FALLS AND FALL RELATED INJURY IN OLDER PEOPLE WITH CHRONIC LIVER DISEASE

DR JAMES FRITH

MB ChB, MRCP (UK)

A thesis submitted to the Institute for Ageing and Health, Newcastle University, in candidacy for the degree of Doctor of Philosophy, September 2010

2. ACKNOWLEDGEMENTS

"Education is not the filling of a pail, but the lighting of a fire."

WB Yeats

My deepest thanks must go to Julia for lighting my fire. She will forever be my inspiration.

My gratitude also goes to those who freely imparted their wisdom on me, namely Professor David Jones, Professor Chris Day, Professor Chris Gray and Dr Louise Allan. The helping hands, provided by both Dr Maw Pin Tan and Dr Simon Kerr, for those moments when I had no idea, were most welcome and gratefully received.

For making doctoral research one of the happiest periods of my life I thank Lisa, Chris, Ruth and Linda. I will miss you.

The staff of Falls and Syncope welcomed me with warmth, friendship and a sense of belonging. I am incredibly grateful to them for inviting me into the family.

Katharine, Jessie and Tilly, without whom I would not have managed, I thank for their relentless hard work, for never saying no and for always being altruistic.

Without the support of my family I would never have been fortunate enough to be here. I owe them so much. I am eternally grateful to them, and to my friends who have become part of my family, for bearing the brunt of my grumpiness.

Introduction

Alongside an ageing population with an increasing prevalence of chronic liver disease (CLD) is an improved survival rate for younger people with CLD who are surviving into older age. Older people often have different, more complex health service needs for which geriatric services exist. However, the rapidly expanding older CLD population may have specific needs or outgrow specialty specific services.

Falls are more common with increasing age in the general population and represent a substantial burden for individuals, families, society and the economy. People with CLD have multiple theoretical risk factors for falling, generating the hypothesis that falls and fall related injury will be common in older people with CLD. However, in order for services to adapt to the changing demographic evidence is required; firstly for an evidence-based management approach for falls intervention and prevention studies and secondly to support setting up of services.

Methods

In Phase 1, self-complete data collection tools were mailed to existing, comprehensive databases of extant cases with primary biliary cirrhosis (PBC), primary sclerosing cholangitis and post-liver transplant (post-LT). The same tools were completed by patients with non-alcoholic fatty liver disease and alcoholic liver disease in the clinic. The tools provided data to define falls and fall related injury prevalence in an older (>65 years) and a younger CLD cohort. An existing database of older, healthy community-dwelling adults was used as a control group. In Phase 2, multidisciplinary falls assessments were performed in a group of people with CLD to explore possible modifiable fall associations in order to inform future intervention/prevention studies. Finally, potential barriers to multifactorial intervention were explored.

Results

Falls are common in older people with CLD with almost 50% having had a fall in the previous year, significantly more so than age- and sex- matched community controls. Falling was unrelated to liver disease but was independently associated with orthostatic dizziness, lower limb strength and fear of falling. Falls were most common in older people with PBC (58%) and least common in ALD (18%). Fall prevalence post-LT is similar to other CLDs and significantly greater than in community

controls; it is associated with orthostatic dizziness and the nadir blood pressure on standing up. Transplantation appears to have no effect on falling. Several barriers to intervention exist, confidence to exercise, understanding the benefits of physical activity, fatigue and FOF which was independently associated with levels of physical activity.

Conclusion

As falls are very common in older people with CLD and represent a substantial problem on an individual and societal level, current services will need to adapt. Several fall associations have been identified, each of which is modifiable and provides evidence for future intervention studies and services. In the general population orthostatic dizziness is amenable to conservative measures and lower limb strength and fear of falling can be improved through physiotherapy. If future studies revealed these to be effective intervention methods a multidisciplinary team consisting of a physician, nurse and physiotherapist would be required.

5. LIST OF TABLES

↑, ↓	Increase, decrease
αfp	Alpha fetoprotein
A1AT	Alpha-1-antitrypsin
AD	Autonomic dysfunction
AI	Autoregulatory index
ALD	Alcoholic liver disease
ALF	Acute liver failure
ALT	Alanine transaminase
ANS	Autonomic nervous system
ASI	Autoregulatory slope index
AST	Aspartate transaminase
AUC	Area under the curve
BEI	Baro-reflex effectiveness index
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BRS	Baro-reflex sensitivity
CA	Cerebral autoregulation
CAMCOG	The Cambridge Cognition Examination
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CBT	Cognitive behavioural therapy
CI	Confidence interval
CLD	Chronic liver disease
cm/s	Centimeters per second
CO_2	Carbon dioxide
CPP	Cerebral perfusion pressure
CSS	Carotid sinus syndrome
CVR	Cerebrovascular resistance
dBP	Diastolic blood pressure

e.g.	Exempli gratia (for example)
ECG	Electrocardiogram
ESLD	End stage liver disease
FES-I	Falls efficacy scale international
FIS	Fatigue impact scale
g	Gram
HAAF	Hypoglycaemia associated autonomic failure
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HF	High frequency
HFnu	High frequency normalised units
HH	Hereditary haemochromatosis
HOMA	Homeostasis assessment model
HR	Heart rate
HRV	Hear rate variability
Hz	Hertz
i.e.	Id est (that is)
IR	Insulin resistance
kg	Kilogram
L	Litre
LF	Low frequency
LFnu	Low frequency normalised units
LFT	Liver function test
LT	Liver transplant
MCA	Middle cerebral artery
MDT	Multidisciplinary team
mm Hg	Millimeters of mercury
mmol/L	Millimoles per litre
MRC	Medical Research Council
MRI	Magnetic resonance imaging

ms^2	Milliseconds squared
NAFLD	Non-alcoholic fatty disease
NASH	Non-alcoholic steato-hepatitis
NHS	National health service
OEES	Outcome expectation for exercise scale
OGS	Orthostatic grading scale
OH	Orthostatic hypotension
OR	Odds ratio
OT	Occupational therapy/therapist
PBC	Primary biliary cirrhosis
PET	Positron emission tomography
PI	Pulsatility index
PNS	Parasympathetic nervous system
POD	Paracetamol overdose
ProFaNE	Prevention of falls network Europe
PROMIS-HAQ	Patient reported outcome measurement information system-Health assessment questionnaire
PSC	Primary sclerosing cholangitis
POTS	Postural tachycardia syndrome
PSD	Power spectral density
RRI	R-R interval
sBP	Systolic blood pressure
SD	Standard deviation
SEES	Self-efficacy for exercise scale
SNS	Sympathetic nervous system
SPECT	Single photon emission computed tomography
STS	Sit to stand test
TCD	Transcranial Doppler
TIPS	Transcutaneous intrahepatic porto-systemic shunt
TUG	Timed up and go
VLF	Very low frequency
VVS	Vasovagal syncope

7. ASSOCIATED PEER REVIEWED PUBLICATIONS

Frith J, Jones D, Newton J. Chronic liver disease in an ageing population. Age and Ageing 2009: 38; 11-8

Frith J, Newton J. Autonomic dysfunction in chronic liver disease. Liver International 2009: 29; 483-9

Frith J, Newton J. Managing abnormal liver blood tests in older people. Geriatrics and Ageing 2009: 12; 295-300

Frith J, Newton JL. Liver disease in older people. CME Geriatric Medicine 2009: 11; 89-128

Frith J, Newton J. Liver transplantation in more elderly age. Transplant International 2009: 22; 599-600

Frith J, Day C, Henderson E, et al. Non-alcoholic fatty liver disease in older people. Gerontology 2009: 55; 607-13

Frith J, Day C, Robinson L, et al. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. Journal of Hepatology 2010: 52; 112-16

Frith J, Kerr S, Robinson L, et al. Primary biliary cirrhosis is associated with falls and significant fall related injury. QJM 2010: 103; 153-61

Frith J, Newton JL. Liver disease in older women. Maturitas 2010: 65; 210-14

Elliott C, Frith J, Newton JL. Occupational therapy in chronic liver disease: a preliminary study to explore the views of occupational therapists and physicians working in the acute medical setting. British Journal of Occupational Therapy 2010: 73; 116-20

Hollingsworth K, Jones D, Taylor R, Frith J, et al. Impaired cerebral autoregulation in primary biliary cirrhosis- implications for the pathogenesis of cognitive decline. Liver International 2010: 30; 878-85

8. ASSOCIATED PEER REVIEWED PUBLISHED ABSTRACTS

Frith J, Robinson L, Jungerius D, et al. Orthostatic grading scale is better than timed up and go at identifying fallers with primary biliary cirrhosis. Age and Ageing 2008: 38; ii48

Frith J, Robinson L, Jungerius D, et al. Falls are common in primary biliary cirrhosis and associate with dysautonomia and lower limb weakness. Hepatology 2008: 48; 1092

Frith J, Jones DEJ, Newton J. Regulation of cerebral blood flow is significantly impaired in primary biliary cirrhosis. Journal of Hepatology 2009: 50; S246

Frith J, Robinson L, Wilton K, et al. Non-alcoholic fatty liver disease is associated with recurrent falls and significant injury. Hepatology 2009: 50; 792A

Frith J, Day C, Henderson E, et al. Non-alcoholic fatty liver disease is more severe in the elderly. Age and Ageing 2009: 38; ii49

Frith J, Robinson L, Elliott C, et al. Recurrent falls and significant injury are common in non-alcoholic fatty liver disease. Age and Ageing 2010: in press

Frith J, Elliott C, Pairman J, et al. Liver transplantation is not associated with significant improvement in functional ability or symptoms. Hepatology: in press

Newton JL, Elliot C, Frith J, et al. Appreciation of the benefits of exercise programmes in non-alcoholic fatty liver disease: implications of fatigue and impact upon activities of daily living. Hepatology 2008: 48; 1136

Elliott C, Robinson L, Jones DEJ, Frith J, et al. Functional impairment is significant in chronic liver disease. Age and Ageing 2010: in press

INTRODUCTION – PART ONE

9.1. INTRODUCTION

All cells within the human body undergo changes related to advancing age, although different cell groups are affected differently. The ageing process affects the liver on a molecular, cellular, tissue and macroscopic level and has implications for both the healthy and the diseased liver. As management of adults with liver disease improves and the population ages we will see an increasing number of older people with longstanding liver disease, and older people presenting with liver disease for the first time. It is essential therefore, that laboratory and clinical hepatologists, as well as geriatricians, have an understanding of the ageing liver.

Cellular, tissue and physiologic age-related changes will be presented here while attempting to maintain a clinical focus. This will lead on to general, clinically relevant issues relating to an older person with chronic liver disease, followed by disease specific age related considerations.

Search Strategy and Selection Criteria

The Ovid MEDLINE® database was searched for relevant publications, written in the English language, from 1950 to 2010. Further publications were identified by selecting appropriate publications from reference lists of relevant papers. Search terms were matched to Medical Subject Headings and consisted of: ageing/aging, hepatocyte, liver function tests, acute liver failure, chronic liver disease, cirrhosis, alcoholic liver disease, fatty liver disease, autoimmune hepatitis, viral hepatitis, HBV, HCV, biliary cirrhosis, sclerosing cholangitis, hepatocellular carcinoma, liver transplant, alpha 1-anti-trypsin, Wilson's disease, haemochromatosis, osteoporosis, bisphosphonates, portal hypertension.

9.2. THE AGEING HEPATOCYTE AND HEPATIC SINUSOID

Hepatocytes increase in size with advancing age, although it is unknown why this occurs it is often thought to be a compensatory hypertrophy related to the reduction in hepatocyte numbers which begins in the sixth decade with a more rapid loss in the eighth decade [1]. As with most ageing tissues within the body increasing numbers of polyploid cells are seen, reflecting the senescent state of the aged liver. Little is known about how advancing age affects the intra-cellular organelles within the hepatocytes. Mitochondria appear to mirror the response of hepatocytes by declining in number but increasing in size. Mitochondrial ATP content is reduced, as is their overall activity

which declines further in response to oxidative stress [2]. Smooth endoplasmic reticulum is decreased in volume in rat hepatocytes which may have important implications for drug metabolism [1]. Some abnormality may be present in ribosomes and polysomes, with abnormal aggregation and binding to endoplasmic reticulum, resulting in abnormal cross-linking of amino acids and an accumulation of redundant proteins [1, 3]. These proteins are believed to be the explanation for the dark macroscopic appearance of the liver as the aged intra-cellular lysosomes are unable to process the accumulating proteins [3].

Age related changes also occur in the hepatic sinusoid, the site of substrate exchange between the blood and the liver. Within the sinusoid the sinusoidal endothelial cells become thickened and defenestrated, collagen is deposited in increasing quantities in the space of Diss and increasing numbers of fat-rich, inactive stellate cells are seen. These changes may result in an increased systemic exposure to toxic macromolecules due to impaired endocytosis. There is also the potential for increased post-prandial hyperlipidaemia as the reduction in fenestrations leads to impaired transfer of lipoproteins [4].

9.3. AGEING AND LIVER FUNCTION

Liver blood flow is estimated to reduce by 35% between the age of 30 and 100 years and is unrelated to the decrease in liver volume [5, 6]. One rodent derived model, suggests that this reduction in blood flow is the result of increasing numbers of leukocytes within the sinusoids, stimulated by the up regulation of intercellular adhesion molecule 1 which occurs with advancing age [7]. This reduction in blood flow may impair hepatic function, particularly following laparoscopic cholecystectomy when there is prolonged recovery of hepatic blood flow following the raised intra-abdominal pressure during the procedure [5]. The reduction in blood flow correlates well with several measures of laboratory liver function (galactose elimination, aminopyrine demethylation, caffeine clearance), providing evidence for decreasing liver function with age [8, 9]. However, these laboratory markers of liver function do not translate into clinically significant impairments. For example, one very important function of the liver is the phase 1 metabolism of drugs. Studies in rats have demonstrated an age associated decline in drug metabolism, which when interpreted alongside the aforementioned changes in liver blood flow, liver volume and laboratory function tests, have lead to the widely held view that phase 1 drug metabolism is impaired with advancing age. Actually, there is little human data to support this; indeed, CYP450 enzyme concentration and activity appear not to decline with advancing age in human liver,

although some results are conflicting [10, 11]. Notwithstanding this, it is important to remember that the absorption, distribution and excretion of medications may be altered. Similarly to CYP450, there is no age related reduction in the activity of hepatic alcohol dehydrogenase with the majority of changes in the metabolism of alcohol occurring in non-hepatic sites (e.g. the age associated reduction in gastric alcohol dehydrogenase) [12, 13]. Declining gastric alcohol dehydrogenase increases the availability of alcohol which, alongside a reduced volume of distribution increases blood alcohol levels per unit consumed [12, 13, 14].

9.4. AGEING LIVER REGENERATION AND RECOVERY

It seems likely that the aged liver has a reduced ability to cope with challenging physiological and pathological insults. Figure 1 outlines the changes seen with advancing age which could, in theory, lead to an increased susceptibility to insults [2, 15, 16, 17, 18].

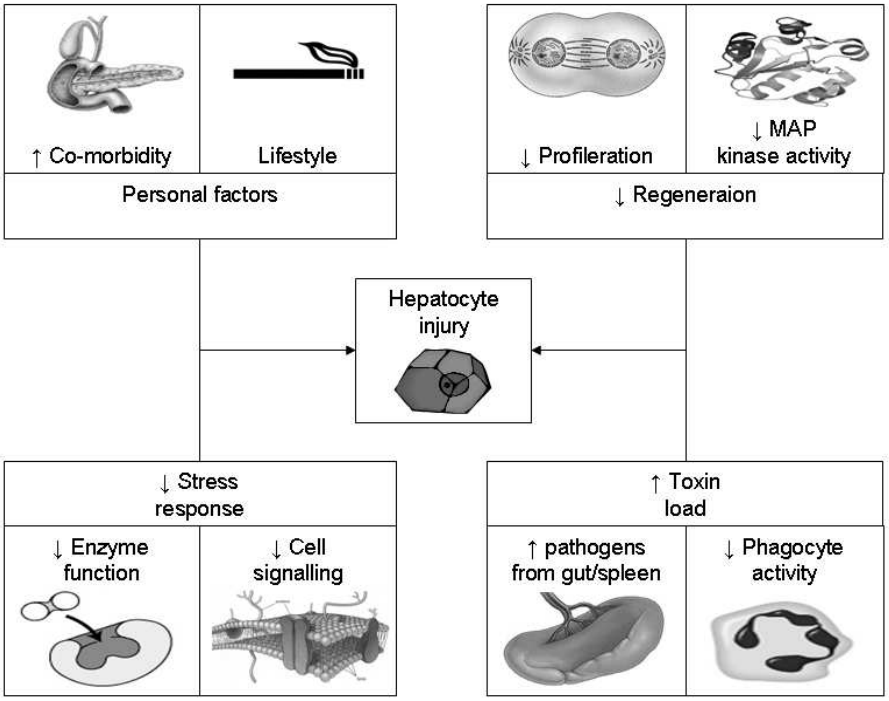


Figure 1. Possible mechanisms behind the increased severity of injury in aged hepatocytes.

It is essential to remember that the liver has a remarkable ability to regenerate and that this ability persists into advanced age. Many of the aforementioned observations are based on rodent livers and have only theoretical translation into humans. Furthermore, many have been inconsistent and difficult to reproduce, highlighting the need for further good quality studies in ageing human hepatocytes. The disadvantage of these molecular rat-based studies is that they have the potential to feed widely held misconceptions that older people will have reduced liver function and the wrongly held assumption that clinically-used laboratory liver function tests (LFTs) can be mildly abnormal as part of the normal ageing process.

9.5. CHRONIC LIVER DISEASE (CLD) IN OLDER PEOPLE

Studies relating to liver disease in older age are uncommon and evidence must therefore be extrapolated from studies of younger people or be based upon expert opinion and experience. As with many diseases in old age, the presentation and clinical course can be subtle, non-specific and easily missed. It is essential to be aware of these non-specific presentations and have a high index of suspicion. Interpretation of hepatic investigations should be with the same vigilance as would be applied to a younger person, as most investigations and treatments are well tolerated and beneficial in the older person. Acute liver failure (ALF) is rare in the older person and will not be covered in this work; however some basic details are provided in Box 1.

Acute liver failure is exceptionally rare in older people and as such evidence based treatment is lacking and should follow that of younger people where appropriate. In a Swedish 10 year study of new cases of ALF the eldest person to have the diagnosis was 59 years [19].

The most likely causes are viral and drug induced hepatitis but ischaemic hepatitis is increasingly being seen in older people [20]. Acute failure secondary to hepatitis A virus is more severe in the elderly with more complications and an increased mortality [21]. Drug-induced ALF is most frequently caused by paracetamol with age over 40 years being associated with a poorer prognosis [22].

Ischaemic hepatitis is seen in approximately 1% of critical care patients and has a mean age of 70 years. Aminotransaminases and LDH levels rise dramatically as a result of hypoxia, hypotension, decreased perfusion or venous congestion. While it is potentially reversible it carries a high mortality rate of 45%. Although it is an increasing cause of hepatitis it is an exceedingly rare cause of liver failure in the elderly.

Box 1. Acute liver failure in the older person.

9.5.1. EPIDEMIOLOGY

Medical management and liver transplantation has transformed the survival of patients with liver disease. As the population ages and medical management of CLD improves, we can expect to see greater numbers of older people with liver disease.

Twenty-eight percent of individuals with alcoholic liver disease (ALD) present over the age of 60 years [23] and 26% of patients with non-alcoholic fatty liver disease (NAFLD) are aged over 60 years [24]. Chronic, autoimmune liver diseases also commonly present for the first time in older age; 50% of patients with primary biliary cirrhosis (PBC) present for the first time over the age of 65 years, and few patients with autoimmune hepatitis (AIH) present before the fifth decade [25]. The exact prevalence of drug-induced liver disease is difficult to define given its challenging diagnosis; however, it is thought to be more common in older age [26]. In line with these statistics, the demand for liver transplantation in older patients is increasing and age is now less of a contraindication (due to technical advances and increased life expectancy); the proportion of those over the age of 60 years who received a liver transplant during 1990–91 was 10%, doubling to 21% during 1997–99 [27].

Viral hepatitis is less common in older age, there are however several considerations with regard to older people. Firstly, fewer older people are vaccinated against hepatitis B (HBV): 0.9% of over 65 year-olds in one hospitalised group, compared with 21% in a 35-45 year-old group [28]. Outbreaks of HBV have been reported in residents of care homes, without the typical blood-borne route of transmission [29]. Possible sources include sharing bath brushes, sexual contact and razor blades [30, 31]. It could therefore be recommended that older people in care homes be vaccinated against HBV, however the response to the vaccine is significantly reduced in older people [32]. Hepatitis C virus (HCV) is also uncommon in older people but there may be a significant few who received blood transfusion prior to screening of donor blood.

9.5.2. PRESENTATION AND CLINICAL FEATURES

Presentation is, on the whole, non-specific, subtle and easily disregarded. The commonest reason for referral (at any age) to a hepatologist is abnormal liver function tests (LFTs) of unknown cause. Fatigue, malaise, anorexia, nausea and vomiting can occur in any form of CLD. However, certain features are more common in older people (Table 1). In general, older people are more likely to

have signs of CLD on examination, possibly because they present later in the course of the disease or have had the disease for longer [23, 33, 34].

Disease	Clinical feature
ALD [23]	Typically non-specific Dizziness more common with increasing age
PBC [35]	Typically asymptomatic Sjorgren's syndrome, pruritus, weight loss, xanthalasma, fatigue, abdominal discomfort
AIH [36]	Typically non-specific 50% have lethargy, pruritus, abdominal pain 25% present with signs of hepatic failure 20% asymptomatic
HBV [37]	Typically asymptomatic Anorexia, vomiting, jaundice
HCV [38]	Variceal bleeding, malaise, abdominal pain, oedema, pruritus
Hepatocellular carcinoma [34]	Weakness, abdominal pain, anorexia, weight loss, nausea

Table 1. Clinical features more commonly seen in an older person with CLD.

