UVB,

		leaving less UVB available to be absorbed by 7-DHC (and subsequently be converted to Vitamin D). However, the results of studies examining the relationship between melanin, UVB exposure and Vitamin D production have been variable, and this issue requires further clarification [110].
	Age	As age increases, the capacity to synthesis D3 from UVB exposure decreases (see 1.10.4.1 for more details) [133].
	Adiposity	Obese individuals have lower serum 25(OH)D concentrations when compared with normal weight individuals (see section 1.10.5.2 for further discussion) [133].
	Health status: Kidney and Liver Function	Reduced liver function can limit conversion of pre-Vitamin D to 25(OH)D and lead to decreased 25(OH)D status and vitamin D deficiency. In addition, decreased conversion of 25(OH)D into 1,25(OH)D by the kidney can lead to decreased availability of active vitamin D and a build-up of 25(OH)D in circulation [110].

Table 1.11: Summary of factors which affect 25(OH)D concentrations.

1.10.5.1 Ageing and Vitamin D deficiency

A combination of these factors including lower dietary intake, lower cutaneous synthesis of D3 and medication use affecting vitamin D metabolism, are likely factors contributing to increased risk of vitamin D deficiency in older people [136]. Reported factors which may contribute to increased risk of vitamin D deficiency in older people include:

a) Low dietary vitamin D consumption

The results of the most recent rolling programme of the NDNS (2008/2009-2011-2012) showed that older adults (>65 years), had an average 25(OH)D concentration which was insufficient (<50nmol/L) for most of the year, with the exception of the summer months when the average 25(OH)D was 50.5nmol/L.

Vitamin D intake from food sources (fortified and natural) and supplements was low, with a mean intake of 5.1 µg/day Vitamin D (51% RNI). However this is 1.5µg/day higher intake of Vitamin D than adults (18-64 years). [130]

b) Adverse effects of institutionalisation

Vitamin D status is significantly lower in the institutionalised older people, with mean values for men and women of 38.1nmol/L and 36.7nmol/L respectively compared with 56.2nmol/L and 48.4nmol/L in free living men and women respectively aged >65years.

Prevalence of deficiency (<25nmol/L) was also higher in institutionalised men and women (30.2% and 32.5% respectively) than free-living men and women (9.6% and 15% respectively) >65years. [110]

c) *Lower 7-dehydrocholestorol availability*

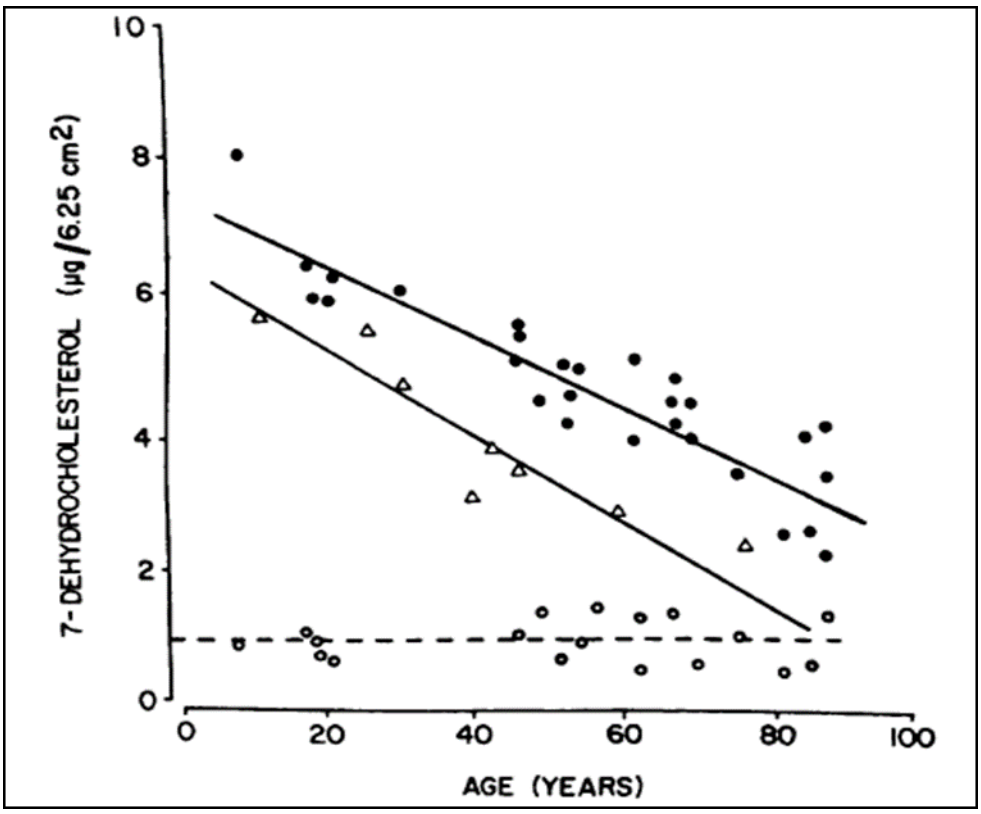


Figure 1.22 Graph demonstrating the effect of age in years (x-axis) on 7-dehydrocholestrol concentration (y-axis) in the dermis and epidermis of Caucasian adults (18-92 years). Taken from Figure 1 [137].

Amounts of 7-dehydrocholestrol in the epidermis decline steadily with increasing age (as depicted in Figure 1.22), probably due to the age associated steady decrease in epidermal mass seen >20years [137] which may reduce the capacity for Vitamin D from cutaneous synthesis. However the most recent SACN report on Vitamin D concluded that current evidence, was insufficient to conclude that 7-DHC was a limiting factor in Vitamin D production in older people [110].

d) *Health status*

Poor health in older age, including conditions affecting the function of the liver and kidneys, may reduce conversion of Vitamin D to 25(OH)D and 1,25(OH)D (the metabolite of Vitamin D capable of exerting Vitamin D related actions). However, low circulating concentrations of 25(OH)D are usually a result of reduced Vitamin D intake (dietary and cutaneous), rather than impairments in Vitamin D metabolism [110].

1.10.5.2 Obesity and Vitamin D deficiency

A negative correlation between vitamin D status and body fat /BMI has been reported in many observational studies. For example, a recent systematic review of 23 observational studies found that Vitamin D deficiency was 35% and 24% higher in obese and overweight respectively, than in normal weight comparators irrespective of age and study location [138].

The reasons for the relationship between vitamin D status and obesity are not clearly understood but may include:

a) 25(OH)D sequestration in adipose tissue

Adipose tissue is the main storage site for vitamin D, confirmed in Vitamin D radio labelling experiments[139]. In obese individuals, this may result in higher amounts of 25(OH)D being 'sequestered' in adipose tissue and not released when required i.e. adipose tissue may act as a vitamin D 'sink', restricting entry to the circulation[110, 112, 140].

This suggests that obese individuals have reduced Vitamin D bioavailability, and require a larger Vitamin D intake to achieve the same serum 25(OH)D concentration as a normal weight individual. In a supplementation study in which obese and normal weight individuals were given 700IU [17.5µg] Vitamin D per day, it was estimated that obese individuals need an additional 17% of Vitamin D for every additional 10kg above 'normal weight' to achieve the same 25(OH)D status as the normal weight group[141].

In support of this Vitamin D sequestration/reduced bioavailability theory, weight loss studies have shown that body fat loss results in higher 25(OH)D concentrations[142].

b) Volumetric Dilution

This theory challenges the sequestration theory by stating that the apparent difference in 25(OH)D concentrations in obese individuals, is simply due to dilution of 25(OH)D across the larger volume of body mass (see Figure 1.22).

In a cross sectional study of 686adults, the differences in 25(OH)D attributed to obesity disappeared when serum 25(OH)D concentrations were adjusted for body

weight/body fat using linear and hyperbolic modelling. The author concluded that this rendered the theory of Vitamin D sequestration unnecessary, since when fat mass is taken into account appropriately, there is no difference in 25(OH)D concentration between obese and lean individuals. In light of this, the author also highlighted the importance of tailoring of Vitamin D intakes according to body size to achieve desirable 25(OH)D status [143].

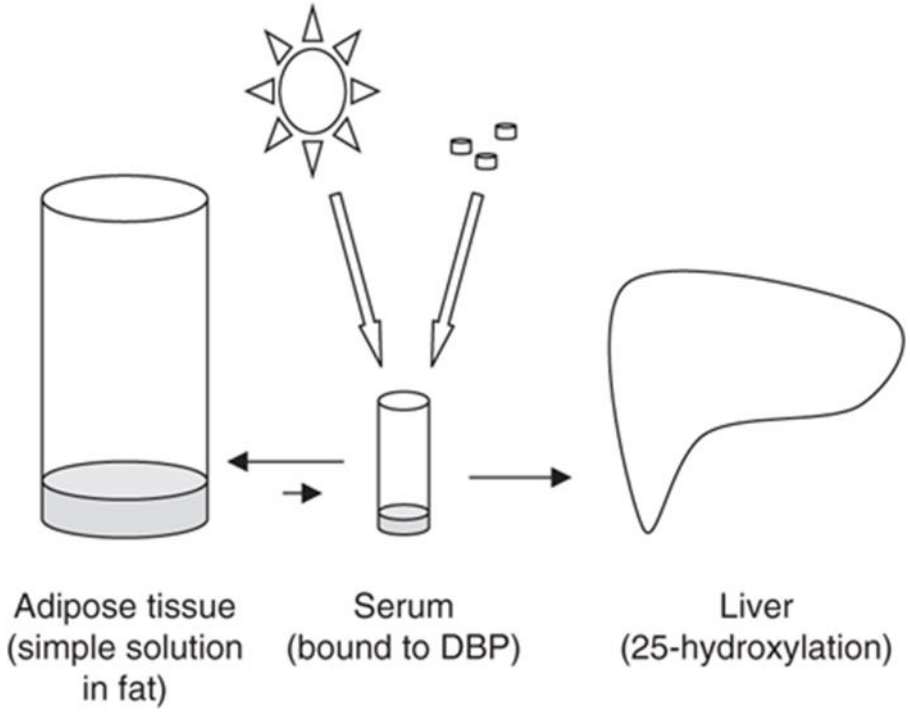


Figure 1.23: 25(OH)D is distribution throughout the body according volumetric dilution. Vitamin D is taken in by cutaneous synthesis or ingestion. This enters the circulation bound to DBP (Vitamin D binding protein) and also passively diffuses into the adipose tissue. It is then taken up into the liver for conversion to 25(OH)D. This means as body mass increases, 25(OH)D dilutes over a larger area, leaving less 25(OH)D diluted in the serum.[143].Taken from Figure 2 [143].

c) Metabolism of Vitamin D in Adipose Tissue

It has been proposed that lower Vitamin D concentrations in obese individuals are due to catabolism of Vitamin D in the adipose tissue via 24 hydroxylases which are expressed in adipose tissue[144].In a study in 37 obese and 20 lean participant's plasma 25OHD concentrations in lean and obese people were 54nmol/L and 29nmol/L respectively (p=0.006), and correlated inversely with BMI (r=-0.38, p=0.017). Expression of CY2J2 (25-hydroxylase which metabolises Vitamin D to 25OHD) and CYP27B1 (1ª hydroxylase which converts 25OHD to 1,25OHD) was decreased by 71% (p=0.0001), and 49% (p=0.05) in the subcutaneous adipose tissue of obese participant's compared with lean participant's. The authors concluded that adipose

tissue has an active role in the metabolism and catabolism of Vitamin D and that this becomes impaired in obesity [145].

1.11 Vitamin D and KOA

I have summarised below the current observational and limited available interventional evidence regarding the relationship between KOA and Vitamin D.

1.11.1 Observational Studies

Several studies have assessed the relationship between serum 25(OH)D concentration and radiographic KOA severity, with mixed results.

The Framingham Osteoarthritis Study, which measured radiographic KOA (K&L grade) in 715 at 2 time points 1993-4 and 2002-5, found only slight, non-significant worsening of OA (measured as proportion of participant's with joint space loss) with low Vitamin D status (lowest tertile) (see Table 1.12). However, it is important to note that the majority of participant's started without evidence of radiological KOA (87% K&L <grade 2), with only 20.3% of these showing joint space narrowing at follow up. In addition, Vitamin D concentration was not measured at the time of radiograph, but was measured between the original visit and follow up visit (1996-2000), so it possible vitamin D status at this time was not representative of that when radiographs were taken [87].

25OHD Tertile	Proportion of knees showing joint space narrowing (%)
High (57nmol/L)	13.9 (65/468)
Medium (42-55nmol/L)	13.4 (63/471)
Low (<40nmol/L)	15.8 (75/474)

Table 1.12: The proportion of knees showing joint space narrowing on follow up by serum 25(OH)D tertile (High, Medium, low) in The Framingham Osteoarthritis Cohort Study. Adapted from Table 2 [87])

A 2013 systematic review of 13 observational studies and 2 RCTs concluded that there was moderate evidence (2 high quality cohort studies) for an association between 25(OH)D concentration and radiological progression of KOA, and strong evidence (4 high quality cohort studies) for an association between 25(OH)D concentration and cartilage loss (measured as changes in joint space narrowing or cartilage volume). This

review also highlighted the limited amount of research available to determine the relationship between 25(OH)D and OA in other joints (hand and hip) and symptomatic OA [93].

There are few observational studies addressing the relationships between serum 25(OH)D status and symptoms of KOA. However, one longitudinal study of 769 older people (50-80yrs) with knee or hip pain, in which hip/knee radiographs and serum 25(OH)D was measured at baseline, and after 2.6 and 5 years concluded that serum 25(OH)D <25nmol/L predicted increases in self-reported knee pain (p=0.002) [89].

In summary, the observational evidence suggests that maintaining sufficient Vitamin D status may slow progression of KOA, but evidence regarding symptom relief is limited and requires further investigation.

1.11.2 Interventional Studies

The first large Vitamin D supplementation (2000IU [50µg]/day over 2 years) study in KOA participant's assessing radiographic and symptomatic outcomes, showed a small non-significant improvement in self-reported knee pain (-2.31 points in vitamin D group vs -1.46 points in placebo group) (p=0.17). However, a sub-analysis of those with serum 25(OH)D<25nmol/L showed a larger (but still non-significant) difference between change in self-reported pain in the Vitamin D supplementation and placebo groups (-2.7points vs -1.0 points respectively). There was no significant change between Vitamin D and Placebo groups for any radiographic measurement, and the authors concluded that there was insufficient evidence that Vitamin D supplementation was beneficial in slowing the progression of KOA in those with serum 25(OH)D <25nmol [92].

A very recent (2016) 3 year vitamin D supplementation study [146] in five UK hospitals of patients with radiographic KOA (K&L score 2-3), showed no significant difference in joint space narrowing (JSN) or self-reported of symptoms of KOA. However, it is important to note that participant's with variable baseline 25OHD were recruited into the Vitamin D supplementation and placebo interventions. However, as we have seen from the McAlindon study above, those with lower baseline 25OHD show larger improvements in KOA outcomes with Vitamin D supplementation. Subgroup analysis of

those with low 25(OH)D (classed as <50nmol/L in this study) showed no statistically significant interaction between baseline 25(OH)D and treatment effect for JSN (Treatment effect -0.06mm, 95% CI -0.20 to 0.32)[90].

1.11.3 Problems regarding current Vitamin D supplementation studies

As highlighted above, there are flaws in the design of the few published studies. The primary problem is recruitment of study participant's without regard to their baseline serum 25(OH)D concentration. One would predict that only those with "insufficient" vitamin D status would benefit from vitamin D supplementation so results could be "diluted" by lack of effect in study participants with adequate vitamin D status. This idea is supported by sub analyses in which those who are 25(OH)D deficient have yielded [92] larger improvements in KOA outcomes with supplementation than all 25(OH)D levels combined [92].

Therefore, studies which examine the effect of vitamin D supplementation on KOA outcomes in 25(OH)D deficient populations are needed. However, this introduces problems in identifying (through screening) and recruiting such specific individuals (this issue is further discussed in Chapter 2)[147]. Pilot studies are therefore needed to identify the potential problems and solutions to recruiting suitable participants for a vitamin D supplementation study in KOA.

1.12 Physical Activity and KOA

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" (WHO, 2017 [148]). This can include any type of activity, taking place when working, playing, carrying out daily activities or as a recreational pursuit. Physical activity is not the same as exercise which is type of physical activity which structured and planned with the specific aim to improve fitness.

Taking part in physical activity has a range of positive general health benefits including improving muscular and cardiorespiratory fitness, improve bone and function health, reducing risk of hypertension, coronary heart disease, stroke, diabetes and various cancers, reducing risk of falls and subsequent fractures and in regulating energy balance and controlling weight. [148]

However despite the massive benefits of physical activity on health, physical inactivity is prevalent. Physical inactivity (definitions of which vary according to different physical activity guidelines) is the fourth leading risk factor for global mortality, causing an estimated 3.2 million deaths globally. In 2010, approximately 23% adults over 18 years old (20% men and 27% women) were not active enough globally. [148] Addressing the current global problem of physical inactivity is essential for the prevention of non-communicable disease (including osteoarthritis), so much so that the WHO has placed great focus on the matter in their 2010 "Global Recommendations on Physical Activity for Health" report. [149]

1.12.1 Physical activity guidelines

1.12.1.1 World Health organisation recommendations

The WHO recommends all adults aged 18-64 years should do at least 150 minutes of moderate intensity (or 75 minutes of vigorous intensity) aerobic PA throughout the week, performed in bouts of 10 minutes. For additional health benefits it is recommended adults increase their PA to 300 minutes of moderate intensity (or 150 minutes of vigorous intensity) PA throughout the week. Muscle strengthening exercise (involving major muscle groups) should also be done on 2 or more days a week. [150]

For older adults (65 years and over), the WHO recommends the same level of activity as specified for adults aged 18-64 years (see above) with these additional recommendations: [151]

- Older adults with poor mobility should perform PA to enhance balance and prevent falls on 3 or more days per week.
- When older adults cannot do the recommended amounts of PA due to health conditions they should be as physically active as their abilities and health allows.

1.12.1.2 UK Department of Health recommendations

Recommendations on physical activity recommended by the UK Department of Health are very similar to the WHO recommendations. For adults aged 18-64 years, it is recommended that adults complete all activity recommended by WHO for that age

group (see section 1.12.1.1), with the addition of minimising the amount of time spent being sedentary for extended periods. [152]

Recommendations for older adults (65 years or over) include all which is specified for older adults by WHO (see section 1.12.1.1) with the addition of minimising the amount of time spent being sedentary for extended periods. [153]

1.12.2 Physical activity and the pathogenesis of KOA

The exact role of physical activity in the pathogenesis of KOA is not currently completely understood. However there are several current theories as to what the role of physical activity may be in KOA, which will be described in this section.

1.12.2.1 Physical activity, mechanical loading and KOA

According to existing evidence, physical activity can have both beneficial and detrimental effects to the knee joint depending on the context.

Under normal conditions, physical activity is beneficial to the knee cartilage as it acts as a mechanical stimuli to the cartilage (within a physiological range), which has several subsequent effects of the cartilage which are important for maintain cartilage homeostasis [154, 155]:

- Increasing hydrostatic pressure, which enhances the profusion of the synovial fluid throughout the cartilage which provides nourishment for mature cartilage cells trapped within the cartilage matrix. This is important as the cartilage has no vasculature and therefore no other means of distributing nutrients.
- Induces (via the action of mechanoreceptors) biosynthesis of components (e.g. type II collagen and aggrecans) of the ECM of the cartilage, thereby maintaining cartilage tissue integrity by preventing cartilage atrophy and ensuring the cartilage maintains deformation capacity
- Induces chondrogenesis (production of new chondrocytes) by simulating the differentiation of undifferentiated stem cells.
- Promotes the release of anti-inflammatory cytokines (e.g. IL-4) which subsequently reduce the expression of inflammatory cytokines (e.g. NFκB and TNFα)

Mechanical loading of the joint (in which physical plays a part) is regulated in the normal cartilage by the high water content within the cartilage which contributes to about 90% load support and shield the ECM from excessive stress or friction. However, changes to the careful balance of the structure of the cartilage (e.g. as a result of injury, repetitive loading or extreme torsional strain which can be induced by certain sporting, occupational or recreational activities) can result in excessive joint loading and induction of proinflammatory cytokine expression which cause subsequent damage to and degradation of the cartilage (a key event in the pathogenesis of OA), even under physiologically normal levels of loading to the joint.[2] And so in the context of other risk factors for the development of KOA (a comprehensive summary of which can be found in section 1.4) like previous injury or surgery to the joint and abnormal joint stability and range of motion, can produce and abnormal joint environment which may result in joint damage under normal physiological loading and activities such as physical activity. [2, 155]

Immobility is also harmful for the joints, causing a loss of flexibility around the knee joint and surrounding tissues, which can lead to impaired or altered gait and unequal distribution of force across the joint, causing pain and dysfunction of the joint. [155]

1.12.2.2 The impact of physical activity on other risk factors of KOA

Physical activity is important for the modulation of other risk factors which contribute to the pathogenesis of KOA by promoting the growth and maintenance of the cartilage (via the mechanism outlined above), strengthening the muscles surround the joint and by regulation of obesity. I have briefly described the potential role physical activity on those risk factors below:

a) Physical Activity and Obesity in KOA

Physical activity, along with diet, is an essential component in maintaining energy balance. When energy input and output becomes unbalanced (due to increased energy intake, reduced energy expenditure, or commonly both) to produce an energy surplus, this results in fat accumulation and obesity. [156] As described in detail in section 1.4.2.1, obesity is an important modifiable risk factor involved in the pathogenesis of KOA. It is therefore logical to assume that as physical activity has an important role in

the maintenance of energy balance and obesity has an important role in KOA pathogenesis, that physical activity may have a beneficial effect of KOA pathogenesis via the prevention or modification of obesity. Interventional studies have investigated the role of physical activity and diet for weight loss with the aim of improving KOA progression and symptoms. For example, a randomised, single blind clinical trial (the ADAPT Trial) of exercise and dietary interventions to reduce weight in community dwelling overweight and obese adults (> 60 years) found that an exercise plus dietary programme n=76) resulted in mean 5.2kg (95% CI 0.85, 9.55) weight loss and resulted in significant improvements in knee pain (p=<0.05), 6 minute walk distance (p=<0.05) and stair climb time (p=<0.05). The exercise only group within this study resulted in a mean 3.46kg (95%CI -0.77, 7.69) of weight loss and achieved significant improvement in 6 minute walk distance (p=<0.05). [157]

b) Physical Activity and muscle in KOA

Physical activity has an important role in strengthening the muscles which surround and support the joints which subsequently reduces risk of injury. [158] Impaired quadriceps strength have been linked to prevention of KOA in cross sectional studies, with increased quadriceps strength found to be protective against cartilage loss at the patellofemoral joint (OR: 0.4 [95% CI 0.2, 0.9] for highest versus lowest tertile of quadriceps strength).Quadriceps strength has also been associated with KOA symptoms in a cross sectional study of 300 KOA participants with knee pain (assessed by WOMAC questionnaire) vs 300 KOA participant without pain, which showed participants with pain had significantly (p=0.005) lower quadriceps strength than those without pain and that quadriceps strength was independently associated with pain (OR: 18.8 [95% CI: 4.8, 74.1).[159]Knee extensor strength has also been associated with decreased risk of developing symptomatic (but not radiographic) KOA in a 2010 longitudinal study of 1617 older adults (aged 50-79 years), with women in the highest tertile of peak knee extensor strength (compared to the lowest tertile) having reduced incident symptomatic KOA with an OR of 0.5 (95% CI 0.3, 0.8). [160]

1.12.3 Physical activity and KOA: Observational Evidence

1.12.3.1 Physical guidelines and KOA

Low levels baseline levels of PA have been consistently reported in those with KOA in the literature. For example, a US study reported that 30% of KOA participant's achieved recommended PA levels (30min/day moderate PA, 5days/week) compared with 45.4% reported by the general US population [161].A 2013 systematic review of 21 studies of KOA patients included n=3266 participants with a weighted mean average age of 64 years, mean BMI 30kg/m2 and 63% had severe KOA (K&L grade III or IV). The weighted mean moderate-vigorous PA (MVPA) in bouts of >10 mins was 50 minutes per week (95%CI 46, 55), weighted mean MVPA was 131 minutes per week (95% CI 125, 137) and weighted mean daily steps per day were 7753 (95% CI 7582, 7924). Proportion of KOA participants meeting physical activity guidelines were also measured calculated and it was found there was high quality evidence that 13% participants met PA guidelines (defined as 150mins/week of MVPA in bouts of >10mins) and moderate quality evidence that 19% participant met the guidelines of 10,000 steps per day. [162] This is low compared to the UK general population in which 66% men and 54% women (>18 years old) met PA guidelines of >150min MVPA/week (according to 2012 data presented by BNF). [163]

It has been hypothesised that pain avoidance contributes to the lower PA patterns observed in KOA sufferers, but this hypothesis has been disputed, with some studies demonstrating that pain does not have a significant relationship with the amount of PA performed in those with KOA [164, 165]

1.12.3.2 Physical activity in preventing KOA

Physical activity alone does not seem to increase risk of developing KOA. Current evidence shows either no associated effect of recreational physical activity on risk of KOA or decreased risk of KOA, e.g. a case control study of men and women (n=281) about to receive knee arthroplasty for primary KOA retrospectively assessed lifetime physical activity and found risk of arthroplasty decreased with increasing cumulative hours of recreational activity. OR (95%CI) in men with low and high (dichotomised by the mean) cumulative exercise hours for knee arthroplasty were 0.91 (95% CI 0.31,

2.63) and 0.35 (95% CI 0.12, 0.95) respectively. The OR for knee arthroplasty by cumulative exercise hours for women were less disparate than in men at OR (95%CI) 0.56 (95% CI 0.3, 0.93) for low cumulative exercise hours and 0.56 (95% CI 0.32–0.98) for high cumulative exercise hours. [166]Studies of the Framingham cohort (n=1279) found that participation in self-reported recreational physical activity (walking, jogging and working up a sweat) was not associated with decreased or increased risk of OA (including in those classed as obese [defined as BMI >30kg/m2]).[167] Another study within the Framingham cohort (n=1415), which assessed self-reported hours per day in different intensities of physical activity ranging from sedentary to heavy activity) found no association with habitual physical activity and KOA after adjusting for age, BMI, knee injury, smoking and education. They also found no increased risk of KOA with increasing PA. [168]

1.12.4 Physical activity and KOA: Interventional evidence

1.12.4.1 Exercise and KOA

Exercise is recommended as one of the first treatment options for KOA by NICE. [10] Many different types of exercise have been trialled in KOA populations but the consensus is that physical activity is beneficial for the joints tissues and improves symptoms and function in people with OA. [169] A Cochrane systematic review of RCTs of exercise interventions for knee osteoarthritis reported that exercise significantly reduced knee pain by 12/100 points (95% CI 10, 15) and improved physical function by 10/100 points (95% CI 8, 13) immediately after treatment. 12 studies also reported significant reductions in knee pain (6/100 points, 95% CI 3, 9) were sustained at 2-6 months post treatment and 10 studies showed improvements in physical function (3/100 points, 95% CI 1, 5) were sustained at 2-6 months post treatment. [170]

Many interventional studies have investigated the effects of certain types of exercise (e.g. aerobic, muscle strengthening, balance and coordination and water based exercises) on KOA outcomes. A systematic review and meta-analysis comparing the effect of aerobic walking exercises (4 studies) and quadriceps strengthening exercises (10 studies) in KOA populations concluded that both aerobic and strengthening exercises resulted in reduction of pain (weighted pooled effect size 0.52 (95% CI 0.34, 0.70) and 0.32 (95% CI 0.23, 0.42) respectively) and reduced self-reported disability

(weighted pooled effect size 0.46 (95% CI 0.25, 0.67) and 0.32 (95% CI 0.23, 0.41)). As both types of exercise resulted in benefits in pain and disability outcomes, it was suggested by the authors of this paper that as both types of exercises produced benefits and adherence is the main predictor to response to exercise, in clinical practice patients should be offered a choice of the type of exercise intervention they would like to participate in. [103] The literature regarding exercise interventions to improve balance are more difficult to summarize due to the variation in their methods and interventions used. Once of the most common types of balance based exercise tested in KOA patients is Tai Chi. An RCT of n=56 participants randomised to a 12-week Tai Chi class or waiting list control group showed mean improvements in pain of 5.2 points (95% CI, −0.8 to 11.1) (0-100 scale) and mean improvement in physical function of 9.7 (95% CI, 2.8–16.7) (0-100 scale). [171] Finally the effect of water based (or aquatic) exercise on knee osteoarthritis outcomes was assessed in a 2015 meta-analysis of 6 RCTs of aquatic based exercise interventions. This meta-analysis concluded that there was no significant effect favouring aquatic exercise on physical function (SMD 0.31, 95% CI 0.01, 0.63), pain (SMD − 0.25, 95% CI 0.74, 0.24) or stiffness (SMD − 0.15, 95% CI 0.47, 0.17), when compared to land based exercise. When compared to no exercise, there was moderate evidence for a moderate effect of aquatic exercise of physical function (SMD − 0.55, 95% CI 0.94, 0.16) but not for pain or stiffness. [172]

1.12.4.2 Physical activity and KOA

Evidence regarding non-structured physical activity programmes for the treatment of knee osteoarthritis is sparser than for structured exercise programmes. It is important to establish if self-managed, lifestyle based physical activity interventions are effective in targeting and changing physical activity behaviours, as this is essential to modifying behaviour in the long term beyond the end of the intervention period. One home based, self-managed 12 week pedometer driven walking programme in older (>60 years), community dwelling adults with symptomatic OA was reported. In this randomised trial, steps increased by 23% in the intervention group and decreased by 15% in the control group but there was no significant difference in change of pain from baseline to 12 weeks between the intervention and control group (F= 0.75, P = 0.40). [173] However more evidence of home based, self-managed PA programmes is needed

to establish their effectiveness in increasing PA, on KOA symptoms and on long term maintenance of activity.

1.12.5 Physical Activity programmes and KOA: Gaps in the literature

Despite the wealth of literature regarding the association between physical activity and KOA and many studies demonstrating that various type of physical activity interventions are beneficial for KOA symptoms (see section1.12.4), there are several gaps in the existing literature regarding the use of physical activity programmes in KOA populations which need to be addressed. These gaps are described below:

Promotion of structured exercise is recommended in KOA [10] but not specifically increasing levels of wider types of physical activity. Therefore there is limited evidence about the effectiveness of interventions to promote PA in people with KOA, particularly in those with higher adiposity.

Lifestyle based PA interventions in other populations of sedentary adults have been recommended as an alternative to more structured exercise programmes, to which there have been many identified barriers (e.g. lack of time and dislike of vigorous exercise). A study of 235 sedentary adults taking part in a two year lifestyle based PA or structured exercise programme concluded that both were equally effective in increasing PA and cardiorespiratory fitness [174]. PA interventions in older population groups can be effective up to 12 months (but beyond this was unclear) and that interventions which included goal setting activities were likely to be the most effective [175, 176]. Investigation of PA interventions in an older population of KOA sufferers is sparse and inconclusive, with no effect on symptoms reported. However, one study demonstrated that an individualised advice-based PA intervention raised PA levels and intention to exercise in sedentary, older OA sufferers [177].

Because PA helps to maintain energy balance and to reduce risk of weight gain, reduced PA can result in a vicious cycle of weight gain and decreased PA, which can exacerbate joint pain and disability in OA sufferers [178, 179]. This suggests that PA interventions could play a part in breaking this destructive cycle and, for this reason, investigations into effective PA interventions for use in obese KOA populations are needed.

This is particularly important given that exercise is recommended by NICE as a core treatment in OA [10] and that problems with exercise adherence and uptake amongst patients are acknowledged.

1.12.5.1 Online Programmes for delivery of Physical Activity and Exercise Interventions.

Home based self-management exercise programmes, such as walking programmes, are popular options for the delivery of interventions in those with KOA [173], and can offer benefits such as easier incorporation into patient lives and are inexpensive alternatives to structured, supervised programmes [173].They can be effective in improving symptoms and can be maintained for up to 1 year [180].

There are few examples of the use of online technology to improve PA in those with KOA. However, a 12 month online PA programme was tested in an older (50-80yrs) population with self-reported HOA or KOA. Subjective PA measures (with a subgroup of objective PA measures) and self-reported pain and quality of life measures were made at baseline, 3 and 12 months. The PA programme involved the completion of a baseline test, goal setting and time limited PA objectives (with prompting tests). Results demonstrated good adherence to the programme (46% completed 6/9 online modules) and increases in self-reported and objective (+24mins activity/day compared to control group) measures of PA. This demonstrates that online PA programme can engage participant's and maintain PA improvements in the medium term [181].

When advising participant's to improve their PA levels, in practice, there are limited options for those in primary care. Due to a lack of time during consultations, a lack of standardised activity advice and lack of facilities to which to refer patients, the development of home based, self-managed activity programmes are ideal, if not essential. With the growing influence of digital technologies and the pervasive availability of such technologies, web-based interventions provide the perfect opportunity to deliver low cost, accessible and flexible PA interventions [181]. However few studies have tested this approach to improving PA in older people, therefore issues such as presentation, accessibility and usage for an older population particularly have not been addressed. An exception is the Live Well programme, which developed and piloted an online intervention platform to deliver personalised lifestyle-

related behaviours (including PA) intervention in older people [182, 183]. Therefore, I aim to develop and test in a pilot study the potential for using an online PA programme in older obese adults with KOA.

1.13 Vitamin D and Physical Activity

Many observational studies have observed a positive relationship between serum 25(OH)D concentrations and increasing physical activity levels. [184-186]e.g. a 2010 longitudinal study with a mean follow up of 2.6 ± 0.4 years found those with low 25(OH)D (defined as <50nmol/L) at baseline had significantly (p=<0.001) lower mean PA (8470.3 ± 3347.5 steps per day) compared to those with high 25(OH)D at baseline (9401.7 ± 3612.9 steps per day). This study also found that change in PA was significantly positively correlated with change in 25(OH)D (r=0.19, p=<0.001). [187] Another study based on 2003-2006 NHANES data from n=6370 participants showed that for every 10 minute increase in moderate or vigorous activity per day, there was a corresponding increase in 25(OH)D of 0.8nmol/L (0.32ng/ml) and 0.45nmol/L (0.18ng/ml) respectively. [188] However, the nature and mechanisms underpinning this relationship are currently unknown.

One theory regarding the relationship observed between 25(OH)D and physical activity is that increased physical activity levels reflect increased time spent outdoors and therefore increased amounts of sunlight exposure. Therefore the relationship observed between 25(OH)D and physical activity may be a result of the confounding effect of sunlight exposure (and the subsequent cutaneous synthesis of vitamin D). However, contrary to this hypothesis, cross sectional studies which have observed a positive relationship between 25(OH)D and physical activity which have also measured sunlight exposure (by dosimetry or self-report) have found this relationship remained even when taking into account sunlight exposure.[184, 187] This may indicate an that the relationship between 25(OH)D and PA is independent of sunlight exposure or may this may be a result of inherent errors with the sunlight exposure measurement, e.g. lack of proper compliance with the dosimetry measurement or as a result of covering the skin while outdoors (thereby preventing cutaneous vitamin D synthesis but still being recorded as being outdoors). [184]

An alternative theory regarding the relationship between 25(OH)D and PA is that people with lower 25(OH)D concentrations may be linked to lower muscle strength or usage which may then impact on ability to perform PA. There is some evidence to support this theory in the literature, as there is some evidence to suggest that vitamin D is stored in the skeletal muscle and can be released during activity, e.g. a study of n=14 young healthy males who took part in indoor muscle building exercise for at least a year had significantly higher 25(OH)D concentrations vs age matched controls (mean 57 ± 5 nmol/L vs. 40 ± 5 nmol/L, p=<0.05). [189] Conversely, there is also some evidence that 25(OH) may have direct effects on the muscle via the action of VDRs in the skeletal muscle which may encourage protein synthesis and muscle mass growth. [190] However a systematic review and meta-analysis of 17 RCTs showed no significant effect of vitamin D supplementation on proximal lower limb strength in patients with 25(OH)D <25nmol/L (SMD 0.1, 95%CI −0.01,0.22). [191]

Based upon the currently literature, it is difficult to determine exactly what the nature of the relationship between 25(OH)D and PA, and therefore further studies, particularly investigating the role of PA alone (controlling for potential confounding factors) on the bioavailability and metabolism of vitamin D are needed. [185] Additionally as vitamin D and PA are both closely linked with many of the same risk factors of KOA (e.g. age, BMI, occupation) and have some reported evidence as (individual interventions) that they could be potentially used as treatments options in KOA, it is worth investigating vitamin D and PA have a potential synergistic relationship in the treatment of KOA. Part of the aim of this study would be to investigate if an investigation of these two interventions combined would be feasible.

1.14 Scientific Justification for this study

It is clear from information presented above that affordable and effective new treatments in KOA are needed. Current management options are limited and focus on the treatment of symptoms rather than slowing the progression of disease. Importance has been placed on the role of lifestyle interventions in OA, with NICE specifying them as core treatments for all with OA, but there are acknowledged problems with delivery, uptake and maintenance of these interventions (particularly exercise programmes)[10].

We therefore, aimed to pilot two lifestyle interventions, for which there was potential evidence for a role in KOA pathogenesis, but where there was insufficient evidence from intervention studies to prove efficacy. These interventions were, Vitamin D supplementation and an online, self-managed physical activity programme.

The current evidence behind and justification for choosing these particular interventions is described below in section 1.11.1.

1.14.1.1 Choosing the Study Population

To test the efficacy of interventions in KOA, we need to choose an appropriate 'at risk' population and, for the purposes of this project, that means those at risk of Vitamin D deficiency, with low PA and who have KOA. Increasing adiposity and age are important determinants of each of these factors.

It was therefore decided that obese (BMI 30-40kg/m2) and older adults (50-70 years) would be chosen to pilot these interventions.

Choosing an 'at risk' population was important because it increases the likelihood of identifying people with the correct profile for our study (low vitamin D, low physical activity levels and presence of KOA) thereby aiding in the identification and recruitment of people into the pilot study who are likely to benefit from such intervention.

1.14.1.2 Piloting Interventions: Why it is important?

The design of a large-scale study testing the effect of Vitamin D supplementation, and online lifestyle based PA programmes in a 2 by 2 RCT factorial design is a complex intervention addressing multiple interventions and outcome measures. Based on the MRC Guidelines for the development of Complex Interventions (displayed in Figure 1.24: Diagram representing the key elements of the development and evaluation process for complex interventions as specified by the MRC. Adapted from Figure 1 [193]), development of such complex interventions starts with the systematic development of interventions using best available evidence followed by pilot testing [192]. Piloting and feasibility testing is required to establish testing procedures, estimating recruitment and retention rates and in determining possible sample sizes.

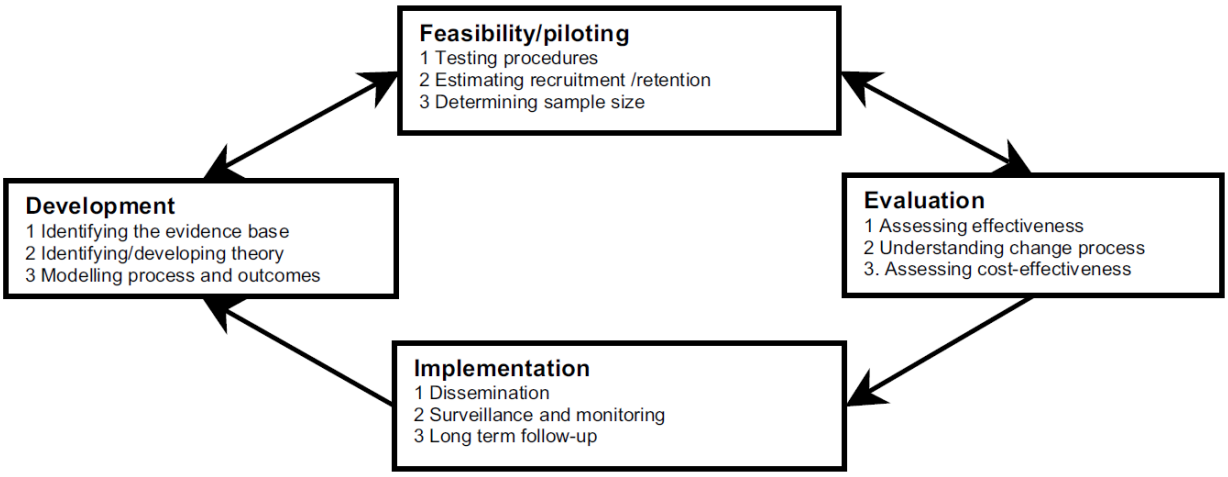


Figure 1.24: Diagram representing the key elements of the development and evaluation process for complex interventions as specified by the MRC. Adapted from Figure 1 [193]

In line with the MRC recommendations, we designed and conducted a pilot and feasibility study to test the feasibility and acceptability of the use of a web-based lifestyle PA and Vitamin D supplementation programme in at-risk KOA population with the aim of informing a more complex intervention.

A pilot study can be defined as a *'test of the methods and procedures to be used a larger scale…to test the feasibility of methods and procedures (pg. 1)* [194].

A pilot feasibility study design is ideal to allow the exploration of issues surrounding the design, planning, recruitment and logistical management of studies. However, there can be variability in what is investigated and reported as part of pilot studies (see Table 1.13) [194].

Elements reported in pilot studies	Explanation
Calculating sample Sizes	Pilot studies can provide initial data (means and SDs for study measurements/outcomes) on which to base sample size calculations.
Testing study protocols	Testing the study protocol using a 'trial run' allows problems or gaps to be identified. This ensures that when the full trial takes place all equipment, materials and training are in place.
Testing study measures	It is important to test study measures, especially if there will be several investigators taking measurements, to ensure consistency and appropriateness of the measurements.
Recruitment strategies	It is important to estimate recruitment rates in order to estimate the time needed for recruitment and to identify issues around recruitment, to ensure enough participants can be recruited into the fully-scale study.

Acceptability of Interventions	Testing the acceptability of an intervention (particularly those which may be concerning, potentially harmful or difficult to administer) in your target population is essential to ensure good retention and adherence during trials. This allows optimisation of the intervention before use in a trial.
Selection of primary outcome measures	There are many factors which can influence the decision of what the best primary outcome measurement should be, including feasibility, acceptability, reliability and confounding factors.
Resource assessment	This allows estimates of the time and resources required to carry out a study and includes a realistic estimation of staff and resource requirements to be made. This is important to avoid wasting resources, whilst ensuring enough resources are available to carry out a high-quality study.
Management and Logistical issues	This allows for the optimisation of practical and logistical issues such as data management and storage and communication with the study team/participant. This ensures the smooth running of the full study in a timely manner.
Scientific Integrity	Assessing the research question using the pilot study can allow for the optimization of the aims and objectives to appropriately address the research question.

Table 1.13: A summary of the variety of aims of pilot studies. Adapted from [194, 195].

It is advisable to pilot studies before conducting large trials for several reasons; to provide rationale for the study, test the feasibility of the procedures and measurements and identify any important logistical, methodological or study design issues to be addressed before running a full-scale trial. This can ultimately save money, prevent unnecessary burden on participants and ensures the usefulness of the research [194, 196].

The definition of what constitutes a feasibility study (distinctly from a pilot study) vary but broadly it can defined as a piece of research done before the main study which are used to estimate important parameters needed to design the main study, such as: [197]

- SD of outcome measures
- willingness of participants to be randomised
- willingness of clinicians to recruit participants
- numbers of eligible participants
- characteristics of proposed outcome measures

- follow-up rates, response rates, adherence and compliance rates

This information can be used to inform the design of the main study but is not used to evaluate outcomes or effect. A sample size calculation is not required in a feasibility study but adequate sample is needed to evaluate feasibility outcomes. [197]

In this study we combined elements of the feasibility study (assessment the acceptability, recruitment, population eligibility, follow-up, response and recruitment rates, compliance to study measures and interventions) and pilot study (testing protocols, study measures and interventions and identifying issues in study design and management) to produce useful data to inform the design of an effective complex intervention.

Using a pilot feasibility study design to trial these interventions is also a good opportunity to trial some of the recommendations made by authors on improving the design of the intervention, e.g. use of Vitamin D deficient KOA populations in the Vitamin D supplementation intervention. Using a pilot study design will allow us to test how feasible and acceptable this study design and interventions will be.

1.15 PhD Aims and Objectives

The aim of this PhD project was to explore relationships between Vitamin D status, habitual PA and KOA symptoms and to pilot an intervention study designed to deliver Vitamin D supplementation and an online PA intervention in older, obese people with symptomatic KOA. We aimed to do this by addressing the following objectives:

1. To explore relationships between circulating concentrations of Vitamin D, objectively measured PA and KOA symptoms in older obese adults with symptomatic KOA using a cross-section study design.

2. To design and implement a pilot intervention study to assess the acceptability and feasibility of an intervention providing Vitamin D supplementation and/or a web-based PA intervention in older obese adults with symptomatic KOA using a pilot intervention study design.

3. Using participant's from the pilot intervention study, to assess the acceptability and feasibility of key aspects of the intervention study including procedures for recruitment, intervention modalities and outcomes measures, using a semi-structured qualitative interview design.

1.16 Study Design Overview

In order to test our aims and objectives, three studies were set up and conducted from September 2013-June 2016 as pictured in Figure 1.25. Each stage of the overall study design is explored in the remaining chapters of this thesis.

Firstly, study participants were recruited by screening of patients from primary (North East site) and secondary (Liverpool site) care sources against the study eligibility criteria (April/September-December 2015). Potentially eligible participants were mailed study information packs and instructed to contact the study team if they were interested in taking part. Respondents were screened by telephone by the researcher and eligible participant's invited to take part in the cross-sectional study. In Chapter 2, the methods and results of the recruitment from primary and secondary care are presented and compared.

Cross-sectional study participant's attended a 90minute cross-sectional study visit at North Tyneside General Hospital (NTGH) where anthropometric and knee function tests and questionnaires were completed and blood samples taken. Accelerometers were provided for wear 3-5 days post study visit which were returned by post to Newcastle University. Chapter 3 addresses the methods and results of the cross-sectional study visits. The compliance and feasibility of the study measures is explored and the relationships between 25(OH)D, objective PA and self-reported KOA outcomes were analysed.

Following completion of the cross-sectional study visit, all study participants were screened for eligibility for the 3-month pilot interventional study using the cross-sectional study results. Eligible participants were invited to take part in the 3-month pilot intervention study, which included an initial study pack mail out (containing their study arm allocation, instructions and materials needed to complete their allocated intervention), and a midpoint (6 week) and end point (12 week) 90min study visit at

NTGH, which repeated the measures taken during the cross-sectional study visit. Chapter 4 will outline the intervention design and pilot intervention study methods. Study and intervention compliance, treatment effect and change in outcome measures are analysed. Finally, Vitamin D and online PA intervention study outcomes are compared.

Directly after the 12week pilot intervention study visit, a 60-minute semi-structured qualitative interview study took place, exploring the participant's views on the acceptability and feasibility of study recruitment, visits, measurements, materials and interventions. Qualitative data, in the form of interview transcripts, were analysed using the thematic framework method to identify qualitative 'themes'. Chapter 5 outlines the process of thematic framework analysis used and the resulting themes which were identified regarding the feasibility and acceptability of recruitment, study measures and materials and study interventions. Based on the themes identified, recommendations for the design and conduct of future studies were compiled.

Finally, this thesis finishes with an overview and discussion of the results from the three research studies. The strengths and limitations of these studies are discussed and recommendations for future work based on the results of this PhD project are presented.

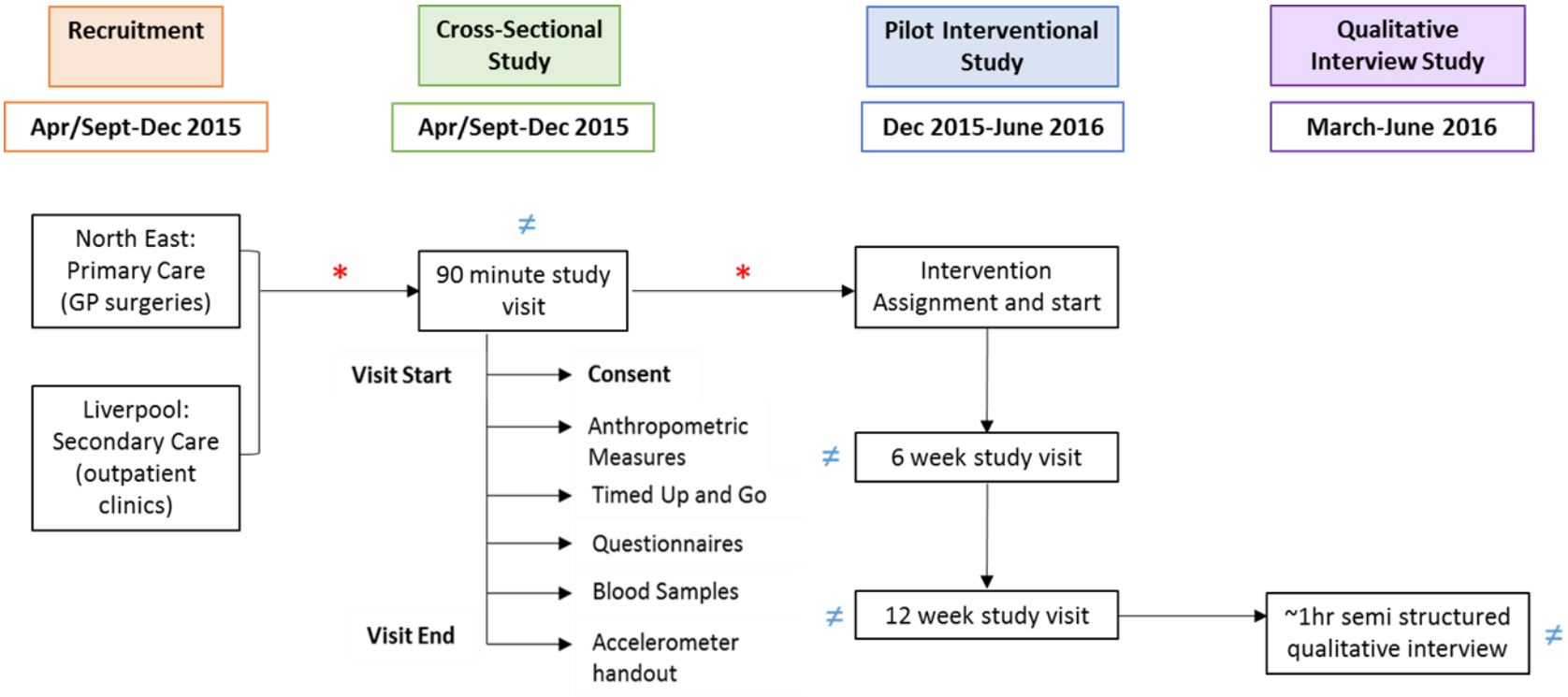


Figure 1.25: Overview of the design of the three studies comprising this PhD project. Study information was posted to potential participants and responders were screened by telephone against the study eligibility criteria. Eligible participants attended a 90-minute cross-sectional study visit at North Tyneside General Hospital where a range of study measurements were taken. At the end of the study visit, participants were provided with an accelerometer to wear for the following 3-5 days which was then returned to the study team by post. When all study measurement results were collected, they were collated into a participant feedback document which was posted to the participant. All cross-sectional study participants were screened for eligibility for the 3-month pilot intervention study. Eligible participants were assigned to study intervention arm (Vitamin D supplementation [2000IU [50µg]/d] and/or online PA programme) in an unrandomised design. Participants were mailed a study intervention starter pack followed up at 6 and 12-week study visits (repeating measurements from cross-sectional study). All pilot intervention participants were invited to take part in the #1hr semi-structure qualitative interview directly after the 12-week pilot intervention study visit. The qualitative interview focussed explored participants views on the acceptability and feasibility of the cross-sectional and pilot intervention studies.

Chapter 2. Study Recruitment

2.1 Introduction

It has been observed that just over half of publically funded clinical trials recruit to their target within their study duration [198]. The consequence of inadequate study recruitment is either the investment of further resources by the funders or a reduction in statistical power, risking the misinterpretation of treatment effect. [198, 199]. Poor recruitment also delays study start and completion and restricts opportunities for participation [200]. As such, most funding bodies now require evidence of feasibility assessment or consideration of pilot study data before funding is allocated to a full scale clinical trial [199, 201]. Therefore the optimization of recruitment strategy, to ensure recruitment numbers are met, should be undertaken before full scale clinical trials are conducted as part of either an external (performed as a standalone study) or internal (performed as part of a clinical study) pilot study[199].

In consideration of this, as part of the pilot study reported in this thesis, two different clinical based recruitment strategies were compared in order to assess the most successful strategy to identify and recruit the target study population.

2.2 Ethics and approvals

2.2.1 REC application

In accordance with Good Clinical Practice, NHS Research Ethics Committee (REC) approval was obtained before commencing the study by proportional review from London City and East Research Ethics Committee on 20/11/2014 ('Impact of Physical Activity and Vitamin D on osteoarthritic knee pain' - IRAS Project ID: 143184) (See Appendix A), using the online IRAS application portal. Permission for the cross-sectional study, pilot intervention study and qualitative interview study were applied for and approved within a single IRAS application form.

2.2.2 Study Permissions and Agreements

All researcher specific permissions were completed prior to commencement of the study, including;

- Research Passport for the primary researcher [RB] to work within the Northumbria Healthcare NHS Foundation Trust (13/10/2016).
- Honorary Contract was also obtained for the primary researcher [RB] for Northumbria Healthcare NHS Foundation Trust (18/12/2014)
- Caldicott Approval for data storage and participant study visits was obtained on 09/12/2014 (ID: C2952).

General study agreements and contracts were also completed prior to commencement of the study including;

- Application for NIHR CRN (Clinical Research Network) support including Research Nurse Support and Financial (recruitment costs) support was granted on 09/01/2015 (CRN Portfolio ID: Study 18199 – Impact of Physical Activity and Vitamin D on osteoarthritic knee pain).
- Study Site approvals were obtained from R&D departments at North Tyneside General Hospital on 19/12/2014 (Northumbria Healthcare NHS Foundation Trust) and University Hospital Aintree on 29/11/2014(Aintree University Hospital NHS Foundation Trust)
- A site agreement contract between Northumbria Healthcare NHS Foundation Trust and Aintree University Hospital NHS Foundation Trust was completed (see Appendix B).
- Sample Transfer agreements between Northumbria Healthcare NHS Foundation Trust and Newcastle University were obtained.

Finally, this study was registered with ClinicalTrials.gov on 13/11/2014 (Identifier: NCT02293889). The study protocol was uploaded and study status was updated as appropriate.

2.3 North East Recruitment

2.3.1 Methods

In the North East, we planned a primary care recruitment strategy which involved recruiting GP surgeries to screen their patient lists against our eligibility criteria. All potential participants identified by the GP surgery were sent the study information and invited to take part in the study. This process (summarised in Figure 2.1) is in more detail below.

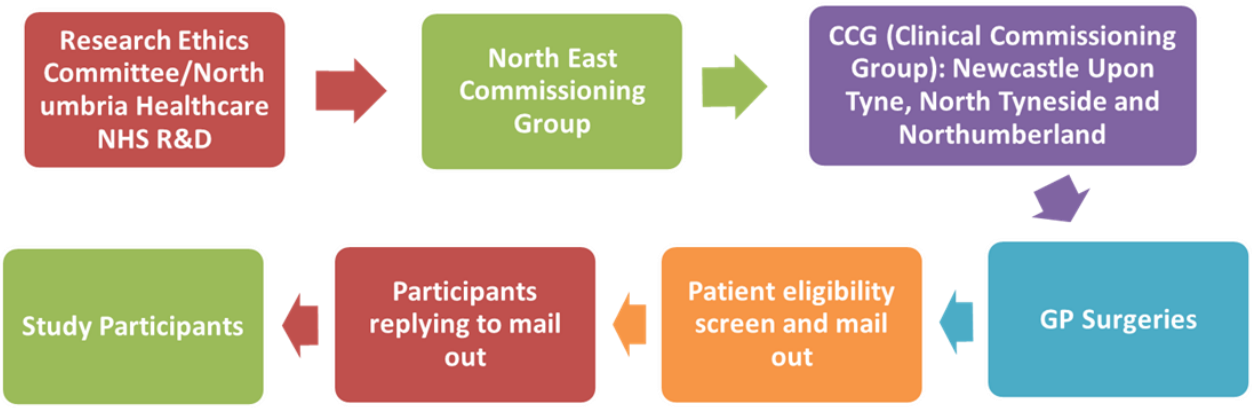


Figure 2.1: Summary flow diagram of the stages involved in the North East Primary Care recruitment strategy

2.3.1.1 North East Commissioning service

A 30 minute face to face meeting (16/09/2014) was arranged with the North East Commissioning Service to review the study design, study recruitment plan and requirements from the NECS.

The proposed primary care recruitment strategy was agreed with NECS and NECS staff was assigned to recruit from each local Primary Care Trust (PCT):

- Northumberland PCT
- North Tyneside PCT
- Newcastle Upon Tyne PCT

A summary sheet of the study eligibility criteria, participant Information Sheet and Consent form was sent to the NECS recruitment staff in order to recruit GP surgeries.

2.3.1.2 GP Practice Recruitment

Due to time and resource constraints, not all GP Practices in our recruitment area were invited to participate in the study. Instead a selection of GP practices in the Northumberland, North Tyneside and Newcastle areas (shortlisted as surgeries with a known interest in or had previously participated in academic research) were approached by NECS with a summary of our study and study criteria (see Appendix C). GP practices who were interested in taking part in the study contacted NECS who confirmed with the study team [RB].

2.3.1.3 Patient Identification and Study Information Mail out

Once GP practices were recruited, they screened their patient lists against our study criteria. Numbers of potential participants identified from this patient list screening was passed on to RB at Newcastle University, who prepared the correct number of prepaid study mail out packs (containing a letter of invitation (see Appendix D), participant information sheet (see Appendix E) and consent form (see Appendix F). These study mail out packs were delivered to the GP surgery who added a study invitation letter on the GP surgeries headed paper to the mail out pack. Potential participants' addresses were added to the completed study mail out packs which were mailed by the GP surgery. GP surgeries were paid a £250 fee for time and labour.

2.3.1.4 Patient Recruitment

As detailed on the patient information sheet in the participant mail out pack, individuals who were interested in participating in the study contacted the study team at Newcastle University using the contact telephone number or email address provided. Potential participants gave their contact details and were further screened for eligibility by telephone using a telephone screening questionnaire (see Appendix G).Eligible participants were invited to a 90 min study visit at North Tyneside General Hospital (NTGH), ineligible participants were informed of the reason(s) for their ineligibility and thanked for their time.

2.3.1.5 Recruitment records

Logs of all individuals who contacted the study team were recorded including information on; date and time of contact, name, contact information, GP surgery, reason for call, eligibility for study and details of study visit arrangement (if applicable). Detailed logs of all recruited participants were kept in the form of a master recruitment log (containing names, study ID assigned, study recruitment date, home address, contact details, appointment details and GP practice). Individual participant contact sheets were also kept in the front of each participant case file detailing all contact with the study team (including date of contact, reason for contact and outcome of contact).

2.3.2 Results

2.3.2.1 Recruitment of GP Surgeries

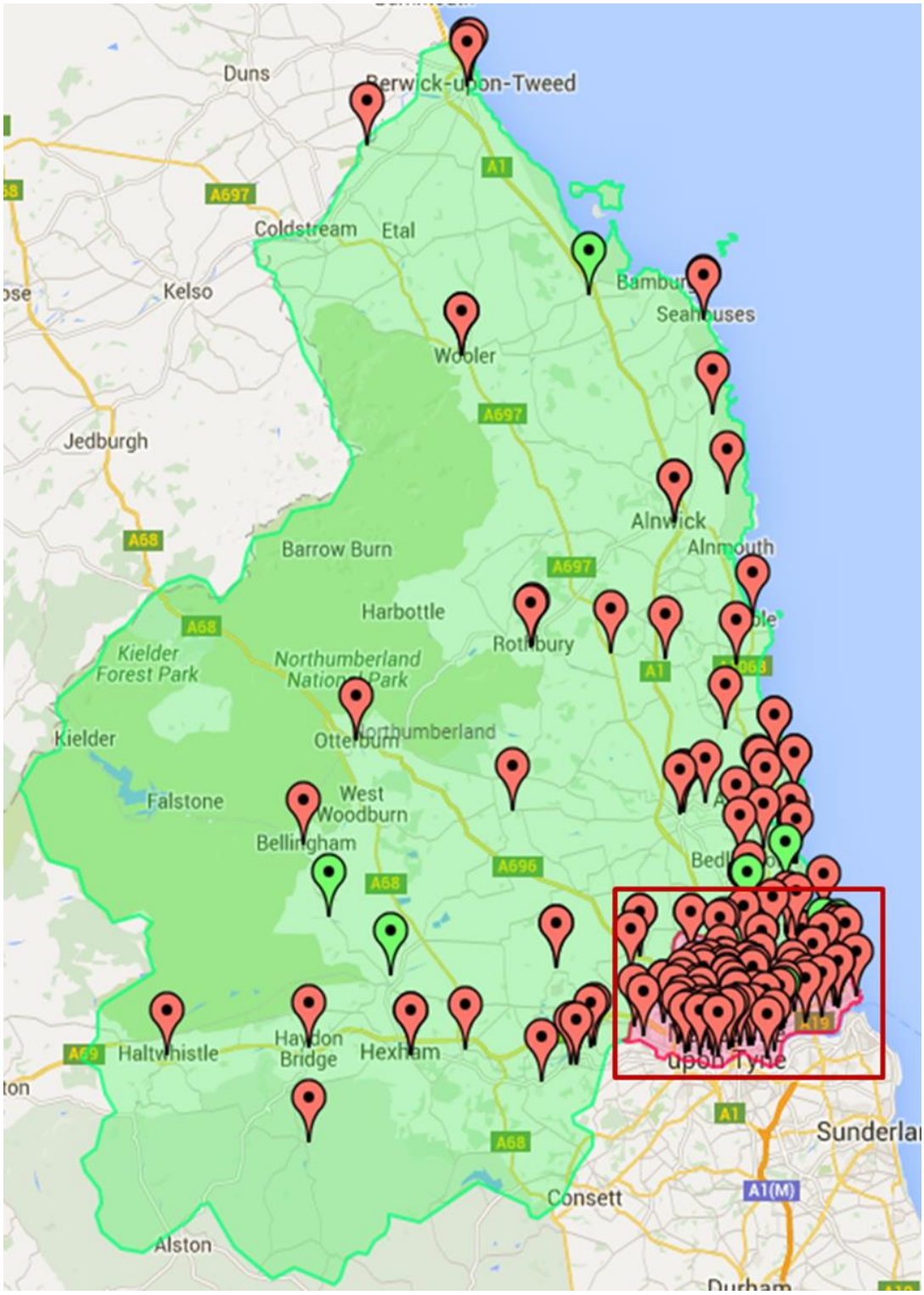


Figure 2.2: Map of the North East (Northumberland area highlighted in green and North Tyneside and Newcastle area highlighted in red), with markers highlighting the location of GP Surgeries. Red markers indicate GP Surgeries not approached or recruited to the study and green markers indicate GP surgeries recruited to the study.

From the Northumberland, North Tyneside and Newcastle PICs, 8 GP surgeries were recruited to the study; 4 from Northumberland, 2 from North Tyneside and 2 from Newcastle PICs from March 2015-October 2015 (see Figure 2.4). A graphical representation of the location and spread of the GP surgeries in the geographical location and which of those took part in the study (highlighted by green markers) can be seen in Figure 2.2 and Figure 2.3.

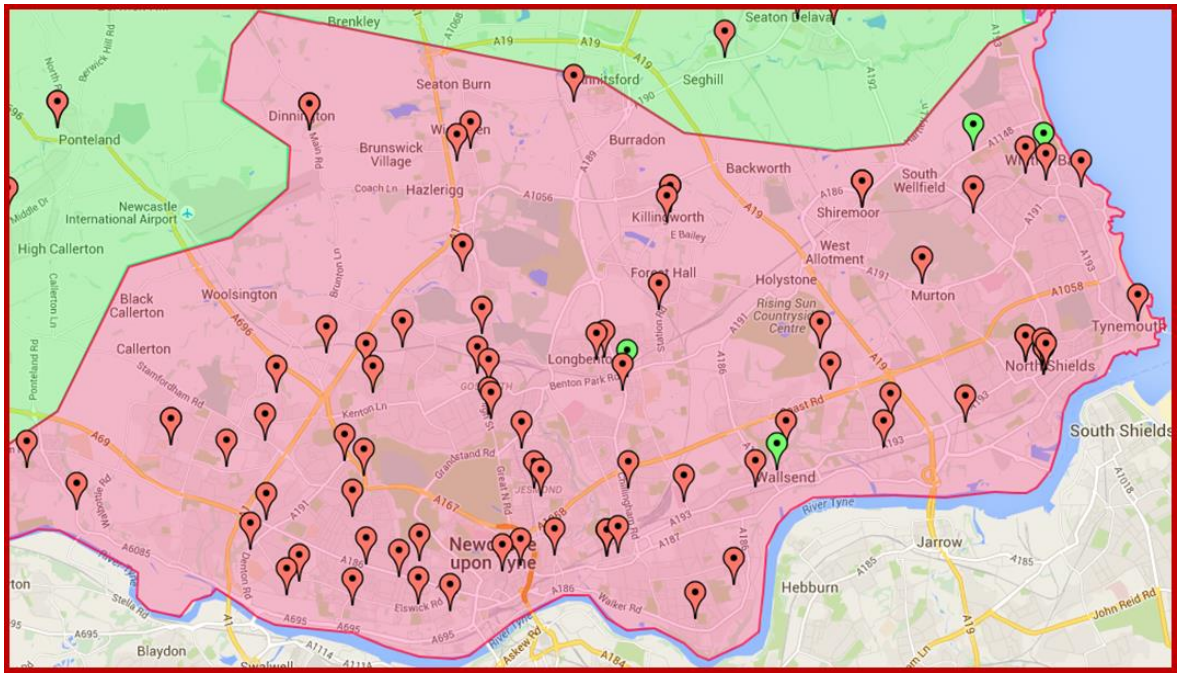


Figure 2.3: Map of Newcastle and North Tyneside area on which markers indicate the locations of GP Surgeries with those GP surgeries who took part in the study highlighted in green

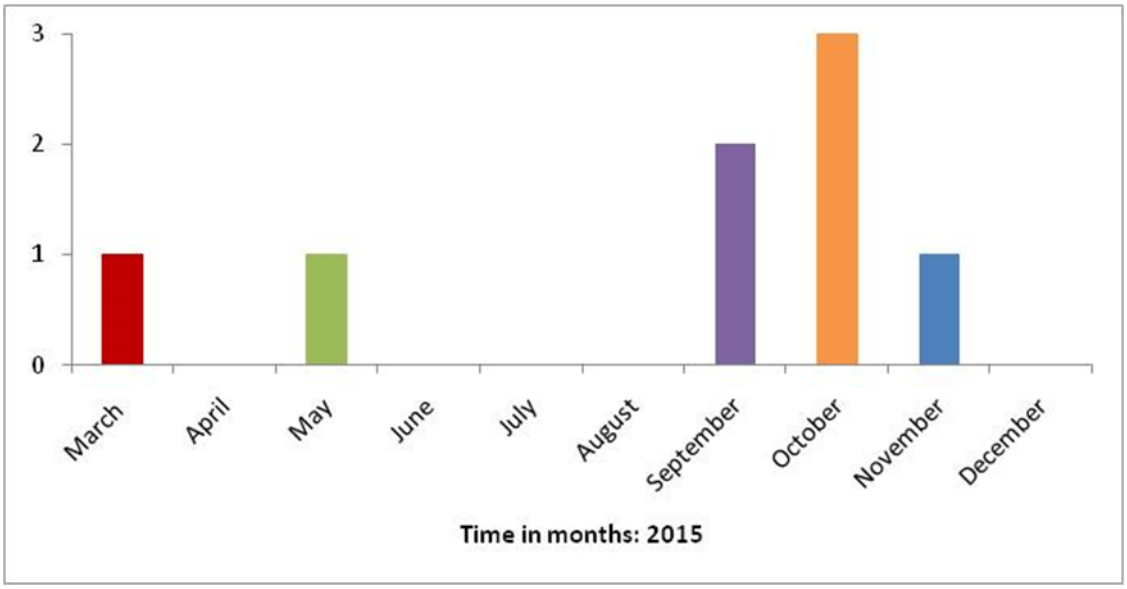


Figure 2.4: Number of GP surgeries recruited in the North East throughout 2015 by month

2.3.2.2 Reviewing GP Surgery Patient Lists (KOA Coding)

The eight recruited GP surgeries then proceeded to screen their GP surgery patients against our study criteria. Screening at all GP surgeries was conducted electronically by identification of correct 'codes' (each surgery, as part of general practice, assigns codes to individual symptoms, signs and conditions which are recorded within every patients electronic medical record). Codes relating to each of our study criteria were searched for and patients which met all of these criteria were identified as potentially eligible for the study.

An issue encountered using this electronic coding system was the variation in the coding terms used for KOA. The variation in the coding used to identify KOA between our 8 GP surgeries can be seen in Table 2.1 below.

GP Surgery	Geographical Location	Codes used to search for KOA
GP Practice 1	Northumberland	Data not obtained
GP Practice 2	Newcastle Upon Tyne	Data not obtained
GP Practice 3	North Tyneside	"Osteoarthritis of knee-X703L" "Osteoarthritis NOS, knee N05zL"

GP Practice 4	North Tyneside	Data not obtained
GP Practice 5	Northumberland	"Knee osteoarthritis" "Osteoarthritis of knee"
GP Practice 6	Newcastle Upon Tyne	"Knee Osteoarthritis NOS – NO5z6-1" "Osteoarthritis NOS, of Knee – NO5zL" "Knee pain – 1M10" "Anterior Knee Pain – NO94W" "Painful Right Knee – EGTON279" "Anterior Knee Pain – 1M12" "Knee Joint Pain – NO946-1"
GP Practice 7	Northumberland	Data not obtained
GP Practice 8	Northumberland	Data not obtained

Table 2.1: Variation in coding of KOA amongst recruited GP surgery electronic patient records.

Anecdotally, the GP practices expressed that, particularly regarding searching for the ACR criteria we specified for defining symptomatic KOA, there was addition manual processing of the electronic records (reading through individual records to note if criteria had been recorded in the patients notes) to ensure this criteria was met in addition to be coded as having KOA by the individual surgery.

2.3.2.3 Potential Participant Mail-out

The numbers of eligible potential participants identified and mailed information can be seen in stratified by month and individual GP surgery in Figure 2.5 and Table 2.2.

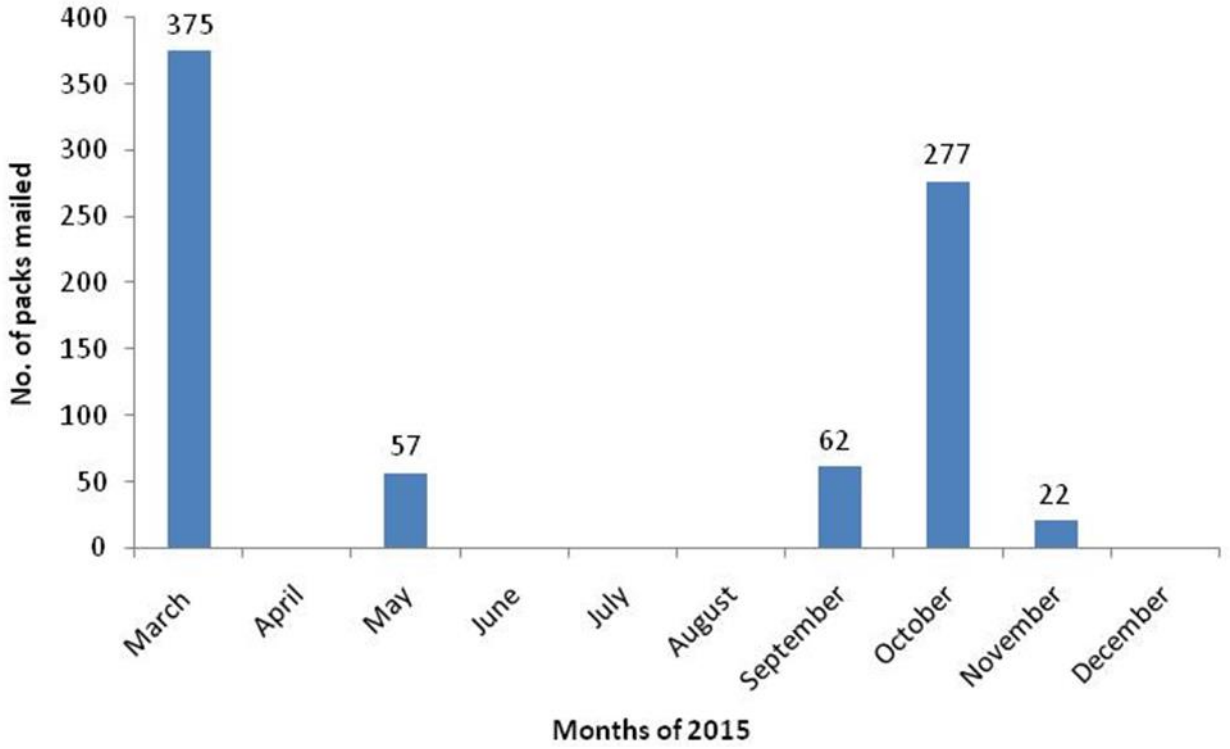


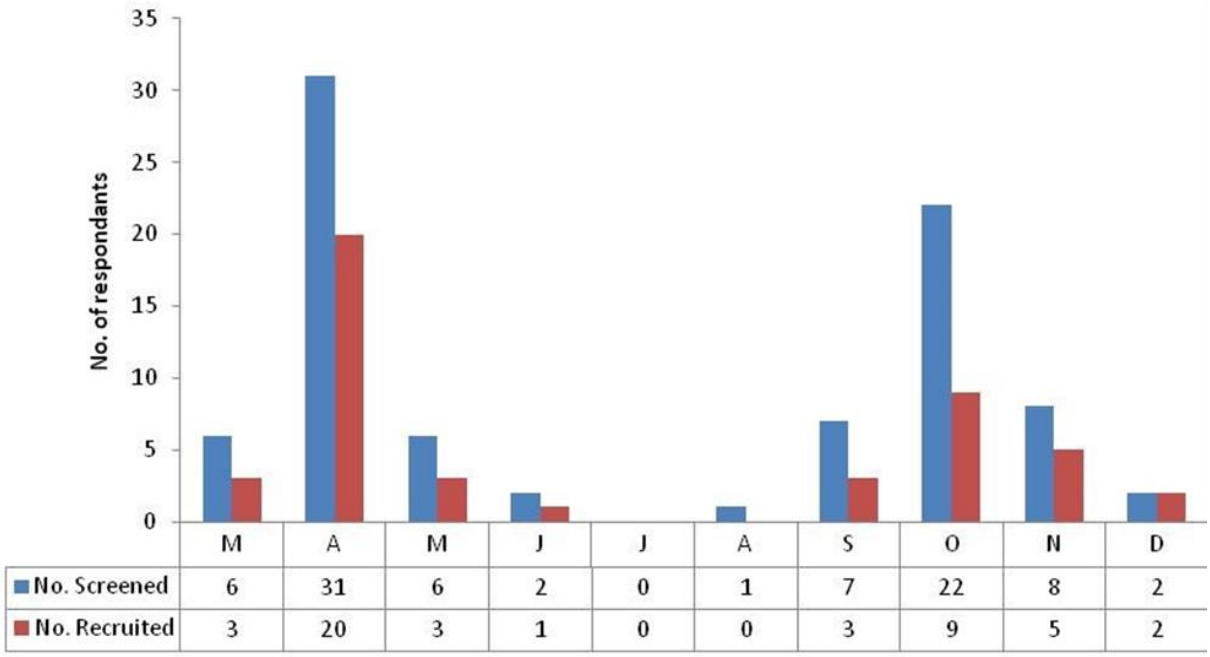
Figure 2.5: Number of study invitation packs mailed by GP surgeries to potential participants throughout 2015.

GP Surgery	Number of packs mailed	No of patients registered to GP practice	% of practice patients eligible for our study
GP Practice 1	375	14165	2.65%
GP Practice 2	57	4429	1.29%
GP Practice 3	43	6647	0.65%
GP Practice 4	17	6063	0.28%
GP Practice 5	121	9259	1.3%
GP Practice 6	134	8576	1.56%
GP Practice 7	22	4463	0.49%
GP Practice 8	22	3627	0.6%

Table 2.2: Number of eligible potential participants identified and mailed participant invitation packs by each GP surgery compared to the total number registered patients to that practice.

2.3.2.4 Study Information Mail-out response and Cross-sectional Study Recruitment

As part of the study information mailed to participants, they were instructed to contact the study team at Newcastle University by telephone or email. A total of 85 people contacted the study team between March and December 2015 (see Figure 2.6), 10.7% of the original 791 people who were mailed study information.



	M	A	M	J	J	A	S	O	N	D
No. Screened	6	31	6	2	0	1	7	22	8	2
No. Recruited	3	20	3	1	0	0	3	9	5	2

Figure 2.6: Number of respondents to the participant information pack which were screened by telephone (depicted in blue) and subsequently recruited into the cross-sectional study (depicted in red).

45/85 of the people screened were deemed eligible to participate in the cross-sectional study visit after completion of a telephone screening questionnaire, 5.7% of the original mail out population. The main reasons for exclusion during the telephone screening were those who inquired with questions but did not reply with interest in taking part in the study (n=12), those who had had knee replacement surgery (n= 10) and those who contacted to confirm they did not wish to take part (n=4) (see Figure 2.7).