9.5.3. INVESTIGATION

As one of the commonest presentations in a person of any age is abnormal LFTs of unknown cause it is important to recognize that there are no age-associated changes in alkaline phosphatase, hepatic transaminases or bilirubin [39]. Therefore all abnormalities in LFTs should be treated with the same diligence in an older person as in a younger person. If clinical features do not direct further investigations a full liver screen should be considered (Box 2). Ultrasound examination of the liver is useful to assess disease severity (specifically to look for a nodular liver and/or evidence of portal hypertension such as splenomegaly) or to identify focal liver lesions. If diagnostic doubt remains a liver biopsy should be considered. In England and Wales 6% of liver biopsies are performed in people aged over 80 years. Mortality from liver biopsy in this age group is approximately 0.2%, with no increase in mortality seen with advancing age [40].

Full blood count
Coagulation
Glucose and lipid profile
Inflammatory markers
Alkaline phosphatase sub typing
Viral hepatitis markers
Immunoglobulins
Auto-antibodies
Ferritin and/or HFE genotyping*
Urinary copper/caeruloplasmin*
Alpha 1-antitrypsin*
Alpha fetoprotein (AFP)
Abdominal/liver ultrasound
Investigations marked with an asterisk may be unnecessary as their respective diseases rarely present in later life

Box 2. Investigations considered for an older person with abnormal liver function of unknown cause.

9.5.4. SPECIFIC LIVER CONDITIONS

9.5.4.1 Alcoholic Liver Disease

Signs and symptoms are more severe on presentation in the older patient with ALD [23, 41] and blood alcohol levels may be higher because of lower body water content. Acute withdrawal may be easily missed, particularly in a population which may be judged to be less likely to consume alcohol. However, 53% of males and 38% of females over the age of 60 years are current drinkers, [42] and almost 10% of acute care of the elderly admissions are abusers of alcohol [43].

9.5.4.2 Non-Alcoholic Fatty Liver Disease

NAFLD is more common and more severe in older people [24]. Patients will typically display features of the metabolic syndrome. Diagnosis can be made clinically, in the presence of risk factors (insulin resistance/diabetes, obesity, dyslipidaemia, and hypertension) and the absence of other causes. Ultrasound showing an 'echo bright' liver supports the clinical diagnosis with a specificity of 95% [44]. Given its prevalence and the expected increase in cases in the older population more studies are required in this age group.

9.5.4.3 Autoimmune Hepatitis

In general AIH has an insidious onset in the old and in the young. AIH in older people is associated with fewer autoimmune diseases than in younger people. The commonest disease associations in older age are rheumatoid arthritis, autoimmune thyroid disease and ulcerative colitis [45]. Treatment outcomes with prednisolone, azathioprine or a combination of both are similar for both older and younger people, and are generally excellent [45, 46].

9.5.4.4 Primary Biliary Cirrhosis

PBC presents similarly in the old and young, although older people have fewer symptoms on presentation (Table 1). Diagnosis can be confirmed without the need for biopsy if a positive serum anti-mitochondrial M2 antibody is positive and the clinical features are consistent with PBC. Treatment strategies are similar regardless of age. Fatigue is a poor prognostic marker, being even more so in older people with PBC [47].

9.5.4.5 Primary Sclerosing Cholangitis (PSC)

Increasing age was found to be an independent risk factor for a poor outcome in one large PSC cohort [48]. However, very little data exists on PSC in the elderly, perhaps because the median age of diagnosis is 40 years with a median survival of 11.9 years, and because it is itself a rare disease. However, being that there is a second peak in the incidence of inflammatory bowel disease in the 7^{th}-8^{th} decade [49], one might expect that with an ageing population, and survival of IBD patients similar to that of the general population, we may expect see more PSC in the elderly [50].

9.5.4.6 Viral Hepatitis B

HBV is not common in older age and is less likely to be treated because markers of active viral replication (HBV DNA, HBeAg) tend be low or absent in older age [51]. The efficacy of some treatments has not been assessed specifically in the elderly, however some trials do include elderly subjects, including a meta-analysis of randomised controlled trials assessing the efficacy of combination interferon with lamivudine versus interferon alone – equally effective in younger and older groups [52]. Assessment of lamivudine in the elderly has been carried out showing that it is as effective in over 60s as in under 60s at reducing ALT and HBV DNA, with resistance no more prevalent in the older than in the young [53].

9.5.4.7 Viral Hepatitis C

HCV presents with signs of severe liver disease in older people (Table 1), although studies are uncommon. Recombinant interferon has a response rate (normalised ALT, improved liver histology) of 62% in the over 65s, compared to 57% in under 65 year olds. Side effects however, are more common in older people (23%) compared to the young (19%) [54]. Combination interferon and ribavirin is as successful in the over 60 year olds as in those under 60 years, with a sustained virological response of 38% in the under 60 year olds and 32% in the over 60 year olds (p=0.36). Combination is also more effective than interferon alone, and is not associated with more side effects than the younger cohort [55].

9.5.4.8 Hepatocellular Carcinoma

HCC is usually detected as an acute deterioration in liver function tests in the presence of existing chronic liver disease. However, the commonest presenting features (if not identified on screening) in patients aged over 65 years are weakness, abdominal pain, anorexia, weight loss and nausea [34]. Ninety per cent of patients with HCC, aged over 65 years, have an alpha-fetoprotein (αfp) level greater than 10 ng/ml [34]. One large, population-based study of older patients with HCC demonstrated some differences in treatment methods used when compared to younger patients (displayed in brackets): transplant 0.9% (1.5%), tumour resection 8.4% (5.9%), ablation 4.1% (4.4%), TACE 4.2% (6.3%) [56].

9.5.4.9 Hereditary Haemochromatosis (HH)

HH is classically diagnosed in middle age, with an average survival of 21 years (with treatment) [57]. However, recent case reports and genetic studies have shown that it can present in old age, and males who are homozygous for the C282Y gene (the commonest genetic abnormally identified) are surviving into old age without clinical or biochemical abnormalities. This is of importance to clinicians who should be aware that patients can present much later than previously thought [58]. As might be expected, females who undergo earlier menopause have a greater concentration of hepatic iron, than females who undergo the menopause after the age of 50, as a result of therapeutic menstruation [59].

Haemochromatosis must also be considered in older patients presenting with neurological complications, as iron overload may be misdiagnosed with movement disorders such as Parkinson's disease or cerebellar syndromes [60]. Treatment by venesection may induce orthostatic

hypotension as a result of volume loss which is likely to be more severe in the elderly; concomitant infusion of intravenous fluids may reduce this risk in those with postural symptoms or drops in blood pressure.

9.5.4.10 Alpha 1-Antitrypsin Deficiency (A1AT)

A1AT is recognised as a possible cause of cirrhosis in older age. In one case review describing 3 patients, aged 66, 71 and 77 years, only one had obstructive airways disease, but each had abdominal swelling or hepatomegaly; with a raised ALP [61]. It can also present with isolated respiratory disease in the elderly, and is more likely to present later in life-long non-smokers [62].

9.5.4.11 Wilson's Disease

Wilson's disease most commonly presents in adulthood with neuro-psychiatric symptoms rather than the hepatic dysfunction seen in childhood [63]. Reports of presentation in the elderly vary from neurological dysfunction in the absence of liver disease and Kaiser-Fleischer rings [64], liver disease with no neurological dysfunction [65], to non-specific presentation (weight loss) [66]. In one review comparing recent diagnoses of WD (1994-2003) to past diagnoses (1976-1993) the age at presentation was greater in the most recent period (35.1 vs. 16.7 years) [67].

9.5.5. MANAGEMENT

9.5.5.1 General Principles

General management strategies apply to people of any age with chronic liver disease, such as lifestyle modification in ALD and NAFLD. Specific points relevant to older people are described below.

9.5.5.1.1 Orthostatic Hypotension (OH)

OH is more common in older people, but may also arise as a consequence of liver disease associated autonomic dysfunction, the processes behind this are discussed in detail in section 11.4 on page 28 [68]. Fluid balance is also disturbed in older cirrhotic patients, and can be aggravated by fluid restriction, diuretics, laxatives and anorexia. Care must be taken when treatments such as diuretics are administered to older patients with liver disease.

9.5.5.1.2 Polypharmacy

This often results when patients develop cirrhosis. They may be prescribed beta-blockers, diuretics, laxatives, vitamin supplements and disease specific medications (e.g. immunosuppressives in inflammatory liver disease). Benzodiazepines can result in prolonged sedation as a result of relatively higher body fat in older people. Adverse effects from benzodiazepines are also significantly more common with age [69]. Some general principles concerning medications used for symptomatic relief of liver disease are described below under palliation. Urinary and faecal incontinence may be exacerbated by the use of diuretics and laxatives, but also as a result of adverse effects of medication such as ursodeoxycholic acid and colestyramine.

9.5.5.1.3 Bone Disease

Bone protection will be an issue facing many older people with CLD. Osteoporosis is common in cirrhosis [70] and risk may increase with the use of steroids in autoimmune liver disease.

9.5.5.1.4 Hepatic Encephalopathy (HE)

HE specific to the older person has little to no evidence base. As clinicians we must therefore extrapolate relevant data from trials concerning younger adults. It can be anticipated that the diagnosis of HE in the elderly will be more challenging given that delirium and dementia secondary to increasing co-morbidity will be more common. Clinicians should therefore consider the diagnosis in older patients presenting with delirium or dementia. Lactulose is recommended in minimal HE to improve cognition and quality of life, however, evidence suggests it has no beneficial effect on survival or progression of HE [71, 72]. When prescribing laxatives in the elderly consideration should be made to the effects it will have on faecal incontinence, gastrointestinal absorption, hydration and electrolyte homeostasis [73]. Previous claims that HE is more common after therapeutic transcutaneous intrahepatic porto-systemic shunting (TIPS) in >60 year olds seem unlikely [74, 75, 76]

9.5.5.1.5 Oesophageal Varices

There is evidence to suggest that older people should be treated as actively as in younger patients (when appropriate), as active management of varices has similar short term survival rates, and similar rates of long-term survival with respect to liver-related mortality [77]. Endoscopy is safe and well tolerated (see below). One small trial has demonstrated higher re-bleeding rates,

complications and overall mortality of injection sclerotherapy in older people compared to younger people [78]. However, this trial was small and did not fully consider co-morbidities. The use of octreotide and terlipressin in the elderly is not well evidence based. They should be considered where appropriate, but may not always be suitable in view of the greater prevalence of heart disease and hypertension.

9.5.5.2 Screening

9.5.5.2.1 Bone densitometry

Assessment of bone density should be considered in all patients who have CLD, particularly in the presence of cirrhosis [79]. However, there is no international consensus and local guidelines may differ. It should be recommended for those who have had a fragility fracture or who are on long term steroid therapy [79] and should form part of the transplant screening process. For patients with PBC bone densitometry is recommended at diagnosis [80].

9.5.5.2.2 Upper gastrointestinal endoscopy

Endoscopy is safe and well tolerated in the older person [81]. The frequency of upper gastrointestinal endoscopies to screen for varices should follow established guidelines [82], regardless of age.

9.5.5.2.3 Ultrasound examination and serum αFP

These are recommended every 6 months in patients with cirrhosis where treatment for early HCC such as resection or ablation would still be feasible. Such treatment may be efficacious and well tolerated by patients over 70 years [56, 83, 84].

9.5.5.3 Liver Transplantation

Following liver transplantation people aged over 60 years have no significant differences in length of hospital stay, repeat admissions, infections, rejection or repeat transplantation compared to younger people [85]. The same study also demonstrated a 5 year survival of 58.1% in transplants performed after 1991. Although this survival rate was significantly less than the younger group (82.3%), a 58% 5 year survival rate must not be undervalued. Some studies, although not all, demonstrate that there are no significant survival differences between older and younger patients if classified as low risk pre-treatment. Factors which contribute to significantly increased mortality in older age include inpatient status pre-transplant, low albumin, raised bilirubin, raised prothrombin

time and high Child-Pugh score [27, 85, 86]. The commonest cause of death in recipients aged over 60 years is malignancy (35%) whereas younger patients are most likely to die from infection [85]. Cerebro- and cardio-vascular death rates are similar in both age groups; the most likely explanation being that the older age group undergo more pre-transplant screening for co-morbidities [85].

9.5.5.4 Palliation

Developments in liver transplantation have transformed the management of liver disease. However, those who are unable to undergo transplantation have almost been left behind in terms of available evidence-based treatments. Transplantation is often denied because of co-morbidities or frailty, resulting in the older person with end stage liver disease (ESLD) requiring palliation. Quality of life is poor for patients with ESLD, with sleep disturbance, pruritus, muscle cramps, ascites, fatigue, pain and cognitive decline [87, 88]. Physicians are perhaps less well able to care for the patient with ESLD than for end stage malignancy, for example. This situation is worse for older patients as most available evidence relates to younger patients. Figure 2 describes the management of some symptoms commonly seen in ESLD [89].

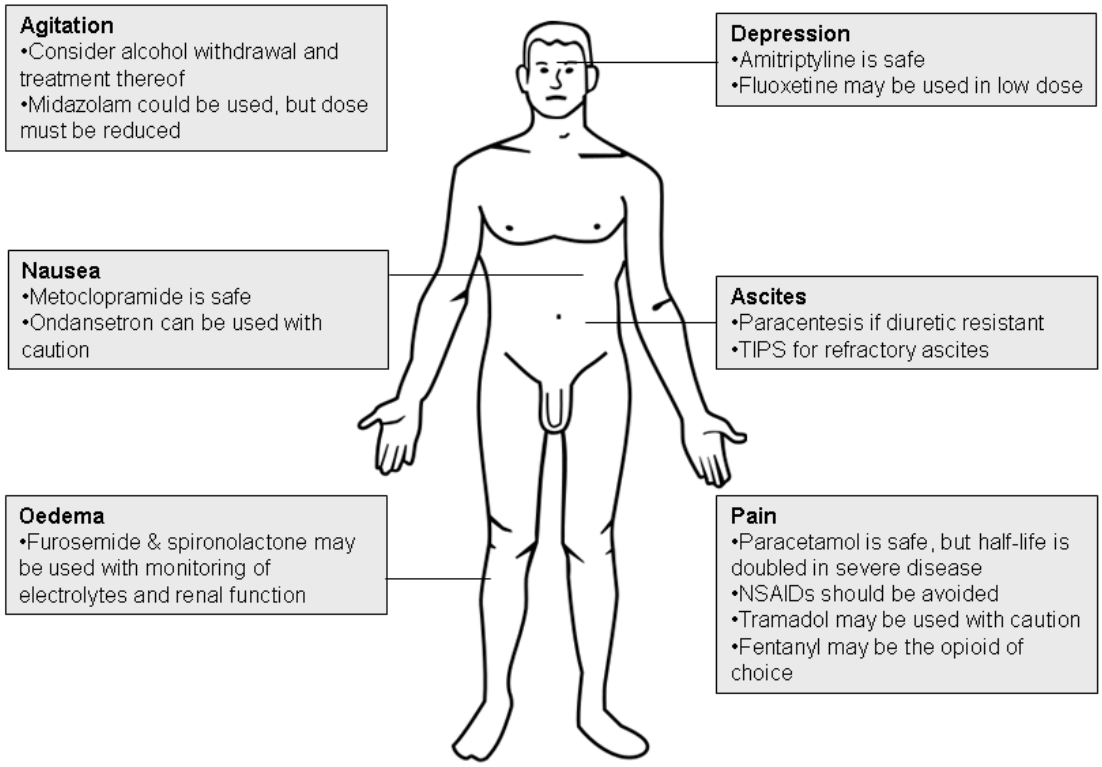


Figure 2. Common symptoms of ESLD and their treatment options.

9.5.6. PROGNOSIS

Not all CLDs increase mortality in older people. The majority of deaths in older people with AIH, PBC and HCV are unrelated to the liver [35, 36, 90]. However, ALD, NAFLD, and older, fatigued PBC patients all demonstrate age-associated increased risk of death [41, 47, 91]. Both HBV and HCV in older people are associated with increased risk of hepatocellular carcinoma [90, 92].

9.5.7. SUMMARY

Clinicians can expect to see increasing numbers of older people with liver disease. Detecting liver disease in older people relies on a high index of suspicion given that presentation is often non-specific. All hepatic investigations should be interpreted with diligence as there are no clinical changes resulting from age alone. There are several considerations when treating older people and transplantation is an option. Those diagnosed with cirrhosis who are otherwise fit should undergo 6-monthly surveillance for HCC. Evidence-based management of end stage liver failure is scanty,

but can be extrapolated from trials in younger people. Prognosis is variable, but the majority of older people with liver disease die of non-liver related causes.

INTRODUCTION - PART TWO

10.1. INTRODUCTION

As has been highlighted in the previous section, an increasingly ageing population and the improving treatments of CLD is leading to an older CLD population. Health care services need to be aware of this as the needs of ageing patients change; it may be anticipated that an older CLD population will face the same 'geriatric syndromes' (e.g. falls) as the general ageing population but that neither geriatricians nor hepatologists will be equipped to deal with these evolving needs. It is therefore essential to begin to define the problems which may be faced in order to develop services appropriately.

Alongside the liver-related problems which affect people with CLD there are significant extra-hepatic sequelae. These non-liver manifestations include bone disorders [79], cardiac and skeletal muscle abnormalities [93, 94], neurological disorders [95, 96, 97] and cognitive disorders [98, 99, 100, 101]. Many of these extra-hepatic manifestations and their consequences are established risk factors for falls and could therefore, in theory, be putting those with CLD at an increased risk of falls.

Accidental falls are estimated to cost the UK National Health Service close to £1 billion annually [102]. Such high costs occur due to the extensive physical, psychological and social sequelae of falls. Approximately 5% of falls, in the general population, result in a fracture, with increasing injury occurring with advancing age such that 15% of over 80 year olds sustain a fall-related injury [103]. Furthermore, 95% of hip fractures in older women are caused by falling and over 80% of older women would rather die than lose their independence from hip fracture [104, 105]. In addition to the morbidity, the mortality associated with falling is also increased; the odds ratio of death at one year following a fall is 2.6 (95% CI 1.4-4.7) [106].

It is not just the physical injury which contributes to the increased morbidity in falls. Psychosocial consequences of falling include loss of confidence, activity avoidance, social isolation and an increased risk of being admitted to long term care facilities [107, 108, 109, 110]. Fear of falling is a particularly complex consequence of falls as fear of falling leads to falls and a vicious cycle is created (Figure 3). It is also independently associated with an increased risk of institutional care [111, 112, 113].

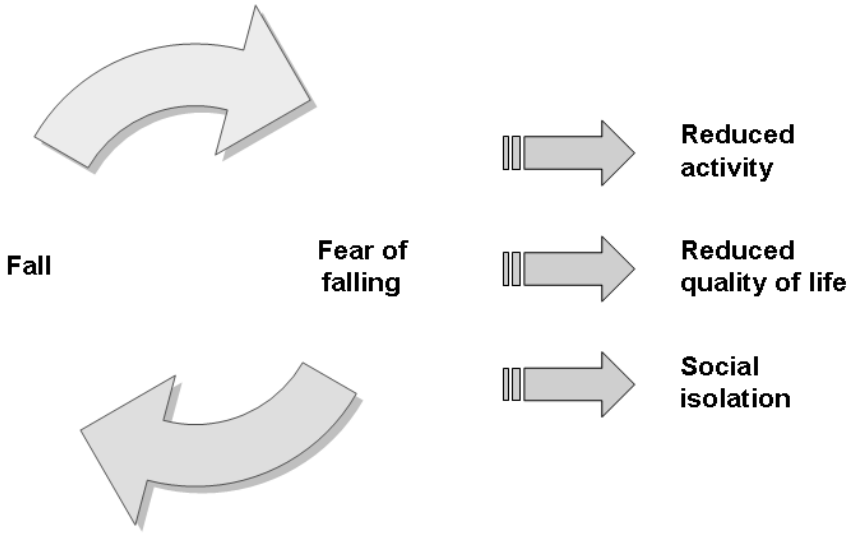


Figure 3. The vicious cycle of falls and fear of falls.

10.2. FALLS IN CLD - EVIDENCE & THEORY

The complexity of falls aetiology and a lack of effective targeted single-interventions is highlighted by the number of identified fall risk factors, over 400 [114]. As it would be impossible to consider every risk factor in all individuals undergoing a falls assessment, the National Institute for Clinical Excellence (NICE) has produced a clinical guideline detailing an appropriate multifactorial falls risk assessment. The falls risk factors discussed here will be based on this NICE guideline, which is specific to older people [115].

Search Strategy and Selection Criteria

The Ovid MEDLINE® database was searched for relevant publications from 1950 to 2010. Papers were excluded if they were not written in the English language or were based on paediatric populations. Chronic liver disease in general was used as a search term as well as searching specifically for fatty liver disease, alcoholic liver disease, primary biliary cirrhosis, autoimmune hepatitis, viral hepatitis, hepatocellular carcinoma and primary sclerosing cholangitis. These search terms were matched to Medical Subject Headings and then searches were combined with the following terms: accidental falls, gait (and ataxia), balance (postural instability), mobility, muscle weakness (and strength), fear of falling, vision, cognition (and cognitive impairment), environment (and home hazard), footwear, assistive devices and polypharmacy.

10.2.1. NEURO-CARDIOVASCULAR INSTABILITY

Orthostatic hypotension (OH), vasovagal syncope (VVS) and carotid sinus syndrome (CSS) can each cause falls as a consequence of syncope, pre-syncope or a loss of balance. Although syncope may be thought of as a separate entity to falls, syncope and falls are closely related. CSS and VVS are more common in people with unexplained falls and the treatment of OH leads to a reduction in unexplained falls [116, 117, 118, 119].

The prevalence of neuro-cardiovascular abnormalities in CLD is well documented and represents a major risk factor for falling in CLD with the prevalence of autonomic dysfunction as high as 87% in some liver disease populations [68, 94, 97, 120, 121, 122, 123, 124]. The importance of autonomic dysfunction in CLD is discussed further in section 11. A summary of the normal, orthostatic, neuro-cardiovascular process is displayed below in Figure 4.

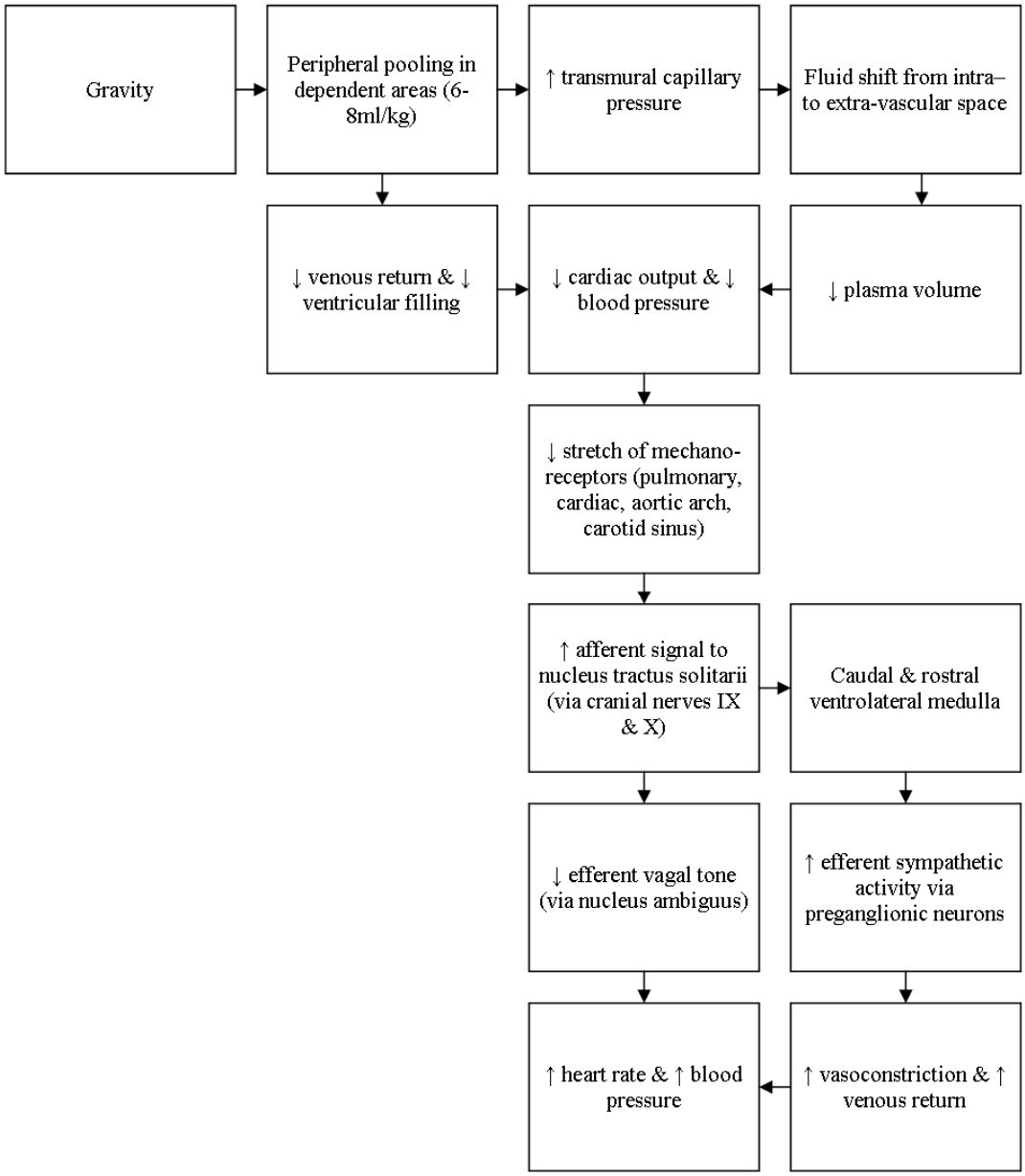


Figure 4. Flow chart of the normal physiological response to orthostasis.

10.2.2. GAIT AND BALANCE

Abnormal gait and balance are associated with an increased risk of falling in the general elderly population and may be the result of a variety of mechanisms [125, 126]. Studies specific to gait and balance in CLD are rare. Gait speed is a commonly used screening tool to identify those at risk of falling, with slower speeds being associated with falling [127]. The search strategy above identified

no publications describing gait speed in people with CLD, although there is evidence that walking distance is impaired [128].

Evidence concerning postural balance in CLD is limited to ALD and Wilson's disease, in which ataxia may be seen [129, 130]. There is surprisingly little data relating to postural instability secondary to cerebellar disease in ALD. While there is a lack of data in CLD theoretically balance may be impaired due to orthostatic intolerance. Postural dizziness is known to be associated with poor balance, is common in both NAFLD and PBC and could contribute to an increase in postural instability in CLD [131].

10.2.3. MUSCLE WEAKNESS

Muscle strength is strongly associated with falls via its influence on gait and balance [132]. While there is much evidence for the biological abnormalities seen in the muscles of people with CLD this has not been translated into pragmatic studies of muscle function and strength in humans with the exception of one study [133]. This was a small study of people with NAFLD which found that all of their participants (*n* 37) had reduced muscle strength. Although the authors did not suggest a cause, theoretically muscle weakness could occur in those with insulin resistance which, via increasingly resistant GLUT-4 transporters, reduces glucose uptake in myocytes [134]. Mitochondria in skeletal muscle appear to have abnormal function in people with PBC and this degree of dysfunction appears to correlate with the degree of exercise performed [93]. Potentially, this abnormality of bioenergetics in the skeletal muscle could result in muscle weakness and thereby, falls.

10.2.4. PREVIOUS FALLS

Those who have fallen are significantly more likely to do so. Those who have fallen recurrently are at particular risk of falling again with a relative risk of falling within the year of 2.4 (95% CI 1.7-7) [135]. Furthermore, recurrent falls are associated with a decline in muscle strength and worsening balance [136, 137].

10.2.5. VISUAL IMPAIRMENT

The risk of falling is doubled in those with visual impairment [138], although interventions to improve vision do not always prevent further falls; indeed some studies have demonstrated an increase in falls following correction of visual impairment [139, 140, 141]. There are several reasons

why people with CLD may develop visual impairment and be at increased risk of falling [142, 143, 144, 145, 146]. These impairments, all of which are uncommon, are summarized in Figure 5 below.

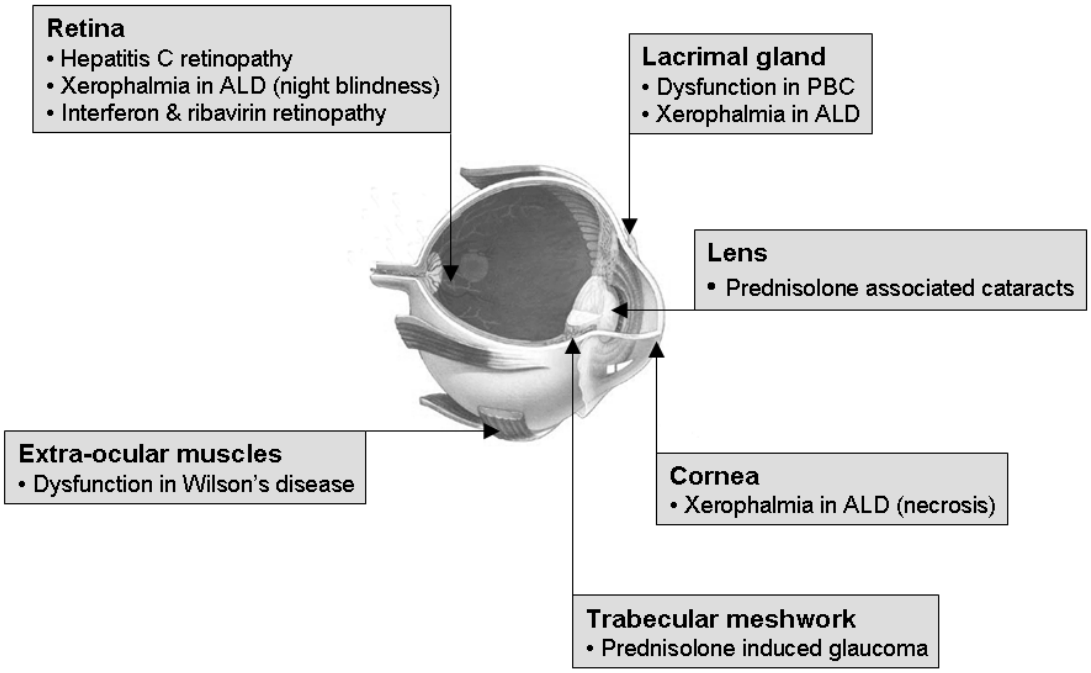


Figure 5. Visual impairment may result from CLD in several locations of the eye.

10.2.6. MEDICATION

Figure 6 displays the odds ratio for having a fall while taking different medications identified from a meta-analysis of studies involving people aged 60 years or more [147]. Individuals who use over 3 medications are also at increased risk of falling, regardless of the class of drug that they're taking [148].

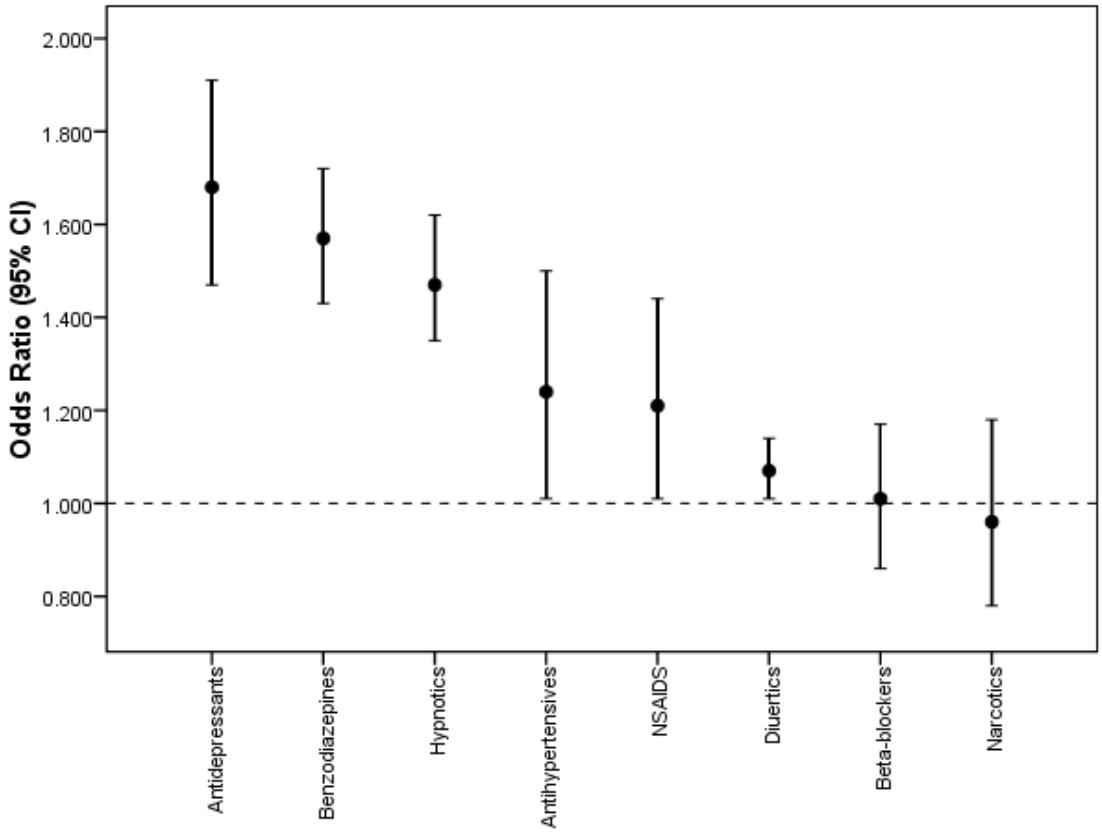


Figure 6. The odds ratio for falling while taking various medications.

The risk of falling in people with CLD who are taking psychotropic drugs may be exaggerated. For the most part psychotropic medications are eliminated by the liver and are associated with dose-dependant adverse reactions [149]. As such those with liver disease may have an increased risk of falling while taking these. A literature search was unable to reveal any data concerning the prevalence of polypharmacy in CLD, but it is possible given the multiple symptomatology in conditions such as PBC.

10.2.7. ENVIRONMENT, ASSISTIVE DEVICES AND FOOTWEAR

The majority of falls, particularly those that are injurious, occur in the home [150]. Environmental hazards are involved in approximately 50% of home-based falls, but the number of hazards present does not appear to increase the risk of falling [151]. There is a lack of data concerning environmental hazards, assistive devices and footwear in people with CLD and it is difficult to find a theoretical basis for an increased risk of falling secondary to these risk factors.

10.2.8. COGNITIVE IMPAIRMENT

The odds of falling in people with cognitive impairment are 5 times higher than in those without cognitive impairment (OR 5, 95% CI 1.8-13.7) [125]. Cognitive deficits are present in a number of CLDs independently of disease severity [99, 101, 152, 153]; an increase in falls related to cognitive impairment could therefore be anticipated.

10.3. SUMMARY

There is little to no data available concerning falls in CLD. The data available concerning risk factors are, on the whole, theoretical only. The high prevalence of autonomic abnormalities in CLD may represent the most important potential risk for falls; particularly as autonomic function plays a role in gait, balance and cognition, each of which is associated with falls.

INTRODUCTION - PART THREE

11.1. INTRODUCTION

Autonomic dysfunction in the context of CLD has been of increasing interest over the last 15 years. During this time it has become widely accepted as a complication of CLD, and a major contributor to the symptomatic burden. As the prevalence may be as high as 67%, and it is associated with an increased mortality, it is of great importance to clinicians who encounter CLD [154]. The autonomic nervous system is complex, with many investigations available. With its high prevalence and clinical significance it is important that clinicians recognise dysautonomia and initiate appropriate investigation and management. In the context of an ageing CLD population, dysautonomia could lead to increased prevalence of cognitive deficits, poor mobility and increased falls and fall related injury.

Search Strategy and Selection Criteria

Journal articles from 1950 to date were searched using Ovid MEDLINE® database. Search terms used included autonomic nervous system, autonomic nervous system diseases, chronic liver disease, fatty liver disease, alcoholic liver disease, biliary cirrhosis, sclerosing cholangitis, viral hepatitis, hepatocellular carcinoma, autoimmune hepatitis and liver transplantation. Search terms were matched to Medical Subject Headings. Excluding non-English papers, 17 publications were identified with additional relevant papers identified through reference lists. Where there is a lack of evidence in the literature regarding a specific point, general principles and expert opinion are applied; these comments are explicit when included.

11.2. THE AUTONOMIC NERVOUS SYSTEM (ANS)

The autonomic nervous system comprises the sympathetic (SNS) and parasympathetic nervous systems (PNS). They are largely responsible for involuntary, subconscious control of viscera, smooth muscle and secretory glands. The autonomic efferent neurones originate in the spinal cord or brain stem (pregangionic), but differ from the somatic nerves in that the second neurone originates in an autonomic ganglion outside the central nervous system (postganglionic).

The sympathetic preganglionic neurones are limited to the thoracic and first three lumbar segments of the spine. The postganglionic neurones of the sympathetic system make up the sympathetic chain, found alongside the spine, and the celiac and mesenteric plexuses. Sympathetic

preganglionic neurones release acetylcholine, whereas postganglionic neurones transmit noradrenalin (with the exception of sweat glands which are cholinergic, and the adrenal medulla which directly synapses with preganglionic neurones). The physiological responses of sympathetic nervous stimulation are increased heart rate (HR) and blood pressure (BP); dilatation of the bronchi; vasodilatation to skeletal muscle; vasoconstriction to the gastrointestinal tract; decreased gastrointestinal motility; increased sweating; smooth muscle sphincter contraction and pupillary mydriasis.

Parasympathetic preganglionic neurones are located in the 3rd, 7th, 9th and 10th cranial nerve nuclei as well as 2nd, 3rd and 4th sacral cord segments. Again the postganglionic neurones are found outside the central nervous system contributing to plexuses such as Auerbach's (myenteric) and Meissner's (sub mucosal). The neurotransmitter of the parasympathetic nervous system is acetylcholine, through which the following clinical responses occur: decreased HR and contractility; vasodilatation; bronchial constriction; increased gastrointestinal motility; relaxation of smooth muscle sphincters and pupilary miosis.

11.3. AUTONOMIC DYSFUNCTION

AD is a change in normal functioning of the ANS which adversely affects health. It can be primary or secondary, acute or chronic and transient or progressive. This review will focus on chronic, secondary AD as a result of CLD.

11.4. PATHOGENESIS

The patho-physiological basis of AD secondary to liver disease is largely unknown. Immunological and metabolic abnormalities may play a role, but the resultant decreased parasympathetic and increased sympathetic activity may in part be explained by the following mechanisms.

In CLD there is a decreased response to vasoconstrictors which may be caused by increased concentration of vasodilators such as nitric oxide. An increase in portal blood pressure, even mild, can lead to an up regulation of nitric oxide synthatase [155]. An increase in vasodilator production, a diseased liver and a porto-systemic circulation bypassing hepatic metabolism will contribute to increased levels of circulating vasodilators. Circulating vasodilators will activate the renin-angiotensin-aldosterone system and increase plasma levels of the vasoconstrictor angiotensin II. Plasma concentrations of angiotensin II, are raised in patients with CLD, and correlate with disease

severity [156]. Understanding angiotensin II in relation to control of the glomerular filtration rate is well understood, but it may also interact with the parasympathetic control of heart rate variability (HRV). Infusion of angiotensin II causes a decrease in HRV and a reduction in vagal discharges to the heart; if the vagus nerve is severed there is no change in HRV when it is infused. Administration of an angiotensin converting enzyme inhibitor improves the HRV confirming that angiotensin II plays a role in AD [157]. In addition, administration of antioxidants to people with CLD seems to reverse blunted BP responses suggesting that oxidative stress may also play a role in AD [158].

Diabetes, which is a common cause of AD is common in CLD [159, 160]. In diabetics who suffer iatrogenic hypoglycaemia there is a hypoglycaemia associated autonomic failure (HAAF) [161]. This is a result of decreased response of adrenaline and the SNS to hypoglycaemia. It may be possible that the hypoglycaemia induced by severe hepatic dysfunction may bring about HAAF. The resultant AD creates hypoglycaemic unawareness, and therefore a vicious circle of worsening AD [162].

AD in advanced liver disease is associated with decreased baro-receptor sensitivity to hypotension, leading to impaired BP and HR responses [163]. Advanced liver disease and cirrhosis result in other complex cardiovascular abnormalities, such as arterio-venous communications, altered sodium handling and cirrhotic cardiomyopathy. These changes will exaggerate the abnormal effects of AD, but are outside the scope of this review.

11.5. PRESENTATION OF AD IN CLD

Disease specific features of AD are described in Table 2 [97, 120, 121, 164, 165, 166].

Disease	Features
Primary Biliary Cirrhosis	PNS dysfunction in 71%, SNS dysfunction in 57%. AD is associated with cognitive decline and fatigue in PBC, but not with disease severity.
Primary Sclerosing Cholangitis	Orthostatic intolerance in 5%.
Alcoholic Liver Disease	PNS dysfunction in 72% of patients, SNS dysfunction in 40%. Prevalence greater in more severe disease. Quantity of alcohol consumed correlates with degree of AD and worsens AD in existing CLD.
HbsAg positive liver disease	PNS dysfunction in 86%, SNS dysfunction in 43%.
Anti-HCV positive liver disease	PNS dysfunction in 58%, SNS dysfunction in 42%.

Table 2. Autonomic dysfunction in specific liver diseases.

The clinical picture of a patient with chronic liver disease presenting with AD is similar for chronic AD of any cause. However, with the aforementioned cardiovascular changes the presentation can be more complex and difficult to distinguish from other sequelae of CLD, such as hypovolaemia (resulting from sepsis, blood loss or over-diuresis).

11.5.1. ORTHOSTATIC HYPOTENSION

One of the commonest consequences of AD in CLD is OH, with 33% of patients having dizziness on standing [122, 123]. The patient typically complains of dizziness or light-headedness on standing from a sitting or lying position. Other symptoms include blurring of vision, discomfort of head, neck or shoulder- the so called 'coat hanger' headache, fatigue and in severe cases, syncope.

11.5.2. FATIGUE

Fatigue is a common complaint of patients with CLD and ranges from slight impairment of daily living to severe debilitation. Liver function tests (LFTs) are often performed in the patient who presents with 'tiredness all the time' and fatigue may therefore be a presenting symptom of CLD. It can develop at any time in patients with existing liver disease, but it does not correlate with disease severity [167, 168]. The severity of fatigue experienced by patients correlates with increasingly

severe autonomic dysfunction, which must therefore be a major contributing factor in the aetiology of this symptom [169]. Other contributing factors may include metabolic disturbance, anaemia, altered sleep patterns and medication (benzodiazepines, antidepressants, beta-blockers).