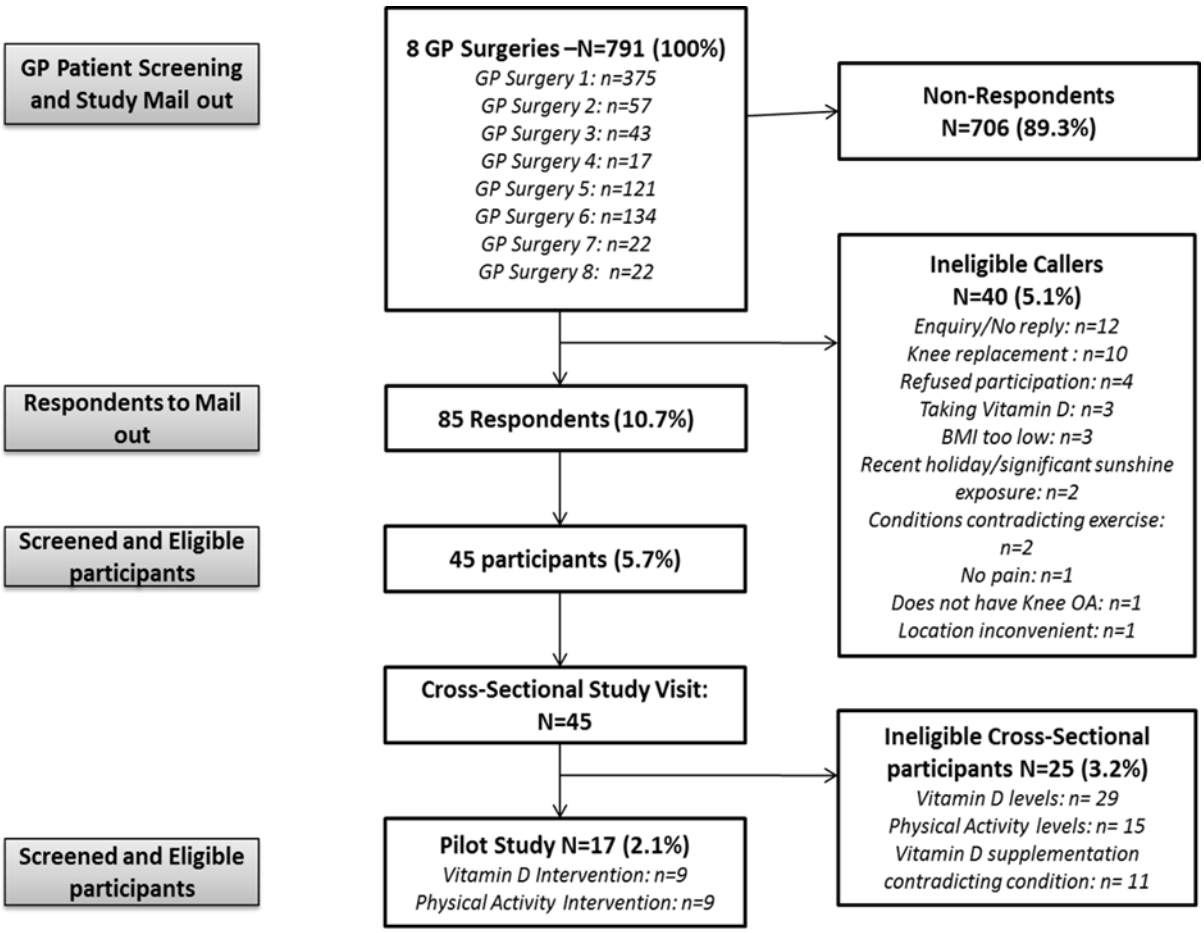


Figure 2.7: Flow diagram depicting the flow of participants from study information mail out, to participant response and recruitment into the cross-sectional study.

2.4 Liverpool Recruitment

In Liverpool we planned a secondary care recruitment strategy involving identifying potential participants from referrals to three hospital clinics in University Hospital Aintree (UHA). This process is summarised in Figure 2.8 below:

Figure 2.8: Summary flow diagram of the stages involved in the Liverpool Secondary Care recruitment strategy

2.4.1 Methods

2.4.1.1 UHA Clinic Recruitment

Through on site negotiations with UHA R&D and hospital departments, we recruited three hospital clinics to recruit for this study and identified persons in charge of recruitment for each clinic:

- Weight Management Clinic;
- Physiotherapy Clinic;
- Musculoskeletal Assessment Service (MCAS)

The recruiters and staff in each clinic screened each referral to that clinic against the study eligibility criteria. Information about the study was disseminated during staff meetings and posters hung in clinics rooms (see Appendix H) to encourage staff screening.

2.4.1.2 Participant Identification and Study Information Hand out

Information provided in participant referral letters to each clinic was screened for study eligibility by clinic staff. Patients identified as potentially eligible from this screening process would be informed about the study and given a study information pack (containing a study invitation letter, participant information sheet and consent form (see Appendix D-F) on their first visit to the outpatient clinic.

2.4.1.3 Patient Recruitment

Patient recruitment was carried out as in the North East (see pg. 91). Potential participants who were eligible for the study would be invited to a 90 min study visit at UHA and arrangements made with CRN research nurses at UHA to conduct the study visit.

2.4.2 Results

2.4.2.1 Recruitment of patients from secondary care

Referrals to the above clinics were screened by clinical staff during the recruitment period (October- December 2015). No referrals were identified which met the study eligibility criteria during the study recruitment period and no study invitation packs were handed out. Several reasons for a lack of success in recruiting patients from this location and environment were concluded from discussions with the recruitment staff at the Liverpool site, including;

a) Recruitment workload vs resources

Steps were taken during the study to engage staff within each participating department at UHA and encourage knowledge of and recruitment for the study. These steps included assigning a named clinician within each clinic tasked with managing and encouraging recruitment and dissemination to the wider clinical staff within each department by presentations regarding the study at departmental meetings and displayed posters (containing the study information and eligibility criteria) in all clinical spaces. However, despite this effort to disseminate knowledge regarding the research study, no recruitment was achieved. Feedback from clinicians involved reported that lack of time during their working day and a lack of eligible participants lead to non-recruitment. Within this study, recruitment was a potentially timely process

considering that refers to each department were paper-based and had to be individually and manually searched for all of the study eligibility criteria. Due to this time intensive process, it was likely the staff within the department did not have time to dedicate to this task.

b) Assessing study eligibility from referral records

It was also highlighted by the UHA staff that information contained within the referral records the departments received for each patient was hugely variable, ranging from a single sentence to a full patient assessment and medical history. This meant that identifying the correct information to assess eligibility of a patient for this study based on the referral was often not possible, due to unavailable or incomplete data. This meant any patients could not be accurately assessed for eligibility into this study.

2.4.2.2 Post hoc referral analysis

To further investigate the issues encountered in recruitment from this site, an exemplar post hoc analysis (Feb-March 2016) was performed by RB of 3 months of historical referrals (November 2015-Feburary 2016) to the Physiotherapy, Weight Management and Musculoskeletal Assessment service clinics. This was done with the aim of identifying patterns in information contained within referrals and patient eligibility which may enlighten any issues which prevented recruitment from this study site.

For each referral, the following information relating to demographics and our study eligibility criteria was extracted where available: age, gender, alcohol consumption, smoking status, date of referral, service/department referred from, primary reason for referral, history of KOA, BMI, and presence of any contradictory conditions.

a) Baseline Statistics

Basic characteristics of patients referred to each clinic were recorded and are summarised in Table 2.3 below.

Baseline characteristics	UHA Hospital Clinics			
	Physiotherapy	MCAS	Weight Management	All clinics
Mean Age (range)	58.2 (31-81)	52.4 (16-98)	NR	44.1 (16-98)
Gender				
Male	39%	40%	26%	38%
Female	61%	60%	74%	62%
Ethnicity				
White (British)	6%	47%	0%	16%
White (European)	0.3%	1.4%	0%	0.6%
Asian	0.1%	0.7%	0%	0.1%
Arab	0%	0.7%	0%	0.2%
Indian	0.1%	0.9%	0%	0.3%
Black	0%	0.7%	0%	0.2%
Other	0%	0.7%	0%	0.3%
Not Reported	93%	49%	100%	82.3%
Alcohol Intake				
Non Drinker	3.9%	33.5%	0%	11.3%
<14 Units/Week	3.9%	33.0%	0%	11.2%
>14 Units/Week	1.1%	10.1%	0%	3.4%
Not Reported	91.1%	23.4%	100%	74.1%
Smoking Status				
Non Smoker	6%	43%	0%	15.4%
Previous Smoker	3%	24%	0%	8.1%
Current Smoker	3%	20%	0%	7.1%
Not Reported	88%	13%	100%	70%

Table 2.3: Demographic characteristics of patients referred to UHA outpatient clinics between November 2015-Feburary 2016

b) Reason for referral to clinics

Analysis of the primary reason for referral to all clinics (represented in Figure 2.9) revealed the most common reason for referral was lower back pain (184 referrals) followed by shoulder pain (128 referrals). People were more likely to be referred for knee symptoms, e.g. knee pain (105 referrals) without a diagnosis of KOA than for confirmed KOA (74 referrals).

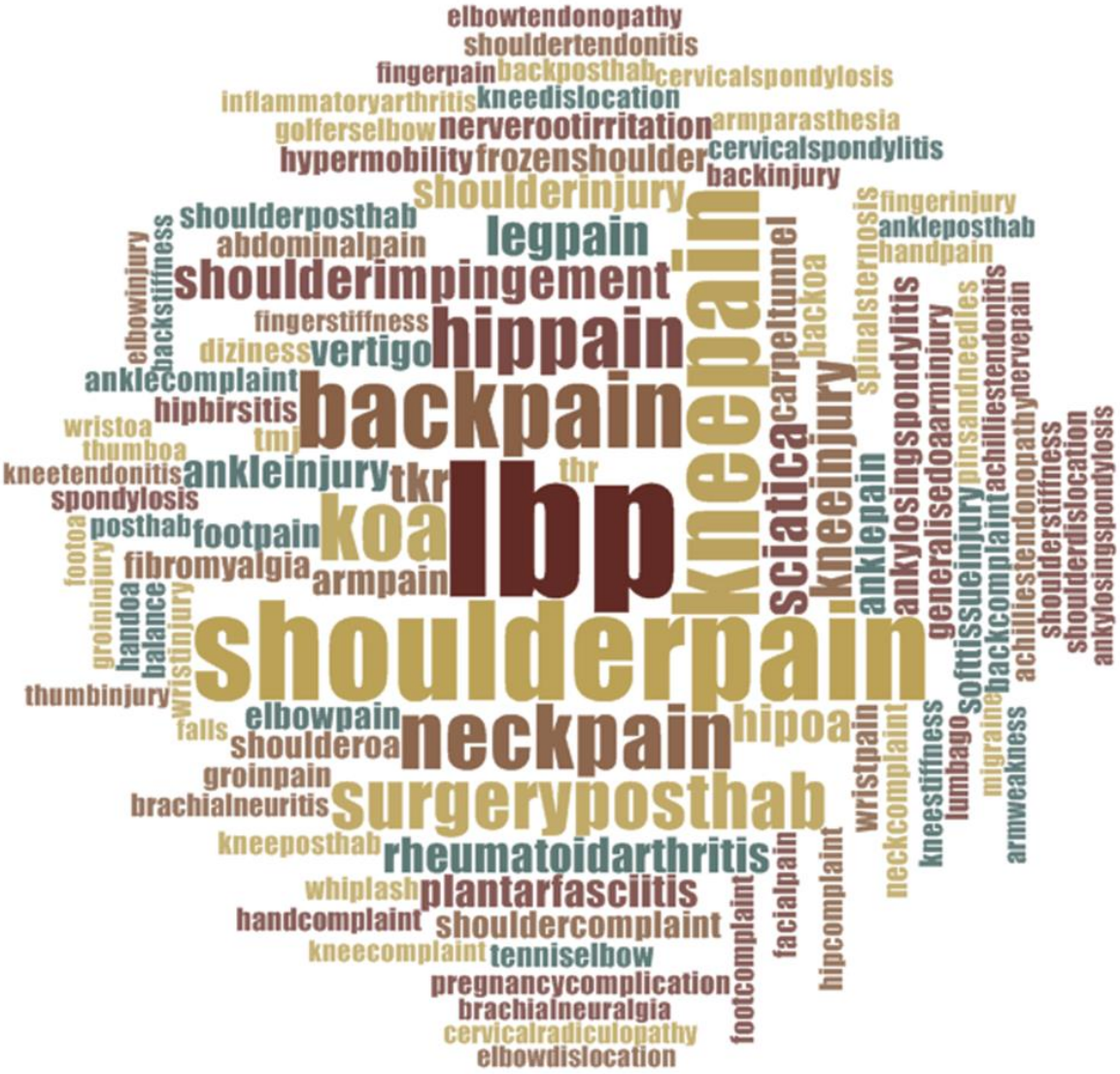


Figure 2.9: Word cloud (produced in Nvivo) representing the primary reasons for referral to Physiotherapy, Weight Management and MCAS UHA clinics. The size of the word represents the frequency of occurrence, with large words occurring more frequently than smaller words. LBP=lower back pain, TKR=total knee replacement, THR=total hip replacement, KOA=Knee osteoarthritis, OA=osteoarthritis

c) Eligibility Analysis

Next we analysed the content of the referrals against each of our main study eligibility criteria (outlined below) to determine how many participants would have been potentially eligible for the study, and to what degree each of these criteria was met among the referrals to the 3 UHA clinics.

i) Age

Age or DOB was consistently reported across all 3 clinics, with only 76 referrals (3.5% all referrals) not containing information on either. There was particularly high non-reporting of age amongst the Weight Management Clinic (37.6% WM referrals) than the physiotherapy (0.6% of physiotherapy referrals).

As can be seen in Figure 2.12, age was the study criteria most likely to be met by referrals when screened. When we look at the proportions of referrals deemed eligible and non-eligible by age criteria between the 3 clinics (see Figure 2.11and Figure 2.12) there were slightly higher numbers of non-eligible referrals, with 56.6% and 53.1% referrals determined ineligible from the Physiotherapy and MCAS clinics respectively and 42.8% and 46.9% referrals determined eligible from the Physiotherapy and MCAS clinics respectively.

ii) Body Mass Index

As can be seen in Figure 2.10, BMI was the criteria which had the highest levels of non-reporting. Incidence of non-reporting was particularly high within the physiotherapy clinic at 95.6%and much lower within the weight management clinic at 14.9%.

Of the referrals which reported information on BMI (see Figure 2.12), the MCAS clinic had the highest number of eligible referrals which met our BMI criteria at 75/573 referrals (13.1%), followed by the Weight Management Clinic at 35/181 referrals (19.3%) and finally the Physiotherapy clinic at 23 eligible referrals (1.5%).

iii) KOA Diagnosis

The KOA criteria specified the referral must confirm a diagnosis of KOA for the individual to be considered eligible. Across all clinics, there were low numbers of

referrals containing information of a positive KOA diagnosis at 171/2201 referrals screened (see Figure 2.12).

The pattern of KOA diagnosis non-reporting and ineligibility varied considerably between clinics. Non-reporting of KOA diagnosis status was high within the weight management and physiotherapy clinics with an incidence of 96% and 66.2% respectively. The MCAS clinic provided good reporting of KOA diagnosis status, however there was a large proportion of ineligible referrals (individuals without diagnosed KOA) compared to eligible referrals at 78.9% and 12.6% respectively.

iv) Presence of Contraindicatory Conditions (CCs)

The presence of conditions which would contraindicate our study interventions were recorded as these would lead to exclusion of potential participants. These included conditions affecting PA participation, e.g. angina and respiratory disease, and conditions which affecting Vitamin D supplementation, e.g. kidney and liver disease. As can be seen from Figure 2.11, there was low levels of referral exclusion based on the presence of contraindicatory disease at 7.2% of total referrals. However there were high levels of non-reporting with over half (56%) of all referrals not reporting on contraindicatory conditions at all.

Age was significantly higher in those with confirmed CCs compared to those confirmed without CCs ($t=16.2$, $p<0.001$), with a mean age of 66yrs and 49 years respectively. There was also a higher proportion of females amongst those with CCs at 65.6% compared to those with no CCs (61.1%) or the whole sample (62%). There was also better reporting of alcohol intake amongst those with confirmed contraindicatory conditions with a non-reporting rate of 26% compared to 47.5% in those with no CCs. Zero alcohol intake reporting was also higher in the group with CCs compared to those without CCs, at 25.6% and 16.9% respectively.

When the contraindicatory conditions recorded are broken down further (see Figure 2.13), you can see the most common contraindicatory condition recorded was stage 3 chronic kidney disease (28.75% of CCs) , followed by COPD (22.5% of CCs) and TKR (total knee replacement) (14.4% of CCs).

v) Diagnosis of Differential/Inflammatory Arthritis (IAs)

The presence of alternate arthritic conditions, particularly inflammatory arthritis, was also excluded. As with contraindicatory conditions, there was low number of referrals excluded based on presence of alternative/inflammatory arthritis diagnosis (4.4% of referrals) however there were high levels of non-reporting of such conditions with 54.9% of referrals containing no information on potential alternative arthritic diagnosis. Non-reporting was particularly high in the Weight Management clinic at 100% rate of non-reporting, followed by the Physiotherapy clinic at a rate of 67% non-reporting.

Age amongst those with IAs was significantly higher than those without IAs (t=3.9, p=<0.001) with mean ages of 57yrs and 51yrs respectively. The proportion of females was also higher in the groups with ICs that the group with no ICs, at 81.25% and 60.9% respectively. Non-reporting of alcohol use was substantially higher in the group with IAs at a prevalence of 74%, compared to those without IAs at a prevalence of 47.7%.

When alternative/inflammatory arthritic conditions were analysed further (see Figure 2.13), it can be seen the most common diagnosis was for Fibromyalgia (35.4% of IAs), followed by Rheumatoid Arthritis (24% of IAs) and Gout (8.3% of IAs).

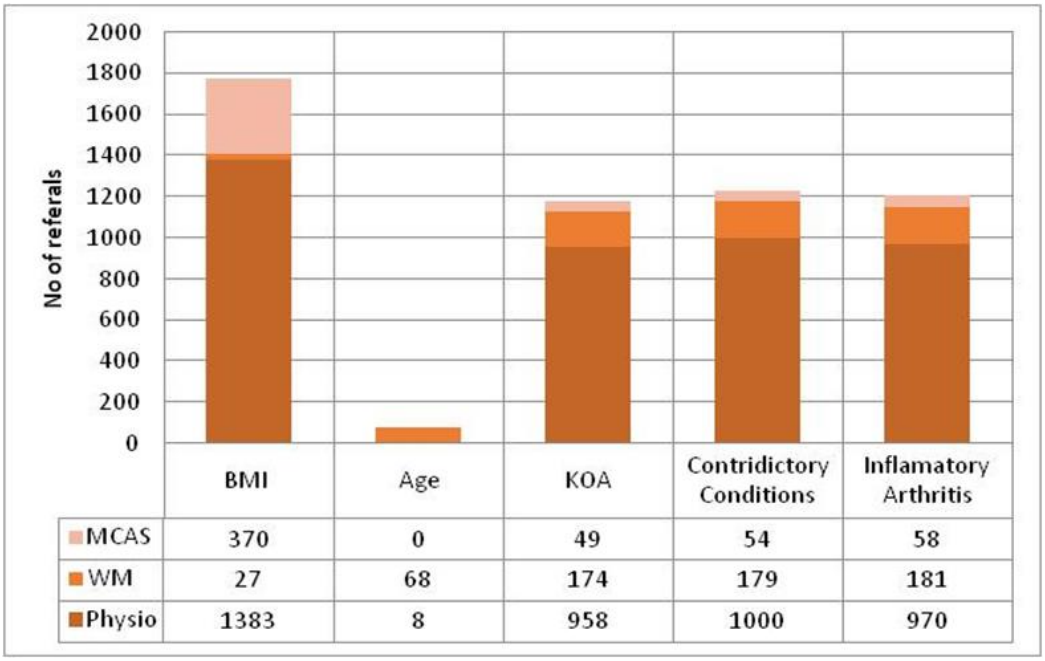


Figure 2.10: Graph depicting the number of referrals not reporting eligibility criteria, stratified by hospital clinic; MCAS: Musculoskeletal Assessment Service, WM: Weight Management and Physio: Physiotherapy

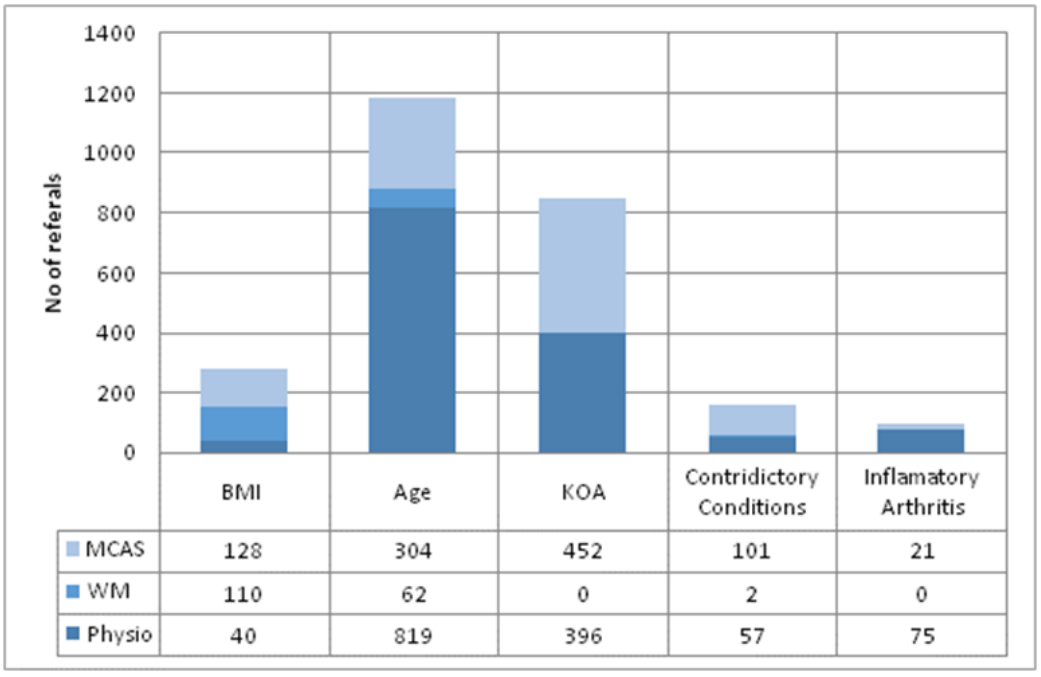
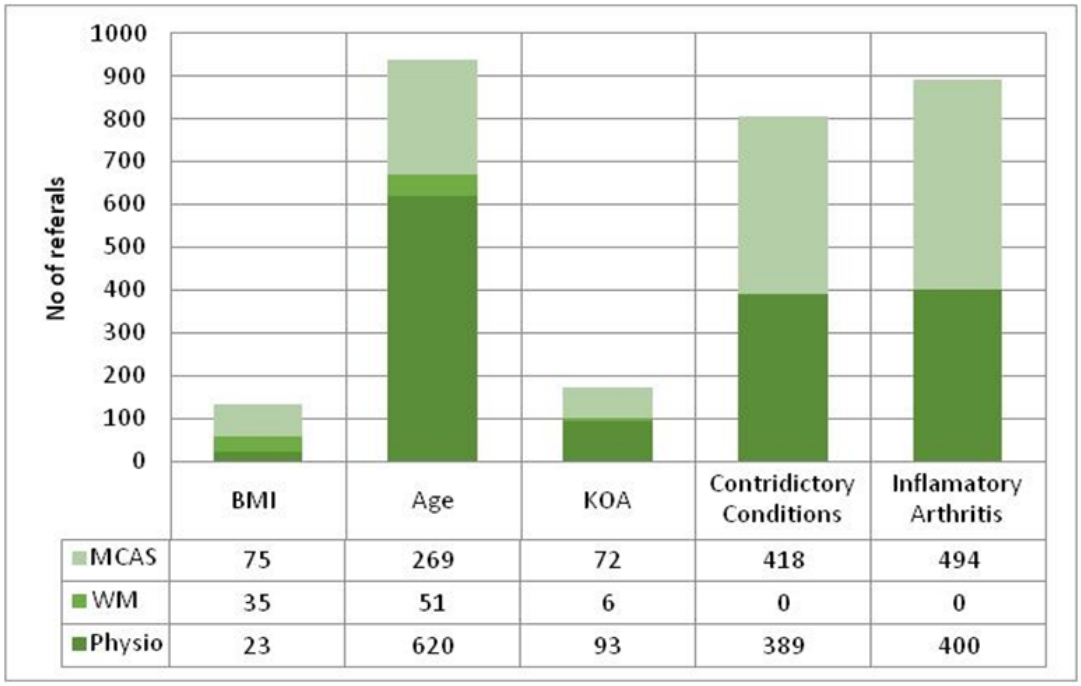


Figure 2.11: Number of referrals deemed ineligible by eligibility criteria, stratified by hospital clinic; MCAS: Musculoskeletal Assessment Service, WM: Weight Management and Physio: Physiotherapy



	BMI	Age	KOA	Contridictory Conditions	Inflamatory Arthritis
MCAS	75	269	72	418	494
WM	35	51	6	0	0
Physio	23	620	93	389	400

Figure 2.12: Number of referrals deemed eligible by eligibility criteria, stratified by hospital clinic; MCAS: Musculoskeletal Assessment Service, WM: Weight Management and Physio: Physiotherapy

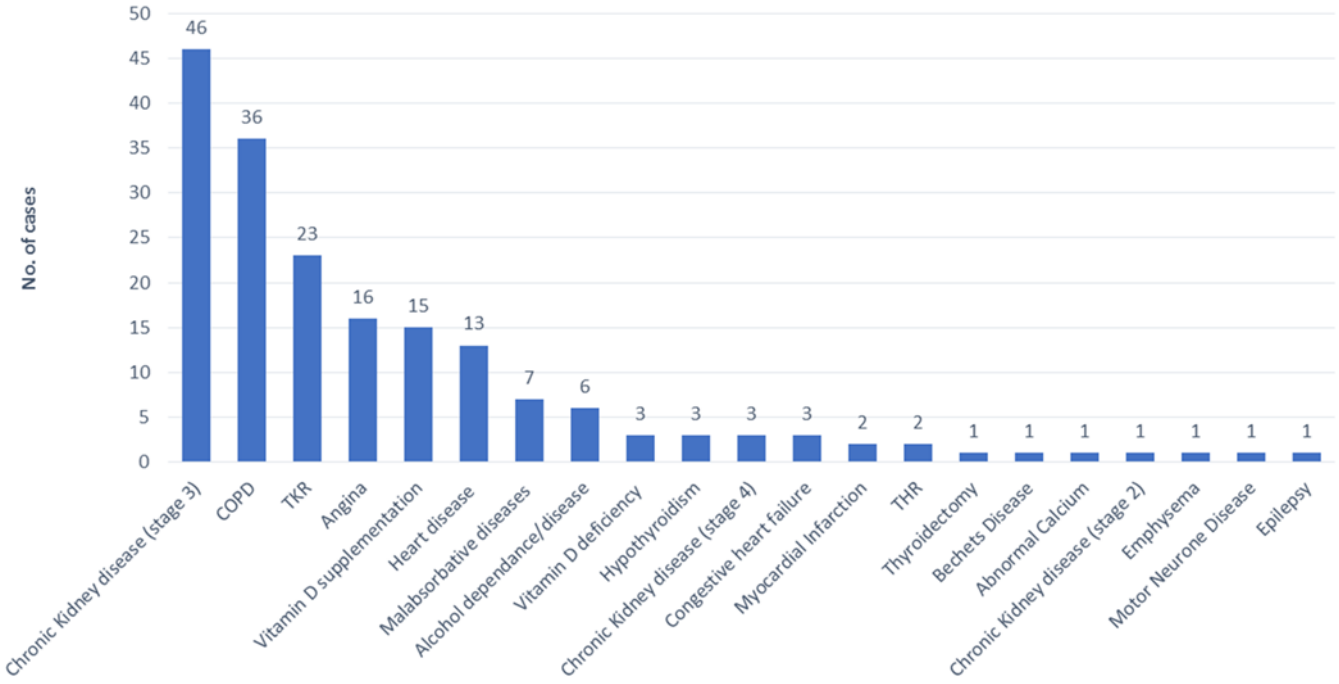


Figure 2.13: Graph depicting the frequency of different contraindicatory conditions recorded from referrals which would result in exclusion from the study. COPD: Chronic Obstructive Pulmonary Disease, TKR: Total Knee Replacement, THR: Total Hip Replacement

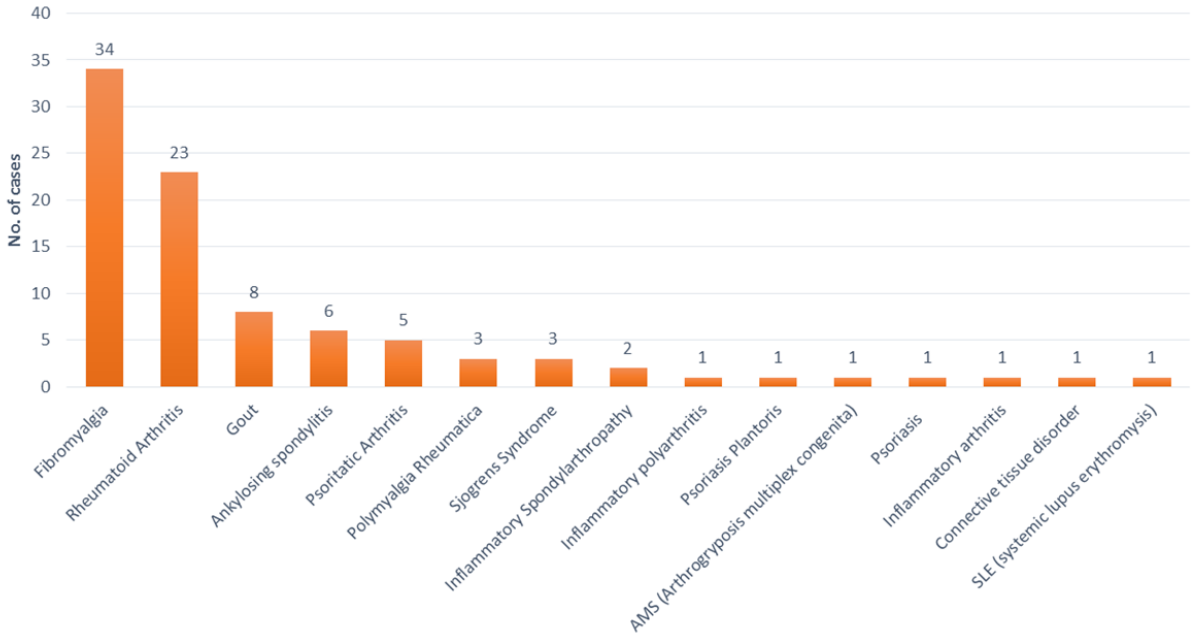


Figure 2.14: Graph depicting the frequency of different alternative/Inflammatory arthritic conditions recorded from referrals which would result in exclusion from the study.

vi) Combining Eligibility Criteria

To determine how many referrals would be considered eligible once criteria were combined, we analysed all the results from each hospital clinic, the outcome of this can be seen in the Venn diagrams in Figure 2.15, Figure 2.16, Figure 2.17 and Figure 2.18. The Venn diagrams display the number of eligible referrals on combination of the study eligibility criteria.

When all criteria were combined to give a final number of potential eligible patients, only 8/2203 were considered eligible, all originating from referrals to MCAS. Of these eight potentially eligible patients, there were five males and three females. 75% were non-smokers and 50% were non-drinkers. Mean age was 52 years and mean BMI was 30.1.

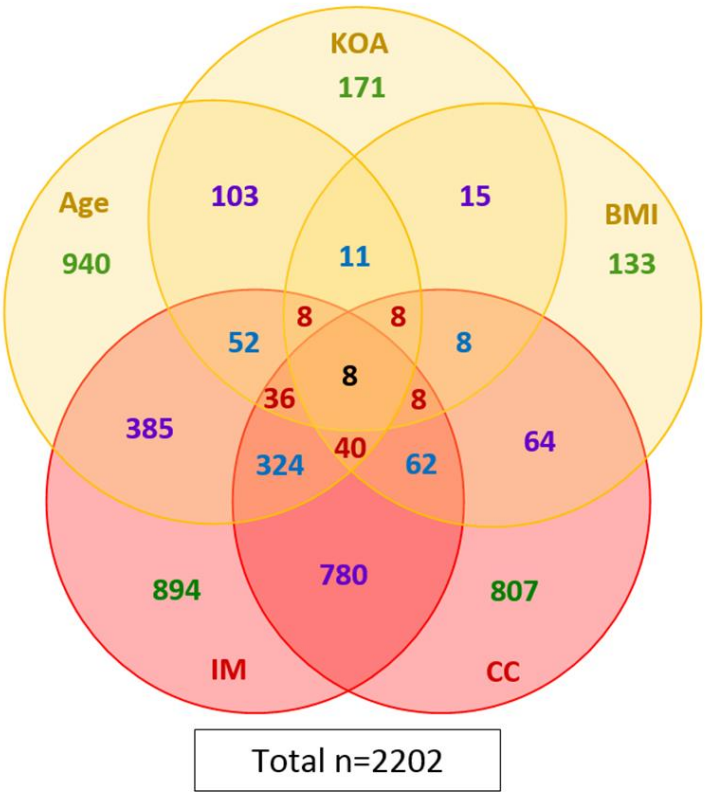


Figure 2.15: Numbers of eligible referrals from all UHA hospital clinics based on combinations of study eligibility criteria, with each circle representing a single study eligibility criteria.

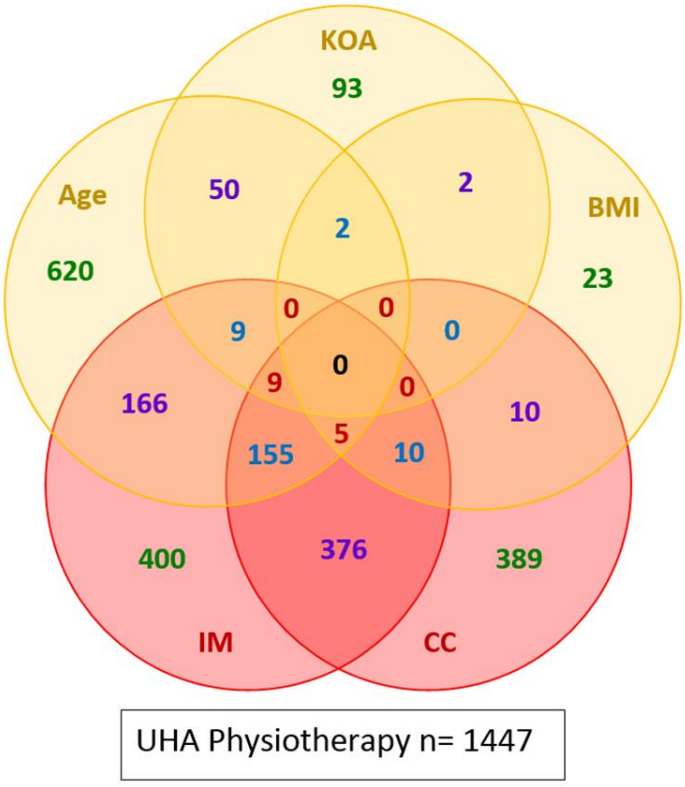


Figure 2.16: Numbers of eligible referrals (from UHA Physiotherapy hospital clinic) based on combinations of study eligibility criteria, with each circle representing a single study eligibility criteria.

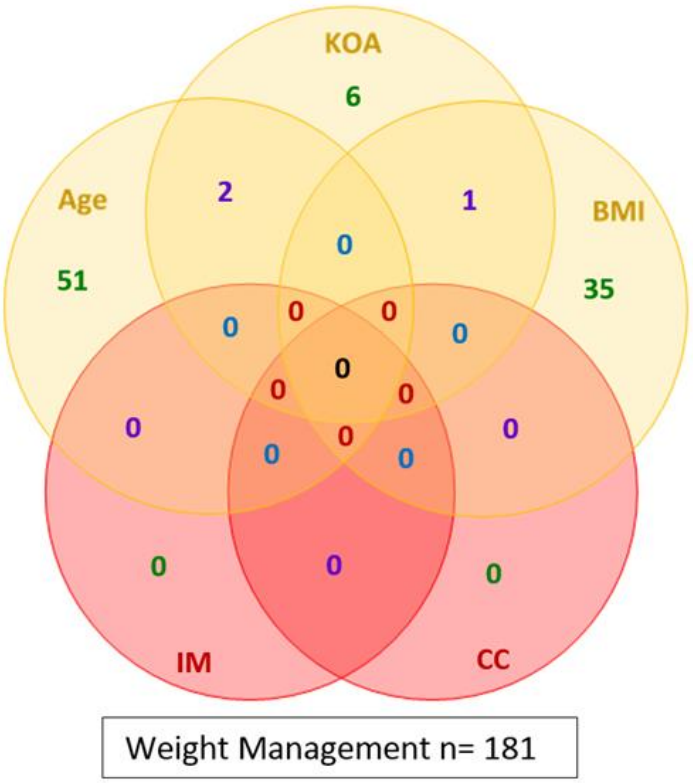


Figure 2.17: Numbers of eligible referrals (from Weight Management clinic) based on combinations of study eligibility criteria, with each circle representing a single study eligibility criteria.

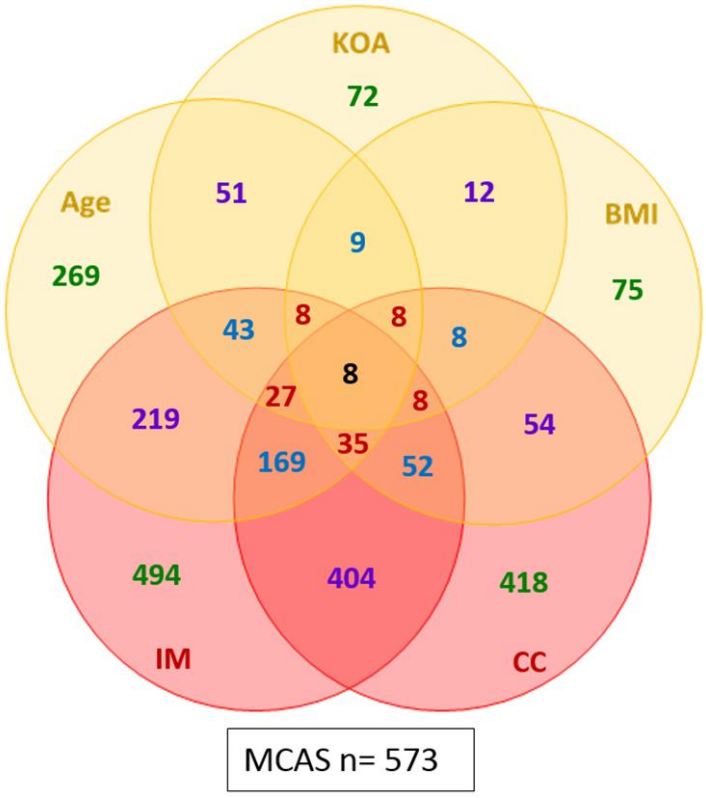


Figure 2.18: Numbers of eligible referrals (from Musculoskeletal Assessment Service clinic) based on combinations of study eligibility criteria, with each circle representing a single study eligibility criteria.

2.5 Discussion

In this chapter, I have reviewed the two recruitment strategies tested as part of this pilot feasibility study with the aim of finding the most effective strategy for identifying an obese, older KOA population for research study participation. A primary care recruitment strategy was conducted in the North East by recruiting GP surgeries across Northumberland, North Tyneside and Newcastle upon Tyne, to screen their practice patient lists against our study eligibility criteria, and mail out study information to identified potential participants. A secondary care recruitment strategy was conducted in Liverpool by recruiting 3 hospital clinics, Physiotherapy, Weight Management and Musculoskeletal Assessment Service, within University Hospital Aintree (UHA) to screen referrals sent to each clinic during our winter recruitment periods (January-April 2015/October-December 2015).

2.5.1 Primary Care Strategy

Our primary care recruitment strategy in the North East was successful in recruiting 8/153 GP surgeries with a combined practice patient number of 57,229. From these surgeries 791 patients were identified as meeting the study criteria (1.38% of total registered to these practices). If we compare this to the reported data from ARUK [202]of those with KOA in the North East (using the closest available filters to our study eligibility criteria; Aged 45-74 and Obese BMI), there are 18,225 people who meet our study eligibility criteria in the whole North East (excluding screening for concurrent alternative arthritis diagnosis and contraindicatory conditions), meaning study information was mailed to approximately 4.3% of the available eligible participants in the North East.

Recruiting participants from primary care introduces specific problems, which have been summarised in a paper by Bower et al. in 2009 [203]. They identified 4 specific stages in the recruitment of patients from primary care to research studies (summarised in Figure 2.19); recruitment of the primary care site, process of

recruitment/screening at the primary care site, patient agreement to take part in research and participant retention after recruitment.

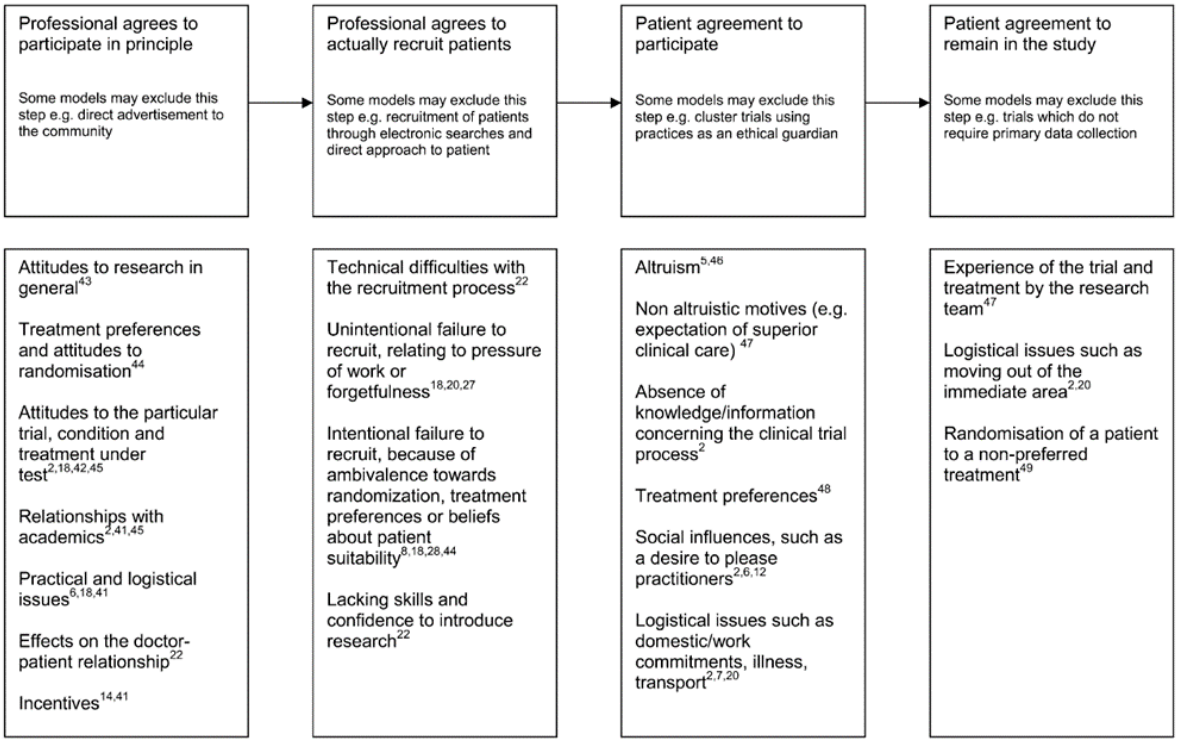


Figure 2.19: Flow diagram summarising the stages of recruitment from primary care and the factors affecting recruitment at each stage. Taken from Figure 1 [203].

As part of this article, a number of factors affecting recruitment from primary care resources were discussed, many of which we encountered during this study, for example the need for development of an infrastructure to allow primary care involvement in research. This was an initiative addressed by the NIHR CRN, which was established to provide support and raise awareness of clinical research involvement among primary care practice [203]. As part of this study, we obtained CRN support provided by NECS (the North East Commissioning Service). NECS supported our study by advertising, liaising and recruiting GP surgeries to partake in our study and provided financial incentives for participation, both previously identified factors (see Figure 2.19) important in the recruitment of primary care sites to research.

An advantage of using of GP surgeries as recruitment sites was access to the use of electronic health records for patient eligibility screening. The use of electronic records is a significantly less time consuming and more efficient process than manual hand searching of records, as condition and symptoms are usually recorded as codes which can be electronically searched and identified. Additionally, this meant we could also

screen an entire practice relatively quickly, with a turnover time of a few weeks. However, the coding of symptoms and conditions was variable between GP practices and therefore led to variation in their use for searching for those with KOA (as can be seen above in Table 2.1). This variation in coding between practices could potentially lead to under or over reporting of these criteria in patients, leading to a loss of eligible participants or potential inclusion of ineligible participants.

After recruiting GP surgeries and screening potential eligible participants, it was the choice of the participant on receiving our study information pack, whether to participant in this study ('opt-in' strategy). It has been suggested in the literature that 'opt in' strategies results in lower response rates and a more biased sample (due to participant self-selection) than an 'opt out' strategy. However the 'opt out' strategy poses many ethical issues, particularly regarding the presumption that individuals would find it acceptable to be contacted repeatedly about a study without specifically expressing willingness to take part[204].As described in Figure 2.19, this willingness to participate in research can depend on a number of different factors and addressing these factors may improve recruitment. For example, a well-established practical strategy to improve recruitment includes conducting telephone reminders after the original study information is sent, which has been shown to increase recruitment by up to 3 times compared to no reminder [205]. Therefore any future studies following on from this pilot study using the primary care recruitment strategy, may consider using reminders as a simple way of increasing recruitment.

2.5.2 Secondary Care Recruitment

As discussed in 2.4.2, our Secondary Care recruitment strategy was unsuccessful in identifying and recruiting any eligible participants during our recruitment period. In an effort to understand why this strategy was unsuccessful, an exemplar post hoc analysis was conducted of referrals sent to our recruited hospital clinics in the 3 months following the close of study recruitment (December 2015-March 2016). Using this post hoc analysis of and through discussion with the recruitment team at UHA, we identified pertinent explanations for the failure of this recruitment strategy: the balance between recruitment workload and available resources and quality and eligibility of referrals to our selected clinics.

Feedback from clinicians involved reported that lack of time and eligible participants lead to non-recruitment. It has been previously reported that lack of allocated or specific time for study recruitment and the demands of working in a busy outpatient environment are well known barriers for clinicians to adherence of recruitment tasks in research. [200] Another potential contributing factor to this was the manual nature of searching the paper based referrals to each clinic, which was a time consuming and inefficient process. Improvements can be made by allocating specific staff, e.g. research nurses, to this particular task, however, this often depends on the amount of resource available to the study team [200].

After our post hoc analysis (section 2.4.2.2) of referrals sent to the three UHA clinics over 3 months, we identified several potential issues. Firstly, as highlighted by the recruitment team, the quantity and quality of information contained within the referrals to these clinics was hugely variable. This meant that identifying information regarding our study eligibility criteria was often not possible. Additionally, as identified in our exemplar post hoc analysis, many eligibility criteria had high levels of non-reporting on referral documents, particularly regarding BMI status (excluding the Weight Management clinic which consistently provided this information as part of their referrals). There were also high levels of exclusion based on lack of specific KOA diagnosis and reporting of KOA symptoms, although 'knee pain' was commonly reported on referrals, but without a KOA diagnosis (see section 2.4.2.2). This lack of clarity regarding study eligibility criteria within referrals could potentially have led to exclusion of eligible participants.

2.6 Conclusions

Overall, the primary care strategy was successful in identifying and recruiting appropriate participants to our study. As this approach included screening medical records for specific KOA diagnosis according to ACR criteria, I believe this is a more relevant and targeted approach than could be achieved by advertisement to the general public, which would potentially lead to greater numbers of non-eligible volunteers, requiring further effort in manually screening people who met our study criteria. The primary care strategy also provided several advantages over the secondary care strategy we reviewed, including:

- Adequate information, via access to electronic patient medical notes, on which to assess study eligibility.
- Availability of adequate resources, e.g. staff with allocated time to recruit for our research study, to allow recruitment
- More efficient screening process, via electronic searching of patient medical notes, allowing screening of large numbers of individuals in GP surgeries compared to secondary care clinics.

In conclusion we have demonstrated the use of a primary care recruitment strategy is feasible for identifying and recruiting an older, obese population with KOA for involvement in a research study investigating the effect of Vitamin D and PA on KOA. However, further improvements to our primary care strategy can still be made by making use of reminders (postal or telephone) during study recruitment, to boost study participation.

Chapter 3. Cross-Sectional Study

3.1 Introduction

Chapter 2 described how people with symptomatic KOA aged 50-70yrs and with a BMI 30-40kg/m^2were recruited from primary and secondary healthcare sources into a cross-sectional study. Chapter 3 includes an overview of the design of this cross-sectional study which aimed to assess KOA symptoms, Vitamin D status and PA in an older aged (50-70yrs), obese (BMI 30-40kg/m^2) people with symptomatic KOA. This chapter also includes details of compliance with the study measurements to assess the feasibility of their use in this study population. Because the relationships between Vitamin D status and KOA symptoms were relatively unexplored at the beginning of this PhD project [93], data from this cross-sectional study were used to look for potential relationships between serum 25(0H)D concentration and outcomes relating to KOA symptoms. In addition, whilst the benefits of increasing PA through structured activities (such as exercise) on KOA symptoms are well-described[103], evidence on the extent to which light activity patterns and unstructured daily activity may relate to KOA symptoms is sparse. In the present chapter, this evidence gap was addressed by investigating potential relationships between PA intensity (assessed objectively using an accelerometer) and outcomes relating to KOA symptoms.

3.2 Methods

3.2.1 Ethics and Consent

REC approval was obtained before commencement of the cross-sectional study as part of an IRAS combined ethical approval form (see Appendix A). Written informed consent was obtained from each participant at the beginning of the cross-sectional study visit.

3.2.2 Study Design

Once recruited into the study, participants were invited to participate in a 90 minute cross-sectional study visit which was designed to obtain quantitative information on Vitamin D status, PA and physical capability and subjective assessment of KOA symptoms as detailed in the SOP (see appendix I).These visits were time-tabled to

occur during the ‘winter period’ (April 2015 and October-December 2015) when cutaneous synthesis of vitamin D was zero. This cross-sectional study provided information about the feasibility of, and experience in, conducting study visits for the measurement of anthropometrics, Vitamin D, PA and KOA symptoms in older obese adults with symptomatic KOA. In addition, data from this study visit were used to assess eligibility of participants for inclusion in the pilot intervention study (described in Chapter 4).

The protocol for the cross-sectional study is illustrated in Figure 3.1and described in more detail in section 3.2.6.

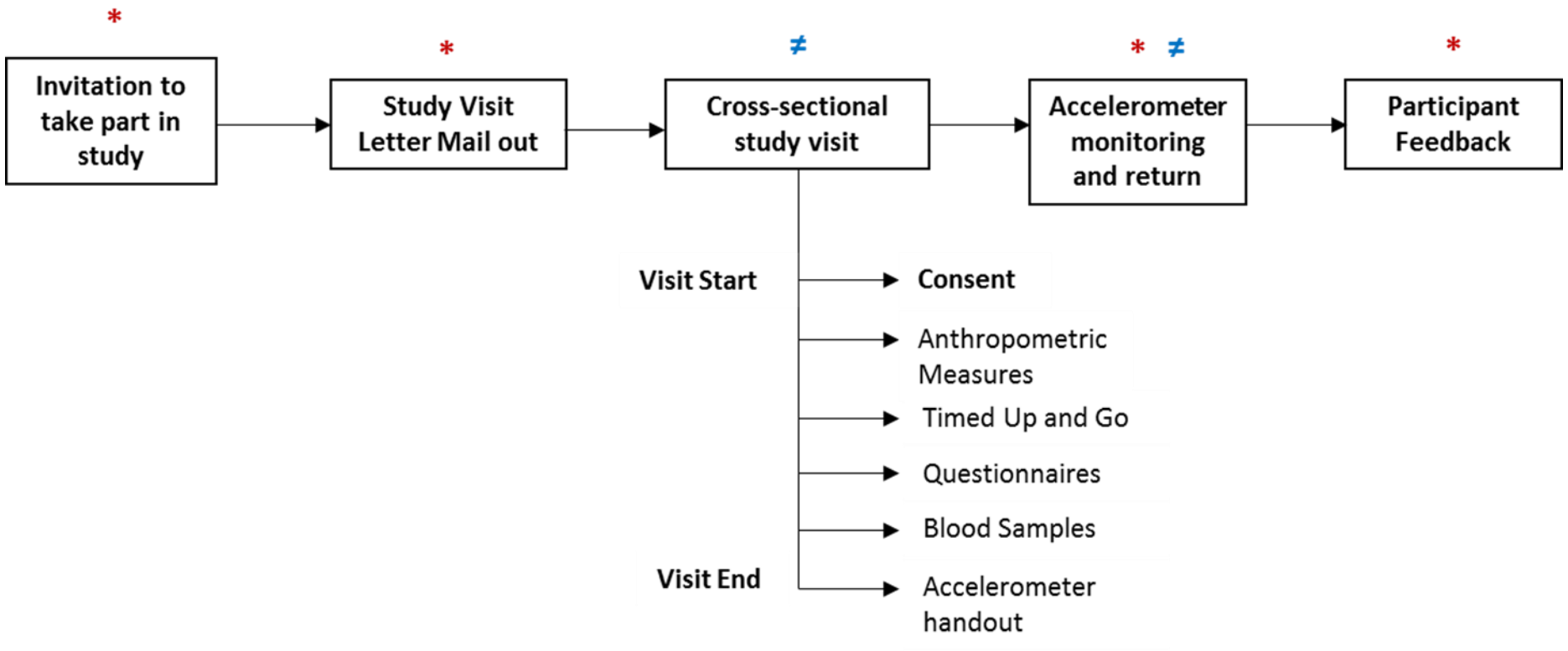


Figure 3.1: Overview of the cross-sectional study procedure. Study information was posted to potential participants and responders were screened by telephone against the study eligibility criteria. Eligible participants were invited to participate in the cross-sectional study visit and an appointment time was arranged. Participants then attended a 90 minute cross-sectional study visit at North Tyneside General Hospital where a range of study measurements were taken. At the end of the study visit, participants were provided with an accelerometer to wear for the following 3-5 days which was then returned to the study team by post. When all study measurement results were collected they were collated into a participant feedback document which was posted to the participant. *= mail outs, ≠=data collection.

3.2.3 Study Participants

3.2.3.1 Participant Sampling and Recruitment

A targeted convenience sample of individuals meeting the study eligibility criteria (see section 3.2.3.2) was recruited to the study in the North East and Liverpool areas.

We opted for an older adult population as the incidence of KOA increases substantially with increasing age. In addition, older adults with a BMI 30-40kg/m2 because an adults classified as obese are more likely to have low Vitamin D and PA levels. Finally we selected people with symptomatic KOA in order to assess KOA symptoms throughout the duration of the study.

As described in Chapter 2, participants were recruited from Primary Care Sites (GP surgeries) in the North East of England. With the assistance of NECS, GP surgeries in the Northumberland, North Tyneside and Newcastle upon Tyne areas were recruited to the study. Recruited GP surgeries then screened their patient lists against the study eligibility criteria and potentially eligible participants were mailed a study pack (including a study invitation letter, a patient information sheet and consent form) which included contact information for the study team at Newcastle University. Individuals were instructed to contact the study team if they were interested in participating. Eligibility was confirmed by telephone in respondents and those who were eligible were invited to take part in the cross-sectional study visit at North Tyneside General Hospital.

For more information regarding recruitment methods, please see section 2.2.

3.2.3.2 Study Eligibility Criteria

a) Study Inclusion Criteria

1. Obese: BMI 30-40kg/m2 as defined by WHO criteria [206]

2. Older adults: 50 – 70 years

3. OA of the knee according to ACR Guidelines on symptomatic KOA criteria (using history and physical examination:

- Pain in the knee

AND 3 OF THE FOLLOWING:

- Over 50 years of age
- Less than 30 minutes of morning stiffness
- Crepitus on active motion
- Bony tenderness
- Bony enlargement
- No palpable warmth of synovium[4]

4. Good understanding of written and spoken English (as no translation services were available to support this study).

b) Study Exclusion Criteria

1. Any other type of arthritic condition, e.g:
    - RA
    - Fibromyalgia
    - Ankylosing Spondylitis
    - Gout
    - Lupus
    - Paget's Disease
    - Polymyalgia rheumatic (PMR)
    - Psoriatic arthritis
    - Scleroderma
    - Sjogrens Syndrome
2. Currently taking part in a different PA or exercise intervention study
3. Taking Vitamin D, cod liver oil or Calcium capsules/supplements (topical/oral/intravenous, prescribed/non-prescribed) above 10µg/day of vitamin D and/or 500µg/day of calcium.
4. Taking part in another intervention study/trial (depending on researcher's discretion)
5. Chronic alcohol abuse (> 21 (women) and 28 (men) SI units/week

3.2.4 Study Materials and Measures

3.2.4.1 Study Measurement Selection

Table 3.1 presents the targeted outcome measurement and the measurement tool selected and summarises the rationale for tool choice.

Outcome	Measurement Tool Selected	Rationale for tool choice
Weight, BMI, Body Fat% and Body Fat Mass	Tanita Bioimpedance Scales	These scales provided an easy, non-intrusive and portable device for measuring body weight and for estimating body fat content by bioelectrical impedance. Compared with body imaging (MRI/CT) and Dual X-ray absorptiometry (DXA), bioelectrical impedance is inexpensive and safe and requires no specially trained staff. Compared with densitometry (underwater weighing), the gold standard of body composition measurement, it is quick and simple [207, 208]
Waist Circumference	Tape Measure	A standardised protocol was selected for waist measurement according to the WHO recommendation. Waist circumference was measured with a flexible tape measure, midway between the lowest rib margin and the iliac crest. Due to potential variability in measurement (even within the same subject depending on stance, respiration and stomach contents), I measured in triplicate and calculated the mean measurement. [208]
Height	Stadiometer	This is a cheap, accessible and reliable method of measuring height and was used in the calculation of BMI.
Knee Function	Timed Up and Go	Timed up and Go is a test of functional mobility and has been widely utilised in older study populations. Monitoring changes in TUG can detect changes in mobility, especially important in those with potentially mobility limiting disease such as OA[209]. TUG has been previously used in KOA populations as a measure of physical function [210]. Additionally it is easy to set up and requires no specialist equipment.

Knee Symptoms	Visual Analogue Scale (VAS), WOMAC Questionnaire	WOMAC is a widely used, validated questionnaire for use in people with OA, which assesses pain, stiffness and physical function. The VAS provides a subjective measurement, on a scale of 0-10, of the participant's perception of their pain level.
Vitamin D	25(OH)D concentration in venous Blood and Dried Blood Spot (DBS)	25(OH)D concentration in serum samples is the most widely used and accepted measurement of Vitamin D status, due to its long half-life [110]. In addition, DBS is emerging as a novel method of collecting blood samples for multiple analyses including 25(OH)D [211]. As part of this study we decided to test the acceptability of using the DBS method for collecting blood for measuring 25(OH)D by comparison with the traditional serum sample method.
Physical Activity	Accelerometer: Actigraph GTM1/GT3X	Accelerometry provides an objective way of measuring PA, which is more accurate than a pedometer and which can measure a range of PA outcomes (including PA intensity, frequency and duration). Compared with self-reported PA e.g. via questionnaires, it is more reliable and not subject to recall bias. Accelerometers are non-invasive and easy to use and practical for use in a lifestyle setting for monitoring PA over several days [212]
Quality of Life	SF-36 Questionnaire	SF-36 is a validated and widely used questionnaire for measuring physical and mental quality of life. This is important as it adds context to participant problems (e.g. any emotional problems which may be contributing to their symptoms) and can be used as a method of assessing participants personal perception of change/response to a treatment [213].

Table 3.1: Outcomes measured in both the cross-sectional (this chapter) and pilot feasibility (Chapter 4) studies, the tool selected for measuring each outcome and the rationale for choice of this tool.

3.2.4.2 Cross-Sectional Study Measurements

During the 90 minute cross-sectional study visit, the quantitative measurements summarised in Table 3.2 were made according to the protocols set out in the study SOP (see Appendix I)

Outcome	Equipment	Procedure	Approximate Time Taken to complete
ACR Symptomatic KOA Criteria	None	Participants were asked to expose their bare knee. The researcher then physically examined the knee for signs of KOA. The method for knee examination has been previously published[214].	5 mins
Height	Stadiometer	Participants were asked to stand with their back towards Stadiometer ruler and the marker was brought down to the top of the head. Height was measured from the marker. Height was measured 3 times.	5 minutes
Weight (kg), BMI, Body Fat%, Fat Mass (kg)	Tanita Bioimpedance Scales	Participants were asked to stand barefoot on Bioimpedance scales and age, body type, gender and height were imputed. Results for anthropometric measures are printed and recorded in the data collection sheet.	5minutes
Waist Size (cm)	Flexible measuring tape (marked in centimetres)	Waist size was measured using a measuring tape halfway between the bottom rib and hip bone.	5 minutes
Physical Function	Marker cone, measuring tape, stopwatch	Participant begins seated and on 'go' the participant rises unaided and walks 2 meters in forward and back, then sits down unaided. This process is timed and repeated 2 more times.	10 minutes
Knee Pain, Stiffness and Function	WOMAC Questionnaire, pen	Each question on the questionnaire was read out by the researcher and the answers provided by the participant were recorded.	10 minutes
Quality of Life	SF-36 Questionnaire, pen	The questionnaire was completed by the participant with the researcher available for assistance if required.	10 minutes
Knee pain	VAS Questionnaire, pen	Each question on the questionnaire was read out by the researcher and the answers provided by the participant were recorded.	5 minutes

Serum Vitamin D, Serum Calcium and Haematocrit	1x Plain, 2x Serum Gel and 1x EDTA Vacutainer Tubes, Butterfly needle, vacutainer tube holder, antiseptic wipe, disposable tourniquet, gauze, plaster, Pathology sample bag	The participants arm is assessed and prepared before blood is taken from the median cubital or cephalic vein, using a vacutainer blood collection system, by RB. If there were problems with blood collection, a research nurse was called.	10 minutes
Serum Vitamin D	DBS (Dried Blood Spot) Kit: containing DBS card, Foil packaging, high flow lancet, plaster, antibacterial wipes and sterile gauze.	The participants washed their hands thoroughly. The researcher disinfected finger before blood is obtained by fingerprick. Blood drops are placed on a filter paper and dried at room temperature.	5 minutes
Physical Activity	Pre-set Actigraph monitor (GTM1/GT3X), elastic waistband, Self-addressed, prepaid envelope, accelerometer instructions and accelerometer log	The accelerometer was presented to the participant and instructions on use were given. A self- addressed, prepaid envelope was provided for return of the device.	3-5 days

Table 3.2: Measurement methods, equipment and duration of the quantitative measurements taken during the cross-sectional study visit

In addition to the equipment specified above for the measurements taken during the cross-sectional study visit each individual participant's file was updated so that it contained:

- 2 copies of consent form (see Appendix F): one copy for participant and one copy for research team.
- Data collection form (see Appendix J): including details on painkiller use, smoking and drinking status, health status, medication status, ACR criteria, anthropometrics, time up and go measurements, checklist for questionnaire completion, checklist for blood collection and processing and checklist for accelerometer provision.
- Sample Tracking Form (see Appendix K): containing instructions on sample processing and checklist for sample collection and processing.

The above documentation was filled out during the cross-sectional study visit and completed questions and blood sample results were also stored in the participant file on their completion and return.

3.2.5 Study Setting

All study visits took place within North Tyneside General Hospital within clinical rooms within the Jubilee Day Hospital. All appropriate staff, equipment and logistical provisions were prepared at each study site before the study visits commenced, as follows:

3.2.5.1 Site staff

One CRN nurse, Ms Kirstie Walker, was allocated to assist RB with study visits between September-November 2015.A team of recruiters at NECS conducted recruitment in the North East and Liverpool study sites.

3.2.5.2 Equipment and Services

-80 freezer space for sample storage was arranged at NTGH pathology labs. Site Initiation Visits, involving presentation of the study aims and methods and a practical study visit run through, was completed at both sites. Site files containing ethical documents, study protocol, study manuals and freezer logs were created.

3.2.6 Procedures

3.2.6.1 Study Visit Invitation

Study Visits were arranged by telephone based on the participant availability and hospital clinic room availability. Once an appropriate time was determined, a study visit appointment letter stating the time and location of the participant's appointment and a map of NTGH was mailed to the participant's address. Transport arrangements were discussed prior to the appointment with taxis offered by the study team if transport was unavailable. If the participant travelled by car, parking charges and mileage were reimbursed, and if participants travelled by bus, cost of bus tickets were reimbursed.

3.2.6.2 Study Visit set up

Before each study visit, a clinical room within the Jubilee Day Hospital, NTGH was booked for the appropriate time. The study team arrived at the booked room 15 mins before the appointment time to prepare and set up all the required equipment for the study visit. This involved preparation of blood collection equipment, set up of Tanita Bioimpedance scales and Stadiometer, set up of the timed up and go test and organisation of the participant's documentation. At the appointment start time, the participant was called from the Jubilee Day Hospital waiting room.

3.2.6.3 The Study Visit

The study visit, conducted by the author of this thesis (RB) began with a discussion about the study (i.e. study aims and objectives and what taking part would involve), and if the participant was happy to take part, written consent was taken. Study measurements (summarised in Table 3.2) were then taken in accordance with the study SOP (see Appendix I). At the end of the study visit, the participant was thanked for their participation and informed that they would receive mailed feedback on their measurements in due course.

3.2.6.4 Data and Sample Storage

Blood samples were centrifuged at 3000rpm for 10mins to separate serum for the measurement of vitamin D and calcium concentrations and spare serum for future analyses (labelled Storage). The serum was transferred to a sample tube labelled with

the participant ID, date, sample type (vitamin D, Calcium or Storage) and Study Visit (CS- cross sectional) and stored in sample storage boxes in a -80C freezer at NTGH R&D department. Sample storage sheets detailing the sample and location within the box were updated as samples were added to the freezer. Frozen samples for Vitamin D and Calcium assay were transferred to Newcastle and NTGH pathology labs in batches (by storage box) for analysis. Spare storage sample boxes were kept at -80C at NTGH until study close, when all samples were transferred to Newcastle University (Biomedical Research Building, Campus for Ageing and Vitality).

All hard copies of participant data were kept in individual participant files labelled with the participant ID and were transferred by RB to Newcastle University after the study visit was completed. All participant files were kept in a locked filing cabinet, within a locked room in a Newcastle University staff and student accessible building (Biomedical Research Building, Campus for Ageing and Vitality). Data was also imputed to SPSS (electronic statistical package) and saved as a database. All information contained within the electronic database was identifiable only by participant code and was password protected and encrypted.

3.2.6.5 Participant Feedback

On conclusion of the cross-sectional study, each cross-sectional study participant was mailed a letter thanking them for their participation in the study and an individual feedback sheet which provided data collected during their study visit. This included:

- Weight (kilograms, stone and pounds)
- BMI
- Waist measurement (centimetres and inches)
- Knee pain (scale of 0-20)
- Knee stiffness (scale of 0-8)
- Blood Vitamin D (25(OH)D) concentrations (nmol/L – deficient, insufficient and sufficient)
- Blood Calcium concentrations (mmol/L – normal, low and high)
- Time spent in physical activity Intensities (% time in sedentary, light and moderate activity)

They were also informed that they would receive a telephone call in due course to inform them of their eligibility for the pilot intervention study (described in Chapter 4).

3.2.7 Data Processing and Analysis

Study data was processed before being entered into an electronic database, as follows:

3.2.7.1 Means of repeated measurements

For measurements taken in triplicate during the study visit (Height, Waist Circumference and Timed Up and Go) a mean and standard deviation was produced, which was entered into the electronic database.

3.2.7.2 WOMAC LK3.1 Questionnaire Scoring

Responses to the WOMAC Questionnaire were calculated for each participant according to the scoring instructions outlined by the questionnaire developer, Nicholas Bellamy, in the WOMAC Osteoarthritis Index User Guide XI [215]. The participant response for each question was calculated (None=0, Mild=1, Moderate=2, Severe=3 and Extreme=4). These question scores were then totalled by section, resulting in WOMAC Pain score (0-20), WOMAC Stiffness Score (0-8) and a WOMAC physical function score (0-68). The results of all the questionnaire sections were also totalled to provide a WOMAC Total score (0-96).

3.2.7.3 SF-36 Questionnaire Scoring

Responses to the SF-36 Questionnaires for each participant were scored using the Quality Metric Health Outcomes Scoring Software 4.5. Responses to each question were imputed into the software. After all responses were recorded, the software calculated a range of outcomes (shown in Table 3.3), each on a scale of 0-100, MCS and PCS were the primary SF-36 Scores used during statistical analysis in the present study.

SF-36 Outcome	Low scores	High Scores
Physical Functioning (PF)	Indicate imitation in performing physical activities	Indicate no/little limitation in physical activities
Role Physical (RP)	Indicate problems with work or other activities due to physical health	Indicate no/little work/activity limitation due to physical health
Bodily pain (BP):	Indicate high pain levels which interfere with daily activities	Indicate no pain with no related effect on activities
General Health (GH):	Indicate poor general health which is likely to decline.	Indicates good general health
Vitality (VT):	Indicate tiredness	Indicates high energy levels
Social Functioning (SF):	Indicate low involvement in social activities due to physical or emotional problems	Indicates normal involvement in social activities without any interference from physical or emotional problems
Role Emotional (RE):	Indicate problems with work or activities due to emotional problems.	Indicates no work/activity limitation related to emotional problems.
Physical Component Score (PCS):	Indicate limitations in PF and participation in work and activities due to physical health	Indicate no physical limitations or disability, high energy levels and good general health.
Mental Component Score (MCS):	Indicate psychological distress, social and work/activity problems due to emotional problems and poor general health.	Indicated no psychological distress of limitations and good general health.

Table 3.3: A summary of the interpretation of different Quality Metric Health Outcomes from SF-36 questionnaire data [216]

3.2.7.4 Actigraph Data downloading and processing:

On return of the accelerometer device to RB, data was downloaded from the Accelerometry device to the Newcastle University computer system using the Actilife 5

software. The accelerometer was connected to the computer using a USB cable and opened using the Actigraph 5 software. Raw data files were saved under each participant IDs in individual participant computer files. Using the Actigraph software, the following outcomes (see Table 3.4) were calculated and downloaded into the participant's computer file, and then inputted into an SPSS database.

PA Outcome	Details
Wear Time Analysis	Includes calculation of times of wear and non-wear of the accelerometer device.
Energy Expenditure	Includes calculation of energy expenditure in kilo-calories (kcals) in total and from physical activity.
Activity Cut Points	The proportion of time spent in different activity cut points (a table of the default cut points used can be seen in Appendix L)
Activity Bouts	Separates activity cut points into bouts of >10mins. All data collected in bouts of <10mins will be discounted (in line with UK government guidance that activity should be performed in bouts of >10mins [217]). Number of bouts, total time spent in bouts and average time in each bout is calculated.
METs	Metabolic Equivalents are calculated (1 MET - 1kcal/kg body mass/hour) as an average over time of wear.

Table 3.4: PA Outcomes calculated using Actilife 5 software[218]

3.2.7.5 Data Management and Analysis

All participant data were kept in hard copy and electronic database format. Electronic databases were created and used to conduct statistical analysis. All statistical analyses were performed using IBM SPSS Statistics Version 23. Descriptive data analysis, including means and standard deviations, were calculated for all outcome measures. Data was also grouped according to established criteria (e.g. PA classifications or

vitamin D status) which are described in detail within the results, and means and standard deviations calculated for outcome measures within those groupings.

3.3 Results

3.3.1 Study Measure Compliance

As part of the assessment of feasibility during this pilot study, I investigated compliance with the study measurements made during the cross-sectional study. The same measurements were used in the pilot intervention study which is described in Chapter 4.

3.3.2 Study Visit Measurements

Compliance with measurements made in the cross sectional study visit are summarised in Table 3.5. Compliance with anthropometric measurements was high with only 1/45 participants missing waist measurement. Compliance in completing questionnaires was also high with 100% compliance for questionnaires completed with the researcher (VAS and WOMAC) and 44/45 completing the questionnaire that was completed independently (SF-36). Compliance with conventional collection of venous blood (44/45) was higher than for the dried blood spot samples (40/45). The single example of non-compliance with venous blood samples was due to difficulty in taking blood from the participant. Non-compliance with DBS samples was due to investigator error (4/45) and refused consent (1/45).

Study Measurements		Compliance
Anthropometric Measures	Height	100%
	Bioimpedance Measurements (Weight, BMI, Body Fat%, Body Fat Mass)	100%
	Waist Circumference	98%
Knee Function Measures	Timed Up and Go	100%
Questionnaires	VAS	100%
	WOMAC	100%
	SF-36	97.8%
Blood Samples	Venous Sample	97.8%
	Dried Blood Spot Sample	88.9%

Table 3.5: Compliance with measurements made during the cross sectional study visit

3.3.3 Accelerometry

3.3.3.1 Use of Activity Monitor and Data Retrieval

Of the accelerometers distributed during the cross-sectional study, all devices were returned by participants. Accelerometry data could not be retrieved from 1 monitor due to a technical fault with the device and step count data was missing for 10 more participants due to errors when setting up the accelerometry devices.

3.3.3.2 Wear Time Analysis

The mean length of time that participants wore the accelerometer per day is summarised in Table 3.6. It is generally accepted that 10hours/day of monitor wear is the minimum acceptable monitoring period when measuring activity using accelerometry[219] so I used this cut off point as the standard for valid accelerometry data within this study.

Only 3/44 (7%) of participants had a mean of <10hours/day of accelerometry monitoring. Table 3.6summarisestotal % wear and non-wear time for all 44 participants, for the 41 participants deemed to have valid data (mean > 10 hours/day monitoring) and the 3 participants without valid (mean < 10 hours/day monitoring) data. There was no observable differences in age or BMI between excluded (3) and included (41) cases.

	All Participants (n=44) Mean (SD)	Participants with valid data (N=41) Mean (SD)	Participants with invalid data (n=3) Mean (SD)
Mean Age (years)	61 (±5.5)	61 (±5.6)	63 (± 3.5)
Mean BMI (kg/m^2)	34 (±4.6)	34 (±4.0)	36 (±11.1)
Mean Daily Wear Time (mins)	779 (±133.0)	798 (±101.0)	514 (±252)
Total Wear time (% of total monitoring time)	59 (±8.5)	60 (±7.8)	47 (±9.7)
Total Non-Wear Time (% of total monitoring time)	40(±9.1)	40 (±7.8)	41 (±23.3)

Table 3.6: Mean (SD) wear time of accelerometers over the activity monitoring period in all participants, participants with valid data (defined as participants with mean >10 hours/day of activity data) and participants with invalid data (defined as participants with mean <10 hours/day of activity data)

As can be seen in Table 3.6, participants with invalid accelerometry data wore the accelerometer for a mean 284 minutes less than participants with valid accelerometry data. Participants with valid data spent 60% of their time wearing the accelerometer compared to 47% in participants with invalid data. This disparity in wear time is reflective in the validity of the participant's data.

3.3.4 Participant Characteristics

A summary of the participant characteristics is provided in Table 3.7. Of the 45 participants in the cross-sectional study, there was 22 females (49%) and 23 males (51%). All participants were Caucasian and the majority were current non-smokers (89%). Mean participant age and BMI was around the middle of our age (50-70 years) and BMI (30-40 kg/m2) eligibility criteria at 61 years and 34.3 kg/m2 respectively. The majority of participants reported Bilateral KOA (69%) followed by Left KOA (22%) and Right KOA (9%).On knee examination, I identified which ACR criteria were met by each participant, the results of which are summarised in Table 3.8.Overall, 31% and 33% of participants reported previous injury or previous surgery to the affected knee joint respectively with no significant relationship between reported previous injury and surgery. 28% of our sample were currently employed with 72% retired or on sickness leave.

Participant characteristics	All Participants (n=45) Mean (SD)	Females (n=22) Mean (SD)	Males (n=23) Mean (SD)
Age (years)	61.2 (±5.31)	59.9 (±4.84)	62.3 (±5.57)
Height (cms)	169.9 (± 8.91)	163.8 (±6.33)	175.4 (±7.19)
Weight (kgs)	106.2 (±23.15)	104.0 (±26.93)	108.3 (±19.33)
BMI (kg/m2)	34.5 (±4.65)	34.5 (±4.32)	34.6 (±5.04)
Body Fat (%)	40.6 (±7.93)	46.1 (±4.35)	35.5 (±7.08)
Body Fat Mass (kg)	40.6 (±11.70)	43.1 (±9.84)	38.3 (±13.04)
Waist Circumference (cms)	112.8 (±12.12)	108.6 (±11.50)	116.8 (±11.57)
Timed Up and Go (secs)	9.5 (±2.19)	9.8 (±2.49)	9.3 (±1.89)
VAS Daily Score (0-10)	4.3 (±1.84)	4.0 (±1.74)	4.6 (±1.94)
WOMAC Pain	8.4 (±3.44)	8.1 (±3.74)	8.5 (±3.20)
WOMAC Stiffness	4.4 (±1.95)	4.3 (±2.02)	4.5 (±1.91)
WOMAC Activities of Daily Living	27.9 (±10.78)	28.0 (±12.05)	27.8 (±9.72)
WOMAC Total	40.6 (±15.25)	40.3 (±17.00)	40.8 (±13.86)
SF-36 MCS (Mental Capacity Score) (0-100)	48.6 (±11.5)	44.9 (±10.81)	52.5 (±11.26)
SF-36 PCS (Physical Capacity Score) (0-100	38.6 (±9.5)	40.9 (±8.76)	36.6 (±10.01)
Serum 25(OH)D (nmol/L)*	43.6 (±23.4)	42.4 (±20.50)	43.6 (±24.12)
Serum Calcium (mmol/L)	2.2 (± 0.28)	3.0 (±0.29)	2.2 (±0.28)
% 25(OH)D Deficient (<25nmol/L)*	27 (12/45)	27 (6/22)	26 (6/23)
% 25(OH)D Insufficient (26-50nmol/L)*	36 (16/45)	32 (7/22)	39 (9/23)
% 25(OH)D Sufficient (<51nmol/L)*	36 (16/45)	36 (8/22)	35 (8/23)
% time in sedentary activity	63 (±10.6)	61.9 (±10.39)	66.5 (±10.36)
% time in light activity	33 (±9.4)	34.2 (±8.75)	29.6 (±10.03)
% time in moderate activity	44 (±3.1)	3.9 (±3.22)	3.9 (±3.34)
Average daily time in sedentary activity (mins)	1276 (±2693.8)	1535 (±3096.3)	1029 (±2296.6)
Average daily time in light activity (mins)	263 (±87.6)	289 (±81.6)	239 (±88.3)
Average daily time in moderate activity (mins)	31 (±26.0)	33 (±29.1)	30 (±23.3)

Table 3.7: Characteristics of participants in the cross-sectional study by gender. *Indicates missing data

When comparing the anthropometrics of male and female participants, differences in height and body fat % can be observed, with females being on average 11.6cms shorter and 10.6% (equating to 4.8kg of fat mass) higher body fat % than the males. However the females did have a smaller waist circumference at a mean 8.6cm less than the males.

When comparing self-reported knee osteoarthritis symptoms, there are no notable differences observed between genders apart from in the SF-36 scoring. Females reported having worse mental health outcomes, with a mean SF-36 MCS 7.6 points lower than the males (on a scale of 0 to 100, with 0 representing worse mental wellbeing and 100 representing best mental wellbeing). Conversely males reported slightly worse physical health outcomes with a mean SF-36 PCS 4.3 points lower than the females (on a scale of 0 to 100, with 0 representing worse physical wellbeing outcomes and 100 representing best physical wellbeing).

There was little difference in vitamin D concentration (nmol/L) and vitamin D status between genders. However there were slight differences in physical activity recorded between the genders. Males spent 4.6% more time in sedentary activity and 4.6% less time in light activity than females, while levels of moderate activity between men and women didn't differ.

ACR Criteria	% participants with criteria
Pain in Knee during last 3 months	96%
>50years old	100%
<30mins knee stiffness in morning	71%
Crepitus on active motion	91%
Bony tenderness	69%
Bony enlargement	69%
No palpable warmth of the synovium	58%

Table 3.8: Proportion (%) of cross-sectional study participants meeting each ACR symptomatic KOA criteria as determined by physical knee examination

Painkiller use in participants of the study was common. Of all participants, 67% (n=), 62% (n=28), 4% (n=2) and 22% (n=10) reported taking paracetamol, NSAIDs, opioid painkillers (e.g. codeine and tramadol) and other painkillers (e.g. amitriptyline and gabapentin) respectively. Interestingly those participants who reported taking NSAIDs also reported higher levels of WOMAC Pain compared to those who did not take NSAIDs (mean WOMAC pain score 9.1 ± 3.1 vs 6.9 ±3.5 respectively).

In addition to KOA, the study participants reported multiple concurrent health conditions the most common of which were hypertension (40%, n=18), cardiovascular disease e.g. angina, arrhythmias (29%, n=23), type 2 diabetes (20%, n=9%) and depression (20%, n=9).

Information was also collected on incidence of previous knee injury or previous knee surgery. Of our study participants, 35% (n=16) reported previous knee injury and 65% (n=29) did not report any previous knee injury. Regarding previous knee surgery (not knee replacement surgery), 38% (n=17) reported having previous knee surgery while 62% (n=28) did not report any previous knee surgery.

When PA status was assessed against the government PA guidelines [217], 18 participants (41%) were classed as ‘inactive’ (<30mins moderate activity/week), 4 participants (9%) were classed as ‘low activity’ (30-59mins moderate activity/week), 10 participants (23%) classed as ‘some activity’ (60-149mins moderate activity/week) and

12 participants (27%) classed as 'met activity guidelines' (>150 mins moderate activity/week)

3.3.5 Physical Activity and KOA symptoms

As part of the aim of this cross sectional study was to investigate the relationship between PA and KOA symptoms, I have performed a descriptive analysis of the PA and KOA symptom data from the cross sectional study participants.

For this analysis participants were classified into groups according to the NHS England PA classification groups (see Table 3.9). [217]

PA Level Classification		Study Sample Size n= (%of total sample)
Inactive	<30mins moderate activity per week	18 (41)
Low	30-59mins moderate activity per week	4 (9)
Some	60-149mins moderate activity per week	10 (23)
Met Guidelines	>150mins moderate activity per week	12 (27)

Table 3.9: Table demonstrating the classification for activity levels by amount of moderate intensity activity completed per week according to UK government guidelines

As can be seen in Table 3.10, time to complete the timed up and go test was a mean 2.0 and 1.9 seconds longer in the inactive participants compared to participants achieving low PA or those which met PA guidelines respectively. Interestingly when observing self-reported pain (WOMAC Pain score, 0-20 scale), those who reported the lowest mean levels of pain were those who achieved low PA levels and those with the highest mean levels of pain were those participants who met PA guidelines (with a difference in mean WOMAC pain score of 3.0 points between these groups). This pattern was also the same for WOMAC stiffness (with a mean difference of 3.0 points on a scale of 0-8) and for WOMAC activities of daily living (with a mean difference of 11.8 on a scale of 0-68).

Measures of KOA symptoms	Physical Activity Level Classification			
	Inactive (n=17) Mean (SD)	Low (n=4) Mean (SD)	Some (n=11) Mean (SD)	Met Guidelines (n=9) Mean (SD)
Timed Up and Go (secs)	10.4 (±2.45)	8.4 (±0.67)	9.4 (±1.91)	8.5 (±1.71)
VAS Daily Score (0-10)	4.0 (±2.24)	3.8 (±1.26)	4.5 (±1.90)	4.3 (±1.67)
WOMAC Pain (0-20)	8.2 (±2.98)	6.3 (±0.96)	7.7 (±4.30)	9.3 (±3.60)
WOMAC Stiffness (0-8)	3.8 (±2.28)	2.5 (±1.73)	4.5 (±2.22)	5.2 (±1.19)
WOMAC Activities of Daily Living (ADL) (0-68)	27.6 (±10.30)	17.5 (±7.33)	27.7 (±12.05)	29.3 (±11.16)
WOMAC Total (0-92)	39.6 (±14.71)	26.3 (±9.22)	39.9 (±17.95)	43.8 (±14.95)

Table 3.10: Mean and SD of measurements of self-reported KOA symptoms by PA Guideline grouping

3.3.6 Vitamin D Status and KOA Symptoms

As part of the aim of this cross sectional study was to investigate the relationship between Vitamin and KOA symptoms, I have performed a descriptive analysis of the Vitamin D and KOA symptom data from the cross sectional study participants.

Vitamin D was organised according to vitamin D status: deficient (25(OH)D <25nmol/L), insufficient (25(OH)D 25-50nmol/L) and sufficient (25(OH)D >50nmol/L). A descriptive analysis of measurements of KOA symptoms by vitamin D status is presented in Table 3.11.

There is little observable difference in time taken to complete time up and go between vitamin D status's, with vitamin D sufficient participants 1.3 seconds faster than the vitamin D deficient group. Regarding self-reported pain, stiffness and activities of daily living, the vitamin D insufficient group had lowest reported severity of symptoms compared to the vitamin D deficient group who reported the highest severity of symptoms.

Measures of KOA symptoms	Vitamin D status		
	Deficient (n=12)	Insufficient (n=16)	Sufficient (n=16)
Timed Up and Go (secs)	10.2 (±2.55)	9.4 (±2.38)	8.9 (±1.41)
VAS Daily Score (0-10)	4.4 (±2.23)	4.2 (±1.65)	4.4 (±1.67)
WOMAC Pain (0-20)	9.1 (±3.80)	8.0 (±2.99)	8.3 (±3.53)
WOMAC Stiffness (0-8)	4.8 (±1.99)	4.1 (±2.31)	4.2 (±1.60)
WOMAC Activities of Daily Living (ADL) (0-68)	31.6 (±9.50)	26.3 (±10.59)	26.2 (±11.46)
WOMAC Total (0-92)	45.5 (±14.71)	38.4 (±14.81)	38.6 (±15.67)

Table 3.11: Mean and SD of measurements of self-reported KOA symptoms by vitamin D status

3.3.7 Vitamin D and Physical Activity status

As part of the aim of this cross sectional study was to investigate the relationship between Vitamin and physical activity, I have performed a descriptive analysis of the Vitamin D and physical activity data from the cross sectional study participants. For this analysis, participants were classified according to NHS England PA classifications (as in section 3.3.5) and vitamin D was measured as serum levels of 25(OH)D in nmol/L.

The participants with the highest serum 25(OH)D concentrations were in the low PA group, while the group with the lowest 25(OH)D concentrations were those in the some PA group (with a total mean difference of 19nmol/L between these groups). Those participants who met PA guidelines had a mean 25(OH)D 4nmol/L higher than the inactive PA group.

	Physical Activity Level Classification			
	Inactive (n=17) Mean (SD)	**Low (n=4) Mean (SD)**	**Some (n=11) Mean (SD)**	**Met Guidelines (n=9) Mean (SD)**
Vitamin D (25(OH)D) concentration (nmol/L)	42 (±23.3)	58 (±35.7)	39 (±21.2)	46 (±22.4)

Table 3.12: Mean (SD) serum 25(OH)D concentrations (nmol/L) of participants according to PA classification

3.4 Discussion

This cross-sectional study was designed to serve two objectives: i) to ascertain the feasibility of measuring Vitamin D, PA and KOA symptoms in older obese adults with symptomatic KOA ii) to explore the relationships between vitamin D, physical activity and KOA symptoms in our study population and iii) to identify potential participants for the pilot intervention study which is described in Chapter 4.

In Chapter 2 the feasibility of recruitment for this cross-sectional study was investigated. This investigation revealed a number of issues affecting recruitment, particularly recruitment from secondary care sources (see section 2.4 for more details). The present chapter focuses on the acceptability, and feasibility, of conducting the relevant measures. The results of this feasibility analysis are discussed below according to study resources, management and scientific data [194].

3.4.1 Study Resources

3.4.1.1 Study Measure Compliance

As can be seen in section 3.3.1, compliance with study measurements was high, with only one individual unable to give blood by venous collection, five people who did not give a DBS sample (one did not give consent and for four there was a lack of DBS kits available when needed). PA data was missing for one participant due to accelerometer malfunction and three participants were excluded from PA analysis due to low compliance with wear time (<10hrs/day). This high level of study measurement compliance demonstrated that overall these measurements seemed to be acceptable

to the participants. This issue is explored further in the qualitative interview study which is reported in Chapter 5.

3.4.1.2 Study Equipment

a) Cost and availability

The cost and availability of equipment, such as accelerometry devices, will inevitably affect the measurements that can be made as part of a study. In the present study, this cost was avoided by borrowing devices from various research departments within Newcastle University.

b) Equipment retention

One of our measurements involved the hand out of equipment (accelerometry devices) to participants to use after the study visit. With this comes the risk of equipment loss or damage. We aimed to reduce the risk of monitor loss or damage by following best practice recommendations [219] including demonstration of how to use the device correctly, provision of written instructions on device use and use of wear logs. All activity monitors in this study were returned using the postal method, which is better than the estimated 5% that are usually lost/missing when using the mail out method of returning the activity monitors [219].

3.4.2 Study Management

3.4.2.1 Study Timescale

Due to a protracted ethical approval process, this study which was designed to start in October 2014 was delayed until April 2015. I had intended to begin recruitment in October 2014 so that participants could be recruited during the winter to reduce the confounding effect of Vitamin D synthesis through sunlight exposure since dermal Vitamin D synthesis is not possible in the UK during the winter months (October to April) [110]. The delay in obtaining ethics committee approval reduced the time frame in which I could perform this study and reduced the sample size that I was able to achieve. Lack of time has often been reported as a major barrier to recruitment, especially in a clinical environment where additional support may be limited [220]. NB Although assistance from a research nurse had been offered originally, shortly before

the main period of recruitment was due to start, this offer was withdrawn because of the unavailability of staff.

3.4.3 Scientific Data

3.4.3.1 Participant characteristics

My participants met my eligibility criteria by being classified as obese (mean BMI: 34.3 ±4.8), reporting mild-moderate knee pain (mean 8.4 ±3.4on a 0-20 scale) and Knee stiffness (4.4 ±1.9 on 0-8 scale) and were aged with the specified age range of 50-70years (mean 61.2 ± 5.3).I had almost equal numbers of men (n=23) and women (n=22) in the study. This observation shows that the recruitment strategy was successful in attracting both genders to volunteer for this study. Note, however, that KOA is diagnosed more often in women than in men [221].

Vitamin D status was assessed by quantifying serum 25(OH)D (nmol/L) concentration This revealed that 27%, 36% and 36% participants were classed as Vitamin D deficient (<25nmol/L), Vitamin D insufficient (26-50nmol/L) and Vitamin D Sufficient (>51nmol/L) respectively[110]. The results of a large UK cohort study of >45 year olds by Hypponen[129] showed vitamin D deficiency (25 (OH)D <25nmol/L) prevalence during Winter/Spring in the UK obese population and residents of Northern England were 13.5%, 17.5% respectively and vitamin D insufficiency (25(OH)D <40nmol/L) prevalence in these groups were 43.3% and 46.6% respectively. If we compare the prevalence of vitamin D deficiency (25(OH)D <25nmol/L) in this study (27%) with the cohort study by Hypponen [129] (17.5%), there is comparatively higher vitamin D levels of vitamin D deficiency within our study cohort.

Analysis of PA data collected in this cross-sectional study when compared against the UK guidelines [217] revealed that 40%, 9%, 36% and 21% of participants were classed as having inactive, low, some and met guidelines levels of physical activity (see Table 3.9for details). These results differ from the UK PA statistics compiled by the British Heart Foundation [163](based on data from the Health Survey for England [HSE]) which recorded 26%, 5%, 14% and 55% of men and 27%, 6%, 12% and 55% of women aged 55-64 years old were classed as having inactive, low, some and met guidelines levels of activity. These results suggest this cross-sectional study cohort had comparatively higher levels of inactivity and lower proportions of individuals meeting

PA guidelines compared to the general UK population surveyed as part of HSE. This difference in recorded PA levels may be due to the prevalence of KOA in this cross-sectional study population which can be supported by evidence from a 2013 systematic review [162] also showed populations with KOA achieved lower levels of PA compared to the general population, with 13% of people with KOA achieving the PA guidelines of >150 minutes of moderate activity per week (in bouts of >10mins). Several non-disease related factors (e.g. sex, age and BMI) and disease related factors (e.g. pain, dysfunction and OA severity) may be responsible for the differences in physical activity levels found in those with, and without, KOA [222-224].

3.4.3.2 The relationship between PA, vitamin D status and KOA symptoms

The results of our descriptive analysis of self-reported KOA symptoms by PA classifications (defined based on guideline produced by NHS England [217]) showed that those participants classed as 'inactive' took a mean 1.9 seconds longer to complete the Timed Up and Go (TUG) test than the participants who 'met activity' guidelines. This may imply that as moderate physical activity (on which these PA guidelines are based upon) increases, physical function (represented by decreased time taken to complete TUG) improves or vice versa. This relationship between physical activity and physical functioning has been observed in other cross-sectional studies, e.g. 2013 cross-sectional study of 160 older and overweight and obese individuals with KOA [225], who found a significant correlation between physical functioning (measured using the Short Physical Performance Battery) and time (minutes) in Moderate/Vigorous intensity physical activity ($r=0.315$, $p=<0.001$). Further evidence from intervention studies with the aim of increasing PA in older individuals with KOA [226, 227]also show improvements in physical function with increased PA, suggesting PA may be the causal factor in this relationship.

Interestingly during this descriptive analysis of PA groups and KOA symptoms it was also observed that the worst reported severity of KOA symptoms were seen in those who 'met PA' guidelines while those with 'low' activity levels had the lowest reported severity of KOA symptoms. This is contrary to most evidence which suggests that exercise programmes which increase physical activity result in improvements in pain and disability outcomes. [103] There are several potential explanations to account for

this observation. Firstly, as the distribution of participants between the different PA classification groups is highly variable (n=4 in the 'low' activity group vs n=9 in the 'met guidelines' group) and the sample size was too small to conduct statistic comparisons, it may be this observation is not due to a true effect but has occurred by chance. The only way to test this assumption would therefore be to collect a larger sample and conduct a statistical analysis. Secondly, as highlighted by the Centers for Disease Control and Prevention (CDC) recommendations on exercising safely with arthritis, it is important that people with arthritis who are generally inactive increase their PA slowly, giving the body time to adjust to the new level of activity and also to choose activities which are 'joint friendly' and therefore provide low risk of injury to the joints. [228] This information was provided as part of our PA intervention, however if participants did overexert or injure themselves this is likely to provide a source of pain. However, as we did not formally record this information, it is not possible to provide data to support this theory from this study.

The results of our descriptive analysis of self-reported KOA symptoms by vitamin D status showed little observable difference between the vitamin D groups in KOA symptoms. This reflects recent evidence collated by a 2013 systematic review by Cao et al [93] which showed limited evidence for an association between symptomatic KOA and 25(OH)D levels. One 2011 cross sectional study showed a significant association between Vitamin D deficiency and KOA symptoms in those <60 years old (OR: 2.26, 95%CI: 1.15-4.4, P=0.018) but not in those >60 years old (OR: 1.01, 95%CI: 0.48-5.9, P=0.96) [229], suggesting it may be an age specific relationship. However due to the narrow age range of our participants (50-70 years) and low numbers of participants it would not be possible to compare the effect of age as a potential factor in the relationship between vitamin D and KOA symptoms in this study.

Finally, in our descriptive analysis of the relationship between 25(OH)D concentrations and PA classification groups, it was observed that those with the lowest serum 25(OH)D concentrations were those in the 'some' activity group and those with the highest serum 25(OH)D concentrations were found in participants achieving 'low' PA levels. This is at odds with much of the existing research literature which consistently demonstrate a positive relationship between serum 25(OH)D concentrations and PA levels, e.g. a US study based on NHANES data showed that for every 10 minute

increase in moderate intensity activity per day there was an associated serum 25(OH)D increase of 0.8nmol/L [230]. Proposed explanations for the relationship between serum 25(OH)D and PA seen in the existing research literature include; i) that those with higher 25(OH)D concentrations are more physically able and are therefore more active, ii) those who are more active may increase their 25(OH)D concentrations through increased sunlight exposure, or iii) an external factor may affect both 25(OH)D and physical activity levels [231].I speculate this difference in what was observed within our cohort and the existing literature is due to the disparity in sample sizes between PA classification groups and that a larger, more equally distributed sample would be required to explore this relationship adequately.

3.5 Summary

This cross-sectional study has shown that it is feasible to assess Vitamin D, PA and KOA symptoms in older obese adults with symptomatic KOA with high adherence to all aspects of the study protocol.

Analysis of this cross-sectional data highlighted interesting areas of future investigation, which have informed the following recommendations:

- KOA populations, including this cross-sectional cohort, have low activity levels compared to the general UK population. Increasing PA, particularly moderate intensity activity, may be beneficial KOA cohorts in order to improve health outcomes [162].
- Moderate intensity activity may be associated with physical function. Promoting increased moderate intensity activity may also be important in improving knee function in those with KOA [225].
- In this sample 25(OH)D concentrations were lowest in those achieving ‘some’ activity and those with the highest 25(OH)D concentrations achieved ‘low’ activity, contrary to the majority of the existing literature. A cross-sectional study with a larger sample size which takes into account potential confounding factors is required to statistically explore the relationship between 25(OH)D and PA in this study population.
- There was no trend observed regarding a relationship between 25(OH)D concentrations and PA classification (which has been observed in the current

literature) in this study, however this may be due to small sample size and unequal distribution of sample size between PA classification groups. In light of previous studies which have observed a relationship between 25(OH)D and PA which has been [230], and evidence of association between 25(OH)D and KOA [93, 103] and PA and KOA [103], further (as yet not conducted) studies investigating the potential cumulative effect and relationship between vitamin D, PA and KOA are needed to investigate this further. Ideally a factorial RCT intervention administering Vitamin D and PA would be conducted to investigate the effect of Vitamin D and PA on KOA cumulatively and separately.

Chapter 4. Pilot Intervention Study

4.1 Introduction

In this chapter, I describe my pilot intervention study which was designed to assess the feasibility of delivering a vitamin D supplementation and web-based PA intervention to obese older adults with KOA. At the start of this PhD, there were few intervention studies which investigated the impact of Vitamin D supplementation on KOA symptoms [147]. In addition, despite evidence supporting a positive relationship between increasing PA levels and KOA symptom relief [103]and recommendations from NICE that PA should be a first line treatment option for those with OA [10], there is little evidence available regarding the effect of home-based web delivered PA programmes [181]. No study to date has conducted a randomised controlled trial assessing the use of both Vitamin D supplementation and web-based PA programmes with the aim of KOA symptom relief. The purpose of this pilot interventional study was to assess the feasibility and acceptability of conducting such a RCT.

4.2 Methods

4.2.1 Ethics and Consent

REC approval was obtained before commencement of the cross-sectional study as part of an IRAS combined ethical approval form (see Appendix A). Written consent was obtained from each pilot interventional study participant at the beginning of the cross-sectional study visit and verbal consent was obtained before commencement of the pilot interventional study.

4.2.2 Study Design

4.2.2.1 Study Design

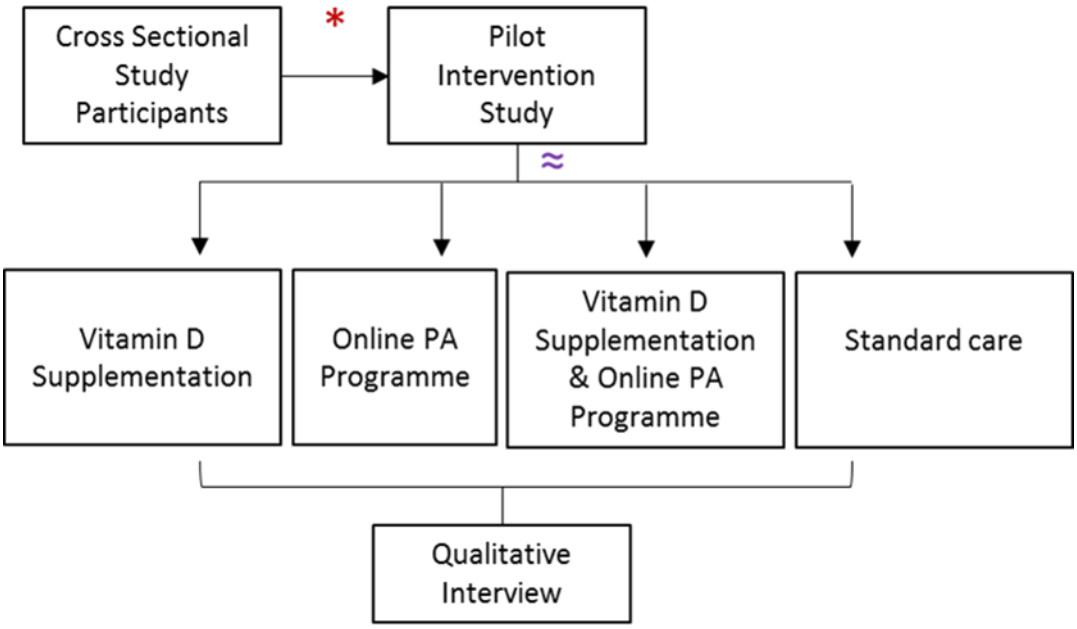


Figure 4.1: Original design of the pilot intervention study. *=screening, ≈=randomisation

The pilot intervention study was designed to assess the acceptability and feasibility of two intervention modalities, Vitamin D supplementation and a web-based PA intervention, over three months. To avoid confounding through cutaneous synthesis of vitamin D the intervention was intended to occur in the winter months (January-March 2015 and January-March 2016). The2x2 factorial design of the study allowed the intervention modalities to be assessed independently and also permitted investigation of any potential interaction. The specific design and content of these interventions is described in section 4.2.2.2-4.

a) Amendments to Study Design

The pilot intervention study design was originally a 2x2 factorial randomised controlled trial design with four study arms (see Figure 4.1). Participants who met the eligibility criteria (see section 4.2.3.2.) were randomly (through random number sequence allocation) allocated to one of these study arms.

However due to low numbers of participants meeting the eligibility criteria for both intervention modalities (required for the fully randomised study design), the study design was changed to an unrandomised design (see Figure 4.2) with those eligible only for the Vitamin D intervention assigned to the Vitamin D intervention, those

eligible for the web-based PA intervention assigned to the web-based PA intervention and participants eligible for both interventions assigned to both. This decision was made so there would be adequate numbers within each intervention group to assess the feasibility and acceptability of the intervention. For more details about the study allocation procedures see section 4.2.6.1.

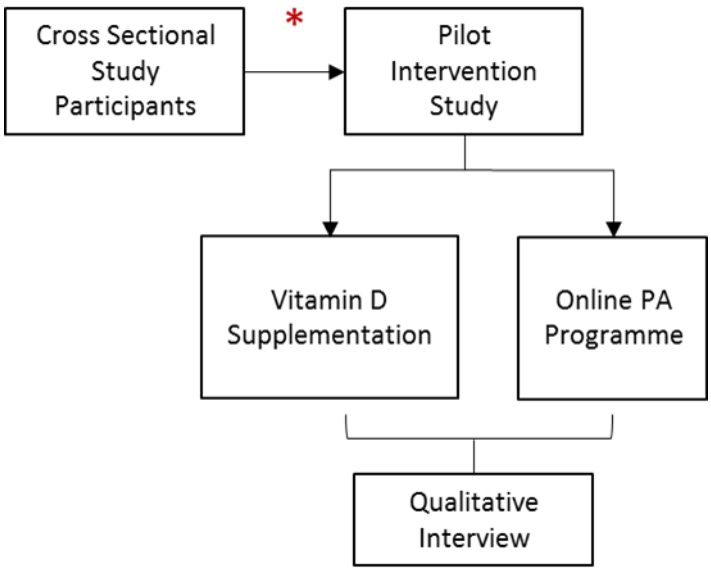


Figure 4.2: Diagramatic representation of the study flow of the amended pilot intervention study design.*=screening

b) Intervention Design

The design of the two study intervention modalities (Vitamin D supplementation and web-based PA intervention) for this pilot intervention study were developed with collaborators at Newcastle University (Dr Thomas Hill and Professor John Mathers) and based on the current academic literature. I have described the rationale, development process and final intervention content for each intervention below.

4.2.2.2 Vitamin D Intervention

When designing the Vitamin D intervention, several issues had to be addressed. Below I have described the evidence base, development process and final intervention content for the Vitamin D supplementation intervention:

a) Vitamin D supplementation Intervention: Evidence Base

Before designing the Vitamin D intervention, I reviewed the existing literature on studies implementing Vitamin D interventions in a KOA population. From this review, I

identified several design issue which were important in informing the design of my study:

- Participant baseline serum 25(OH)D concentrations: Any response to supplemental vitamin D is likely to depend on the vitamin D status of the participants at baseline. In the only published RCT of Vitamin D supplementation in KOA patients available at the time of intervention design [92], the authors reported a small non-significant improvement in WOMAC Pain Score among those supplemented with Vitamin D who had low baseline 25(OH)D concentrations (<37.44nmol/L).
- Vitamin D administration and delivery: Vitamin D supplementation is available as a subcutaneous depot injection or for oral ingestion in the form of capsules, tablets, powders or sprays.[110] Most Vitamin D supplementation interventions for older populations in clinical studies have used oral supplementation methods [92],[232],[233]. Vitamin D supplements are also available as Vitamin D2 or Vitamin D3, with evidence that D3 is significantly more effective in raising serum 25(OH)D concentrations than D2 [234, 235].
- Vitamin D dosage: The amount of Vitamin D given daily in Vitamin D supplementation studies is highly variable. The dosage used in McAlindon's RCT of [92] Vitamin D and KOA was 2000IU (50 µg) Vitamin D/day. A dose of 1000-2000IU (25-50µg) daily (10,000IU or 250µg monthly) is also recommended clinically for Vitamin D deficient and insufficient individuals over 3 months to raise 25(OH)D concentrations to sufficiency (>50nmol/L) [134].
- Vitamin D supplementation confounders: The main contributor to 25(OH)D concentrations is sunlight exposure, followed by dietary ingestion (consumed as supplements or food) [110].
- Vitamin D supplementation safety: There is no official 'cut off point' for Vitamin D toxicity specified and estimates of the serum Vitamin D concentrations indicative of toxicity in the literature are variable [236-238]. However, it is generally recognised that Vitamin D toxicity is rare and occurs at high Vitamin D doses, consistently reported as above 375-500nmol/L [239]. Additionally the side effects from Vitamin D toxicity are not thought to be a direct result of Vitamin D itself, but a result of its effect on calcium metabolism. Vitamin D

toxicity may lead to hypercalcemia which produce the side effects experienced during toxicity [240, 241].

b) Vitamin D Intervention: Interventional Development

Based on the literature reviewed above, I developed my own Vitamin D intervention. The rationale and development process for this is reviewed below:

- Participant baseline serum 25(OH)D concentrations: Based on the evidence suggesting that those with low baseline 25(OH)D concentrations may benefit through improvement in KOA symptoms after Vitamin D supplementation [92], I decided to also recruit Vitamin D insufficient (26-50nmol/L 25(OH)D) individuals. Vitamin D deficient (<25nmol/L 25(OH)D) individuals were excluded on ethical grounds (I had originally intended that some participants would be Controls and so not receive vitamin D – see Fig 4.1) and so, with the participant's permission, they could be referred directly to their GP for follow up[134].
- Vitamin D administration and delivery: As Vitamin D3 is more effective than D2 in raising vitamin D status and as this form of the vitamin is more readily available as a supplement, I chose to use a Vitamin D3 preparation. Due to logistical issues and availability of trained staff to administer injections, we rejected delivering Vitamin D by depot injection. The use of powders and spray mechanisms for supplementation were rejected due to product availability and cost issues. This left the study team with a choice of capsules or tablet supplement. Commercially available products were reviewed according to product composition and cost and Boots Pharmaceuticals Vitamin D 25µg tablets were selected for use in the study.
- Vitamin D dosage: I decided to administer the clinically recommended dose of 2000IU (50µg)/day of Vitamin D deficient individuals over 3 months with the aim of raising serum 25(OH)D concentrations of Vitamin D insufficient participants to Vitamin D sufficiency (>50nmol/L).
- Vitamin D supplementation confounders: As cutaneous synthesis is the largest contributor to 25(OH)D, sunlight exposure presented as a potential confounder to our Vitamin D supplementation intervention by providing an unregulated

Vitamin D source during the study. In addition, dietary supplements e.g. multi-vitamin tablets are a potential source of vitamin D. I therefore took several steps to attempt to reduce the amount of cutaneous Vitamin D production during the study and confounding from dietary sources:

- No consumption of any other Vitamin D containing supplements.
- No sunbed use by participants during the pilot intervention study.
- No holidays to areas where exposure to significant sunlight exposure is anticipated which is likely to cause cutaneous 25(OH)D production.
- Conduct of pilot interventional study during the UK 'winter' months, October-April, when cutaneous 25(OH)D production is not possible [110].

- Vitamin D supplementation safety: Participant safety with regards to Vitamin D supplementation was fully considered and the following procedures were in place:
  - Serum concentrations of 25(OH)D were monitored at each study time point (6 week and 12 week) to ensure they had not surpassed current safe upper limits>100ng/ml (220nmol/L) [241].
  - Serum calcium concentrations were monitored to ensure observed concentrations remained within the normal physiological range.
  - Individuals allocated to the Vitamin D supplement only group were asked to limit non-essential Vitamin D supplementation.
  - Participants were monitored (by observation/reporting of any symptoms of hypercalcemia/Vitamin D toxicity and monitoring of serum 25OHD and Calcium during the study) to identify any hypercalcaemic/Vitamin D toxicity symptoms.
  - Participants with health conditions/taking medications that could exacerbate the effect of Vitamin D or make Vitamin D supplementation dangerous were excluded (see section 4.2.3.2.)

c) Vitamin D Intervention: Final Intervention Content

In summary, the study intervention involved participants taking 2000IU (50µg) (in the form of 2x1000IU [25µg] tablets/day) D3 per day. These tablets were provided to participants in 6 week batches (refilled with more D3 tablets at the week 6 study visit)

in pill boxes, which included a separate box for each day of the 6 weeks. Each separate days box was filled with 2x 1000IU (25µg) tablets (see Figure 4.3). Participants were instructed to leave any missed tablets in their original position in the pill box to allow compliance to be measured at each study visit. At the start of the study intervention, the participants were provided with their pill box and a Vitamin D Intervention manual (see Appendix M) containing instructions on following the intervention.

Figure 4.3: (Top) Picture of pill case give to participants as part of the Vitamin D intervention, containing 3 weeks supply of Vitamin D supplements. (Bottom) Picture of the contents of each individual's day's pill box.

4.2.2.3 Online PA Intervention

The online PA intervention, 'POW' (People with Osteoarthritis Walking programme) aimed to increase PA, walking in particular, among older obese adults with KOA

through goal orientated lifestyle changes. POW was adapted from the 'moving more' module of the LEAP (Living, Eating, Activity and Planning in Retirement) intervention that formed part of the 'Livewell' project, developed at Newcastle University [182]. LEAP is a web-based intervention accessible by PC, tablet and smartphone and the 'moving more' module supports participants to be more physically active. Each participant is given a pedometer at the start of the intervention and encouraged to record their daily step counts and set step count goals. They are also provided with access to information on how to be more PA in different ways, with links to PA information in the local community, and provided with a diary feature which allows them to schedule and record any PA they have undertaken [183]. The POW intervention involved adapting the LEAP 'moving more' module in the following ways:

- An introduction page was added that provided information on exercising safely with KOA (see Figure 4.4) (adapted from ARUK 'Knee Pain and Exercise' Information Sheet[242].
- Content on KOA and general goals to be achieved through being more active were added (see Figure 4.5)
- Content on KOA specific barriers and solutions to performing additional physical activity (identified through review of the literature [243-255]) were added (see Figure 4.6).

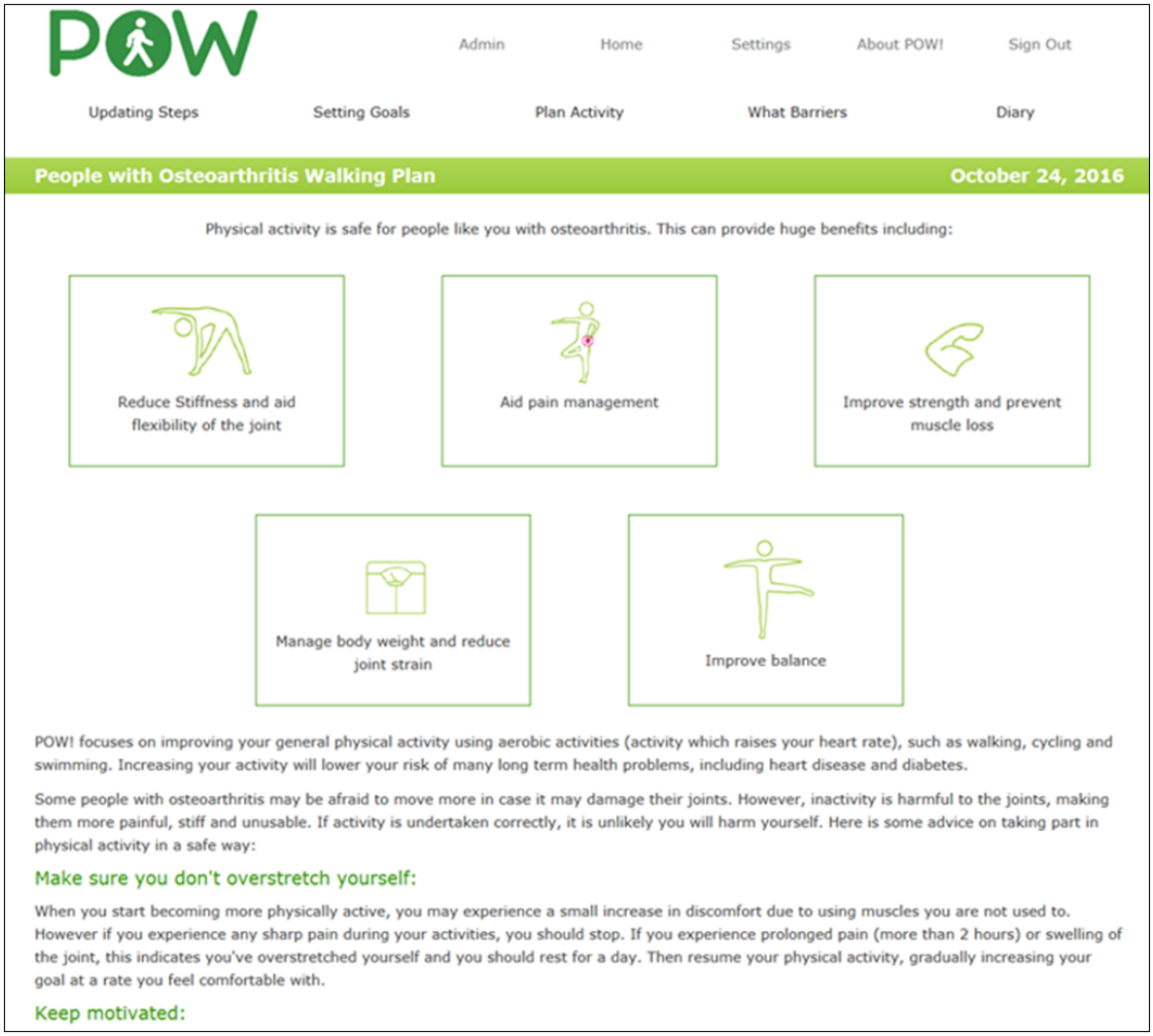


Figure 4.4: Screenshot of the Online POW PA programme introduction page outlining the purpose and use of the website and advice on exercising safely in KOA.

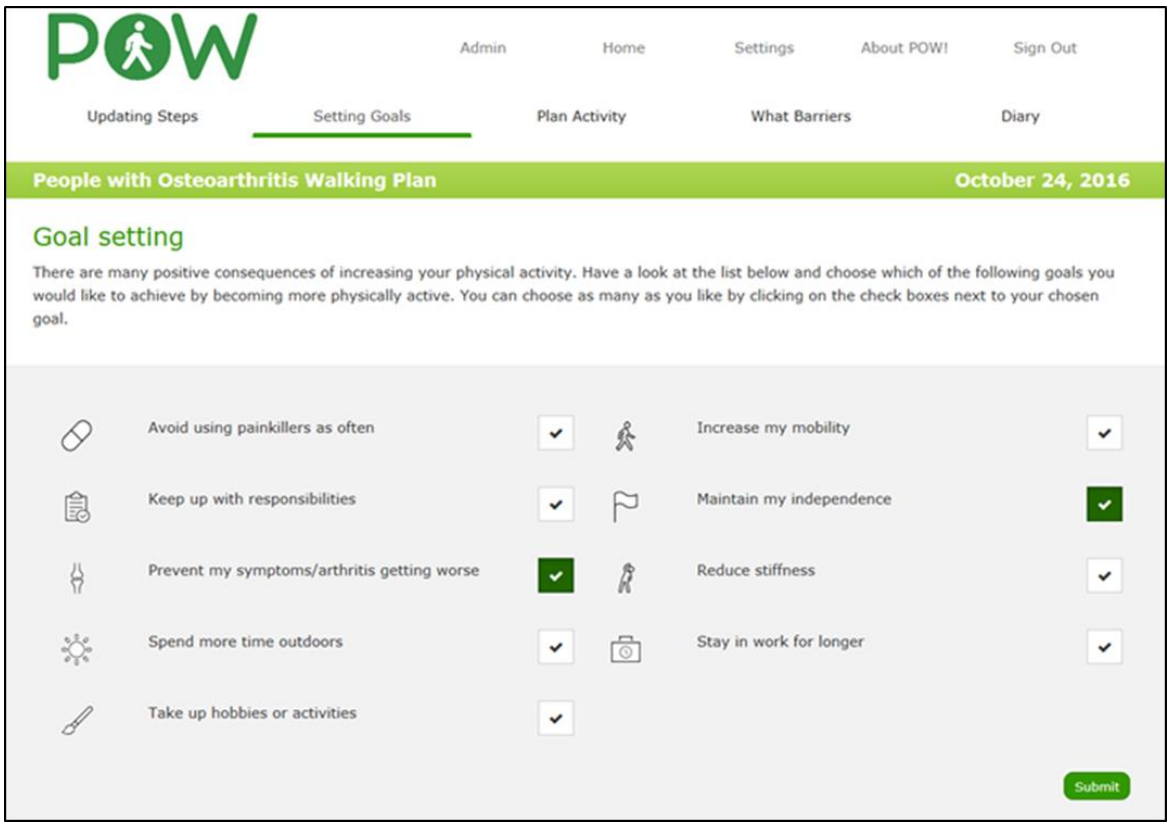


Figure 4.5: Screenshot of the Online POW PA programme goal setting page where users can set goals they would like to achieve by becoming more active.

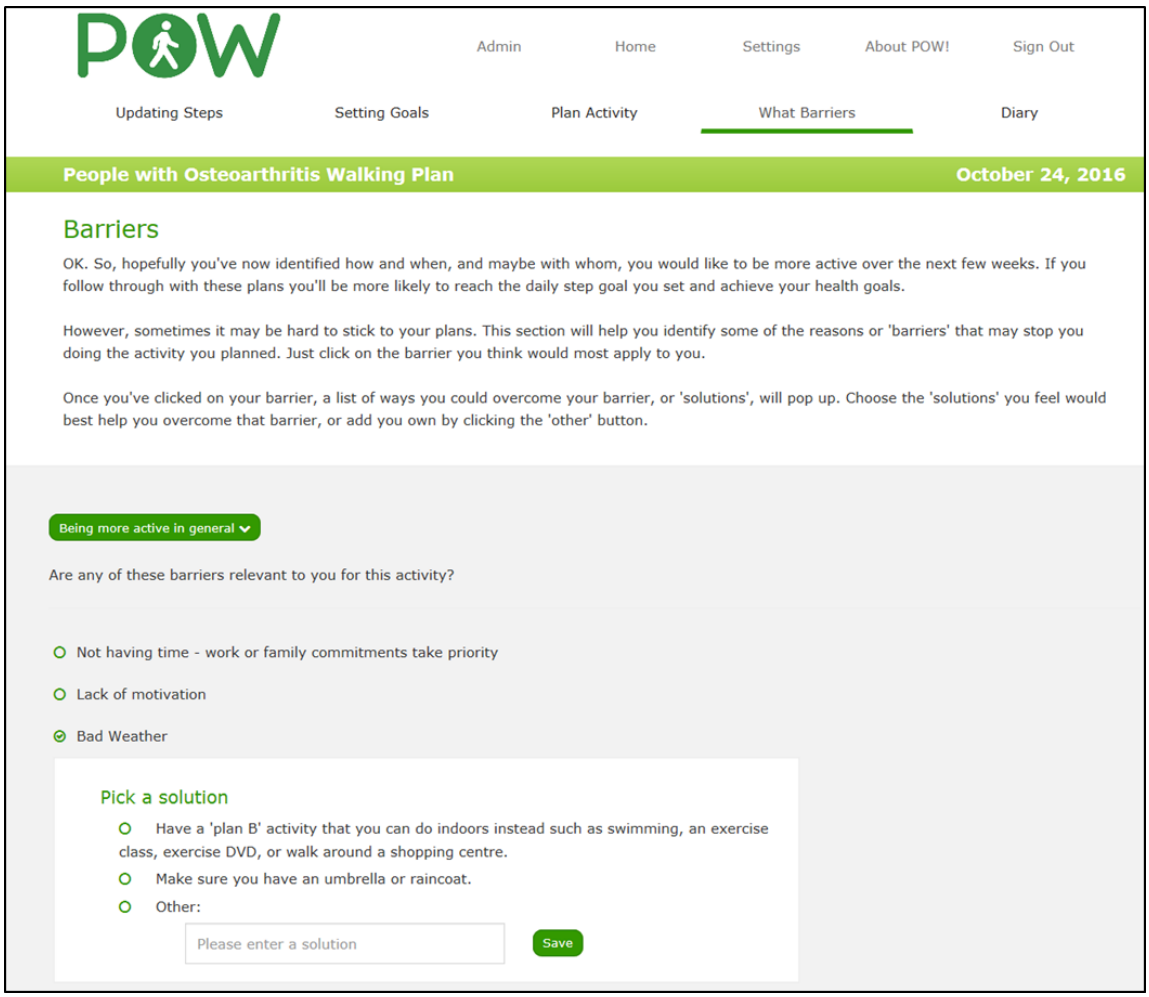


Figure 4.6: Screenshot of the Online POW PA programme barriers and solutions page where participants can select a barrier they might anticipate in completing an activity, and POW! offers a number of possible solution to that barrier from which the participant may choose.

This KOA specific PA intervention was renamed 'POW' (People with Osteoarthritis Walking programme), as the main activity promoted was walking supported by the use of pedometers that were provided. In collaboration with Hippo (www.hippomarketing.eu), the web-based intervention was designed. Hippo hosted the website, carried out website maintenance and amendments and provided reports on website use (i.e. using Google analytics, PiWik and raw CSV data files).

a) PA Intervention

Promotion of the use of the online PA programme (POW) was the main focus of the PA intervention. Instructions on pedometer use and a PA specific intervention manual (including instructions of website use – see Appendix N) were developed and provided to participants at the start of the intervention. Paper activity sheets were also provided to participants to allow them to record step data if they were unable to go online.

4.2.2.4 Standard Care

This study arm was designed as a comparison group for the Vitamin D and PA groups and involved administering a daily placebo identical to the Vitamin D supplement provided to those in the Vitamin D supplementation arm. These details were outlined as part of Standard Care Instruction manual (see Appendix O) which was mailed to participants at the start of the pilot intervention study.

a) Changes to Design

Due to logistical issues (regarding length of time required and cost to produce a placebo supplement), the production of a placebo and identical Vitamin D supplement was not possible during the study timeframe. Therefore this group was changed to a standard care group, which would receive neither the Vitamin D supplementation nor web based PA intervention, but were instructed to continue their usual care practices regarding their KOA. Standard Care participants were instructed not to deliberately alter their Vitamin D (through use of supplements, sunbeds or sunny holidays) or PA (through structured exercise programmes or deliberate exercise increase) patterns during the duration of the study.

4.2.3 Study Participants

4.2.3.1 Participant Sampling and Recruitment.

A targeted sampling method was used to recruit into the pilot intervention study. Participants who took part in the cross-sectional study were screened against the pilot intervention study eligibility criteria. Those who met the eligibility criteria for the Vitamin D supplementation intervention were entered into the Vitamin D supplementation intervention and those who met the eligibility criteria for the Online PA intervention were entered into the Online PA intervention.

4.2.3.2 Study Eligibility Criteria

The eligibility criteria for the pilot interventional study are detailed below with * indicating those criteria which related specifically to the Vitamin D intervention and ≠ indicating those criteria which related specifically to the online PA intervention.

a) Inclusion Criteria

The same inclusion criteria as used in the cross-sectional study (see Chapter 3) were adopted with the addition of:

1. Low objectively measured concentrations of Vitamin D, defined as:*

Insufficient (25-50nmol/L), and excluding those considered vitamin D deficient (<25 nmol/L).

2. Low PA recorded from accelerometers defined as: ≠

<60min/week of moderate PA, <30min/week vigorous PA (2*credit of moderate activity) defined as being 'inactive' and 'low' in activity by UK government guidelines. Activities only counted if they occurred in >10mins bouts[217]. Activity was defined as moderate if it made the participant 'breathe faster, feel warmer or sweat' and increased heart rate. Activities identified as moderate included: brisk walking, cycling, gardening, housework, DIY, climbing stairs and carrying heavy loads.

b) Exclusion Criteria

The same exclusion criteria used in the cross-sectional study were adopted with the addition of:

1. Health conditions which can interfere with Vitamin D supplement absorption: *

- Malabsorption syndromes: e.g. cystic fibrosis, celiac disease, Whipple's disease, Crohn's Disease, bypass surgery, short bowel syndrome,
- Diagnosed restrictive eating disorder
- Hypercalcaemia (albumin-adjusted plasma calcium > 2.60 mmol/l)
- Hypocalcaemia (albumin-adjusted plasma calcium < 2.15 mmol/l)
- Renal Stage 4-5 Chronic Kidney Disease: GFR < 30 ml/min/1.73m2
- Primary hyperparathyroidism

2. Health conditions that can affect normal baseline concentration of vitamin D:*

- Current pregnancy, delivery of child/breast feeding 1 year prior to recruitment
- Holiday with significant sunlight exposure (specified by list of sunny destinations) in the last 3 months and plans for holidays to sunny/skiing destinations for the duration of the study.
- Current Anticonvulsant drug therapy
- Current Glucocorticoid use
- Current HIV/treatment with Antiretroviral drugs
- Current anti-oestrogen (aromatase inhibitors, oestrogen receptor inhibitors and selective oestrogen receptor moderators) such as used to treat breast cancers
- Those currently taking cytostatic/anti-tumour drugs
- Granulomatous disorders: sarcoidosis, TB, Lymphomas

3. Current health conditions which may be made worse by vitamin D consumption*

- Chronic Renal Disease: stage 4 and 5 (see above)
- Liver disease
- Histoplasmosis
- hyperparathyroidism

- Hypocalcaemia or hypercalcemia (as defined above)
- Lymphoma
- Current/recent (in the last 6 months) supplementation(topical/oral/intravenous, prescribed and non-prescribed) with: Phosphorous, >10µg/day Vitamin D and >500mg/day Calcium

4.2.4 Study Materials and Measures

4.2.4.1 Study Measures

All study measurements made during the cross-sectional study visit (see section 3.2.4.2) were repeated at the 6 week and 12 week pilot interventional study visits. Study Intervention compliance was also measured at each study visit.

4.2.4.2 Study Materials

All pilot intervention study materials were developed and compiled prior to commencement of the pilot intervention study. These included all materials for the Vitamin D, Online PA and standard care interventions as specified in Appendix P.

4.2.5 Study Setting

All study visits took place within North Tyneside General Hospital in clinical rooms within the Jubilee Day Hospital. All appropriate staff, equipment and logistical provisions were prepared as described in section 3.2.

4.2.6 Procedure

Standard Care participants attended a 6 week and 12 week intervention visit, where cross-sectional study visit measures were repeated and intervention compliance assessed.

4.2.6.1 Study Arm Allocation

In accordance with the original study protocol, all cross-sectional study participants were screened against the pilot intervention study criteria and randomised (using an online random number allocator) to one of four study arms (Vitamin D, PA, Vitamin D & PA or standard care).

a) Study Arm Allocation Amendment 1

The above randomised allocation yielded only 4 eligible participants from the pool of 45 cross-sectional study participants. Due to these small numbers, an amendment was submitted to the research ethics committee to revise pilot intervention study criteria. This allowed inclusion of participants with low activity levels (<60mins moderate activity/week) as well as sedentary activity levels (<30mins moderate activity/week) to increase the study numbers. This change yielded an additional 2 eligible participants for the pilot intervention study, who were subsequently randomised (using an online random number allocator) to a study arm.

b) Study Arm Allocation Amendment 2

It was concluded that 6 participants were insufficient to test our pilot interventional study aims of testing acceptability and feasibility of the study interventions, therefore the decision was made by the study team to abandon the randomisation procedure to increase participant numbers in the pilot intervention study, allowing us to test our study aims. Therefore, participants who were eligible for the Vitamin D intervention according to the pilot intervention study Vitamin D eligibility criteria were entered into the Vitamin D study and participants who were eligible for the online PA activity intervention according to the pilot intervention study PA criteria were entered into the Online PA intervention (see Figure 4.7). By opting for an unrandomised study design, increased participant numbers were obtained to facilitate an assessment of acceptability and feasibility of study procedures and Vitamin D and PA interventions.

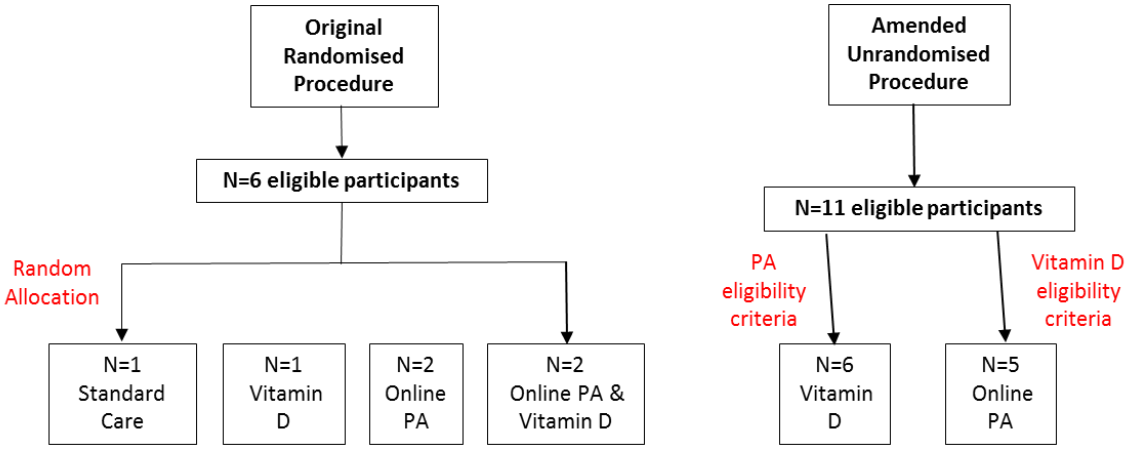


Figure 4.7: Diagram representing allocation procedures used during the pilot intervention study.On the left is the original planned randomised allocation procedure for pilot interventional study, where participants are randomly allocated to 1 of 4 study arms. On the right is the unrandomised allocation procedure where participants are allocated to the study arm which they meet the study criteria for (Online PA or vitamin D).

4.2.6.2 Pilot Intervention Initiation

Following completion of eligibility screening, eligible participants were contacted by telephone to inform them of their eligibility. Once verbal reconsent was obtained from participants, they were allocated to the appropriate intervention arm using the allocation procedures detailed in section 4.2.6.1. Once study arms were allocated to each participant, the appropriate study intervention starter pack and study materials were mailed out to the participant's home address.

Participants were informed by telephone when their starter pack was mailed and were instructed to read the intervention instructions and familiarize themselves with the study materials on the starter packs arrival, but not to start the intervention. Participants were also instructed to complete and return (by self-address, prepaid envelope) the study starter pack receipt and consent slip to the research team as soon as they received the study starter pack.

On receipt of the consent slip, each participant was contacted to review the intervention instructions and to answer any participant questions. Once the participant understood the intervention and felt they were able to complete it, an intervention start date was set (see Figure 4.8below) for summary of study initiation process.

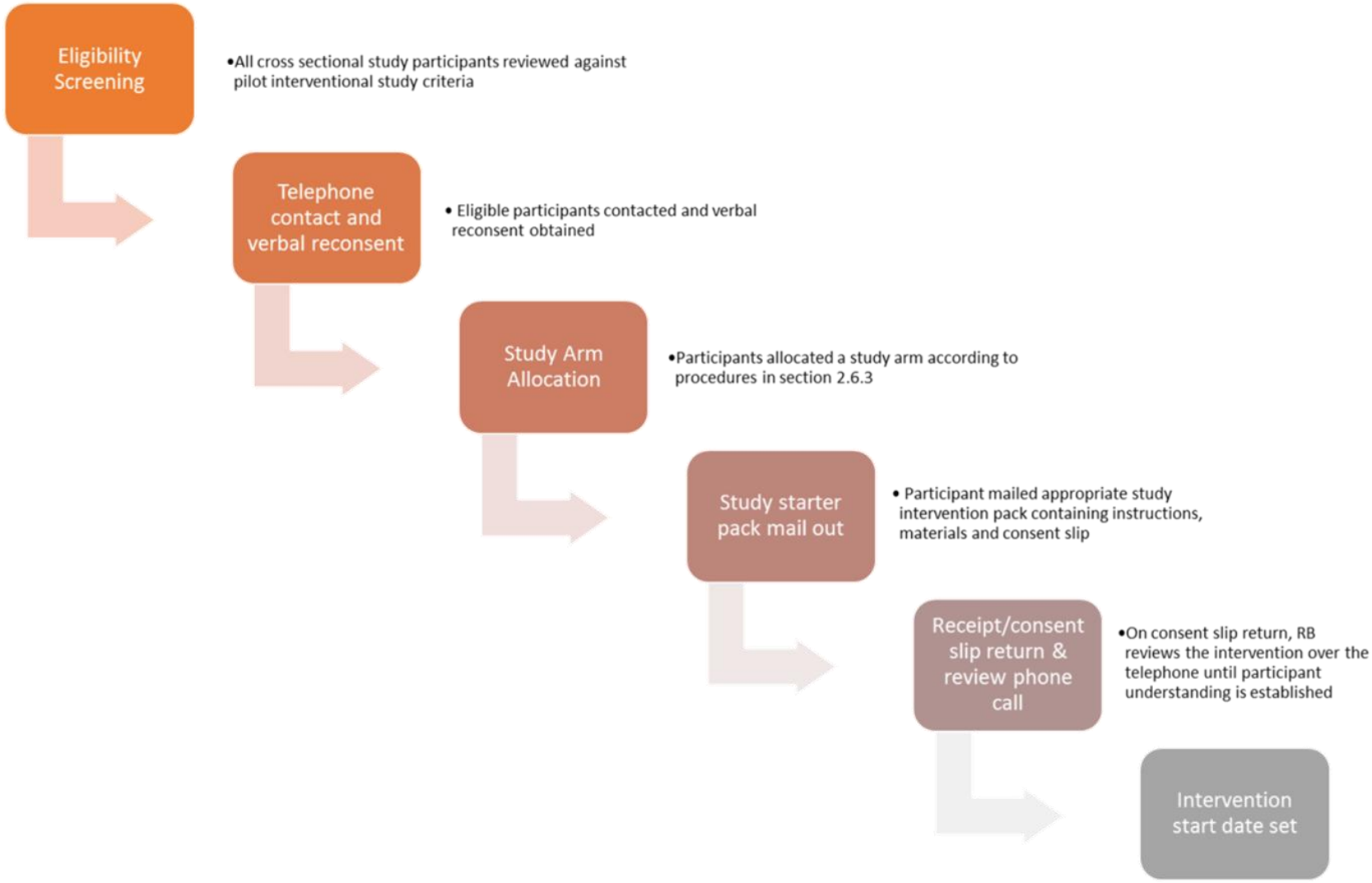


Figure 4.8: Process of recruiting cross-sectional study participants into the pilot intervention study and the initiation of the pilot interventional study.

4.2.6.4 Six week Follow-Up Visit

Participants were invited to attend a follow up visit at approximately 6 weeks from the start of the pilot intervention study. An appointment was made according to participant and clinical room availability and an appointment letter and hospital map was mailed to each participant. The study visit began with a short review of the participant's intervention progress and collection of details regarding intervention compliance. The study visit then proceeded in the same way as the cross-sectional study visit except the consenting process. All data and samples were stored as specified in sections 3.2.7 and, and data was processed and analysed as outlined in section 3.2.7.

4.2.6.5 Twelve week Follow-Up Visit (study close)

Participants were invited to attend a follow up visit at approximately 12 weeks after the start of the pilot intervention study. An appointment was booked as described above and the participant was reminded the qualitative interview would take place directly after this appointment. An appointment letter and hospital map was mailed to the participant. The study visit was conducted as described for the six week follow up visit above.

4.2.6.6 Participant Feedback

On conclusion of the pilot interventional study, each pilot intervention study participant was mailed individual feedback based on the data collected over their 3 study visits, including information on:

- Weight (kilograms, stone and pounds)
- BMI
- Waist measurement (centimetres and inches)
- Knee pain (0-20)
- Knee stiffness (0-8)
- Blood Vitamin D levels (nmol/L – deficient, insufficient and sufficient)
- Blood Calcium levels (mmol/L – normal, low and high)
- Steps

Participant feedback additionally contained a letter thanking participants for their participation in the pilot interventional study. A feedback evening on 17/11/2016 was also arranged where mean data for weight, BMI, waist circumference, TUG, serum 25(OH)D concentrations and Physical Activity levels (sedentary, light and moderate intensities) by intervention group (Vitamin D supplementation and web based PA interventions) as a PowerPoint presentation.

4.2.7 Data Processing and Analysis

4.2.7.1 Data Processing

All study data, labelled by participant code and study visit, were entered into electronic databases for analysis. All repeated measurements, WOMAC and SF-36 Questionnaire data and accelerometry data were scored and processed as described in section 3.2.7.

4.2.7.2 POW Website Usage Data Extraction

Data on the usage of the POW Website was collected using csv. files (provided by hippo) or data imputed into step graphs by users. Data on frequency, time and duration of POW website use for each PA intervention participant was collected using the PiWik Website Analysis website.

4.2.7.3 Data Analysis

a) Primary Outcomes

- Recruitment rates (numbers/% recruited from general population and from potential participants identified)
- Dropout rates (at each study time point)
- Compliance to study measurements at each time point
- Compliance to Vitamin D intervention (pill counts)
- Compliance to PA intervention (frequency of use/time spent on online system, data input to online system and comparison of compliers to non-compliers.

b) Secondary Outcomes

- Anthropometric Measurements

- KOA Symptoms
- Physical Activity
- Vitamin D

All statistical analyses were performed using IBM SPSS Statistics Version 23. Baseline data for pilot intervention study participants are the data collected for the cross-sectional study. Change in variables were calculated by subtracting the data point from Week 12 of the intervention from the data point for baseline (measurement taken for the cross-sectional study). Descriptive statistics summarising primary and secondary outcomes at each study visit and change in outcomes over study visits for each intervention group are reported using mean and median values with variance reported as standard deviation or 95% confidence intervals.

4.3 Results

17 eligible people from the cross-sectional study were recruited into the pilot intervention study between December 2015-April 2016. Nine participants were assigned to the Vitamin D supplementation intervention and nine participants were assigned to the Online PA intervention (due to the change in study arm allocation during the study from randomised to unrandomised, n=3 participants took part in both the physical activity and vitamin D intervention study concurrently, resulting in 17 participants with 9 participant allocated to each intervention group).

4.3.1 Primary Outcomes

4.3.1.1 Study Retention

As displayed in Figure 4.9below, retention throughout the 3 month pilot intervention was 100%. Mean follow up time (days) from pilot intervention start to the week 6 study visit was 46.7 days (±5.0) and mean follow up time (days) from week 6 study visit to week 12 study visit was 49.3 days (±7.8).

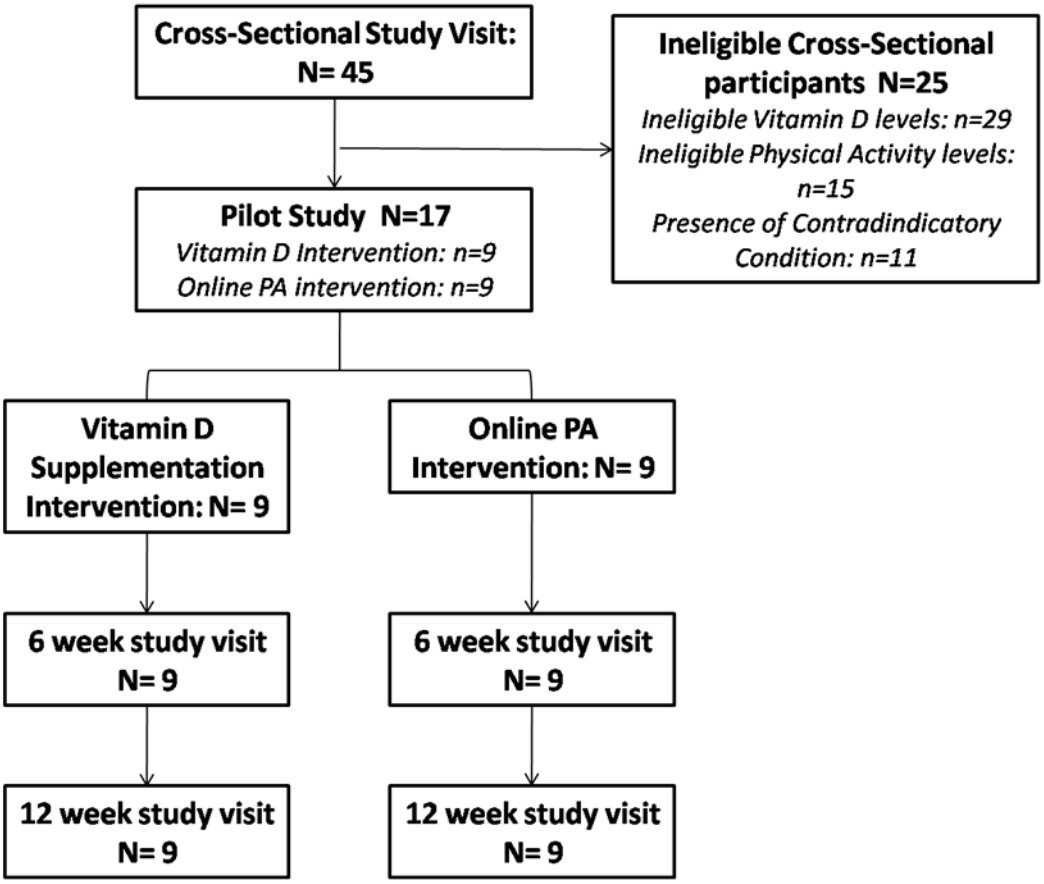


Figure 4.9: Summary of recruitment and retention throughout the pilot intervention study

4.3.1.2 Measurement Compliance

Study Measurements		Compliance (N=17)		
		Baseline	Week 6	Week 12
Anthropometric Measures	Height	100%	100%	100%
	Bioimpedance Measurements (Weight, BMI, Body Fat%, Body Fat Mass)	100%	100%	99%
	Waist Circumference	94%	100%	100%
Knee Function Measures	Timed Up and Go	100%	100%	100%
Questionnaires	VAS	100%	100%	100%
	WOMAC	100%	100%	100%
	SF-36	100%	100%	100%
Blood Samples	Venous Sample	100%	99%	100%
	Dried Blood Spot Sample	88%	94%	88%

Table 4.1: Compliance to study measures at baseline, week 6 and week 12 of pilot intervention study across all participants

Compliance to anthropometric study measurements was high, with only 1/17 participants missing body fat mass data at the 12 week visit and 1/17 participants missing waist circumference data at the baseline visit, due to investigator error. Compliance in completing questionnaires was 100% across all time points. Compliance for venous blood samples was high, with only 1/17 participants missing a blood sample at 6 weeks due to difficulty in accessing a vein. Compliance to the fingerprick DBS blood sample method was lower than the venous method at 88% (15/17 participants) at baseline, 94% (16/17 participants) at week 6 and 88% (15/17 participants) at week 12. One participant refused to give a DBS sample at all time points due to a dislike of having blood taken. At baseline one other participant sample was not taken due to investigator error and at week 12 another participant refused consent for the DBS sample due to side effects (pain and bruising at the site of fingerprick) from the DBS procedure at their previous study visit.

4.3.1.3 Activity Monitor compliance and Data Retrieval

All activity monitors were returned and data downloaded and retrieved at each time point (baseline, week 6 and week 12) of the pilot intervention study.

4.3.1.4 Wear Time Analysis

	Mean Baseline (n=17) Mean (SD)	Mean Week 6 (n=15) Mean (SD)	Mean Week 12 (n=17) Mean (SD)	Change in measures (n=17) Mean (95% CI)
Mean Age (years)	62 (±5.5)			N/A
Mean BMI (kg/m^2)	34 (±3.7)	33 (±2.4)	34 (±3.9)	-0.11 (-0.73, 0.51)
Mean Wear Time (mins)	3093 (±824.6)	3990 (±400.0)	3728 (±630.8)	636 (198, 1073)
Total Wear time (% of total monitoring time)	60 (±6.0)	59 (±6.0)	55 (±9.4)	0.4 (-5.5, 6.2)
Total Non-Wear Time (% of total monitoring time)	40 (±6.1)	41 (±6.0)	45 (±9.4)	5.3 (0.1, 10.4)

Table 4.2: Mean wear time of accelerometers over the activity monitoring period at baseline, week 6 and week 12 of the pilot intervention study. Data only refers to participants with valid data (>10hours wear time/day) (n= 15)

Compliance to PA measurement by accelerometry was analysed by study visit, results of which are summarised in Table 4.2. As with the cross-sectional study, a mean of >10

hours/day of monitor wear was determined as an acceptable length of daily wear to provide valid PA data [219]. For baseline and week 12 study visits, valid data (calculated from average wear time/day over the monitoring period) was obtained for all pilot study participants (n=17). At week 6 study visit, valid data (calculated as described above) was not obtained for two participants, leaving 15 participants with valid data. When analysed by individual day, of the nine participants monitored for 3 days at baseline, 89% and 11% of participants achieved three or two days of valid data respectively and of the seven participants monitored for five days at baseline, 71%, 14% and 14% achieved valid data for five, four and 3 days respectively. At week 6 (during which all participants were monitored for five days) 63%, 25% and 13% of participants achieved five, four and three days of valid data respectively. At week 12 (during which all participants were monitored for five days) 56%, 25%, 13% and 6% of participants achieved five, four, three and one day valid data respectively.

Mean total wear time increased from baseline to week 12 by a mean 636 mins (95% CI: 198, 1073) of the pilot intervention study. There was a slight mean increase in % wear time from baseline to week 12 of 0.4% (95 CI: -5.5, 6.2) and a mean increase in non-wear time of 5.3% (95% CI: 0.1, 10.4) from baseline to week 12 study visits.

4.3.1.5 Vitamin D Supplementation Intervention

78% (7/9) participants took 100% (168/168 tablets) of the Vitamin D supplements. 1/9 (11%) took 99% (167/168) vitamin D supplements and 1/9 participants (11%) took 93% (156/168). Averaged across all participants, Vitamin D supplement compliance was 99% (1499/1512).

4.3.1.6 Online Physical Activity Intervention

Compliance with the POW! Website was measured by frequency of website usage. Those who did not log on to POW! After the initial registration visit were considered ‘non-compliers’. 3/9 (33%) PA intervention participants were POW non-compliers. There were no differences in baseline measurements between POW compliers and non-compliers.

Use of the POW website by intervention participants was analysed using website analytics programme PiWik. We a variety of POW! Website usage outcomes, which are summarised below in Table 4.3.

POW! Usage Outcomes	Mean (SD)
No. of POW! visits	11.3 (±6.28)
Total time (secs) spent on POW!	5820.2 (±4694.52)
Mean number of actions per visit	9.1 (±3.24)
Total number of website actions	112.3 (±75.86)
Average time (days) between visits	4.0 (±2.09)

Table 4.3: Table summarising POW! Website usage outcomes amongst PA intervention compliers (n=5).

The usage of the primary individual web pages within the POW Website were analysed as % of total POW Usage (see Table 4.4).The most frequently visit page on the POW website was the step graph (54%) followed by the dashboard (9%) and the goal setting page (5.4%).

POW Web Page	% of overall usage
Introduction	3.1
Activity Questionnaire	1.5
Step Graph	54.0
Goal Setting	5.4
Activity Planning	4.3
Activity Barriers	2.3
Diary	2.8
Dashboard	9.0
Other	17.6%

Table 4.4: Table summerising the % of usage of each web page on the POW website by PA participants

4.3.2 Participant Characteristics

4.3.2.1 Cross-sectional study group vs. Pilot intervention study group

Study Measurements	Cross-sectional Study Cohort (n=45)	Pilot Interventional Study Cohort (n=17)
Age (years)	61(±5.3)	61(±5.4)
Height (cms)	170 (± 8.8)	170 (±9.7)
Weight (kgs)	106 (±23.2)	98 (±12.4)
BMI (kg/m2)	34 (±4.8)	34 (±3.9)
Body Fat (%)	40 (±8.1)	40 (±8.6)
Body Fat Mass (kg)	40 (±11.9)	39 (±10.1)
Waist Circumference (cms)	113 (±12.1)	111 (±8.8)
Timed Up and Go (secs)	9.5 (±2.2)	9.9 (±2.6)
VAS Daily Score (0-10)	4.3 (±1.8)	4.3 (±2.1)
WOMAC Pain	8.4 (±3.4)	7.5 (±3.5)
WOMAC Stiffness	4.4 (±1.9)	3.7 (±2.4)
WOMAC Activities of Daily Living (ADL)	28.1 (±10.7)	25.5 (±12.7)
WOMAC Total	40.8 (±15.2)	36.7 (±17.8)
SF-36 MCS (Mental Capacity Score) (0-100)	48.6 (±11.5)	46.8 (±9.2)
SF-36 PCS (Physical Capacity Score) (0-100)	38.6 (±9.5)	41.9 (±9.9)
Serum 25(OH)D (nmol/L)	44 (±23.4)	43 (±20.5)
Serum Calcium (mmol/L)	2.2 (±0.3)	2.3 (±0.2)
% 25(OH)D Deficient (<25nmol/L)	27 (12/45)	12 (2/17)
% 25(OH)D Insufficient (26-50nmol/L)	36 (16/45)	65 (11/17)
% 25(OH)D Sufficient (<51nmol/L)	36 (16/45)	18 (3/17)
% time in sedentary activity	63 (±10.6)	69 (±9.7)
% time in light activity	33 (±9.35)	29 (±9.5)
% time in moderate activity	3.5 (±3.1)	2.7 (±2.7)
Average daily time in sedentary activity (mins)	1027(±2247.6)	591 (±21.3)
Average daily time in light activity (mins)	273 (±81.3)	241 (±75.3)
Average daily time in moderate activity (mins)	29 (±25.5)	21 (±19.6)

Table 4.5: Means and SD of participant characteristics of cross-section and pilot intervention study participants. [1] = non parametric data.

Baseline participant characteristics for the cross-sectional study and the pilot intervention study cohorts are summarised in Table 4.5. There were n=45 participants in the cross-sectional study 49% of which were female and n=17 participants enrolled into the pilot intervention study of whom 44% were female. Overall, participants in both studies were very similar between the cross-sectional study and pilot interventional study cohort. Measurements were similar between the cross-sectional and pilot intervention study participants. However baseline WOMAC Pain (0-20) 0.9 points higher in the cross-sectional participants compared to the pilot intervention participants. Physical activity measures were also different between the groups, with % sedentary time 6% higher and % light and moderate time 4% and 0.8% lower in the pilot intervention participants compared to the cross-sectional study participants.

4.3.2.2 Vitamin D Intervention group vs. Online PA Intervention group

Study Measurements	Vitamin D Intervention Cohort (n=9)	Online PA Intervention Cohort (n=9)
Age (years)	60.4 (±4.7)	61.9 (±5.4)
Height (cms)	173.4 (±8.6)	169.3 (±11.6)
Weight (kgs)	99.2 (±9.2)	98.6 (±14.6)
BMI (kg/m2)	33.2 (±4.2)	34.5 (±3.5)
Body Fat (%)	39.1 (±9.7)	38.3 (±8.0)
Body Fat Mass (kg)	38.8 (±10.7)	37.6 (±9.3)
Waist Circumference (cms)	110.3 (±6.5)	112.9 (±9.9)
Timed Up and Go (secs)	9.6 (±2.9)	9.8 (±2.2)
VAS Daily Score (0-10)	4.4 (±1.8)	4.1 (±2.2)
WOMAC Pain	7.4 (±3.8)	7.7 (±3.2)
WOMAC Stiffness	3.4 (±2.4)	3.3 (±2.5)
WOMAC Activities of Daily Living (ADL)	24.6 (±13.5)	25.7 (±12.1)
WOMAC Total	35.4 (±18.8)	36.7 (±17.1)
SF-36 MCS (Mental Capacity Score) (0-100)	47.0 (±10.1)	49.0 (±9.0)
SF-36 PCS (Physical Capacity Score) (0-100	41.63 (±10.1)	40.9 (±11.0)
Serum 25(OH)D (nmol/L)	38.3 (±9.1)	47.0 (±26.0)
Serum Calcium (mmol/L)	2.3 (±0.3)	2.3 (±0.2)
% 25(OH)D Deficient (<25nmol/L)	0 (0/9)	22.2 (2/9)
% 25(OH)D Insufficient (26-50nmol/L)	100 (9/9)	44.9 (4/9)
% 25(OH)D Sufficient (<51nmol/L)	0 (0/9)	33.3 (3/9)
% time in sedentary activity	64.5 (±9.6)	74.2 (±6.1)
% time in light activity	31.6 (±7.9)	24.4 (±6.0)
% time in moderate activity	3.8 (±3.4)	1.4 (±0.6)
Average daily time in sedentary activity (mins)	539.8 (±105.8)	647.4 (±179.8)
Average daily time in light activity (mins)	259.4 (±72.5)	208.7 (±55.8)
Average daily time in moderate activity (mins)	30.4 (±23.7)	11.8 (±5.3)

Table 4.6: Mean and SD of study outcomes for the Vitamin D supplementation and web-based PA interventions.

Baseline participant characteristics for both intervention modality groups are summarised in Table 4.6. Of the n=9 participants enrolled in the Vitamin D supplementation intervention, 44% were female, and of the n=9 participants enrolled into the web-based PA intervention 33% were female. The Vitamin D supplementation intervention group had a mean 25(OH)D concentration which was 8.7nmol/L lower than the Online PA intervention group. Mean % sedentary activity in the Online PA group was 9.7% higher than the Vitamin D supplementation group. Mean % light and

moderate activity was -7.2% and 2.4% lower respectively in the Online PA intervention group compared to the Vitamin D supplementation group. These differences in baseline Vitamin D and PA measures between intervention modalities is likely reflective of the eligibility criteria for each intervention, e.g. a low 25(OH)D concentrations (25-50nmol/L) were required for the Vitamin D intervention and low PA levels (<60mins/week of moderate intensity activity) were required for the Online PA intervention.

4.3.3 Secondary Outcomes

4.3.3.1 Changes to Anthropometric Measures

Anthropometry Measures	Vitamin D supplementation N= 9			Online PA programme N= 9		
	Baseline Mean (SD)	Week 12 Mean (SD)	Change in measurement Mean (95% CI)	Baseline Mean (SD)	Week 12 Mean (SD)	Change in measurement Mean (95% CI)
Weight (kgs)	101.7 ± 11.4	102.6 ± 10.4	1.4 (-0.4, 3.1)	98.6 ± 14.6	96.9 ± 14.8	-1.8 (-4.6, 1.1)
BMI (kg/m2)	33.4 ± 10.4	33.8 ± 4.1	0.6 (-0.05, 1.2)	34.5 ± 3.5	33.8 ± 3.7	-0.7 (-1.7, 0.4)
Body Fat (%)	38.5 ± 9.2	38.6 ± 9.6	0.1 (-1.1, 1.2)	38.3 ± 8.0	36.5 ± 7.2	-2.0 (-5.2, 1.2)
Body Fat Mass (kg)	39.1 ± 10.0	39.5 ± 10.6	0.7 (-0.6, 2.1)	37.6 ± 9.3	34.6 ± 10.0	-2.4 (-6.2, 1.5)
Waist Circumference (cms)	110.3 ± 6.5	111.4 ± 6.1	0.1 (-2.8, 3.0)	112.9 ± 9.9	111.7 ± 7.8	-1.1 (-4.1, 2.0)

Table 4.7: Change in anthropometric measurements from baseline to week 12 of pilot interventions

Participants in the Vitamin D intervention group had slight mean increases in anthropometric measurements. However, there were mean decreases in all anthropometric measurements in the Online PA intervention group. Online PA intervention participants lost an average 1.8kg over the 3 month intervention compared to the average 1.4kg increase in body weight in the Vitamin D intervention group. Body Fat % decrease by 2.4% on average in the Online PA intervention in contrast to the Vitamin D supplementation group who increased body fat % by 0.7%.