11.5.3. EXERCISE INTOLERANCE

In addition to fatigue, autonomic dysfunction can also reduce exercise tolerance. In patients with dysautonomia secondary to diabetes a blunted response of HR, BP, adrenaline and noradrenalin is seen [170]. The same response could be anticipated in those with AD in CLD.

11.5.4. URINARY SYMPTOMS

Bladder dysfunction is a feature of AD; 10% of patients with CLD have symptoms of 'bladder disturbance' and 14% of pre-transplant patients use incontinence pads [123, 171]. Although there is very little data concerning bladder dysfunction in CLD we know from other AD associated diseases that it may also manifest as urinary frequency, hesitation or retention; the consequences of which include urinary tract infections, renal failure and indignity [172]. Incontinence in CLD may be exacerbated by prescribing diuretics.

11.5.5. GASTRIC SYMPTOMS

In patients with CLD there is both delayed gastric emptying of liquids and solids and a prolonged transit time from mouth to caecum [173, 174]. Symptoms include early satiety, nausea, vomiting, weight loss and epigastric pain. The decrease in small bowel motility resulting from AD is particularly important as it can cause bacterial overgrowth, with increased risk of HE and peritonitis. Delayed gastric emptying is associated with post-prandial hypoglycaemia, and may therefore worsen AD [175]. Changes in gastrointestinal motility alongside disturbances of sphincter control can cause diarrhoea, constipation and incontinence which may be exaggerated by laxatives.

11.5.6. SEXUAL DYSFUNCTION

Similar to fatigue LFTs may be performed when investigating a patient who presents with sexual dysfunction, and may identify liver disease (13% of men presenting with erectile dysfunction have abnormal LFTs) [176]. Sexual problems may arise either from fatigue, altered body image, AD, haemodynamic changes or from alterations in circulating sex hormones. Females show higher levels of dysfunction in end stage liver disease, although in cirrhotic patients males place greater

importance on it [177, 178]. Diuretics, beta-blockers and antidepressants can all exacerbate sexual dysfunction.

11.5.7. HIDROSIS

Despite 5% of patients with CLD have sweating abnormalities it is uncommon to encounter either a patient who complains of excess or impaired sweating as it has little impact on daily life [123]. Unless questioned specifically patients may not appreciate the significance of symptoms of temperature regulation and sweating. Clinically the usefulness of this in relation to diagnosing AD is questionable.

11.6. INVESTIGATING THE ANS

The simplest, clinical method to test for AD is to test for OH. Baseline BP is recorded in a resting supine position; the patient then stands and the BP is recorded immediately and repeated at 3 minutes standing. A diagnosis of OH is made if there is a systolic drop in BP of ≥20mmHg or a diastolic drop of ≥10mmHg within 3 minutes [179]. In patients with CLD, before a diagnosis of OH is made, hypovolaemia should be excluded (typically hypovolaemia will cause an isolated systolic drop with no diastolic drop in pressure, however this is unreliable) and causal medications should be reviewed.

Another simple clinical test is a resting electrocardiogram. A normal resting HR would lay between 60 and 80 bpm, levels above this could indicate parasympathetic dysfunction. However anaemia, hyperthyroidism, sepsis, hypovolaemia, arrhythmias and phaeochromocytomas can also cause resting tachycardias. The presence of rate limiting medication can also mask parasympathetic dysautonomia.

Other tests of autonomic function are available (Table 3), but these are specialised and not practicable in every clinic [180]. However an understanding of them is of value in order to understand specialist investigation and research. Measuring autonomic function is unreliable in those patients who are on beta-blockers, as normal sympathetic responses will be blunted.

Investigation	Method	Interpretation
Active standing (Parasympathetic 30:15 ratio)	Using ECG monitoring, the patient rests supine for a stable HR. The patient then stands up with the ECG monitoring. The ratio of longest RRI (around the 30th beat) to the shortest RRI (around the 15th beat) following standing is calculated.	≥1.04 normal 1.01-1.03 borderline <1.0 abnormal
Response to deep breathing (Parasympathetic)	After resting in a sitting position, whilst recording the HR, the patient breathes deeply and evenly at 6 breaths per minute. The maximum and minimum HR during each breath cycle is noted for 3 consecutive cycles. The mean difference between maximum and minimum HR is calculated.	>9 bpm normal (age >60) ≥15 bpm normal (age <60) 11-14 bpm borderline ≤10 bpm abnormal
Valsalva (Parasympathetic)	After resting in a sitting position, with HR monitoring, the patient expires for 15 seconds against a closed glottis (pressure of 40 mm Hg). The ratio of the longest RRI just after releasing the valsalva, and the shortest RRI during it is calculated.	≥1.11 normal (age >60) ≥1.21 normal (age <60) 1.11-1.2 borderline
Valsalva (Sympathetic)	The same method as for valsalva (parasympathetic) but BP is recorded.	Normally there will be a BP overshoot shortly after releasing the strain.
Isometric exercise (Sympathetic)	Using a dynamometer, hand grip is maintained at 30% of maximum grip for 5 minutes. An alternative is to ask the patient to sit up from supine position, leaving their legs on the couch. Baseline diastolic pressure is measured before exercise and just before releasing the grip, the difference is calculated.	≥16 mmHg normal 11-15 mmHg borderline ≤10 mmHg abnormal
Cold pressor (Sympathetic)	One hand is held in iced water for 1 minute. Diastolic BP is measured, before and after, the increase is calculated.	≥15 mmHg normal 11-14 mmHg borderline ≤10 mmHg abnormal

Table 3 continues…

Using Ewing and Clarke's criteria, severity of dysautonomia is classified as:
Normal: all tests normal or borderline
Early dysautonomia: one abnormal HR test or two borderline
Definite dysautonomia: two or more abnormal HR tests
Severe dysautonomia: two or more HR rate tests abnormal, plus one borderline or abnormal BP test
Atypical: any other combination of abnormal tests

Table 3. Tests of autonomic function, and classification of severity.

11.7. TREATING AD IN CLD

There are numerous factors which complicate the treatment of dysautonomia in the patient with CLD. Patients may be on diuretics, beta-blockers, antidepressants or sedatives all of which affect the autonomic nervous system. Lactulose and diuretics as discussed previously can contribute to incontinence or sexual dysfunction, and a risk/benefit analysis may need to be undertaken with the patient.

Pronounced splanchnic vasodilatation following paracentesis of ascitic fluid results in a prominent activation of the SNS [181] leading to, at worst, circulatory collapse [182]. This is avoided by infusion of intravenous albumin to maintain a normovolaemic circulation [181].

11.7.1. ORTHOSTATIC HYPOTENSION

Specific treatment options for patients with CLD and OH are lacking, therefore therapeutic options for OH of other causes may be applied with expert opinion. OH is often the most troublesome of dysautonomic symptoms but is usually treated successfully with conservative measures. A typical recommendation for patients with OH of any cause is to maintain their intravascular volume by drinking at least 2 – 2.5 litres of fluid per day. This may however, complicate CLD, especially those who are fluid overloaded but who are unable to maintain their fluid in the intravascular compartment. Compression stockings help to redistribute extra-vascular fluid, and also prevent peripheral venous pooling on assuming an upright posture. Large meals should be avoided to minimise postprandial hypotension, and all patients should adopt a slow, gradual staged movement on rising into standing position. Pharmacological options are available for those few who do not respond to conservative measures. Fludrocortisone can improve OH of any cause by

causing sodium and water retention, but may be contraindicated or used with great caution in CLD where secondary hyperaldosteronism may already be present. Midodrine, an α1-adrenoreceptor agonist, which is used off-licence in the UK, may be used to treat OH. Extreme caution should be taken when using in patients with CLD, as it can worsen liver function. Other agents which have been used for OH (but not specifically used in CLD) are beta-blockers, clonidine, pyridostigmine, erythropoietin and selective serotonin re-uptake inhibitors.

11.7.2. FATIGUE

Fatigue is often multi-factorial and difficult to manage. In CLD associated fatigue patients should be encouraged to adopt a steady state of activity, and avoid intense bouts of activity when energy is present. In resistant cases of Primary Biliary Cirrhosis (PBC) where fatigue is associated with excessive daytime sleepiness modafinil has been used successfully [183]. It is relatively contraindicated in hypertensive patients, and BP should be monitored while on treatment. Starting dose is 50-100mg and titrated accordingly. Side effects include headaches, sleep disturbance and hypertension. In those who suffer from insomnia a sedative may improve sleep thereby improving daytime wakefulness. In those who suffer broken sleep or display risk factors for sleep apnoea a referral for sleep studies should be considered. In patients on beta-blockers a risk/benefit analysis should be undertaken on an individual basis, as beta-blockers can cause profound fatigue [184].

11.7.3. GASTROINTESTINAL SYMPTOMS

Current treatments for delayed gastric emptying are, on the whole, disappointing. There are no trials addressing this issue in CLD specifically and evidence must therefore be taken from trials assessing delayed gastric emptying of other causes. Medical management includes erythromycin which improves motility but does not improve symptoms, and domperidone which seems to be more effective at symptom control, in diabetic patients with gastroparesis [185]. Surgical options as yet are limited as trials have been retrospective and uncontrolled, but gastrostomy, botulinum neurotoxin and implantable electrodes to stimulate motility have shown promise [185, 186, 187].

Gastrointestinal mobility disorders may be initially managed with diet, followed by medications such as laxatives or bulking agents, and constipating agents with planned enemas, although specific evidence in relation to CLD is lacking, expert opinion would suggest using the above simple measures as a first line treatment. For severe, resistant cases with significant impact on daily living surgical options exist (evidence not specific to CLD). For incontinence the anal

sphincter can be repaired or substituted, but with disappointing long term success [188]. For incontinence and constipation colectomy with or without stoma formation may improve symptoms [189].

11.7.4. URINARY SYMPTOMS

Treatment options for neurogenic bladder dysfunction are generic and expert opinion allows us to apply the evidence to any causal disease. Evidence suggests that urodynamic studies will help direct appropriate management [190]. First line treatment for urinary frequency includes bladder retraining (increasing time between voiding) or regular toileting (micturating every 2-4 hours) [172]. Pharmacological treatments include antimuscarinics which can worsen AD and alpha-blockers which can cause profound OH [191]. For severely hypotonic bladders intermittent catheterization may reduce incontinence, infections and renal failure [192].

11.7.5. SEXUAL DYSFUNCTION

It is difficult to distinguish between AD, medication adverse effects and psychological disturbance as the cause of sexual dysfunction. Contributing medications should be reviewed. Despite lower levels of testosterone and increased levels of oestrogen, supplementing testosterone is not effective at improving erectile dysfunction [193]. Unsurprisingly sexual dysfunction does improve in alcoholic men who abstain [194]. The incidence of erectile dysfunction more than doubles in men who undergo TIPS [195]. There is evidence that the pharmacokinetics of phosphodiesterase type-5 inhibitors in those with hepatic impairment is not altered [196], however there are also case reports of hepatotoxicity associated with sildenafil [197].

11.7.6. HYPERHIDROSIS

Although not specific to CLD, disorders of sweating, especially axillary, palmar and gustatory hyperhidrosis, may respond to treatment with botulinum neurotoxin [198].

11.8. AUTONOMIC FUNCTION FOLLOWING LIVER TRANSPLANTATION

The majority (87%) of patients who undergo liver transplantation suffer from AD [124]. The degree of dysautonomia improves after liver transplantation in 63% of patients at 6-7 months; however in a very small number it gets worse despite successful grafting and in patients whose allograft function

is impaired dysautonomia persists [124, 199]. Although the aforementioned studies had relatively short follow up, studies of spontaneous baro-reflex sensitivity have shown improvements which remain at 18 months [200].

The effects of LT on sexual and urinary dysfunction are much less impressive, with no improvements in symptoms. This confirms the complex nature of these problems with medication and psychological factors perhaps having a greater effect than AD [171, 177].

11.9. PROGNOSIS

The association between liver disease severity and the incidence of AD is equivocal with conflicting results [95, 96, 154, 201]. Mortality is increased in patients with CLD and AD; 4 year mortality is 30% in CLD with AD compared to 6% in CLD without AD [202]. AD is an independent risk factor for mortality in both compensated and decompensated cirrhotic patients [154]. In one study which followed patients awaiting LT for 10 months, 6 patients died, each had AD leading the authors to conclude that consideration should be given for early LT in those with AD [154]. In addition to increased mortality in those with cardiovascular abnormalities, patients with PBC who suffer from fatigue have an increased mortality [203].

The aforementioned sequelae of AD add significantly to poorer quality of life in patients already burdened with chronic disease. Recent studies are also beginning to define additional potential consequences of AD in those with liver disease such as cognitive impairment [99]. As dysautonomia is increasingly common in older age we should expect to see more consequences of AD as the liver disease population ages. Falls, OH, incontinence and cognitive impairment are all more common with age and will pose significant problems in this population.

Although the increase in mortality associated with AD is significant, hepatologists should not solely focus on survival or laboratory markers, but address symptomatic burden and quality of life. Challenging, vague symptoms can often be improved through active listening and empathy, improving patients' expectations and satisfaction. If patient care is to be improved, outcome measures which enable patients to represent the treatment effects which make a real difference to their lives must be incorporated into routine clinical practice [204].

11.10. CONCLUSIONS

Although greater understanding of the pathogenesis of AD in CLD is required its effects on patients are becoming increasingly recognised. The symptomatic burden of patients with CLD and dysautonomia is high, but may be overlooked in favour of laboratory markers of disease severity. Many of the symptoms, such as fatigue and sexual dysfunction, pose difficulties for clinicians, as they may be considered low priority, ubiquitous and un-modifiable. Simple measures such as reviewing medications (beta-blockers, diuretics, and antidepressants) may lead to improvements in the patients' symptoms and quality of life. Recognising AD will help to identify those patients who are at increased risk of death, and may contribute to the consideration for LT.

The role of autonomic dysfunction in older people with CLD who fall remains to be seen. It seems likely that abnormal blood pressure responses to standing could contribute to falls in CLD and if so, represents a potential therapeutic and preventative target.

INTRODUCTION – PART FOUR

12. ORIGINAL HYPOTHESES

- Falls are common in older people with CLD
- Factors contributing to falls in older people with CLD include autonomic dysfunction, muscle abnormalities, gait and balance impairments and cognitive decline
- Fall related injuries are severe due poor protective mechanisms resulting from a transient loss of consciousness caused by autonomic dysfunction

13. AIMS

- To define the prevalence of falls and recurrent falls in older people with CLD
- To establish the prevalence of fall related injury in older people with CLD
- To identify modifiable factors associated with falling in older people with CLD

14. SECONDARY AIMS

- To determine if falls prevalence differs between specific CLDs
- To explore fall associations in specific CLDs to identify whether associations contribute to falls differently in different CLDs
- To define the prevalence of falls in a post-LT population
- To explore the effect of transplantation on falls
- To understand the relationship between falls and fall associations
- To identify potential barriers to uptake and adherence to a falls prevention/ intervention programme
- To produce evidence to support the design of a future falls prevention/ intervention programme

METHODS – PART ONE

15.1. BACKGROUND

The Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University in collaboration were awarded Biomedical Research Centre status in 2007. The National Institute for Health Research Biomedical Research Centre in Newcastle is one of 12 Biomedical Research Centres in the UK, but is unique in its specialist status of Ageing; the centre is composed of seven strands, one of which is Liver Disease in Ageing. The importance of such a theme has been described earlier in the introduction to this thesis.

One of the principle aims of the Liver Disease in Ageing Strand is to define the burden of liver disease and to establish therapeutic needs with the overarching aim of having direct benefits to patients. The work presented in this thesis addresses this aim in relation to falls and fall-related injury.

15.2. RESEARCH DESIGN

Although the Medical Research Council (MRC) came under criticism for being narrow and misconceived with it's framework for developing and evaluating complex interventions in 2000, it has stimulated and promoted discussion about research methodologies and helped researchers to contextualise their research [205, 206]. Context is crucial to understand whether a problem exists, the extent of that problem and whether the problem could be susceptible to intervention [207]. Context can be set through literature review, seeking expert opinion and undertaking epidemiological research. While the MRC updated its guidance in 2008 there was little reference to the 'contextualising phase' of research apart from the updated cyclical/non linear model of the research process. Although the linear model in the original framework was criticised for being too rigid with no feedback loops it is often useful to think of research in stages and the linear model assists understanding of the context of this thesis. Figure 7 attempts to explain how the work of this thesis fits into the service development and research setting, although it is important to recognise that the process is rarely linear and realistically would have many feedback loops. The top row of the Figure represents generic research stages; the middle row represents the stages involved in forming this thesis and the bottom row displays the 2 phases which will be used to present the findings.

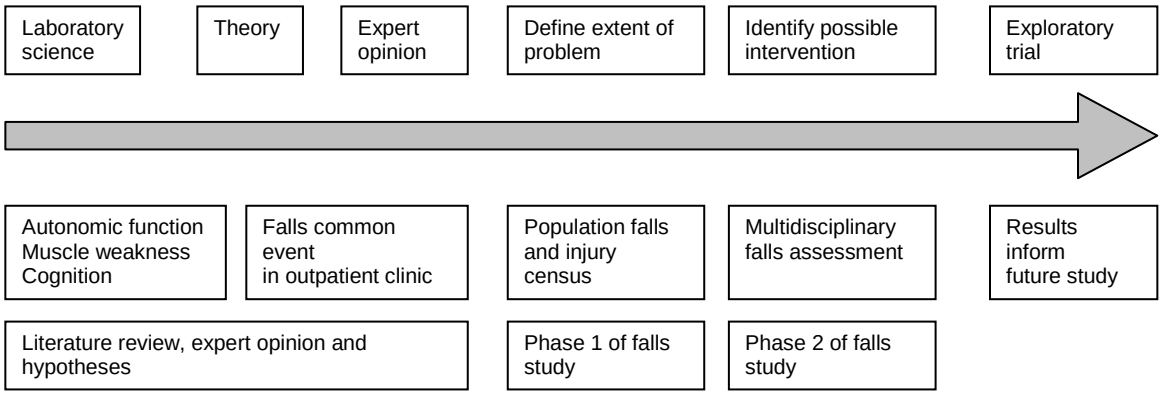


Figure 7. Diagram of the processes involved in designing and testing the hypotheses of this thesis.

The first stage of literature review, expert opinion and hypothesis generation is covered in the introduction of this thesis.

15.2.1. PHASE 1- DEFINING FALLS AND INJURY PREVALENCE

To define the extent of the problem of falls and fall related injury in CLD an epidemiological cross sectional approach was undertaken. The CLD population would be identified from the comprehensive databases of patients maintained by the Hepatobiliary department of Newcastle upon Tyne Hospitals NHS Trust. These databases provide an ideal method of data collection on a relatively large scale as they hold details on all existing cases.

In order to specifically define the problem in relation to older people with CLD the cohort was divided into 2 age groups, a younger age group (aged <65 years) and an older group (aged ≥65 years). Data collected from the over 65 years CLD group could then be age and sex matched to non-liver disease cases in an existing community control database, in which data concerning falls is stored. Further details are described below.

15.2.2. PHASE 2- MULTIDISCIPLINARY ASSESSMENT

Once the scale of the problem was defined, falls and injury associations could be explored in detail on multidisciplinary assessment in representative samples of the database populations.

15.3. ETHICAL APPROVAL

15.3.1. PHASE 1

Each of the CLD databases has approval from the Newcastle Upon Tyne Hospitals NHS Trust Caldicott Guardian. The Caldicott Principles were reviewed at outset and strictly adhered to during all stages of the study. The databases were interrogated for patient identifiable data only when absolutely necessary and on a strictly need to know basis. All participants who were contacted had provided prior, fully informed consent to be contacted regarding audit, service evaluation and research purposes.

The existing community control falls database contained no patient identifiable data and permission for the recruitment of this cohort and the data collection was granted by County Durham and Darlington Local Research Ethics Committee in April 2002.

15.3.2. PHASE 2

The study design was submitted to Newcastle and North Tyneside 1 Research Ethics Committee for consideration. Permission to perform the study was granted in the form of Service Development. The principles behind service development/evaluation allowed collection of data from individuals who would typically benefit from the existing service, where the service is typical of and unchanged from usual service delivery. The MDT assessments used in phase 2 of this study were based on best current practise and were performed in the Falls and Syncope Service of Newcastle upon Tyne Hospitals NHS Trust. In order to adhere to the ethical principles of service evaluation participants who underwent MDT assessment were typical of usual service users in that they had either fallen or had risk factors for falling. Data collected from the assessment could, ethically, be used for research as long as the data was anonymous, results from data analysis could not be used to identify individuals and the results could not cause harm or distress.

The service development was undertaken with participants aged over 18 years residing in the North East of England between December 2007 and December 2009.

15.4. SAMPLE SIZE

Using available databases, which have a total population size of 871, a response size of 267 would be required to establish the estimated population prevalence of falls with a 95% confidence level and a sampling error of ±5%.

Estimating that the prevalence of falls in the community control group would be similar to those in the published falls literature (~30%) and using a power level of 0.8 with an alpha of 0.05, to detect a difference of 10% between the controls and those with CLD aged ≥65 years would require sample sizes of 356. However, as there are 229 individuals aged ≥65 years in the full database population it would not be possible to reach this sample size. With identical power and alpha, to detect a difference of 20% would require a sample size of 93 in the CLD group aged over 65 years which was considered achievable as a response rate of 41% would be required.