Measures of KOA symptoms	Vitamin D supplementation N= 9			Online PA programme N= 9		
	Baseline Mean (SD)	Week 12 Mean (SD)	Change in measurement Mean (95% CI)	Baseline Mean (SD)	Week 12 Mean (SD)	Change in measurement Mean (95% CI)
Timed Up and Go (secs)	9.7 ± 2.7	8.3 ± 2.5	-1.4 (-2.2, -0.5)	9.8 ± 2.2	7.8 ± 1.4	-2.0 (-3.0, -0.88)
VAS Daily Score (0-10)	4.4 ± 1.7	4.8 ± 1.8	0.4 (-0.3, 1.2)	4.1 ± 2.2	3.8 ± 2.4	-0.2 (-1.2, 0.8)
WOMAC Pain (0-20)	7.6 ± 3.6	7.7 ± 4.6	0.1 (-2.4, 2.6)	7.7 ± 3.2	5.6 ± 3.9	-3.0 (-5.2, -0.8)
WOMAC Stiffness (0-8)	3.7 ± 2.4	3.4 ± 2.0	-0.2 (-1.3, 0.8)	3.3 ± 2.5	2.6 ± 1.7	-0.8 (-1.9, 0.4)
WOMAC Activities of Daily Living (ADL) (0-68)	24.8 ± 12.7	24.8 ± 11.4	0.0 (-5.2, 5.2)	25.7 ± 12.1	18.3 ± 12.9	-7.3 (-13.7, -1.0)
WOMAC Total (0-92)	36.0 ± 17.7	35.9 ± 17.4	-0.1 (-7.7, 7.5)	36.7 ± 17.1	26.8 ± 17.6	-9.9 (-17.6, -2.2)
SF-36 MCS (0-100)	57.0 ± 3.8	59.3 ± 0.5	5.1 (0.7, 9.4)	57.0 ± 3.8	59.3 ± 0.5	5.6 (-1.2, 12.3)
SF-36 PCS (0-100)	36.3 ± 16.5	35.9 ± 10.9	-2.7 (-7.5, 2.0)	36.3 ± 16.5	35.9 ± 10.9	0.9 (-9.7, 11.4)

Table 4.8: Changes in KOA symptoms from baseline to week 12 of pilot intervention

Comparison of KOA symptoms at baseline and week 12 in the Vitamin D supplementation group (see Table 4.8) showed a mean decrease of 1.4 seconds to complete the TUG test, indicating improved function. Changes in WOMAC measures were similar at baseline and week 12. SF-36 MCS (0-100) increased mean 5.1 points in the Vitamin D supplementation group to mean 59.3/100 points, indicates an improvement of mental quality of life throughout the study. Conversely physical health related scores (SF-PCS) improved throughout the Vitamin D supplementation intervention, decreasing by 2.7 points from a mean 36.3/100 at baseline to a mean of 35.9/100 at week 12 suggesting a worsening of physical health during the study.

Comparison of KOA symptoms at baseline and week 12 in the online PA programme group (see Table 4.8) also showed decreases in time taken to complete TUG by mean 2.0 secs, indicating improved function. Decreases in WOMAC Pain (0-20), WOMAC ADL (0-68) and WOMAC Total scores of an average of 3.0, 7.3 and 9.9 points respectively were observed in the Online PA intervention indicating improved self-reported pain, function and overall KOA symptoms. An increase in mean SF-36 MCS of 5.6 points was seen in the online PA intervention, indicating an improvement of mental quality of life.

4.3.3.2 Changes to 25(OH)D Levels

Mean change in 25(OH)D concentration from baseline to week 12 in the Vitamin D supplementation group was 51 ±23.1nmol/L (95% CI 33.2, 68.8) (see Figure 4.10). Change in 25(OH)D concentration from baseline to week 6 was 39.9nmol/L ±17.0 (95% CI: 26.8, 52.9) and change in 25(OH)D concentration from week 6 to week 12 was smaller at 11.1 ±11.6 nmol/L (95% CI: 2.2, 2.0.0).

Mean change in 25(OH)D concentration from baseline to week 12 in the Online PA group was smaller than the Vitamin D supplementation group at 14.9 ±41.1 (95% CI: -16.7, 46.5) (see Figure 4.11). Change in 25(OH)D concentration from baseline to week 6 was 11.0 ±39.0 (95% CI: -19.0, 41.0) and change in 25(OH)D concentration from week 6 to week 12 was smaller at 3.9 ±4.5 (95% CI: 0.4, 7.4).

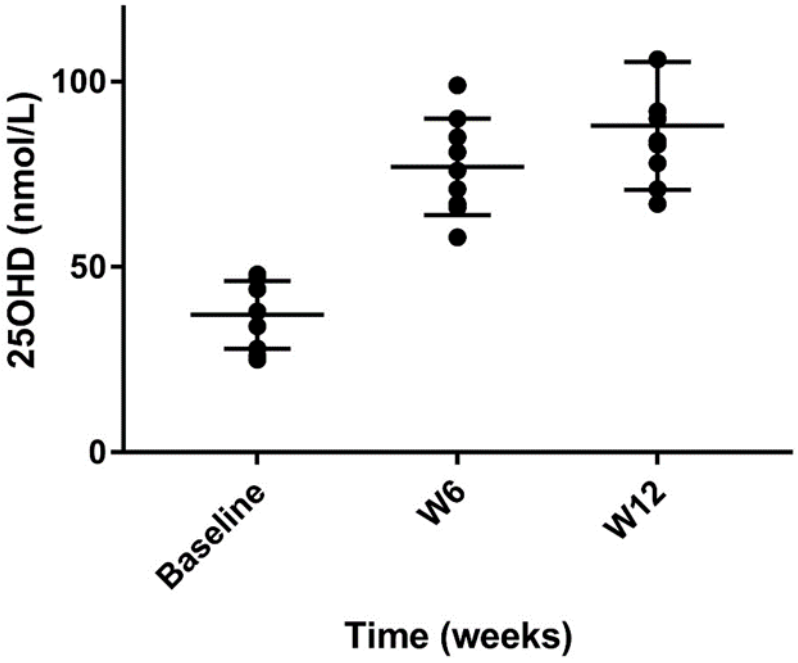


Figure 4.10: Individual participant 25(OH)D concentrations (y axis) by time point in the pilot intervention study (x axis) in the Vitamin D supplementation group

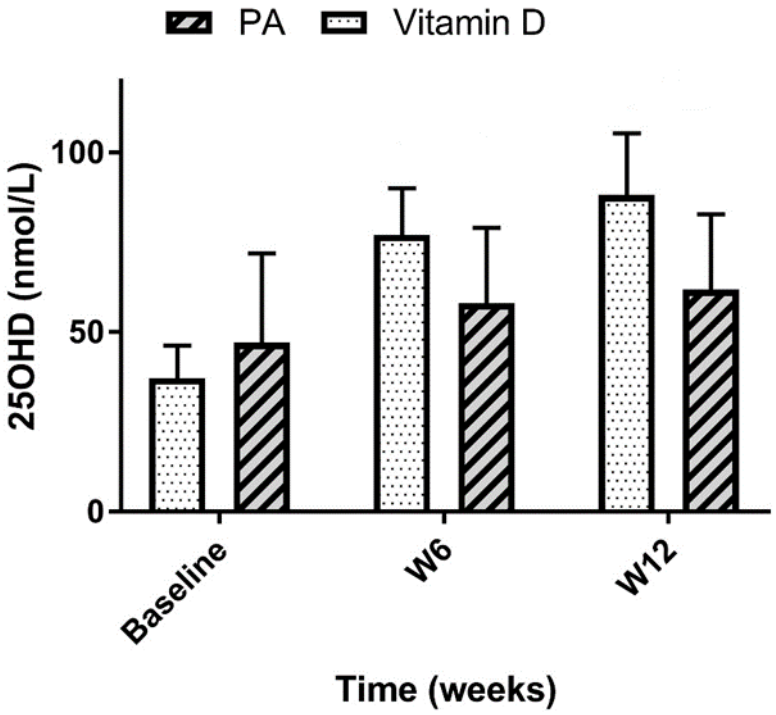


Figure 4.11: Mean (SD) 25(OH)D concentrations (y axis) by time point in the pilot intervention study (x axis) in the Vitamin D and PA intervention groups.

Vitamin D Status	Vitamin D Group		PA Group	
	Baseline	Week 12	Baseline	Week 12
Vitamin D deficient (<25nmol/L 25(OH)D)	N= 0 0%	N= 0 0%	N= 2 22.2%	N= 0 0%
Vitamin D Insufficient (26-50nmol/L 25(OH)D)	N= 9 100%	N= 0 0%	N= 4 44.4%	N= 2 22.2%
Vitamin D sufficient (>50nmol/L 25(OH)D)	N= 0 0%	N= 9 100%	N= 3 33.3%	N= 7 77.8%

Table 4.9: Change in Vitamin D status by intervention group

In the Vitamin D intervention group there was 100% change from Vitamin D insufficiency to Vitamin D sufficiency (see Table 4.9: Change in Vitamin D status by intervention group). In the PA group there was a 45% increase in Vitamin D sufficiency with 3/9 people moving from insufficiency to sufficiency and 2/9 people moving from deficiency to sufficiency (see Table 4.9).

4.3.3.3 Changes to objective PA

PA Measures	Vitamin D supplementation N=9			Online PA programme N=9		
	Baseline Mean (SD)	Week 12 Mean (SD)	Change in Measures` (95% CI)	Baseline Mean (SD)	Week 12 Mean (SD)	Change in Measures (95% CI)
% time in sedentary activity	62 (±10.9)	62 (±13.6)	-0.1 (-5.9, 5.6)	74 (± 6.1)	68 (±7.3)	-5.0 (-9.7, -0.2)
% time in light activity	34 (±9.5)	34 (±11.8)	0.1 (-5.9, 6.1)	24 (±6.0)	29 (±7.0)	4.7 (0.4, 9.1)
% time in moderate activity	3.9 (±3.16)	3.9 (±3.55)	0.0 (-1.1, 1.1)	1.4 (±0.65)	2.4 (±1.28)	1.0 (-0.1, 2.1)
Average daily time in sedentary activity (mins)	516 (±121.4)	507 (±139.2)	-8.8 (-91.1, 73.4)	647 (±179.8)	540 (±157.7)	-107.4 (-259.8, 45.0)
Average daily time in light activity (mins)	303 (±148.8)	270 (±86.1)	-33.1 (-130.7, 64.5)	209 (±55.8)	199 (±38.1)	-9.5 (-44.3, 25.2)
Average daily time in moderate activity (mins)	31 (±22.2)	33 (±30.9)	1.9 (-11.5, 15.2)	12 (±5.3)	16 (±7.7)	4.4 (-3.0, 11.8)

Table 4.10: Changes in PA measures from baseline to week 12 of pilot intervention.

Comparison of PA measures in the Vitamin D supplementation group (see Table 4.10) showed similar % time in sedentary, light and moderate intensity activity at baseline and week 12. Average daily time (mins) in sedentary and light activity decreased by 8.8 (95% CI: -91.1, 73.4) mins and 33.1 (95% CI: -130.7, 64.5) mins respectively. Average moderate activity increased by 1.9 mins (95% CI: -11.5, 15.2) from baseline to week 12 in the Vitamin D supplementation intervention group.

Comparison of PA measures at baseline and week 12 in the Online PA programme group showed a decrease in % time in sedentary activity of -5.0% (95% CI: -9.7, -0.2) and an increase in % time in light and moderate activity of 4.7% (95% CI: 0.4, 9.1) and 1.0% (95% CI: -0.1, 2.1) respectively (see Table 4.10). Average daily time (mins) in sedentary and light intensity activity decreased throughout the PA intervention by -107.4 (95% CI: -259.8, 45.0) and -9.5 (95% CI: -44.3, 25.2) respectively from baseline to week 12 measures (see Table 4.10).

At the end of the 3 month intervention, % time in sedentary activity was 6% higher in the online PA intervention group compared to the Vitamin D supplementation group.

% time in light activity and % time in moderate activity was 5% and 1.5% lower respectively in the Online PA intervention group compared to the Vitamin D supplementation group. These differences in the PA measures between intervention groups at 12 weeks may reflect differences in baseline PA measures between the intervention groups which showed significant differences between baseline % time in sedentary, light and moderate activity and average daily time in light and moderate activity (see Table 4.6). However the differences in physical activity between the two intervention groups reduced at week 12 compared to baseline, which considering the change observed in PA measures in the online PA intervention group, suggest an overall improvement in physical activity in the online PA intervention group.

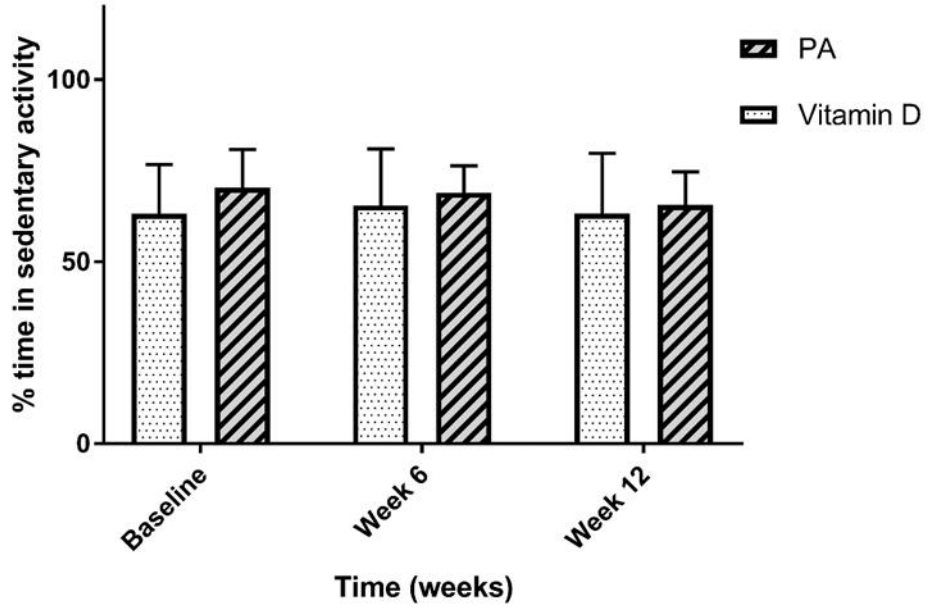


Figure 4.12: % time in sedentary intensity activity by pilot intervention study time point in Online PA and Vitamin D supplementation intervention groups.

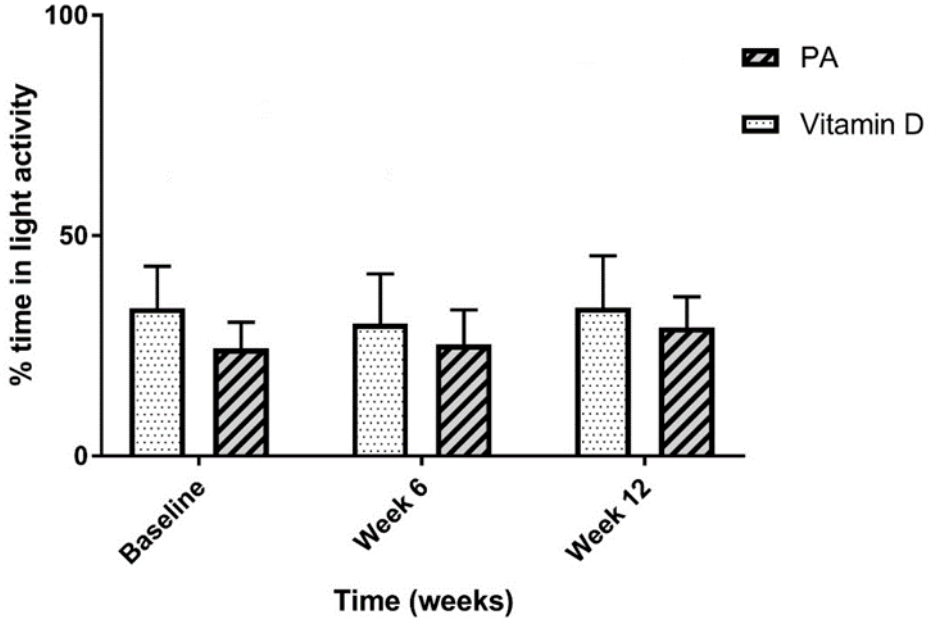


Figure 4.13: % time in light intensity activity by pilot intervention study time point in Online PA and Vitamin D supplementation intervention groups.

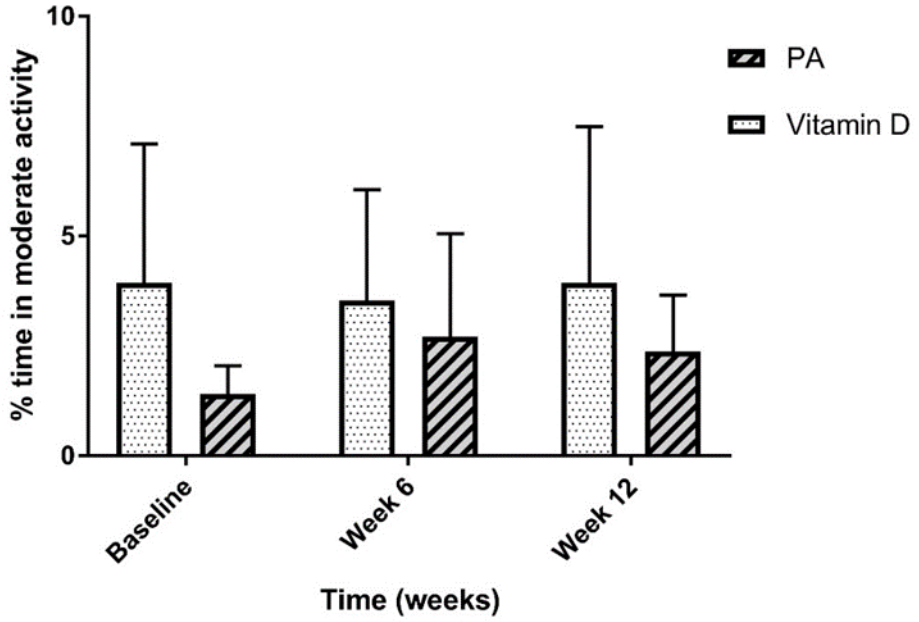


Figure 4.14: % time in moderate intensity activity by pilot intervention study time point in Online PA and Vitamin D supplementation intervention groups.

4.3.3.4 PA Measures by Online PA intervention compliance

Differences were observed between POW Compliers (participants who logged onto the POW website beyond the registration visit) and non-compliers (participants who did not log on to the POW website beyond the registration visit) in PA outcome change during the 3 month PA intervention (see Table 4.11). This analysis showed that POW compliers had substantially reduced their average sedentary time during the 3 month intervention by -169.71 (±215.3) min compared to POW non-compliers who increased their sedentary time during the intervention by 17.1 (±80.27). However interestingly POW non-compliers increased their moderate activity by 7.2mins more than the POW compliers, which may be an example of study participation effect (otherwise known as the Hawthorne effect in which awareness of being studied can impact behaviour [256]).

PA Measure	POW Compliers (n=5)	POW Non compliers (n=4)	Mean Difference
Change in % time in sedentary activity	-5.6 (±7.01)	-3.7 (±5.24)	1.9
Change in % time in light activity	4.9 (±6.18)	4.5 (±5.60)	-0.4
Change in % time in moderate activity	0.7 (±1.66)	1.5 (±0.89)	0.8
Change in Average daily time in sedentary activity (mins)	-169.71 (±215.3)	17.1 (±80.27)	186.81
Change in Average daily time in light activity (mins)	-3.7 (±27.43)	-21.3 (±77.42)	-17.6
Change in Average daily time in moderate activity (mins)	2.0 (±10.37)	9.2 (±7.28)	7.2

Table 4.11: Table summarising the change in PA measures during the PA intervention between POW compliers and non-compliers.

4.4 Discussion

This pilot intervention study was designed to test the feasibility and acceptability of two interventions, daily vitamin D supplementation and online PA programme interventions, in older obese adults with KOA. As part of this pilot intervention study we tested study arm allocation procedures, study retention and intervention compliance and effect. The results of this pilot study are discussed below according to study design and procedures, study compliance and intervention effect.

4.4.1 Study Design and Procedures

As part of the original design of this pilot study, eligible participants would be randomised to one of 4 study arms; daily vitamin D supplementation of 2000IU (50µg) D3, access to an online PA programme (POW), both or standard care, as part of a 2x2 factorial randomised control trial design. However due to the low numbers (six participants) of cross-sectional study participants eligible for inclusion into the random study arm allocation (requiring participants to meet the eligibility criteria for both the Vitamin D and Online PA intervention), the decision to unrandomise the study arm

allocation process was made. This decision meant 17 participants were deemed eligible to receive one of the study interventions and who were entered into the pilot intervention study. This allowed sufficient participant numbers to test the pilot intervention study aims of assessing the feasibility and acceptability of the pilot interventions.

Another consequence of the unrandomised study design was that we could not assess the effect of the vitamin D supplementation and online PA interventions in combination, as originally planned. Additionally because of the different eligibility criteria employed for each intervention group, there were differences in baseline measurements between groups, as demonstrated in Table 4.6. The PA intervention group had 12% higher sedentary time and 10% and 2.5% lower % light and moderate time at baseline compared to the Vitamin D intervention group. There was also a difference in baseline 25(OH)D concentrations between intervention modalities, with the Vitamin D supplementation group having 8.7nmol/L lower baseline 25 (OH)D concentrations than the Online PA intervention group.

However, as a pilot intervention study, it is important to highlight the feasibility of randomisation and study arm allocation procedures, and how many participants are required to screen in order to recruit sufficient participants into a RCT. Therefore, the information collected by this pilot study on the number of participants eligible for randomisation (6 [0.8%] of an original 791 originally identified potential participants) based on our eligibility criteria and recruitment rates (5.7%) will be important in informing recruitment targets for future RCTs using this study population and interventions. For example, if this data is extrapolated to the entire older obese KOA population of north east England (n= 1,203,453) according to data on prevalence published by ARUK[17]), we could expect approximately 9627 participant to be eligible for and participate in a randomised control trial of Vitamin D supplementation and Online PA programme interventions.

4.4.2 Study Compliance

4.4.2.1 Study Visit and Measurement Compliance

As discussed in section 4.3.1, study visit retention was 100% at each time point. As with the cross-sectional study, compliance to study measures was very high at each

time point of the pilot intervention study for anthropometric and questionnaire data. Compliance to blood samples was high for venous blood samples with only one blood sample missing at week 6 due to difficulty in accessing the participant's vein. Compliance with DBS blood samples was lower than venous samples, with one participant refusing to give DBS samples at all time points due to a dislike of needles, one participant refusing DBS samples at week 12 due to side effects (bruising and pain) and one DBS sample missing at baseline due to investigator error (no DBS kit available). However, despite the lower level of compliance with the DBS blood collection method compared to venous collection, there are many potential benefits to collecting blood samples by the DBS method. The DBS method is minimally invasive, is easy to conduct (not requiring specially trained medical staff), is easy to transport and store and are low in cost [257]. This makes DBS ideal for use in clinical trials and population based studies for screening and collecting baseline measurements [258]. The use of DBS has been validated for use in many biomarkers, including for the detection of 25(OH)D [259], which has been previously applied in a large multisite population based nutrition study, Food4Me [260].

Compliance to accelerometer use was analysed using wear time in minutes and as a % of the total 24hr day. Valid data was classed a day with >10hrs wear time [219]. Over our five day accelerometer monitoring period, we found 71%, 63% and 56% of pilot intervention study participants had valid data for all 5 days at baseline, week 6 and week 12 time points respectively. This was slightly lower than the compliance found in the NHANES (National Health and Nutritional Examination Survey) 2003-2004 dataset, with 74% of men and 68% women aged 40-59 years achieving 5 days valid data (classed as >10hours wear time/day) and 80% of men and 77% of women aged 60+ years achieving 5 days valid data [261].

4.4.2.2 Intervention Compliance

Compliance to the Vitamin D supplementation was measured using pill counting at 6 and 12 week study visits, which showed compliance was high in this pilot study at 99% over the 3 months intervention period. This is comparable with the 2013 RCT by McAlindon [147] which showed 96% adherence to vitamin D supplementation over 24 months.

Compliance to the Online PA intervention (defined as repeated use of the POW website beyond the initial registration visit) in the pilot intervention study was 66% (6/9 participants) over the 3 month intervention period. Similarly on the only currently available online PA intervention for older obese adults with KOA, the 'Join2Move' intervention, which concluded of the 100 participant assigned to the online 'Join2Move intervention', 94% started the programme and 46% adhered to the set adherence level (completion of 6/9 online 'modules')[262].

4.4.3 Intervention Effect

In this pilot study, we administered Vitamin D supplementation and Online PA interventions to an older obese KOA population and tracked subsequent changes in 25(OH)D concentrations and objective PA measures.

During the 3-month Vitamin D supplementation intervention, a mean increase of 51 ±23.1nmol/L (95% CI 33.2, 68.8) was observed in the Vitamin D supplementation group, from 38.3 (±9.1) at baseline to 88.1 (17.2) at week 12. Increases in 25OHD concentrations were higher in this pilot intervention study than those reported in another D3 supplementation study [263], which also supplemented deficient participants (defined as <50nmol/L 25(OH)D concentration, mean 25(OH)D 41.2nmol/L) to receive 2000IU (50µg) of cholecalciferol/day for 3 months, and found an increase of 34.1 nmol/L 25OHD. The disparity in 25OHD may be due to cutaneous Vitamin D synthesis as the supplementation regime ran into the 'summer months' (April-September) when exogenous synthesis of Vitamin D in the UK occurs [110]. However when mean 25OHD concentration change was analysed according to those who finished D3 supplementation before (46 [95%CI -195.4, 2.87.4]) and after (52.4 [30.1, 74.7) April 2016 there was little difference observed. 25(OH)D concentrations also increased by 14.9 ±41.1 (95% CI: -16.7, 46.5) (see Table 4.9) in the Online PA intervention group despite not being supplemented as part of the study and being instructed not to take supplement containing Vitamin D at home. It is therefore likely to be a result of cutaneous synthesis as this intervention also ran into the summer months. Seasonal variation in Vitamin D synthesis are summarised in the introduction chapter, however briefly a British cohort study showed average 25OHD varied by 20.8nmol/L in men and 17.4nmol/L in women between Winter/Spring (December-

May) and Summer/Autumn (June-November) [129]. As this pilot intervention took place January-June, it is likely this change in 25(OH)D in the Online PA intervention group reflects this previously reported season variation in 25(OH)D production between Spring and Summer.

No trends for change in self-reported KOA symptoms (assessed using WOMAC Questionnaire and VAS in this pilot intervention study) were observed in the Vitamin D supplementation group after 3 months (see Table 4.8). This is consistent with the results of more recently released published RCTs [146, 147] which supplemented symptomatic KOA participants with 24,000-50,000IU (600-1250µg) Vitamin D/per month for 2-3 years showed no significant improvements in KOA symptoms measured by the WOMAC Questionnaire. However one Vitamin D supplementation study [147] did see a statistically significant improvement in knee pain measured by Visual Analogue Scale (0-100) (p=0.48) in the Vitamin D supplemented group compared to the placebo group at 2 years. The benefit of this RCT was that, like this pilot intervention study, only those considered Vitamin D insufficient were included in the study, ensuring those supplemented would be those most likely to benefit from supplementation. Despite these similarities with this pilot intervention study, we were unable to replicate this previously improvement in knee pain VAS and we saw no trend for improvement in VAS (0-10) (change of 0.4 [95%CI -0.3, 1.2]) over 3 months of Vitamin D supplementation.

The Online PA intervention (POW) aimed to increase PA among older obese adults with KOA using a goal orientated lifestyle changes to increase PA. This was based previous work as part of the LEAP (Living, Eating, Activity and Planning in Retirement) intervention that formed part of the 'Livewell' project, developed at Newcastle University [182]. As part of the online PA intervention, various behaviour change techniques (BCT)[264], such as goal setting, action planning, barrier identification and problem solving, setting of graded tasks and self-monitoring of physical activity (using the pedometers provided), were delivered as an online programme. The evidence regarding which BCTs are most effective in promoting physical activity change are mixed. A systematic review [265] of BCTs in obese individuals with the aim of increasing PA concluded many BCTs when present as part of a physical activity intervention were associated with significantly higher PA. The strongest associations

were found in interventions incorporating teaching to use prompts and cues (where participants are taught environmental prompts/cues which remind them to perform a behaviour [264]), prompt practice (where the participant is prompted to repeat a behaviour [264]) and prompt rewards contingent on effort or progress towards behaviour (using praise/rewards for attempts at achieving behavioural goal [264]) [265]. However another systematic review [266] of BCTs in physical activity interventions observed only 3 BCTs which were significantly associated with higher PA when present in an intervention. These BCTs included barrier identification and problem solving, providing rewards contingent on successful behaviour and demonstrating the behaviour[266]. The effect of BCTs on physical activity was not specifically explored as an outcome of this pilot intervention study, however participants views on some of the BCT used in the intervention were discussed as part of the qualitative interview study (see chapter 6).

The effect of the Online PA intervention on objective PA measures was assessed as part of this pilot intervention study. Due to the variable nature of physical activity interventions, the ability of the intervention to change physical activity in the target population can be considered a measure of effectiveness and feasibility. During the 12 week intervention, the Online PA group experienced changes in % time in sedentary, light an moderate intensity PA of -5.0% (95% CI: -9.7, -0.2), +4.7% (95% CI: 0.4, 9.1) and +1.0% (95% CI: -0.1, 2.1) respectively. Comparatively the Vitamin D intervention groups experience minimal change in % time in sedentary, light an moderate intensity PA throughout the intervention at -0.1% (95% CI: -5.9, 5.6), +0.1% (95% CI: -5.9, 6.1) 0.0% (95% CI: -1.1, 1.1) respectively. This disparity in PA change between intervention modalities suggests the Online PA intervention was successful in promoting increased PA in the participants. In a published online based PA intervention study [262] in older obese individuals with KOA, objective PA levels (measured as mean total mins/day in PA light, moderate and vigorous intensity activity) were not significantly different between the PA intervention group and controls (361 [95% CI: 312-411] vs 358 [95% CI: 310-407] respectively) at 3 months. Indeed average mins/day in PA between baseline and 3 months (369 [95%CI: 299-439] vs 361 [95% CI: 312-411] respectively) decreased in this PA intervention group [262]. This suggests that compared to the only

other published Online based PA intervention for KOA patients, this pilot intervention was more effective in increasing PA in this population over 3 months.

Changes in self-reported KOA symptoms were observed from baseline to week 12 of the Online PA intervention. Changes in WOMAC pain (0-20) and activities of daily living (0-64) of -3.0 (95% CI: -5.2, -0.8) and -7.3 (95% CI: -13.7, -1.0) were seen respectively. Change in time taken to complete TUG (secs) also changed from baseline to week 12 of the Online PA intervention by -2.0 (95% CI: -3.0, -0.88). Overall, the existing research literature support the observation that increasing PA improves self-reported KOA pain and disability. A systematic review of four RCTs of aerobic walking exercise interventions on KOA symptoms showed weighted pooled effect sizes of 0.52 (95% CI: 0.34-0.70, n=449) for pain and 0.46 (95% CI: 0.25-0.67, N=385) for disability [103]. A RCT of exercise and dietary weight loss interventions of 316 obese adults >60 years with KOA showed there were also improvements in mean WOMAC Pain and Function over 18 months of −0.40 (95% CI: −1.32-0.52) and -3.07 (95% CI: 1.91-6.13) respectively within the exercise group, however these improvements were not as large as recorded in this pilot intervention study [157].

4.5 Conclusions

During this three month pilot intervention study, we aimed to assess the feasibility of delivering a Vitamin D supplementation and Online PA intervention to obese older people with symptomatic KOA. Secondary aims were to assesses the effect of the interventions delivered on anthropometric measures, self-reported KOA symptoms, serum 25(OH)D concentrations and objective PA measures. From this study, we have concluded:

- There were insufficient numbers (n=6) of participants eligible to participate in both of the pilot interventions. Therefore, only 6 participants were randomised according to the original RCT design. After un-randomisation, an additional 11 participants were recruited. This highlights the feasibility of randomisation and study arm allocation procedures, which will inform how many participants are required to screen in order to recruit sufficient participants into a RCT design trial. Extrapolation to the older obese KOA population of north east England (n= 1,203,453) according to data on prevalence published by ARUK[17]), estimates

9627 participants to be eligible for and participate in a randomised control trial of Vitamin D supplementation and Online PA programme interventions.

- Study retention was excellent in this study at 100% at week 6 and week 12. Compliance with study measurements was high (see Table 4.1). Assessing compliance with the accelerometry data was particularly important to ensure valid PA data (classed as >10hours wear/day) was used in our analysis. We found total days of valid PA wear reduced from baseline (71%, 14% and 14% achieved valid data for five, four and three days respectively) to week 12 (56%, 25%, and 13% of participants achieved five, four and three day valid data respectively) of the pilot intervention study.
- Compliance to the Vitamin D supplementation intervention showed high compliance in this pilot study at 99% over the 3 months intervention period, comparable with the vitamin D supplementation study by McAlindon [147] which showed 96% adherence to vitamin D supplementation over 24 months. Compliance to the Online PA intervention was 66% (6/9 participants) over the 3 month intervention period, higher than the 'Join2move' online PA intervention for older obese people with KOA [262], with 46% adhering to the studies set adherence level (completion of 6/9 online 'modules').
- Participation in the Vitamin D supplementation intervention led to substantial increases in serum 25(OH)D levels over 3 months of a mean 51 ±23.1nmol/L (95% CI 33.2, 68.8). Increases in 25(OH)D were also seen in the Online PA intervention group, however this change was not as large as the Vitamin D intervention group, at a mean 14.9 ±41.1 (95% CI: -16.7, 46.5). This was possibly a result of cutaneous Vitamin D synthesis as the study ran into the 'summer' months when Vitamin D production was possible in UK. No trends for change in self-reported KOA symptoms (assessed using WOMAC Questionnaire and VAS in this pilot intervention study) were observed in the Vitamin D supplementation group after 3 months (see Table 4.8). This is consistent with the results of more recently released published RCTs [146, 147] no significant improvements in KOA symptoms measured by the WOMAC Questionnaire.
- Changes in objective PA were seen in the Online PA intervention group from baseline to week 12 in % time in sedentary, light an moderate intensity PA of -5.0% (95% CI: -9.7, -0.2), +4.7% (95% CI: 0.4, 9.1). This change in objective PA

was not observed in the Vitamin D supplementation group with % time in sedentary, light an moderate intensity PA throughout the intervention at -0.1% (95% CI: -5.9, 5.6), +0.1% (95% CI: -5.9, 6.1) 0.0% (95% CI: -1.1, 1.1) respectively. This suggests the Online PA intervention was successful in promoting increased PA in the Online PA intervention participants. Changes in self-reported KOA symptoms were observed from baseline to week 12 of the Online PA intervention in WOMAC pain (0-20) (mean difference -3.0 [95% CI: -5.2, -0.8]) and activities of daily living (0-64) (mean difference -7.3 [95% CI: -13.7, -1.0]). This observation has also been observed in other clinical trials of PA interventions [103, 157].

Chapter 5. : Assessing acceptability and feasibility of study procedures and interventions: A Qualitative Interview study

5.1 Introduction

Chapter 1 presented the aims and objectives of the pilot study, i.e. to explore the issues around design, planning, recruitment, conduct and logistical management to potentially inform a future trial [194]. This can be achieved using quantitative and/or qualitative data collection techniques. The advantage of collecting qualitative data is that it can provide context and meaning and can raise unanticipated ideas or insights regarding the study and its participants [267].

A qualitative interview study was selected to explore participant views on the cross-sectional and pilot study presented earlier in the thesis (chapters 3 and 4). Detailed aims and objectives are summarised in section 5.2.

5.2 Aims and Objectives

The aim was to assess the acceptability and feasibility of several aspects of the cross-sectional and pilot studies, in particular:

1) Recruitment:
    a. Are GP surgeries an effective setting for recruitment
    b. What were people's reasons for participating in the study?
2) Study Measurements and Study Visits
    a. What were the participant's views on the organisation, timing and structure of study visits?
    b. What were the participant's views on the measurements taken during study visits?
3) Study materials
    a. What were the participants opinions on the information provided at the beginning of the study (i.e. the participant information sheet)
    b. What were the participant's opinions on the materials provided as part of the interventions?
4) Pilot Study Interventions:

a. Were the interventions usable and acceptable to participants?
b. Were there any issues with using the interventions?

5) Study Experience:
   a. What was the participant's experience of taking part in the study? In particular would they recommend any changes to study interventions or procedures?
   b. Were there any recommendations/changes the participants could offer regarding the study?
   c. How acceptable in general was participation in the study?

5.3 Methods

5.3.1 Ethical Considerations

A favourable ethical opinion was provided by London City and East Research Ethics Committee (REC)prior to commencement of the study (see Appendix A).Written informed consent to conduct and audio record interviews was obtained at the beginning of the study as part of the overall study consent procedure (see appendix F).The consolidated criteria for reporting qualitative research (COREQ) checklist was used to guide to the development and reporting of the qualitative research study [268].

Verbal consent for participation in qualitative interviews was obtained prior to the interviews taking place. Participants were informed that they had the right to withdraw from the interview at any point and that interview recordings would be transcribed verbatim and audio recordings would be deleted.

5.3.2 Study Design

Semi-structured, one to one, face to face interviews, lasting between 35-80 minutes were conducted with the aim of assessing the acceptability and feasibility of study procedures and interventions and providing recommendations for a future trial.

5.3.3 Study Participants

5.3.3.1 Inclusion Criteria

- All Pilot Intervention study participants were eligible to take part in an interview

5.3.3.2 Exclusion Criteria

- Participants who did not take part in the pilot intervention study
- Participants who refused to provide consent to take part in a qualitative interview
- Participants who refused to provide consent to having the interview audio recorded

5.3.3.3 Sampling Strategy

A purposive sample of those who participated in the pilot intervention study were invited to be interviewed. This sample could be split into two sub-samples according to the study interventions to which the participants were allocated (i.e. Vitamin D supplementation and Online PA programme).

5.3.4 Materials and Measures

Prior to the commencement of the qualitative study, a topic guide was developed with the advice from two health psychologists with expertise in health behaviour change (NO'B and LA). The topic guide comprised of a set of questions designed to assess acceptability and feasibility of study procedures and interventions and was used to guide each interview (see appendix Q). A qualitative interview protocol was developed which outlined and standardised all procedures for setting up and conducting qualitative interviews, ensuring essential equipment and procedures (e.g. consenting) were adhered to and that all interviews were consistent (see appendix R).

5.3.5 Study setting

The interviews took place within North Tyneside General Hospital.

5.3.6 Study Procedure

The interviews took place directly following the pilot intervention 12 week study visit and were all conducted by the author of this thesis (RB).

The interview adhered to the interview protocol (see appendix R). The topic guide and prompts were used to encourage and probe participant responses. At the end of the interview, the recording was stopped and the participant thanked for their involvement.

5.3.7 Methodological Quality

As part of the qualitative approach undertaken, issues affecting methodological quality were taken into consideration during the design, conduct and analysis of the qualitative interview study with the aim increasing the trustworthiness of the qualitative data.

We employed many methodological techniques to improve different quality concepts regarding the overall trustworthiness of the data, as described below.

5.3.7.1 Dependability and confirmability

In order to ensure this data was dependable (that methods of obtaining study findings are clear [269]) and confirmable (that the findings of the study a representative of the study aims and topic rather than the researchers beliefs [269]), we ensured the following:

Clear audit trails were maintained throughout this qualitative study. Rationale for study aims, design, participant sample, data collection and analysis are clearly detailed as part of this thesis.

Data was analysed and coded by the primary researcher (RB), with a subsection of interviews (n=4) also analysed and coded by a second researcher (LA). After each of the first four interview transcripts were analysed and coded, RB and LA met to compare and discuss the resulting themes (defined as prevalent ideas or concepts expressed by participants and identified from the transcripts), with any discrepancies resolved through discussion (triangulation [269]).

5.3.7.2 Credibility

To ensure the themes derived from the data were reflective of the participants opinions and experiences, direct quotes from participants on which themes and subthemes have been based have been presented in Appendix S. The relevant direct quotes are used as supporting evidence for the interpretation of themes and subthemes throughout the results section of this chapter.

Another aspect of the study, which may have increased the credibility of the data collected, was the participant's relationship with the interviewer. As RB had conducted all study visits (3 face-to-face visits before the qualitative interview was conducted) and was the primary contact for participants therefore familiarity and rapport with participants was established before the interview. This important as it has been recognised it may help participants to relax, leading to a more productive interview [270].

5.3.7.3 Transferability

In order to ensure this qualitative data is transferable (to other studies and contexts) details of the characteristics of the study population are reported in the results of this chapter. The context of the subject matter of this interview (involvement in the cross-sectional and pilot intervention studies) are described in detail in chapter 3 and 4.

Another aspect worthy of note when considering context is the environment in which the interviews were conducted. Interviews were conducted in a clinical room (Jubilee Day Hospital, NTGH), following the participants final study visit. This was done primarily to reduce participant burden (i.e to keep number of visits to a minimum that would hopefully maximise recruitment to the study). As the interview took place in the same room and environment participants had completed their previous study visits, it was a familiar environment which may have been helpful when discussing procedures which had occurred previously (i.e. recall). However, as a clinical environment, this may have influenced the participant's responses to what they believed appropriate to that environment.

It has been recognised that many of the researcher's personal characteristics (e.g. background, experience and training, and preconceptions) can have an effect on the

research process, and that these characteristics should be acknowledged (reflexivity) [271].

5.3.8 Data Processing and Analysis

5.3.8.1 Data Processing

All interviews were audio recorded and transferred to a Newcastle University password protected computer. All recordings were transcribed verbatim into word documents by an approved external transcription service (Type it Write).

All transcripts were checked against the audio recordings and any errors or gaps in transcription were corrected. Transcripts were stored in electronic form in files on a Newcastle University password protected computer, identifiable only by participant ID.

5.3.8.2 Data Analysis

All data were analysed by the author of this thesis [RB] and 25% (4/16 transcripts) analysed by LA. Transcripts were analysed using a structured thematic analysis. [269] Briefly, the main themes were determined based on the responses of participants to a standardised topic guide asking questions in relation to recruitment, study materials, study visits, pilot interventions and study experience.

A random selection of four transcripts were selected initially and independently coded by RB and LA. Opinion on preliminary themes identified were discussed until agreement was reached. This process allowed early themes to be reviewed and agreed before the remaining transcripts were analysed by RB.

Remaining data from the interview transcripts were coded into these themes and themes were redefined/revised where appropriate. In some instances, it was appropriate to generate sub-themes[272]. Themes and sub themes were summarized in table form along with supporting quotes (with appropriate participant ID) from transcripts. A narrative description of the themes and subthemes were then discussed as part of the results section of this chapter.

5.4 Results

5.4.1 Participants

17 participants who took part in the pilot intervention study, and of these 16 (nine men and seven women) provided informed written consent to take part in an audio recorded qualitative interview. One participant refused to participate due to lack of available time. Of those participating, eight took part in the online PA intervention and eight took part in the Vitamin D supplementation intervention. Of those who took part in the Vitamin D intervention, four were female and four were male, with a median age of 62 years (range: 51-68 years), median BMI of 31.5 (range: 29-41) and median WOMAC Pain (0-20) of 7.8 (range: 1-12) at baseline and 7.8 (range: 2-16) at week 12. Of those who took part in the Physical activity intervention, three were female and five were male, with a median age of 63 years (range: 52-69), median BMI of 34 (range: 30-41) and median WOMAC Pain (0-20) of 7.9 (range: 3-12) at baseline and 5.4 at week 12 (range: 0-11).

5.4.2 Qualitative Interview Findings

The qualitative interview data were analysed according to each of the main study aims (see section 5.2) relating to study recruitment, study visits and procedures, study materials, pilot interventions and overall study experience. The results, including themes and sub-themes are summarised below. Since responses given by males and females were similar, they are presented together. A table summarising all of the themes and subthemes identified can be found in Appendix S.

5.4.3 Theme 1: Study Recruitment

5.4.3.1 Sub theme 1.1: Motivations to recruitment

Two main motivations for participation in the study were identified, both regarding improving health. The first motivation regarded personal benefit, primarily the hope that participation in the study would improve their KOA and the willingness to try anything to improve their health condition and symptoms.

> "I thought I would try anything. If anything works, I will try it. I know it's just a test at the minute [the study interventions], but…Only to get rid of the pain. (*Participant 033, Male, Vitamin D Intervention*)

A subset of participants also hoped the study may aid them in increasing their activity levels and to lose weight

> "I was hoping my weight would go down." (*Participant 004, female, Online PA Intervention*)

The second main motivation for participation was the desire to help other individuals with KOA by contributing to medical research. The hope was that in the future the information gained from this study would be used to treat and improve KOA.

> "I thought, well, what the hell, because, if I'm not mistaken, on the first letter [participant information sheet] it said it [study] will be for future references, for people that have got arthritis, and it may be beneficial, the findings, to help somebody else, so I thought why not (participate in study)." (*Participant 032, male, Online PA intervention*)

Interestingly, for those who did not comply with the PA intervention, the main motivations for participations seemed to be altruism (help other in the future by contributing to research) and 'disproving the research team' in reaction to being labelled 'obese', which the participant found personally offensive.

> "Yes, because, relating back to the first one, [cross-section study] on the letter, in my words to my wife, "I'll bloody show her who's obese', and that's what I've been trying to do, I've been trying too...you were the cause of it. So I did take part in the second one [pilot intervention study], and I was determined to lose some weight, and I feel better for it. (*Participant 032, male, Online PA intervention*)

Compliers to the PA intervention were more likely to be motivated to part for personal benefit, with no non-compliers stating this as a motivator for participation.

5.4.3.2 Subtheme 1.2: Barriers to recruitment

In addition to identified facilitators, several potential barriers to study recruitment emerged. The use of specific terms within the study information provided and used to screen for eligibility were sometimes viewed negatively by participants such as the use of terms relating to age, particularly 'older', and the use of the term 'obese' which were viewed as potentially offensive. For some participants, being identified as obese was also surprising and unexpected and one participant particularly expressed they would have preferred to have discussed their weight with the GP before recruitment to the study:

> Well a bit cross that somebody had the nerve to call me obese, that was the first thing…I think if one had been prepared, if the GP had talked it through and said, 'You know you're a little bit overweight and they are looking for people who might join this thing [study]. (*Participant 026, female, Vitamin D intervention*)

One participant, a non-complier to the online component of the PA intervention, explained that their family had discouraged their involvement in the study due to a distrust of medical research and concern that it may be harmful. Although this did not prevent the individual taking part it does highlight the perception of some members of the public that medical research is unregulated and potentially harmful.

> I was advised by my daughter and son in law not to take part in it [study], because I think the word was, 'don't let them get their claws in you, or you might not come out alive', you know…it's common knowledge that, sometimes, doctors get their hands on you, and they start feeding you all kinds of things, and you end up a zombie." (*Participant 032, male, Online PA intervention*)

5.4.3.3 Subtheme 1.3: Facilitators to recruitment

Various facilitators, which mediated motivation to participate or retention in the studies, were identified. The main facilitator to recruitment was the involvement of GP surgeries. The majority of participants (including compliers and non-compliers to the interventions) expressed that they felt recruitment from the GP surgery was a good method of recruitment. Recruitment through GP surgeries was also viewed as a form of 'endorsement' from a professional medical body. This was important for facilitating participation into the study as this 'endorsement' seemed to reassure participants that the study was safe and legitimate:

> "I felt it [the study] was important because the GP was behind it, it was authentic, it had the authority. It was women my age who had these problems [knee osteoarthritis], and because the doctor's names and surgeries was on it, that gave it a good okay." (*Participant 022, female, Online PA intervention*)

Alternatively, it was felt by two participants that recruiting from GP surgeries by screening patient records, that they had been nominated for the study without their permission to be referred or recommended to the university study team.

> "The doctor hadn't asked my permission or done anything in that nature about the referral [for study recruitment]. She'd [GP] just done it. (*Participant 026, female, Vitamin D Intervention*)

It was suggested that discussions with GPs about the patient's willingness to be recommended for participation in research studies may be preferable regarding recruitment from GP surgeries.

> "I think possibly if the GP had have mentioned it [research study] beforehand rather than a letter coming, you know, if I had been at the GP or something like that and he'd [GP] said, 'how do you feel about taking part in these things [research studies]'" (*Participant 007, male, both interventions*)

As well as identifying motivators to participation in the study, several other facilitators (factors aided study recruitment and retention) emerged. These included personal interest in the study topic, the hope that study results will inform primary care practice (i.e. to improve care provision) and study appointment flexibility. Provision of transport was an important facilitator for study participation in non-compliers to the online PA intervention who saw arranging travel to the study site as a barrier to their participation.

> "…I didn't think I would be accepted [recruited to the study] because I didn't drive, and I was worried about getting to this place, and you explained that you would provide transport, and I was relaxed after that, because my major…I didn't want the worry of trying to jump on two buses to get here, getting home, and as soon as you said transport, I thought, well, there's no problem." (*Participant 032, male, Online PA intervention*)

One participant's views deviated from that of the majority and it was likely due to having been a medical researcher. They highlighted their previous career had increased the likelihood of them taking part in the study because they felt that they could not reasonably decline participation as they were aware of the importance of participants.

> "how could I possibly disagree (taking part in the study) having had a career that is related to medical research myself? I wouldn't dream of standing in anybody's way if there was any way that I could help out by being a participant although (*Participant 026, female, Vitamin D intervention*)"

5.4.4 Theme 2: Study Visits and Measures

5.4.4.1 Sub theme 2.1: Study Setting

The use of the hospital as a setting for the study was discussed with mixed opinions. It was generally agreed that the hospital was an appropriate setting for the study. For some attending a hospital for a research study was reassuring and gave the study credibility and for others it evoked anxiety over what the visit may involve.

> "At first you think 'hospital' what are they going to do, but once you've been here, and you've been through the first session, there wasn't a problem with it." (*Participant 032, male, Online PA intervention*)

It emerged that the participant who expressed anxiety over the study setting was also the participant whose family members expressed distrust of medical research and a non-complier to the online PA intervention.

Accessibility to the hospital was discussed and opinions were mixed. A reoccurring theme was issues with parking (i.e. lack of parking space) and in particular parking charges. This led to some participants parking outside of the hospital grounds or seeking alternative travel arrangements.

> Sometimes I brought the car down and parked in the local housing estate because I refuse point blank to pay parking in a hospital, even if you were going to pay it back, which I haven't asked you to do with any of it." (*Participant 026, female, Vitamin D Intervention*)

Most participants preferred to travel to their study appointment by car. Problems with using public transport were identified by one participant.

> I don't live on a METRO route, and I've got quite a walk to get to a bus which, because of the condition I've got, and getting on and off [the bus]…fair enough, one of the buses that lower down, they're alright, but using public transport is a problem for me because, even having to stand up, in preparation to get off, the bus is moving, and my knees aren't steady enough. I just very, very rarely use public transport" (*Participant 029, female, Online PA intervention*)

5.4.4.2 Sub theme 2.2: Wearing the accelerometer

Wearing an accelerometer or activity monitor presented as a challenge for some participants who reported that they found wearing the device (worn on an elasticated

belt) irritating, noting the belt seemed to move around and the elastic belt as uncomfortable to wear.

> It kept slipping up and down, I don't know why. Then I couldn't sometimes tell whether I was putting it in the right place. I just found it just irritating. That's the only bit I didn't really enjoy." (*Participant 003, female, Vitamin D intervention*)

Alternately, some participants reported noted after wearing the activity monitor that they did not realise it was there. Some concern also revolved around the concept of being monitored. These concerns primarily regarded being perceived as lazy when participants were not being active and embarrassment over the monitor recording personal activities such going to the toilet, which seemed to stem from a misunderstanding of what the activity monitor was able to record.

> "It's embarrassing actually if you're on the loo and so on, you think they might know what you're doing…It's probably handy for you to know that I can get on and off the loo or not but it's a bit embarrassing. It's like having someone watching you." (*Participant 026, female, Vitamin D intervention*)

5.4.4.3 Sub theme 2.3: Completing the consent form

Views on the measurements taken during the study visits was discussed. One study procedure which generated a range of opinions was completion of the consent form at the start of study visit 1. Many participants reported preferring to complete the consent form with the researcher because this provided them with an opportunity to ask questions face to face.

> "No I think it was easier doing it [consent form] here [study appointment], because if you're unsure about some of the questions, you'd [researcher] be able to help us answer them, whereas if you're at home on your own, you're on your own, unsure." (*Participant 037, male, Vitamin D intervention*)

However, there was some confusion amongst participants as to why the consent form was required. Most participants correctly assumed that consenting was a necessary part of the research study process. Some participants viewed completion of the consent form as confirmation of the participants understanding and to outline what was to happen in order to prevent any abuses of power by the study team. Alternatively, anxiety was expressed by one individual about the need to complete a

consent form which seem to suggest to them that the study would involve invasive or unpleasant procedures. However, following consent and once the study visit was completed the same individual expressed confusion over why consent was required for the measurements taken.

> "…bit it's funny, when you start talking about consent forms, then what the wife was saying, and what the daughter was saying, 'hold on, are they going to take your leg off you', you know what I mean? Consent you know, it's in the back of your mind, 'hold on, I'm signing a consent form, why?'. Once it was all explained, it was no problem…Well, I mean, for what treatment I've had, I don't know why we had a consent form. I mean, basically, I'd already been doing it, taking a weight, height and a little bit of blood, and monitoring my activities, but I don't know what the law is." (*Participant 032, male, Online PA intervention*)

This particular participant seem to express anxiety and distrust of medical research and seemed wary regarding the concept of medical research. However this did not deter his participation within the study although he did not comply with the online PA intervention.

5.4.4.4 Sub theme 2.4: Questionnaire completion

Several problems with the completion of questionnaires were identified by participants including concern over unintentional variation in their answers to questions between study visits which are not due to any perceived variation in their condition or wellbeing. For example, one participant described what they perceive to be a 'mild' symptom may change between study visits depending on external factors such as sleep or mood.

> "I'm never terribly sure because we never keep a record, whether mine are consistent answers or not from one period to the next. That slightly worries me because in my head I might be using a different understanding of mild each time I come in, slightly depending on my mood or slightly depending on whether I had a good night's sleep or something like that." (*Participant 026, female, Vitamin D Intervention*)

Other issues emerged regarding confusion over the wording of questions in the questionnaires. They were described as ambiguous or and sometimes difficult to

understand, e.g. it was felt some questions were phrased as double negatives and therefore the true meaning of the question was difficult to decipher.

> "Yes, there were two questions when I did it [questionnaires] today…but they were almost like double negatives, I thought, "I don't know if I'm reading this properly or not."(*Participant 038, female, Vitamin D intervention*)

A further issue that emerged was the dislike of admitting perceived personal limitations and accepting there are activities oneself cannot do anymore.

> "No, the only bad point is me; I don't like accepting what I can and can't do, so I sometimes think, well, it's really that but I'm going to say this, but that's my problem. Even after all these years, I still don't like saying, 'I can't do'…"(*Participant 029, female, Online PA intervention*)

However, having the researcher present during completion of the questionnaires was reported to encourage participants to answer more honestly.

> Yes, and discuss [the questions], and then you're sitting there thinking, 'I want to say I'm that good, but I'm really not that good', so I think, for me personally, it helped me be more honest, with which one [answer] to tick." (*Participant 029, female, Online PA intervention*)

5.4.4.5 Sub theme 2.5: Taking blood Samples

Giving venous blood samples was reported as acceptable by all participants and most were familiar with the process of having blood taken due to previous experience in donating blood or having blood taken in other contexts.

> "I am a blood donor any way so it wasn't a problem. (*Participant 033, male, Vitamin D intervention*)"

5.4.4.6 Sub theme 2.6: External factors on study measurement performance

Participants also highlighted the importance of external factors affecting physical activities which may not be taken into account by the activity monitors such as other health conditions, e.g. arthritis at other sites, which restricted movement or illness.

> The last time [participant wore the activity monitor] I wasn't very well so I was in bed so I didn't probably use it [activity monitor] as

much as I could have done but I was ill in bed at the time." (*Participant 003, female, Vitamin D intervention*)

The impact of movement restrictions due to other medical problems including pain and arthritis at other anatomical sites and time of day was also highlighted concerning performance during the timed up and go function test performed during the study visit. This highlighted the need to record and consider such contextual factors when carrying out this test.

" That was fine [time up and go test], except I think, the last one I came to, when my back was still a problem, and I couldn't…I think I only managed one walk." (*Participant 029, female, Online PA intervention*)

5.4.4.7 Sub theme 2.7: Uncertainty over what was being measured

There was some isolated instances of uncertainty over exactly what a measurement was measuring and why it was being measured. One participant was unclear as to why some measurements (e.g. height and waist circumference) was repeated and taken three times.

"Basically, you took my height three times, you took my waist measurement three times. Well, either you're very insecure, or is that because of the study, you've got to do it three times? I mean, I'm not going to get any smaller… (*Participant 032, male, Online PA intervention*)"

One other participant described a misunderstanding of what the accelerometer was able to measure, thinking that it was able to record activities such as going to the toilet, which they found embarrassing.

"It's embarrassing actually if you're on the loo and so on, you think they might know what I'm doing. It's a bit of an embarrassment, especially for older ladies I would say, yes. I took it off for showers and baths and things. I might have been tempted to take it off for other things but I didn't. It's probably handy for you to know that I can get on and off the loo or not but it's a bit embarrassing. It's like having someone watching you." (*Participant 026, female, Vitamin D intervention*)

5.4.4.8 Sub theme 2.8: Embarrassment over terminology used during study visits

There was some embarrassment over terminology used during the study visits, particularly terms relating weight such as 'obese'. One participants highlighted their relief that the subject of their weight was not discussed explicitly during the study visit.

> "I'm pleased you didn't say that I was overweight because normally they do. That was a plus, that you didn't make any comment at all actually. I don't need to be told I need to lose weight because I know that." (*Participant 003, female, Vitamin D intervention*)

5.4.4.9 Sub theme 2.9: Study Visit length

Most people felt that the duration of the study visits was acceptable and as they expected.

> "You have certain things that you want to do as part of your study then I don't think it's probably unreasonable. It's normally about an hour, I think, isn't it, so that's not a huge amount of time out of my day." (*Participant 043, male, Online PA intervention*)

However, one participant highlighted they found the study visits were more time consuming than they anticipated. They also expressed the idea that just because they were retired, that did not mean they had a lot of free time to be called upon to attend study visits.

> "Just because we're retired, we're not sitting around waiting to be called into the hospital and entertained for a whole morning. We have plenty of other things to do, like everybody does. So it was probably more time consuming, these little sessions than I thought from the outset. (*Participant 026, female, Vitamin D intervention*)

5.4.4.10 Sub theme 2.10: Concern over investigator qualification

One participant expressed concern about a student researcher taking blood samples, feeling it would be more appropriate for medically trained professional, such as a nurse, to carry out what was viewed as a medical procedure.

> I would have expected a trained medical worker to do those [take blood samples], a nurse. You tell me you've done a course to enable you to do that and I take that at face value…I would have probably stayed with the nurse doing it throughout." (*Participant 026, female, Vitamin D intervention*)

5.4.5 Theme 3: Study Materials

5.4.5.1 Sub theme 3.1: Acceptability of patient information sheet

When asked about the materials mailed to participants regarding recruitment to the study (study invitation pack containing invitation letter from GP surgery, patient information sheet and consent form) most felt that the information was easy to understand, straightforward and helpful. However, as discussed earlier in the context of study recruitment, there were objections to some of the terminology used in the patient information sheet, particularly terms relating to weight ('obese') and age ('older'), which were viewed by some as offensive and carried a stigma.

> " I read it [patient information sheet], but that was good; if that word hadn't have been on…'overweight', I would have said…but 'obese' has got that tinge to it, that meaning…it just hits you where it hurts." (*Participant 032, male, Online PA intervention*)

> "So I didn't know what to be more offended by, being called older or being called obese [laughter]…It's the fact that when you see it just written like that, it's quite stark, isn't it?" (*Participant 038, female, Vitamin D intervention*)

Some participants expressed shock at being labelled as obese or older as they had not previously considered themselves to be either.

> …And actually, I mean I just don't consider myself an older person but maybe I am you know…" (Participant 038, female, Online PA intervention)

> "Well, being selected on that criteria. I've never thought of myself as being obese…but it just came out of the blue, the letter." (*Participant 007, male, Online PA intervention*)

5.4.5.2 Sub theme: Provision of appointment letters

One participants mentioned the advantages of being provided with appointment letter for remembering the appointment date and time and in being provided with evidence to present to their employer so they could leave work early to attend a study visit.

> "So a letter is good for me because I can show my boss and I'm not just, you know, having a sneaky early finish. So the letter is useful for me to show him, rather than just tell him. So that was fine. Plus, I think, if you've got something tangible, you know, you can put in your handbag and you remember. Whereas, if you've just had a

phone call, you write it in your diary or you stick it on a calendar or something like that, but you could forget." (*Participant 004, female, Online PA intervention*)

5.4.5.3 Sub theme 3.3: Participant feedback

There was great interest in study feedback amongst participants, with a number of reasons for this emerging. Participants felt generally that in receiving feedback on their results from the measures taken during the study visit, they were 'getting something back' from participating and that research studies should be a two way process, with information benefiting both the research team and participant.

> Really important [feedback], I think. As I say, it's a two way process I believe, so I'm happy to participate and it's always very interesting to see what the results have actually brought up." (*Participant 043, male, Online PA intervention*)

Participants were also interested in receiving individual feedback in order to inform them on their current health status with a view to improving their condition and overall health. Particular emphasis was placed on the role of feedback in not only providing results from the study visits but in providing advice on how to 'improve' their results in the future.

> " But as long as it's a coherent set of information with some possible pointers and what one might do to continue to manage the condition." (*Participant 022, female, Online PA programme*)

> "…[feedback] telling me how much exercise I did or didn't do. Well I could have told them that. That was foolish. I mean that's a piece of information. More to the point, it's how can you do some more or whatever you can do. (*Participant 026, female, Vitamin D intervention*)

It was suggested that the feedback from the study could also be potentially feedback to and inform primary care (GP surgeries), with the aim of improving the participants future health.

> "Obviously any diet warnings, if you picked something really foul up you would have obviously contacted the GP and put matters in hand to do something about it. So it's a good thing"(*Participant 026, female, Vitamin D intervention*)

There was also interest in feedback of the results from the study as a whole, particularly regarding comparing different intervention groups (Vitamin D supplementation and Physical Activity groups) to establish whether there were any differences in outcomes at the end of the study according to intervention group.

> "…people who've had the placebo, people who've had the Vitamin D and then the people who've had the activity programme, I think it will be interesting to see how to results differ, if at all." (*Participant 004, female, Online PA intervention*)

5.4.5.4 Sub theme 3.4: Intervention study pack and instructions

Materials provided as part of the pilot interventions were also discussed with participants. It was felt that the pilot intervention starter pack (containing the pilot intervention study invitation letter, study intervention manual and study materials) was generally clear and easy to understand. This promoted an understanding and confidence in conducting the interventions and using the intervention materials provided.

> "I thought they were quite good [study intervention manual]. They were concise and I knew what I was doing" (*Participant 003, female, Vitamin D intervention*)

> "That was really useful to read through all of that (study intervention instructions). I found the whole thing really helpful. I had my pedometer and I read that, knew how to work that. So that was fine. I was raring to go really."(*Participant 004, female, Online PA intervention*)

The mode of delivery of the pilot intervention starter pack (posted to the participant's home address at the start of the pilot intervention study) also seemed preferable to collecting the pack in person

> "Yes, obviously it's a cheaper way for me [to have pack posted] because I don't have to come down [to collect the pack]. (*Participant 033, male, Vitamin D intervention*)

5.4.5.5 Sub theme 3.5: Use of the pill cases

Intervention specific materials delivered as part of the study intervention starter pack were also discussed. As part of the Vitamin D supplementation intervention, six-week supply pill cases containing the vitamin D supplements were provided to participants.

With the exception of one participant who reported difficulty in opening and closing the pill cases, all participants found the pill cases easy to use.

> "…the whole thing has been a disaster as far as my thumb nails have been concerned. That's why I don't want those things [pill boxes] back. They're the most…if you honestly think that people with any degree of arthritis in their hands could possibly manage those, they can't. It was awful." (*Participant 026, female, Vitamin D intervention*)

In addition to being generally easy to use, the use of pill cases in delivering Vitamin D supplements was reported to facilitate compliance to the intervention by reminding participants if they had taken their supplements every day (i.e. it worked as a behavioural prompt).

> "Like I said, if you didn't know whether you had taken a tablet, you would know as soon as you opened the box. I mean I didn't miss one." (*Participant 033, male, Vitamin D intervention*)

5.4.5.6 Sub theme 3.6: Pedometer as an incentive to increase PA

As part of the physical activity intervention, a pedometer was provided to enable participants to track and monitor their daily steps if desired. All participants in the online PA intervention used the pedometers provided to monitor their activity. It was reported to work as an incentive to motivate people to monitor and increase their activity when using the POW website.

> …I thought they [pedometer] were a tool, and it was an incentive for me to have around." (*Participant 032, male, Online PA intervention*)

> No I think the pedometer is the key thing. It's a daily thing that I check up on. That's really important." (*Participant 022, female, Online PA intervention*)

Interestingly, the participants who reported that the pedometer was effective as an incentive to increase their PA were mostly non-compliers to the online component of the PA intervention.

5.4.6 Theme 4: Pilot Intervention

Themes emerging with regards to the acceptability of the pilot intervention study related to the acceptability of study procedures and the interventions themselves including specific issues.

5.4.6.1 Sub theme 4.1: Study arm allocation

Themes regarding the acceptability of study procedures such as study arm allocation and study retention was discussed. Views on study arm allocation varied with some participants expressing a preference for participation in a particular study arm, specifically for either of the intervention arms. However, participants did not suggest they would withdraw from the study if they were allocated to a study arm which was not preferred by themselves. The study arm allocation procedure was unclear to one particular participant.

> "Well, I'm not sure why, or how, you selected who does what **[which study arm participant is allocated to];** you must have your reasons, but I just took it as this is the way you wanted it, that I would be taking part in this." (*Participant 032, male, Online PA intervention*)

One participant who had taken part in the Vitamin D intervention expressed their preference for this study arm because it was perceived as being 'easier' in terms of fitting into everyday life when compared to the PA intervention.

> "As I say, it's easy to take. If you have got to do some sort of exercise before you go to bed and you are tired you just say, 'I will miss it tonight', whereas with a tablet you just take it and because I was taking the statin as well, it made sure that I was taking that regularly…It was easier taking them than doing an activity one because, you know, I can't be bothered." (*Participant 033, male, Vitamin D intervention*)

However overall the majority of participants expressed a preference for participation in the online PA intervention. This was due to them seeing it as motivation to start increasing their activity levels or as giving them a feeling they were 'doing something' or achieving something as part of participating in the study.

> "I was hoping I would be in one of the groups that did more of the exercise than just take the pills…Yes I thought it might give me a kick

start in doing something" (*Participant 003, female, Vitamin D intervention*)

"Well I suppose you just would feel you were not doing anything differently, whereas if you were in one of the others, provided with an exercise programme or…so you were just doing something differently I suppose." (*Participant 038, female, Vitamin D intervention*)

One participant also expressed relief at not being allocated to a placebo or standard care group, claiming they would have been disappointed to be allocated to this group. However, they did not suggest they would withdraw from the study if they were allocated to the placebo/standard care arm.

"Because one of them [study arm] was no intervention, wasn't it? Yes I'd have been a bit disappointed if I'd been given…you know, so I was glad to get…" (*Participant 038, female, Vitamin D intervention*)

5.4.6.2 Sub theme 4.2: Study retention

Participants identified a variety of different facilitators to retention within the three-month pilot intervention study. These included the desire that something beneficial may result from the intervention, which may benefit other, interest in the study, not wanting to disappoint the researcher and the need to finish the study and see it through to the end.

All I have given up here is my time, you know, everything else is…something good might come out of it and like I say if not for myself then it might for somebody else. (*Participant 033, male, Vitamin D intervention*)

Well I was quite happy to do that because I've got the time and I was just quite interested really (*Participant 038, female, Vitamin D intervention*)

I saw it through. I didn't like taking the tablets. I knew they weren't having a beneficial effect on me, but I saw it through. (*Participant 045, male, Vitamin D intervention)*

One participant identified the pain they experienced during the study as a barrier to study retention, as they perceived the pain as a result of the Vitamin D supplements they were taking as part of the Vitamin D intervention.

If I had, I would have...the agony I was in, it didn't seem to be improving. That was the real reason why I nearly gave up. I didn't think they were doing any good at all[Vitamin D supplements].
(*Participant 026, female, Vitamin D intervention)*

5.4.6.3 Sub theme 4.3: Facilitators to intervention success

A number of facilitators to participants remaining in the study were reported. Facilitators to study retention varied between individuals, including a need to finish what they had started (regarding the study), the feeling of contributing towards something potentially beneficial for others, personal interest in the study topic and not wanting to disappoint the research team. Interestingly, many of these facilitators to remaining in the study were similar to the motivations identified for entering the study initially (see section 5.4.3.1).

"I didn't want to disappoint you. I knew you'd be heartbroken so I thought I'll keep taking them [Vitamin D supplements] to the end"
(*Participant 045, male, Vitamin D intervention*)

The majority of study facilitators related to participation in the physical activity intervention with social support heavily influencing adherence (e.g., having someone else there to encourage you to carry on with the intervention, such as a spouse).

"If it's just you, you'll think, oh I'll not bother going [to exercise], but if somebody else wants to go with you, or comes to pick you up or jollies you along a little bit, I think it's easier to do it with someone."
(*Participant 004, female, Online PA intervention*)

Pets also played a role with encouraging adherence to the physical activity intervention by encouraging regular walking (e.g. a dog walking).

"Oh like I say, my daily activities more or less revolve around my dog." (*Participant 041, male, Online PA intervention*)

In addition, anticipated regret played a role in facilitating adherence to the physical activity intervention. Some participants reported guilt or fear of 'not doing enough' or not complying with the intervention as a reason for continuing compliance.

"…gave me a big push to get going and then I would be so guilt ridden if I didn't do it, I would continue doing it [PA intervention].
(*Participant 003, female, Vitamin D intervention*)

Barriers to intervention acceptability, feasibility or adherence related to the disruption of the participant's regular routines, such as staying away from home (e.g. holidays, social events and work), environmental factors (e.g., bad weather), and personal factors (e.g., injury, illness and lack of time). These factors often made it difficult to access study materials (e.g. pill cases and the online PA website) and adhere to the intervention. People further reported that other events meant they sometimes did not have time to participate in the intervention.

> "I mean sometimes we were doing bed and breakfast and sometimes they [pill cases] were packed in the car and so on so I couldn't do them [take Vitamin D supplement] that day." (*Participant 026, female, Vitamin D intervention*)

> If I'm staying in a hotel overnight, they haven't always got any facilities [for activity] (*Participant 004, female, Online PA intervention*)

5.4.6.4 Sub theme 4.4: Barriers to intervention retention

A specific barrier to study retention was expressed by one participant relating to the level of pain they experienced throughout the study. However facilitators to retention included not wanting to disappoint the researcher and eventually feeling an improvement with longer term participation.

> "…the agony I was in, it didn't seem to be improving. That was the real reason why I nearly gave up. I didn't think they were doing any good at all…I nearly came in to give it up then too but I was so sorry for you doing this wretched study, I thought, " Well I better hang on". Then it did, in the end, finally kick in to be some use but it got worse before it got better." (*Participant 026, female, Vitamin D intervention*)

Other barriers to intervention adherence referred specifically to the PA interventions. For example, bad weather disrupted and discouraged outdoor based activities such as gardening and walking and higher levels of activity in general.

> "So it wasn't really the weather to garden. That's why we decided to do swimming. It was the easiest option to do because I haven't got a bike…And now that the weathers better and it's a bit lighter at night, especially when the clocks go forward, it will be lighter again, so I think we will get out and about a lot more often. It will make us walk more often." (*Participant 004, female, Online PA intervention*)

The importance of sedentary working environments in preventing increased activity was also highlighted by one participant. They described how their working environment prevented them from being active at work and left little time remaining to do more activity outside of work.

> "I just felt I haven't maybe helped as much as I could if I was only working 38 hours a week. Because if I worked 38 hour a week I could put in more exercise." (*Participant 022, female, Online PA intervention*)

The contribution of periods of illness and other injuries/health conditions on the amount of activity the individual was able to undertake was discussed by several participants.

> "I was having problems with my neck at the time so the swimming was out" (*Participant 007, male, both interventions*)

> "As I said, there was a complaint, and when my back had gone [injured] unfortunately I couldn't do any real sort of exercise or anything additional certainly at that time." (*Participant 043, male, Online PA intervention*)

5.4.6.5 Sub theme 4.5 Intervention safety concerns

Continued participation for both interventions relied on confidence of some participants that the intervention was safe. Most of these safety concerns related to fear of side effects of taking Vitamin D supplements and injury during increasing PA as part of the online PA intervention.

> "Well I did ask you, 'Can you overdose on this stuff [vitamin D supplements]?' and you reassured me there. (*Participant 026, female, Vitamin D intervention*)

> "I think the day my knee almost locked, I was a bit worried then that I was overdoing it [with the PA intervention]." (*Participant 004, female, Online PA intervention*)

5.4.6.6 Sub theme 4.6: Taking Vitamin D supplements

In terms of acceptability of the Vitamin D intervention, several improvements were recommended by participants. For example, some participants occasionally did not take the Vitamin D supplements during the intervention. This was the primary reason reported for forgetting to take the supplements. However, if they missed these

supplements participants carried on taking supplements for additional days at the end of the supplementation period. This ensured all participants took the full dose of vitamin D supplements.

> "If I did miss some, I had them the next day but not in double quantities, I merely went on for a little bit longer, which is why I've got one more lot to do." (*Participant 026, female, Vitamin D intervention*)

5.4.6.7 Sub theme 4.7: Barriers to POW website usage

In terms of barriers to engagement with POW, participants, particularly those who did not comply with the online component of the PA intervention, reported a preference for paper-based resources and little or no experience of using the internet previously.

> "No problem [paper activity sheets], it was part of what I used to do at work; I used to fill a log in, I used to write a log, it was all written. If I had to write it in, on the computers, I would have, probably, been on until twelve o' clock at night…Yes if it had all been on the computer, I wouldn't have taken part; I would have phoned you up and said I don't want to take part anymore." (*Participant 032, male, Online PA intervention*)

Non-compliers to the online PA intervention particularly expressing the perception the internet version of the PA intervention as a barrier due to fear of using the internet correctly or expressing the perception that being 'old' was a barrier to internet use and therefore avoided using the POW website.

> "And it's my generation that never grew up with computers, so we often, some of us find it harder than others [using POW]" (*Participant 022, female, Online PA intervention*)

Some participants began to engage with the website, but subsequently lost confidence with it after experiencing functional/technical problems with the POW activity graph feature. This meant that imputed steps were not correctly represented on the online activity graph. Some participants reported consequently losing confidence in the function of the website.

> 'I think it wasn't transferring the data in the way that you were expecting it to, which I lost a bit of confidence in the online part then." (*Participant 043, male, Online PA intervention*)

5.4.6.8 Sub theme 4.8: Facilitators to POW usage

An important part of continued participation in PA was engagement with the physical activity intervention, POW. An important facilitator to compliance with the online PA intervention was familiarity with or previous experience of the internet as part of work or personal use.

> "I do most things online, even although I work on a computer at work, when I come home at night, I check my emails and have a look on Facebook and chat to my friends. Then I buy stuff, online shopping, I do the ASDA shopping. So I use it a lot. So, for me, it was just second nature to go onto the website and have a look at stuff on there and input my steps. So I found it really great." (*Participant 004, female, Online PA intervention*)

5.4.6.9 Sub theme 4.9: Activity monitoring to increase activity

The importance of monitoring activity in order to increase PA was discussed by the Online PA intervention participants. The majority of PA intervention participants mentioned at the start of the intervention they conducted a period of monitoring their PA, without making any changes to their PA, in order to obtain a 'baseline' PA level for reference, which they could the subsequently build upon for the rest of the intervention period.

> "...didn't set any goals on purpose for the first two or three weeks because I just wanted to see how everything was working. I wanted to get a picture of where I was at before I started trying to push myself further." (*Participant 007, male, both interventions*)

Participants then highlighted the importance of continuously building on their PA by competing with themselves. Participants described wanting to achieve the level of PA (usually counted in steps using the pedometers provided as part of the intervention) they had obtained the day before and feeling disappointed if they were unable to do this. It can be inferred from this that the monitoring PA itself was motivation to maintain or increase PA.

> Well, as I say, that's the sort of thing that keeps me going; I'm checking it all the time, I'm trying to beat yesterdays figures, and, when I find out I've been doing my gardening, and I'm nackered, an I haven't beaten yesterdays figures, it's a little bit disappointing, but it's just a game, isn't it? (*Participant 032, male, Online PA intervention*)

5.4.6.10 Sub theme 4.10: Improvements to POW step graph

When exploring the acceptability of POW, many functionality improvements to the website were suggested, mostly regarding the online step graph used to visualise the amount of daily activity undertaken by the participant. One participant suggested that the graph could visualise the pattern of activity achieved more effectively by including a summary of the activity achieved on each day of the week. This would allow participants to identify any particular days of the week where their activity was particularly low.

> "It was to try and help identify to me, is there a same day, or days in the week, when I have less steps, and I look and think 'right is that because on the Saturday night, because I go down to the so-and-so, and then I'm sick on the Sunday', and that's where I would have liked to have seen it, over the week, and then looked at the next week and thought, hang on a minute, Sunday was the same last week, or, you did better on a Wednesday because that's your day off." (*Participant 029, female, Online PA intervention*)

It was also suggested that a weekly email notification and summary of the participant's activity would be preferable to visualise activity week to week.

> "I find that, if that side of it could be sorted out [online step graph]. Even if you sent the sheets [paper based activity sheets] away and they fed them in and put it onto the graph and maybe once a week you got an email or something, or 'this is how you've done this week', something to look at. I think you do need to have something to look at for your progress because there's nothing more motivational than looking at something and saying, oh I dipped last week, I'll sort it out this week. So I did find the visual side of it could be helpful, but I just didn't think it was working properly. Sorry. (*Participant 007, male, both interventions*)

5.4.6.11 Sub theme 4.11: Use of POW website pages

Most comments on the use of specific web pages within the POW website mentioned the use of the interactive step graph page, where participants could impute their daily steps as recorded by the pedometer.

> "Obviously I used the step page on a weekly basis to begin with and then more frequently once it went on to day." (*Participant 004, female, Online PA intervention*)

It was mentioned by one participant that the POW page summarising activities available in the local area was useful in aiding them to think of different activities that were available and which they could try.

> No, it was good, it made you think about different things, that you could, perhaps, try, if you haven't already tried them. (*Participant 029, female, Online PA intervention*)

One participant mentioned they did not like using the POW page allowing the participant to set PA goals for the coming week as they felt when they set the goal too high, and they were unable to achieve that goal, it was discouraging and when they set the goal too low, and they consistently achieved the goal, that there was no point to it.

> Not for me, no, because, if I don't achieve them, I get annoyed and irritated with myself, and then, if I'm achieving them every day, I think, 'I set those too low', so what's the good of that? (*Participant 029, female, Online PA intervention*)

One participant also mentioned the POW page summarising possible barriers and solutions to increasing PA. They felt the barriers were not applicable to them and the solutions provided were not helpful.

> Probably a bit of both. Certainly the answers weren't helpful, but the barrier side of it, I think if somebody wants me to do something, they'll do it. The barriers, to me, they just didn't apply to me. (*Participant 007, male, both interventions*)

5.4.6.12 Sub theme 4.12: Continuing the intervention beyond the study period

When asked about the participant's capability to continue with their assigned intervention beyond a 12 week period. Most responses which indicated a preference or capability for continuing with the intervention beyond 12 weeks regarded the PA intervention. Most participants involved in the PA intervention stated they would like to 'stick to' or keep up their increased PA beyond the end of the study.

> Now that I understand it a little bit more, it's probably been life changing because I'll stick to it now. I'll stick to what I'm doing. I realise how many steps I need to do a day and okay it might be chucking it down with rain or blowing a gale, but I know that I still need to do something (*Participant 007, male, both interventions*)

5.4.7 Theme 5: Study Experience

There were many important aspects of the study experience which emerged during interviews. These included the importance of the participant's relationship with the researcher, the level of communication between the researcher and participant throughout the study and maintaining a professional appearance when conducting the study.

5.4.7.1 Sub theme 5.1: Voluntary nature of involvement

No financial incentive was offered as part of this study, however when asked participants expressed that they would be uncomfortable accepting a monetary reward in exchange for study participation, highlighting the voluntary nature of participation.

> "That's not why I did it. I didn't expect anything back. Actually I'd feel uncomfortable with that…because I think if you do something like this there shouldn't be a monetary reward. You're doing it to help yourself, not for what money you can gain out of it." (*Participant 003, female, Vitamin D intervention*)

5.4.7.2 Sub theme 5.2: Participants relationship with the researcher

Some participants viewed it as important that the researcher puts the participant at ease during study appointments in order to 'get the best' out of the participant. The level of familiarity and rapport with the researcher was also important with participants preferring to maintain contact with the same researcher throughout the study duration.

> "I think it's been nice having the same person each time. I mean I don't know how other studies particularly work but, you know, so that by the time you've been more than once you're coming to see someone you've already met. I think that's good." (*Participant 038, female, Vitamin D intervention*)

5.4.7.3 Sub theme 5.3: Communication

The speed and consistency of communication throughout the study was also viewed as important. One participant referred specifically to a 'gap' between the first 6 weeks of their pilot intervention study and the study visit which would begin their second 6

weeks of the pilot intervention study. This gap or lag in communication was viewed as potentially off putting.

> "Like I said earlier, I think that might have out a lot of people off [time delay in responses from researcher], you know, because, I don't know, it might be down to me, but when I commit to something, I'm gonna do something. I'm up for it, ready to, you know, right, let's get started! That's probably down to me more than anything else." (*Participant 007, male, both interventions*)

5.4.7.4 Sub theme 5.4: Professional demeanour

One participant specified the importance of a professionally run study through the allocation of appropriately trained staff. One participant spoke about the provision of a receptionist rather than fellow students to the study to take study calls and pass on messages to the researchers. This kind of professional approach was thought to increase the credibility of the study.

> "The people who were answering the phone were hardly what you would call receptionists. They were probably fellow students and they didn't know when you were coming in or they might or might not take the information. I mean that really was rather poor quite frankly because you weren't put in the mood for believing it to be a doctoral student's piece of work…" (*Participant 026, female, Vitamin D intervention*)

5.4.7.5 Sub theme 5.5: Hope the study will provide future benefit

Finally participants reported hope in that the results of the study would provide future benefit by informing future healthcare and giving benefit to other patients. It was hoped that the results from this study contribute towards medical advancements which could be used in the treatment of KOA in the future.

> "I feel as if I've helped in some capacity to develop for the future, trying to relieve pain in the knees. If I can help in that way, at least I've tried and done something." (*Participant 037, male, Vitamin D intervention*)

> I hope that whatever you've found can be, in the fullness of time, given in advice to the management of the condition of people." (*Participant 026, female, Vitamin D intervention*)

5.5 Discussion and Recommendations

This qualitative interview study established that participants generally felt the study interventions and conduct acceptable and feasible, although some barriers were reported and should be considered when planning a future trials.

5.5.1 Comparison with existing literature and future implications

5.5.1.1 Recruitment

Regarding recruitment into the cross-sectional study, the majority of participants felt that the method of recruiting through GP surgeries was acceptable. In addition to this many participants felt that being identified by their own GP surgery gave the study authenticity, as if the study was 'endorsed' by the surgery. In support of this, a 2015 report for the Health Research Authority (HRA) which collected the opinions of 110 members of the public about their opinions of recruitment into clinical trials expressed, when asked about searching of GP records to identify patients for clinical trials research, that most people supported the searching of records by research nurses and non- clinical NHS doctors, with the caveat that high levels of data security and patient anonymity were observed[273].

When investigating reasons people had for participating in the study, it was found that motivations centred on a desire to improve their overall health and wellbeing by improving their KOA or losing weight, and a desire to help others by contributing to research. A systematic review of the barriers to participation in clinical trials[220] also found the most commonly mentioned motivation for participation in clinical research studies was identified as altruism.

We also identified as part of this study many facilitators to participation such as provision of transport and appointment flexibility. It has been previously reported that travel related costs were potential reasons for refusing participation or poor retention [220] and that making sure study visits take place at convenient times (e.g. after participant working hours or weekends) and locations were an important facilitator[220]for participation in their study [274]. The importance of addressing these 'patient related barriers' to participation in clinical studies has been previously emphasised as a means to improve study recruitment and retention [275].

Finally, participants identified several potential barriers to participation in the studies. One participant described how his family had discouraged his involvement in the study due to a distrust of medical research. The influence of 'important people' to the participant (e.g. family members, spouses and friends) has been previously acknowledged, with participation more unlikely if these important people are against participation[220]. Mistrust of medical research is a factor which and been linked to low participation and retention in research studies [275]. Many participants also expressed they found the use of certain terms in the recruitment materials as potentially off-putting and offensive, such as the terms 'obese' and 'older'.

5.5.1.2 Study Measures and Visits

The majority of participants reported that the hospital was an appropriate setting for conduct of the study and felt this location provided the study with credibility and a higher level of safety. However, transport to the hospital was identified as an issue, with a particular dislike of hospital car parking charges and finding a place to park.

There were many thoughts on the consenting process, with some participants confused about why consent was required while other participants saw it as a normal part of participating in a research study. However, a systematic review surmised that in general, study participants prefer to sign a consent form even if they don't fully understand the purpose of the consent form [220]. One participant reported concern over the consent form rooted in a distrust of medical research, with some fear that they may be giving consent to something unpleasant. This may be unsurprising considering, in a study examining 732 participants views on the consent process before surgery, that 10% participants did not understand what they agreed to on the consent form[276]. This suggests that greater time and clarity may be required when the researcher reviews the consent form with the participant. Previous literature suggests such a strategy would be successful in improving participant understanding of consent. A 2004 systematic review assessing interventions to improve participant understanding of the consent process showed extending the duration of the consent discussion between the researcher and participant significantly improved participant understanding [277]. In support of this, a quarter of the participants of this pilot intervention study noted they preferred completing the consent form in discussion

with the researcher during the study visit as this provided the participant with the opportunity to ask questions.

Most study participants expressed that having blood samples taken during the study was acceptable as they were used to having blood taken and had experienced this previously in a clinical setting. However, some participants reported a dislike of the DBS blood collection method, with the main reason for this being a dislike of the associated pain and of giving blood samples. However despite this, (as reported in Chapter 4) compliance to DBS measurements across all time points in the pilot intervention study was high at 90%. This level of compliance to DBS measurements and the concepts expressed regarding issues in providing DBS samples is similar to what has been reported in a2009 study, which assessed the use of the DBS methodology and resulted in84% participants agreeing to provide DBS samples. The main reported reasons for refusal to provide a DBS sample in this study was use of medications (e.g. use of blood thinners), dislike of potential pain, blood and needles and belief the procedure was unnecessary, invasive or dangerous [278].

Many issues regarding the monitoring of participants' activity post visit using activity monitors (accelerometers) were discussed. These issues mostly concerned comfort (with some participants commenting that the elastic belt was irritating and itchy), the concept of being monitored (with the fear of being seen as lazy when they were not moving) and the impact of external factors (such as illness) on the amount of activity recorded. There are few studies that have qualitatively assessed the views of participants on accelerometer use for clinical trials. One study comparing the acceptability of accelerometers, pedometers and questionnaires for assessing PA in bronchiectasis patients found the accelerometers (actigraph 9.42) easy to use. However, as with this study, participants found the elasticated belt uncomfortable and experienced problems with the belt moving or twisting. One of the strategies employed by participants to address this problem was by putting the elastic belt through belt loops[279].

5.5.1.3 Study Materials

Through the qualitative interview study we also gained insight on the appropriateness of study materials regarding their comprehensiveness and clarity. Through this

examination of the study materials we were also able to highlight several improvements which could be made which could potentially increase participant recruitment and understanding of the study, e.g. changing of the terms used to describe obesity and age which were thought to be 'off putting' and 'offensive'. Sensitivity to terminology used in the way certain treatment conditions are described is recommended. It is suggested to avoid use of potentially off putting terminology, members of the study population are consulted at the design phase of study documents to identify any necessary changes, ensuring the documents are appropriate for the target study population [275].

Participants stated the intervention instructions were easy to understand. The majority of the Vitamin D intervention participants stated that the pill cases containing the Vitamin D supplements were easy to use and facilitated compliance by allowing the participants to visualise and track which supplements they had taken. One exception was a participant who stated that they found it difficult to open the pill cases and open the blister packs containing the Vitamin D supplements. The use of pill cases in delivering drug interventions is common; [280]however, the effectiveness of their use, particularly in nutritional supplementation interventions, has been rarely reviewed. One study, the TRACE study delivering daily Vitamin C and E supplements in a 2x2 factorial placebo controlled design over 2 months, found99% supplements were taken without pill organisers and 100% taken with pill organisers (no significant difference) [280]. Another study, the VITAL study, a 4 month placebo controlled antioxidant supplementation study comparing 7 day pill organisers (n=148) and blister packs marked with days of the week (n=149),found adherence significantly (p=0.05) differed according to supplement delivery method, with adherence higher in the blister pack delivery group in the lowest tertile of pill count (lowest number of pills taken)[280].

The pedometer provided as part of the online PA programme was routinely used by participants and was seen as a motivator and facilitator to monitoring daily activity. The use of pedometers in physical activity interventions is widespread and has been seen to significantly increase activity by a mean 2491 steps/day compared to controls (p=<0.001) according to a systematic review of 8 RCTs[281]. Pedometers as facilitators and motivators for activity has been explored before in a 2016 study of 12 cardiac rehabilitation patient provided with a pedometer based tele-rehabilitation PA

intervention. Themes which emerged from analysis of qualitative interviews were that patients gained awareness of their PA and consequently were able make personalised PA goals. This allowed participants to tailor their PA to fit into their daily lives and provided them with independence to choose when and how they increased their PA [282].

5.5.1.4 Pilot Intervention Study

Most importantly, during this study we explored the acceptability of the pilot study interventions. This was important to assess as both of these pilot interventions (Vitamin D supplementation and online physical activity programme) had not been administered in this particular study population (older, obese adults with symptomatic KOA) as part of a clinical trial before this PhD project began. It was therefore important to determine if these interventions were acceptable and appealing to participants as part of a pilot study before conducting a full scale RCT [195]. As part of this qualitative interview study, rich data on practical issues which occurred as part of the interventions was collected and analysed to provide recommendations on how to improve these pilot interventions to make them more acceptable to the study population.

We established many motivations and barriers to intervention retention and engagement. The barriers and motivators to PA in KOA patients have been well explored in other qualitative studies [243, 246-248, 252, 254, 283]. Many of the themes which emerged from our own qualitative study reflected what was found in other qualitative studies looking at barriers to exercise interventions in older participants with KOA, including lack of suitable environments for activity (due to bad weather, lack of facilities and equipment), poor personal health, current injury, fear of side effects or 'pushing oneself too far' and competing responsibilities and life events [243, 248, 252].Themes regarding motivators and facilitators to exercise from this study also reflected those found previously on exercise interventions in older adults with KOA, including the influence of social support (including friends, family and pets) and desire to lose weight [248, 252]. In addition to this, our study identified that guilt of not complying or 'letting down the researcher' also facilitated adherence to the interventions, suggesting the participant's relationship with the researcher is also an

important aspect of the interventions. A less well-explored area of research is the use of web based physical activity interventions, particularly in older and KOA populations. A recent systematic review [284] of internet based physical activity interventions showed 54/72 of the paper intervention identified used health adults. Of the 18/72 PA interventions in disease populations, the majority of online PA interventions were targeted to Type 2 diabetes populations (7/72 papers) followed by Heart disease (3/72) and MS (2/72) populations. Only one online PA intervention was found in an arthritic/fibromyalgic population, which provided online PA lessons and self-assessments to an intervention group and a standard care group. No improvement in self-reported PA measures was observed between the online PA and standard care groups [285]. Most of these existing studies of online PA interventions were also conducted in a younger to middle aged population, with an average age of 40.2years in the healthy populations and 51.6 years in disease populations [286]. While there have been no studies investigating the use of an online platform for delivery of PA intervention to older adults with KOA, studies have been conducted to understand the views of older people on internet use. Many of the barriers to internet use we identified such as 'being too old' and 'difficulty in using the internet' have been identified in other qualitative studies, suggesting these are prevalent views amongst the older population [287]. Considering the gaps identified in the current literature, the themes which have emerged regarding the use of our online PA programme in older obese adults with KOA is therefore unique data which can be applied to the future design and conduct of studies delivering online PA interventions to the same study population.

5.5.1.5 Study Experience

Regarding study experience, it was concluded the participant's relationship with the researcher, particularly the familiarity and rapport developed throughout the study, was an important aspect of the study experience, which meant during the study visits, participants were more at ease. This concept of 'building trust' has been reported previously, specifically in the context of qualitative research. Prolonged engagement with participants in studies allows the building of trust and rapport between participant and researcher, which means the participant may be more comfortable disclosing information about themselves[288].

The appropriateness and effectiveness of providing monetary compensation for participation in research studies is unclear [289]. Previous studies have noted that participants who express financial incentives as the main motivator for participation in studies are more likely to have high attrition. This highlights that although financial incentives may trigger interest in a study, it is not the key factor in maintain engagement with a study till the end [275]. The views of the participants of this study was that they would not be comfortable receiving monetary incentives and that they felt participation should be voluntary without the need for payment. However, as no financial incentives were offered as part of this cross-sectional or pilot intervention studies, beyond compensation for travel, this participant population may be biased as a self-selected set individuals who ascribe to this belief (individuals who would prefer monetary compensation may not have participated in this study).

5.5.2 Study Strengths and limitations

One of the strengths of this qualitative study is that it could be combined with the objective data from the cross-sectional and pilot intervention studies to provide a mixed methods design, which has allowed us to review the feasibility and acceptability of the study measures, materials and interventions. This mixed methods approach is important in providing multiple views, approaches to review during our pilot study, as a measure or procedure may be accurate, and clinically relevant however, it may be affected by factors independent to the study. E.g. within this study accelerometers were used as an accurate, objective method of measuring activity however due to technical issues (such as monitor placement and movement) and external factors (such as injury and illness), the activity data collected may not be representative of the participants usual activity at that time point. Therefore piloting the study measures helps to identify what the most feasible and realistic outcome measure may be, while ensuring accuracy and relevance of the measure to the aims of the study [195].

Another strength of this study was the approach to a deviant case which emerged within our study sample. To explain why the views of the deviant case differed from the rest of the study sample, we drew upon several comments from the participant regarding her previous career and experiences. As this particular participant's previous career was within a research environment, many of the views expressed by this

participant were contradictory or unique due to the different perspective this participant had regarding the research studies they had conducted themselves. The participant therefore had very specific views on methodology and quality within the study which were unique to their specific experiences and views as a researcher themselves. [271]

There were a number of limitations to our qualitative interview study which should be highlighted. Firstly to obtain sufficient data, all participants who took part in the pilot intervention study (n=17) were invited to take part in the qualitative interview study (of which only 1 refused to participate. Due to the low participant pool for the qualitative study we were unable to obtain a purposeful sample of participants and instead obtained a convenience sample based availability. Despite this all participants had taken part in the pilot intervention study, and therefore were able to provide their views on each of the qualitative interview study aims (see section 5.2). Therefore I do not believe this alteration in sampling method significantly impacted on the fulfilment of the aims and objectives of the study. However ideally a larger sample would allowed us to have picked a purposeful sample of participants we believed could have provided rich and varied data on each of the study aims.

Secondly, due to our sampling only pilot intervention participants, we obtained a relatively homogenous study population. Therefore the qualitative data collected reflects the view of those participants who consented to recruitment and participation in the studies. In order to collect a more heterogeneous view of issues such as recruitment and compliance, interviews need to be conducted with those people who, for example, refused recruitment to the original cross-sectional or pilot intervention studies, or who did not adhere to the studies.

5.5.3 Implications for further research

We aim for the results from the cross-sectional and pilot intervention studies in combination with the context provided by the qualitative interview study to provide recommendations for conduct of future trials of vitamin D and online based PA interventions in this study population. Below the recommendations based upon the results of the qualitative interview study (in the context of the categories explored) are summarised.

5.5.3.1 Study Recruitment

- Based on the finding that recruitment from GP surgeries was feasible (resulting in recruitment of n=45 participants) and acceptable (with participants expressing they felt recruitment from their GP surgery gave the study a sense of authenticity and safety), we therefore recommend that follow on studies should consider this method of recruitment.
- Resulting from concerns discussed in the interviews regarding 'permission to be contacted' for participation in research studies, we suggest that future researchers or GPs discuss potential participation in a research study with individual participants before study recruitment materials are mailed out.
- The importance of appointment flexibility in facilitating study participation has been highlighted in previous literature [220]. In this qualitative interview study, we also found that participants felt flexible appointment times facilitated study participation. We therefore recommend study teams make sure a range of appointment dates and times (morning to evening) are available for participants and that appointments are organised by telephone so participants can suggest the most suitable time and date for themselves.

5.5.3.2 Study Visits and Measures

- In this study, participant's identified several issues regarding accessibility to the study site, including difficulty finding parking bays within the hospital site, hospital parking charges and difficulty in using public transport. Provision of transport (e.g. taxis) or compensation for travel (e.g. reimbursement of bus tickets or car journeys) has also been highlighted in previous literature as a facilitator to study participation [220]. As it is essential can access the study site without difficulty to facilitate participation and retention we therefore recommend the provision of travel as part of future studies e.g. provision of taxis to take participants to and from study visits, and/or recompensation for parking charges, bus fare and mileage if participant choose to travel by car or bus to study visits.

- As some participants expressed confusion over what the consent form meant and why it was required, we recommend extending the consent discussion between the researcher and participant, splitting the consent form into simple bullet points and providing participants with their own copy of the consent form to review later if desired (all strategies previously reported to improve participant understanding of the consent process [277]).
- Some participants expressed a misunderstanding of what the activity monitors were able to record and felt it may be recording things which were intrusive. We therefore recommend that researchers provide further explanation of the activity monitor, how it works and what it records, with a small example of the activity monitor output. This information should also be included in the activity monitor information sheet so participants can review the information at a later date if they wish.
- Some participants highlighted instances where they felt external factors (e.g. illness) affected their activity levels, and therefore they felt the activity levels recorded by the activity monitor may not have been representative of their usual routine. We therefore recommend extending the activity monitor recording period from 5 days to 7 days. 7 days activity monitoring is routinely used as the 'gold standard' of activity monitoring time in PA research as this allows monitoring of all weekdays and weekends, allowing patterns of weekly activity to be measured. Increased monitoring time also accounts for greater within participant and between participant variation[219]. We also recommend participants use of a log to record significant events during activity monitoring, e.g. injury preventing activity, to monitor any deviations in regular activity.

5.5.3.3 Study Materials

- Some terminology used as part of the recruitment materials, particularly regarding obesity and age, was considered insensitive and potentially offensive to potential participants. We therefore recommend avoiding use of the terms 'older' and 'obese' as part of participant materials and recommend piloting materials amongst groups with similar demographics to the to identify optimal terms (prior to study recruitment) regarding weight and age to use within materials.

- Receiving individual feedback in this study was viewed positively and additions to the data included in this feedback were recommended by participants (e.g. feedback on how to improve individual health status). Based on this we recommend the participant should be sent written feedback on the measurements taken as part of the study with a clear explanation of what the measures mean. Feedback should also be sent to the participant's GP surgery if participant's wish it, including recommendations to the GP to follow up any abnormal results with the participant.
- We conclude the mode of delivery (post) of the pilot intervention materials employed in this pilot intervention study was acceptable to participants. We therefore recommend that future studies use a similar approach by posting materials required for the pilot intervention to the participant's home address and therefore reducing burden on the participant. To ensure an accurate tracking of materials, the pilot intervention pack should include a receipt to confirm correct delivery which should be returned to the study team and we recommend the mail out should be followed a phone call by the study team to the participant to review instructions and confirm participants understanding of the intervention.
- This study confirmed that delivery of vitamin D supplements in pill cases was acceptable for participants of the Vitamin D intervention and facilitated compliance to the vitamin D intervention. However previous literature suggests use of blister packs labelled with days of the week is more effective in facilitating compliance to medication [280], and so we recommend a trial of the use of labelled blister packs for delivery of vitamin D supplements/matching placebos in future studies.
- Participants of the online PA intervention felt that provision of pedometers for activity monitoring was motivating for participants to increase their PA. We therefore recommend pedometers should be provided to all participants as part of the online physical activity intervention to allow participants to monitor their own PA and as a motivation tool to increase PA.

5.5.3.4 Pilot Interventions: Vitamin D supplementation and Online PA Intervention

- As some participants expressed confusion about the study arm allocation process (specifically how participants are allocated to each study arm), we recommend in future studies the study arm allocation process should be clearly and adequately explained in the PIS and discussed face to face with participants during recruitment to the intervention study to ensure understanding.
- As there were participant concerns over intervention safety in both intervention groups(specifically fear of side effects in the Vitamin D supplementation group and fear of injury in the online PA group), we recommend intervention safety is thoroughly discussed before the participant commences the intervention. It should also be made clear that participants can contact the research team should there be any issues or concerns over safety and that specific signs and symptoms of potential intervention side effects should also be assessed during all intervention study visits.
- As some participants expressed a specific dislike of the online format of the PA intervention and a preference for a paper based intervention, we recommend an individualised approach to the PA intervention, offering the POW programme as both a paper based and an online based intervention, thereby providing participants with a choice of intervention format.
- As during the pilot intervention study there was a lack of confidence regarding using the POW website due to technical difficulties with the function of websites step graph feature, we recommend full pilot testing the POW website (with a subsection of age appropriate pilot testers) before the further studies commence to identify any technical or usage problems.
- We recommend the implementation of some of the recommendation made by participants for improving the functionality of the POW website, e.g. changes the activity graph output to display individual days of the week so participants can identify patterns in activity and the addition of weekly email activity summaries to participants.

5.5.3.5 Study Materials

- Familiarity and rapport with the researcher was identified as an important aspect of the study experience by participants in this study. We therefore

recommend the same researcher/staff are maintained for participants throughout the duration of future studies.

- The maintenance of a professional demeanour during the study e.g. by allocation of a receptionist rather than students, was highlighted particularly by one participant. Therefore, if resources allow, allocations of specialised staff e.g. receptions, clinicians and researchers, should be allocated to appropriate roles within the study.
- Speed and consistency of the communication throughout the study was highlighted as an issue to participants, with some expressing they felt 'forgotten about' during large gaps in communication with the study team. To avoid gaps in communication, we recommend the allocation of dedicated research or administrative staff to maintain consistent and timely communication with participants during studies.

5.6 Conclusions

This qualitative interview has identified participant views on the acceptability and feasibility of the whole study process from recruitment to participation in the vitamin D supplementation and online PA interventions, as specified in the study aims. We believe we obtained a sufficient participant sample from our pilot intervention study participants (n-=16) to achieve data saturation (evidenced as no new themes emerged within analysis of the final two interview transcripts). During analysis of the qualitative interview data, we identified prevalent themes, which have informed the many important recommendations for future studies of this kind, including:

- Recruitment from the screening of GP surgeries in northeast England was generally acceptable to participants however concerns regarding 'permission to contact' for study participation need to be addressed in future studies.
- Most participants found the study measures and procedures acceptable, with only few minor issues identified. Comfort (particularly regarding the elasticated belt) and movement of the accelerometer were identified as issues by participants, which have been reflected by the results of a previous study [279]. We therefore recommend the placement of accelerometers through belt loops where possible.

- When reviewing written study materials, participants found some of the terminology used potentially offensive. We therefore recommend piloting when designing study documents to ensure the documents are appropriate for the target study population.
- Pilot intervention participants generally viewed the materials provided as part of each intervention as acceptable and useful, and in some instances facilitated intervention compliance (e.g. pill cases and pedometers)
- Several key facilitators (social support and activity monitoring) and barriers (disruptions to daily routine, bad weather, illness or injury and sedentary work environments) to increasing physical activity were identified and could be addressed to provide a more effective interventions.
- Lack of compliance to the POW programme depended on a preference for a paper based intervention and a fear of using the internet 'incorrectly' while compliance was mediated by previous experience with using the internet. More flexibility in mode of physical activity intervention delivery according to participant's preferences is recommended to increase intervention compliance.

Chapter 6. General Discussion

6.1 Main Findings and Relation to the Literature

This PhD project aimed to explore relationships between vitamin D status, physical activity and KOA symptoms as part of cross-sectional study and to pilot an intervention study designed to deliver Vitamin D supplementation and an online physical activity intervention in older, obese people with symptomatic KOA. The project had several distinct, but inter-related, objectives which are summarised in Table 6.1.

Study Design and Date Conducted	**Study Objective**
Cross-sectional study *(April 2015, October-December 2015)*	To explore relationships between circulating concentrations of Vitamin D, objectively measured PA and KOA symptoms in older obese adults with symptomatic KOA.
Pilot intervention study *(January-July 2016)*	To design and implement a pilot intervention study to assess the acceptability and feasibility of a vitamin D supplementation intervention and/or a web-based PA intervention in older obese adults with symptomatic KOA.
Qualitative interview study *(March-July 2016)*	To assess participant's views on the acceptability and feasibility of key aspects of the intervention study including procedures for recruitment, intervention modalities and outcome measures.

Table 6.1: Summary of the objectives and specific studies conducted in this PhD project

The three studies were set up and conducted from September 2013-July 2016. During this time participants were recruited and screened against the study eligibility criteria. Eligible participants were invited to take part in a single 90 minute cross-sectional study at NTGH. In addition, cross-sectional study participants were screened against the pilot interventional study criteria. Eligible participants were invited to take part in

the 3 month pilot intervention study, which included an initial study pack mail out, and a midpoint (6 week) and end point (12 week) study visit at NTGH. The qualitative interview study took place directly after the 12 week pilot intervention study visit.

The main findings from these three studies were:

1. That recruitment of older obese patients with symptomatic KOA though a clinical route is best achieved using primary care (North East GP surgeries) sites rather than secondary care sites (Liverpool hospital outpatient clinics). The availability of formal support mechanisms, including specialist recruitment staff, (through CRN and the local NHS commissioning group), aided with recruitment of primary care sites (GP surgeries). Recruiting from primary care enabled the screening of large numbers of North East population (n=57,229) across 8/153 GP surgeries. From those screened, n=791 (1.38% people registered to the recruited GP practices) met our study eligibility criteria. When these data are compared with the prevalence data for individuals with KOA in the North East (using the closest available filters to our study inclusion criteria. aged 45-74 and BMI >30kg/m^2) reported by ARUK [202], this showed that I identified and contacted 4.3% of potentially available potentially eligible participants in Northumberland, Newcastle Upon Tyne and North Tyneside. However, for this pilot study, I recruited only 8 of the 153 GP practices in the North East. These 8 practices are responsible for 7.2% of Northumberland, Newcastle upon Tyne and North Tyneside (areas where recruitment took place in this study) so, extrapolating to all GP practices, these data suggest that this recruitment strategy has the potential to identify 55.2% (n=11,155) of the total potentially eligible patients in this region.
2. Recruitment from secondary care sites (Liverpool UHA outpatient clinics) was unsuccessful in recruiting any potential participants for this study. To determine the reasons for this failure, I undertook a post hoc analysis in which I reviewed the case notes for n=2202 hospital referrals sent to UHA outpatient clinics between November 2015 and February 2016. This revealed that the two most common reasons for potential participant exclusion during referral screening were the non-reporting of patient BMI on referrals (1780/2202) and low number of patients diagnosed with KOA (171/2202). As a result only n=8

potential participants, who met all study eligibility criteria, were identified from hospital referral screening of 2202 referral notes. Additionally there was no formal support processes, unlike primary care recruitment, to aid with recruitment in the outpatient clinics. Also as referral documents sent to the outpatient clinics were paper based, this meant referrals had to be screened manually, which was both labour and time intensive. Lastly, most KOA patients are managed in primary care (according to NICE guidelines [10]), and those referred to secondary care clinics for specialist services, e.g. physiotherapy and manual therapy, or for more advanced treatment, e.g. joint surgeries and procedures, are likely to be the more difficult/ advanced cases. The latter may also have more concurrent disease which would make them ineligible for my study.

3. The cross-sectional study confirmed that objectively measured activity levels in older, obese people with KOA were low in comparison with the general UK population. In summary, 41% of my participants were classed as physically inactive (<30mins moderate activity/week) and only 27% met the UK Department of Health (DoH) PA guidelines[217]. This compares with the general UK population in which 26-27% were classed as inactive and 55% met the UK guidelines(based upon PA data compiled by the BHF)[163]. A 2013 meta-analysis of 2 studies (n=1250) in KOA populations which reported only 13% participants met the DoH PA guidelines (>150mins MPA per week) and the total sample had a weighted mean average of MVPA at 50mins/week[162].It has been suggested that this disparity in PA amongst KOA and non-KOA groups is due to both disease related (e.g. pain, dysfunction and disease severity) and non-disease related factors (e.g. age, sex and BMI) [223, 224, 290]. The low levels of activity seen in people with KOA in comparison to the general UK population as defined by DoH PA recommendations highlight the need to increase PA in this clinical population, not only as a means to managing their disease [10] but also because of the positive effects of greater PA on many aspects of physical and mental health [291]. Closing the PA gap between people with KOA and the general population by increasing levels of moderate activity, may improve both KOA symptoms and overall health. In the cross-sectional study, it was observed that time to complete the timed up and go test

was a mean 1.9 seconds longer in the inactive participants compared to participants which met PA guidelines. This suggests that the participants who met PA guideline had better physical function than those who were classed as inactive. This observation has been reported previously in a cross-sectionals study of160 older overweight and obese adults with KOA in which there was a significant correlation between Short Physical Performance Battery Score (SPPB) (a 10 minute battery of test designed to measure lower extremity function [292]) and time (mins) spent in MVPA (r=0.315, p=<0.001) [225].

4. In this cross sectional study, there was little observable differences in KOA symptoms by vitamin D status. In the literature, the previous evidence regarding relationships between serum 25OHD concentrations and KOA symptoms is limited. A systematic review [93] concluded that there is limited evidence (only 2 cross-sectional studies) which have reported the relationship between symptomatic KOA and 25OHD concentrations. However a more recent cross-sectional study of 256 adults aged 45-85 years with ACR defined symptomatic KOA showed a significant negative correlation between self-reported KOA pain (WOMAC pain scale 0-20) and serum 25OHD concentrations (r=-0.25, p<0.01) and significant differences in WOMAC pain score observed between participants with adequate (>75nmol/L) Vitamin D concentrations and participants with deficient (<50nmol/L) (p<0.001) and insufficient (51-74nmol/L) (p= <0.016) Vitamin D concentrations[293]. However another cross sectional study of 148 patients explored the association between 25OHD concentrations and presence of diagnosed symptomatic KOA by age and found a positive relationship in those <60 years (OR: 2.26, 95%CI: 1.15-4.4, P=0.018) but not in those >60 years old (OR: 1.01, 95% CI: 0.48-5.9, P=0.96)[229]. Several theories about how 25OHD status may relate to knee pain in KOA have been proposed including : i) the increased bone turnover which occurs during KOA leads to increased sensitivity to normal mechanical forces [294] and ii) that decreased 25OHD promotes a chronic pro-inflammatory state which increases pain sensitivity [295-297].
5. During this pilot intervention study we were able to test the feasibility of randomisation and study arm allocation. We found that given our study eligibility criteria for the Vitamin D supplementation and web-based PA

programme, there were very few of our cross-sectional study cohort who met both of these criteria, 6/45 (13%), and were therefore able to be randomised to one of the 4 originally planned study intervention arms (standard care, vitamin D supplementation, web-based PA programme, or both interventions). This suggests you would need to screen and invite very large numbers of people to achieve a RCT design. E.g. if we extrapolate our pilot study recruitment and retention data to the number of participants estimated to be eligible for our study in north eastern England by ARUK[17], from a pool of 9619 potential participants (who have been screened for eligibility and sent study information) we could expect 72 participants to be eligible for and recruited to a RCT study. It is therefore clear that conducting a RCT study would be a large undertaking and may involve the collaboration of several study teams as part of a multisite study approach.

6. The 12 week pilot interventional study demonstrated that Vitamin D supplementation and Online PA interventions were feasible and effective in their intended purpose. Supplementation with 2000IU (50µg) of D3/day increased 25OHD concentrations by 51(±23.1) nmol/L(95% CI 33.2, 68.8) and compliance to the Vitamin D intervention was high (99.1% i.e. 1499/1512 supplements taken). In contrast, compliance with the web-based PA programme was lower (66.6%; (6/9)) participants logged onto the online PA programme beyond the registration. The amount of time that participants spent using the online PA programme was highly variable with an average total 97 (±78) minutes and a mean interval of 4 days (±2.1) between visits. From baseline to week 12 of the PA intervention, % time sedentary decreased and time spent in moderate intensity activities increased by 5.8% and 1.0% respectively. Change in average daily time spent in sedentary activity throughout the 3 month intervention increased from baseline to week 12 in non-compliers (participant who did not utilise the POW website) (+17 (±80.3) mins) while sedentary time reduced in compliers (participants who did utilise the POW website) by -170 (±215.3) mins. Interestingly non-compliers achieved greater increases in average daily time in moderate activity from baseline to week 12 of the pilot intervention study of +9 (±7.3) mins compared to +2 (±10.4) mins in compliers. Evidence of the effectiveness of 72 web-based PA

programmes was summarised in a 2013 systematic review [286]. This review found that 37 studies targeted PA as the sole intervention outcome and only 1 paper was conducted in an arthritic population. Only 7 studies assessed PA objectively using accelerometers or pedometers and significant improvements in PA were seen in 86% (6/7) of these studies [286]. The sole RCT reporting the use of a web-based PA intervention in an osteoarthritic populations tested the use of a 9 week web-based intervention ("Join2move" intervention) in 100 older (50-75 years) KOA/HOA participants. Engagement with this PA programme resulted in no improvement in PA at 3 months but there was evidence of improvement in subjective (+ 21.2 points, 95% CI 3.6-38.9) and objective (+24 mins Light/Moderate/Vigorous PA, 95% CI 0.5-46.8) measures of PA after 12 months [262].

7. In the pilot intervention study, there was no evidence that increasing 25OHD status changed any self-reported KOA symptom. However, it is important to note that this was a pilot study designed to investigate acceptability and feasibility and was not powered to detect effects of the intervention modalities on KOA symptoms. Evidence from RCTs of the effects of vitamin D supplementation on KOA symptoms is very limited. A 2013 RCT delivering 2000IU (50µg) (with subsequent dose adjustment) Vitamin D over 2 years in a symptomatic KOA population found although knee pain (WOMAC, 0-20 points) decreased in both the Vitamin D supplementation (-2.31, 95% CI -3.24, -1.38) and placebo group (-1.46, 95% CI -2.33, -0.60), this was not significant and there was no significant difference in change in knee pain between the 2 treatment groups at 2 years (p=0.17). A more recent 2016 UK randomised, double blinded multisite study [146] recruited 474 patients >50 years and supplemented them with 800IU (20µg)/day cholecalciferol or a placebo over 3 years. The authors found no significant change in KOA symptoms (WOMAC pain, stiffness and function, scale 0-100) with Vitamin D supplementation and no significant differences between the Vitamin D and placebo groups [146]. The fact that both of these intervention studies did not observe any relationships between 25OHD concentrations and KOA symptoms may be due to a major limitation of all currently published Vitamin D supplementation studies in that they did not recruit those with low 25OHD concentrations exclusively. Vitamin

D supplementation would be more likely to benefit those with low baseline 25OHD concentrations, therefore supplementing those with sufficient 25OHD concentrations is unlikely to demonstrate any effect. This may be supported by the fact that sub analysis of participants in the 2013 RCT Vitamin D supplementation study [92] showed that change in WOMAC Pain (baseline to 22 months) in participants with low baseline 25OHD were greater than the whole sample, however not significantly so (change in pain −2.7 vs. −1.0, [95% CI of difference, −5.3, 1.9], p = 0.36, effect size = 0.4). The advantage of this pilot study is that an exclusively 25OHD insufficient population participated in the Vitamin D intervention, therefore testing supplementation in the population most likely to demonstrate any potential effect.

8. The pilot intervention study showed several significant changes in KOA symptom measures from baseline to week 12 in the Online PA intervention group, particularly in WOMAC pain (0-20) (mean difference -3.0 [95% CI: -5.2, -0.8])and activities of daily living (0-64) (mean difference -7.3 [95% CI: -13.7, -1.0]). The only other web-based PA programme in KOA participants [262] showed no significant difference in self-reported KOA symptoms in response to the intervention. However results from a systematic review of home-based or supervised aerobic or strengthening exercises in KOA patients concluded that there were positive effects on pain and on self-reported disability [103].
9. Finally my qualitative study in which I interviewed participants (n=16) who took part in the pilot intervention study provided insights into what did or did not work well from the participants' perspective. Many of the barriers and facilitators to recruitment reported here had been reported in previous studies, such as a dislike of travel and travel related costs and a distrust of medical research [220]. The primary motivation for participation in clinical research studies was identified as altruism [220], which we also identified as part of this study as well as a desire to improve personal health.
10. The qualitative interview study revealed that the terminology used in some of the study materials was insensitive to this particular audience and requires revision. Terms relating to weight, specifically 'obese' and 'obesity', and age, specifically 'older', were considered insulting by some, who felt the use of such language may be enough to 'put people off' participating in the study. The

importance of using the correct terminology in study documents for the study target population has been highlighted previously and the involvement of the study population at the document design stage, to ensure their appropriateness for that population, is a strategy to ensure this [275]. Some participants expressed they felt surprised at being identified as obese or older as they had not previously considered these terms applicable to them. This highlights the importance of piloting studies and of the involvement of the lay public in the development of study materials.

11. The interviews with participants showed that the Vitamin D intervention was acceptable and the way it was delivered (e.g. via a pill case) facilitated compliance with the intervention. The effectiveness of use of pill cases and blister packs to increase compliance have also been demonstrated in previous vitamin supplementation studies [280]. Most participants took the Vitamin D supplements with their other prescribed medication, and so it became part of their 'daily routine'. This is reflected in the excellent compliance with this intervention modality (99.1%). Minor concerns regarding potential side effects of Vitamin D supplementation were expressed by some participants but they were reassured after discussions with the researcher.
12. Qualitative data suggested reasons why some participants did not engage with the web-based PA programme through the different themes which emerged from POW programme compliers (participants who demonstrated use of the POW website beyond the initial visit) and non-compliers (participants who did not log on to the POW website beyond an initial visit), with previous experience and confidence in using the internet expressed as key factors relating to the compliance with the POW programme. This highlights the need for a more personalised and multifaceted (using paper and online based interventions) approach to PA interventions and that a 'one size fits all' approach is unlikely to be successful in maximising compliance [298].

6.2 Study strengths and limitations

6.2.1 Study Strengths

The pilot design of this study was important to test our study aims (to test the feasibility and acceptability of measuring Vitamin D and PA and providing Vitamin D supplementation and online PA intervention studies in this study population), especially as these interventions were being applied in a novel way. By exploring issues of study design, study management, and feasibility and acceptability of study recruitment, measures and interventions, I was able to provide useful recommendations (see section 7.4 below) for the effective conduct of a full scale study with the potential to save time and money and to reduce participant burden in subsequent studies of these interventions in this study population. The mixed methods design allowed me to produce quantitative data which can be used practically to estimate expected recruitment rates (55% of potentially eligible population), pilot intervention study recruitment numbers (n=234) adherence and outcomes for a north eastern England population, while the qualitative information provided insight into the context and reasons for my findings, particularly in regards to participants views on acceptability. Both of these data collection methods provided useful information which can be used to provide recommendation for future studies.

Another major strength of this study was the development and implementation of an evidenced-based set of inclusion and exclusion criteria. By focussing on older people with obesity, I attempted to maximise the ability to recruit participants with symptomatic KOA who would have inadequate Vitamin D status and low PA [133, 299]. Recruitment of this sub-population for the cross-sectional study potentially increased the number of participants eligible for the subsequent intervention study. Additionally, application of these criteria meant that we targeted individuals who may benefit most from a Vitamin D supplementation and PA intervention to improve KOA symptoms. By recruiting those with symptomatic (and not radiographic diagnosed) KOA, we could test the effect of the effect of Vitamin D and PA interventions on symptoms more effectively. Not everyone with radiographic KOA has symptoms and not everyone with symptomatic KOA will have evidence of radiographic KOA [300].

Another study strength is that I recruited participants from primary (and attempted to recruit from secondary) care NHS sites using ACR defined symptomatic KOA criteria and excluded any other arthritic condition (e.g. Rheumatoid Arthritis). By using a healthcare based recruitment strategy rather than advertising to the general public, I hoped to prevent contamination of our participant sample with those with alternative or undiagnosed arthritic conditions and those who self-report KOA but may not have the condition. While this may make the recruitment strategy more complicated and time-consuming initially, in the long run I expect it to save time and resources by ensuring that non-eligible participants are not invited to a study visit.

This pilot intervention study is novel in that, in contrast to previous Vitamin D supplementation studies, it was the first which has attempted to deliver a Vitamin D supplement people with symptomatic KOA who were known to be 25OHD insufficient. I recruited into the intervention study pre-screened participants who were defined as 25OHD insufficient (25OHD 25-50nmol/L) (deficient participants, 25OHD <25nmol/L, were referred back to their primary care provider for medical treatment for ethical reasons). Previous vitamin D supplementation studies have included participants, regardless of baseline 25OHD status [90, 92]. This problem with this approach is that participants who are deficient in 25OHD potentially may benefit from an increase in 25OHD. Indeed, a case could be made that those already sufficient in 25OHD may be unresponsive to supplementation. This is supported by the results of subgroup analysis of one Vitamin D supplementation study in KOA [92] in which participants with low 25OHD concentrations (<38nmol/L) at baseline had slightly greater, but non-significant, improvements in KOA pain at two years (measured by WOMAC Questionnaire, 0-20 scale) (-2.7 [95%CI -5.3, 1.9], p=0.36, ES=~0.4) compared with the total treatment group (-2.31 [95%CI -3.24, -1.38], p=0.17, ES=~0.2)[92].

Another strength of this study is the use of objective measures, specifically accelerometry, to measure PA at baseline, half way point (6 weeks) and end point (12 weeks) of the pilot intervention study. Previous studies comparing the use of accelerometry and self-reported questionnaires for measuring PA have shown that participants self-report significantly less sedentary intensity activity and higher vigorous intensity activity than was measured objectively [301, 302].However despite the clear advantages in using objective PA measures, the use of objective measures to

monitor PA during previous web-based PA intervention studies are sparse. A 2013 systematic review of internet based PA interventions concluded, that from 72 studies, only 16 studies measured PA using an objective PA method and only 4 of the studies used accelerometers [284]. Further, the only other published internet-based intervention study in a KOA population [262] used a self-report PA questionnaire (n=199) to measure PA with only a subset of participants provided with accelerometers (n=83). The latter paper did not provide any statistical comparison between the self-reported and objective measures used.

6.2.2 Study Limitations

The first limitation of this study is that due to administrative problems we were unable to adhere to the timelines originally laid out this study. This pilot study was originally designed so the cross-sectional and pilot interventional studies would take place during the annual 'winter' period (October-April [110]) when Vitamin D cannot be synthesised in the skin in the UK. This would ensure there would be no confounding effect of additional cutaneous synthesis of Vitamin D throughout the intervention period. However, due to the time required for an ethical amendment application to update and amend the eligibility criteria for the pilot intervention study, some participants were delayed from entering into the pilot intervention study. This meant that the last participant started the pilot intervention study on 02-04-2016 and therefore finishing the 3 month intervention on 25-06-2016. This means that cutaneous synthesis of Vitamin D may have occurred in some participants. This is confirmed by evidence that the Online PA intervention group increased mean 25OHD concentrations by 14.9nmol/L over the 3 month intervention, without any Vitamin D supplementation. However there were no significant differences in median 25OHD concentrations (nmol/L) Vitamin D supplemented participants who finished the intervention before or after April (end of 'winter' period) at baseline (34.5 [95%CI 86-155] and 38 [95%CI 30-46] respectively) and week 12 (81 [95%CI -40-201] and 84 [95%CI 73-107] respectively).

The original study design included the piloting of a randomised 2x2 factorial intervention study. However the lower than anticipated numbers of participants recruited to the cross-sectional study and, of those, meeting both eligibility criteria for the intervention study (low 25OHD concentrations and low activity levels) meant that I

had to alter the design of the pilot study. Since the focus was on acceptability and feasibility of the study interventions, the decision was made to amend to study design to a unrandomised design allowing those eligible for only the Vitamin D intervention (having low 25OHD concentrations) to be assigned to the Vitamin D supplementation intervention and those eligible for the online PA intervention (low PA levels) to the online PA intervention. This change allowed us sufficient numbers of participants in each intervention group to assess the interventions acceptability and feasibility. However, the limitations of changing the study design to an unrandomised design means we were unable to obtain data on participant acceptance and retention rates when randomised according to a 2x2 randomised design. We have only obtained data on the acceptance of each intervention individually and not a standard care or combined intervention arm. We therefore cannot, as a result of this unrandomised pilot study, inform a power calculation for a full scale RCT study of Vitamin D supplementation and Online PA interventions in this study population. We can however estimate the numbers of participants required for each individual intervention based on previously published studies e.g. McAlindon calculated for their Vitamin D supplementation study [92] that in order to detect a change of 2.2 units (effect size 0.54) in WOMAC Pain (scale 0-20) detectable to 80% power, 114 participants are needed. Based on the screening and recruitment rates obtained for this pilot intervention study, 387,786 would need to be screened to obtain 114 participants for a full scale RCT Vitamin D and Online PA intervention with similar power to previous full scale Vitamin D supplementation RCTs [92].

Another limitation of this study was the lack of success of our secondary care recruitment strategy which resulted in no recruitment of participants from the Liverpool study site. The failure of the recruitment strategy to recruit reduced participant numbers and resulted in some of the study design amendments discussed above. This also meant we were unable to explore the acceptability of recruitment from secondary care in participants. However large amounts of resultant feasibility data were collected from the secondary care site at Liverpool which allowed me to determine why this strategy was unfeasible in this study.

Lastly, as the pilot intervention study was 3 months (12 weeks) in duration, it can only give us data on the feasibility of running and maintenance of the study interventions

over a short time period and not on feasibility and maintenance in the long term. This is important to establish, particularly regarding the PA intervention, as it has been reported that long term adherence to PA programmes (12 months) by older people (aged 55-70 years) lead to significant improvements in PA which are likely to improve overall health and to reduce risk of age-related diseases [175].

6.3 Recommendations and Future Research

6.3.1 Recommendations from this PhD Project

The results of this study are intended to inform the design of future trials of the interventions investigated. In light of the results from this pilot study, it may be more practically feasible to recommend a three arm RCT design, with a Vitamin D supplementation, Online PA intervention and control arm, where the effectiveness of intervention can be compared to controls. This design would require fewer participants and could estimate based on power calculations from existing studies of Vitamin D supplementation [90, 92] and Online PA interventions [262] in this study population and by incorporating recommendations from this pilot study. Recommendations based on the results of this study are summarised in Table 6.2.

Future Study Recommendations	
Study Design	- Providing the Vitamin D supplementation intervention during the winter period (October-April) would be ideal to avoid the confounding effect of cutaneous synthesis of Vitamin D from sunlight.
Study Recruitment	- Recruitment from primary care sites allows easy and quick screening of large numbers of people resulting in sufficient numbers of eligible study participants and is an acceptable form of recruitment for most participants. - Recruitment can be boosted using follow up mail outs or phone calls from the study team. - Assistance from the local commissioning group (North East Commissioning Service) was essential in the recruitment of GP practices in this study. Therefore obtaining the support of the local healthcare authority,

	or commissioning group, should be sought when recruiting from primary care.
Study Materials	- Completion of the consent form during the study visit was preferable to participants, giving participants the opportunity to ask questions and the researcher to check participant understanding of the study requirements. - Terminology regarding obesity and age should be presented with care to avoid offense to participants. Conducting a focus group with target population to select acceptable terms may be useful before finalising study materials. - Make the study design and allocation process simple, clear and understandable within the patient information sheet (PIS). - Delivery of study intervention materials by post was convenient and acceptable to participants. This should be followed up by a phone call from the researcher to talk through the study intervention instructions, to check participant understanding and to answer any participant questions. - Receipt of personal feedback on study outcome measures was important to participants. Participants recommended that in addition to information on study measures there should be information on how to continue improving their health after the intervention and that GPs are sent a copy of their feedback for review.
Study Measurements	- There were some minor issues raised by participants regarding accelerometers which included; o Comfort of the elastic belt used to attach accelerometer to trunk: advise participants to wear the device above clothing where possible. o Movement of the accelerometer and belt with activity: advise participants to pull belt through clothing belt loops, where possible, to keep belt in place. If this is not possible, provide alternative accelerometer attachment options (belt clips or watch straps).

	○ Concern of being monitored and what activities the monitor can record: during the study visit, the researcher should explain the nature of the device and what data are collected. In addition, include this information of the written instructions. ○ Concern that injury or illness reduces 'normal' activity at time of monitoring: provide participants with a log where they can note down any important occurrence such as illness or injury if they feel this would affect their activity results.
Study Arm allocation/ Randomisation	- Participants expressed a dislike of the idea of being allocated to a standard care group in this intervention study. Therefore, if resources allow, a placebo group should be used for the vitamin D intervention.
Vitamin D intervention	- As participants expressed concerns over side effects and intervention safety during the intervention, care should be taken to reassure participants of intervention safety and potential risks. Therefore all reported medical incidences and suspected side effects should be recorded carefully and reviewed by a clinician during the study. Serum 25OHD and Calcium should also be monitored throughout the study to ensure toxicity is not experienced.
Web-based PA intervention	- Provide training sessions before commencement of the pilot intervention study on the use of the POW Programme as well as written instructions and materials. - A subset of participants disliked the web-based format of the PA intervention. Therefore a multimodal method of intervention delivery should be considered with a web-based and paper based PA intervention formats offered to boost intervention engagement. - Concerns over potential injury and intervention side effects were mentioned by participants, such as flare up of symptoms by increasing activity. Therefore, as in this pilot study, researchers and study materials should

	clarify the importance of gradually increasing activity to avoid injury and recommendation of appropriate types or activity for those with KOA. All side effects and injuries should be carefully recorded and reviewed by a clinician, with adjustments in PA adjusted during the study if necessary. - A part of the qualitative interview study participants suggested a range of improvements to the POW system which should be applied to future studies, including; improvements in the ease of use/clarity of the website's design and layout, reformatting of the online activity graph to display total activity per day rather than total activity per week, allowing participants to identify patterns of activity and setting up email updates on weekly activity for participants.
Study Resources and Management	- Study recruitment is labour and time intensive and therefore, if resources permit, specific study staff should be allocated to recruitment and assistance from research (e.g. CRN) and local authorities (e.g. commissioning groups) sought. - If study is conducted across different study sites, a study manager should be appointed at each site, with responsibility for promoting and running the study at that site. This splits the burden of study management amongst staff, reducing burden and improving study recruitment and outcomes.

Table 6.2 Recommendations for improvements to protocols when conducting full-scale intervention studies based on pilot study findings

6.3.2 Intervention applications and Scalability

Our final recommendation for future work is to test these interventions in a large population in order to assess the intervention's appeal and scalability amongst the older, obese population with KOA. The is important to establish in full scale studies if there are potential beneficial effects of our pilot interventions on KOA symptomatic outcomes, as it is important to determine if these interventions can be delivered on a large scale.

The advantage of the web-based PA intervention is that the online delivery means it is practically scalable to a large number of people simultaneously, cheap and easy to

deliver. It may also be possible to expand this intervention further to include a module within the web-based intervention regarding weight loss. This would be particularly relevant to our study population (identified as obese) and was a topic many pilot study participants expressed interest in during the qualitative interviews. It was remarked by some participants they had hoped to lose weight by participating in the PA intervention and so I surmise that adding a weight loss aspect to the intervention would be appealing to study participants. Additionally despite existing evidence that weight loss is beneficial in reducing risk of [303] and improving KOA progression and outcomes[107, 157, 304, 305], no web-based weight loss specific programme has been trialled amongst obese KOA participants with this aim of improving symptoms. This is a research gap which needs addressing and could potentially form part of a web-based self-help programme including a PA and weight loss intervention.

Scaling out Vitamin D interventions may be more difficult to achieve as provision of supplements and medical monitoring (for clinical safety reasons) will be required, resulting in associated costs. Approaches which could be considered include prompts for GPs and clinics to perform regular serum 25OHD screening in KOA populations and provision of information regarding how to maintain sufficient Vitamin D levels throughout the year and the importance of this regarding health.

As part of further pilot testing of these interventions I suggest a co-design approach with involvement and input from different user groups, e.g.

- PPI to provide a participant centred input, particularly regarding materials and processes directly affecting participants in the study
- Clinical management organisations, e.g. commissioning groups and CRN to suggest appropriate pathways for patient recruitment and to provide assistance in access to potential participants.
- Clinical teams to suggest how the study may designed to successfully engage clinicians in research and identify which member of the clinical team may have capacity to engage with research

By collating input from different potential user groups, it may be possible to provide further recommendations to refine and design an effective complex intervention to assess the effectiveness of vitamin D and online based PA in obese older KOA patients.

Appendix A.

NHS
Health Research Authority

NRES Committee London - City & East
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421386
Fax:01173420445

29 November 2014

Miss Rebecca Brown
Human Nutrition Research Centre
Insitute of Cellular Medicine
Newcastle University
NE4 5PL

Dear Miss Brown

Study title:	**The Impact of Physical Activity and Vitamin D status on osteoarthritic knee pain in older obese adults: a cross sectional study and pilot RCT**
REC reference:	**14/LO/2184**
IRAS project ID:	**143184**

The Proportionate Review Sub-committee of the NRES Committee London - City & East reviewed the above application on 26 November 2014.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation

with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

The Committee agreed that the application did not present any material ethical issues.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP surgery study invitation and information]	1	12 November 2014
GP/consultant information sheets or letters [Letter to GP on patient involvement in study: North Tyneside v1]	1	12 November 2014
GP/consultant information sheets or letters [Letter to GP on patient involvement in study: Liverpool Aintree v1]	1	12 November 2014
GP/consultant information sheets or letters [Letter to GP on patient involvement in RCT: North Tyneside v1]	1	12 November 2014
GP/consultant information sheets or letters [GP letter on patient involvement in RCT: Liverpool Aintree v1]	1	12 November 2014
GP/consultant information sheets or letters [Letter to GP about study close v1]	1	12 November 2014
GP/consultant information sheets or letters [Letter to GP on study close: Liverpool Aintree v1]	1	12 November 2014
Interview schedules or topic guides for participants [Topic guide for qualitative interview v1]	1	12 November 2014
IRAS Checklist XML [Checklist_20112014]		20 November 2014
Non-validated questionnaire [Potential participant telephone screening]	1	12 November 2014
Other [Supervisor CV: Dr Nicola O'Brien]	1	13 November 2014
Other [Standard operating proceedures manual for study visits]	1	20 November 2014
Participant consent form [Consent form North Tyneside v1]	1	12 November 2014
Participant consent form [Consent form Liverpool Aintree v1]	1	12 November 2014
Participant information sheet (PIS) [Participant Information sheet North Tyneside v1]	1	12 November 2014
Participant information sheet (PIS) [Participant Information Sheet Liverpool Aintree v1]	1	12 November 2014
REC Application Form [REC_Form_20112014]		20 November 2014
Research protocol or project proposal [Study Protocol]	1	12 November 2014
Summary CV for Chief Investigator (CI) [Chief Investigator CV]	1	12 November 2014
Summary CV for supervisor (student research) [John Mathers CV Supervisor V1]	1	12 November 2014
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary of protocol v1]	1	12 November 2014
Validated questionnaire [WOMAC LK3.0 Questionairre]	1	12 November 2014
Validated questionnaire [SF-36v2 Questionairre]	2	12 November 2014

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

There were no declarations of interest.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

14/LO/2184	Please quote this number on all correspondence

Yours sincerely

pp Dr John Keen
Chair

Email: nrescommittee.london-cityandeast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Professor John Mathers*
Ms Caroline Potts, Northumbria Healthcare NHS Foundation Trust

Appendix B.

Northumbria Healthcare NHS
NHS Foundation Trust

Research Support Unit

Prof Richard Walker
Director of Research & Development

Direct Line: 0191 293 2709
Fax: 0191 293 2709

Research and Development Office Direct dial 0191 2934087 or Tel: 0844 811 8111

Caroline Potts	*Head of Research and Development*	*Caroline.potts@nhct.nhs.uk*	*0344 811 8111 Ex 2842*
Lynn Mann	*Research Governance Manager*	*Lynn.mann@nhct.nhs.uk*	*0191 2932511*
Andrew West	*R&D Facilitator*	*Andrew.west@nhct.nhs.uk*	*0344 811 8111 Ex 2816*
Peta Heslop	*Senior Research Nurse*	*Peta.Heslop@nhct.nhs.uk*	*0191 293 2684*
Ann Wilson	*Senior Research Nurse*	*Ann.Wilson@nhct.nhs.uk*	*0191 293 4163*
Norma Cardill	*Office Co-ordinator*	*Norma.cardill@nhct.nhs.uk*	*0191 293 4087*
Liz Costigan	*Admin Assistant*	*Liz.costigan@nhct.nhs.uk*	*0344 811 8111 Ex 2829*
Toni Renwick Smith	*Admin Assistant*	Toni.Renwick-Smith@nhct.nhs.uk	0344 811 8111 Ex 4576

19 December 2014

Miss Rebecca Brown
Human Nutrition Research Centre
Institute of Cellular Medicine
Newcastle University
NE4 5PL

Dear Rebecca

Re: The Impact of Physical Activity and Vitamin D status on osteoarthritic knee pain in older obese adults: a cross sectional study and pilot RCT

R&D Ref: 0173

REC Ref: 14/LO/2184

I confirm that I am happy to give approval and provide indemnity for the above study to take place within this Trust. I am authorised by the Chief Executive to do so on his behalf.

Please note that it is a condition of this agreement that the Research Support Unit ***must*** be notified of:

- Any significant changes to the study design.
- Commencement and completion of the study.
- Any decision made by a Research Ethics Committee regarding this study.
- Any adverse effects upon subjects.
- Any suspension or abandonment of the study.
- All funding, awards and grants pertaining to this study, whether commercial or non-commercial.
- All final reports, publications and/or conference presentations of the findings of the study.

Commencement of any work related to this study, using Trust resources or premises, implies agreement with the above conditions.

Yours sincerely

Caroline Potts
Head of Research & Development

In association with the University of Newcastle upon Tyne

LP30055

NHS CONFIDENTIAL

Ref: **HW/RP**

18th December 2014

Miss Rebecca Brown
1st Floor, Biomedical Research Building
Campus for Ageing & Vitality
Newcastle University
NE5 4QJ

Dear *Miss Brown*

Honorary research contract issued by Northumbria Healthcare NHS Foundation Trust

I am pleased to offer you an honorary research contract in Northumbria Healthcare NHS Foundation Trust. I should be grateful if you would sign the attached three contracts, keep one yourself and return the other two to Human Resources, Northumbria House, Unit 7/8 Silver Fox Way, Cobalt Business Park, Newcastle upon Tyne, NE27 0QJ. We will send a copy of the contract to your substantive employer.

The contract if accepted by you begins on 29th December 2014 and ends on 31st August 2016 unless terminated earlier in accordance with the clauses in the contract. Please note that you cannot start the research until the Principal Investigator has received a letter from us giving permission to conduct the project.

A reservation has been made for you to attend the following Trust Induction Programme to be held on:-

Monday 29th December 2014, in Room, at Cobalt Conference Suite, Northumbria House, Unit 7/8 Silver Fox Way, Cobalt Business Park, from 08:30 am to 4.30 pm.

Please complete the ID application form and bring along to the Trust Induction in order that a Human Resources Representative can issue you with your ID badge.

We will not reimburse any expenses you incur in the course of your research unless we have agreed to do so by prior arrangement. Similarly, we accept no responsibility for damage to or loss of personal property.

Your Research Passport may be subject to random checks carried out by us within the lifetime of the project. The information it contains must therefore remain up to date and accurate.

If your circumstances change in relation to your health, criminal record, professional registration or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform your employer through its normal procedures. You must also inform your nominated manager in this NHS organisation.

NHS CONFIDENTIAL

Honorary Research Contract

HONORARY RESEARCH CONTRACT BETWEEN

NHS organisation(s): Northumbria Healthcare NHS Foundation Trust

AND

Name: Rebecca Brown

Place of Study: Newcastle University

Report To: (Principal Investigator/Head of Department) Dr Fraser Birrell

PERIOD of AGREEMENT

From: 29th December 2014 To: 31st August 2016

SIGNATURES

Researcher: R Brown Date: 22/12/2014

Name: Rebecca Brown

On behalf of the NHS organisation(s) H. Webster Date: 18/12/2014

Name: Hannah Webster

Appendix C.

Research Project Summary – information for GP practices

NHS
North of England Commissioning Support Unit

Study Title: The Impact of Physical Activity and Vitamin D supplementation on knee osteoarthritis pain in older obese adults

Brief summary of the project	The aim of this research is to examine the relationship between Vitamin D status, obesity and osteoarthritic knee pain and to conduct a pilot RCT to test the feasibility of a behavioural intervention to increase PA and a vitamin D supplementation intervention to improve pain in in older obese adults with knee OA. The research aims will be implemented using the following Objectives: Objective 1: To undertake an observational (cross sectional) study to investigate the relationships between Vitamin D status, objectively measured PA, obesity and knee pain in older people with OA. Objective 2: To test the feasibility of an intervention to increase PA and/or to provide Vitamin D supplementation to improve pain in older obese people with knee OA. Objective 3: To explore the acceptability of the two studies in a subsection of the cross-sectional study and pilot RCT trial participants using qualitative interviewing.
What will the practice be expected to do?	A database search and mail out
What will patients be expected to do?	Potential participants will be screened for eligibility by telephone and invited to attend a single session at Newcastle or Liverpool Universities. During this visit they will provide formal written consent and will then be assessed on a battery of measures including: questionnaires, blood samples and physical function and body composition measures. They will be given at that time, an accelerometer to wear for 7 days, which they will then send back to the University in a prepaid envelope. **>64** participants with low Vitamin D and PA status (32 participants per study intervention: vitamin D and PA) will be recruited from the cross-sectional study cohort for a pilot 2*2 factorial blinded RCT to test the feasibility and acceptability of a 3 month Vitamin D and PA intervention to reduce knee pain. Participants will be randomised to receive one of 4 conditions: 1) Behavioural PA intervention and Vitamin D placebo 2) Vitamin D intervention 3) PA and Vitamin D intervention 4) Vitamin D Placebo only Participants will be invited back to the University for Follow-up

Vit D and OA – GP practices Version 1 (NECS) August 2014

	assessments at 6 and 12 weeks, where they will repeat the tests applied during the cross-sectional study. After completion of the study, some participants will be invited to participate in a qualitative interview to assess the feasibility and acceptability of the study.

Inclusion/ exclusion criteria	*Inclusion Criteria* 1. Obese: BMI 30-40kg/m2 as defined by WHO criteria [40] 2. Older adults: 50 – 70 years 3. OA of the knee according to ACR Guidelines on symptomatic Knee OA criteria (using history and physical examination: • Pain in the knee AND 3 OF THE FOLLOWING: • Over 50 years of age • Less than 30 minutes of morning stiffness • Crepitus on active motion • Bony tenderness • Bony enlargement • No palpable warmth of synovium [2] 4. Good understanding of written and spoken English (as no translation services will be available to this study). *Exclusion Criteria* 1. Any other type of arthritic condition, e.g.: o RA o Fibromyalgia o Ankylosing Spondylitis o Gout o Lupus o Paget's Disease o Polymyalgia rheumatic (PMR) o Psoriatic arthritis o Scleroderma o Sjogrens Syndrome 2. Previous joint injury 3. Currently taking part in an PA/exercise regime 4. A medical condition for which exercise is not recommended e.g. unstable angina pectoris or recent myocardial infarction. 5. Taking vitamin D/Calcium supplements 6. Taking part in another research trial/intervention (dependant on the type of study – under researcher opinion) **From the original group above a further group will be highlighted for objective 2:** *Inclusion Criteria (Pilot RCT)* Same inclusion criteria as the cross-sectional trial with addition of: 1. Low objectively measured levels of Vitamin D, defined as: Deficient and insufficient (<50ng/ml) as in accordance with the IOM Guidelines [35], excluding the most deficient (<12.5 nmol/L, the 25OHD concentration at which symptoms as a result of Vitamin D

	deficiency commonly occur). 2. Low PA recorded from accelerometers defined as: <30min/week of moderate PA, <15min/week vigorous PA (2*credit of moderate activity) defined as being 'inactive' by UK government guidelines. Activities only counted if they occurred in >10mins bouts. Activity was defined as moderate if it made the participant 'breathe faster, feel warmer or sweat' and increased heart rate. Activities identified as moderate included: brisk walking, cycling, gardening, housework, DIY, climbing stairs and carrying heavy loads [41]. <u>*Exclusion Criteria (Pilot RCT)*</u> The same exclusion criteria as 5.3.2 1. Conditions which can interfere with Vitamin D supplement adsorption: o Malabsorption syndromes: e.g. cystic fibrosis, celiac disease, whipples disease, Crohns Disease, Bypass Surgery, short bowel syndrome, o Diagnosed restrictive eating disorder 2. Conditions which can affect normal baseline levels of vitamin D: o Current pregnancy, delivery of child/breast feeding 1 year prior to recruitment: as requirement for Vit D is increased at this time. Large Vit D doses have also the potential to harm a foetus. o Holiday with significant sunlight exposure in the last 6 -8 weeks [42] o Current Anticonvulsant drug therapy: this decrease vit D levels as it leads to inactivation of 25OHD in the liver to inactive metabolites. o Current Corticosteroid use: cause severe vitamin D deficiency so may not respond to supplementation in the same way as non-corticosteroid takers. 3. Current conditions which may be made worse/prompts complications of by vitamin D consumption o Chronic Renal Disease o Liver disease o Histoplasmosis o Atherosclerosis o Granulomatous disorders: sarcoidosis, TB, Lymphomas (due to the conversion of 25OHD into 125OHD by macrophages) o hyperparathyroidism o Hypocalcaemia or hypercalcemia o Lymphoma 4. Use of medications/treatments which require caution when taken with vitamin D: o Aluminium Antacids: increases aluminium adsorption (problematic esp. in kidney disease)

	○ Calcipotriene (Dovonex): topical vitamin D The following drugs when taken with Vit D supplements leads to an increase in blood calcium levels which can lead to irregular heartbeat in these people. ○ Digoxin (Lanoxin): used to treat congestive heart failure/arrhythmias ○ Statins: Atorvastatin (Lipitor) ○ Diltiazem: used to treat angina, high blood pressure and heart conditions ○ Verapamil: used to treat angina, high blood pressure and heart rhythm disorders a. Water pills (Thiazide diuretics) 5. Current/recent (in the last 6 months) supplementation with: ○ Phosphorous: phosphate supresses 25OHD conversion into 125OHD by the kidneys so decreases the effectiveness of Vit D ○ Calcium ○ Vitamin D: including prescribed and non-prescribed vitamin D supplements/analogues and any supplements containing fish oil supplements during the past 6 weeks
Study Costs	

If you are interested in taking part or would like more information please contact Norah Phipps on 07467 337836 or norah.phipps@nhs.net

Appendix D.

GP letter head (to be confirmed)

A REQUEST FROM YOUR GP
[Firstname] [Surname]
[Patient Address Line 1]
[Patient Address Line 2]
[Patient Address Line 4]
[Patient Address Line 6]

Date:

Dear **[Title] [Surname]**

The impact of Physical activity and Vitamin D supplementation on Knee Osteoarthritic pain in older adults

Your General Practice is working with Newcastle and Liverpool Universities on a study to measure levels of physical activity and Vitamin D in people with knee osteoarthritis, in order to see whether this is linked to levels of pain experienced in the joint. Eligible people will then take part in a 3 month intervention where they will be given either: daily vitamin D supplements, daily physical activity programme, both or neither.

We are looking for adults 50-70 years old with a BMI 30-40 kg/m^2 with knee osteoarthritis to take part.

Please take time to read and understand the information provided in this form. If you are interested in taking part or have any queries, please contact Miss Rebecca Brown on **0191 248 1131** (9am – 5pm, Monday-Friday) or at **rebecca.brown2@ncl.ac.uk** (at any time) who will be happy to provide you with more information.

It is your decision whether you would like to take part in this study. If you decide to take part, you will have to sign a consent form (a copy of this has been enclosed for your interest). If you decide not to participate, you do not have to respond to this letter.
Thank you for your time and consideration, it is much appreciated

Thank you for your help.

On behalf of xxxx Medical Practice

R&D No: 0173 Participant Invitation letter V3
13/08/2015

Appendix E.

Study Title: The impact of Physical activity and Vitamin D supplementation on Knee Osteoarthritic pain in older adults

Participant Information Sheet

Dear Sir/Madam,

We would like to invite you to take part in our research project being conducted by Newcastle and Liverpool Universities. Before you decide, we would like to describe to you why the research is being conducted and what involvement would mean for you. Please read the information carefully and feel free to discuss it with your relatives, friends or GP. If you would like more information or something is unclear to you, please contact our research team on the contact details provided below.

Do I have to take part?

It is completely your choice whether to take part in this project; you will not experience any negative repercussions if you decide not to take part. You will also be free to withdraw your consent at any point, without providing a reason, which will not affect your future treatment.

Why have I been invited to take part in this study?

You have been identified by your GP surgery as meeting our criteria needed to take part in our project. These are:

- Between 50-70 years old
- A BMI between 30-40 kg/m^2
- Have been diagnosed with knee osteoarthritis or have long term knee pain

Why is the study being conducted?

Osteoarthritis is a common disease of joints and can lead to pain and disability. There are no effective treatments for osteoarthritis, meaning most people will eventually need a joint replacement. Increasing physical activity is often recommended to those with osteoarthritis to

improve symptoms, but the pain experienced by people with osteoarthritis can often prevent them from doing this. This can result in weight gain, which has been shown in other studies to further increase joint pain in osteoarthritis.

Recently, studies have shown that low levels of Vitamin D (essential for bone health) may be linked to worsening of osteoarthritis. As Vitamin D levels are more likely to decrease with increasing age and body weight, these people are more at risk of having low Vitamin D levels.

What does this project involve?

This project includes 2 studies:

Study 1

This study will measure levels of physical activity and Vitamin D to see if this is linked to knee pain in older obese people with knee osteoarthritis. This will involve inviting approx.200 people to attend a one off visit to North Tyneside General Hospital where we will take some measurements during October-December 2015

Study 2

The second study will last 2-3 months, where we will split people randomly into one of 4 groups:

- daily vitamin D supplements
- daily walking programme
- daily vitamin D supplements and walking programme
- Standard care (will not receive a vitamin D supplement or walking programme)

We will need 64 people (16 people per group) who completed Study 1and who have low levels of Vitamin D and physical activity, to see if the above treatments would be convenient and easy to achieve as well as if they have any positive effect on joint pain.

At the end of every month of Study 1 (end of October, November and December) we will review everyone who has completed study 1 to see if they are eligible for Study 2. If you are, we will contact and inform you of this.

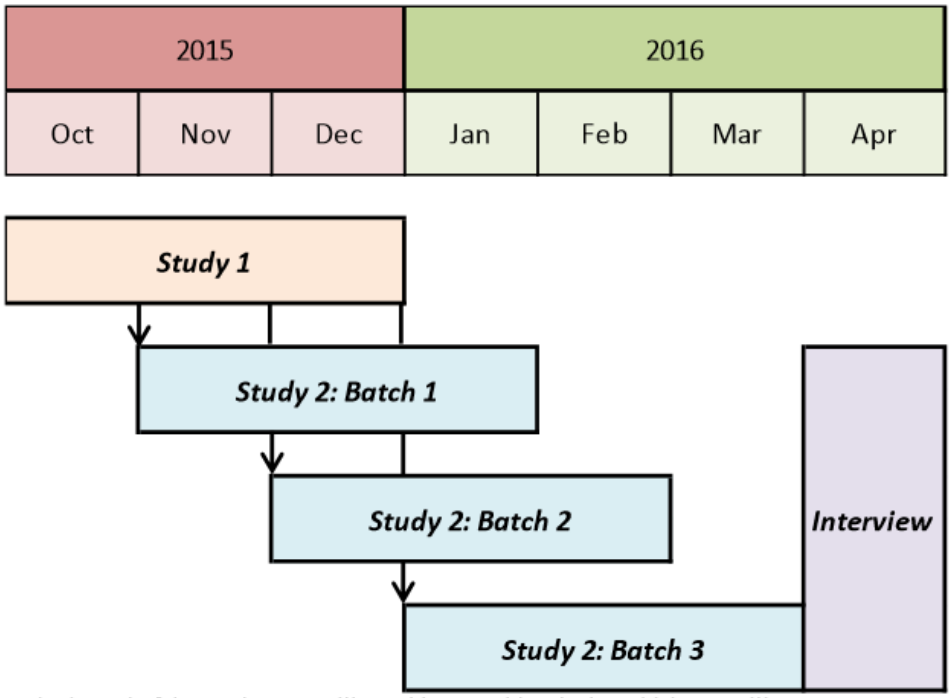
What will I have to do as a participant?

Study 1

If you are interested in taking part in the study, please contact our research team using the details provided below. The researcher will first tell you about the study and ask you some questions; this should take about 10-15 minutes. Please have a list of any medications you are currently taking at the time you call. We will then arrange to attend a visit with us a North Tyneside General Hospital.

The visit will last 1 hour-1 hour 30 mins, during which we will:

- Recap the study information and complete the consent form
- Take measurements on your body weight and height, BMI, Body Fat, waist circumference
- Complete a basic function test: walking and getting up and down from a chair.
- Give you questionnaires to complete concerning any pain you have experienced, and your wellbeing.
- Take blood samples to measure your vitamin D levels



At the end of the session, we will provide you with a device which you will wear on your body for the following 5 days after the visit, which measures your movement and allows us to measure how physically active you are. You will be provided with a pre-paid envelope to post this back to us.This will be the end of the first study. We will contact you within a month after this, to inform you if you are eligible for *Study 2*and to provide you with your study results.

Study 2

If you are eligible and if you are interested in participating in the second study we will mail you a study starter kit, with:

- A leaflet recapping what the study involves. The group you have been randomly assigned to (described below)
- Information on how to complete your intervention and any materials you will need.
- A self-addressed pre-paid card to send back to the study team as acknowledgement of receipt.

After you have received your study starter kit and mailed back your receipt, we will arrange a telephone meeting with you to run though the instructions you have received.

This study will be 3 months long and will involve 2 follow-up visits: 4-6 weeks and 8-12 weeks into your intervention. These follow-up visits will last approx. 1hour 30mins, during which we will:

- Retake all of the measurements we took during study 1
- Ask you questions about and monitor the progress of your intervention

At the end of the study, we may invite you to an additional hour long interview session to explore your opinions on your experience during the study. This will help us highlight important issues which will improve the participant's experiences in future studies.

What will the intervention involve?

We will assign you a group randomly, meaning you have equal chance of being assigned to each group. You will be informed what group you are taking part in at the start of the intervention.

1. ***Vitamin D group***

You will be provided with 90 (3month supply) Vitamin D capsules (2000 international units each) to be taken daily. This aims to increase your Vitamin D levels to within a normal range.

2. ***Physical Activity group***

You will be provided with personal login details to an online system which you will use to record your daily steps and set goals. We will also give you a pedometer for you to wear and count your daily steps.