15.5. IDENTIFYING COHORTS

Databases of prospectively diagnosed patients with CLD who attend the Newcastle upon Tyne Freeman Hospital liver outpatient clinics are continuously updated. When the databases were established existing cases were identified from the following sources: patient lists of Consultant Gastroenterologists practising in the area, the health authority hospital admission data, autoantibody records (for autoimmune cases of CLD) stored in the immunology laboratory and data from death certificates from the office of national statistics. Patients who met the diagnostic criteria, as described below, and who provided fully informed consent for their data to be stored, used for research and to be contacted regarding future studies are included. Data stored on the databases include contact details, date of birth, sex, medical history, drug history and results of investigations.

15.5.1. NON-ALCOHOLIC FATTY LIVER DISEASE

All patients who attend the outpatient liver clinic who meet the inclusion criteria are included on this existing database. To be eligible for a diagnosis of NAFLD, and therefore included in the database, patients had to have 1) elevated aminotransferases (either ALT or AST), 2) a liver biopsy which showed at least 10% of hepatocytes were steatosed, 3) exclusion of other liver diseases with clinical, biochemical, radiological or histological data, 4) a weekly alcohol intake of less than 140 g for females and less than 210 g in males (reported by patient, a close relative in most cases and measurement of random serum alcohol level).

In addition to the data described above the NAFLD database also includes BMI, insulin resistance level [graded with the homeostasis assessment index (HOMA) [208]], lipids and histological grade (steatosis, NASH or cirrhosis).

15.5.2. ALCOHOLIC LIVER DISEASE

All patients with ALD attending the outpatient liver clinic are included in this existing database, if eligible and consenting. Patients are eligible if they had consumed at least 80 g of alcohol per day for the previous 10 years and had had other causes of liver disease excluded on the basis of clinical, biochemical, radiological or histological data. Diagnosis was confirmed histologically in all patients.

15.5.3. PRIMARY BILIARY CIRRHOSIS

The existing PBC database comprises patients who reside within the postal codes NE1 to NE25 and who meet the inclusion criteria described here. The rationale behind this is that the geographical cohort enables descriptions based on a well defined population irrespective of hospital attendance, and thus a more accurate reflection of the population rather than hospital attendees. Patients on the PBC database are eligible for inclusion if they meet at least 2 out of the following recognised criteria: 1) evidence of a serum anti-mitochondrial antibody or PBC specific anti-nuclear antibody at a titre of ≥1:40 by immunofluorescence, 2) a cholestatic abnormality of LFTs, 3) compatible liver histology [209, 210].

15.5.4. PRIMARY SCLEROSING CHOLANGITIS

The existing PSC database is also defined geographically by the postal code NE1 to NE25 and includes individuals who have had a diagnosis confirmed by magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography and had confirmation of PSC on liver biopsy.

15.5.5. POST LIVER TRANSPLANTATION

Details of those liver transplant recipients who received their liver transplant, in Newcastle upon Tyne Hospitals NHS Trust, within the previous 5 years, for any reason, are stored in an existing database. As Newcastle Upon Tyne Hospitals NHS Trust is one of 5 centres which perform liver transplantation in the UK patients on this database includes individuals living anywhere within the UK.

15.5.6. CONTROLS

An existing database of community dwelling individuals who had previously undergone multidisciplinary falls assessment was used to identify controls. The participants were recruited from a single primary care provider in the North East of England, within the same postal code as the CLD databases. A computer-generated random sample of patients was identified from the primary care provider's patient list, and contacted via post. Those living in residential or nursing home were excluded prior to recruitment. Those who responded were offered a clinical assessment which included medical history drug history and falls history. The database was interrogated to identify and thereby exclude participants with a history of liver disease.

15.6. DATA COLLECTION

15.6.1. DEFINING THE PREVALENCE OF FALLS AND INJURY

In order to quantify the problem of falls in this novel service development programme a self-reporting falls and injury screening tool was posted out to the participants on the databases. Its purpose was to identify those who had not fallen in the previous year, a Non-Faller and those who had fallen, Fallers. Those who had fallen were then considered as either a Single-Faller (one fall in the previous year) or as a Recurrent-Faller (2 or more falls). Data concerning fall-related injury was also collected (soft tissue injury, attendance at Accident and Emergency, bone fractures and hospital admission, 32, page 219). A pre-paid return envelope was included alongside the postal tool, along with a letter explaining the purpose of the data collection.

This tool was used for the PBC, PSC and transplanted cohorts. This data was already available on the existing controls database. As response rates to postal data collection are notoriously low for ALD and NAFLD cohorts a different approach was used to collect falls and injury prevalence. All consecutive patients with ALD and NAFLD attending the liver outpatient clinics in June 2009 were asked to complete the falls and injury self-reporting tool while in the waiting room, irrespective of whether they had fallen or not.

15.6.2. MULTIDISCIPLINARY ASSESSMENT

All participants who attended for MDT assessment refrained from caffeine and nicotine to reduce possible effects on circulating, serum catecholamine levels and ate a light breakfast only [211]. All assessments took place in the morning to remove the influence of diurnal autonomic variation, in a

clinic which was kept at constant room temperature. Evaluation took approximately 75 minutes and is summarised in Figure 8. This is followed by a more detailed description of the assessments.

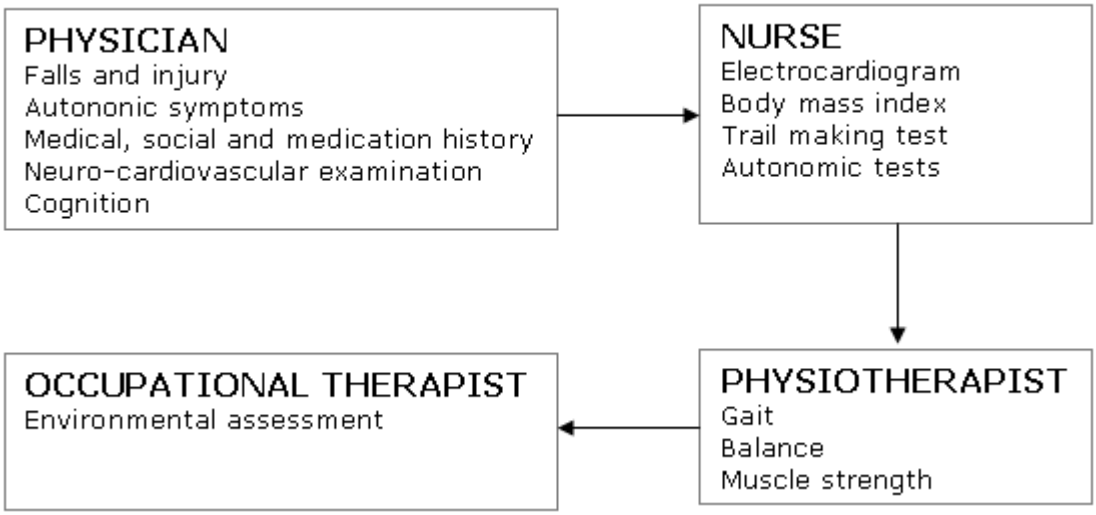


Figure 8. A schematic of the MDT assessment.

15.6.2.1 Medical Assessment

This included self-reported past medical history, systems review, autonomic symptom review, falls and injury review, social history, medication review and a neuro-cardiovascular examination which included visual acuity and a cognitive assessment. Vision was classed as normal or abnormal [cataracts, retinopathy, binocular acuity less than 6/9 (which is the local falls service trigger for further optical testing)]. Clinical records were examined for serum albumin, bilirubin, ALP and ALT levels. Participants with NAFLD, ALD and PSC were considered to have cirrhosis if there was evidence on biopsy. In PBC cirrhosis was considered if there was evidence on biopsy, or if biopsy had not been performed, it was considered if an individual had bilirubin over 18 μmol/L, albumin below 40 g/L, platelets below 222 $x10^9$ and spleen length over 12 cm on ultrasound [212].

Cognition was assessed with the cognitive component of the Cambridge Examination for Mental Disorders (CAMCOG) [213]. This sensitive, specific and comprehensive cognition scale is comprised of 11 subsections which make up the total CAMCOG score out of a possible 105. The sensitivity of this tool was particularly advantageous over other cognitive tools as the aim was not to screen for dementia but to detect small differences between individuals in order to accurately

identify differences between individuals. The sensitivity is particularly useful at discriminating between individuals who perform at the higher end of cognitive ability and is therefore useful, in the absence of a ceiling effect, in these populations where dementia was not expected to be a large occurrence [213].

The Orthostatic Grading Scale is a 10 item scale on which participants rate the severity of their dizziness, if any, from 0 (never experiences) to 4 (always experience severe dizziness) in various postural situations. It is fully validated against full physiological autonomic function testing [214].

15.6.2.2 Nursing Assessment

Participants' height, weight, BMI and the Trail Making Test [215] were recorded. A 12 lead ECG was performed (Philips Page Writer 300 PI) and reviewed by the Physician, to identify participants with arrhythmias which would preclude them from HRV analysis. The participant was then connected to the continuous ECG and beat-to-beat blood pressure monitoring equipment (Taskforce® Monitor 3040i, CN systems Medizintechnik GmbH, Graz, Austria) for analysis of the ANS.

Participants rested in the supine position, undisturbed, for 10 minutes whilst wearing the Taskforce® Monitor equipment. Following 10 minutes rest the participants were helped into a standing position where they remained for 3 minutes. Following the active stand a valsalva was performed. Detailed methodology concerning analysis of autonomic function is described below.

15.6.2.3 Physiotherapy Assessment

Muscle strength was assessed using a digital handheld dynamometer (TKK 5401 GRIP-D; Smedley, Takei, Tokyo, Japan). Participants were positioned in a straight-backed chair, shoulders adducted in a neutral position, arms unsupported and feet flat on the floor. The elbows were flexed at 90 degrees with the forearm in neutral position (neither prone nor supinated) and the wrist was dorsiflexed 0 to 30 degrees with 0 to 15 degrees of ulnar deviation. Once in the correct position, participants held the dynamometer in their dominant hand, and when instructed flexed their fingers to achieve maximal grip strength. The strongest grip of three attempts was recorded (unit of measurement kg), with a 15 second interval between each attempt.

Dynamic lower limb strength was also recorded using the Sit to Stand Test (STS). Participants sat in a standard clinic chair with no armrests and were asked to cross both arms across their chest.

Participants were then asked to stand up and sit down 5 times without the use of their arms; the length of time taken from first attempting to stand up until the final seated position was recorded. The Sit to Stand Test is predominantly a measure of lower limb strength, but it must be acknowledged that there will be some degree of sensory influence (for example proprioception and vestibular function) on the outcome. As this test is performed under time higher values (measured in seconds) indicate weaker lower limbs.

A timed walking test, the Timed Up and Go Test (TUG), was performed as gait speed is associated with falls. Participants began in a sitting position, with their back against a standard clinic chair, upper limbs placed on the arm rests and walking aid at hand, if required. Participants were then asked to stand up and walk at their usual pace to a mark on the floor 3 meters away, turn around, walk back and sit down [216]. This is performed twice so that the first attempt familiarises the participant with the procedure; the second attempt is scored. As the test is timed (in seconds) a longer value indicates a slower 'up and go' and is associated with an increased risk of falling [127].

The performance orientated assessment of mobility was performed by each participant [217]. This provides a measure of both gait and balance and has previously been shown to have sound levels of validity and reliability [218]. Nine gait manoeuvres are performed and scored 0 (abnormal) or 1 (normal) to give a total possible gait score of 9. The balance component is comprised of 13 manoeuvres, each of which is scored 0 (abnormal), 1 (adaptive) or 2 (normal), giving a total possible balance score of 26.

15.6.2.4 Occupational Therapy (OT) Assessment

As part of the novel, multidisciplinary service development programme participants also underwent an OT assessment. The resulting information gained from this will be presented in a separate thesis by the Occupational Therapist working in the Newcastle Biomedical Research Centre Liver Theme.

15.6.2.5 Symptom Assessment Tools

Falls Efficacy Scale International (FES-I) is a self-completed tool which quantifies an individual's concerns about falling while performing 16 different activities [219]. Participants rate their concern as 'not concerned at all' (scored 1) through to 'very concerned' (scored 4) giving a minimum score of 16 and maximum score of 64. One disadvantage of this tool is that it is not fully validated in younger individuals. However, no such tool for younger people exists. The FES-I is considered the

best available validated tool to assess fear of falling and is recommended by ProFaNE, a European falls prevention network [220].

The Patient Reported Outcome Measurement Information System- Health Assessment Questionnaire (PROMIS-HAQ) allows quantification of functional ability [221]. Individuals rate their ability to complete 20 different functional activities from 'completely' (scored 0) through to 'not at all' (scored 4). This tool is reliable, valid and sensitive to change [222]; it is particularly useful at identifying how disease impacts upon functional ability rather than quality of life in general. The advantage of exploring functional ability is that it highlights key areas of weakness which are modifiable, whereas quality of life measurement does not specifically identify modifiable targets.

15.6.3. AUTONOMIC FUNCTION TESTING

The MDT nurse, trained and experienced in the use of the Task Force® Monitor performed all cardiovascular assessments. Three electrodes (CNSystems Medizintechnik GmbH, accessory 01616) were attached to each individual; 1 on the anterior surface of the left shoulder, 1 on anterior surface of the right shoulder and 1 over the lower left thorax in the anterior axillary line, providing a 3 channel ECG. For continuous beat-to-beat BP recording the appropriate size "Flying-V" finger cuff and oscillometric BP cuff were selected. The appropriate finger cuff was then connected to the "Task Force® Vascular Unloading Monitor" and placed over 2 fingers, proximally, while the "Task Force® Vascular Unloading Monitor" was attached to the forearm using a Velcro fixing cuff. The oscillometric BP cuff was placed on the opposite upper arm.

ECG recordings were based on the bipolar principles of Einthoven with anti-drift to suppress/compensate electromagnetic noise. The manufacturer stated level of accuracy is ± 5 μV and is able to measure band width frequencies between 0.08 and 150 Hz. Oscillometric and continuous beat-to-beat BP recording has an accuracy of ± 5 mm Hg between 50 and 250 mm Hg.

Task Force® Monitor programme version 2.2 was used to record and analyse ECG and BP recordings. This provides a report for each individual detailing, for each intervention/time period, the mean heart rate [bpm (beat per minute)], mean systolic BP (sBP, mm Hg), mean diastolic BP (dBP, mm Hg), mean LFnu (low frequency normalised units, %), mean VLF (very low frequency, ms^2), mean LF (ms^2), mean HF (ms^2), mean power spectral density [PSD, ms^2), LFnu:HFnu, LF:HF, baro-receptor slope mean (ms/mm Hg) and BEI (%).

15.6.3.1 Heart Rate Variability

The Fast Fourier Transformation, performed by the Task Force® Monitor programme version 2.2, produces a measure of how variance distributes as a function of frequency rather than time [223]. This method separates the HR fluctuations into the LF, VLF and HF spectral bands, which together comprise PSD. Figure 9 displays this graphically using an example from an individual; the z axis relates to time with a 10 minute supine rest between 4 and 14 minutes. During this time the parasympathetic predominance can be seen as the large peaks (y axis) between 0.15 and 0.4 Hz (x axis). Following the rest period the individual stands upright at 15 minutes. The parasympathetic withdrawal and sympathetic activation can be seen as the peaks change from high to low frequency (0.04 to 0.15 Hz).

This method is not recommended for analysis of recordings lasting less than 5 minutes but is a justified method for the 10 minute recordings collected during the individuals' 10 minute supine rest [223]. In addition to providing the 3 frequency domains the Task Force® Monitor programme also provides normalised units of the LF and HF spectral components (LFnu and HFnu respectively). The normalised values provide a measure of the proportion that each domain contributes towards total PSD minus the contribution of VLF. Therefore normalised units provide a measure of the balance of the 2 arms of the ANS, particularly when expressed as a ratio (LFnu:HFnu).

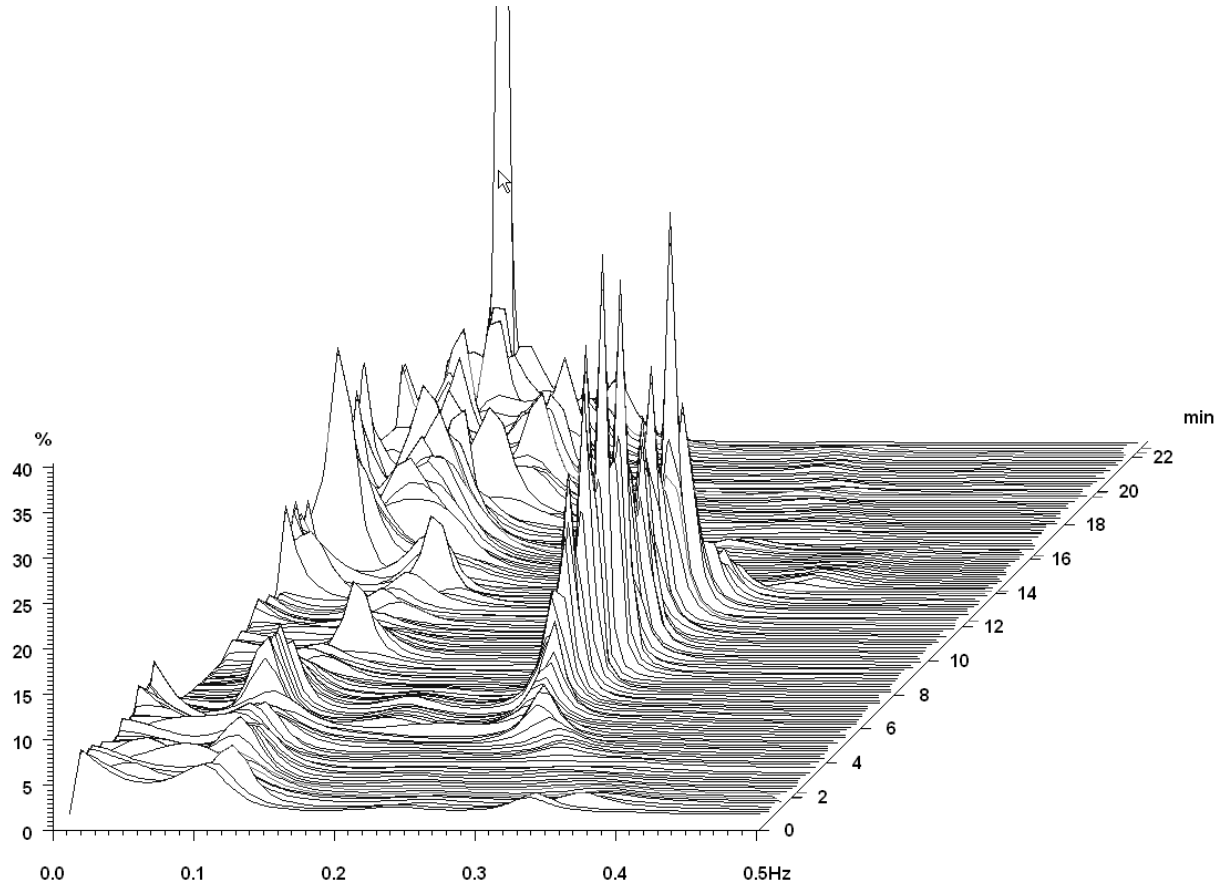


Figure 9. Spectral analysis of HRV.

15.6.3.2 Baro-reflex Sensitivity

Task Force® Monitor programme version 2.2 uses the sequence method to calculate a measure of BRS. This method identifies consecutive increases or decreases in sBP which occur in association with a prolonged RRI or shortened RRI for 3 or more beats. The gradients of the resulting sBP-RRI associations are calculated and a mean value is provided for the 10 minute supine rest and is referred to as the slope mean. In addition to the baro-receptor slope mean the baroreceptor effectiveness index (BEI) is calculated. This is the ratio of spontaneous sBP increases or decreases to the corresponding, appropriate changes in RRI and is a proportion (%) of how many times the baro-reflex is effective [224].

15.6.3.3 Active Standing

An orthostatic challenge can provide both a measure of the sympathetic and parasympathetic nervous system. The degree to which sBP or dBP drops on standing is a measure of the sympathetic nervous system; international consensus defines an abnormal BP response to standing as a sBP drop of ≥20 mm Hg or a dBP drop of ≥10 mm Hg; if either of these criteria are met a diagnosis of OH can be made [179]. However, these strict criteria do not take into account prolonged smaller drops in BP. For example, an asymptomatic 5 second sBP drop of 22 mm Hg could be considered an abnormal response to standing but a symptomatic 60 second sBP drop of 15 mm Hg with a prolonged recovery could be, strictly, considered as a normal response. For this reason, in place of a formal diagnosis of OH, the area under the curve (AUC) has been determined. This is calculated in software developed by the medical physics department of Newcastle upon Tyne Hospitals NHS Trust and is demonstrated in Figure 10: The dotted horizontal line represents the baseline sBP and is based on the stable sBP values at the end of the supine rest period. The dotted vertical line indicates the point of standing erect from the supine position, this coincides with a drop in sBP which reaches it's nadir at the horizontal dashed line. The vertical dashed line is the moment when sBP returns to baseline. From this the AUC can be calculated and is represented by the shaded area.