3. ***Vitamin D and Physical Activity group***

You will receive both the treatments outlined in 1 and 2 above for 3 months.

4. ***Standard Care***

You will not receive either the vitamin D supplement or the walking programme. You will continue with your usual care routine as your doctor recommends.

We will ask you, as part of the study, **not** to use sunbeds, go on a sunny holiday or spend time deliberately lying in direct sunshine. We ask this because this will affect your Vitamin D levels and therefore will affect our study.

What are the risks of taking part?

You may experience some mild discomfort when the blood sample is taken and possible mild bleeding or bruising afterwards.

What are the benefits of taking part?

You will gain access to information on your physical activity and Vitamin D levels, information GPs will not routinely have access to.

Will my expenses be covered?

We will cover the expenses of your travel to and from the visits, if you could keep your tickets or receipts.

What will happen if anything goes wrong?

If you have been harmed in this study as a result of someone else's negligence or wrong doing, you may have grounds for legal action against the Northumbria Healthcare NHS Foundation Trust, but you may have to pay for legal costs.

If you wish to make any complaints throughout or following the study, you may contact the research team or, if preferable, the NHS Complaints system and Newcastle University to make a more formal complaint.

Will my information be confidential?

Yes. Only the researchers involved will have access to the information you provide. Information which identifies you (e.g. your name and address) will be destroyed at the end of the study. Any remaining information after this will not be identifiable as belonging to you; this includes all publications and meetings. You may also specify on your consent form whether your GP should be informed of your participation in this study.

What do I do if I decide I no longer want to take part?

If at any point before, during or after the study visit, you wish to no longer take part, just contact the research team to inform them.

Who is performing the research?

The members of our research team include:

- Study Manager: Miss Rebecca Brown, PhD Student, Newcastle University
- Professor John Mathers, Professor of Human Nutrition, Newcastle University
- Dr Nicola O'Brien, Research Associate in Health Psychology, Newcastle University
- Dr Daniel Cuthbertson, Clinician and Research Associate of Obesity and Endocrinology, Liverpool University.
- Ms Caroline Potts, Research and Governance Manager and Study Sponsor, Northumbria Healthcare NHS Foundation Trust
- Mr Andrew Irwin, Research Nurse, University Hospital Aintree, Liverpool University.

What do I do next?

If you are interested in taking part in this study or have any questions concerning the information above, please contact Miss Rebecca Brown by email or telephone, who will be happy to answer your enquires and make appointments for study visits.

Contact details

Miss Rebecca Brown:

Telephone: 0191 248 1131 (please call between 9am and 5pm, Monday-Friday)

Email: rebecca.brown2@ncl.ac.uk (contact at any time)

We hope to hear from you soon, thank you for reading and considering the above information.

Yours Sincerely

Miss Rebecca Brown (Study Manager)

Human Nutrition Research Centre

Institute of Cellular Medicine

Newcastle University

Newcastle upon Tyne

NE4 5PL

This work is supported by the Medical Research Council and Arthritis Research UK as part of the MRC-Arthritis UK Centre for Integrated research into Musculoskeletal Ageing (CIMA).

Appendix F.

Centre: **North Tyneside General Hospital**

Patient Identification Number for the trial: #

CONSENT FORM

Title of the Project: **Impact of Physical Activity and Vitamin D status on Knee Osteoarthritis (KOA) pain in older obese adults**

1. I confirm that I have read and understand the information sheet dated 16/02/2015 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected ☐
3. I understand that my participation involves additional invasive tests or samples required for research purposes only and that this data may be retained for use in future studies. ☐
4. I understand that, where it is relevant to my taking part in this research, individuals from the Newcastle and Liverpool Universities research team, from regulatory authorities or from the NHS Trust, may look at data collected during the study. I give permission for these individuals to have access to my information. ☐
5. I agree to my GP being informed of my participation in the study. ☐
6. I agree to take part in the above study. ☐
7. I would like to be contacted about and take part in the pilot RCT (study 2) if I am eligible to do so. ☐

8. I would like to be contacted about taking part in an interview about my experiences of the studies ☐

9. I agree to the use of audio recording equipment during the interview ☐

10. I agree that the research team can retain my details and contact me for further research. ☐

Name of Participant	Date	Signature

Name of Researcher	Date	Signature

Appendix G.

Screening Questionnaire

Participant Details

Date..... Institution.....

Name of researcher completing form.....

Participant Name.....

Participant telephone contact number.....

Participant email.....

Participant Address.....

..... Postcode.....

Participant D.O.B..... Participant age.....

Gender: MALE/ FEMALE

Weight (approx. as last measured).....

Height.....

BMI.....

Occupation.....

Do you smoke? YES/ NO/ PREVIOUSLY

Participant Ethnicity

White

□ English/Welsh/Scottish/Northern Irish/British

□ Irish

□ Gypsy or Irish traveller

□ Any other white background (describe).....

Mixed/Multiple ethnic groups

□ White and Black Caribbean

□ White and Black African
□ White and Asian
□ Any other mixed/multiple ethnic group (describe).....

Asian/Asian British
□ Indian
□ Pakistani
□ Bangladeshi
□ Chinese
□ Any other Asian Background (describe).....

Black/African/Caribbean/Black British
□ African
□ Caribbean
□ Any other Black/African/Caribbean background (describe).....

Other ethnic group
□ Arab
□ Any other ethnic group (describe) .....

Criteria for knee OA

1. Have you ever been diagnosed with knee osteoarthritis or 'knee pain' by a doctor? YES/ NO
2. If yes, which knee? RIGHT/ LEFT/ BOTH
3. Do you currently experience pain in the affected knee? YES/ NO
4. Is there 'morning stiffness' in the knee reported, which eases within 30 mins? YES/NO

Recent Travel

1. Have you been on holiday in the last 3 months? YES/ NO
2. If yes, where did you visit on holiday? .....
3. What date did you leave for holiday? .....
4. What date did you return from holiday? .....

Knee Injury

1. Have you ever injured your painful/OA affected knee? YES/ NO
2. Have you ever had any surgery performed on your knee? YES/ NO
3. If yes to Q2 please specify.....

Current health status

1. Are you currently taking part in a PA/exercise programme or class? YES/ NO
2. Do you currently drink more than 21 (women)/28 (men) units of alcohol per week? YES/ NO
3. Apart from knee pain/osteoarthritis, do you have any other health conditions? YES/ NO
4. If yes to Q3, please specify conditions by name.....

Current Medications

1. What medications are you currently taking (prescribed or non-prescribed)

Current Medications

2. Are you currently taking any supplements (prescribed or non-prescribed)? YES/ NO
3. If yes, specify below:

.....
.....
.....
.....
.....
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.....
.....

Patient Eligibility

1. Does the participant meet any exclusion criteria? YES/ NO
2. Based on this questionnaire, is the participant eligible to be invited into the cross-sectional study? YES/ NO
3. Based on this questionnaire, is the participant potentially eligible for the pilot RCT? YES/ NO
4. If potential participant is eligible, are they interested in taking part in the study? YES/ NO
5. If yes to Q4, book and confirm appointment details:

Appointment details

Location..... Date and Time.....

Appendix H.

Vitamin D, Obesity and Knee OA study

What's the study?

The aim of this study research is to examine the relationship between Vitamin D levels, obesity and osteoarthritic knee pain. This year **(September-December 2015)** we will be recruiting patients from secondary care physio clinics in University Hospital Aintree for a one off **1.5 hour study visit at Liverpool University** (Clinical Sciences Centre) to measure vitamin D, physical activity and pain levels in eligible people.

Recruitment:

We would like you to recruit referrals to your clinic at their assessment visit against the following criteria:

INCLUSION CRITERIA

1. Obese: BMI 30-40kg/m2

2. Older adults: 50 – 70 years

3. Diagnosed OA of the knee (use ACR Guidelines on symptomatic Knee OA criteria to check against):

- Pain in the knee

AND 3 OF THE FOLLOWING: <30 minutes of morning stiffness, Crepitus, Bony tenderness, Bony enlargement, No palpable warmth of synovium

4. Good understanding of written and spoken English

EXCLUSION CRITERIA

1. Any other type of arthritic condition, e.g. RA, Fibromyalgia, Ankylosing Spondylitis, Gout, Lupus

2. Chronic alcohol abuse (> 21 (women) and 28 (men) SI units/week)

If patient meets the criteria above, please provide with patient information envelope!!

If you have any questions about the study, please contact Miss Rebecca Brown:

Email (rebecca.brown2@ncl.ac.uk) Phone: 0191248 1131

Standard Operating Procedures Manual

The role of Vitamin D and Physical activity in knee osteoarthritic pain in older obese people: a cross-sectional and pilot RCT study

Miss Rebecca Brown

19/10/2015

Human Nutrition Research Centre,

Institute of Cellular Medicine,

Newcastle University

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Recruitment

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

Cross-Sectional Study

Two different recruitment strategies will be used for the 2 different research sites at North Tyneside and Liverpool. North Tyneside will use GP surgery list screening to recruit potential participants and Liverpool Aintree will recruit directly from physiotherapy clinics.

North Tyneside

1. GP surgeries, approached by the North East Commissioning service, will be recruited to recruit for this study
2. Interested surgeries will search their patient databases for potential participants and mail out the study information (invitation letter, participant information sheet and consent form) to eligible people.
3. Interested individuals will call the study team (Rebecca Brown, Newcastle University) where a short telephone questionnaire will be conducted to confirm eligibility.

If person is eligible and willing to participate in the study, a study visit will be arranged:

- General availability of the potential participant will be determined (enquire of availability for the next couple weeks)
- Availability of Room and Nurse will be booked at NTGH Education Centre
- Researcher will call back potential participant to confirm a time and date for study visit
- Study visit will be booked and confirmed with the Education centre NTGH
- Appointment letter for study visit (and map indicating where they need to go) will be mailed to participant.

Liverpool

Potential participants will be identified in physiotherapy clinics by physiotherapist (Paul West) at University Hospital Aintree.

Study information (invitation letter, participant information and consent form) will be handed out to potential participants.

Interested people will call the study team (Rebecca Brown, Newcastle University) where a short telephone questionnaire will be conducted to confirm eligibility.

If person is eligible and willing to participate in the study, a study visit will be arranged:

- General availability of the potential participant will be determined (enquire of availability for the next couple weeks)
- Availability of Room and nurse will be enquired at Clinical Sciences Centre, Aintree Hospital.
- Researcher will call back potential participant to confirm a time and date for study visit .
- Study visit will be booked and confirmed with the Clinical Sciences Centre, Aintree Hospital.
- Appointment letter for study visit (and map indicating where they need to go) will be emailed to participant.

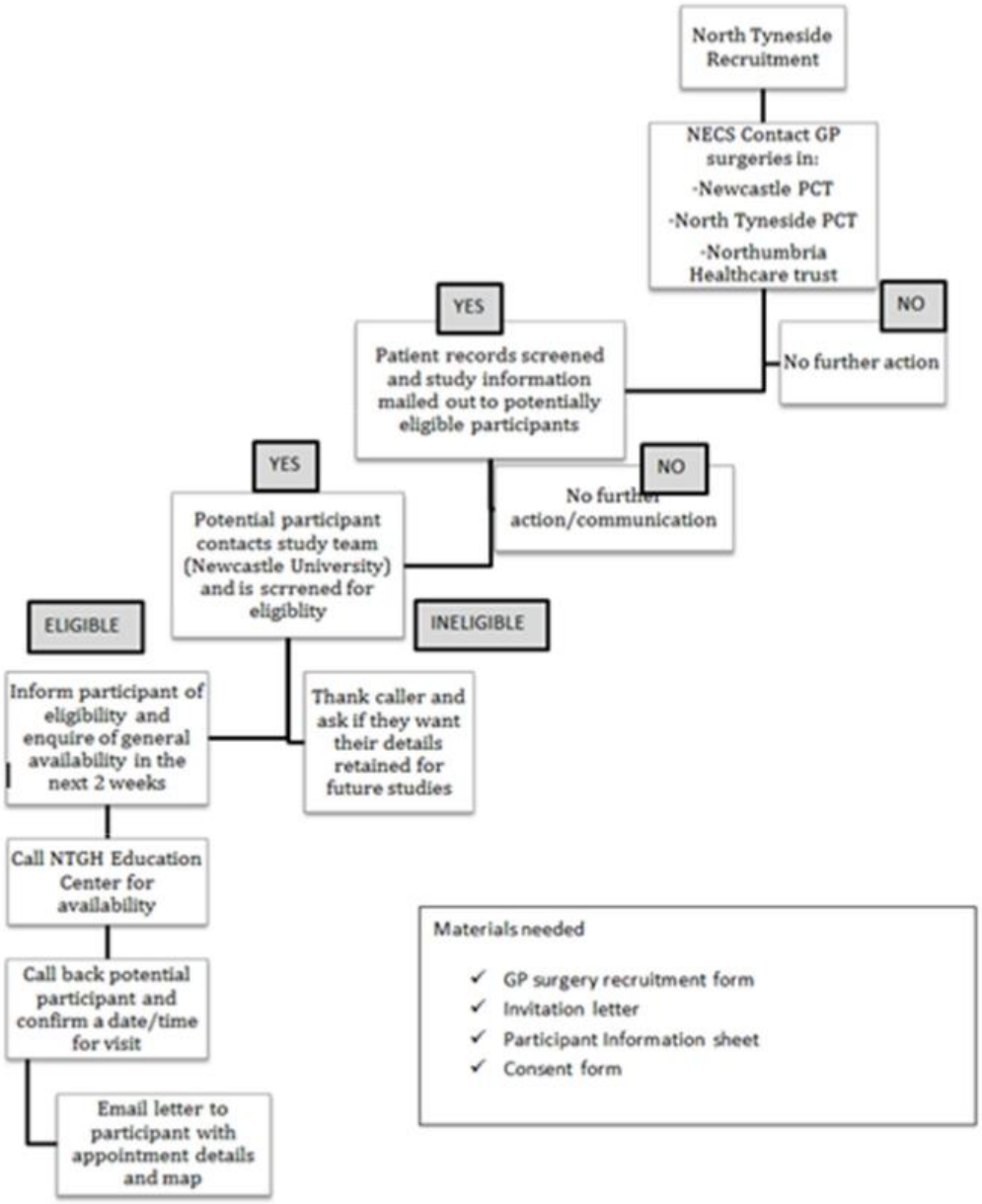

Figure 1: Participant Recruitment at North Tyneside

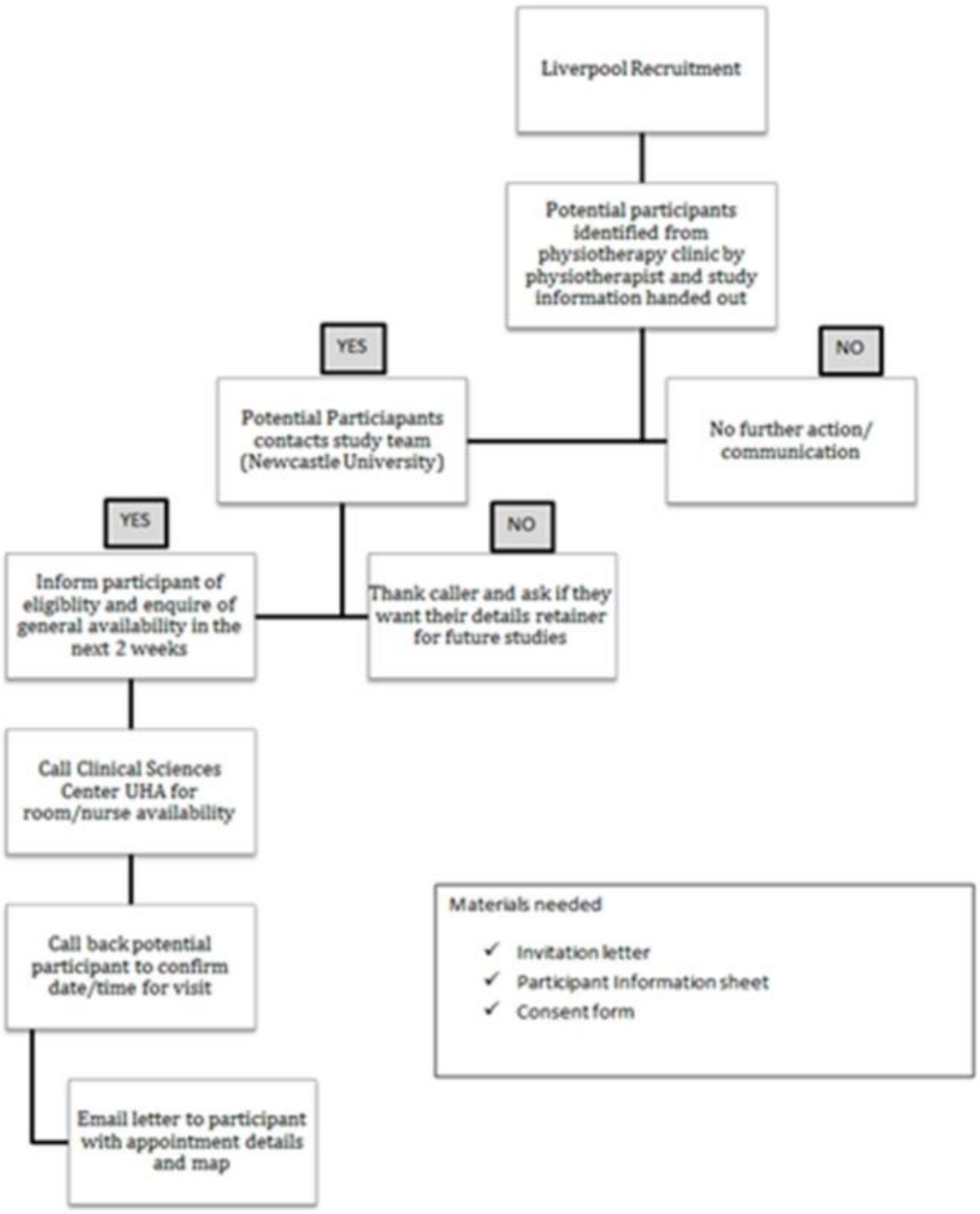

Figure 2: Participant Recruitment at Liverpool

Pilot RCT (North Tyneside and Liverpool sites)

Participants for the Pilot RCT study will be recruited from the existing pool of participants who have completed the Cross-sectional Study and have indicated in the written consent form they would like to participate in the pilot RCT study.

1. Recruitment for the pilot RCT will be staggered, into 3 'batches', with the cross-sectional study participants assessed for eligibility (using the cross-sectional study results) into the pilot RCT study study at the end of every month of the cross-sectional study period (October-December 2015): see Figure 3.
2. All individuals identified as eligible for the pilot RCT will be contacted and informed, and verbally reconsented into the pilot RCT study.
3. All eligible and willing participants for that batch of pilot RCT will then be randomly allocated to an intervention arm;
    a. Vitamin D supplementation
    b. Online PA intervention
    c. Vitamin D supplementation and Online PA Intervention
    d. Standard Care
4. Participants will be sent an intervention pack corresponding to their allocated intervention arm, containing: Instructions on how to follow their intervention, materials required for the intervention and a postcard to return to the study team (to markk receipt of the intervention pack0
5. If receipt of the intervention pack is not indicated within a week of intervention pack post out, the participant will be contacted and followed up by the study team.
6. After receipt of the intervention pack is confirmed, the study team will arrange a telephone meeting with the participant to: explain the intervention, the steps involved and allow the opportunity for the participant to ask any questions. The participant will also be asked to repeat back their understanding of the intervention and instructions to ensure the participant has full understanding of what is required.
7. After the telephone meeting is completed, the pilot RCT will officially begin for that participant.

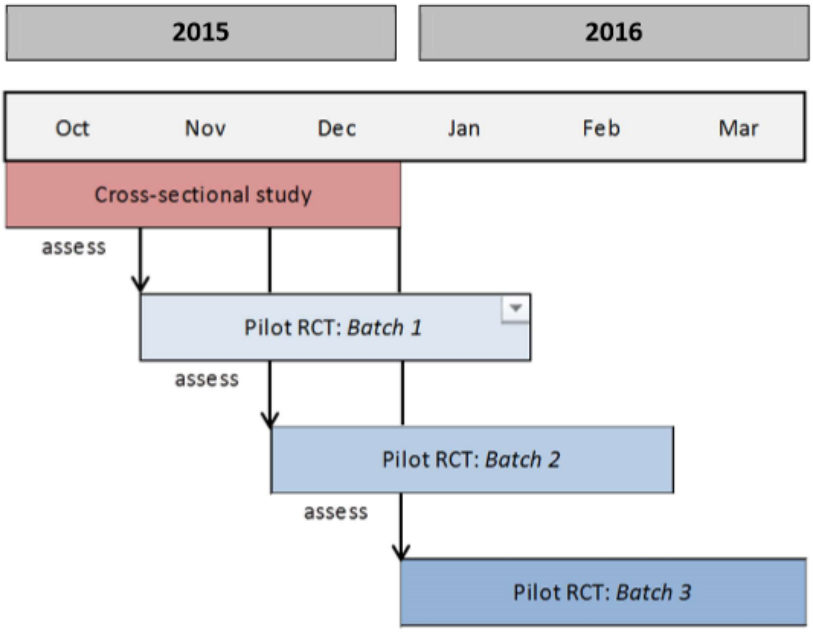

Figure 3: Diagram summarising the recruitment strategy for the pilot RCT study. Participants who have completed the cross-sectional study (October-December 2015) are assessed at the end of every month (October, November and December 2015) for eligibility into the pilot RCT. Eligible and willing individuals are then immediately entered into and begin the pilot RCT at the start of the subsequent month (November, December 2015 and January 2016), create 'batches' of participants within the pilot RCT study.

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Screening

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

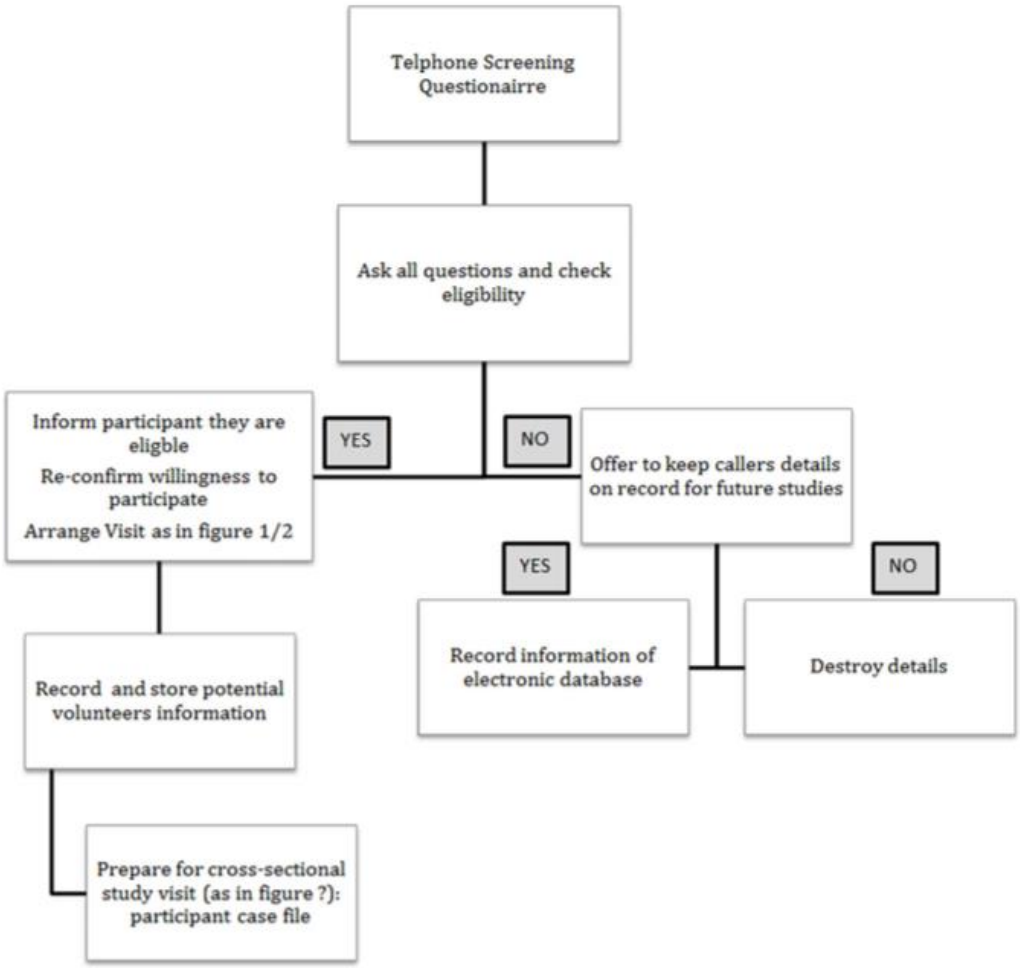

Figure 3: Telephone screening questionnaire procedure

Materials needed

- ✓ Telephone screening questionnaire
- ✓ Telephone screening guide
- ✓ BMI chart

Consent Form

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

Completing the consent form

Equipment needed:

- Pen
- Consent for
- Participant Information sheet

Method:

1. Ask if the participant has read the participant information sheet and understand what is involved in the study.
2. Explain in detail what the study involves:
    a. What is the purpose of the study
    b. What are the aims of the study
    c. What measurements will we perform and why?
    d. Notify participants will receive basic feedback after the study results have been analysed
3. Ask participant if they have any questions and provide appropriate answers.
4. Ask if they would like their GP informed of their participation in the study.
5. If they have understood this and are happy to proceed with the study, provide the participant with the consent form. Explain they will sign to declare they understand what is involved in the study and they agree to participate.
6. Once form is completed, make one copies (one for participant, one for study file

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Anthropometric Measurements

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

Waist Circumference:

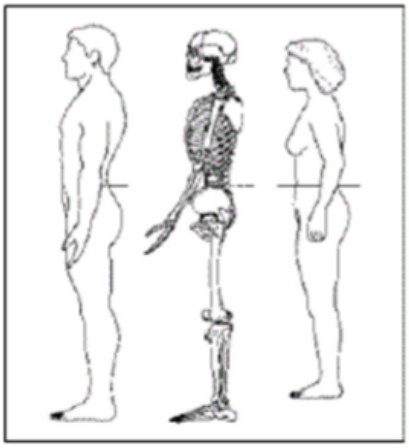
Equipment required:

- Tape measure

Instructions:

1. Ask the participant to remove any heavy upper garments. Inform the participant this is necessary to obtain an accurate measurement.
2. Ask the participant to identify the 2 bone landmarks: the lowest rib and iliac crest.
3. Measure the waist at the midpoint between the lowest rib and iliac crest (see diagram below).
4. Make sure the tape is not too tight or too loose. Ensure the tape is lying flat on the skin and is horizontal.
5. The measurement should be made during exhalation
6. Note down the measurement
7. Inform the participant the measurement is finished.

Figure 1: Measuring tape position for waist circumference



Body Height:

Equipment required

- Stadiometer (height ruler)

Instructions:

1. Ask the participant to remove their shoes.
2. Ask the participant to step onto the height scale.
3. Stand straight with feet together, arms by the side. Heels, buttocks and upper back should also be in contact with the wall when the measurement is made.
4. Gently lower the ruler until it reaches the **highest point of the head.**
5. Note down the measurement.
6. Inform the participant the measurement is finished and they can step off the scale.

Bio impedance

Equipment:

- Tanita 300 bio impedance scales

Instructions:

1. Ask the participant to empty his/her pockets and to remove shoes and socks/tights
2. Press the ON/OFF button to turn on the power
3. Enter 0.5 kg to allow for clothing weight. Then enter the gender and body type of the participant (1 of 4 body types): Standard Male and Female and Athletic Male and Female. Athletic is defined as a person who is involved in intense physical activity (will not apply to anyone in our study)
4. Enter the age and height of the participant
5. Wait till the device flashes 'step on'
6. When ready, ask the participant to place feet **wholly** on both anterior and posterior electrodes and remain still until the measurement is complete.
7. When measurement is complete ask participant to step down.

Timed up a go test

Equipment:

- Chair (standard height 40-50cms from ground)
- Floor marker/cone
- Tape measure
- Timer/stopwatch

Demonstration:

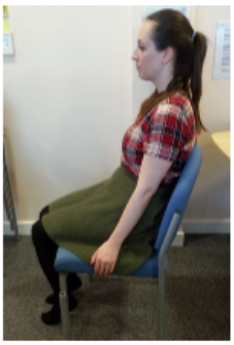
1. Show them the course.
2. Say 'this activity involves sitting on a chair, standing up, walking 2 meters at a **normal pace**, turn, walk back to the chair and sit down. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street'.
3. Examiner then physically demonstrates the task: 'let me show you what I want you to do….'

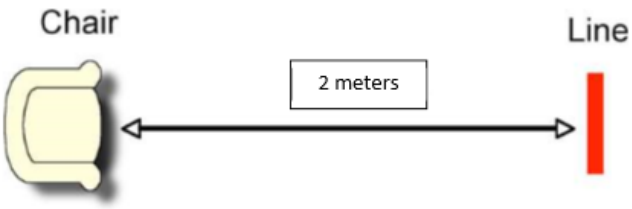
Participant practice trial run

1. Say 'now you try. Remember to walk at your usual speed. Ready? 3, 2, 1, go!'. Give encouragement.
2. Ask if they have any questions and answer.

Instructions:

1. First go through the demonstration procedure.
2. Then allow the participant a practice run (go through participant practice procedure). Do not record/note down the results of this go.
3. Start the first trial: Say 'This time I am going to time you. Are you ready? 3, 2, 1, go!' Begin timing with the stopwatch on the word 'go' and finish timing when the subjects back has touched the backrest of the chair.
4. Repeat 2 more times with a short rest between each turn.





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Questionnaires

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

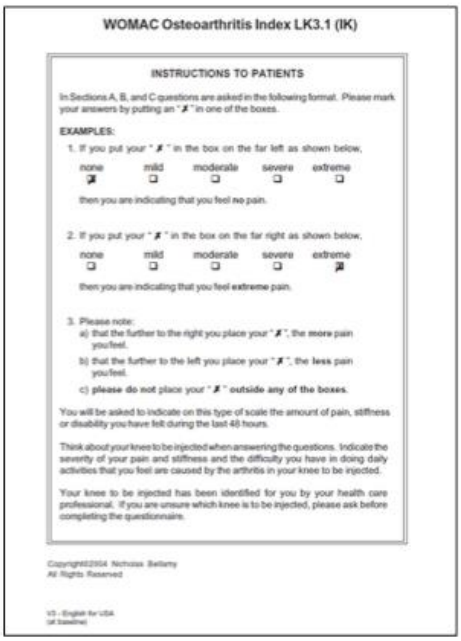
WOMAC Questionnaire

Equipment:

- WOMAC Version 3.1 Questionnaire: paper copy
- Pen
- Desk and Chair

Instruction:

1. Describe the purpose of the questionnaire. Say 'This is a questionnaire to measure your pain stiffness and function in your OA joint. There are 24 questions and it should take about 10 minutes to complete'.
2. Describe how to complete the questionnaire: say 'Next to each question are 5 options corresponding to how strongly you agree with the question: none, mild, moderate, severe and extreme. Please pick one as your answer to the question. Please let me know if you need any help or have any questions'
3. Allow participant time to complete the questionnaire.
4. Write participant ID onto questionnaire and store in participant case file.



WOMAC Osteoarthritis Index LK3.1 (IK)

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an "✗" in one of the boxes.

EXAMPLES:

1. If you put your "✗" in the box on the far left as shown below,

none	mild	moderate	severe	extreme
☒	☐	☐	☐	☐

then you are indicating that you feel no pain.

2. If you put your "✗" in the box on the far right as shown below,

none	mild	moderate	severe	extreme
☐	☐	☐	☐	☒

then you are indicating that you feel **extreme** pain.

3. Please note:
   a) that the further to the right you place your "✗", the **more** pain you feel.
   b) that the further to the left you place your "✗", the **less** pain you feel.
   c) **please do not** place your "✗" **outside any of the boxes.**

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your knee to be injected when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your knee to be injected.

Your knee to be injected has been identified for you by your health care professional. If you are unsure which knee is to be injected, please ask before completing the questionnaire.

V3 - English for USA
(IK baseline)

VAS Pain Scale

Equipment:

- VAS Pain Scale: paper copy
- Pen
- Ruler
- Desk and Chair

Instruction:

1. Provide the participant with the paper VAS scale and explain the purpose of the scale. Say 'This is a question to measure your pain. Please put a mark along the line which describes the level of everyday pain you usually experience., where 0 is no pain and 10 is the worse pain you could experience'.
2. When the participant has completed this, measure (using a ruler) the distance between 0 and the participants mark in mm. Note this down on the data collection sheet.
3. Write participant ID onto questionnaire and store in participant case file.

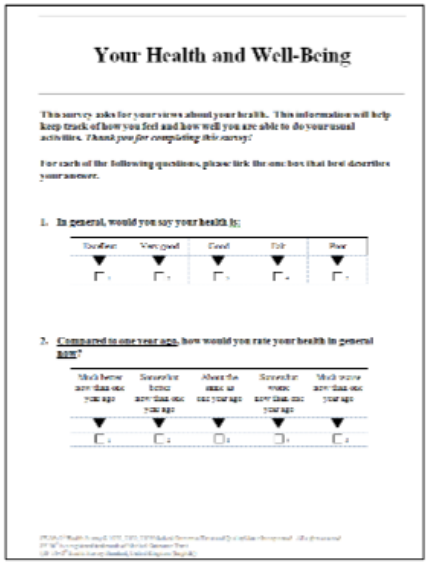
SF-36 Questionnaire

Equipment:

- SF-36 Version 2 Questionnaire: paper copy
- Pen
- Desk and Chair

Instruction:

1. Describe the purpose of the questionnaire. Say 'This is a questionnaire asking about your views on your health. This gives us an idea of how you feel and how well you're able to do your usual activities. There are 11 questions and it should take about 15 minutes to complete'.
2. Describe how to complete the questionnaire: say 'Next to each question please pick the answer you feel is most appropriate for the previous 4 weeks. Please let me know if you need any help or have any questions'
3. Allow participant time to complete the questionnaire.
4. Write participant ID onto questionnaire and store in participant case file.


Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

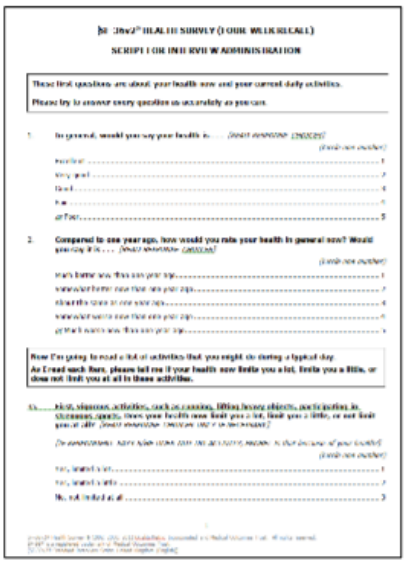
For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5


SCRIPT FOR INTERVIEW ADMINISTRATION

These first questions are about your health now and your current daily activities.

Please try to answer every question as accurately as you can.

1. In general, would you say your health is: ..... [READ RESPONSE CHOICES]

(Circle one number)

excellent 1
very good 2
good 3
fair 4
poor 5

2. Compared to one year ago, how would you rate your health in general now? Would you say it is ..... [READ RESPONSE CHOICES]

(Circle one number)

much better now than one year ago 1
somewhat better now than one year ago 2
about the same as one year ago 3
somewhat worse now than one year ago 4
much worse now than one year ago 5

Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities.

3. ..... [list, vigorous, activities, such as running, lifting heavy objects, participating in strenuous sports]. Does your health now limit you a lot, limit you a little, or not limit you at all? [READ RESPONSE CHOICES] [DO NOT PROMPT]

(Circle one number)

yes, limited a lot 1
yes, limited a little 2
no, not limited at all 3

Blood sample Collection

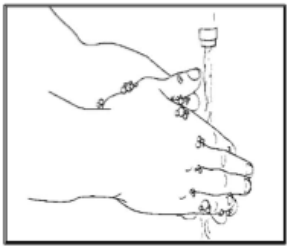
Rebecca Brown R&D 0173

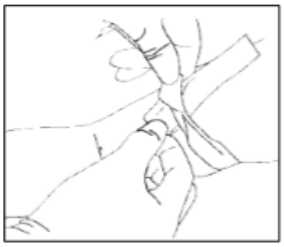
Version: 3.0 19/10/2015

Venous Blood Sample

Equipment

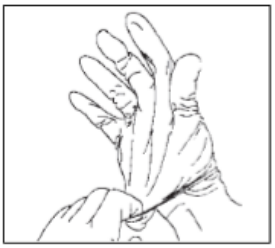
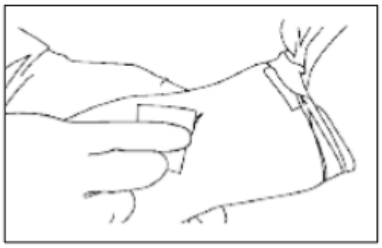
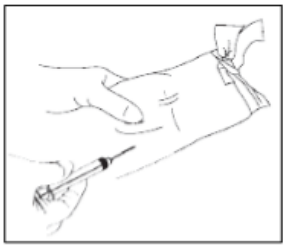
- Chlorhexidine Gluconate 2% in 70% isopropyl alcohol
- Non sterile gloves
- Apron
- Tourniquet
- Sterile gauze swab
- Sharps bin
- Gold top Vacutainer blood collection tube
- Vacutainer winged butterfly system blood collection system
- Spot plaster





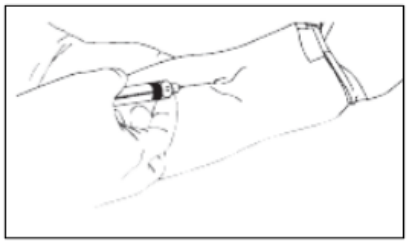
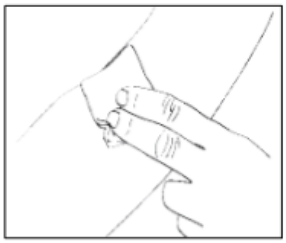
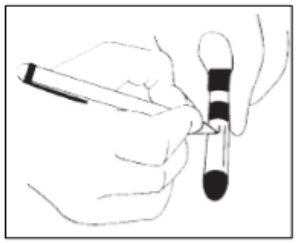
Instruction:

1. Wash hands with antiseptic solution
2. Ensure the participant is comfortable and their arm is well supported.
3. Apply a clean tourniquet about 5-10cm above the intended insertion site
4. Inspect, palpate and identify a suitable site: if this is difficult use measures to encourage venous filling such as warm compress.

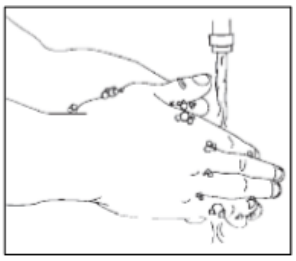
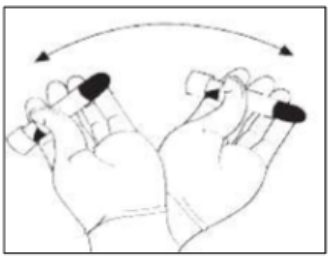




5. Put on non-sterile gloves
6. Clean the intended insertion site using a single use 2%chlorhexidine in 70% alcohol for 20-30 seconds and allow the skin to completely dry (do not repalpate the skin after this)

7. Access the vein using the ANTT (aseptic non-touch technique)
8. With the bevel of the needle pointing uppermost, enter the vein at 30 degree angle.
9. Withdraw the blood slowly and check the bottle is full.

10. Release the tourniquet
11. Place the gauze swab over the site and withdraw the needle from the vein. Do not apply pressure until the needle has been fully removed. Ask participant to continue to apply pressure to the site.
12. Dispose of sharps and equipment immediately and dispose of gloves then wash hands.
13. Ensure blood flow has stopped at the insertion site and apply spot plaster.
14. Invert the tubes and label the bottle with participant ID, date and time.

Dried Blood Spot Sample

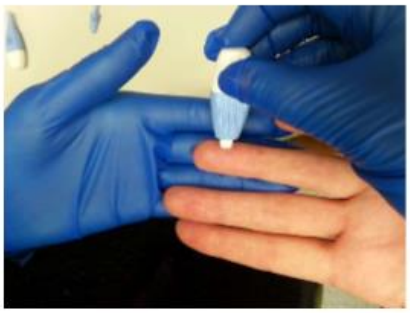
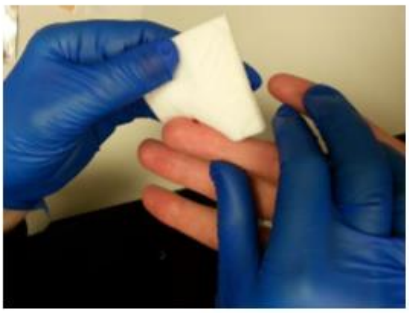
Equipment:

- Whatman Protein Saver 903 Card
- Sealable plastic bag (sealable, heavy duty and waterproof)
- Desiccant pack
- Non-sterile disposable Gloves
- Sharps bin
- Chlorhexidine Gluconate 2% in 70% isopropyl alcohol swabs
- Sterile blood lancet
- Sterile gauze
- Spot plaster

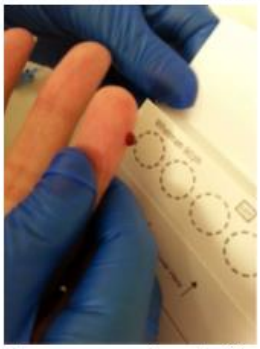
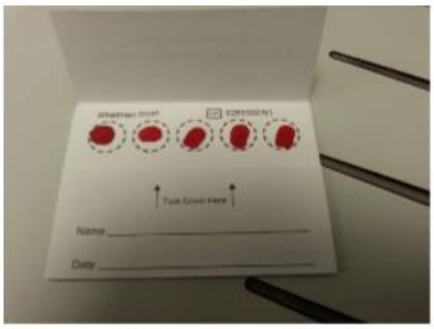
Instruction:

1. Explain what will happen to the participant: say 'I am now going to take a drop of blood from your finger and place it on this card. We'll use this to measure your Vitamin D levels'
2. Take equipment out of the plastic bag and arrange in from of you (remove card from packet and open the card (do not touch the filter paper).
3. Wash hands and don gloves
4. Ask participant to wash their hands with soap and warm water for 1-2 mins and dry their hands well.

5. Ensure the participant is sat comfortably with their arm extended. Use the third or fourth fingers of the hand (these are the best to perform a fingerprick on). Don't use the tip or centre of the finger.
6. Clean the fingerprick site with the alcohol swab for 20-30 seconds and allow the skin to completely dry.

7. Warn the participant they will feel a sharp scratch and using a sterile lancet, penetrate the skin just off the centre of the finger pad.
8. With a sterile gauze, wipe away the initial spot of blood.
9. Apply gentle pressure to the finger and allow a large drop of free flowing blood to collect at the fingerprick site
10. Hold the DBS card by the edges and touch it gently against the large drop of blood (do not

press the paper against the finger), allowing a sufficient amount of blood to saturate a fill the circle on the paper (do not layer blood drops onto the same circle). This spot should contain about 100µl blood.

11. When all 5 spots on the card have been filled with blood, have the participant hold sterile gauze against the fingerprick site for a couple minutes so the bleeding stops. Place a spot plaster on the site.
12. Write on the participants study ID and the date and time the sample was taken in permanent marker.
13. Allow the card to air dry completely in a horizontal position (at least 3 hours at room temperature). Keep away from direct sunlight and open window as this will compromise the sample. During this time do not stack or heat the cards or allow the blood to come into contact with any surfaces. It will turn from bright red to dark red when it dries.
14. Once dry package the cards for storage and transportation:

15. Place card into the sealable bag (ensure decissicant packet is inside)
16. Using a permanent marker, clearly label the bag with the contents (Study Site, Date and participant ID)

Accelerometry

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

Preparing the accelerometer

Equipment needed:

- GT3X accelerometer
- connecter cable
- Actilife software
- Actilife manual

Method:

Before the study visit:

Accelerometers will be charged, initialised and data downloaded by Rebecca Brown, Newcastle University as Actilife software is required to carry this out:

1. Ensure the Actigraph is fully charged. Devices can be charged by attaching the device to computer using the USB cable. Once fully charged the light will remain on in the device.
2. Initialise the device by connecting the device to the computer via USB cable. Open Actilife 5 software. Select the check box next to the device to be initialised and click the 'initialise' button.

Demonstrating accelerometer use and providing the accelerometer to the participant

Equipment needed:

- GT3X accelerometer (initialised)
- Elastic belt
- Participant instructions on accelerometer use
- Accelerometer log (participant)
- Accelerometer tracking log (case form)

Method:

1. Explain to the participant what the device is and why it is being used. E.g. 'this is a device to measure how active you are. We need this to track how active you usually are'.
2. Explain how to use the device and demonstrate on self. Points to cover include:
    a. How to wear the device: 'you must wear this around you hips. It attaches using the elastic belt' (put device on around the hips to demonstrate)
    b. How the device should feel: 'It can be worn above or beneath you clothing e.g. through your belt loops. It must be snug against your body (but doesn't have to touch your skin) to stop it moving around.'
    c. Practical requirements: 'the device is not waterproof so avoid submerging it in water', 'the device needs to be worn for 3 full days for at least 10 hours a day, so please wear the device as long as you can. It can be taken off for showers and sleep. Please record when you take off/put on the device using the log we have provided you'.
    d. Declare when recording will start and stop. 'the device will start to record at 00:00 on the 00/00/0000 (this is also written on your log form) and will stop recording 00:00 on the 00/00/0000'.
    e. Instructions on return of the device. 'you will need to return the device on 00/00/0000 using the self-addressed/prepaid envelope we have provided you with. Please return the device, the elastic belt, and log form in the envelope (this will be covered on the written instructions).
3. Provide the participants with the equipment above (except tracking log) , explaining what each one is.
4. Make sure the participant is happy they know what to do.
5. Fill out the accelerometer tracking form as indicated on the form.

NB: Self-addressed envelopes will be addressed to the Biomedical Research Building in Newcastle University for data downloading and initialisation. From here devices for Liverpool will be sent back to University Hospital Aintree (Liverpool)

Qualitative Interview

Rebecca Brown R&D 0173

Version: 3.0 19/10/2015

Qualitative Interview

Equipment needed:

- Topic guide
- Pen and paper
- Audio recorder
- Extra recorder tape
- Extra batteries

Method:

Before the interview

1. Ensure the voice recorder is fully charged and working
2. Familiarise self with topic guide

In the interview

3. Welcome the participant and ask them to make themselves comfortable.
4. Offer to get the participant a drink/refreshment.
5. Explain what will happen and confirm the participant is happy to continue:
    a. Explain why the interview is being conducted and why it is important for this research.
    b. Explain the interview will take about an hour
    c. Explain that the researcher will ask questions but that the participant should feel free to talk about anything they feel is relevant.
    d. Explain that they are free the withdraw from the interview at any point and withdraw their consent
    e. Explain anything they say will be strictly confidential and that any quotes although quotes may be used, they will not contain any identifying information.
    f. Ensure they are happy to be recorded (explain this is so the interview may be transcribed and that audio material will be destroyed after the close of the study)
    g. Ensure they are happy to proceed.
6. Proceed with the interview, starting with the first question in the topic guide. As a semi-structured interview, the interviewer should attempt to cover the questions on the guide, however allow flexibility for the interviewee to explore and answer freely without input. Use of follow-up questions for interesting and relevant lines of participant thought will be employed.
7.

8. Conclude the interview when all relevant question have been covered and the participant has felt they have finished their answers/or when the time runs out. If time left, ask the participants if they have any other comments regarding the study they had not covered yet.
9. Thank the participant for their involvement in the interview and recap what will happen with the information they have provided.
10. Ensure the participant has adequate travel arrangements in place to return home.

Appendix J.

Data Collection Form

V2 05-08-15

V2 05-08-2015

The Impact of Physical Activity and Vitamin D supplementation on osteoarthritic knee pain in older obese people: a cross-sectional and pilot RCT study

Participant Information

Participant ID…… **Gender:** **Male** ☐ **Female** ☐

Date of Birth…… **(dd/mm/yyyy)**

Date…… **Time**……..

Study Visit (circle as appropriate) : **1 (cross-sectional)**

3 (pilot RCT)

4 (pilot RCT)

Consent

Was a signed consent from obtained? **YES** ☐ **NO** ☐

Was a copy given to the participant? **YES** ☐ **NO** ☐

Relevant Health Information

1. Have you EVER smoked Tobacco?

   NEVER ☐ CURRENT SMOKER ☐ EX-SMOKER ☐

   If current smoker or ex-smoker:

   a)Approximately how many cigarettes do you (or did you) smoke per day?

   ……

   b)How long have you smoked (or did you smoke)?

   ……

   c)If an ex-smoker, when did you give-up smoking?

   ……

2 a) Have you had an alcoholic drink in the past year? YES ☐ NO ☐

If yes to Q2a:

c)Approximately how many units of alcohol do you consume per week (now and in the past year)?

.....

ALCOHOLIC UNIT GUIDE

Wine: a small **(125 ml)** glass is **~1.5 units**; a standard **(175 ml)** glass is 2 units and a large **(250 ml)** glass is **3 units.**

Half pint of **(4%) beer**/ cider is **1 unit**; stronger **(6.5%) beer** is **2 units** per half pint.

A **single (25 ml)** tot of **spirits is 1 unit.**

Please review the participant's medication list (in the medication section of the screening questionnaire) to confirm correctness.

3. Have you ever been diagnosed with (or had):	**YES**	**NO**
Cystic Fibrosis	☐	☐
Celiac Disease	☐	☐
Whipples Disease	☐	☐
Crohn's Disease	☐	☐
Short Bowel syndrome	☐	☐
Gastric bypass/weight reduction surgery	☐	☐
Chronic Renal Disease (Stage 4 or 5)	☐	☐
Liver disease	☐	☐
Histoplasmosis	☐	☐

4. Do you currently have:		
Restrictive Eating Disorder	☐	☐
Hyper/Hypocalcaemia	☐	☐
Hyperparathyroidism (primary)	☐	☐
Are pregnant or breastfeeding	☐	☐
Lymphoma/Sarcoidosis/TB	☐	☐

5. Are you currently taking:	**YES**	**NO**
Anticonvulsant drugs	☐	☐
Glucocorticosteroids	☐	☐
HIV Treatment	☐	☐
Antiretroviral drugs	☐	☐
Anti-oestrogen drugs	☐	☐
Cytostatic/anti-tumour drugs	☐	☐
Vitamin D/Calcium/Phosphorous Supplements above certain dosage	☐	☐

6. Painkiller use:

a) Do you use any painkillers? YES NO

b) What condition do you use these painkillers for?

.....

.....

.....

.....

c) What painkillers do you use/how often (per week)/what dose:

.....

.....

.....

.....

7. <u>ACR Criteria checklist – has the participant experienced any of the following in the last 2 weeks</u>

Pain in the knee (essential)	☐
And 3 of the following:	
Over 50 years old	☐
Less than 30mins morning stiffness in morning	☐
Crepitus on active motion	☐
Body tenderness	☐
Bony enlargement	☐
No palpable warmth of the synovium	☐

Anthropometric Measurements

See SOP Manual pgs 5-8

Measurement	First attempt	Second attempt	Third attempt
Height (cm)*			
Waist Circumference (cm)*			
Body Weight (kg)*		**N/A**	**N/A**
BMI (kg/m^2)		**N/A**	**N/A**
Body Fat %		**N/A**	**N/A**
Total Fat Mass		**N/A**	**N/A**
*Height and Waist Circumference should be measured to the nearest 0.0, Body weight should be measured to the nearest 0.00.			

Musculoskeletal Function: Timed Up and Go (TUG) Test

See SOP Manual page 9

Test start time: .....

	MM:SS:00	Unable to complete?	Comments
Practice run	N/A		
TUG Trial 1			
TUG Trial 2			
TUG Trial 3			
TUG Mean Score			

Test end time.....

V2 05-08-2015

Questionnaires

See SOP Manual pages 10-13

Was the Questionnaire understood and completed by the participant?

	YES	NO		YES	NO
WOMAC	☐	☐	**IPAQ**	☐	☐
SF-36	☐	☐	**Vit D FFQ**	☐	☐
VAS Pain Scale	☐	☐	**Sun Exposure**	☐	☐

Blood Samples

See SOP Manual pages 14-19

a) Venous Blood Sample

Was consent to take blood given? **YES** ☐ **NO** ☐

Was sufficient volumes blood collected for the following (tick box if collected) and sample spun correctly?:

	Collected	Centrifuged
Vitamin D analysis (SG)	☐	☐
Haematocrit analysis (EDTA)	☐	☐
Sample Storage (Plain)	☐	☐
Calcium analysis (SG)*	☐	☐

*collected for Study Visits 3 and 4 only.

Notes.....

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V2 05-08-2015

b) Dried blood spot test

	YES	NO
Was the dried blood spot test card filled?	☐	☐

If not how many blood spots were collected?.....

Notes.....

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Accelerometry

	YES	NO
Was instruction on how to use Actigraph described to the participant?	☐	☐

	YES	NO
Was the device, written materials and envelop provided to the participant?	☐	☐

	YES	NO
Was the tracking log filled out?	☐	☐

Appendix K.

Northumbria Healthcare NHS Foundation Trust

CIMA The Centre for Integrated research into Musculoskeletal Ageing

Newcastle University

Sample tracking form

Participant ID: _____

Date: _____

Time: _____

Investigator: _____

Serum extraction and aliquot Protocol

4 tubes of blood should be taken per participant:

- Vitamin D analysis (SST/Serum Gel Vacutainer tube – Yellow)
- Haemocrit analysis (EDTA Vacutainer tube)
- Sample storage at Newcastle University (Plain Vacutainer tube – Red)
- Calcium analysis (SST/Serum Gel Vacutainer tube – Yellow)

Sample Processing

Blood samples should be processed as follows:

1. Label each Vacutainer tube with participant ID and date and sample type (see key below)
2. Store in sample bag on ice till processing (apart from EDTA Sample).
3. Centrifuge at 3000rpm at 4◦C for 10 mins

4. Using a Pasteur pipette remove serum from separated sample into prelabeled Eppendorf tubes as follows:
    a. 1ml serum calcium sample
    b. 0.5 ml for each vitamin D sample
    c. 0.5-1ml serum per storage sample

Note at this point any haemolysis of the samples on the data collection form. Ensure the labelling on the Vacutainer tube matches that on the aliquot tubes.

5. All used pipettes, sharps and recapped used sample tubes should be disposed of in the sharps/biohazard bins.

Sample Storage

Serum samples should then be transferred and stored as follows:

Vitamin D and Calcium Aliquots:

- Should be stored on ice till transported to the -80C freezer facility (**North Tyneside General Hospital)**
- Tubes should be stored in the correct sample box (large sample box) and the location of each sample recorded on the sample storage form, dated and signed by investigator (hard and electronic copy)
- Samples will be transported for analysis to the Freeman Hospital, Newcastle Upon Tyne at the end of each month September 2015-March 2016.

Haemocrit:

- Whole blood sample (in Vacutainer) should be transferred to NTGH pathology labs for analysis **on the day of collection**. Do not be freeze/cool (will lyse RBC).
- Place Vacutainer tube in specimen bag and complete lab request with participant ID, sex and age of participant.

Storage Aliquots:

- Aliquots 1 and 2 should be stored on ice till transported to the -80C freezer facility (**North Tyneside General Hospital).**
- Tubes should be stored in the correct sample box (small sample box) and the location of each sample recorded on the sample storage form, dated and signed by investigator (hard and electronic copy)
- Samples will be transported for storage to Newcastle University, (Centre for ageing and Vitality, NE4 5PL) at the end of each month September 2015-March 2016.

Checklist

1. Was blood sample taken for:

SG/VD	☐
P/S	☐
EDTA/H	☐
SG/CA	☐

2. Were samples appropriately stored till storage? ☐

3. Were samples store in -80◦C in the appropriate location? ☐

NOTES

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Appendix L.

Accelerometer activity intensity cut points	
Activity Intensity	**Total Counts**
Sedentary	<100
Light	101-1952
Moderate	1953-5724
Vigorous	>5725

Appendix M.

Your Intervention Guide: Vitamin D supplements

YOUR GROUP:

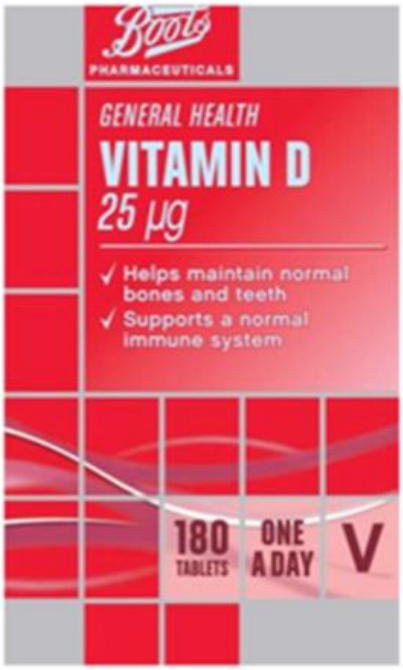
You have been assigned to receive the vitamin D supplement intervention. This will involve you taking vitamin D supplements every day for 3 months with the aim of increasing your vitamin D levels.

The aim of this intervention is to see whether taking Vitamin D supplements has any effect on your knee pain. To measure this we will invite you to see us at North Tyneside General Hospital half way through, and at the end of, your study to repeat the measurements we took during your first study visit.

Please follow the instructions in this guide carefully and if you have any queries, please contact us by telephone (0191248 1131) or email (rebecca.brown2@ncl.ac.uk).

THE SUPPLEMENT:

You will be taking a Vitamin D supplement provided by Boots pharmaceuticals. You will be taking 2x 1000IU (international unit) tablets per day, a total of 2000IU each day for 3 months. This should raise your Vitamin D levels from low/moderate to ideal levels.



WHAT DO I NEED TO DO?

Step 1: Receiving your intervention pack

The study team will have called you to inform you that you're eligible for the study and that an intervention pack will be posted to you.

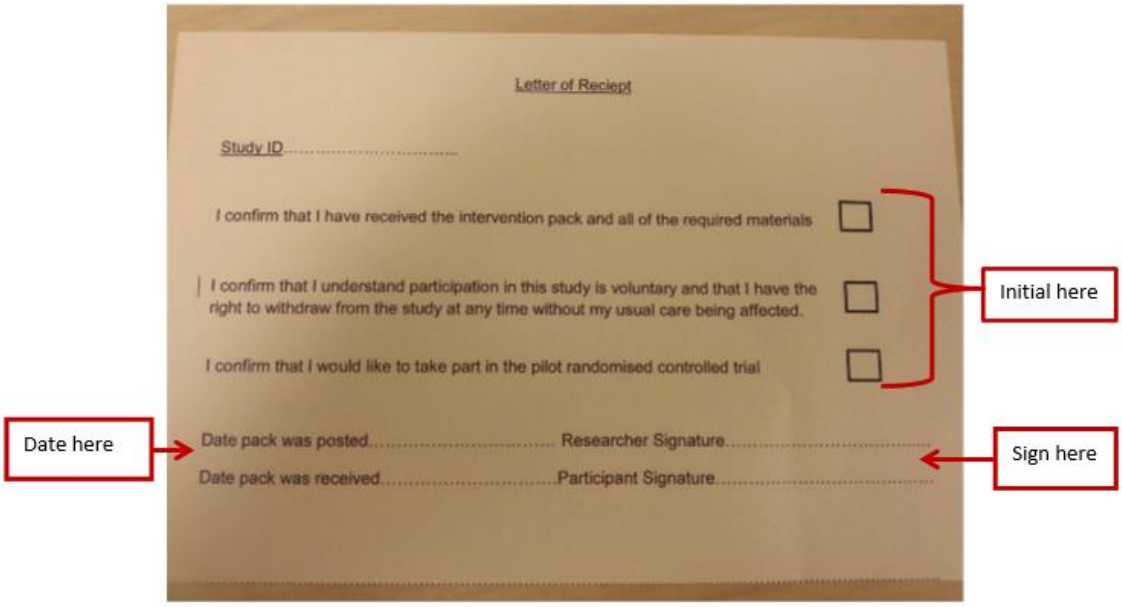
When the intervention pack arrives, it should contain:

- A letter of invitation (informing you which intervention you are receiving)
- An Intervention guide (containing instructions on how to complete the Intervention)
- A letter of receipt to complete (see step 2) and return (see step 3) using the prepaid self-addressed envelope provided.
- Intervention materials (6 weeks supply)

Step 2: Acknowledging Receipt of your pack

Please complete and return the letter of receipt as follows:

- Read and Initial the boxes next to the points you agree to
- Make a note of the date you received your pack
- Sign your name next to the 'Participant signature'
- Place the letter of receipt in the pre-paid, pre-addressed envelope provided.
- Post in the usual way



Step 5: Continuing your supplements

Each compartment within the pill box contains 2 capsules to be taken on that day. Please take both of these together. You can take them any time of the day but try to take them at approximately the same time every day. They can be taken with or without food.

Continue taking the supplements for the full 6 weeks.

Step 6: First Hospital Visit

1-2 weeks before your tablets are due to run out, the research team will call to arrange your first hospital visit as part of this trial. The visit will take place at North Tyneside General Hospital.

During this visit we will repeat all of the measurements we took during your study 1 visit. We will also provide you with another 6 weeks of Vitamin D supplements. Please continue taking your Vitamin D supplements in the same way as the previous 6 weeks.

Step 7: Second Hospital Visit

1-2 weeks before your tablets are due to run out, the research team will call to arrange your second hospital visit as part of this trial. The visit will take place at North Tyneside General Hospital.

During this visit we will repeat all of the measurements we took during your study 1 visit.

This visit will mark the end of the trial.

Step 8: After the end of the study

Now that the study is over, you will be offered the opportunity to receive the intervention you did not receive as part of your study (in your case, this will be the online activity programme).

You do not have to accept this offer but if you do we will provide you with all of the materials and instructions you need in an intervention pack similar to this one. However this further intervention will not be supervised by the study team and you will not attend any hospital visits. If you have any questions, please contact your GP surgery.

What do I do if I miss a day?

If you forget or miss taking a day's supplements, please don't worry, just continue to take the supplements as normal the next day. Do not take 2 days doses together to catch up.

Please leave any unused tablets in the box in its original compartment. That way we can dispose of any leftover supplements correctly and safely.

What if I have any questions?

Please contact the study team at any time if you are unsure of anything or have any questions.

Contact by telephone (0191 248 1131) 9am-5pm Monday to Friday or by email (rebecca.brown2@ncl.ac.uk).

Step 3: Telephone Interview

When the letter of receipt is received by the study team, a member of the team will call you to review the instructions provided in this guide and to answer any questions you may have (this shouldn't take more than an hour).

PLEASE DO NOT START TAKING YOUR VITAMIN D CAPSULES BEFORE THIS PHONE CALL HAS TAKEN PLACE

Step 4: Starting your supplements

You can now begin to take your Vitamin D supplements. Start taking your supplements on the day of your introductory phone call.

Begin with the box called 'Vitamin D - Week 1-3'.

Each box contains 3 weeks of Vitamin D supplements which are labelled according to the days of the week and the number of the week (see below). Once you have finished the first box of supplements, move on to the second box labelled 'Vitamin D - Weeks 4-6'.

NOTES

Appendix N.

Your Intervention Guide: Online Physical Activity Programme

YOUR GROUP:

You have been assigned to the online physical activity programme group. This will involve you using an online programme called "POW" to increase your physical activity. To help with this, you will monitor your daily steps using a pedometer, schedule and record any new activities and set yourself weekly activity goals.

The aim of this intervention is to see whether increasing your everyday activity has any effect on your knee pain. To measure this we will invite you to see us at North Tyneside General Hospital half way through, and at the end of, your study to repeat the measurements we took in your first study visit.

Please follow the instructions in this guide carefully and if you have any queries, please contact us by phone (0191248 1131) or email (rebecca.brown2@ncl.ac.uk).

THE ONLINE PROGRAMME

The "POW" online programme you will be using has been developed by Newcastle University with the aim of helping you to increase your physical activity levels. This guide will take you through the features of this online programme.

- Monitoring and recording your daily steps
- Scheduling physical activities
- Setting yourself physical activity goals
- Identifying barriers to doing physical activity and finding solutions to these.

WHAT DO I NEED TO DO?

Step 1: Receiving your intervention pack

The study team will have called you to inform you that you're eligible for the study and that an intervention pack will be posted to you.

When the intervention pack arrives, it should contain:

- A letter of invitation (informing you which intervention you are receiving)
- An Intervention guide (containing instructions on how to complete the intervention)
- A pedometer guide (containing instructions on how to use your pedometer)
- A letter of receipt to fill out (see step 2) and return (see step 3) using the prepaid self-addressed envelope provided.
- A paper step log (to record your daily steps)
- Intervention materials: pedometer

Step 2: Acknowledging Receipt of your pack

Please fill out and return the letter of receipt as follows:

- Read and initial the boxes next to the points you agree to
- Note down the date you received you pack
- Sign your name next to the 'Participant signature'
- Place the letter of receipt in the pre-paid, pre-addressed envelope provided.
- Post in the usual way

Step 3: Telephone Interview

When the letter of receipt is received by the study team, a member of the team will call you to review the instructions provided in this guide and to answer any questions that you may have (this shouldn't take more than an hour).

PLEASE DO NOT START USING THE ACTIVITY PROGRAMME BEFORE THIS PHONE CALL HAS TAKEN PLACE

Step 4: Setting up a POW account

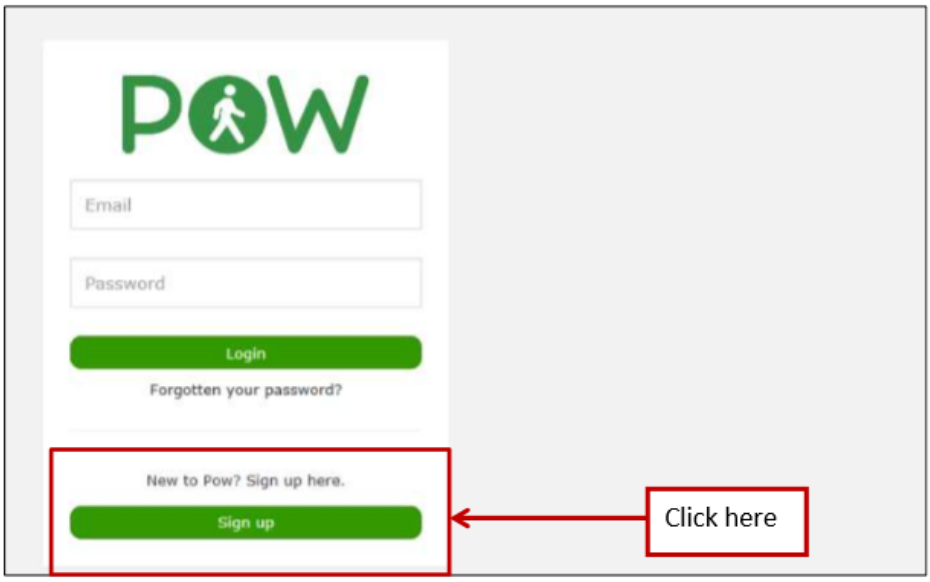
Before you are able to use the online programme, you will need to create a username and password.

Start by typing in this web address:

www.powactive.co.uk

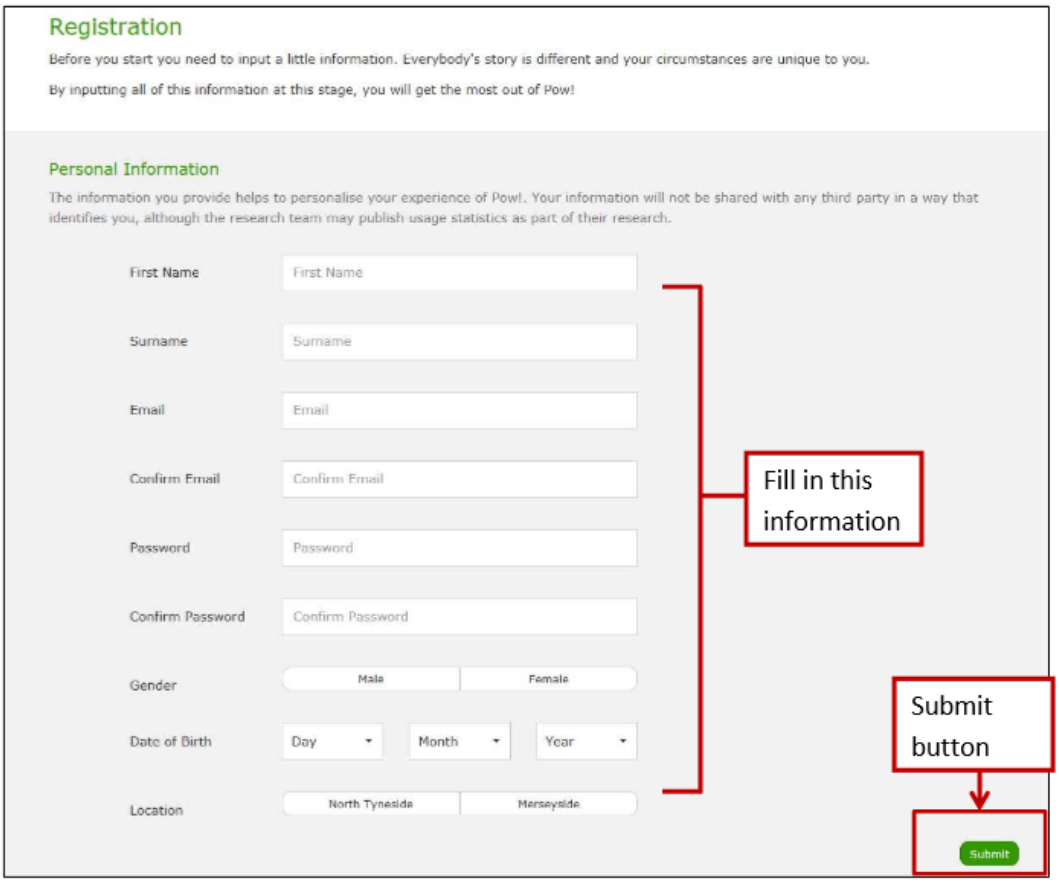
When the online programme loads you should see and introductory screen as in the picture below.

For your first visit, you will need to click on the sign up button to create a new username, which will be your email address, and a password.



This button should load the page below.

Please fill in all of the necessary information on this page and when you have finished, click the submit button on the bottom right of the page.



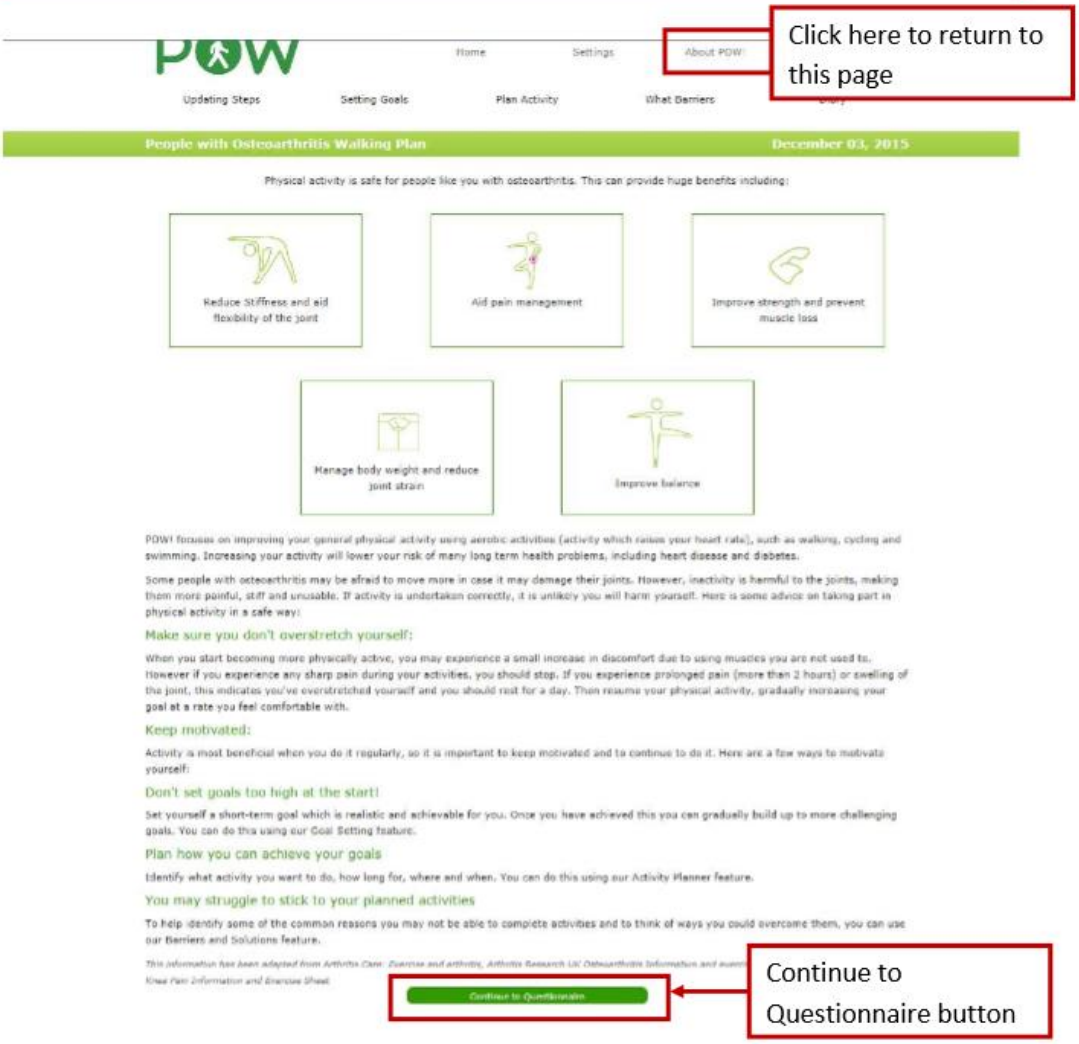
Step 5: Introduction to the programme

After you have submitted your information, the online programme will automatically log you onto the system. Your username will be the email address you provided and you will use the password you provided. For more information of how to log on to POW later, look at the 'How do I log on to POW?' box later in the guide.

The first page you see should look like the one below. Please take the time to read this page as it contains useful advice about how to perform physical activity safely.

When you are ready to move on, please click the 'Continue to Questionnaire' button at the bottom of the page.

You can return to re-read this information at any time by clicking on the 'About POW' tab at the top of the page.



Step 6: Filling in the activity questionnaire

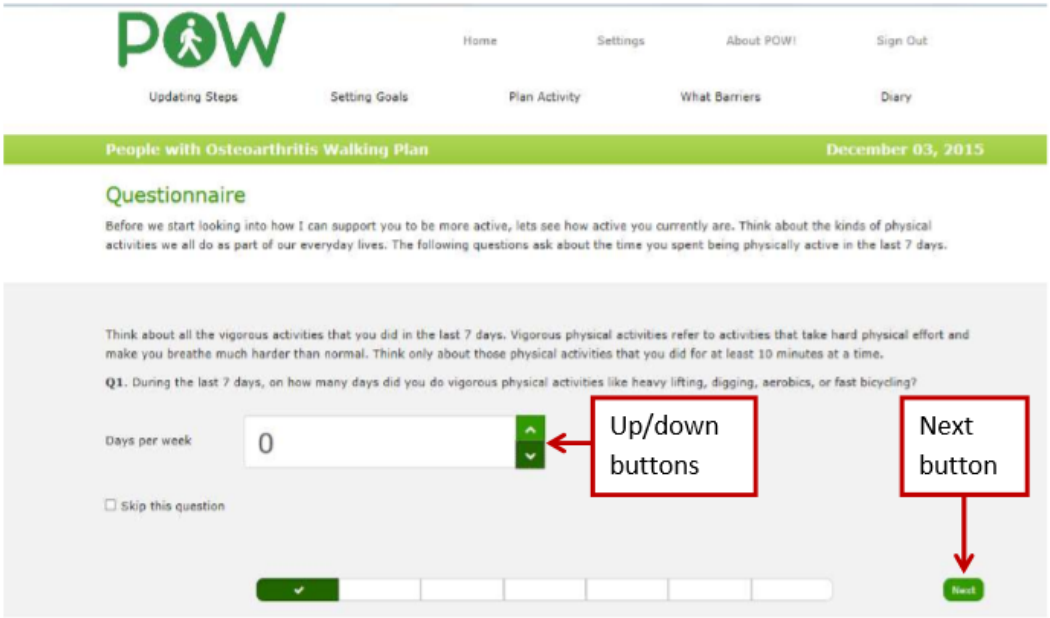
Clicking on the 'Continue to Questionnaire' button takes you to a page which looks like the one below.

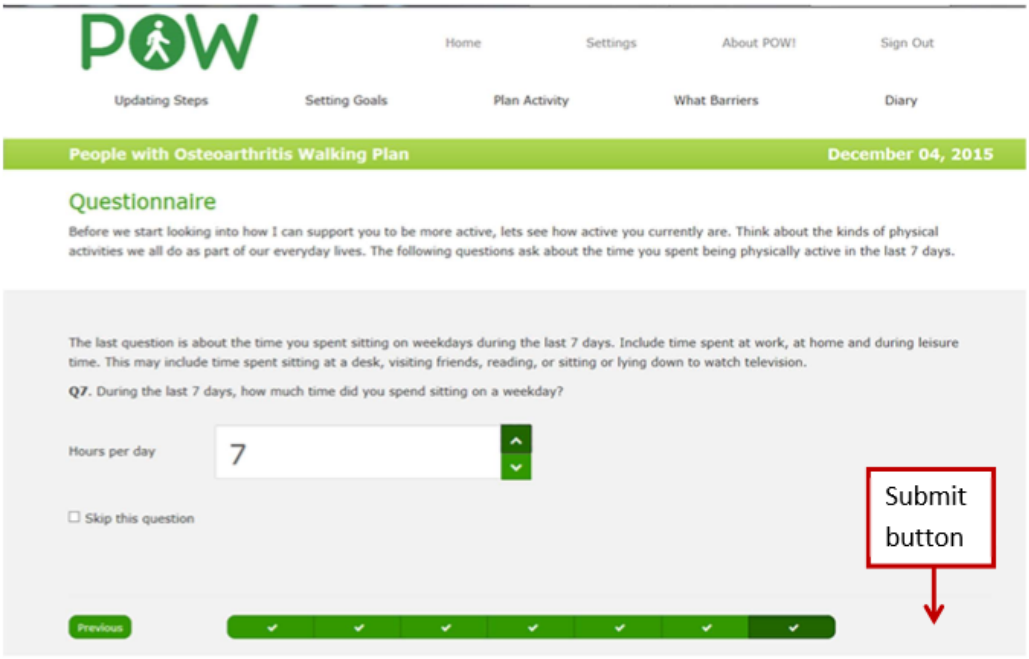
This is a questionnaire to help us measure your usual physical activity levels. Later, POW will give you feedback on your answers to the questionnaire.

Please read the question carefully and when you are ready to answer, use the up and down buttons to put in your answer.

Then click the 'next' button on the bottom right to move on to the next question.

Continue until you reach the last question. When you have answered the last question, please click the 'submit' button in the bottom right corner to finish the questionnaire.




POW
Home
Settings
About POW!
Sign Out
Updating Steps
Setting Goals
Plan Activity
What Barriers
Diary
People with Osteoarthritis Walking Plan
December 04, 2015
Questionnaire
Before we start looking into how I can support you to be more active, lets see how active you currently are. Think about the kinds of physical activities we all do as part of our everyday lives. The following questions ask about the time you spent being physically active in the last 7 days.
The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.
Q7. During the last 7 days, how much time did you spend sitting on a weekday?
Hours per day
7
Skip this question
Submit button
Previous

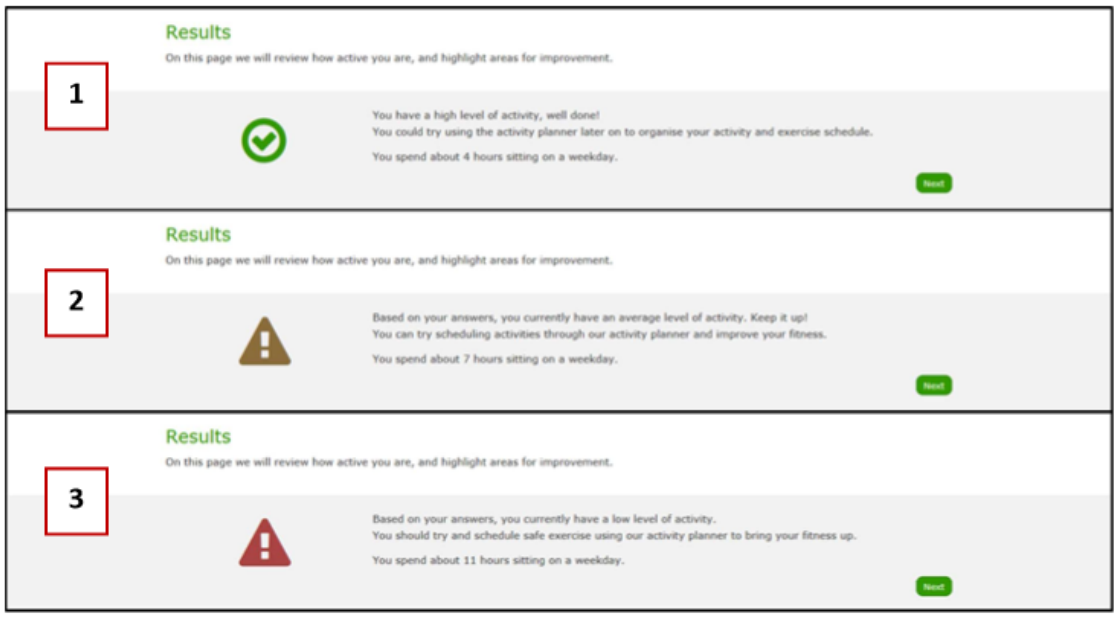
Step 7: Questionnaire Results

When you have submitted your answers for the physical activity questionnaire, the next page will bring you to your results from the questionnaire. These results are an estimate of how much physical activity you usually do during a typical week.

The results will be one of the following:

1. High physical activity level: you are doing enough physical activity
2. Average physical activity level: you are doing some physical activity but could be doing more
3. Low physical activity level: you are not doing much physical activity; you should use the programme to carefully increase your physical activity.

When you have looked at your results and are ready to move on, click on the 'Next' button in the bottom right corner.



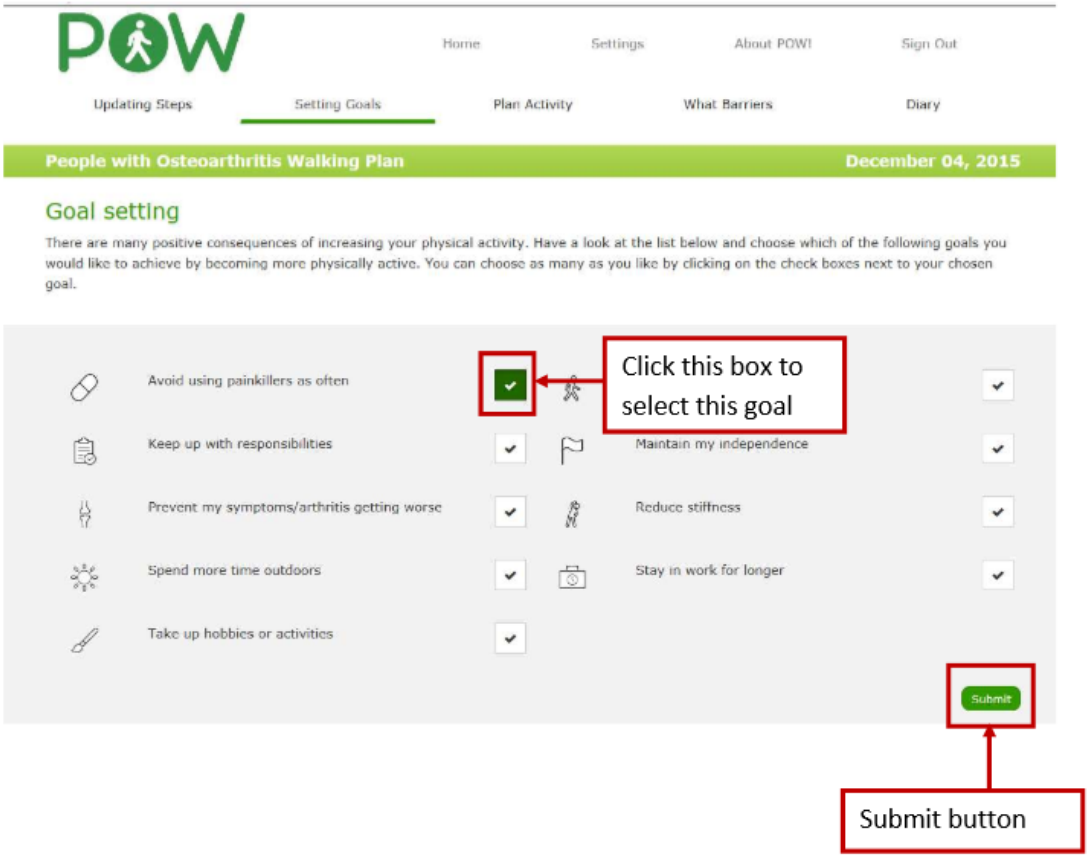
Step 8: Choosing your goals

There are many benefits to increasing your physical activity levels for your general health as well as for your knees.

We realise everyone will have different reasons for wanting to increase their physical activity. Therefore we have provided a page where you can set your own physical activity goals and what you would like to achieve by increasing your physical activity levels.

To select a physical activity goal, just click on the ticked box next to the goal you want so that it turns green (see below). You can select as many goals as you like.

When you have finished, click on the submit button in the bottom right corner.

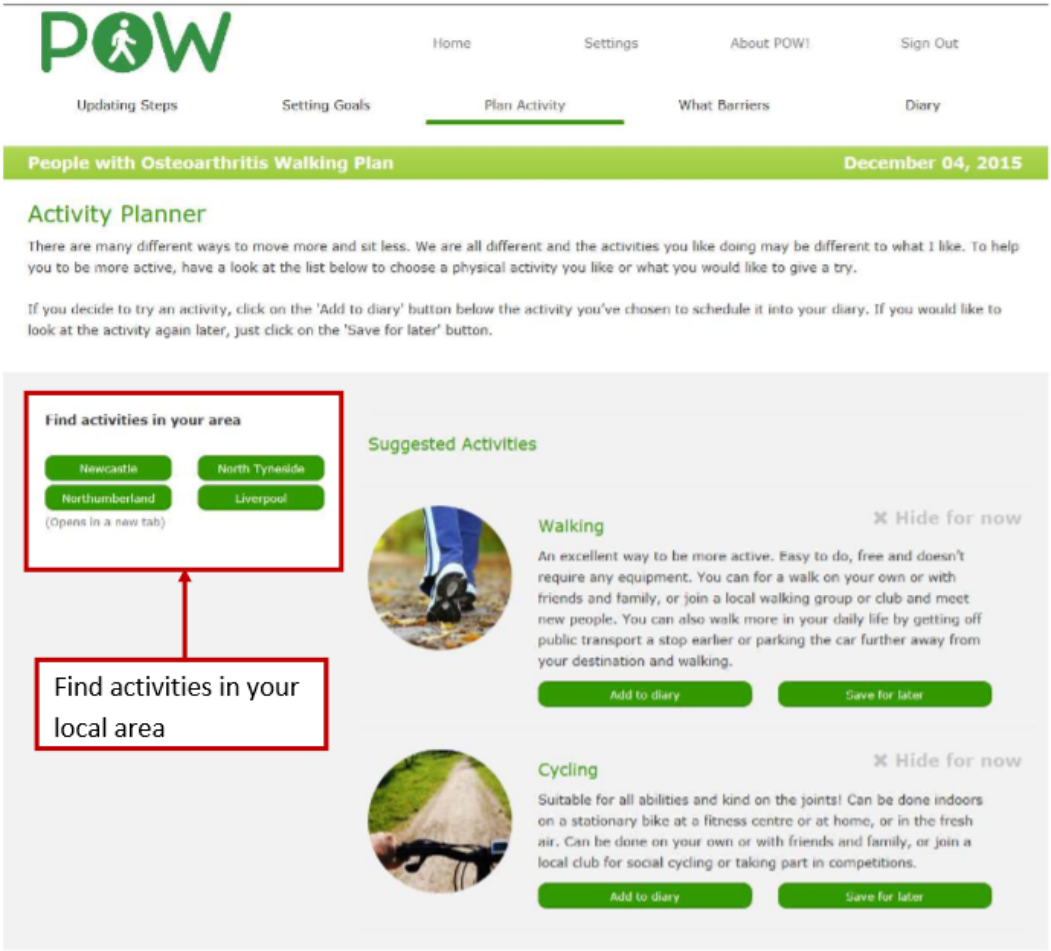


Step 9: Using the Physical Activity Planner

This page allows you to look at the different ways you could increase your physical activity levels.

Firstly you can look at all of the physical activities such as exercise classes and facilities available in your local area. Just click on the button for your location (either Newcastle, Northumberland, North Tyneside or Liverpool) in the 'find activities in your area' section. This will take you to a separate webpage.

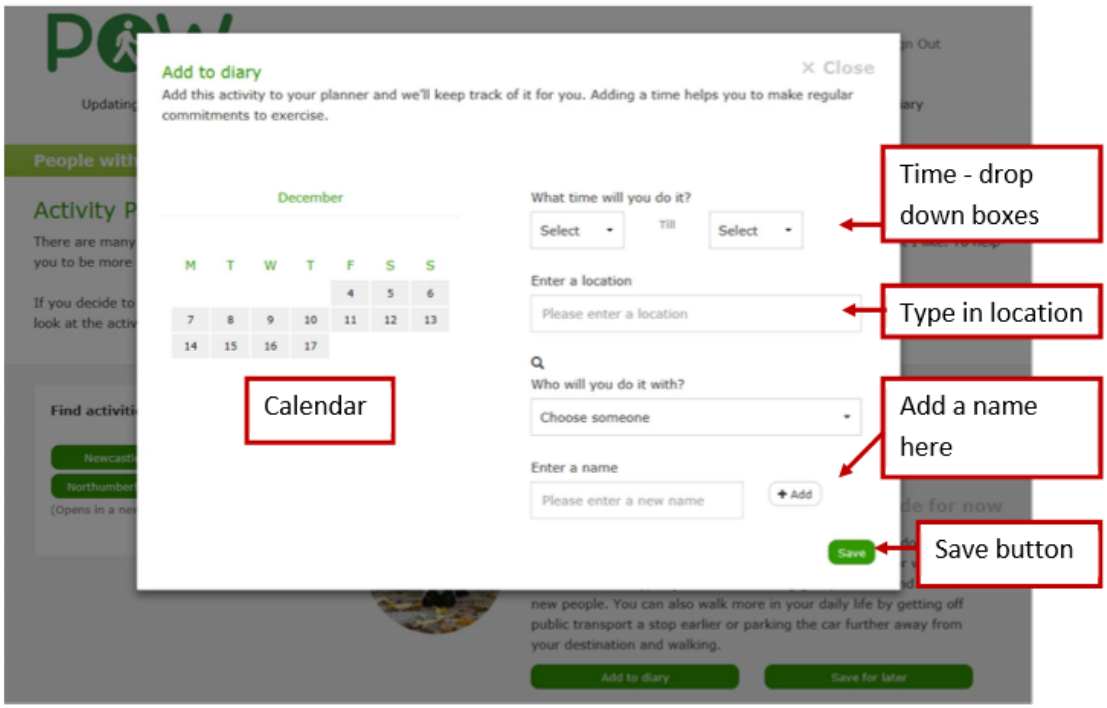
There are also 'suggested activities' to give you ideas of the kinds of activities you could do as part of your day to increase your physical activity levels. You can choose to save these activities to look at them latter by clicking on the 'Save for later' button or you can organise a time to do this activity clicking on the 'Add to diary' button. POW provides an online diary to help you keep track of your plans for activities.



Step 10: Using the Diary feature

If you would like to add a physical activity to your online diary and have clicked the 'add to diary' button, the following window should appear (see below). To save an activity to your diary, fill in the information in this window as follows:

1. Select a day to do the physical activity using the 2 week calendar at the left hand side of the window by clicking on the day you would like.
2. Choose times to start and to finish your activity by clicking on the scroll down boxes in the 'What time will you do it?' section.
3. Choose a place to do it by typing your chosen location into the 'Enter a location box'
4. If you would like to do the activity with someone else, enter their name in the 'Enter a name' box and click the add button.
5. When you are happy with all of these details, click on the 'save' button in the bottom right.
6. Once you have clicked 'save', the question 'Do you have any barriers to completing this' will appear. Please click 'yes'.

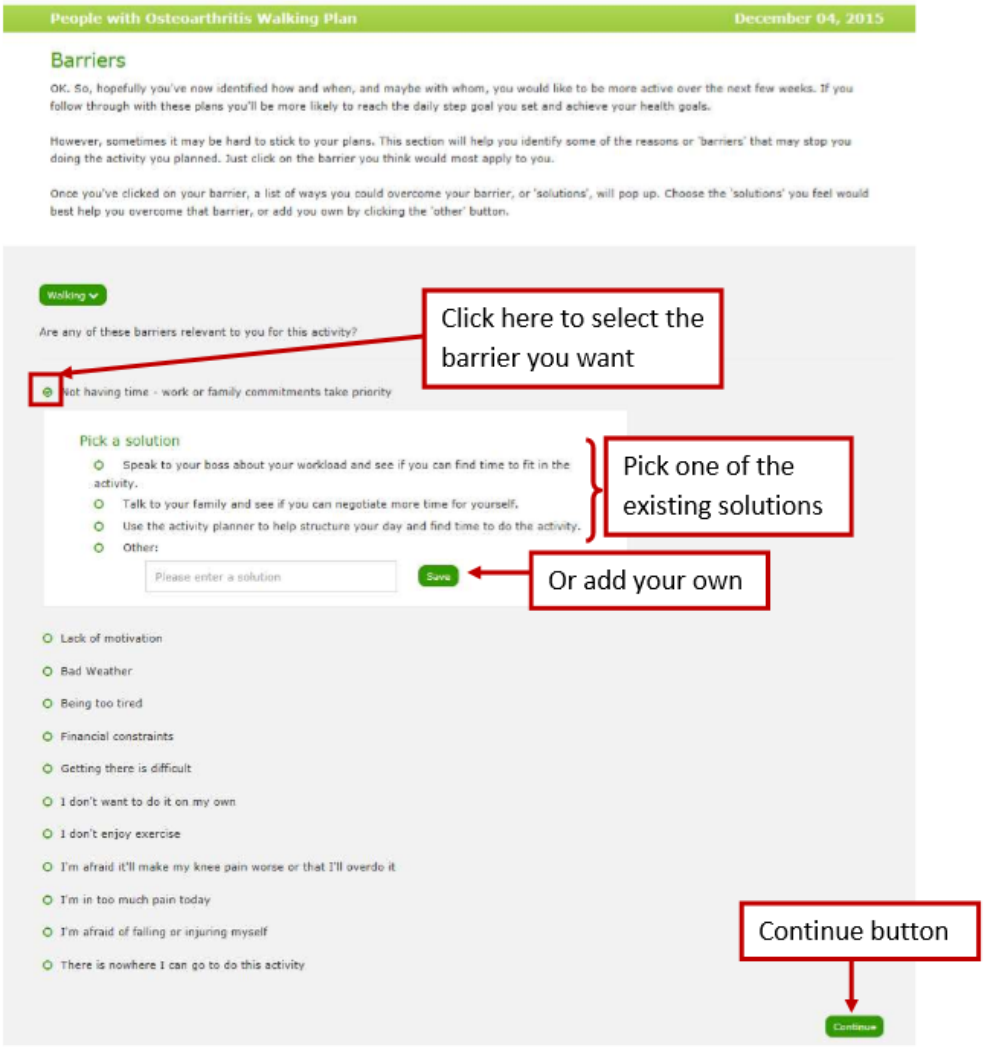


Step 11: Selecting your barriers and solutions

There may be many reasons why you may not be able to do your physical activity as and when you planned to. To help you identify some of the reasons or 'barriers' that may stop you doing a physical activity, we have listed some suggestions. If there is a barrier listed which you think may apply to you, click on the green dot next it.

A box will appear under your chosen barrier called 'pick a solution'. This box contains suggestions of how you could overcome that barrier to complete your physical activity. Choose the solution that you feel would best help you. If there are no solutions listed which you would feel would help you, you can enter your own solution by typing it into the box below and clicking the 'save' box.

When you are finished selecting your barriers and solutions click the 'Continue' button in bottom right of the screen.

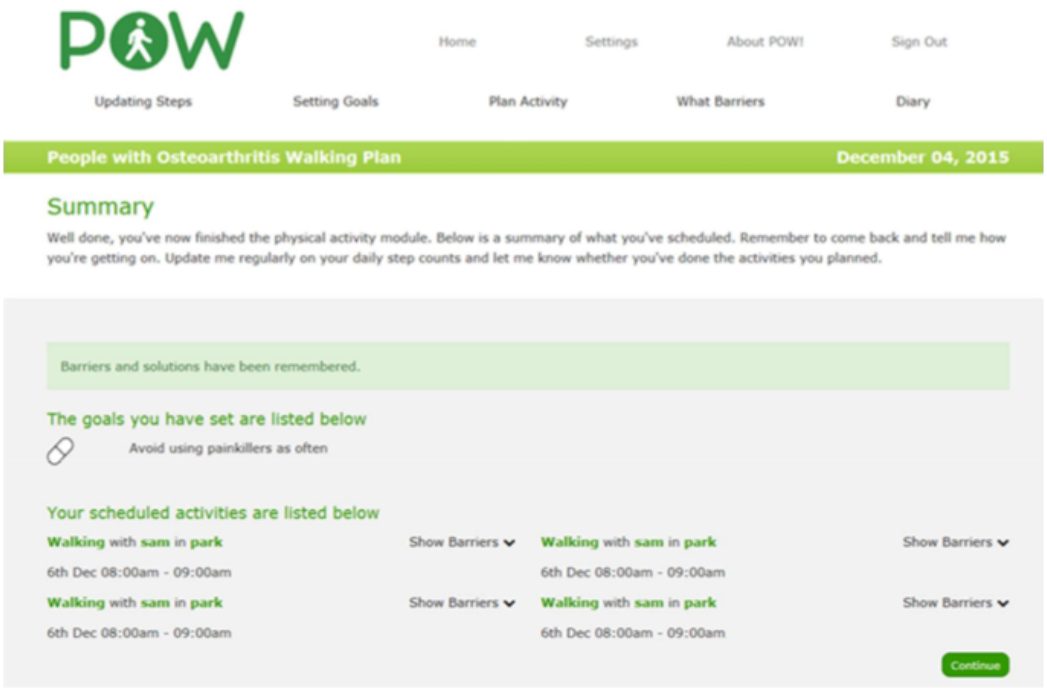


Step 12: Summary Page

The next page will display a summary of what you have just completed, including:

- Any scheduled physical activities
- Any physical activity goals you have selected
- Any barriers and solutions you have selected for your chosen physical activity

When you have finished, click on the 'continue' button on the bottom right of the screen.



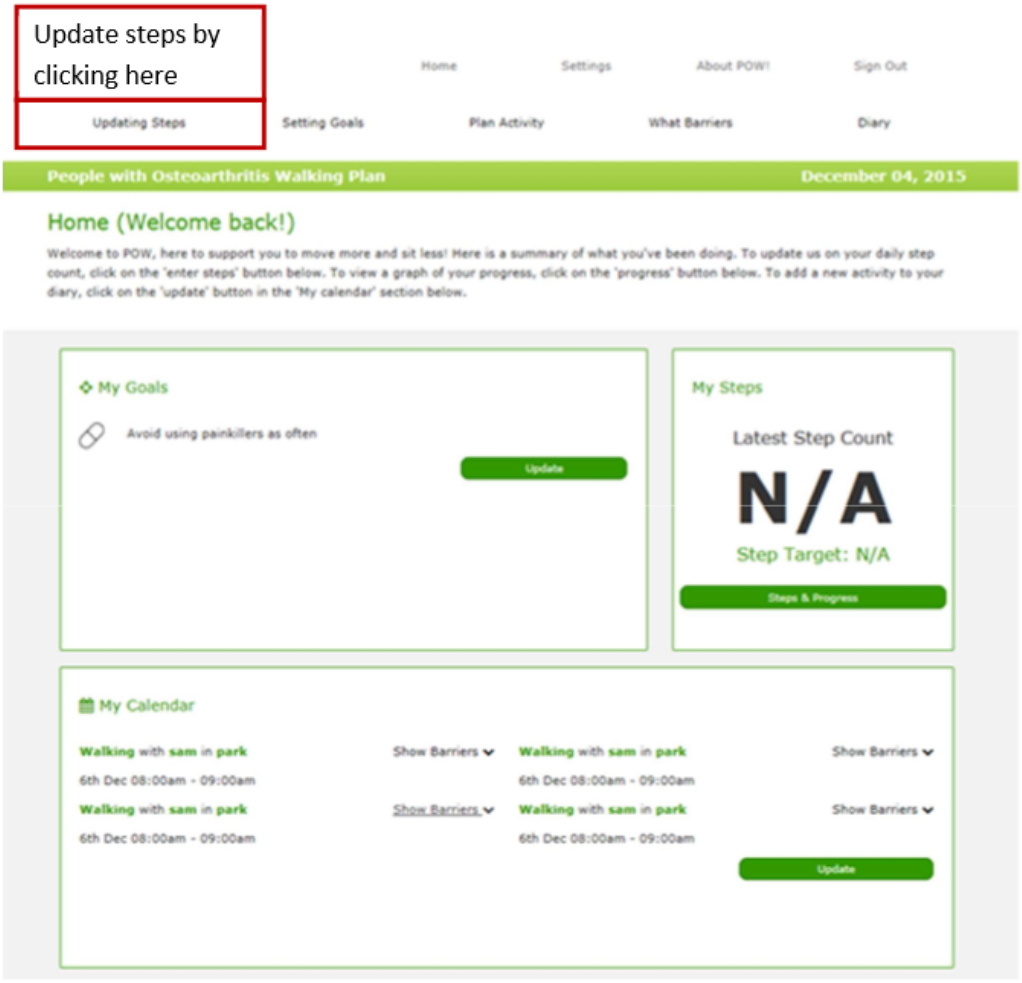
Step 13: Home Page

The home page provides a summary of the:

- physical Activities that you have scheduled in your calendar
- The physical activity goals you have selected
- Step count summary (based on the step count feature – see below)

In order to use the step count feature, click on the ‘Steps and Progress’ button in the ‘My Steps’ section. Or you can click on the ‘Update Steps’ tab at the top of the page.

You can return to this page at any time by clicking on the 'Home' tab at the top of the page.



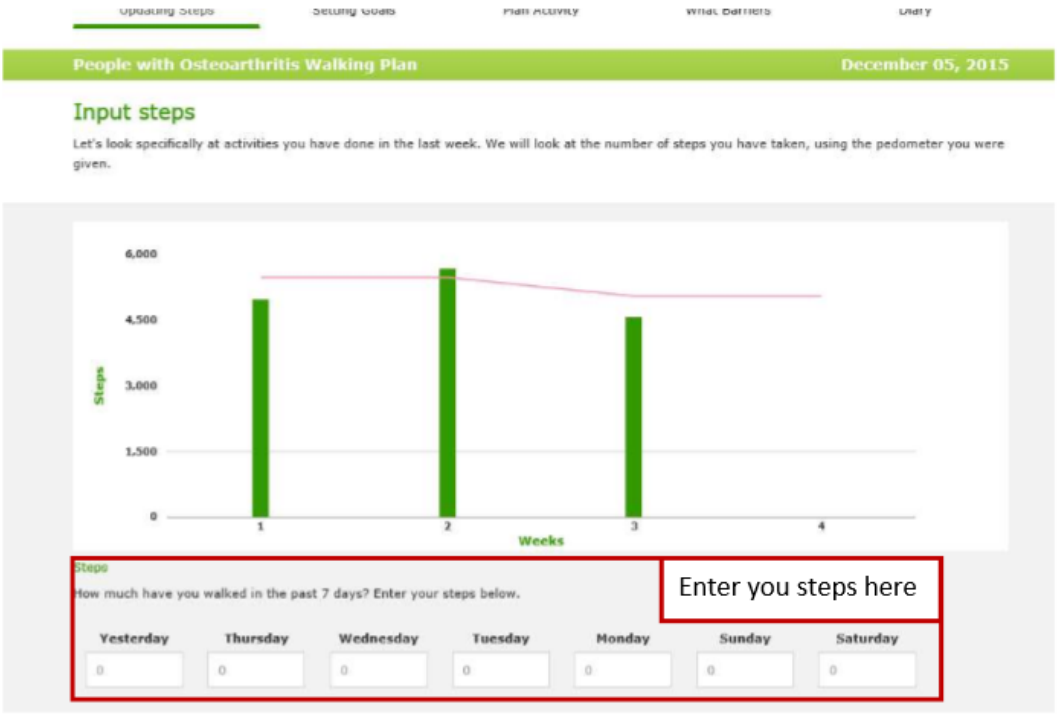
Step 14: Updating your Steps

The 'Updating Steps' feature allows you to track your daily steps and make physical activity goals to help you to steadily increase the amount of physical activity that you are doing.

You'll remember that we gave you a pedometer to wear each day to measure your steps. Please make good use of this throughout your intervention. If you are unsure of how to use your pedometer, please look at the separate guide within this pack called 'Using your pedometer'.

You should wear your pedometer everyday. That way you can get an accurate idea of how much you are moving around every week.

To input your steps, click on the 'Updating steps' tab across the top of the page. You will see a steps section with the days of the previous week.



Please enter the steps that you recorded for each day using your pedometer by clicking on the box below that day and typing your number in. Please enter your steps for the whole week in one go (copying from the paper step log we gave you as part of the intervention pack). Do this on the same day every week. If you enter steps for one day only, the system will presume you have only recorded 1 days of steps that week and your results will be wrong!

The steps you input for each week will be summarised into a graph so that you can see your progress from week to week.

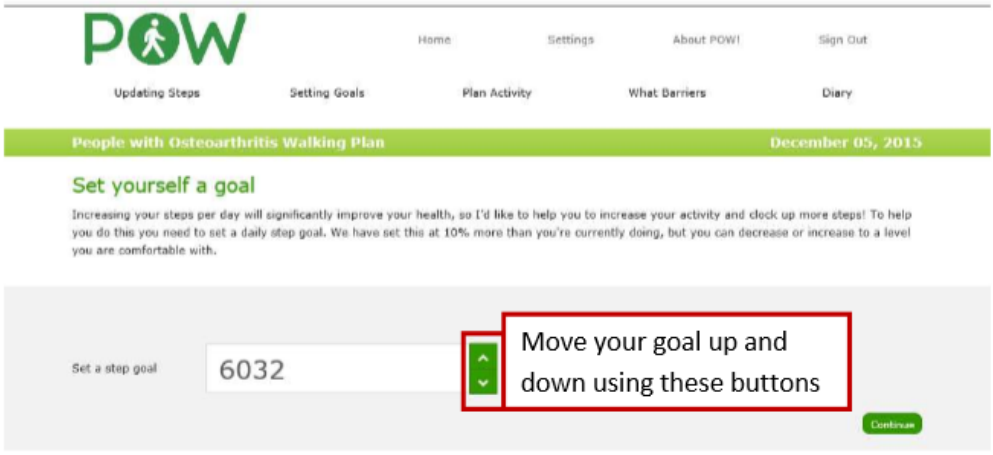
There are also similar sections below to record any cycling or swimming. These activities cannot be picked up by the pedometer and so you will need to enter the details yourself.

When you have finished inputting your steps and physical activities for the day, click on the 'submit' button in the bottom right.

The next page will give you your average daily number of steps for the week.

There will also be a recommendation as to whether this is low, average or an ideal number of steps.

When you have finished, click on the 'continue' button in the bottom right corner.



Step 15: Setting your step goal

This page allows you to set yourself a target or 'goal' for the number of daily steps to do over the next week.

This page will give you a pre-set step goal, set at 10% more than the number of daily steps that you are already doing.

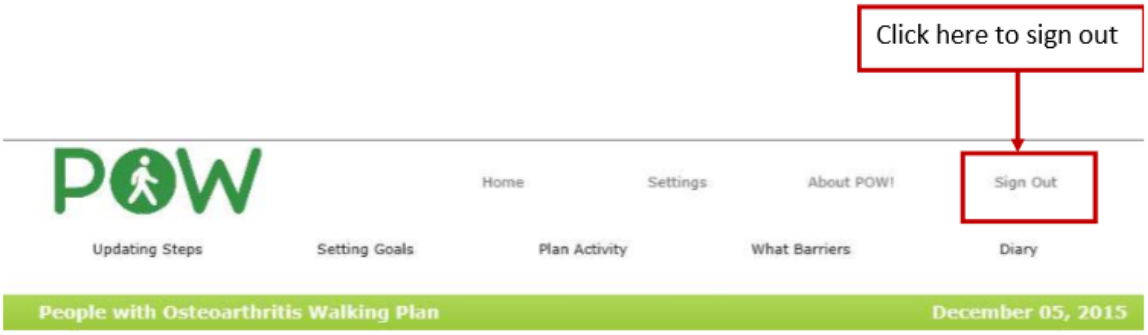
If you feel like this goal is too much or too little you can increase or decrease the number of steps using the up and down arrows. You will be making these changes every week, so you will soon get an idea of how ambitious your weekly goals can be.

When you are happy with the number of steps, click on the 'continue' button in the bottom right corner.

Step 16: Logging Out

When you have finished using POW, you can log out of your account.

To log out, click on the 'sign out' tab at the top right of the page.



Step 16: Signing back in

You can sign back into POW at any time. To do this, log back onto the website **(www.powactive.co.uk)**

Then enter the email address you signed up with as your username and enter the password you chose at the beginning.

If you forget your password at any point, click on 'Forgotten your password?', which will send you a new temporary password to your email address.

What if I have any questions?

Please contact the study team at any time if you are unsure of anything or have any questions.

Contact by telephone (0191 248 1131) 9am-5pm Monday to Friday or by email (rebecca.brown2@ncl.ac.uk).

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Appendix O.

Your Intervention Guide: Standard Care

YOUR GROUP:

You have been assigned to standard care. This will involve you carrying on your usual routine of care with no additional intervention from the study team.

The aim of this is to act as a comparison to the intervention groups. As part of this we will invite you to see us at North Tyneside General Hospital half way through, and at the end of, the study period to repeat the measurements we took during your first study visit.

To avoid disappointment we will offer both interventions given as part of this study (vitamin D supplements and Online Physical Activity Interventions) at the **end of the study period.** We just ask you do not any significant changes to your usual routine **during the study period.**

Please follow the instructions in this guide carefully and if you have any queries, please contact us by telephone (0191248 1131) or email (rebecca.brown2@ncl.ac.uk).

WHAT DO I NEED TO DO?

Step 1: Receiving your intervention pack

The study team will have called you to inform you that you're eligible for the study and that an intervention pack will be posted to you.

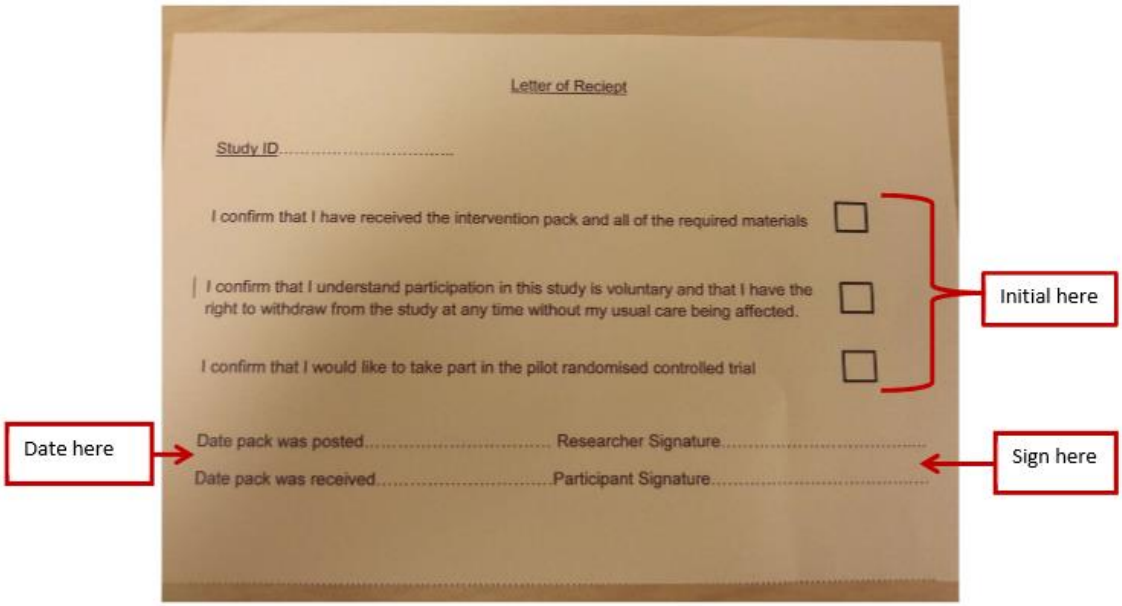
When the intervention pack arrives, it should contain:

- A letter of invitation (informing you which intervention you are receiving)
- A guide (containing instructions on what you need to do during the study)
- A letter of receipt to complete (see step 2) and return (see step 3) using the prepaid self-addressed envelope provided.

Step 2: Acknowledging Receipt of your pack

Please complete and return the letter of receipt as follows:

- Read and Initial the boxes next to the points you agree to
- Make a note of the date you received your pack
- Sign your name next to the 'Participant signature'
- Place the letter of receipt in the pre-paid, pre-addressed envelope provided.
- Post in the usual way



Step 3: Telephone Interview

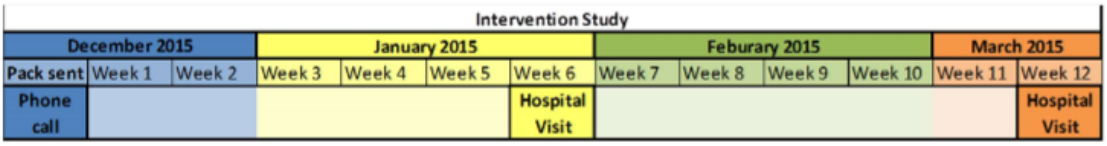
When the letter of receipt is received by the study team, a member of the team will call you to review the instructions provided in this guide and to answer any questions you may have (this shouldn't take more than an hour).

Step 4: Standard Care

What we would like you to do for the next 3 months is continue with your standard care.

What we mean by this is that you should continue to treat and deal with your knee as you usually do without starting any new treatments during the period of the study.

This is important, as we need a standard group to compare our other groups to.



Step 6: First Hospital Visit

During week 4-5 of the study (Mid-January 2016), the research team will call to arrange your first hospital visit as part of this trial. The visit will take place at North Tyneside General Hospital.

During this visit we will repeat all of the measurements we took during your study 1 visit. Please continue maintain your standard care after this visit.

Step 7: Second Hospital Visit

During week 10-11 of the study (Start of March 2016), the research team will call to arrange your second hospital visit as part of this trial. The visit will take place at North Tyneside General Hospital.

During this visit we will repeat all of the measurements we took during your study 1 visit.

This visit will mark the end of the trial.

Step 8: After the end of the study

Now that the study is over, you will be offered the opportunity to receive the interventions you did not receive as part of your study (in your case, this will be the vitamin D supplements and online activity programme).

You do not have to accept this offer but if you do we will provide you with all of the materials and instructions you need in an intervention pack similar to this one. However this further intervention will not be supervised by the study team and you will not attend any hospital visits. If you have any questions, please contact your GP surgery.

What if I have any questions?

Please contact the study team at any time if you are unsure of anything or have any questions.

Contact by telephone (0191 248 1131) 9am-5pm Monday to Friday or by email (rebecca.brown2@ncl.ac.uk).

NOTES

Appendix P.

Pilot Intervention Materials

Vitamin D Intervention

- 2x 3 week pill boxes per person
- 180 1000IU D3 supplements per person (2xsupplements per day =2000IU)
- Instructions for Vitamin D intervention (see appendix)
- Pilot Intervention invitation letter: specifying allocation to Vitamin D intervention
- Study Starter pack receipt and consent slip (see appendix)

Online PA Intervention

- Access to POW website
- 1x SW-200 Digi walker Pedometer per person
- Paper activity sheets (see appendix)
- Instruction sheet on use of pedometer (see appendix)
- Instruction manual for PA intervention (see appendix)
- Pilot intervention invitation letter: specifying allocation to Online PA intervention
- Study Starter pack receipt and consent slip

Standard Care Intervention

- Instructions for Standard Care (see appendix)
- Pilot Intervention invitation letter: specifying allocation to Standard care
- Study Starter pack receipt and consent slip

Appendix Q.

Topic Guide

Study Title: The impact of Physical activity and Vitamin D supplementation on Knee Osteoarthritic pain in older obese adults

Beginning of the interview:

- Turn on recorder. State the date, time and location. Identify self and identify participant (using ID code)

- Thank the participant for agreeing to talk to me

- Explain the purpose of today's interview: to explore your views on being involved in the Physical activity and Vitamin D in KOA study. I am particularly interested in your views on the intervention you took part in as part of the study so improvements can be made to this.

- The interview will last around 1hr.

- The interview will be audio recorded so this can be transcribed into a word document. The audio recording will then be destroyed.

- Nothing will be labelled with the participants name, so it is completely anonymous. Anything the participant says as part of the interview will not be identifiable to themselves. If any direct quotes are used in e.g. any written reports or presentations, these will again be anonymous.

- Ask the participant to provide verbal consent if they agree to take part in the interview and ask if there are any questions before we begin.

CROSS-SECTIONAL STUDY PARTICIPANTS ONLY

Section 1: Participant Background

I would first like to ask you for some background about your knee osteoarthritis:

- Which knee you have OA in?
- How long have you known you have OA in the knee?
- Are there any events or past experiences you feel may have contributed to developing your Knee OA?
- Have you received any past treatments for your knee? What impact did these have on you knee?
- Can you describe any symptoms you may have? (Follow up on these: questions about duration, intensity, importance to the participant, impact on daily living)

Section 2: Participation in the cross-sectional study

I would now like to ask you about the beginning of this study and how you came to take part in it.

- How were you first approached (how did you first find out about the study)
  - Do you feel that was an appropriate way to be approached?
  - Was the information given to you clear/written in a way you could understand/helpful
  -Is there anything you would change about this information? Any improvements which could be made to it?

- Why did you agree to participate in the cross sectional study?
  - Was there any reason/motivations behind taking part?

Section 3: The Study Visit

I would now like to ask you some questions about your first visit (Study 1 Visit) and what we did:

- How was the organisation of your visit to the hospital? How was the appointment made and could this have been improved?
- Was the location convenient for you? Was it easy to find? Would you have preferred the visit to take place anywhere else?
- Were the instructions on how to get to your appointment adequate (directions given by the study team)? Did you encounter any issues getting to your appointment? Were you offered reimbursement for your travel costs?
- Did you feel happy with the consenting process? Was the study adequately explained to you before you began the study visit?
- What did you think of the measurements taken during the visit:
  - Were they explained to you before they were carried out?
  - Were there any measurements you felt were uncomfortable to carry out?
  - How appropriate do you feel the measurements were for the study? Were there any issues with any of the measurements taken? Did find difficult to do/understand?
  -What did you think of the number of measurements taken? Too many or sufficient?
  - Were you able to use/understand the questionnaires used in the study? Any improvements you would make on these?
  -What did you think of the length of the visit: was it an appropriate length of time?
  -How did you find using the activity monitor after the study visit? Were the instructions adequate on using and returning the device? Were there any issues with using the device?

- What did you expect from Study 1 and were your expectations met?

Section 4: Study 1 Close

I would now like to ask you some questions about the end of study 1

- How was the feedback you were provided with about your study 1 visit?
  - Did it contain all of the information you wanted?
  - Was there anything left out of the feedback sheet?
- Did you receive any information about the next part of the study?
- How was the contact from the study team regarding the study after study 1 visit?
  - how was communication with the study team in general?
- How did you feel about the organisation of the study? Anything which could be improved on?

Section 5: Pilot RCT none-participation

How did you feel about not participating in the pilot RCT?

- Why did you not participate in the pilot study?
- If were not eligible:
  - Did you understand why you were not eligible
  - How did you feel about not being eligible
- If you were eligible but chose not to participate:
  - What were your reasons for declining participation
  - What may have encouraged you to remain in the study?

PILOT STUDY PARTICIPANTS

Section 6: Recruitment into Pilot study

I now want to ask you some questions about Study 2 (the intervention study). Again we will start at the beginning, when you first began Study 2.

How were you approached to take part in the pilot study (study 2)? What did you think about:

- way you were approached

To start your intervention, you were posted a starter pack with materials and instructions inside. What did you think about the starter pack?

  - Was what you needed to do adequately explained by the researcher
  - Were the written materials helpful? What would have improved them (e.g. bigger text, diagrams, pictures)
  - Were you provided with all the materials you needed? Was there anything additional which you feel would have been useful? Was there any of the materials you were given you found particularly useful?

- What did you think of the phone call before you started the intervention? Was everything discussed? Was there any information missed from the conversation?

Section 7: Intervention: Acceptability and feasibility?

I would now like to ask you some questions about what you thought about the intervention you took part in?

What did you think of your assigned intervention arm?

- Was it the group/intervention you wanted to participate in?
- Was easy to stick to the intervention? If so, why? If not why?

VITAMIN D ONLY

- Did you receive all of the instructions and materials you needed in your starter pack?
  - Did you use any additional materials which were not provided to you as part of the pack?
  -Were there any tools/materials you felt were particular useful/ you used alot?
- Was the intervention easy to stick too (e.g. remembering to take the pill 1x/daily)
- Did you miss any tablets? If so was there a particular reason why?
- Was the intervention convenient? How did you incorporate the intervention into your everyday life? How much effort did this involve?
- Were there any instances where you forgot to take the capsule. If yes why, if no why?
- Would you want to continue the intervention? How able would you feel doing this outside the context of this study?
- Did you have any issues or concerns about the intervention? If so were the raised to the study team and were they appropriately addressed?
- Is there anything else about the intervention you would like to mention?

PA INTERVENTION ONLY:

- Did you receive all of the instructions and materials you needed in your starter pack?
  - Did you use any additional materials which were not provided to you as part of the pack?
- What was your understanding of what you needed to do as part of the intervention?
  - What materials did you use which we provided you with: pedometer/online programme/activity sheets). If not, why not?

- What did you think of the online programme?
- Did the online format present any particular challenges/benefits?
- Did each of the different module features (introduction, step counter, goal setting, etc):
  make sense?
  Were they useful?
  Were they clear/easy to use?
  Were there any features you used more than others? Why? If you didn't use a feature, why was that?

Do you feel they system had an impact on your PA?

- Was the intervention convenient? How did you incorporate the intervention into your everyday life? How much effort did this involve?
- Were there any days you didn't use the intervention? If so why?
- Would you want to continue the intervention? How able would you feel doing this outside the context of this study?
- Did you have any issues or concerns about the intervention? If so were the raised to the study team and were they appropriately addressed?
- Is there anything else about the intervention you would like to mention?

CONTROL

- How did you feel about being in the control group?
- Did you receive all of the instructions and materials you needed in your starter pack? Were they easy to understand/follow?
- How did you find taking part in the control group?
- Were there any challenges you encountered from being in the control group?
- Did you have any issues or concerns about being in the control group

Section 8: Pilot Study Visits

I would like to ask some questions about the Study Visits you completed at the hospital as part of the intervention study?

- How did you feel about coming back for 2 additional study visits at the hospital?
  - Was this convenient for you to do? Were you able to fit this into your daily life?
- How was the organisation of your visit to the hospital? How was the appointment made and could this have been improved?
- Were there any issues or comments on the pilot study visits?

Section 9: End of Study 2

Lastly I would like to talk about the end of the intervention study

- How did you feel about taking part in the interview? Did you have any concerns or thoughts about this?
- Would you have liked to have participated in a different study intervention? Why?
  - how do you feel about being offered the other intervention (if applicable) at the end of the study. Is this important to you?
- How did you feel about the close of the study? What did you expect to happen at the end of the study?
- Would you want feedback on the general findings of the study? Do you feel this is important to provide to people?
- Is there anything additional you would like to have been offered at the end of the study?

Section 10: Summary

Lastly I would like to ask some questions to summarise your overall experience of the study:

- What were your overall feelings on taking part in the study?
- Was there anything you disliked about the study?
- Was there any aspect of the study you particularly liked?
- What do you think about the way the study was conducted and organised?
- Is there anything you feel should be added to or changed about the study?
- Do you have any questions? Is there anything you would like to add or feel we did not talk about which is relevant?

Appendix R.

Qualitative Interview Protocol

Before the Visit

- Make sure all of the equipment is collected:
  - Pens
  - Paper
  - Topic Guide
  - Field note sheet
  - Audio Recorder
  - Spare Batteries
  - Stopwatch
- Make sure the POW system is set up on the computer for reference

During the Visit

- Make a note of the participant ID, date, time and verbal consent of participant (including statement of right to withdraw) at start of recording
- Make field notes on, e.g. long hesitations, changes in mood, context to conversation

After the study visit

- Stop the recording when interview is finished.
- Reiterate to the participant what will happen to the interviewing data - this data will be confidential and anonymous. Quote may be used in publications and presentations however these will contain now identifiable data.
- Transfer audio recording to PC as soon as possible labeled with participant ID, date and time of interview

Appendix S.

1.0 Category: Study Recruitment	
1.1 Theme: Motivations for participation	
1.1a Sub theme: Personal Benefit	I thought it might benefit me, maybe I should be doing more exercise than I'm doing, I don't know. (003) Yes, my hope that this would help me, point me in the direction what I'm doing wrong really.(003) **(motivation to take part)** To develop for the knees and that, do you know what I mean? And hopefully it might improve mine.(037) Yes, because if it works, this will be brilliant; all very personal, I'm afraid, hoping that I would benefit from it, and that it would improve things. (029) ...and I thought, well, I'll give anything a go if it helps, or if it improves **(the knees)**. (029) It was quite selfish. I have got problems with my knee and I thought, right I'll take part with this if it can help other people, that's fine. But the main thing was, if it can help me or give me a better lifestyle to help my knee, I was keen for that (007) I thought I would try anything. If anything works, I will try it. I know it's just a test at the minute, but...Only to get rid of the pain. (033) So I mean you want to take care of one's health as far as possible, both for oneself but also for others who love you, to put it crudely. (026)
1.1b Sub theme: Helping others in the future by contributing to research	I thought, well, what the hell, because, if I'm not mistaken, on the first letter it said it will be for future references, for people that have got arthritis, and it may be beneficial, the findings, to help somebody else, so I thought why not. (032) ...so I think that because people value the NHS, value medicine, value doctors and nurses, the whole admin and research; I just feel, yes, this is what I need to do to help people. (022) The spin-off is I've been helped but that was not the motive, it was to help people. (022) Well, it's just, I don't know if it will do me any good but it might help people five, or ten, years down the line, with

	the results of the study. (045) I suppose I thought it might benefit somebody else (003) So I'd helped in the past and would do anything to help the NHS and people's health and life. It goes along with what is important. (022) Well I think all the research is going to help and you need people to volunteer, so I would. (031) All of us benefit, I hope, from medical research at the end of the day. This is a good thing. It comes under my idea of a good thing. (026) ...I wasn't really expecting anything, I was just taking part and I thought in a sort of trial of some sort and to see what happens and if it doesn't help me then it might help somebody else. (033) Yes, it helps the NHS, helps research, helps you, helps people with arthritis, and helps people like my age (022) I quite like doing things like this and I think if you don't research into different things, how are people, you know, how are things going to move on really? You do need people to take part in research to discover what works and what doesn't work. So I was quite excited about joining, yeah. (004)
1.1c Sub theme: Disproving the research team	Yes, because, relating back to the first one, on the letter, in my words to my wife, 'I'll bloody show her who's obese', and that's what I've been trying to do, I've been trying to ... you were the cause of it. So, I did take part in the second one, and I was determined to lose some weight, and I feel better for it. (0.32)
1.2 Theme: Barriers to recruitment	
1.2a Sub-theme: Objection to being called 'Obese'	Yes. I was quite shocked that someone said this is a study for obese older people. Well I can work out that 63 is not a spring chicken but I would query very strongly the notion, and I didn't think much of it, that completely out of the blue one is told one's obese. I mean I'm aware I'm overweight but that's a very sensitive thing to say in a letter. I mean it actually was just the title of the study. (026) Well, I was quite flattered, in a way, that they'd considered me. But then when I read the criteria, I was thinking, hmm, overweight? Over 50? You sort of look at yourself and think, oh well, I am all of those, all of the above, so yeah. (004) I think if one had been prepared, if the GP had talked it through and said, "You know you're a little bit overweight

	and they are looking for people who might join this thing. You do meet the criteria," you'd have been a bit more prepared for it. (026) Well a bit cross that somebody had the nerve to call me obese, that was the first thing. (026)
1.2b Sub-theme: Permission to use personal details for recruitment	Well I would have preferred someone to have suggested, saying that, "The hospital is putting on one of these studies, I think you might meet the criteria. Would you be happy for me to put your name forward?" That would seem like a) polite and b) more sensible. (026) ...as I say, it wasn't discussed with me that the referral **(for recruitment)** should be made. (026) The doctor hadn't asked my permission or done anything in that nature about the referral **(for recruitment)**. She'd just done it. (026) I think possibly if the GP had have mentioned it beforehand rather than a letter coming, you know, if I had been at the GP or something like that and he'd said, "how do you feel about taking part in these things?" (007)
1.2c Sub theme: Uncertainty of capability of a student to undertake research	I didn't realise it was, forgive my saying so, a doctoral students research project. That wasn't made clear. At least I don't think it was. Well I'm fairly certain it wasn't.(026) You have a position in the university, in the hospital and I think for a student to be undertaking that, greater care by the authority needs to be taken so that you can perform what you need to do appropriately (026)
1.2d Sub-theme: Distrust of medical research	No, it seemed presented alright but, to be quite honest, I was advised by my daughter and my son-in-law not to take part in it, because I think the word was, 'don't let them get their claws in you, or you might not come out alive', you know (032) ...but it's common knowledge that, sometimes, doctors get their hands on you, and they start feeding you all kinds of things, and you end up a zombie (032)
1.3 Theme: Facilitators to recruitment	
1.3a Sub-theme: Authenticity given by GP support	I felt it was important because the GP was behind it, it was authentic, it had the authority. It was women my age who had these problems, and because the doctors names and surgeries was on it, that gave it a good okay. (022) It would. I think because you've got the NHS label or the doctor's label or whatever, you just feel this is good. This is okay. You've got to be careful these days, haven't you, with people and what they're about.

	So with that NHS and the local doctor giving me, 'Yes, you're eligible for this'. It was safe. (022) I think the only other way would have been if I'd been contacted directly by yourselves but I think having the GP was probably quite good. Yes, actually it was good because the GP, he was endorsing it, wasn't he? I suppose by the GP saying, "I've given your name, I've put your name forward," that's sort of saying it's okay, I suppose. Do you know what I mean? (038) I think if you'd phoned me without any letter, yes, I would have been a bit more suspicious I think maybe. (038) No, I think that's the best way, through your GP surgery. I mean, it is confidential, but it's not a problem. (045) Well I think the GP is the best because they know my medical history, so goes through that. So that's probably the best way. (031) …I think it was ideal going through your GP, and then, at least, you get the right candidate, hopefully. (029)
1.3b Sub-theme: Research informing primary care practice	…but I would like to think that any findings **(from this study)** would go back to the **(GP)** surgery, do you know what I mean? (032) And in the future, it might help people to learn about diet, exercise, how important it is that GP surgeries deliver this sort of information. We should have classes and this sort of thing. Yes, really important. (022) It makes me think that at least they **(GP Surgery)** are doing something. (033)
1.3c Sub-theme: Potential for weight loss	I think weight wise as well, I wanted to see how much of an affect my weight actually had on the research, because I know I'm overweight, and I need to do something about it. I have since joined slimming world, you know. But it is a struggle because of my mobility. So I did want to give it a try and see how I got on, definitely (004) Yes. I was hoping that my weight would go down. (004)
1.3d Sub theme: Personal interest in the study topic	Because I could see the point in this one. Yes, I had been selected on the grounds I probably was a little bit overweight, but I could see the goal with this, this was gonna help my knee problems and that's a problem I did have; so that's why I wanted to take part in this one. I could see the point in that one. The other one, the point is just getting your BMI down under a certain number, for what reason, I couldn't see. I couldn't see that. (007) I just really wanted to see if there was any effect on it because when you explained about the vitamin D and the

	sunshine etc. I thought, I'd be interested to see whether there is something in that. (004)
1.3e Sub theme: Previous employment in research	…how could I possibly disagree **(taking part in the study)** having had a career that is related to medical research myself? I wouldn't dream of standing in anybody's way if there was any way that I could help out by being a participant although (026) I mean when I realised it was a PhD student I thought, "Yes, well you can't drop out now, poor girl. She's got to try and get on with this hasn't she?" (026) Well as I say, it's been my life career so therefore if there was any way I could be of any help, I would do so. (026)
1.3f Sub theme: Prevention of animal research	I'm all for this cancer research, or research into arthritis. I don't like animals being treated **(tested on)**. (041) I love my dogs. I disapprove of any research on animals. And if you can get a cure for arthritis, cancer, heart disease or anything without animals I'm all for it. Even if I'm the guinea pig myself. (041)
1.3g Sub theme: Provision of transport	It was alright, I mean, to be quite honest, I didn't think I would be accepted **(recruited to the study)** because I didn't drive, and I was worried about getting to this place, and you explained that you would provide transport, and I was relaxed after that, because my major … I didn't want the worry of trying to jump on two buses to get here, getting home, and as soon as you said transport, I thought, well, there's no problem. (032) That was okay. I have a very busy life but having a taxi was a really good thing, because if I'd come by myself I would have had to set off at least an hour earlier. I'd have had a challenge to get the car parked at this time in the day, so taxi rides cuts down the time. So it comes here and they will take me back, that is a really good thing.(022)
1.3h Sub theme: Appointment Flexibility	Well it was in the letter, wasn't it, do this or ring up or something or other, fix a time I think it was. I think that's a much better way. I mean if I remember this correctly, you asked us to phone so a time could be fixed rather than sending out letters and saying, "An appointment has been made." At least I don't think you did but if you did, it might have said within it, "Ring up to change it." So I know I ended up doing some ringing up. That's sensible. (026) Well the study has coincided with me not working so I've been able to be quite flexible. You know, it might have been a bit more of a challenge if I'd been working but it wasn't a problem for me at all. (038) It was entirely my decision on what day, what time, which was ideal, so I have no complaints. (032)
1.4 Theme: Participation without fully understanding study procedure	
	I got the first one, and it explained the different procedures you were going to go through; some would be

	selected to do this, some would be selected to do that, and I, basically, accepted it and came. (032) Well, we didn't really know what was going to be involved; you read this paper, and it says you want to do tests… (032) I think a got a letter, and it just said I've got to go through the second phase, and that was it, I think. Well, I know what the first phase was, and the second can't be any worse. (032)
1.5 Theme: Familiarity with researcher for recruitment into pilot intervention study	
	I felt absolutely fine about that **(recruitment to pilot intervention)** because I knew who you were, so that was fine. (038)
2.0 Category: Study Visits and Measures	
2.1 Theme: Study Setting	
2.1a Sub theme: Hospital as the study setting	It gives it more credibility I think (**hospital setting).** You just feel like you're in a safe place. (022) Well, as I say, I could never get here by bus, and there is a bloody hospital just up the road from where I live, a brand new one; it would have been nice if it had been in the – (032) …it's probably ideal**(hospital setting).** At first you think 'hospital', what are they going to do, but once you've been here, and you've been through the first session, there wasn't a problem with it. (032)
2.1b Sub theme: Accessibility of public transport to access study visits	It's very, very good it's on a bus route. I mean every single bus in North Tyneside comes past Rake Lane virtually. I mean honestly they do. It's very, very good. (026) I don't live on a Metro route, and I've got quite a walk to get to a bus which, because of the condition I've got, and getting on and off … fair enough, one of the buses that lower down, they're alright, but using public transport is a problem for me because, even having to stand up, in preparation to get off, the bus is moving, and my knees aren't steady enough. I just very, very rarely use public transport. (029)
2.1c Sub theme: Dislike of hospital parking access and charges	Parking is a devil because they still make you pay I think, yes. (026) Sometimes I brought the car down and parked in the local housing estate because I refuse point blank to pay parking in a hospital, even if you were going to pay it back, which I haven't asked you to do with any of it. (026) I've gone and you've got me a taxi back and that's been it. Absolutely no hardship. If I had have come in my own car, there would be a problem parking. Hospital car parks are notorious for parking spaces. (041)

	Parking is not good in hospitals. I always find it stresses me out trying to find a space and by the time I get here I'm stressed to smithereens. I'm hyper and swearing at people I shouldn't swear at in car parks. No, so I prefer getting public transport. (003) For me personally it's fine because it's not that far but I do find the parking stressful. (038) It was fine because, obviously, Rake Lane is ideal; the only downside is parking… (029) It's fine. It's easy to get to for me and you can nearly always get a parking space. Not always but most of the time. (033)
2.2 Theme: Wearing the accelerometer	
2.2a Sub theme: Views on being monitored	That's not the worst one, it's having to wear the monitor for five days. It's a little bit inconvenient, but it's okay. (037) I feel as if, obviously, it's **(accelerometer)** monitoring your movement, but there was one day I was just sitting, driving all day, and I kept thinking, "This monitor's not moving, and they must just think I'm sitting about all day," but it's just because I was driving, doing an inspection. But it was in my mind, thinking, "Am I being lazy because I'm not moving?" It was on my mind a little bit. (037)
2.2b Sub theme: Appearance of monitors	No, no. I suppose they could be a little bit more discreet. But again, it's not a bad thing. No hardship. (045) It's always under my clothing, I always wear long shirts so it's out of sight out of mind. (041) Yes, it was important **(that people did see the accelerometer)**… Because I don't want to explain it to them…. I just didn't want to explain what it was, what I was doing probably because I just don't think it's any of their business. Sometimes I get like that. Other times I will explain it to people and sometimes I just didn't want to. At that time I didn't want to explain. (003)
2.2c Sub theme: Wearing the accelerometer	It's probably just me. It kept slipping up and down, I don't know why. Then I couldn't sometimes tell whether I was putting it in the right place. I just found it just irritating. That's the only bit I didn't really enjoy. (003) I do remember that **(wearing the accelerometer)**. I'm not very keen on that for some reason. I couldn't tell you why. I found it irritating. (003) There was the itchy thing **(accelerometer belt)**. I don't like that elastic stuff it's on next to your skin. For a long

	period of time it's a bit of a bind and it does make me itch. It's not good for my skin. But there again, on the grounds of medical research I decided to put up with it. A bit of a bind having to wear it, I will say that, yes. (026) Yes, it wasn't ideal for me; it would slide upside down, and most of my trousers don't have belt-loops, so I couldn't even put it through the belt-loop, and then it was like, going to the toilet, 'have I put myself upside down, moving it?', and the moving of it. Once you actually got yourself dressed, and it was on, it was easier underneath my trousers, that one, and that tended to keep it in place, especially if I had these tighter fitting trousers on, and that was fine, but, apart from, like I say, going to the toilet and thinking, 'shit'... (029) I thought, 'what?', and I think it depends on ... because I'm putting it on the waistband, and I found it depends on the style of trousers, and I think the baggier, loose ones, it wasn't; it mustn't have been enough for it to have registered actual physical movement, so I got wise to that. (029) It was alright. It wasn't a problem **(wearing the accelerometer)**. I was wondering if I had put it on the right way up **(accelerometer)** but I noticed that it had a mark at the top so I know that's the top. (033) You don't really realise it's **(accelerometer)** there once it's on. (037) You don't even realise it's **(accelerometer)** there for the rest of the day... (043)
2.2d Sub theme: Interest in accelerometer feedback	Yes, I liked that, yes **(using accelerometer)**. I mean I was keen to do that and get some feedback, results and things from that. So, yes, that was fine. It didn't intrude, it was easy, you know. The form **(activity log)** was easy too. (038) I mean I kind of enjoyed doing the five day monitor, although I saw the results from the first one, so I haven't seen them from the other two, but, yes, I thought that was quite interesting, my activity levels. (038)
2.3 Theme: Completing consent forms	
2.3a Sub theme: Completing the consent form with the researcher	No, I think it was easier doing it **(consent form)** here **(study appointment)**, because if you're unsure about some of the questions, you'd **(researcher)** be able to help us answer them, whereas if you're at home on your own, you're on your own, unsure. (037) Well, it answered all the questions because I had some questions in my head, and you answered all the questions really well. So I knew exactly what I had to do and what I was getting into as well. So that was good. (004)

	I suppose the thing about doing it **(consent form)** here, in the appointment, is if I had any queries about it, you were there to ask you about them. (038) It was nicer going through it with you, because you became more of a person, rather than just someone there to gather the data; it made it more comfortable, for me anyway, me personally. (029)
2.3b Sub theme: Concerns over identifiability	I thought it was very thorough and it was possible for me to ask questions because the big question for me is is my voice identifiable? You've not told me it will be transcribed and all the rest of it. I mean you will understand, for me, that that's actually a big issue because it's possible for people to identify me. But I don't think anybody should be in a position that their stuff will be identified. (029)
2.3c Sub theme: 'why consent forms are required?'	Well, I mean, for what treatment I've had, I don't know why we had a consent form. I mean, basically, I'd already been doing it, taking a weight, height and a little bit of blood, and monitoring my activities, but I don't know what the law is. (032) Yes, it was quite straightforward really. I suppose it was sort of outlining the obligations on both parts, wasn't it? Do you know what I mean? Yes, I suppose I'm sort of used to things like that, so it wasn't a problem for me.(038) Fine, I just think that you needed to have these things, so somebody can't come back and point the finger of blame, 'you said, or you did', and you think, well, no, you've signed that you've read and you've understood what was actually going to happen, and I do think you need that kind of thing in place, to stop any abuse. I don't mean as nasty abuse, but abuse of power, or information being passed around, that you, perhaps, don't want passed around; you know it's going to stay within this group. (029) When you're willing to do things to help, of course you've got to give consent. That's what you legally have to do. (031)
2.3d Sub theme: Concern over what you are giving permission for	I can understand exactly, but it's funny, when you start talking about consent forms, then what the wife was saying, and what the daughter was saying, 'hold on, are they going to take a leg off you', you know what I mean? Consent, you know, it's in the back of your mind, 'hold on, I'm signing a consent form, why?'. Once it was all explained, it was no problem. (032)
2.4 Theme: Questionnaire completion	
2.4a Sub theme: Ease of use	They **(the questionnaires)** were pretty simple… (032) Yes, fine. It was a good question, it was easy to answer. The tick box helped on things (022)

2.4b Sub theme: Possible variation in answering questions	But some of the questions like when you say your movement restriction, like in the morning, afternoon And evening, bedtime. Progressively through the day it gets worse. There's no measure for doing that. You've got none/moderate/severe/extreme…You can't say well it's extreme at night, it's moderate at dinner time and it's non-existent on the morning. (041) No If you want to ask a certain question, then ask it and I will answer it but sometimes the answers from time to time are different but then that's because the thing you are asking about it's easier or got worse so let's say it's not ABC, ABC, ABC all the time, is it? (033) I'm never terribly sure because we never keep a record, whether mine are consistent answers or not from one period to the next. That slightly worries me because in my head I might be using a different understanding of mild each time I come in, slightly depending on my mood or slightly depending on whether I had a good night's sleep or something like that. So I have problems with subjective measures, everybody does but on the other hand, there's little point in trying to do just objective measures without realising what impact it has on people and what they say the problems are. (026)
2.4c Sub theme: Phrasing of questions	Yes, there were two questions when I did it today…but they were almost like double negatives, I thought, "I don't know if I'm reading this properly or not." But personally, I'd rather just tick a box than write something. (038) Yes, I felt absolutely fine doing them. Actually there were a couple of them that I felt the questions were a little bit ambiguous. And I think it is hard to be absolutely accurate, you know, to know which box to mark really so… (038)
2.4d Sub theme: Researcher presence important in answering honestly	No, the only bad point is me; I don't like accepting what I can and can't do, so I sometimes think, well, it's really that but I'm going to say this, but that's my problem. Even after all these years, I still don't like saying, 'I can't do', so no, they were entirely spot on. I think that, especially with sitting and talking to you, talking through them, I was probably more honest than I would have been if I had done them myself. (029) Yes, and discuss, and then you're sitting there thinking, 'I want to say I'm that good, but really I'm not that good', so I think, for me personally, it helped me be more honest, with which one to tick. (029)
2.5 Theme: Taking blood samples	
2.5a Sub theme: Willingness to donate blood	I am a blood donor any way so it wasn't a problem. (033) I don't mind donating the stuff **(blood)**… (026) I realised that you can get a lot of results from blood tests, so it's all part of the process. (032)

	Yes, it makes sense. Blood has got a lot of information in it. (022) Yes, no problems, at all. I'm a blood donor, you know? (045) Well I have had quite a bit of blood taken for various things. Apart from the fact I know you can't always find my veins, I was prepared for that. (003) I think the first time it was a little bit… I think you couldn't take it the first time, someone else took it and he was a little bit heavy-handed I think. (038) I think particularly as you were talking about Vitamin D as being the main part of your study then obviously the only way you're going to be able to read levels of Vitamin D is by taking blood, so, yes, I had a fair understanding that that would probably be a part of the trial, you would be taking bloods of some kind to get the measurements that you needed. So, yeah, there was no problem for me. (043)
2.5b Sub theme: Views on giving DBS blood sample	I was interested when you took the blood out my finger and put it on the little dots. I was interested in how that worked… (004) I don't like the pinprick one though, that hurt (029)
2.6 Theme: External factors on study measurement performance	
	Walking around, I just couldn't understand, and then, again, if you'd asked me to do that as soon as I got out of bed, things might have been slightly different; my times would have been slightly different, but, during the day, you're more mobile, but I couldn't understand, but I did it, and I did okay through it. (032) As I said earlier, people, of course, don't just have knee problems and you have to understand that there might be other problems with hips and the spine, back, other elements of arthritis and pain that people have that will impact on their ability to stand up and sit down and move around, so as long as you're building that into your trials… There are other factors that can quite often impact on how easily you can do those exercises. (043) The last time I wasn't very well so I was in bed so I didn't probably use it **(accelerometer)** as much as I could have done but I was ill in bed at the time. (003) That was fine, except I think, the last one I came to, when my back was still a problem, and I couldn't … I think I

	only managed one walk **(timed up and go test)**... (029)
2.7 Theme: Uncertainty over what was being measured	
2.7a Sub theme Unclear why measures are repeated	Basically, you took my height three times, you took my waist measurement three times. Well, either you're very insecure, or is that because of the study, you've got to do it three times? I mean, I'm not going to get any smaller... (032)
2.7b Sub theme Embarrassment over what accelerometer is measuring	It's embarrassing actually if you're on the loo and so on, you think they might know what I'm doing. It's a bit of an embarrassment, especially for older ladies I would say, yes. I took it off for showers and baths and things. I might have been tempted to take it off for other things but I didn't. It's probably handy for you to know that I can get on and off the loo or not but it's a bit embarrassing. It's like having someone watching you. (026)
2.8 Theme: Embarrassment over terminology used during study visits	
	I thought I wouldn't be selected for the second one, and that was the one where we had the obese mentioned, and I thought, well, if I bloody do this, I should get some weight off. (032) Yes, well, the weight is embarrassing, for me (032) It was one I didn't enjoy but I know it has to be done. I'm pleased you didn't say that I was overweight because normally they do. That was a plus, that you didn't make any comment at all actually. I don't need to be told I need to lose weight because I know that. (003)
2.9 Theme: Study Visit Length	
	Just because we're retired, we're not sitting around waiting to be called into the hospital and entertained for a whole morning. We have plenty of other things to do, like everybody does. So it was probably more time consuming, these little sessions than I thought from the outset. (026) It's one of them things I think it takes what it takes, isn't it. You have certain things that you want to do as part of your study then I don't think it's probably unreasonable. It's normally around about an hour, I think, isn't it, so that's not a huge amount of time out of my day. (043) It was fine. Well, I expected to be there about an hour, so it met my expectations. (004) It's fine. I don't like being rushed (003)
2.10 Theme: Concern over investigator qualifications	
	I would have expected a trained medical worker to do those, a nurse. You tell me you've done a courseto enable

	you to do them and I take that at face value. I believe you but you hadn't when we started and the nurse did them. Again, I'm not too sure if I had been supervising a project, whether I would have...I would have probably stayed with the nurse doing it throughout. (026) Marginally, only a titchy bit surprised that one had to do them. I mean that's obviously the most intrusive test and on one level I almost feel I might not have expected a student to do those. (026)
3.0 Category: Study Materials	
3.1 Theme: Acceptability of PIS	
3.1a Sub theme Clarity of PIS	But no, I can remember, you know, reading through the papers **(PIS)**, it was quite straightforward really. (038) Yes, that was very helpful. I read it through **(PIS)** and I through I would find that helpful and I'd like to participate in it. (03) I could easily understand it **(PIS)**, yes... (03) Well I think it **(PIS)** was self-explanatory, it was clear, it was easy to understand. It was quite, it was straightforward. (038) Yes. I understood some of it **(PIS).** (031) It told me quite a lot **(PIS)**, quite informative. There was quite a lot in it. When I first came, I had some questions in my head. I thought, I'll ask all about this when I get there, but I was quite impressed with it. I thought it was quite informative, yes. (04) It **(PIS)** was quite professionally laid out, yeah. (04)
3.1b Sub theme Objection to terms used within PIS	...that completely out of the blue one is told one's obese. I mean I'm aware I'm overweight but that's a very sensitive thing to say in a letter. I mean it actually was just the title of the study. (026) It was a letter came from my doctor to say he put my name downand I was—I'll be honest, I was quite shocked when I got the letter because it had me down, 'you are being selected because you are obese' and that was, that was quite a shock. (07) Well, being selected on that criteria. I've never thought of myself as being obese...but it just came out of the blue,

	the letter. (07) I'm just trying to think because, obviously, the doctor sent an accompanying letter to say how my name was put forward, but no, it was very nicely put together, and yes, overweight people, but it wasn't exactly a slap in the face that, because you are overweight, you're being picked on, so no, it was nice and, like I say, if it can help future people, I'm all for it. (029) I did read it, but that was good; if that word hadn't have been on … 'overweight', I would have said … but 'obese' has got that tinge to it, that's meaning, you know, and I can't remember anything else on that sheet, barring obese, and I think it said it three times… Yes, it just went straight into my mind, and thought 'yes'. You know, you go out on a Saturday night pint with the lads, and you take the up, put the weight on, and this kind of thing, but if I said, 'you're obese you', it'd probably be fisticuffs, so it's a good word, it just hits you where it hurts. (032) Well, I was quite flattered, in a way, that they'd considered me. But then when I read the criteria, I was thinking, hmm, overweight? Over 50? You sort of look at yourself and think, oh well, I am all of those, all of the above, so yeah…I can understand because I know that obviously age plays a factor in it because you've been around a long time and your joints do get worn, and I know that weight does have a bearing on it as well. So I totally understood really. I had a bit of a laugh about it actually when I told the girls at work. (04) No, I think it was excellent what came through. I cried of course because it says, 'Women your age', but I mean, it's reality, isn't it? [Laughter]… It's reality. You are the age you are, you are overweight, it's reality…. I think it's a good thing. It said you were eligible because you were overweight, because you are the age you are and because you've had problems. So factually right. It needed to be said outright. (022) So I didn't know what to be more offended by, being called older or being called obese [laughter]… Well, I mean we've had a good laugh at it, you know. As I say, the title, you know, 'Research Study for Obese Older People with Knee Pain', I think probably (unclear 0:09:54) an older person probably… It's the fact that when you see it just written like that it's quite stark, isn't it? And actually, I mean I just don't consider myself an older person but maybe I am, you know….But I mean it was funny, do you know what I mean? I mean I've told a few friends about it, they all think it's quite funny really. When I did speak to you about it and you said that you'd been told you had to use…I think it perhaps could have been softened a bit. (038)
3.2 Theme: Provision of appointment letters	
	And then that was followed up with a letter. And everything's been followed up with a letter, which is good. (038)

	It was fine because first of all you rang me, then a letter followed up. So a letter is good for me because I can show my boss and I'm not just, you know, having a sneaky early finish. So the letter is useful for me to show him, rather than just tell him. So that was fine. Plus, I think, if you've got something tangible, you know, you can put in your handbag and you remember. Whereas, if you've just had a phone call, you write it in your diary or you stick it on a calendar or something like that, but you could forget. I'm not one of those people who puts it in my phone, like some people do, but maybe I should start. Yeah. (04)
3.3 Theme: Participant Feedback	
3.3a Sub theme Getting something back from participating	Really important, I think. As I say, it's a two way process, I believe, so I'm happy to participate and it's always very interesting to see what the results actually have brought up. (043) But I mean obviously, if you're being sufficiently intrusive into people's lives to capture them for taking these tablets and wearing things and bringing them into hospital for two hours at a time then clearly you need to give them as much information as you can about their state of health. (026) Yes it gives it some meaning **(the study)** I suppose, doesn't it? If you get some feedback from it, yes. (036) Yes, I think that is important because if we didn't get any feedback it means, for me, it wouldn't be worth…why did I do it? It's important. (03) As long as I get the feedback, I'm more than content with that, yes, because then it makes me feel as if I've done something. (03)x
3.3b Sub theme Learning more about current health	No, I like things like that. Yes, I thought that was really interesting, yes, just to get an idea of where you are on different things, yes. (038) Yeah, like I said, there wasn't any problems. It's nice to get feedback that where you're at, you know, if your weight's gone down or what your blood tests were. I do enjoy the feedback back on it. (07) I would like to get as much information back on my results. It will be interesting to know how my vitamin D levels have fared since I've been taking it. Are they where they should be? Do I need to continue taking the Vitamin D? It would be good to find that out. Just as much feedback as I can get on the results and that for me to keep and look at and say, they're my goals. (07)
3.3c Sub theme	Well I think it impacts on lifestyle, I think you feel you're doing something to help others, it's very important to

Advice on improving health/conditions	have the feedback. (022) Oh yes, I did. It was quite alright, telling me how much exercise I did or didn't do. Well I could have told them that. That was foolish. I mean that's a piece of information. More to the point, it's how can you do some more or whatever you can do. (026) But as long it's a coherent set of information with some possible pointers and what one might do to continue to manage the condition. (022)
3.3d Sub theme Feedback to primary care	Obviously any diet warnings, if you picked something really foul up you would have obviously contacted the GP and put matters in hand to do something about it. So it's a good thing. (026) If they got anything out of it and it was positive, let me know and if I couldn't get it off the doctor I can get it myself.
3.3e Sub theme Feedback on weight was poignant	It was interesting to use as a baseline because when I read it, I'll say I was quite shocked at some of the stats, particularly my weight… (04) Yes, I read that **(feedback)**. I glossed over the weight bit, naturally, but the rest was fine. (03) Well the feedback is so important because it clarified the fact I needed to lose weight, really (022)
3.3f Sub theme Importance of whole group feedback – what did the study find as a whole	That's the bit I'm most interested in really. It will be interesting to see what things have changed over the twelve weeks. (04) I'd expect to get some feedback, for me, just individual feedback as well as the group feedback (03). …people who've had the placebo, people who've had the Vitamin D and then the people who've had the activity programme. I think it will be interesting to see hoe the results differ, if at all. (04) Yeh. I mean to say, feedback on myself is great, but it would be nice to see what your total figures were- how many people took part, what you thought you had achieved; the project itself. It would be interesting to see what the results were of that. Not just my own personal ones. Just to see what, as a group of people, whether you think you have achieved anything. Whether the exercise has helped people. Whether the vitamins have helped people (07).
3.3g Sub theme	It was easy to read. It was very well set out, I thought. (04)