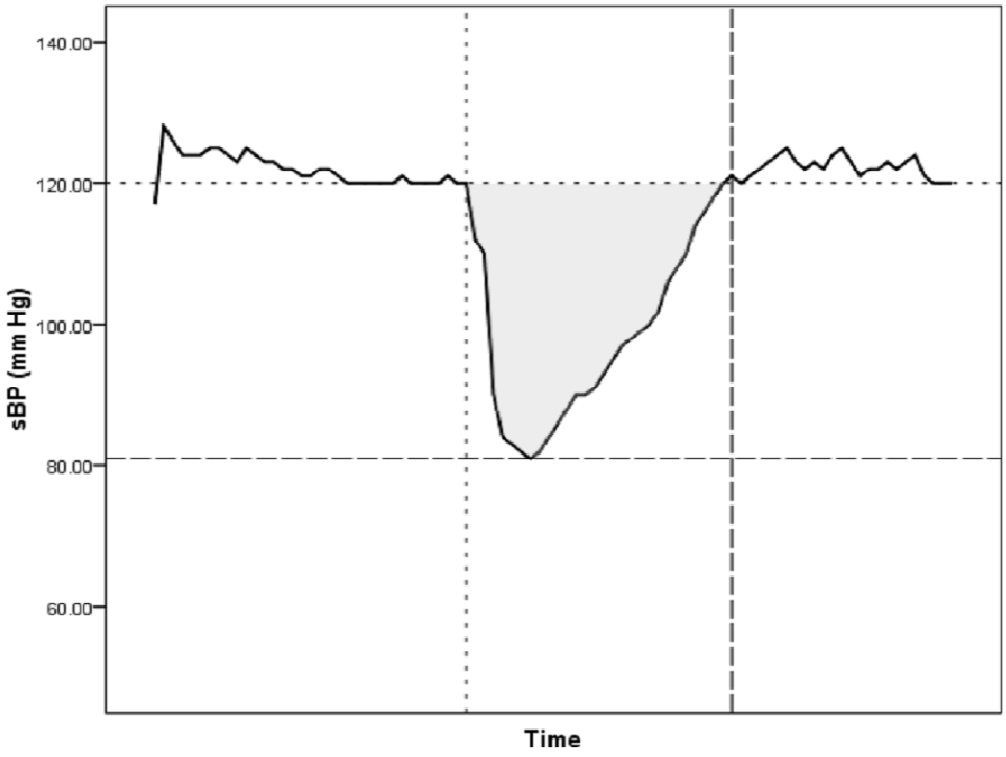


Figure 10. The AUC of sBP upon standing.

A measure of dynamic, parasympathetic activity during active standing is the 30:15 ratio. This is the ratio of the longest RRI around the 30th beat to the shortest RRI around the 15th QRS complex immediately on standing with smaller ratios considered as abnormal. In a normally functioning ANS there would be parasympathetic (vagal) withdrawal on standing resulting in an unopposed sympathetic drive to increase the HR followed by a return in parasympathetic activity and a slowing of the HR, this is similar to the response seen in Figure 9, the difference being that Figure 9 is based on frequency domain analysis whereas the 30:15 ratio is based on time analysis.

15.6.3.4 Valsalva

Following the active standing the participant sat on the edge of the bed quietly for 2 minutes to regain cardiovascular stability. The valsalva was clearly explained to the participants to optimise good technique. The plunger of a 10 ml syringe was discarded and the syringe tube was pierced with a pin so that the circuit was not fully closed. The circuit was created by connecting the tip of the syringe to an aneroid sphygmomanometer (manual, dial display, non-mercury) via plastic tubing. The sphygmomanometer provided a visual display to guide the nurse/physician and

participant to maintain a constant expiratory pressure of 40 mm Hg. Participants placed the 'open plunger-end' into their mouth and were asked to form a strong seal with their lips, they then blew into the syringe for 15 seconds while watching the sphygmomanometer display and were encouraged by the nurse/physician if pressure deviated from 40 mmHg. Two attempts were made with a 2 minute quiet rest between each attempt to regain cardiovascular stability; the 2 attempts were reviewed on the basis of participant effort/technique and visually on the Task Force® Monitor programme, if they were considered poor then a 3rd attempt was made. A normal cardiovascular response to valsalva includes a sympathetically driven BP overshoot on release of the strain and an appropriate increase in heart rate followed by a decrease in heart rate (parasympathetic).

15.7. DATA ANALYSIS

All data analysis was performed using Statistical Package for Social Sciences (SPPS) version 17. To classify distribution of data as normal or non-parametric histograms were plotted and interpreted alongside the Kolmogorov-Smironov normality test. Where data is considered as normally distributed it is summarised with mean and standard deviation (SD) whereas non-parametric data is described as median with the minimum and maximum.

Relationships between 2 categorical variables were assessed by performing the chi-square test. If 20% or more of the expected frequencies of the categorical variables were less than 5 then Fisher's exact test (FET) was performed. Chi-square is reported with its statistic alongside the degrees of freedom and significance level [χ^2 (df), p]. For 2 sets of related categorical data McNemar's test was used to examine marginal homogeneity; to identify changes in a dichotomous, categorical response.

To compare the location between 2 non-parametrically distributed samples the Mann-Whitney test was used and is described with the Mann Whitney U and z statistics alongside the significance value. As the Mann-Whitney test is not well powered for small sample sizes the Kolmogorov-Smirnov Z test was used when comparing 2 non-parametric data sets with numbers less than 25 per group.

Where multiple comparisons were made between non-parametric data sets the Kruskal-Wallis test was performed, the result of this is displayed with the Kruskal-Wallis statistic (H), degrees of freedom and significance level.

Non-parametric associations are described using the Spearman rho (r_s) alongside a significance value.

Negative binominal regression was performed when the dependent variable was count data (for example number of falls) and the distribution of the count was highly skewed to the right (Figure 11). The negative binominal model is more accurate than a multiple linear regression model when the variance of the dependent variable is greater than the mean, taking into account large numbers of zero counts and the possibility of recurrent episodes (for example recurrent falls) [225]. The model fit will be described with the likelihood ratio χ^2, degrees of freedom and p value. The model will be tabulated with the unstandardised beta coefficient (b), standard error (SE), odds ratio (OR) with the 95% confidence intervals (CI) and p.

To identify variables which are independent predictors of a dichotomous, categorical, dependent variable binary logistic regression was performed. Assumptions which were verified were multicollinearity of the independent variables and linearity of the continuous independent variables with the natural log of the dependent variable. Independent variables violating these assumptions were excluded from the model. The goodness of fit of the model is described with Cox's R^2, the -2 log-likelihood and its associated χ^2 statistic and significance value (a χ^2 statistic below 0.05 indicates that the model is a significant fit of the data). The regression coefficient (b), standard error (SE) the significance level (p), the odds ratio (OR) and the 95% confidence intervals are tabulated.

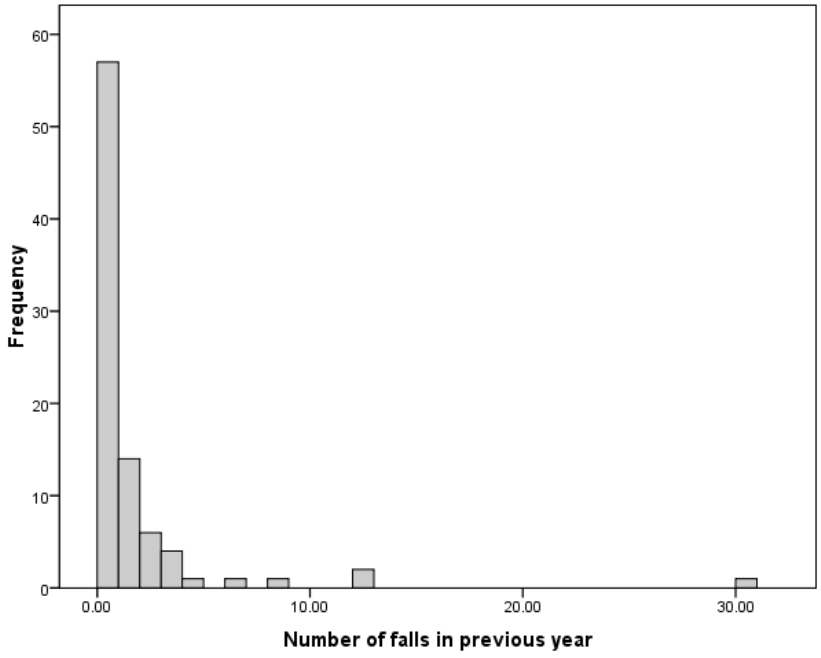


Figure 11. The typical distribution of fall count data distribution.

METHODS – PART TWO

16.1. PHASE 1 RECRUITMENT

The process of Phase 1 recruitment is displayed in Figure 12. A number of individuals who are included on the databases had previously expressed a wish not to be contacted for research, service evaluation or teaching and as such were excluded. The remaining individuals from the PBC and PSC databases were contacted via post as described in section 15.6.1, page 47. The NAFLD and ALD individuals were recruited from the clinic and the rationale for this was detailed in section 15.6.1, page 47. The LT cohort were considered separately as it may be considered that those post-LT no longer have CLD.

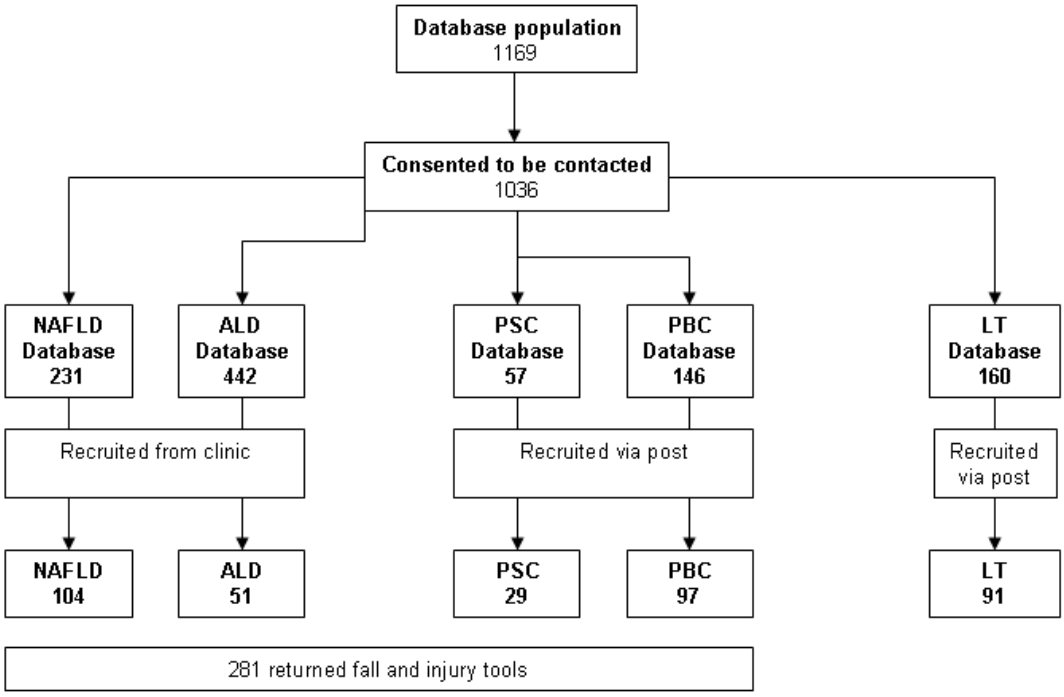


Figure 12. Flow chart of the Phase 1 recruitment.

The response rates (which is the number of completed data collection tools expressed as a percentage of the number of individuals in the corresponding database) for each cohort are displayed in Figure 13, bearing in mind the differing methods of recruitment.

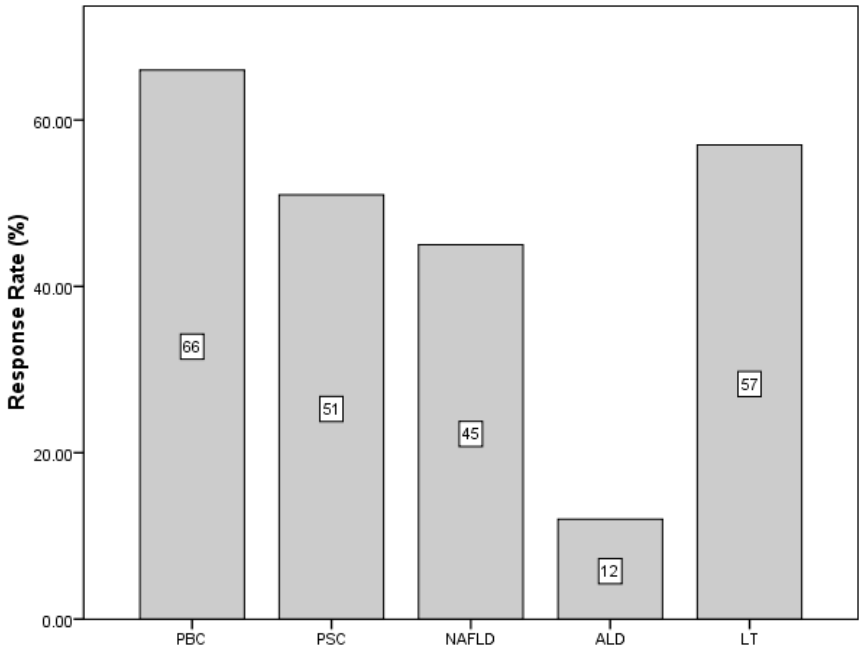


Figure 13. Response rate of the Phase 1 cohorts.

The final Phase 1 cohort, which consisted of 281 individuals was composed of 4 CLDs. The proportion that each disease contributed to the cohort is displayed in Figure 14.

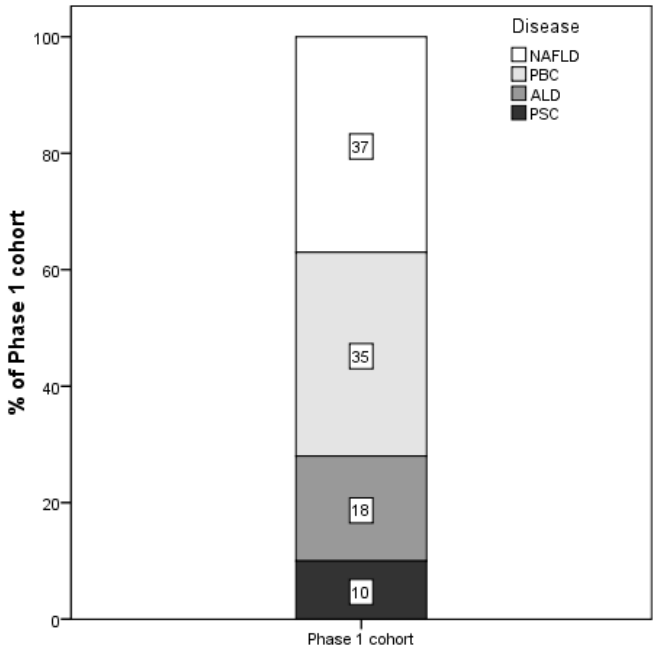


Figure 14. The composition of the Phase 1 cohort.

In an attempt to analyse whether the responders were representative of the populations they were compared to the demographic data of those who did not respond. The results are displayed in Table 4. In general, those who responded were similar to those who did not. The exceptions were a slighty lower albumin in those who responded with NAFLD and a lower age of those with PBC who responded.

	Demographics	Responders	Non-responders	Significance (*U, Z, p)*
NAFLD	Age [years]	59 (19-79)	60 (19-85)	8872, -0.732, 0.464
	Female	55	40	5.833 (1), 0.016
	Albumin [g/L]	44 (35-50)	45 (31-54)	7794, -2.115, 0.041
	Bilirubin [μmol/L]	9 (3-37)	10 (1-107)	8009, -1.785, 0.074
	ALP [U/L]	92 (11-246)	91 (39-468)	8822, -0.545, 0.586
	ALT [U/L]	56 (15-267)	60 (13-504)	8668, -0.778, 0.436
ALD	Age	58 (31-83)	58 (19-77)	3510, -0.027, 0.978
	Female	14	230	0.012 (1), 0.913
	Albumin	38 (29-46)	38 (20-49)	1152, -0.333, 0.74
	Bilirubin	14 (8-79)	15 (4-316)	1151, -0.163, 0.871
	ALP	95 (40-300)	91 (47-392)	2021, -1.828, 0.068
	ALT	39 (11-248)	39 (11-3210)	1599, -3.529, <0.001
PBC	Age	68 (40-95)	73 (42-95)	1463, -2.186, 0.029
	Female	94	93	0.036 (1), 0.85
	Albumin	41 (26-49)	42 (29-47)	746, -0.083, 0.934
	Bilirubin	9 (4-75)	8 (4-49)	670, -0.026, 0.979
	ALP	148 (48-1033)	124 (69-1149)	750, -0.039, 0.969
	ALT	34 (10-220)	29 (10-148)	706, -0.47, 0.639
PSC	Age	59 (27-80)	53 (29-64)	574, -0.781, 0.435
	Female	33	15	2.798 (1), 0.094
	Albumin	42 (30-51)	41 (30-46)	156, -0.641, 0.521
	Bilirubin	12 (7-67)	12 (6-40)	171, -0.365, 0.715
	ALP	161 (60-981)	190 (90-759)	175, -0.26, 0.795
	ALT	41 (11-189)	59 (24-206)	116, -1.794, 0.073

Table 4 continues…

	Demographics	Responders	Non-responders	Significance (*U, Z, p)*
LT	Age	60 (27-79)	52 (20-74)	1761, -4.612, <0.001
	Female	41	42	0.049 (1), 0.825
	Albumin	43 (30-50)	43 (21-48)	1371, -0.242, 0.809
	Bilirubin	9 (3-46)	9 (2-32)	1393, -0.31, 0.757
	ALP	110 (50-799)	111 (48-919)	1404, -0.244, 0.807
	ALT	27 (8-235)	23 (7-123)	1339, -0.624, 0.533

Statistics are calculated with Mann-Whitney *U* with the exception of Female, in which case the χ^2 (df) was used

Table 4. Representativeness of the Phase 1 CLD cohorts.

16.1.1. MATCHING

The CLD participants were divided into the 2 age groups resulting in 143 (38%) participants in the ≥65 years group and 229 (62%) in the <65 years group. Each of the participants in the ≥65 years group was matched for identical age and gender to a participant in the Community Control group. Once those who had sustained a fall had been identified they were then age and sex matched to an individual who had fallen in the community control group in order to compare injury prevalence in matched cases.

16.2. PHASE 2 RECRUITMENT

As part of Phase 1 recruitment individuals were able to express an interest in undergoing a MDT assessment. From the 281 respondents 107 indicated they would be willing to be contacted to discuss the assessment. This process is summarised in Figure 15.

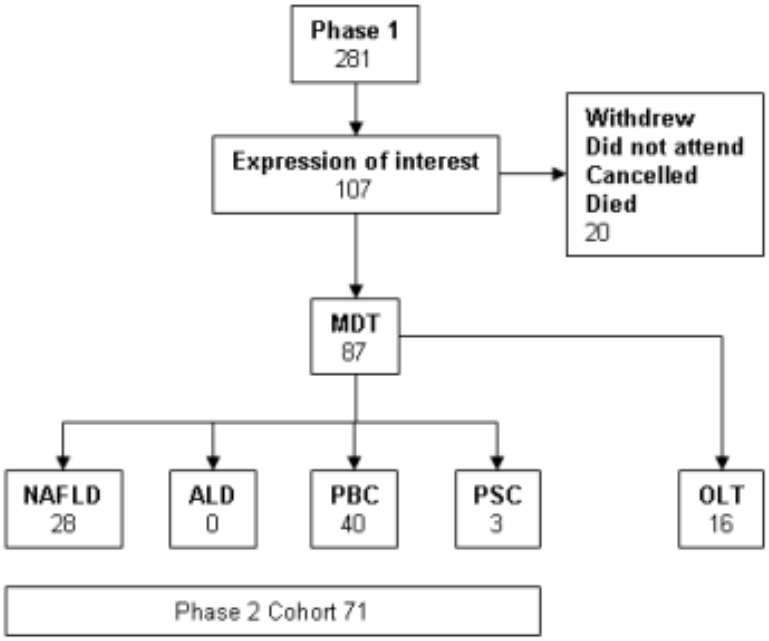


Figure 15. Phase 2 recruitment.

The differences between the Phase 1 and Phase 2 cohorts are described below (Table 5) in order to consider the representativeness of the Phase 2 cohort. Liver disease severity was similar between the cohorts with the exception of age, in which case the Phase 2 cohort was significantly older. This difference was considered when performing statistical analyses and where appropriate age was controlled for.

	Phase 1 Cohort	**Phase 2 Cohort**	***U, z, p***
Age [years]	60 (19-95)	66 (31-81)	13117, -3.281, 0.001
Albumin [g/L]	42 (26-51)	43 (29-51)	11837, -1.274, 0.203
Bilirubin [µmol/L]	10 (3-75)	9 (4-44)	11769, -1.048, 0.294
ALP [U/L]	108 (11-1033)	114 (39-477)	12800, -0.372, 0.71
ALT [U/L]	38 (8-267)	41 (10-357)	12762, -0.412, 0.68
Cirrhosis (%)	63 (17)	8 (9)	*χ^2 (1), 0.088*

Table 5. Representativeness of the Phase 2 cohort.

Although there were no exclusion criteria for the recruitment of the Phase 2 participants it is notable that no participant within the Phase 2 cohort was encephalopathic. Medical history and/or clinical notes were reviewed and in all cases no individual had had a history of HE. In addition, at the time of MDT assessment no individual displayed clinical feature suggestive of encephalopathy, which alongside the result of the Trail Test [median total 121 seconds (49-424), allowed confidence in excluding clinical HE.

RESULTS - PART ONE

17.1. CHAPTER AIMS

- To define falls prevalence in older people with CLD
- To establish the prevalence of fall related injury in older people with CLD
- To explore factors associated with falling in older people with CLD

17.2. INTRODUCTION

This chapter concerns CLD as a whole and is divided into the younger and older age groups in order to address the main objective, falls in older people with CLD. In addition to the younger CLD group the Community Control group is used for comparison.