Feedback presentation	Yes, it's **(feedback)** very plainly set out, yes. (038) I prefer it written **(feedback).** I'm quite shy so I don't like going into a room where I don't know anybody (03).
3.4 Theme: Intervention study pack and instructions	
3.4a Sub theme Study intervention instruction pack delivery mode	I think it was useful to get it posted out and read it before I started. So it was good. Rather than you just handed me a bulk of stuff when I came out. I'd read it before I met you so therefore I knew what to expect. (04) Yes, obviously it's cheaper way for me because I don't have to come down. (033)
3.4b Sub theme Study intervention instruction pack clarity	I found them OK **(study intervention instructions)**. I found them fine. I managed to get on the website, no bother, registered on the website and just filled in the charts on a daily basis. Then I used to put them in on a Sunday night. That was the time I did it. So I found it really well. (04) That was really useful to read through all of that **(study intervention instructions)**. I found the whole thing really helpful. I had my pedometer and I read that, knew how to work that. So that was fine. I was raring to go really. (04) Straightforward, even a dummy like me can understand it **(study intervention instructions)**. (033) No, they were easy to understand. It wasn't difficult. Not a problem **(study intervention instructions)**. (007) No I don't think so, no. I understood it all for a change **(study intervention instructions)**. (003) I thought they were quite good **(study intervention instructions)**, they were concise and I knew what I was doing. (003).
3.5 Theme: Using the pill cases	
3.5a Sub theme Pill cases facilitated compliance	I thought the pill boxes were really good. I have to use them in any case because you sometimes forget if you've taken something. So I found it handy. (03) I think the colour coded boxes, you know, they were marvellous. For me, seriously, I think if it had been a box of Vitamin D tablets and you'd said, 'Take two a day for the next 12 weeks', it would have been easy to forget. But because it was in the pill boxes, I supposed they're called, it made it much easier to remember to take them every morning. (038)

	Like I said, if you didn't know whether you had taken a tablet, you would know as soon as you opened the box. I mean, I didn't miss one. (033) Oh, it was dead easy. Just two tablets. It was easy. Just did it every morning. I thought the little boxes they came in made it simple. (031) I thought it was brilliant. I wondered, "Did I take those tablets this morning?" and I knew I hadn't because it says on the box if you have taken them. (033)
3.5b Sub theme Pill cases easy to use	Well the only general thoughts, the whole thing has been a disaster as far as my thumb nails have been concerned. That's why I don't want those things **(pill boxes)** back. They're the most…if you honestly think people with any degree of arthritis in their hands could possibly manage those, they can't. It was awful (026) Well I don't know, I'd have them in a bottle or something**(Vitamin D supplements).** You see even once you get into the wretched things **(pill cases)**, you've then got to manipulate getting titchy little pills out of a titchy little but of silver foil or whatever it calls itself. I can't tell you the number of times the wretched thing broke, crumbled, fell on the floor. (026) Well I would think that a four-year-old child would be able to work it out. It's simple. **(regarding pill box use)** (045) It was simple. You couldn't make a mistake with it. **(pill boxes)** (033)
3.6 Theme: Pedometer as incentive to increase PA	
	…I thought they **(the pedometer)** were a tool, and it was an incentive, for me, to have around. I told the wife last night, I was saying this would be the last one **(study visit)**, and I wouldn't have any monitors, and she said 'well, are you going to still-?' and I said, 'I'll try and keep my weight down'. (032) No I think the pedometer is the key thing. It's a daily thing that I check up on, that's really important. (022) …and the pedometer was the key because you were watching how little exercise or what a lot you (022)

	I had the step counter on every day. Well I forgot one day, missed half a day before I put it on. But other than that, yes, pretty easy. (031)
4.0 Category: Pilot Interventions	
4.1 Study arm allocation	
4.1a Sub theme Clarity of study arm allocation	Well, I'm not sure why, or how, you selected who does what; you must have your reasons, but I just took it as this is the way you wanted it, that I would be taking part in this. (032)
4.1b Sub theme Participant Preference for Vitamin D supplement intervention	As I say, it's easy to take. If you have got to do some sort of exercise before you go to bed and you are tired you just say, "I will miss it tonight", whereas with a tablet you just take it and because I was taking the statin as well, it made sure that I was taking that regularly (033) Oh yes. It was easier taking them than doing an activity one because, you know, I can't be bothered (033)
4.1c Sub theme Participant Preference for PA intervention: feeling of doing something	I was hoping I would be in one of the groups that did more of the exercise than just take the pills…Yes I thought it might give me a kick start in doing something (03) No I would have welcomed any of them really, but I think, of them all I was glad that I got one where I actually had to get up and do something (04) I was quite pleased. I was pleased that I'd been given the activity one, rather than just being just some sort of tablet to take, or a placebo to take. I thought, well, I've got this activity thing. I need to make it work for me (04). Well I suppose you just would feel you were not doing anything differently, whereas if you were in one of the others, provided with an exercise programme or…so you were just doing something differently I suppose. (038) Quite thrilled that I was picked to do the activity side of it because it's given me the motivation to get up and do stuff that I probably wouldn't be doing otherwise (04).
4.1d Sub theme Preference not to have placebo/standard care group	No I was happy with that. Because one of them was no intervention, wasn't it?…Yes, I'd have been a bit disappointed if I'd been given…you know, so I was glad to get… (038)
4.1e Sub theme No preference for study arm	It doesn't bother me. It's to try and help in any way. I would have done either one. (037)
4.2 Theme: Study retention	
4.2a Sub theme	All I have given up here is my time, you know, everything else is…something good might come out of it and like I

Facilitators to retention	say if not for myself then it might for somebody else. (033) Not a problem. If you volunteer for something, you volunteer and that's it. (033) I nearly came in to give it up then too but I was so sorry for you doing this wretched study I thought, "Well I better hang on." Then it did, in the end, finally kick in to be some use but it got worse before it got better.(026) Well I was quite happy to do that because I've got the time and I was just quite interested really. I suppose (unclear 0:36:13) it was interesting to come back at three monthly periods and today. (038) I didn't want to disappoint you. I knew you'd be heartbroken so I thought I'll keep taking them **(vitamin D supplements)** to the end. (045) I saw it through. I didn't like taking the tablets. I knew they weren't having a beneficial effect on me, but I saw it through. (045)
4.2b Sub theme Barriers to retention	If I had, I would have…the agony I was in, it didn't seem to be improving. That was the real reason why I nearly gave up. I didn't think they were doing any good at all. (026) I mean I nearly gave up in the first week. I mean how did I feel being told which group I was in? Neither here nor there but when it happened I nearly gave up in the first week, I was in such agony. It had got so much worse by taking this Vitamin D tablets compared with the other things that I'd been taking. Whether that's just my mental approach but my God it was awful. I mean to the point that I nearly gave it up. At the end of the first batch of the six weeks, I nearly came in to give it up (026)
4.3 Theme: Facilitators to intervention success	
4.3a Sub theme Personal motivations	You've got to want to do it, as well; it's no good just … I wanted to do this, because I wanted to lose some weight so, basically, you helped me, and I've helped you, which is like smoking really, isn't it? You either want to give in, or you won't, and I wanted to lose weight, and I'm pleased I've done it. (032) I've got two little granddaughters and I don't want to be like this old woman that follows them round everywhere. I want to be able to do what they do and go out with them and walk along the beach, and walk along the seafront with them. (04)
4.3b Sub theme	It is important because I think sometimes if you do it off your own bat you tend to be a bit, "I'll put it off. I'll not do

Social support	that." But if I know somebody wants me to do it and I have to explain to somebody why I haven't done it, I'm more inclined to do it.(03) ...sometimes that's even worse if you go on your own because you've only got yourself to let down. If you go with somebody else, you don't like to let them down. (03) So I think if somebody is there to go along with, you're more likely to continue than you are if you're on your own. If it's just you, you'll think, oh I'll not bother going, but if somebody else wants to go with you, or comes to pick you up or jollies you along a little bit, I think it is easier to do it with someone.(04) ...you need somebody there, your wife or your partner, to keep you going and, normally, she, the wife, is doing the same thing; she's going on the exercise bike, she's walking up the road. (032)
4.3c Sub theme Guilt about not complying	Yes, and give me a big push to get going and then I would be so guilt ridden if I didn't do it, I would continue doing it (**referring to PA intervention).** (03) But again, it was down to feeling guilty. Have I done enough? (041)
4.3d Sub theme Exercising pets	Oh like I say, my daily activities more or less revolve around my dog (041) Part of the reason is I would like a dog but the other part is you've got to take a dog for a walk (03) So it did take us a while to into it **(PA Intervention)**, but I'm retired, so I can plan my day. I've also got a dog, so, you know, the dog is going to have a walk... (07)
4.4 Theme: Barriers to intervention success	
4.4a Sub theme Disruption of regular routine: staying away from home	The danger is the holiday, or the weddings we're going to; everything goes out the window, but we're going to carry it on. (032) As I say, my major worry is, when we get away from the norm, get away from the home, and everything changes, you've got to try and get straight back into the zone again, (032) When we went off to our Outer Hebrides holiday it was a bit more difficult. I mean sometimes we were doing bed and breakfast and sometimes they were packed in the car and so on so I couldn't do them that day but if I did I would just tag them on to the end of the final thing, which I have done. (026)

	We didn't but they were in the car sometimes when I would have wanted them at breakfast and you think, "I can't send my husband out just as he's starting his breakfast to go ferreting in the car and get the things for me," that's a bit mean. Then by the time we'd left, I'd forgotten. So I think even non-chaotic lives and fairly routine lives have breaks in the routine, which might make for difficulty in keeping on with something like that, whether it's on a trial or a real life thing. (026) But, I didn't always do that **(input steps online)** because when I was away I would just note down what I had done and then I would do it—because the Wi-Fi access in hotels isn't always that great. So I would wait until I came home and do it then. (04) If I'm staying in a hotel overnight, they haven't always got any facilities **(for activity)**. (04) You've just got no time to do any activities. You don't get home till nine o'clock at night and then all you want to do is have a bath and go to bed. So it's really difficult those days when I'm away. (04)
4.4b Sub theme Bad weather disrupts PA	When the weather was fine I was doing gardening. I did intend doing some swimming but just getting down to the pool and that, it just didn't fit in. (07) So it wasn't really the weather to garden. That's why we decided to do swimming. It was the easiest option to do because I haven't got a bike. (04) Well, when the weather got better, I included gardening in it because I do like gardening. But the weather was just so poor and the back garden was like a quagmire so we waited till the warmer weather came and it wasn't so damp outside and the garden wasn't so muddy to start doing the garden. So I do spend a lot of time in the garden when the weather's nice. (04) And now that the weather's better and it's a bit lighter at night, especially when the clocks go forward, it will be lighter again, so I think we will get out and about a lot more often. It will make us walk more often. (04) ...but unfortunately at the time that we were doing it the weather was so atrocious that I wasn't able, if you like, in the May to perhaps push myself or achieve perhaps some of the stuff that I'd wanted to do because the weather simply was not really good for getting out and about and doing that. (043)
4.4c Sub theme Sedentary working day restricts	I just felt I haven't maybe helped as much as I could if I was only working 38 hours a week. Because if I worked 38 hours a week I could put in more exercise. (022)

activity	But sometimes, because like if I go to a day conference and I just can't exercise because you have to sit there, so you didn't notice how work impacts on lifestyle. (022) That was really important because, you know, the times when it was lowest was when I was at work and had to be at meetings, had to drive around, had to sit around all day one Saturday at a conference, and you realised how work impacted on lack of exercise. (022)
4.4d Sub theme Injury/other painful conditions prevent PA	I was having problems with my neck at the same time so the swimming was out. (07) I've got other problems apart from my knees and that, so what I've got to make sure is that I don't overdo things that aggravate something else, where I'm going to end up two days not doing anything at all. (07) I do it as I felt I could do it, because apart from my knee, I have lots of other joint problems. So I know that I've got to do so much a day. I do that and if I'm feeling well, I do extra. If I don't; I don't. The bit where, are you putting barriers in to stop you doing the exercise and that, I didn't find that helpful at all. (07) As I said, there was a complaint, and when my back had gone unfortunately I couldn't do any real sort of exercise or anything additional certainly at that time. (043) Well, obviously my hips and my back. You know, things like that are all things that will then impact on the level of activity that you might have in a particular day, you know. It's the nature of the complaint. (043) Again, it was alright, but, really, what stopped me doing as much walking was my back, and, unfortunately, it took about five weeks for that … well, ten days for that to calm down to a point where I could, actually, straighten up and walk. There were spasms shooting up and down my leg, and up my back, so it was, perhaps, a little wasted on me, but, I think, only because I had that problem, and I had to get that problem sorted. It wasn't anything to do with not being able to get somewhere, to be able to do it, well, apart from not being able to, physically, walk; the restrictions weren't on that side, it was what was happening to me… (029)
4.4e Sub theme Christmas holidays disrupts PA	Christmas day. Family, family here, you know, not going out for a walk as much. Bad weather. I did have—I was in hospital for some injections a couple of days, injections into my joints and my neck so I did have a couple of days where I didn't feel too well. So things like that, but other than that, even the weather, I was still trying to get out for a walk. (007)

	I might have had—the other thing is, I think I started my programme a few days before Christmas, which, you know, there's a lot goes on at Christmas. I think it might have been those days that I'd forget. It might have been, actually, when I think back, it might have been better to start just after Christmas or earlier. I think I started three or four days before Christmas or something like that. (007)
4.5 Theme: Intervention safety concerns	
4.5a Sub theme Vitamin D supplement safety: concern of overdose	Well I did ask you, "Can you overdose on this stuff?" and you reassured me there. (026) Well the only issue for me was just towards the end there when I was wondering about side-effects because of another condition I've developed but I don't think there's been any connection. So at the very end I was glad it was coming to an end because I was having problems with my scalp and I thought if it is responsible I didn't want to keep taking them. But I don't think it probably was anything to do with it. (038)
4.5b Sub theme Activity safety: fear of 'pushing self to far'	I was conscious of how much I was doing. And like you say, at certain times I'd push myself. Sometimes if I pushed myself that far, I'd end up with the aching later. (041) I think the day my knee almost locked, I was a bit worried then that I was overdoing it. But it only lasted a day and then I got up in the morning and I couldn't walk very far. I was really concerned (04)
4.6 Theme: Taking Vitamin D supplements	
4.6a Sub theme Routines in taking supplements	But with this, it was downstairs on the windowsill so when I was filling the kettle in the kitchen it caught my eye straight away (038) No problem at all. It was part of my breakfast routine really (038) I took them with the rest. I always take them first thing in the morning because I find if you space them out I forget to taken them. (03) Not a problem **(taking Vitamin D supplements)**. I took them at night before I went to be so that was it. (033)
4.6b Sub theme Reasons for missing supplements	Yes. I think I only missed a day and God knows why I did that. (03) It was the first Sunday. I just thought I had to be honest. If somebody had asked me, I would have said I had taken them. I didn't notice until the Monday I hadn't taken them. I don't know why. (03) If I did miss some, I had them the next day but not in double quantities, I merely went on for a little bit longer, which is why I've got one more lot to do. (026)

	I think I went on holiday for a long weekend, and I think I rang up and I might have mentioned it. I missed, I think it was three or four days **(of vitamin D supplements)** out of the six weeks…I forgot to take them **(vitamin D supplements)** with me to be honest. (037)
4.7 Theme: Barriers to POW Website Usage	
4.7a Sub theme Personal preference for paperwork over IT	No problem **(paper activity sheets)**, it was part of what I used to do at work; I used to fill a log in, I used to write a log, it was all written. If I had to write it in, on the computer, I would have, probably, been on until twelve o' clock at night. (032) Well, at the time, the filling in **(online step graph)**, I thought, am I doing this right? So, I preferred the manual **(paper based)** notes, but other people who are, perhaps, savvier on computer; I like the see what I've done, but it's personal preference. (029) Both would be good **(website and paper formats)**, more help. But also, it was a great thing to just fill in the paper (022)
4.7b Sub theme Lack of confidence in the function of the website	But every time I went on it **(POW website)** to do anything, it wouldn't let me… (041) Well if they **(other people)** have the same sort of problems I had, they would throw the towel in because if there's anything that stresses me out more, its computers that say you can do this but won't let you do it. (041) **(referring to website)** If it's not actually giving you the imagery that you think it's going to then you get a bit confused and then you're worrying if you're doing it right, so it's as I say, unfortunate for me that it meant I lost a bit of confidence in it. (043) I think I had some problems with the online system obviously at the start I think it wasn't transferring the data in the way that you were expecting it to, which I lost a bit of confidence in the online part then (043) The programme changed after the first six weeks. To be honest, I'm not sure quite how it worked after that. It came up again, there was no instruction after it changed (007)

	...sometimes it didn't work, and I was getting really disappointed I found that looking at the graph **(online step graph)** and looking at that side of it was good, but with it not working properly**(online step graph)**, I even, kind of, lost interest in that after the second part**(last 6 weeks of intervention)** (07)
4.7c Sub theme Being 'old' as a barrier to internet use	To me it would have been a doddle for the young'uns, I mean, the young people who were involved, to do it, but to me, it would cause fret; I would have been on for hours (032) And it's my generation that never grew up with computers, so we often, some of us find it harder than others (022)
4.7d Sub theme Fear of using the internet incorrectly	I think I'm frightened of it; I just don't want to look a fool, is all. (032)
4.7e Sub theme Dislike/avoidance of website	Yes, if it had all been on the computer, I wouldn't have taken part; I would have phoned you up and said I don't want to take part anymore. The paper worked, the paper is in the kitchen; it's there, the pen is there, the pedometer comes off, it's what time of night, open it up, write it in, write in the activities, goes fast (032) It was mentioned in the letter, that you wouldn't like me to go online, I thought, "I want nothing to do with this", but, thankfully, you'd put in the paperwork in case of problems. (0
4.8 Theme: Facilitators to POW use	
4.8a Sub theme Familiarity with IT	Really useful. I mean, I've always used IT cause it was my line of work for quite a lot of years. In the early 1980s I went into IT work so I've always had a keen interest in IT and so I've always used IT wherever possible, and I'm not afraid of IT, or anything like that.(043) I found that useful. I used that a lot, yeah. I do most things online, even although I work on a computer at work, when I come home at night, I check my emails and have a look on Facebook and chat to my friends. Then I buy stuff, online shopping, I do the Asda shopping. So I use it a lot. So, for me, it was just second nature to go onto the website and have a look at stuff on there and input my steps. So I found it really great.(04)
4.9 Theme: Activity monitoring to increase activity	
4.9a Sub theme Building on the norm	I think the first week, all i did was walk. I didn't do anything other than walk. Then when I started to put my steps into the programme and it brought up your goal for the following week. (04)

	So the first thing I did was I established what my normal day would be and the number of steps I would take in a normal day...And then try to obviously build in extra walks, and what have you, to see how far I could then go beyond that norm for a day, like. (043) ...didn't set any goals on purpose for the first two or three weeks because I just wanted to see how everything was working. I wanted to get a picture of where I was at before I started trying to push myself further. So really the goal setting and then putting it up by 10%, I didn't find helpful, at all, in the early stages. (07) I would also like to see what is the norm? What is the norm; am I below, or above? (32)
4.9b Sub theme Tracking steps to track activity	All in all, it's always been in my mind; have I walked far enough? Am I doing this? Am I doing that? I never used to think before. I used to take my dog for a walk wherever and back. (041)
4.9c Sub theme Continuously building on activity: in competition with self	While I was counting my steps, I used to go as far as I could just to maximise kind of thing. (041) Oh yeh, because I wanted it to go up every day. If it went down, I was quite annoyed with myself (04) I was more or less governed by that, and if it showed that I wasn't doing all that well, I'd go and push myself a bit further (041) I just, I think it did make me much more aware of what I was doing. I just wanted to do more and more and more as the weeks went on. (04) Well, as I say, that's the sort of thing that keeps me going; I'm checking it all the time, I'm trying to beat yesterdays figures, and, when I find out I've been doing my gardening, and I'm nackered, an I haven't beaten yesterdays figures, it's a little bit disappointing, but it's just a game, isn't it? (032)
4.10 Theme: Improvements to POW step graph	
4.10a Sub theme	It was ideal, but I would like that piece I said, added to it, so I can see if there's a pattern that emerges, from one week to the next **(refering to step counts).** (029) I find that, if that side of it could be sorted out **(online step graph)**. Even if you sent you sheets away and they fed them in and put it onto the graph and maybe one a week you got an email or something, or 'this is how you've done this week', something to look at. I think you do need to have something to look at for your progress because

	there's nothing more motivational than looking at something and saying, oh I dipped last week, I'll sort it out this week. So I did find the visual side of it could be helpful, but I just didn't think it was working properly. Sorry. (07) It was to try and help identify, to me, is there a same day, or days in the week, when I have less steps, and I look and think, 'right is that because on a Saturday night, because I go down to the so-and-so, and then I'm sick on the Sunday', and that's where I would have liked to have seen it, over th week, and then looked at the next week and thought, hang on a minute, Sunday was the same last week, Or, you did better on a Wednesday because that's your day off. (029) I just, purely, preferred what was on those sheets, to just this graph, and I just stoppe using that because I thought, well, that wasn't relaying any information to me. It was, yes, you've done better/worse, better/worse, better/worse, but it wasn't, perhaps, telling me why, wheras I looked back over the sheets, and I can think 'right, I don't work a wednesday, but I travelled down to my brother's that day in York, so I was sitting a long time, so the next day I was very sore. Right, so at least I could put a reason to why I didn't have such a good day, and that made me feel better, rather than thinking what went wrong on that day, whereas I could see on the charts what I'd done. (029)
4.11 Themes: POW Website pages	
	Obviously I used the step page on a weekly basis to begin with and then more frequently once it went on to day. But certainly, the what's on in your area? I used that tab quite a bit. (04) I used to just look and see what I had on at work and think, I can do that that day, I can do this this day. So I just had it in my head after that. (04) It was pretty easy. Just put in the number of steps that I walked in there on a weekly basis. It was no problem (031) Not for me, no, because, if I don't achieve them, I get annoyed and irritated with myself, and then, if I'm achieving them every day, I think, 'I set those too low', so whats the good of that? (029) No, it was good, it made you think about different things, that you could, perhaps, try, if you havn't already tried them. (029) Probably a bit of both. Certainly the answers weren't helpful, but the barrier side of it, I think if somebody wants

	me to do something, they'll do it. The barriers, to me, they just didn't apply to me. (07)
4.12 Theme: Carrying on the intervention beyond study period	
	I think I would probably be more capable now than I was because I think I'm more focused now than I was twelve weeks ago, definitely. I do want to continue to get more active because I think I became a couch potato (04) Oh the pedometer I use it every day now and will continue with that (022) Well like I say, when it got to twelve weeks I was getting a bit cheesed off (04) Now that I understand it a little bit more, it's probably been life changing because I'll stick to it now. I'll stick to what I'm doing. I realise how many steps I need to do a day and okay it might be chucking it down with rain or blowing a gale, but I know that I still need to do something (07) Yeh, because I will definitely keep it up **(exercise)** (031)
5.0 Category: Study Experience	
5.1 Theme: Voluntary nature of involvement – wouldn't take payment	
	No I mean it was voluntary, and it's just the same as me doing the next door neighbour's garden, basically; I wouldn't accept any money. (032) **(...some studies would offer you some kind of monetary gift or something you take away)** That's not why I did it. I didn't expect anything back. Actually, I'd feel uncomfortable with that...Because I think if you do something like this there shouldn't be a monetary reward. You're doing it to help yourself, not for what money you can gain out of it. Maybe I'm the only who thinks that, I don't know but no, I didn't do it for that. I did it hopefully to benefit my health. (03)
5.2 Theme: Participant relationship with researcher	
5.2a Sub theme Temperament of the researcher/study visit	And it was nice and relaxing, I think that's the important thing. You know, sometimes you think, 'Hmm, clinical trial, I'm a bit nervous', but it's been very relaxed (043) And then you get the best out of it, I think when people are at ease, so, no, I think that was just right. Yeah, (043)
5.2b Sub theme Familiarity with researcher	Nice and personal because I knew you, I'd met you before. (022) I think it's been nice having the same person each time. I mean I don't know how other studies particularly work but, you know, so that by the time you've been more than once you're coming to see someone you've already

	met. I think that's good. (038) Well I just think you've just got a little bit of rapport and a bit of a starting point. And you don't have to start from scratch sort of thing…Yeah, I think if you have the same person you get to know them and it's easier to talk. It's more relaxing. (037)
5.3 Theme: Communication	
5.3a Sub theme Mode of communication	I prefer face to face **(communication)**. I don't mind over the phone. As long as it's not on those damn computers I don't mind. (03)
5.3b Sub theme Speed of communication/study: study progressed slowly	As long as I knew what was happening, it might have been done a little bit quicker but as I said, I don't know what you have to do and how long it takes you to go through everything. Maybe I was just being a bit impatient, which is my tendency. (03) It was after; it was halfway through the programme. I had done the first six weeks and I was taking the vitamins and doing the exercises, there seemed to be like a ten day low in the middle. I thought it would've carried straight on, but it seemed to be in limbo for about ten days until we got the second part away again. I was only criticising what happened with that really. (07) Like I said earlier, I think that might have put a lot of people off**(time delay)**, you know, because, I don't know, it might be down to me, but when I commit to something, I'm gonna do something. I'm up for it, ready to, you know, right, let's get started! That's probably down to me more than anything else. (07)
5.4 Theme: Professional appearance to study – study staff	
	But I think there was one time when there was a, probably even possibly the first time, they **(hospital receptionists)** didn't know who you were. I think it's not your fault It's probably worth checking up on as the morning starts **(before study visits)**…because that might put people off if they felt they weren't expected. Yes, that might really because some people might be daunted about coming to a hospital and if they think they're not wanted or expected they might think, 'Golly, what's going on?' (026) The people who were answering the phone were hardly what you would call receptionists. They were probably fellow students and they didn't know when you were coming in or they might or might not take the information. I mean that really was rather poor quite frankly because you weren't put in the mood for believing it to be a doctoral student's piece of work… (026)

	...but the people standing in were not...it wasn't a receptionist. It might have been a fellow student and it isn't their priority to answer the phone on behalf of somebody else whose desk happens to be in the room and all that sort of thing. So no, that was not very professional. It might have put some people off. I mean it almost did me, I will say that. That bit almost did put me off. (026)
5.5 Theme: Hope of study providing future benefit	
5.5a Sub theme Study in informing future healthcare/treatment	I mean, you know, there's a great opportunity for the surgeries and the hospitals. You could do a course on it and invite people so people can learn it. It actually benefits the NHS because then there will be less ill health. (022) ...make that you go into doctors surgeries. Because you go into doctors surgeries, you have those televisions going. Now that's and ideal opportunity for you to share the information (022) And I have worked in a healthcare setting and if you don't get people that are prepared to be involved in things like this, things don't change, medical developments or whatever. Nothing would progress if people weren't prepared to be involved in things, would it? (038) I hope that whatever you've found can be, in the fullness of time, given in advice to the management of the condition to people. (026) I feel as if I've helped in some capacity to develop for the future, trying to relieve pain in the knees. If I can help in that way, at least I've tried and done something. (037) If your results show that Vitamin D did have a wondrous effect on people, I probably would have gone out and bought it myself, if that was the case. (04)
5.5b Sub theme Study in giving benefit to others	Although I'm not too sure just how much, but hopefully there will be some benefits come out of it all, you know. But, no, been really useful. (043)

References

1. Miller, M., *The Little Black Book of Rheumatology*. Little Black Book Series, ed. O.D. K. 2009, London: Jones and Bartlett Publishers.
2. Felson, D.T., et al., *Osteoarthritis: New Insights. Part 1: The Disease and Its Risk Factors.* Annals of Internal Medicine, 2000. **133**(8): p. 635-646.
3. Goldring, S.R. and M.B. Goldring, *Clinical aspects, pathology and pathophysiology of osteoarthritis.* J Musculoskelet Neuronal Interact, 2006. **6**(4): p. 376-8.
4. Altman, R., et al., *Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.* Arthritis Rheum, 1986. **29**(8): p. 1039-49.
5. Kellgren, J.H. and J.S. Lawrence, *Radiological Assessment of Osteo-Arthrosis.* Annals of the Rheumatic Diseases, 1957. **16**(4): p. 494-502.
6. Cooper, C., et al., *Radiographic assessment of the knee joint in osteoarthritis.* Annals of the Rheumatic Diseases, 1992. **51**(1): p. 80-82.
7. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthrosis.* Ann Rheum Dis, 1957. **16**(4): p. 494-502.
8. Peat, G., et al., *Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care.* Ann Rheum Dis, 2006. **65**(10): p. 1363-7.
9. Excellence, N.I.f.H.a.C. *NICE: What we do*. 2016 05/09/2016]; Available from: https://www.nice.org.uk/about/what-we-do.
10. NICE, *Osteoarthritis: Care and Mangement*, NICE, Editor. 2014.
11. Cross, M., et al., *The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study.* Annals of the Rheumatic Diseases, 2014.
12. Kim, C., et al., *Prevalence of radiographic and symptomatic hip osteoarthritis in an urban United States community: the Framingham osteoarthritis study.* Arthritis Rheumatol, 2014. **66**(11): p. 3013-7.
13. Felson, D.T., et al., *The prevalence of knee osteoarthritis in the elderly. the framingham osteoarthritis study.* Arthritis & Rheumatism, 1987. **30**(8): p. 914-918.
14. Haugen, I.K., et al., *Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study.* Annals of the Rheumatic Diseases, 2011. **70**(9): p. 1581-1586.
15. Oliveria, S.A., et al., *Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization.* Arthritis & Rheumatism, 1995. **38**(8): p. 1134-1141.
16. UK, A.R., *Arthritis in the UK: Fats and Statistics*, A.R. UK, Editor. 2014.
17. UK, A.R. *Arthritis Research UK: Musculoskeletal Calculator*. 2016 07/09/2016]; Available from: https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/musculoskeletal-calculator/analysis.aspx?ConditionType=1,2&ChartType=1.
18. Pereira, D., et al., *The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review.* Osteoarthritis and Cartilage, 2011. **19**(11): p. 1270-1285.

19. Farr Ii, J., L.E. Miller, and J.E. Block, *Quality of Life in Patients with Knee Osteoarthritis: A Commentary on Nonsurgical and Surgical Treatments.* The Open Orthopaedics Journal, 2013. **7**: p. 619-623.
20. Hoogeboom, T.J., et al., *Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative.* Rheumatology (Oxford), 2013. **52**(3): p. 543-6.
21. Muraki, S., et al., *Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study.* Osteoarthritis Cartilage, 2010. **18**(9): p. 1227-34.
22. Murray, C.J.L., et al., *Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2012. **380**(9859): p. 2197-2223.
23. Bitton, R., *The Economic Burden of Osteoarthritis.* The American Journal of Managed Care, 2009. **15**(8): p. S230-S235.
24. Leardini, G., et al., *Direct and indirect costs of osteoarthritis of the knee.* Clin Exp Rheumatol, 2004. **22**(6): p. 699-706.
25. Chen, A., et al., *The Global Economic Cost of Osteoarthritis: How the UK Compares.* Arthritis, 2012. **2012**: p. 6.
26. Felson, D.T., *Osteoarthritis of the Knee.* New England Journal of Medicine, 2006. **354**(8): p. 841-848.
27. Birrell, F., Howells, N., Porcheret, M., *Osteoarthritis: Pathogenesis and Prospects for treatment.* Reports on Rheumatic Diseases: Topical Reviews, 2011. **6**(10).
28. Porcheret, M., Healey, E., Dzeidzic, K, Coup, N., Howells, N., Birrell, F., *Osteoarthritis: A modern approach to diagnosis and management.* Reports on Rheumatic Diseases: Hands On, 2011. **6**(10).
29. Berenbaum, F., *Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!).* Osteoarthritis and Cartilage, 2013. **21**(1): p. 16-21.
30. D'Agostino, M.A., et al., *EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: Prevalence of inflammation in osteoarthritis.* Annals of the Rheumatic Diseases, 2005. **64**(12): p. 1703-1709.
31. Pelletier, J.P., Martel-Petetier, J. and Abramson, S. B. , *Osteoarthritis, and inflammatory disease: Potential implication for the selection of new theraputic targets.* Arthritis & Rheumatism, 2001. **44**: p. 1237-1247.
32. Kapoor, M., et al., *Role of proinflammatory cytokines in the pathophysiology of osteoarthritis.* Nat Rev Rheumatol, 2011. **7**(1): p. 33-42.
33. Goldring, M.B. and M. Otero, *Inflammation in osteoarthritis.* Current opinion in rheumatology, 2011. **23**(5): p. 471-478.
34. Goldring, M.B. and S.R. Goldring, *Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis.* Annals of the New York Academy of Sciences, 2010. **1192**(1): p. 230-237.
35. Goldring, M.B. and K.B. Marcu, *Cartilage homeostasis in health and rheumatic diseases.* Arthritis Research & Therapy, 2009. **11**(3): p. 224-224.
36. Loeser, R.F., *Molecular Mechanisms of Cartilage Destruction: Mechanics, Inflammatory Mediators, and Aging Collide.* Arthritis and rheumatism, 2006. **54**(5): p. 1357-1360.

37. Findlay, D., *Subschondral bone in Osteoarthritis*, in *Principals of Osteoarthritis - its definition, charcter, derivation and modality-related recognition*, B. Rothschild, Editor. 2012. p. 139-154.
38. Radin, E.L. and R.M. Rose, *Role of subchondral bone in the initiation and progression of cartilage damage.* Clin Orthop Relat Res, 1986(213): p. 34-40.
39. Day, J.S., et al., *A decreased subchondral trabecular bone tissue elastic modulus is associated with pre-arthritic cartilage damage.* J Orthop Res, 2001. **19**(5): p. 914-8.
40. Hunter, D.J., et al., *Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized.* Arthritis Research & Therapy, 2009. **11**(1): p. 1-9.
41. Felson, D.T., et al., *The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis.* Annals of Internal Medicine, 2001. **134**(7): p. 541-549.
42. Felson, D.T., et al., *Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis.* Annals of Internal Medicine, 2003. **139**(5_Part_1): p. 330-336.
43. Hunter, D.J., et al., *Increase in bone marrow lesions associated with cartilage loss: A longitudinal magnetic resonance imaging study of knee osteoarthritis.* Arthritis & Rheumatism, 2006. **54**(5): p. 1529-1535.
44. Wenham, C.Y.J. and P.G. Conaghan, *The Role of Synovitis in Osteoarthritis.* Therapeutic Advances in Musculoskeletal Disease, 2010. **2**(6): p. 349-359.
45. Myers, S.L., et al., *Synovial inflammation in patients with early osteoarthritis of the knee.* J Rheumatol, 1990. **17**(12): p. 1662-9.
46. Sellam, J. and F. Berenbaum, *The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis.* Nat Rev Rheumatol, 2010. **6**(11): p. 625-635.
47. Scanzello, C.R. and S.R. Goldring, *The role of synovitis in osteoarthritis pathogenesis.* Bone, 2012. **51**(2): p. 249-57.
48. Kapoor, M., et al., *Role of proinflammatory cytokines in the pathophysiology of osteoarthritis.* Nat Rev Rheumatol, 2011. **7**(1): p. 33-42.
49. UK, A. *Osteoarthritis: data and statistics*. 2016 06/09/2016]; Available from: http://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/data-by-condition/osteoarthritis.aspx.
50. Shane Anderson, A. and R.F. Loeser, *Why is osteoarthritis an age-related disease?* Best Practice & Research Clinical Rheumatology, 2010. **24**(1): p. 15-26.
51. Silverwood, V., et al., *Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis.* Osteoarthritis and Cartilage, 2015. **23**(4): p. 507-515.
52. Loeser, R.F., *Age-Related Changes in the Musculoskeletal System and the Development of Osteoarthritis.* Clinics in geriatric medicine, 2010. **26**(3): p. 371-386.
53. Loeser, R.F., *Aging and Osteoarthritis.* Current Opinion in Rheumatology, 2011. **23**(5): p. 492-496.
54. Blagojevic, M., et al., *Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis.* Osteoarthritis and Cartilage, 2010. **18**(1): p. 24-33.
55. Grotle, M., et al., *Obesity and osteoarthritis in knee, hip and/or hand: An epidemiological study in the general population with 10 years follow-up.* BMC Musculoskeletal Disorders, 2008. **9**(1): p. 132.

56. Nevitt, M.C., et al., *Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures Research Group.* Arch Intern Med, 1996. **156**(18): p. 2073-80.
57. Zhang, Y., et al., *Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham Study.* Arthritis Rheum, 1998. **41**(10): p. 1867-73.
58. Roman-Blas, J.A., Castaneda, S., Largo, R., Herrero-Beaumont, G., *Osteoarthritis associated with estrogen deficicency.* Arthritis Research and Therapy, 2009. **11**(5): p. 241.
59. Hannan, M.T., et al., *Bone mineral density and knee osteoarthritis in elderly men and women. The Framingham Study.* Arthritis Rheum, 1993. **36**(12): p. 1671-80.
60. Jordan, J.M., et al., *Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project.* The Journal of Rheumatology, 2007. **34**(1): p. 172-180.
61. Spector, T.D. and A.J. MacGregor, *Risk factors for osteoarthritis: genetics1.* Osteoarthritis and Cartilage, 2004. **12, Supplement**: p. 39-44.
62. Fernández-Moreno, M., et al., *Genetics in Osteoarthritis.* Current Genomics, 2008. **9**(8): p. 542-547.
63. Panoutsopoulou, K., et al., *Insights into the genetic architecture of osteoarthritis from stage 1 of the arcOGEN study.* Annals of the Rheumatic Diseases, 2011. **70**(5): p. 864-867.
64. Kiel, D.P., et al., *Genome-wide association with bone mass and geometry in the Framingham Heart Study.* BMC Med Genet, 2007. **8 Suppl 1**: p. S14.
65. Styrkarsdottir, U., et al., *New sequence variants associated with bone mineral density.* Nat Genet, 2009. **41**(1): p. 15-7.
66. Hofman, A., et al., *The Rotterdam Study: 2016 objectives and design update.* Eur J Epidemiol, 2015. **30**(8): p. 661-708.
67. Miyamoto, Y., et al., *A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis.* Nat Genet, 2007. **39**(4): p. 529-33.
68. Valdes, A.M., et al., *The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance.* Annals of the rheumatic diseases, 2011. **70**(5): p. 873-875.
69. Pan, F., et al., *Association between GDF5 rs143383 polymorphism and knee osteoarthritis: an updated meta-analysis based on 23,995 subjects.* BMC Musculoskeletal Disorders, 2014. **15**(1): p. 404.
70. Rodriguez-Fontenla, C., et al., *Assessment of Osteoarthritis Candidate Genes in a Meta-Analysis of Nine Genome-Wide Association Studies.* Arthritis & Rheumatology (Hoboken, N.j.), 2014. **66**(4): p. 940-949.
71. Nasonov, L.A.a., *Osteoarthritis and comorbidities.* Medicographica, 2013. **35**: p. 152-157.
72. Berenbaum, F., F. Eymard, and X. Houard, *Osteoarthritis, inflammation and obesity.* Curr Opin Rheumatol, 2013. **25**(1): p. 114-8.
73. Grotle, M., et al., *Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up.* BMC Musculoskelet Disord, 2008. **9**: p. 132.

74. Hu, P.-f., J.-p. Bao, and L.-d. Wu, *The emerging role of adipokines in osteoarthritis: a narrative review.* Molecular Biology Reports, 2011. **38**(2): p. 873-878.
75. Sowers, M.R. and C.A. Karvonen-Gutierrez, *The evolving role of obesity in knee osteoarthritis.* Curr Opin Rheumatol, 2010. **22**(5): p. 533-7.
76. Ruhl, C.E., et al., *Serum leptin concentrations and body adipose measures in older black and white adults.* The American Journal of Clinical Nutrition, 2004. **80**(3): p. 576-583.
77. Lee, J.H., et al., *Resistin is elevated following traumatic joint injury and causes matrix degradation and release of inflammatory cytokines from articular cartilage in vitro.* Osteoarthritis Cartilage, 2009. **17**(5): p. 613-20.
78. Wandel, S., et al., *Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis.* BMJ, 2010. **341**.
79. Kongtharvonskul, J., et al., *Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis.* European Journal of Medical Research, 2015. **20**(1): p. 24.
80. Reichenbach, S., et al., *Meta-analysis: chondroitin for osteoarthritis of the knee or hip.* Ann Intern Med, 2007. **146**(8): p. 580-90.
81. Zeng, C., et al., *Effectiveness and safety of Glucosamine, chondroitin, the two in combination, or celecoxib in the treatment of osteoarthritis of the knee.* Scientific Reports, 2015. **5**: p. 16827.
82. Brien, S., et al., *Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis.* Osteoarthritis and Cartilage, 2008. **16**(11): p. 1277-1288.
83. Kim, L.S., et al., *Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial.* Osteoarthritis and Cartilage, 2006. **14**(3): p. 286-294.
84. Usha, P.R. and M.U. Naidu, *Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and their Combination in Osteoarthritis.* Clin Drug Investig, 2004. **24**(6): p. 353-63.
85. Bookman, A.A.M., K.S.A. Williams, and J.Z. Shainhouse, *Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial.* Canadian Medical Association Journal, 2004. **171**(4): p. 333-338.
86. Eberhardt, R., T. Zwingers, and R. Hofmann, *DMSO in patients with active gonarthrosis. A double-blind placebo controlled phase III study.* Fortschritte der Medizin, 1995. **113**(31): p. 446-450.
87. Felson, D.T., et al., *Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies.* Arthritis Rheum, 2007. **56**(1): p. 129-36.
88. Glover, T., et al, *A Cross-Sectional Examination of Vitamin D, Obesity, and Measures of Pain and Function in Middle-age and Older Adults with Knee Osteoarthritis.* Clinical Journal of Pain, 2015. **31**(12): p. 1060-1067.
89. Laslett, L.L., et al., *Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study.* Ann Rheum Dis, 2014. **73**(4): p. 697-703.
90. Arden, N.K., et al., *The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial.* Osteoarthritis and Cartilage.

91. Jin, X., et al., *Effect of vitamin d supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: A randomized clinical trial.* JAMA, 2016. **315**(10): p. 1005-1013.
92. McAlindon, T., et al., *Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial.* Jama, 2013. **309**(2): p. 155-62.
93. Cao, Y., et al, *Association between serum levels of 25-hydroxyvitamin D and Osteoarthritis: a systematic review.* Rheumatology, 2013. **52**: p. 1323-1334.
94. Blotman, F., et al., *Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial.* Rev Rhum Engl Ed, 1997. **64**(12): p. 825-34.
95. Appelboom, T., et al., *Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study.* Scand J Rheumatol, 2001. **30**(4): p. 242-7.
96. Lequesne, M., et al., *Structural effect of avocado/soybean unsaponifiables on joint space loss in osteoarthritis of the hip.* Arthritis Rheum, 2002. **47**(1): p. 50-8.
97. Ameye, L.G. and W.S.S. Chee, *Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence.* Arthritis Research & Therapy, 2006. **8**(4): p. 1-22.
98. Cao, Y., et al., *Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review.* Rheumatology, 2013. **52**(7): p. 1323-1334.
99. Rossignol, M., et al., *Primary osteoarthritis of hip, knee, and hand in relation to occupational exposure.* Occupational and Environmental Medicine, 2005. **62**(11): p. 772-777.
100. Gelber, A.C., et al., *Joint Injury in Young Adults and Risk for Subsequent Knee and Hip Osteoarthritis.* Annals of Internal Medicine, 2000. **133**(5): p. 321-328.
101. Palmieri-Smith, R.M., et al., *Isometric Quadriceps Strength in Women with Mild, Moderate, and Severe Knee Osteoarthritis.* American journal of physical medicine & rehabilitation / Association of Academic Physiatrists, 2010. **89**(7): p. 541-548.
102. Tanaka, R., et al., *Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials.* Clin Rehabil, 2013. **27**(12): p. 1059-71.
103. Roddy, E., W. Zhang, and M. Doherty, *Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review.* Annals of the Rheumatic Diseases, 2005. **64**(4): p. 544-548.
104. Felson, D.T., et al., *Osteoarthritis: New Insights. Part 2: Treatment Approaches.* Annals of Internal Medicine, 2000. **133**(9): p. 726-737.
105. Excellence, N.I.f.H.a.C., *Osteoarthritis: the care and management of osteoarthritis in adults (CG59)*, NICE, Editor. 2008.
106. NICE, *Obesity: identification, assessment and management*, NICE, Editor. 2014.
107. Christensen, R., et al., *Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis.* Annals of the Rheumatic Diseases, 2007. **66**(4): p. 433-439.
108. Kraus, V.a.D.M., *Osteoarthritis*, in *ABC of Rheumatology*, A. Adebajo, Editor. 2010, Wiley-Blackwell: UK.

109. Brubacher, G., *The role of the fat soluble vitamins in human nutrition.* Prog Clin Biol Res, 1981. **77**: p. 97-8.
110. Nutrition, S.A.C.o., *SACN Vitamin D and Health Report*. 2016, Public Health England.
111. Pitt, G., Bates, C., Bender, D., Lawson, D., Muller, D., Poskitt, E., Shearer, M., Thurnham, D., *18. Vitamin D*, in *Dietary Reference Values for food energy and nutrients for the United Kingdom: Report of the panel on dietary reference values of the committee on medical aspects of food policy*. 2013, Department of Health. p. 123-127.
112. Medicine, I.o., *Dietary Reference Intakes for Calcium and Vitamin D*. 2011.
113. Chen T., L.Z., Holick M., *Photobiology of Vitamin D*, in *Vitamin D: Physiology, Molecular Biology and Clinical Application* H. M., Editor. 2010, Human Press.
114. Haddad, J.G., et al., *Human plasma transport of vitamin D after its endogenous synthesis.* Journal of Clinical Investigation, 1993. **91**(6): p. 2552-2555.
115. White, P. and N. Cooke, *The Multifunctional Properties and Characteristics of Vitamin D-binding Protein.* Trends in Endocrinology & Metabolism, 2000. **11**(8): p. 320-327.
116. Ross, A.C., et al., *The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.* J Clin Endocrinol Metab, 2011. **96**(1): p. 53-8.
117. Holick, M.F., *Vitamin D Deficiency.* New England Journal of Medicine, 2007. **357**(3): p. 266-281.
118. Society, N.O., *Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Mangament*, in *National Osteoporosis Society Practical Guidelines*. 2013, National Osteoaporosis Society.
119. Black, L.J., et al., *Analytical Bias in the Measurement of Serum 25-Hydroxyvitamin D Concentrations Impairs Assessment of Vitamin D Status in Clinical and Research Settings.* PLoS ONE, 2015. **10**(8): p. e0135478.
120. Plum, L.A. and H.F. DeLuca, *The Functional Metabolism and Molecular Biology of Vitamin D Action.* Clinical Reviews in Bone and Mineral Metabolism, 2009. **7**(1): p. 20-41.
121. Bastiani, M. and R.G. Parton, *Caveolae at a glance.* Journal of Cell Science, 2010. **123**(22): p. 3831-3836.
122. Haussler, M.R., et al., *Vitamin D receptor (VDR)-mediated actions of 1alpha,25(OH)(2)vitamin D(3): genomic and non-genomic mechanisms.* Best Pract Res Clin Endocrinol Metab, 2011. **25**(4): p. 543-59.
123. M, H., *Vitamin D and Health: Evolution, Biological Functions and Recommended dietary intakes for Vitamin D*, in *Nutrition and Health: Vitamin D*, F.M. Holick, Editor. 2010, Springer Science + Business Media.
124. Shore, R.M. and R.W. Chesney, *Rickets: Part I.* Pediatric Radiology, 2013. **43**(2): p. 140-151.
125. Thacher, T.D. and S.S. Oberhelman, *Vitamin D deficiency in the 21st century: an overview*, in *Handbook of vitamin D in human health: Prevention, treatment and toxicity*, R.R. Watson, Editor. 2013, Wageningen Academic Publishers: Wageningen. p. 12-36.
126. Heaney, R.P. and M.F. Holick, *Why the IOM recommendations for vitamin D are deficient.* J Bone Miner Res, 2011. **26**(3): p. 455-7.
127. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin / Bnf, 2014. **39**(4): p. 322-350.

128. Wahl, D.A., et al., *A global representation of vitamin D status in healthy populations.* Archives of Osteoporosis, 2012. **7**(1): p. 155-172.
129. Hypponen, E. and C. Power, *Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors.* Am J Clin Nutr, 2007. **85**(3): p. 860-8.
130. B. Bates., A., Lennox., A. Prentice., C. Bates., P. Page., S. Nicholson. and G. Swan, *National Diet and Nutrition Survey: Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009-2011/2012)*, P.H.E.a.F.S. Agency, Editor. 2014.
131. Excellence), N.N.I.f.C., *Vitamin D: increasing supplement use in at risk groups (PH56)*, P.H. England, Editor. 2014.
132. Ruston, D., Hoare, J., Henderson, L., Gregory J., Bates, C., Prentice, A., Brich, M., Swan, G. and Farron, M., *National Diet and Nutrition Survey: Adults aged 19 to 64, Volume 4* D.o.H.a.F.S. Agency, Editor. 2004, Department of Health.
133. Prentice, A., *Vitamin D deficiency: a global perspective.* Nutrition Reviews, 2008. **66**(suppl 2): p. S153-S164.
134. Pearce SHS., a.C.T., *Diagnosis and management of vitamin D deficiency.* Clinical Review 2010. **340**: p. 142-147.
135. Hagenau, T., et al., *Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis.* Osteoporos Int, 2009. **20**(1): p. 133-40.
136. Holick, M., *High prevalence of vitamin D inadequacy and implications for health.* MayoClin Proc, 2006. **81**.
137. MacLaughlin, J. and M.F. Holick, *Aging decreases the capacity of human skin to produce vitamin D3.* J Clin Invest, 1985. **76**(4): p. 1536-8.
138. Pereira-Santos, M., et al., *Obesity and vitamin D deficiency: a systematic review and meta-analysis.* Obes Rev, 2015. **16**(4): p. 341-9.
139. Rosenstreich, S.J., C. Rich, and W. Volwiler, *Deposition in and release of vitamin D(3) from body fat: evidence for a storage site in the rat.* Journal of Clinical Investigation, 1971. **50**(3): p. 679-687.
140. Wortsman, J., et al., *Decreased bioavailability of vitamin D in obesity.* The American Journal of Clinical Nutrition, 2000. **72**(3): p. 690-693.
141. Blum, M., G.E. Dallal, and B. Dawson-Hughes, *Body size and serum 25 hydroxy vitamin D response to oral supplements in healthy older adults.* J Am Coll Nutr, 2008. **27**(2): p. 274-9.
142. Themistoklis, T., et al., *Rising Serum 25-Hydroxy-Vitamin D Levels after Weight Loss in Obese Women Correlate with Improvement in Insulin Resistance.* The Journal of Clinical Endocrinology & Metabolism, 2010. **95**(9): p. 4251-4257.
143. Drincic, A.T., et al., *Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity.* Obesity (Silver Spring), 2012. **20**(7): p. 1444-8.
144. Earthman, C.P., et al., *The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications.* Int J Obes, 2012. **36**(3): p. 387-396.
145. Wamberg, L., et al., *Expression of vitamin D-metabolizing enzymes in human adipose tissue[mdash]the effect of obesity and diet-induced weight loss.* Int J Obes, 2013. **37**(5): p. 651-657.

146. Arden, N.K., et al., *The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial.* Osteoarthritis Cartilage, 2016. **24**(11): p. 1858-1866.
147. McAlindon, T., M. LaValley, and B. Dawson-Hughes, *VItamin d supplementation in patients with osteoarthritis—reply.* JAMA, 2013. **309**(15): p. 1583-1584.
148. Organisation, W.H. *Physical activity: Fact sheet*. 2017 04/12/2017]; Available from: http://www.who.int/mediacentre/factsheets/fs385/en/.
149. Organisation, W.H., *Global Recommendations on Physical Activity for Health*. 2010.
150. Organisation, W.H. *Physical Activity and Adults: Recommended levels of physical activity for adults aged 18 - 64 years*. 2017 04/12/2017]; Available from: http://www.who.int/dietphysicalactivity/factsheet_adults/en/.
151. Organsiation, W.H. *Physical Activity and Older Adults: Recommended levels of physical activity for adults aged 65 and above*. 2017; Available from: http://www.who.int/dietphysicalactivity/factsheet_olderadults/en/.
152. Health, U.D.o., *Physical activity guidelines for Adults (19–64 years)*. 2011.
153. Health, U.D.o. *Physical activity guidelines for older Adults (65+ years)*. 2011; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213741/dh_128146.pdf.
154. Musumeci, G., *The Effect of Mechanical Loading on Articular Cartilage.* Journal of Functional Morphology and Kinesiology 2016. **1**: p. 154-161.
155. Esser, S. and A. Bailey, *Effects of Exercise and Physical Activity on Knee Osteoarthritis.* Current Pain and Headache Reports, 2011. **15**(6): p. 423-430.
156. Organisation, W.H., *Obesity and overweight: Fact sheet*. 2017.
157. Messier, S.P., et al., *Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: The arthritis, diet, and activity promotion trial.* Arthritis & Rheumatism, 2004. **50**(5): p. 1501-1510.
158. Cheng, Y., et al., *Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor?* Journal of Clinical Epidemiology, 2000. **53**(3): p. 315-322.
159. O'Reilly, S., et al., *Quadriceps weakness in knee osteoarthritis: the effect on pain and disability.* Annals of the Rheumatic Diseases, 1998. **57**(10): p. 588-594.
160. Segal, N.A., et al., *Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort.* Arthritis Care & Research, 2009. **61**(9): p. 1210-1217.
161. Farr, J.N., et al., *Physical activity levels in patients with early knee osteoarthritis measured by accelerometry.* Arthritis Rheum, 2008. **59**(9): p. 1229-36.
162. Wallis, J.A., et al., *What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis.* Osteoarthritis and Cartilage, 2013. **21**(11): p. 1648-1659.
163. Townsend, N., Williams, J., Bhatnagar, P and Rayner, M., *Physical Activity Statistics 2015*. 2015.
164. White, D.K., et al., *Do radiographic disease and pain account for why people with or at high risk of knee osteoarthritis do not meet Physical Activity Guidelines?* Arthritis and rheumatism, 2013. **65**(1): p. 139-147.
165. Tonelli, S.M., et al., *Women with knee osteoarthritis have more pain and poorer function than men, but similar physical activity prior to total knee replacement.* Biology of Sex Differences, 2011. **2**: p. 12-12.

166. Manninen, P., et al., *Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty.* Rheumatology, 2001. **40**(4): p. 432-437.
167. Felson, D.T., et al., *Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: The Framingham Study.* Arthritis Care & Research, 2007. **57**(1): p. 6-12.
168. Hannan, M.T., et al., *Habitual physical activity is not associated with knee osteoarthritis: the Framingham Study.* J Rheumatol, 1993. **20**(4): p. 704-9.
169. Golightly, Y.M., K.D. Allen, and D.J. Caine, *A Comprehensive Review of the Effectiveness of Different Exercise Programs for Patients with Osteoarthritis.* The Physician and sportsmedicine, 2012. **40**(4): p. 52-65.
170. Fransen, M., et al., *Exercise for osteoarthritis of the knee: a Cochrane systematic review.* British Journal of Sports Medicine, 2015.
171. Fransen, M., et al., *Physical activity for osteoarthritis management: a randomized controlled clinical trial evaluating hydrotherapy or Tai Chi classes.* Arthritis Rheum, 2007. **57**(3): p. 407-14.
172. Lu, M., et al., *Effectiveness of aquatic exercise for treatment of knee osteoarthritis.* Zeitschrift für Rheumatologie, 2015. **74**(6): p. 543-552.
173. Talbot, L.A., et al., *A Home-Based Pedometer-Driven Walking Program to Increase Physical Activity in Older Adults with Osteoarthritis of the Knee: A Preliminary Study.* Journal of the American Geriatrics Society, 2003. **51**(3): p. 387-392.
174. Dunn, A.L., et al., *Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: a randomized trial.* Jama, 1999. **281**(4): p. 327-34.
175. Hobbs, N., et al., *Are behavioral interventions effective in increasing physical activity at 12 to 36 months in adults aged 55 to 70 years? a systematic review and meta-analysis.* BMC Medicine, 2013. **11**(1): p. 75.
176. O'Brien, N., et al., *The features of interventions associated with long-term effectiveness of physical activity interventions in adults aged 55-70 years: a systematic review and meta-analysis.* Health Psychol Rev, 2015. **9**(4): p. 417-33.
177. Halbert, J., et al., *Primary care-based physical activity programs: effectiveness in sedentary older patients with osteoarthritis symptoms.* Arthritis Rheum, 2001. **45**(3): p. 228-34.
178. Steultjens, M.P., J. Dekker, and J.W. Bijlsma, *Avoidance of activity and disability in patients with osteoarthritis of the knee: the mediating role of muscle strength.* Arthritis Rheum, 2002. **46**(7): p. 1784-8.
179. Andersen, R.E., et al., *Relationship between body weight gain and significant knee, hip, and back pain in older Americans.* Obes Res, 2003. **11**(10): p. 1159-62.
180. Deyle, G.D., et al., *Physical Therapy Treatment Effectiveness for Osteoarthritis of the Knee: A Randomized Comparison of Supervised Clinical Exercise and Manual Therapy Procedures Versus a Home Exercise Program.* Physical Therapy, 2005. **85**(12): p. 1301-1317.
181. Bossen, D., et al., *Effectiveness of a Web-Based Physical Activity Intervention in Patients With Knee and/or Hip Osteoarthritis: Randomized Controlled Trial.* Journal of Medical Internet Research, 2013. **15**(11): p. e257.
182. O'Brien, N., et al., *Integrating Evidence From Systematic Reviews, Qualitative Research, and Expert Knowledge Using Co-Design Techniques to Develop a*

Web-Based Intervention for People in the Retirement Transition. J Med Internet Res, 2016. **18**(8): p. e210.
183. Lara, J., et al., *Pilot Randomised Controlled Trial of a Web-Based Intervention to Promote Healthy Eating, Physical Activity and Meaningful Social Connections Compared with Usual Care Control in People of Retirement Age Recruited from Workplaces.* PLoS One, 2016. **11**(7): p. e0159703.
184. Brock, K., et al., *Effects of diet and exercise on plasma vitamin D (25(OH)D) levels in Vietnamese immigrant elderly in Sydney, Australia.* The Journal of Steroid Biochemistry and Molecular Biology, 2007. **103**(3–5): p. 786-792.
185. Brock, K., et al., *Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women.* J Steroid Biochem Mol Biol, 2010. **121**(1-2): p. 462-6.
186. Scragg, R. and C.A. Camargo, *Frequency of Leisure-Time Physical Activity and Serum 25-Hydroxyvitamin D Levels in the US Population: Results from the Third National Health and Nutrition Examination Survey.* American Journal of Epidemiology, 2008. **168**(6): p. 577-586.
187. Scott, D., et al., *A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults.* Clin Endocrinol (Oxf), 2010. **73**(5): p. 581-7.
188. Wanner, M., et al., *Associations between objective and self-reported physical activity and vitamin D serum levels in the US population.* Cancer Causes & Control, 2015. **26**(6): p. 881-891.
189. Bell, N.H., et al., *The effects of muscle-building exercise on Vitamin D and mineral metabolism.* Journal of Bone and Mineral Research, 1988. **3**(4): p. 369-374.
190. Boland, R., *Role of vitamin D in skeletal muscle function.* Endocr Rev, 1986. **7**(4): p. 434-48.
191. Stockton, K.A., et al., *Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis.* Osteoporosis International, 2011. **22**(3): p. 859-871.
192. Craig, P., et al., *Developing and evaluating complex interventions: the new Medical Research Council guidance.* BMJ, 2008. **337**.
193. Craig, N., et al., *Developing and evaluating complex interventions: the new Medical Research Council guidance.* BMJ, 2008. **337**.
194. Thabane, L., et al., *A tutorial on pilot studies: the what, why and how.* BMC Medical Research Methodology, 2010. **10**(1): p. 1-10.
195. Lancaster, G.A., S. Dodd, and P.R. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* J Eval Clin Pract, 2004. **10**.
196. Lancaster, G.A., S. Dodd, and P.R. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* J Eval Clin Pract, 2004. **10**(2): p. 307-12.
197. Arain, M., et al., *What is a pilot or feasibility study? A review of current practice and editorial policy.* BMC Medical Research Methodology, 2010. **10**(1): p. 67.
198. Hampson, L., et al., *Recruitment progression rules for internal pilot studies monitoring recruitment.* Trials, 2015. **16**(Suppl 2): p. O89-O89.
199. Lancaster, G.A., S. Dodd, and P.R. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* Journal of Evaluation in Clinical Practice, 2004. **10**(2): p. 307-312.

200. Adams, M., L. Caffrey, and C. McKevitt, *Barriers and opportunities for enhancing patient recruitment and retention in clinical research: findings from an interview study in an NHS academic health science centre.* Health Research Policy and Systems, 2015. **13**: p. 8.
201. Craig, P., Dieppe, P., MacIntyre, S., Michie, S., Nazareth, I and Petticrew, M, *Developing and Evaluating complex interventions: new guidance*. 2008, Medical Research Council.
202. UK, A.R. *Musculoskeletal Calculator: Analysis*. 2016 [cited 2016 29/11/2016]; Available from: https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/musculoskeletal-calculator/analysis.aspx?ConditionType=2&ChartType=2&Region-0=E08000021&Gender=1,2&AgeBracket=3,2&Bmi=4.
203. Bower, P., et al., *Improving recruitment to health research in primary care.* Family Practice, 2009.
204. Junghans, C.e.a., *Recruiting patients to medical research: double blind randomised trials of 'opt in' versus 'opt out' stratergies.* BMJ, 2005. **331**(940).
205. Watson, J.M. and D.J. Torgerson, *Increasing recruitment to randomised trials: a review of randomised controlled trials.* BMC Medical Research Methodology, 2006. **6**(1): p. 34.
206. WHO. *BMI Classification*. 2006 28/03/2017]; Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
207. Wells, J.C.K. and M.S. Fewtrell, *Measuring body composition.* Archives of Disease in Childhood, 2006. **91**(7): p. 612-617.
208. WHO, *Waist circumference and waist-hip ratio : report of a WHO expert consultation, Geneva.* 2008.
209. Podsiadlo, D. and S. Richardson, *The timed "Up & Go": a test of basic functional mobility for frail elderly persons.* J Am Geriatr Soc, 1991. **39**(2): p. 142-8.
210. Lin, Y.C., R.C. Davey, and T. Cochrane, *Tests for physical function of the elderly with knee and hip osteoarthritis.* Scand J Med Sci Sports, 2001. **11**(5): p. 280-6.
211. Hoeller, U., et al., *Application of dried blood spots to determine vitamin D status in a large nutritional study with unsupervised sampling: the Food4Me project.* British Journal of Nutrition, 2016. **115**(2): p. 202-211.
212. F., H., *Physical Activity Measurements in Obesity Epidemiology*, ed. H. F. 2008, USA: Oxford University Press.
213. Higginson, I.J. and A.J. Carr, *Using quality of life measures in the clinical setting.* BMJ, 2001. **322**(7297): p. 1297-1300.
214. ArthritisUK, *Clinical Assessment of the Musculoskeletal system: a guide for medical students and healthcare professionals*. 2011: ArthritisUK. p. 20-22.
215. Bellamy, N., *WOMAC Osteoarthritis Index User Guide XI*. Vol. 11. 2014.
216. Ware J, K.M., Bjorner J, Turner-Bowsker D, Gandek B, Maruish M. , *SF-36V2 Health Survey: Administration guide for clinical trial investigators*. 2008.
217. Scholes, S.a.M.J., *Health Survey for England: Chapter 2 Physical Activity in Adults*, H.a.S.C.I. Centre, Editor. 2012, NHS England.
218. Manual, A.U., *ActiLife 5 -User's Manual*. 2011, Actigraph.
219. Matthews, C.e.a., *Best practices for using physical activity monitors in population based research.* Medicine & Science in Sports & Exercise, 2012. **44**(1): p. S68-S76.
220. Ross, S., et al., *Barriers to participation in randomised controlled trials: a systematic review.* J Clin Epidemiol, 1999. **52**.

221. O'Connor, M.I., *Sex differences in osteoarthritis of the hip and knee.* J Am Acad Orthop Surg, 2007. **15 Suppl 1**: p. S22-5.
222. Veenhof, C., et al., *Factors associated with physical activity in patients with osteoarthritis of the hip or knee: a systematic review.* Osteoarthritis Cartilage, 2012. **20**(1): p. 6-12.
223. Lee, J., et al., *Obesity and other modifiable factors for physical inactivity measured by accelerometer in adults with knee osteoarthritis: data from the Osteoarthritis Initiative (OAI).* Arthritis Care & Research, 2013. **65**(1): p. 53-61.
224. Manheim, L., et al *Relationship between physical activity and health related utility amoung knee osteoarthritis patients* Arthritis Care & Research, 2012. **64**(7): p. 1094-1098.
225. Chmelo, E., et al., *Physical Activity and Physical Function in Older Adults With Knee Osteoarthritis.* Journal of physical activity & health, 2013. **10**(6): p. 777-783.
226. Ettinger, W.H., Jr., et al., *A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST).* Jama, 1997. **277**(1): p. 25-31.
227. Focht, B.C., et al., *Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis.* Arthritis Rheum, 2005. **53**.
228. Prevention, C.f.D.C.a. *Physical Activity for Arthritis*. 2017 09/11/2017 07/12/2017]; Available from: https://www.cdc.gov/arthritis/basics/physical-activity-overview.html.
229. Heidari, B., P. Heidari, and K. Hajian-Tilaki, *Association between serum vitamin D deficiency and knee osteoarthritis.* Int Orthop, 2011. **35**(11): p. 1627-31.
230. Wanner, M., et al., *Associations between objective and self-reported physical activity and vitamin D serum levels in the US population.* Cancer Causes Control, 2015. **26**(6): p. 881-91.
231. Birrell, F. and R.M. Francis, *Invited Commentary: Physical Activity and Vitamin D.* American Journal of Epidemiology, 2008. **168**(6): p. 587-589.
232. Dawson-Hughes, B., et al., *IOF position statement: vitamin D recommendations for older adults.* Osteoporos Int, 2010. **21**(7): p. 1151-4.
233. Ooms, M.E., et al., *Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial.* J Clin Endocrinol Metab, 1995. **80**(4): p. 1052-8.
234. Trang, H.M., et al., *Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2.* Am J Clin Nutr, 1998. **68**(4): p. 854-8.
235. Tripkovic, L., et al., *Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis.* Am J Clin Nutr, 2012. **95**(6): p. 1357-64.
236. Selby, P.L., et al., *Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate.* Clin Endocrinol (Oxf), 1995. **43**(5): p. 531-6.
237. Blank, S., et al., *An outbreak of hypervitaminosis D associated with the overfortification of milk from a home-delivery dairy.* Am J Public Health, 1995. **85**(5): p. 656-9.
238. Pettifor, J.M., et al., *Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity.* Ann Intern Med, 1995. **122**(7): p. 511-3.

239. Jones, G., *Pharmacokinetics of vitamin D toxicity.* The American Journal of Clinical Nutrition, 2008. **88**(2): p. 582S-586S.
240. Vieth, R., *Vitamin D toxicity, policy, and science.* J Bone Miner Res, 2007. **22 Suppl 2**: p. V64-8.
241. Jones, G., *Pharmacokinetics of vitamin D toxicity.* Am J Clin Nutr, 2008. **88**(2): p. 582s-586s.
242. ArthritisUK, *Hands on: Osteoarthritis knee pain information and exercise sheet,*. 2005, ArthritisUK.
243. Marks, R. and J.P. Allegrante, *Chronic osteoarthritis and adherence to exercise: a review of the literature.* J Aging Phys Act, 2005. **13**(4): p. 434-60.
244. Rasinaho, M., et al., *Motives for and barriers to physical activity among older adults with mobility limitations.* J Aging Phys Act, 2007. **15**(1): p. 90-102.
245. Callahan, L.F., et al., *The People with Arthritis Can Exercise (PACE) Program: A Qualitative Evaluation of Participant Satisfaction.* Preventing Chronic Disease, 2005. **2**(3): p. A11.
246. Schutzer, K.A. and B.S. Graves, *Barriers and motivations to exercise in older adults.* Prev Med, 2004. **39**(5): p. 1056-61.
247. Buman, M.P., L. Daphna Yasova, and P.R. Giacobbi Jr, *Descriptive and narrative reports of barriers and motivators to physical activity in sedentary older adults.* Psychology of Sport and Exercise, 2010. **11**(3): p. 223-230.
248. Wilcox, S., et al., *Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study.* Arthritis Rheum, 2006. **55**(4): p. 616-27.
249. Fisken, A., et al., *Perceived Benefits, Motives, and Barriers to Aqua-based Exercise Among Older Adults With and Without Osteoarthritis.* Journal of Applied Gerontology, 2012. **34**(3): p. 377-396.
250. Brawley, L.R., W.J. Rejeski, and A.C. King, *Promoting physical activity for older adults: the challenges for changing behavior.* Am J Prev Med, 2003. **25**(3 Suppl 2): p. 172-83.
251. Booth, M.L., et al., *Physical activity preferences, preferred sources of assistance, and perceived barriers to increased activity among physically inactive Australians.* Prev Med, 1997. **26**(1): p. 131-7.
252. Hendry, M., et al., *Why should we exercise when our knees hurt? A qualitative study of primary care patients with osteoarthritis of the knee.* Fam Pract, 2006. **23**(5): p. 558-67.
253. Bennell, K.L., F. Dobson, and R.S. Hinman, *Exercise in osteoarthritis: moving from prescription to adherence.* Best Pract Res Clin Rheumatol, 2014. **28**(1): p. 93-117.
254. Holden, M.A., et al., *Role of exercise for knee pain: what do older adults in the community think?* Arthritis Care Res (Hoboken), 2012. **64**(10): p. 1554-64.
255. Murphy, S.L., et al., *Effects of activity strategy training on pain and physical activity in older adults with knee or hip osteoarthritis: a pilot study.* Arthritis Rheum, 2008. **59**(10): p. 1480-7.
256. McCambridge, J., J. Witton, and D.R. Elbourne, *Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects.* Journal of Clinical Epidemiology, 2014. **67**(3): p. 267-277.
257. McDade, T.W., S. Williams, and J.J. Snodgrass, *What a drop can do: dried blood spots as a minimally invasive method for integrating biomarkers into population-based research.* Demography, 2007. **44**(4): p. 899-925.

258. C., V.A.P.a.W., *The application of dried blood spot sample in glovbal clinical trials.* Bioanalysis, 2010. **2**(11): p. 1783-1786.
259. Kvaskoff, D., et al., *Minimizing Matrix Effects for the Accurate Quantification of 25-Hydroxyvitamin D Metabolites in Dried Blood Spots by LC-MS/MS.* Clinical Chemistry, 2016. **62**(4): p. 639-646.
260. Hoeller, U., Baur, M., Roos, F., Brennan, L., Daniel, H., Fallaize, R., Weber, P. et al (2016). *Application of dried blood spots to determine vitamin D status in a large nutritional study with unsupervised sampling: The Food4Me project.* British Journal of Nutrition, 2016. **115**(2): p. 202-211.
261. Troiano, R.P., et al., *Physical activity in the United States measured by accelerometer.* Med Sci Sports Exerc, 2008. **40**(1): p. 181-8.
262. Bossen, D., et al., *Effectiveness of a web-based physical activity intervention in patients with knee and/or hip osteoarthritis: randomized controlled trial.* J Med Internet Res, 2013. **15**(11): p. e257.
263. Diamond, T., Y.K. Wong, and T. Golombick, *Effect of oral cholecalciferol 2,000 versus 5,000 IU on serum vitamin D, PTH, bone and muscle strength in patients with vitamin D deficiency.* Osteoporosis International, 2013. **24**(3): p. 1101-1105.
264. Michie, S., et al., *A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy.* Psychol Health, 2011. **26**(11): p. 1479-98.
265. Olander, E.K., et al., *What are the most effective techniques in changing obese individuals' physical activity self-efficacy and behaviour: a systematic review and meta-analysis.* International Journal of Behavioral Nutrition and Physical Activity, 2013. **10**(1): p. 29.
266. French, D.P., et al., *Which Behaviour Change Techniques Are Most Effective at Increasing Older Adults' Self-Efficacy and Physical Activity Behaviour? A Systematic Review.* Annals of Behavioral Medicine, 2014. **48**(2): p. 225-234.
267. Borkan, J.M., *Mixed Methods Studies: A Foundation for Primary Care Research.* Annals of Family Medicine, 2004. **2**(1): p. 4-6.
268. Tong, A., P. Sainsbury, and J. Craig, *Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups.* Int J Qual Health Care, 2007. **19**(6): p. 349-57.
269. Thorogood, J.G.a.N., *Analysing Qualitative Data*, in *Qualitative Methods for Health Research*. 2009, SAGE: London.
270. Gill, P., et al., *Methods of data collection in qualitative research: interviews and focus groups.* Br Dent J, 2008. **204**(6): p. 291-295.
271. Mays, N. and C. Pope, *Assessing quality in qualitative research.* BMJ, 2000. **320**(7226): p. 50-52.
272. Ritchie J and Lewis J, *Qualitative Research Practice: A guide for Social Science Students and Researchers* 2nd ed. 2010, London: Sage Publications Ltd.
273. Bedford, T., Wilson, S. and Richie, O., *Identifying and recruiting participants for health research*. 2015, Health Research Authority.
274. Gross, D., Julion, W. and Fogg, L., *What motivates participation and dropout amoung low income urban families of colour in a prevention intervention?* Family Relations, 2001. **50**: p. 246-254.
275. Gul, R.a.A.P., *Clinical trials: the challange of recruitment and retention of participants.* Journal of Clinical Nursing, 2010. **19**: p. 227-233.

276. Akkad, A., et al., *Patients' perceptions of written consent: questionnaire study.* BMJ, 2006. **333**(7567): p. 528.
277. Flory, J. and E. Emanuel, *Interventions to improve research participants' understanding in informed consent for research: A systematic review.* JAMA, 2004. **292**(13): p. 1593-1601.
278. Williams, S.R. and T.W. McDade, *The Use of Dried Blood Spot Sampling in the National Social Life, Health, and Aging Project.* The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 2009. **64B**(Suppl 1): p. i131-i136.
279. O'Neill, B., et al., *Comparing accelerometer, pedometer and a questionnaire for measuring physical activity in bronchiectasis: a validity and feasibility study?* Respiratory Research, 2017. **18**: p. 16.
280. Huang, H.Y., et al., *Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials.* Am J Epidemiol, 2000. **152**(8): p. 780-7.
281. Bravata, D.M., et al., *Using pedometers to increase physical activity and improve health: A systematic review.* JAMA, 2007. **298**(19): p. 2296-2304.
282. Thorup, C.B., et al., *Pedometer use and self-determined motivation for walking in a cardiac telerehabilitation program: a qualitative study.* BMC Sports Science, Medicine and Rehabilitation, 2016. **8**(1): p. 24.
283. Schoster, B., et al., *The People with Arthritis Can Exercise (PACE) program: a qualitative evaluation of participant satisfaction.* Prev Chronic Dis, 2005. **2**(3): p. A11.
284. Joseph, R.P., et al., *Internet-Based Physical Activity Interventions.* American journal of lifestyle medicine, 2014. **8**(1): p. 42-68.
285. Lorig, K.R., et al., *The internet-based arthritis self-management program: a one-year randomized trial for patients with arthritis or fibromyalgia.* Arthritis Rheum, 2008. **59**(7): p. 1009-17.
286. Joseph, R., Durant NH., Benitez, TJ and Pekmezi DW., *Internet Based Physical Activity Interventions* American Journal of Lifestyle Medicine, 2013. **8**(1): p. 42-67.
287. Morris, A., J. Goodman, and H. Brading, *Internet use and non-use: views of older users.* Universal Access in the Information Society, 2007. **6**(1): p. 43-57.
288. D, C.J.a.M., *Determining validaity in qualitative inquiry*, in *Theory into practice*. 2000. p. 124-130.
289. Bonner, S.E. and G.B. Sprinkle, *The effects of monetary incentives on effort and task performance: theories, evidence, and a framework for research.* Accounting, Organizations and Society, 2002. **27**(4–5): p. 303-345.
290. Veenhof, C., et al., *Factors associated with physical activity in patients with osteoarthritis of the hip or knee: a systematic review and meta-analysis.* Osteoarthritis and Cartilage, 2013. **21**(11): p. 1648-1659.
291. Ding, D., et al., *The economic burden of physical inactivity: a global analysis of major non-communicable diseases.* Lancet, 2016. **388**(10051): p. 1311-24.
292. Fish, J., *Short Physical Performance Battery*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 2289-2291.
293. Glover, T.L., et al., *A Cross-Sectional Examination of Vitamin D, Obesity, and Measures of Pain and Function in Middle-Aged and Older Adults with Knee Osteoarthritis.* The Clinical journal of pain, 2015. **31**(12): p. 1060-1067.

294. Bergink, A.P., et al., *Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study.* J Clin Rheumatol, 2009. **15**(5): p. 230-7.
295. Hunt, K., Walsh BM., Voegeli D., Roberts, HC. , *Inflammation in ahing part 1: Physiopathology and immunological mechanisms.* Biological Research for Nursing, 2010. **11**(3): p. 245-252.
296. Wang, X., et al., *Metabolic triggered inflammation in osteoarthritis.* Osteoarthritis and Cartilage, 2015. **23**(1): p. 22-30.
297. Tetlow, L.C. and D.E. Woolley, *Expression of vitamin D receptors and matrix metalloproteinases in osteoarthritic cartilage and human articular chondrocytes in vitro.* Osteoarthritis and Cartilage, 2001. **9**(5): p. 423-431.
298. Celis-Morales, C., J. Lara, and J.C. Mathers, *Personalising nutritional guidance for more effective behaviour change.* Proc Nutr Soc, 2015. **74**(2): p. 130-8.
299. Milanović, Z., et al., *Age-related decrease in physical activity and functional fitness among elderly men and women.* Clinical Interventions in Aging, 2013. **8**: p. 549-556.
300. C. Cooper, E.D., M. Edwards, A. Litwic, *Epidemiology of osteoarthritis.* Medicographia, 2013. **35**: p. 145-151.
301. Dyrstad, S.M., et al., *Comparison of Self-reported versus Accelerometer-Measured Physical Activity.* Medicine & Science in Sports & Exercise, 2014. **46**(1): p. 99-106.
302. Prince, S.A., et al., *A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review.* The International Journal of Behavioral Nutrition and Physical Activity, 2008. **5**: p. 56-56.
303. Felson, D.T., et al., *Weight loss reduces the risk for symptomatic knee osteoarthritis in women: The framingham study.* Annals of Internal Medicine, 1992. **116**(7): p. 535-539.
304. Rejeski, W.J., et al., *Obese, older adults with knee osteoarthritis: Weight loss, exercise, and quality of life.* Health Psychology, 2002. **21**(5): p. 419-426.
305. Christensen, R., A. Astrup, and H. Bliddal, *Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial.* Osteoarthritis and Cartilage, 2005. **13**(1): p. 20-27.