Table 6 describes each cohort in terms of demographic data and liver disease severity. Individuals in the older CLD group are matched for age (± 0 years) and sex to individuals in the Community Control group (with the exception of the oldest CLD participants who was 4 years older than the eldest community control).

	CLD <65 years (*n* 169)	**CLD ≥65 years (*n* 111)**	**Community controls (*n* 111)**	**Differences**
Age [years]	55 (19-64)	72 (65-95)	72 (65-91)	
Female (%)	83 (49)	82 (74)	82 (74)	χ^2 (2) 25.288, <0.001
Diabetic (%)	83 (49)	23 (21)	8 (7)	χ^2 (2) 62.298, <0.001
Albumin [g/L]	43 (26-50)	41 (28-47)	43 (36-49)	*H* (2) 18.563, <0.001
Bilirubin [μmol/L]	12 (4-75)	10 (4-68)	7 (2-24)	*H* (2) 30.941, <0.001
ALP [U/L]	104 (11-1033)	129 (57-879)	74 (45-142)	*H* (2) 67.723, <0.001
ALT [U/L]	51 (12-267)	34 (10-204)	19 (9-45)	*H* (2) 115.855, <0.001
Cirrhosis (%)	63 (37)	24 (22)	0	χ^2 (2) 53.853, <0.001

Table 6. CLD. Demographic details.

17.3. FALLS PREVALENCE

The greatest proportion of Fallers was seen in the older CLD group, this group also demonstrated the greatest proportion of Recurrent-Fallers. The proportion of Fallers in the older CLD group was significantly greater than in both the younger CLD group [χ^2 (1) 9.927, p 0.002] and in the Community Control group [χ^2 (1) 4.22, p 0.04]. The same observation is also true when comparing the proportion of Non-, Single- and Recurrent-Fallers in the older CLD group to the younger CLD group [χ^2 (2) 11.523, p 0.003] but not when comparing the older CLD group to the Community Control group [χ^2 (2) 4.417, p 0.110]. These differences can be seen in Figure 16.

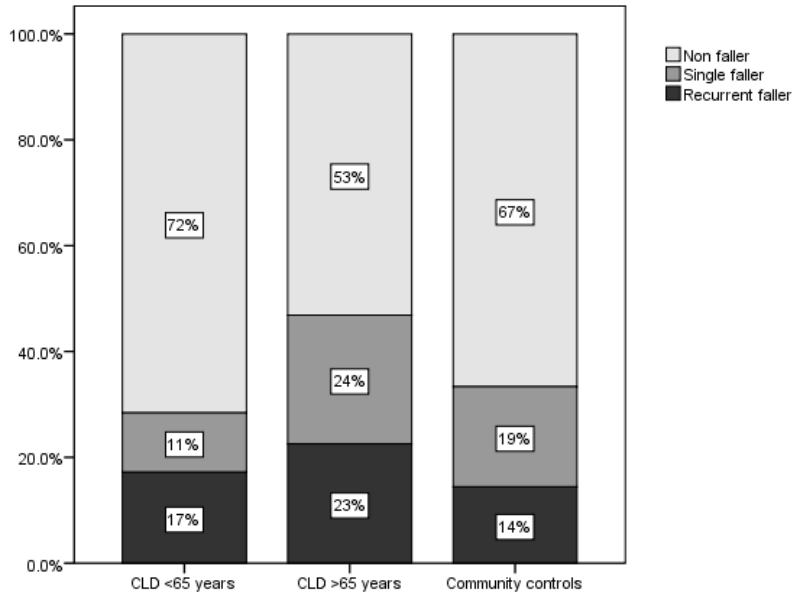


Figure 16. CLD. Falls prevalence.

While this data suggests that falls are very common in older people with CLD (47% fallen in the previous year), it also suggests that recurrent falls are also common. In order to explore this further the number of falls in those who had fallen was compared between the cohorts. There was no significant difference across the groups with similar number of falls [CLD <65 years median 2 (1-52), CLD >65 years 1 (1-10) and Community controls 1 (1-50), H (2) 3.607, p 0.165], Figure 17.

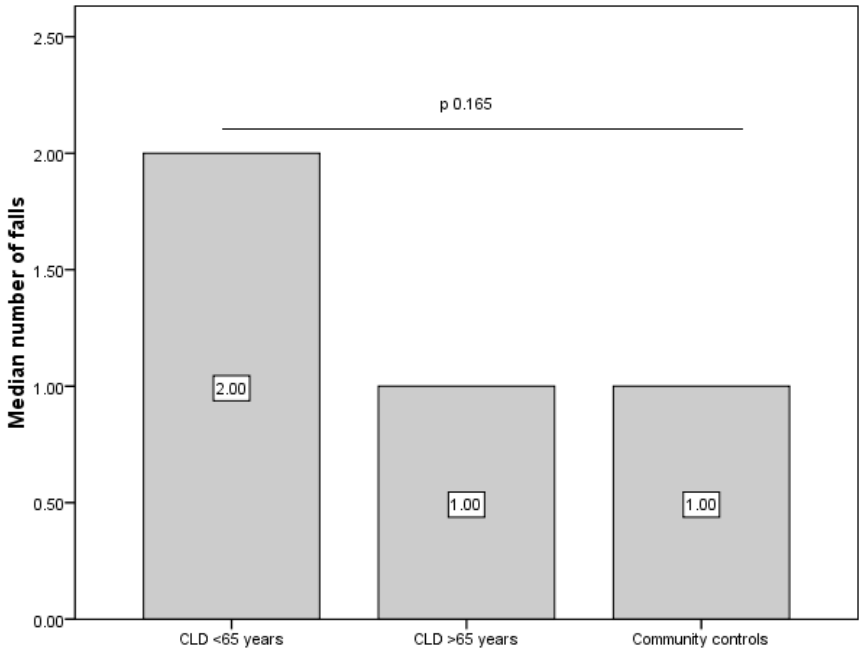


Figure 17. CLD. The number of falls experienced by Fallers.

17.4. INJURY PREVALENCE

Individuals in the older CLD group who had fallen were then matched to a community control who had fallen. Individuals were matched for age (± 1 year) and sex with the exception of the eldest CLD Faller who was 9 years older than the eldest control and was therefore excluded from analysis.

Given the high prevalence of falls in the previous year it could be expected that the older CLD group would sustain more injuries. Indeed, the more serious injuries of fractures and admission to hospital were more common in the older CLD group, but not significantly so (Figure 18,Table 7). Unexpectedly the frequency of soft tissue injury was significantly more common in the Community Controls. However some consideration must be given to the limited numbers and the impact that this has upon statistical analysis.

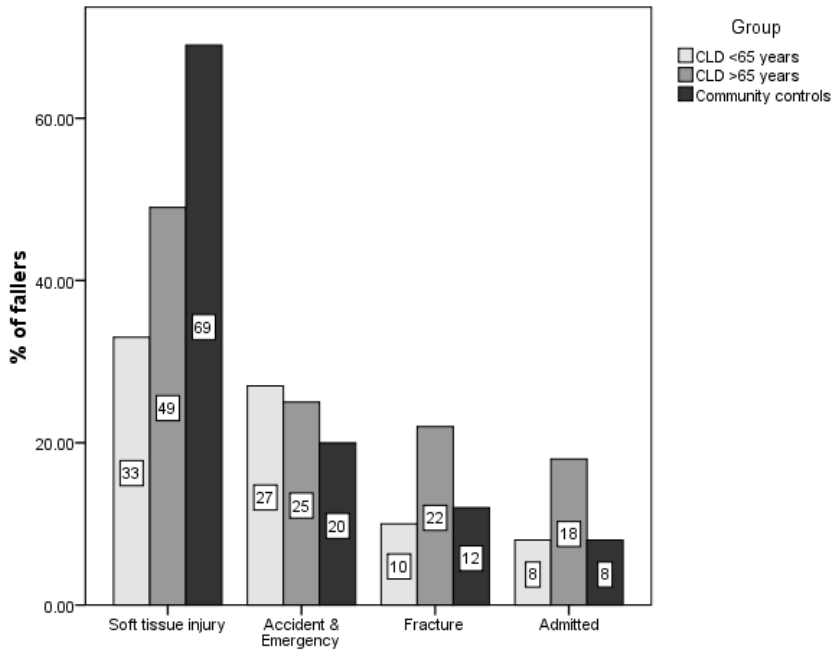


Figure 18. CLD. Fall related injury prevalence.

	CLD <65 years (*n* 48)	**CLD >65 years (*n* 51)**	**Community controls (*n* 51)**	**χ^2 (df), *p***
Any injury	22	27	36	0.5 (1), 0.48[A] 3.363 (1), 0.067[B]
Soft tissue injury	16	25	35	2.508 (1), 0.113[A] 4.048 (1), 0.044[B]
Accident and Emergency	13	13	10	0.032 (1), 0.857[A] 0.505 (1), 0.477[B]
Fracture	5	11	6	2.27 (1), 0.132[A] 1.765 (1), 0.184[B]
Admitted	4	9	4	1.88 (1), 0.17[A] 2.204 (1), 0.138[B]

A= CLD<65 years versus CLD>65 years, B= CLD>65 years versus Community Controls

Table 7. CLD. Fall related injury.

17.5. FALL ASSOCIATIONS

Identifying modifiable factors which were associated with falling was particularly important once it became established that falls were a common event in the older CLD group. As age and markers of liver disease (albumin, bilirubin, ALP, ALT) were available in the Phase 1 cohort these associations were explored first. The remaining associations were explored with the comprehensive MDT assessment data. Non significant correlations are displayed in Appendix B.1, page 220.

17.5.1. PHASE 1- ASSOCIATION WITH AGE AND DISEASE SEVERITY

There was a significant difference in age between Fallers and Non-Fallers when analysing the Phase 1 cohort as whole [66 (19-95) and 60 (19-91), U 7090.5, z -2.942, p 0.003], Figure 19, and this difference was also demonstrated through correlation analysis with number of falls (r_s 0.154, p 0.01). It was interesting to demonstrate that there was no association between number of falls and albumin, bilirubin, ALP or ALT. Consistent with this finding there was no difference in the number of falls between those with cirrhosis [0 (0-12)] and those without cirrhosis [0 (0-52), U 3470.5, z -1.175, p 0.241].

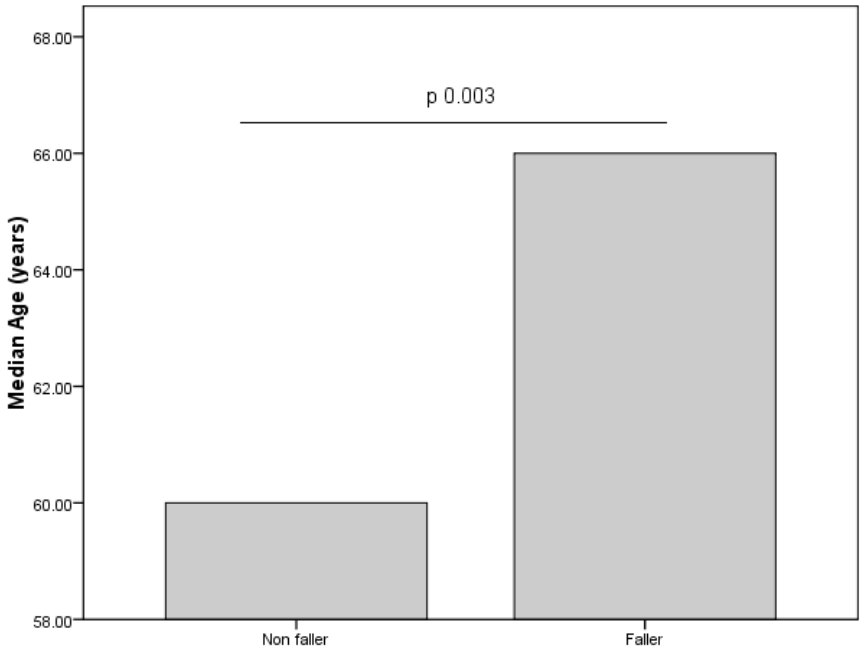


Figure 19. CLD. The Fallers were significantly older than the Non-Fallers.

17.5.2. PHASE 2- MDT ASSOCIATIONS

Data from the MDT assessments were analysed including all ages. All ages were included in order to maximise sample size. However, as a significant association was demonstrated between age and number of falls, age would be adjusted for in further analyses. There were 71 participants in the MDT cohort: Twenty-one (30%) were diabetic, 43 (61%) were on antihypertensive medication, 8 (11%) were cirrhotic, 30 (42%) had abnormal vision and 9 (13%) were being treated for osteoporosis.

The results from the physician assessment which included medical history, medications and vision were as follows. There was a significant difference in the number of falls between diabetics and non diabetics [0 (0-12) and 0 (0-8), *U* 381.5, z -2.215, *p* 0.024, Figure 20]. Between those taking or not taking antihypertensives there was no significant difference in the number of falls [0 (0-12) and 0 (0-8), *U* 468, *z* -1.931, *p* 0.054] although this difference did approach significance. Falls were no more prevalent in those with normal vision compared to those with abnormal vision [0 (0-8) and 0 (0-12), *U* 517.5, *z* -1.39, *p* 0.167], nor were falls more common in those with osteoporosis [0 (0-1)] compared to those without [0 (0-12), *z* 0.638, *p* 0.272].

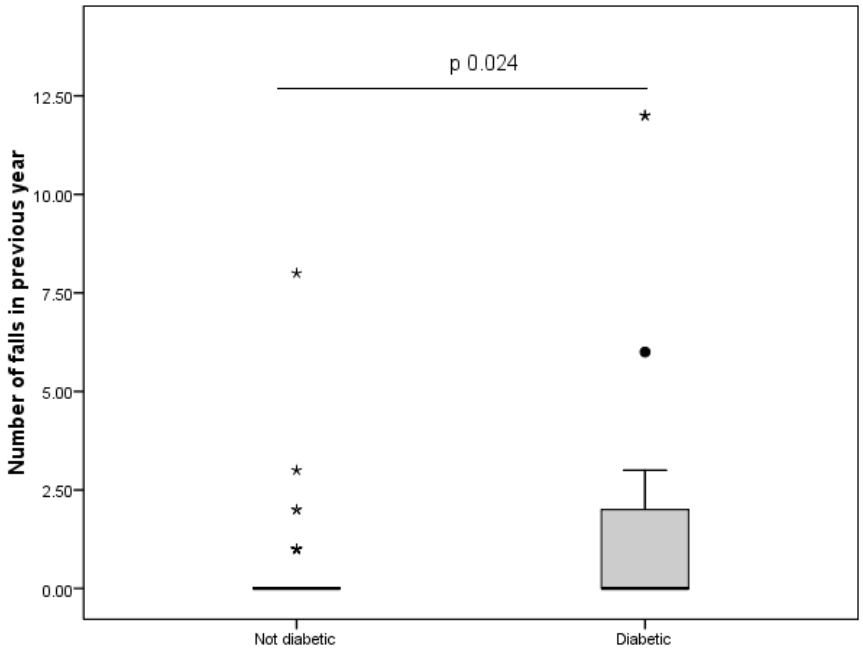


Figure 20. CLD. Falls in Diabetics.

On autonomic assessment it was interesting to find that symptoms of postural dizziness were associated with number of falls in the previous year (Table 8) whereas all other autonomic measures showed no association. The physiotherapy assessment revealed several measures which were associated with falling (Table 8).

	Variables	r_s p
Autonomic assessment	Orthostatic Grading Scale	0.25 0.042
Physiotherapy assessment	Sit to Stand Test	0.379 0.001
	Timed Up and Go	0.336 0.004
	Balance	-0.251 0.035
	Gait	-0.303 0.01
	Fear of falling	0.536 <0.001

Table 8. CLD. Phase 2 correlations with the number of falls.

Two regression models were analysed to identify independent associations with falling. Firstly, binary logistic regression which has a dependent variable of fall or no fall and secondly negative binomial regression which is a form of linear regression more appropriate when analysing data which have a high frequency of negative counts.

Binary logistic regression was performed to identify factors which were independently associated with whether a participant had fallen in the previous year or not. Variables included in the model are shown in Table 9 which displays the model parameters. The variables which remained in the model did not violate the assumptions of binary logistic regression. The 4 residual cases were not removed from the model as they did not exhibit any extreme results which could potentially affect

the model. The final model, which had a poor overall fit, is displayed in Table 9, with the ORs and 95%CIs in Figure 21.

Variable	***b***	**SE**	**OR**	**95% confidence interval (OR)**		***p***
				Lower bound	**Upper bound**	
Constant	-14.296	7.973	0			0.073
Age	0.015	0.044	1.015	0.932	1.106	0.73
OGS	-0.04	0.148	0.961	0.719	1.284	0.786
Diabetes	0.366	1.049	1.441	0.185	11.257	0.727
STS	0.22	0.103	1.246	1.018	1.526	0.033
TUG	-0.215	0.224	0.806	0.52	1.251	0.337
Balance	0.309	0.245	1.362	0.843	2.199	0.207
Gait	-0.211	0.402	0.81	0.368	1.782	0.6
FES-I	0.145	0.06	1.156	1.029	1.299	0.015

R^2 0.356 (Cox), Hosmer & Lemeshaw χ^2 (8) 5.895, p 0.659

Table 9. CLD. Binary logistic regression model for Faller or Non-Faller.

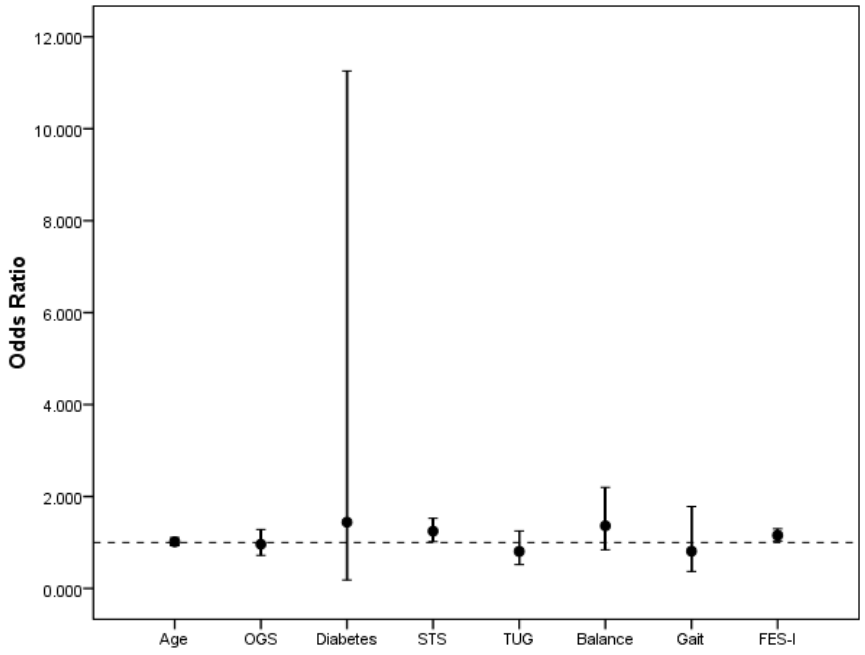


Figure 21. CLD. The 95% CI for the ORs derived from the binary logistic regression model.

Table 9 and Figure 21 show that Sit to Stand time (STS, lower limb strength) and fear of falling (FES-I) were statistically independent associations with the binary outcome. The model corrects for age and diabetes which were found not to be independent associations. This result has important implications as both lower limb strength and fear of falling are modifiable.

Negative binomial regression was performed to identify factors associated with the number of falls in the previous year. No cases were excluded due to undue influence or being significant outliers and the variables met regression analysis assumptions. The model is displayed in Table 10 and Figure 22.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-13.172	4.536	1.903	2.619	0.014	0.004
Age	0.007	0.024	1.007	0.96	1.057	0.761
Diabetes	-0.302	0.726	0.74	0.178	3.068	0.678
OGS	0.169	0.085	1.185	1.002	1.4	0.047
STS	0.157	0.061	1.17	1.039	1.318	0.01
TUG	-0.085	-0.356	0.919	0.701	1.205	0.54
Balance	0.187	-0.102	1.206	0.903	1.611	0.205
Gait	0.359	-0.228	1.432	0.796	2.577	0.231
FES-I	0.073	0.007	1.075	1.007	1.148	0.03

Model likelihood ratio χ^2 (8) 46.713, p <0.001

Table 10. CLD. Negative binomial regression model for number of falls.

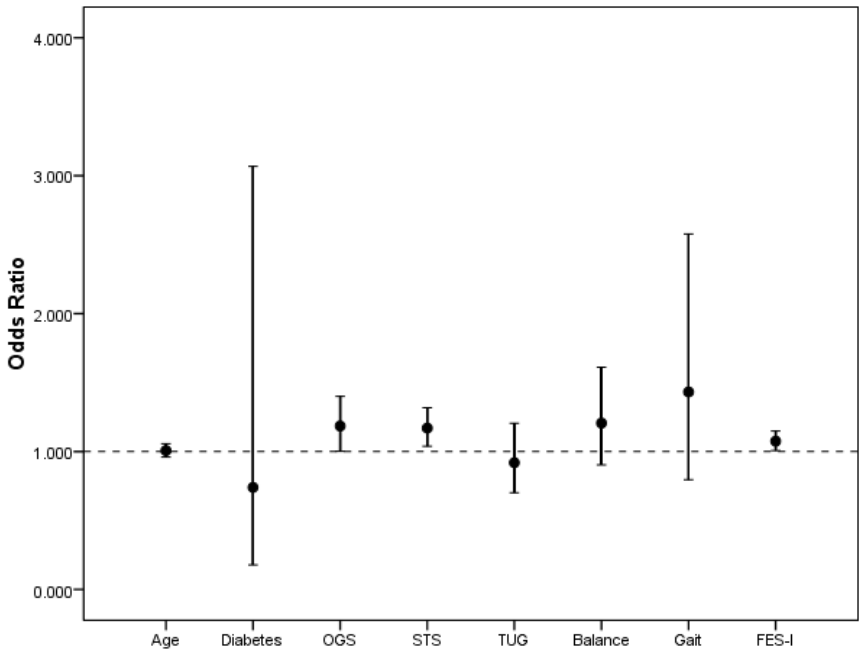


Figure 22. CLD. The 95% CI for the ORs derived from the negative binomial regression model.

The model is a significant fit of the data and demonstrates several significant and independent associations which exist independently of age and diabetes. These were orthostatic symptoms, lower limb strength/function and fear of falling.

17.6. FALLS AND FUNCTIONAL ABILITY

As physical injury is not the only significant consequence of falling, quality of life was estimated. Functional ability was assessed in the older CLD Phase 1 cohort using the PROMIS-HAQ tool.

The number of falls in the previous year was strongly related to functional ability (r_s 0.303, p 0.008) such that increasing number of falls correlated with increasing difficulty. Dividing the cohort into Recurrent-Fallers, Single-Fallers and those who had not fallen in the previous year there was a significant difference in functional ability [Non-fallers 3.75 (0-75), Single-Fallers 7.5 (0-43.75) and Recurrent-Fallers 46.88 (0-72.5), H (2) 7.345, p 0.025 (Figure 23)].

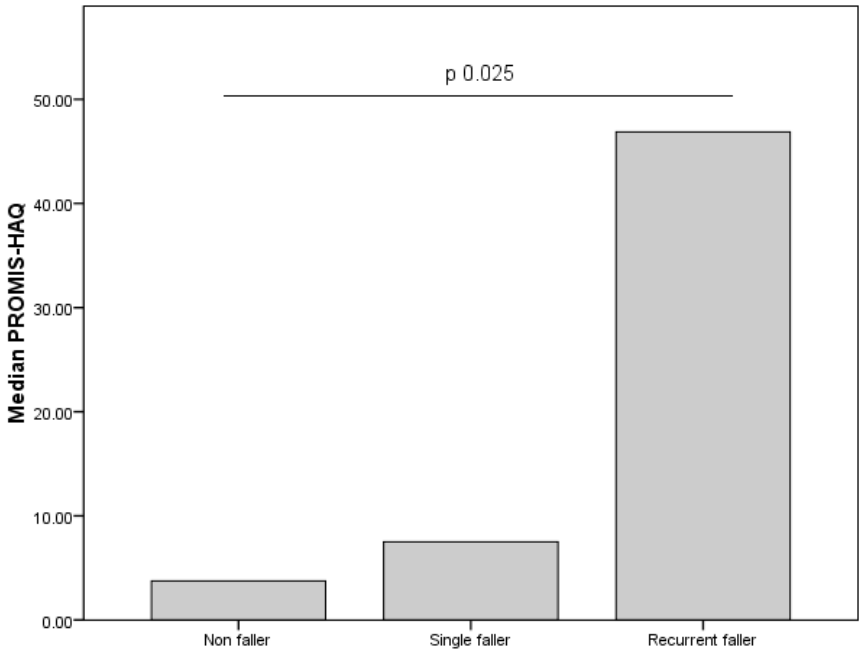


Figure 23. CLD. Functional difficulty and falls.

17.7. SUMMARY

Falls are common in older people with CLD with almost 50% having had a fall in the previous year, and significantly more common than in age and sex matched Community Controls. Fall related injury rates were similar between the cohorts; however there were significantly more soft tissue injuries seen in Community Controls than the older CLD group. There was a tendency for the more serious injuries to be more common in the CLD participants but this difference did not reach statistical significance.

Falls were not associated with markers of liver disease severity but were associated with age, diabetes, orthostatic symptoms, lower limb strength, walking speed, balance, gait and fear of falling. Regression analyses revealed three independent associations, lower limb strength, orthostatic symptoms and fear of falling.

17.8. DISCUSSION

This unique study is the first of its kind, in the English language, to describe falls, fall related injury and fall associations in people with CLD, specifically older people with CLD. The need for this type of study is great given the expansion of the older population, the increasing prevalence of CLD (particularly NAFLD) and the possible 'double-whammy' effect of these factors combined. As falls and fall-related consequences cost the UK NHS approximately £1 billion per year it is essential to identify groups at risk of falling and potential therapeutic/preventative strategies [102, 226]. Older people with CLD represent an ideal population to study given the aforementioned changing demographics.

The results provided here highlight the importance of this study. With close to 50% of older people with CLD falling in the previous year the results can not and should not be ignored. It comes as quite a surprise to reveal such a high prevalence of falls in the absence of any other existing literature on the subject. While it may be anticipated that some would argue that the falls prevalence is high because the participants are elderly, the falls prevalence was significantly greater than in age matched, non-liver disease Community Controls. The falls prevalence was also significantly higher than in the younger CLD cohort which may suggest that there is a combined effect of CLD and ageing which contributes to falling.

The study was unable to demonstrate a significantly increased rate of fall-related injury in older people with CLD. This finding was contrary to the original hypothesis which anticipated fall-

related injury would be common as a result of the increased prevalence of autonomic dysfunction in CLD. Fracture rates and hospital admissions did appear to be more common but, perhaps because of low numbers, the difference was not significant. There was a surprisingly significant difference between the older CLD cohort and the Community Controls with regard to the proportion of Fallers who sustained a soft-tissue injury. However, it is recognised that numbers were small and the analysis was likely underpowered. In addition, caution is required when interpreting soft-tissue injury as this type of injury is felt to be a poor reflection of falls and injury prevalence because of the lack of rapid and independent assessment [227].

It is short sighted to regard physical injury as the sole important consequence of falling. There are personal, social and societal consequences which must be considered. Although this study does not describe each of these it does demonstrate a significant association between falling and functional ability. While it is not possible to determine whether the functional ability contributes to falls or whether it is falling which results in functional impairment, it is likely that both factors interact bidirectionally. Furthermore, the relationship between fear of falling and falls is strong and as was described in section 10.2 fear of falling can result in activity restriction, social isolation, frailty and an increased chance of being admitted to institutional care [228].

An important observation demonstrated in this study is that liver disease severity, as judged by the LFTs and the presence of cirrhosis, is unrelated to falling and falls can occur at any stage of disease. As such, if services were to be developed for people with CLD it would be important not to use markers of liver disease severity, such as LFTs, as a tool for identifying appropriate service users. The observation is in keeping with other quality of life issues faced by people with CLD; for example, fatigue and symptoms of cognitive dysfunction in CLD are unrelated to liver disease severity [99, 167, 229]. Accordingly, this study contributes to the emerging wealth of data that quality of life issues are substantial and of importance to the patient who is sitting in clinic, regardless of their LFT, ultrasound or biopsy result.

As described in section 15.2 context is crucial to understand whether a problem exists, the extent of that problem and whether it could be susceptible to intervention. The Phase 1 data provides evidence that there is a substantial problem and rather valuably, the Phase 2 data provides evidence for the susceptibility to intervention. Indeed, as the Phase 2 MDT assessments were based on the NICE guidelines each fall association which was identified is potentially modifiable.

Although causation can not be determined from this cross-sectional study the associations with falling in CLD which were found are age, diabetes, postural dizziness, lower limb strength, gait abnormality, gait speed, balance and fear of falling. With the exception of age, each of these falls risk factors is modifiable with the potential to prevent falls and fall related sequelae. The range of associations identified here would suggest that an appropriate therapeutic/preventative strategy would be to employ the skills of a multidisciplinary team. The UK NICE Clinical Guideline 21 recommends a MDT assessment and intervention of older people who are at risk of falls. This would seem appropriate for the older CLD population with input from a physician to optimise diabetic control and diabetes related complications such as neuropathy and retinopathy. A physician could also to address orthostatic symptoms/orthostatic hypotension which would need input from nursing staff to assess blood pressure responses. Physiotherapy would be required for gait, balance, muscle strength and fear of falling. An additional intervention for fear of falling would be cognitive behavioural therapy (CBT). The NICE falls guidelines do not recommend the use of CBT to prevent falls, however, CBT can reduce fear of falling and the activity avoidance associated with fear of falling [230]. Indeed, one large, recent, randomized controlled trial which compared usual care to a multicomponent CBT intervention demonstrated a significantly greater reduction in fear of falling and activity avoidance at 8 months follow-up and a continued reduction in fear of falling at 14 months. This trial is in conflict to previous similar studies which did not show sustained improvements following intervention [231]. Furthermore, the recent trial had high drop out rates and a relatively intense and time-demanding intervention, the cost benefits of which are unknown. The NICE guidelines also recommend employing the skills of an occupational therapist for home hazard assessment and intervention. While this study does not comment on home hazards it does demonstrate an increase in functional difficulty in those who fall and that OT input may be required to improve daily functional ability. Overall, it appears that MDT assessment and intervention would be the most appropriate service for older people with CLD who fall or who are at risk of falling.

17.9. LIMITATIONS

This study was prospectively powered to detect a significant difference of 20% in falls prevalence. As the difference between the older CLD group and the Community Controls was 14%, this study was not adequately powered to detect this difference as significant. This limitation is exaggerated when analysing for differences in the prevalence of fall-related injury, given the smaller numbers.

The lack of significance may be due to small numbers of Fallers sustaining an injury, but it must also be considered that the hypothesis of increased fall-related injury in CLD is incorrect.

Comparison of the CLD group with the Community Control group is somewhat limited. The existing database of falls and injury in community controls was collated in 2002, before the NICE guidelines for the prevention of falls were published. However, the falls prevalence seen in this control cohort is similar to rates expressed in falls literature and has the advantage when compared to the CLD cohorts because it is derived from the same geographical region. Furthermore, it allows for age and sex matching of individuals and for exclusion of individuals with a history of liver disease.

Retrospective recall of falls is well known to have its limitations. Restricting retrospective recall to the previous year was an attempt to temper these limitations, but nevertheless they remain. However, as the principle limitation of retrospective recall is under-reporting of events it is likely that the falls prevalence demonstrated is an underestimate and the true prevalence is higher, albeit in each cohort [232]. Approximately 27% of falls studies use retrospective recall, however a preferable method of data collection would be to collect it prospectively [233]. However, this is not without its own limitations such as lengthy data collection periods, lack of validity and some degree of retrospective recall (e.g. monthly reporting of falls) and would likely have resulted in a smaller sample size than seen in this study [233]. The self-reporting of injuries also is subject to the limitations of recall, but is also subject to unconfirmed diagnoses. For example, a person who has fallen and has injured their chest may be informed by their General Practitioner, or indeed conclude for themselves, that they have fractured their ribs, without radiological evidence of such an injury. Conversely, some may fall and sustain an injury but disregard it as negligible, whereas another individual with the same injury may seek urgent medical attention

A prospective sample size calculation was not performed with respect to the Phase 2 MDT assessments. This phase was intended to be exploratory and used to inform future therapeutic or preventative studies if appropriate. A number of factors limited the number of MDT assessments which could be carried out. The principle limiting factor was the availability of the MDT team. Sessions were booked when each team member was available so that the participants would have to attend only once. Two sessions per week were scheduled but this was often not practicable due to annual leave, study leave, sick leave and other factors. Furthermore, the number of MDT assessments was limited by cancellations, non-attendance and the length of time of a full MDT

assessment. As each participant was evaluated by three team members, in a 'rotating clinic', during each session it was only possible to see three participants.

It is appreciated that while efforts were made to prevent bias, those who responded to the data collection tools may have been those who have had problems with falls as they may have felt most likely to benefit from the study. This bias may have been further exaggerated in the Phase 2 MDT assessments, and while attempts were made to assess a wide spectrum of 'phenotypes' bias can not be completely excluded.

During the Physician assessment the participants self-reported their past medical history and medications. In nearly all cases this was verified from the participants' clinical records but in a couple of cases, where clinical records were not available, medical history was dependent on the participants' recall. Where medical records were available, blood results and evidence of cirrhosis were noted. In the majority of cases blood results were available within 4-6 months of the MDT assessment. In the few participants who did not have results within 6 months of the assessment their closest sample was used, but only if the results had previously been stable and the participant was stable clinically.

It seems likely, in retrospect, that the physiotherapy assessment was limited by the ceiling effect during the gait and balance assessment. The tool, which is widely used in clinical practice, may have lacked sensitivity to identify subtle gait or balance abnormalities. However, whether subtle gait and balance abnormalities would have a significant association with falls is unknown.

Unfortunately the FES-I has only been validated in older people. No such tool exists for younger people and as such it seems an appropriate choice especially as it widely used and recommended by the European Falls Prevention Network. However, if it had have been practicable, it would have been preferable to perform at least a small validity study in younger people prior to data collection.

Limitations to the autonomic assessment were minimal. The Task Force® equipment is reliable within a range of 50-250 mm Hg BP which was not an issue for any of the participants assessed. Where limitations may have arisen was in the quality of an individual's valsalva. A poor valsalva could cause erroneously abnormal BP and HR responses from a lack of increase in intra-thoracic pressure. In participants who were judged to have a poor technique the best of three attempts was selected, but this may still have been poor.

As has been mentioned, some of the statistical analyses were limited by the small sample sizes, particularly once the cohorts had been divided into Fallers and Non-Fallers and then sub-divided into injured or not injured. The goodness-of-fit Chi squared statistic for the binary logistic regression model had a p value of greater than 0.05 and as such this model was no better at predicting the outcome (Faller) than using the constant alone (i.e. including the variables in the equation does not improve the model). Conversely, the model-fit of the negative binomial regression was significantly better than the constant alone and the results of this model are significant.

RESULTS – PART TWO

18.1. CHAPTER AIMS

- To define the prevalence of falls in a NAFLD population
- To identify modifiable fall associated risk factors
- To establish whether falling in NAFLD is related to the presence of diabetes
- To establish the rate of fall related injury

18.2. INTRODUCTION

The previous chapter demonstrated that the number of falls was significantly more common in those with diabetes and as such, the high prevalence of diabetes in the NAFLD population could be expected to contribute to high rates of falls. This hypothesis is supported by the multiple falls risk factors which can result from diabetes: visual impairment, sensory disturbance, autonomic dysfunction and polypharmacy. Diabetes was not independently associated with falling however and there may be other factors contributing to falls in this population.

18.3. DEMOGRAPHICS

In Phase 1 there were 32 individuals with NAFLD who were aged 65 years or more (31% of Phase 1 NAFLD cohort) and each of these was age and sex matched to a community control. Details of these cohorts are displayed in Table 11. It was not surprising to note that diabetes was more common than in the community controls.

	NAFLD <65 years (*n* 72)	**NAFLD ≥65 years (*n* 32)**	**Community controls (*n* 32)**	**Differences**
Age [years]	54 (19-64)	70 (65-79)	70 (65-79)	
Female (%)	39 (56)	17 (53)	17 (53)	χ^2 (2) 0.015, *p* 1
Diabetic (%)	45 (63)	19 (59)	1 (3)	χ^2 (2) 33.551, *p* <0.001
Albumin [g/L]	44 (38-50)	44 (35-47)	44 (40-48)	χ^2 (2) 3.72, *p* 0.156
Bilirubin [μmol/L]	11 (4-37)	9 (4-24)	9 (4-18)	*H* (2) 0.087, *p* 0.957
ALP [U/L]	83 (11-233)	102 (57-150)	78 (48-112)	*H* (2) 11.031, *p* 0.004
ALT [U/L]	64 (19-210)	47 (15-204)	21 (9-35)	*H* (2) 50.028, *p* <0.001
Cirrhosis (%)	17 (24)	11 (35)	0	χ^2 (2) 12.419, *p* 0.002

Table 11. NAFLD. Demographic details.

18.4. FALLS PREVALENCE

The relatively small size of the older NAFLD group resulted in small numbers in each of the fall categories and interpretation of the statistical comparisons must take this into consideration. In the older NAFLD group 12 (38%) individuals had fallen in the previous year. There were significantly more Fallers in the older NAFLD cohort than in the matched Community controls [χ^2 (1) 3.925, *p* 0.048, Figure 24]; this significance remained when the Fallers were sub-divided into Single- and Recurrent-Fallers [χ^2 (2) 5.515, *p* 0.019]. These differences were not demonstrated between the older and younger NAFLD groups [χ^2 (1) 1.686, *p* 0.194 and χ^2 (2) 1.929, *p* 0.381].

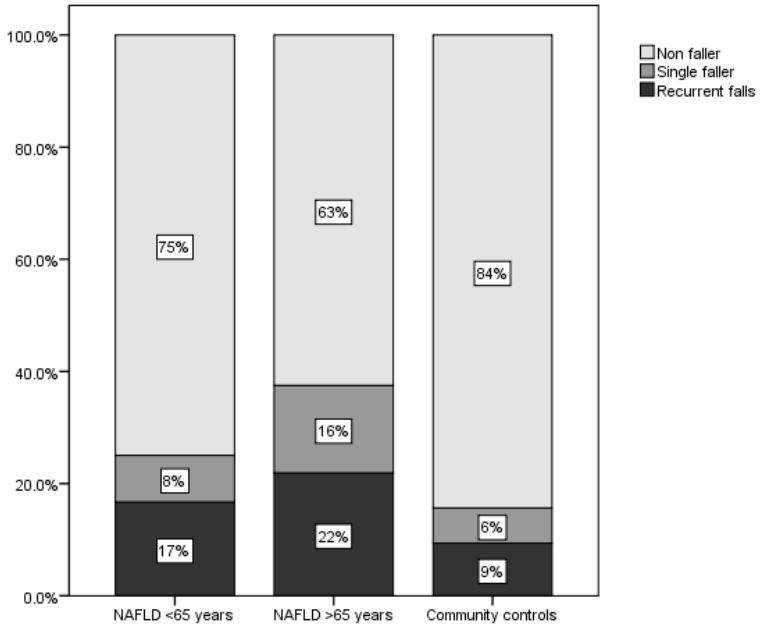


Figure 24. NAFLD. Falls prevalence.

To investigate the difference found between the three different fall categories in the cohorts the number of falls in those who had fallen was compared. No difference was identified (Table 12).

	NAFLD <65 years (*n* 18)	**NAFLD >65 years (*n* 12)**	**Community controls (*n* 5)**	***H* (df), *p***
Median number of falls (range)	2 (1-52)	2 (1-10)	2 (1-2)	1.301 (2), 0.534

Table 12. NAFLD. The number of falls experienced by Fallers.

18.5. INJURY PREVALENCE

Individuals from the older NAFLD group who had fallen were age- (±0 years) and sex-matched to community controls. However there were only 12 Fallers from the older NAFLD group and

although the fall related injury counts have been displayed in Table 13, it is not possible to draw statistical conclusions as the numbers are too small.

	NAFLD <65 years (n 18)	**NAFLD >65 years (n 12)**	**Community controls (n 12)**
Any injury (%)	6	4	10
Soft tissue injury (%)	3	3	10
Accident & Emergency (%)	4	3	3
Fracture (%)	2	2	1
Hospital admission (%)	0	2	1

Table 13. NAFLD. Fall related injury prevalence.

18.6. FALL ASSOCIATIONS

NAFLD is the most common cause of abnormal liver function in the Western world and its prevalence is increasing, with this in mind the need for falls intervention in NAFLD may increase [234, 235]. Given that the prevalence of falls is significantly greater in NAFLD than in Community Controls it became important to explore possible associations.

18.6.1. PHASE 1- ASSOCIATION WITH AGE AND DISEASE SEVERITY

Increasing age showed no association with number of falls in the previous year; nor was falling associated with the LFTs which suggests that falls are unrelated to NAFLD severity; however this could be explored further using the histological staging in the Phase 2 cohort.

18.6.2. PHASE 2- MDT ASSOCIATIONS

As 28 individuals with NAFLD underwent MDT assessment, associations were analysed in the whole group in order to maximise numbers. The aforementioned Phase 1 results demonstrated that

age was not associated with falls and therefore the younger participants were included in the analysis. Twenty individuals in the MDT (71%) were aged 65 years or older, 17 (61%) were diabetic, 22 (79%) were taking anti hypertensive medication and none had a diagnosis of osteoporosis. Histological staging was available in all 28 participants; 14 (50%) had simple steatosis, 10 (36%) had NASH and 4 (14%) had cirrhosis. None had been diagnosed with osteoporosis or were taking prophylactic bisphosphonates.

The number of falls in the previous year did not correlate significantly with BMI or insulin resistance level. In keeping with this there was no difference in the number of falls between diabetics [0 (0-12)] and non diabetics [0 (0-2), z 0.525, p 0.476]. This suggests that falls in people with NAFLD are unrelated to the presence of diabetes or the metabolic syndrome. Four participants had a peripheral neuropathy on examination and interestingly each of these individuals had fallen recurrently in the previous year. While this number may be too low to draw robust statistical conclusions, theoretically a peripheral neuropathy could contribute to falls.

In keeping with the Phase 1 results there were also no difference in the number of falls between each histological stage [steatosis 0 (0-6), NASH 0.5 (0-3), cirrhosis 1 (0-12), H (2) 3.601, p 0.157).

Other falls risk factors assessed included vision, which was not associated with number of falls [abnormal vision 0 (0-12) and normal vision 0 (0-3) respectively, z 0.406, p 0.725] and antihypertensive medication. The difference in number of falls between those taking and those not taking antihypertensive medication approached significance but did not reach the 5% value [0.5 (0-12) and 0 (0-12), z 1.086, p 0.064].

Number of falls did correlate with several autonomic measures including resting and nadir dBP and AUC, the results of which are displayed in Table 14. Additionally, the physiotherapy assessment revealed an association between number of falls and fear of falling, Table 14, which is in keeping with the previous chapter concerning CLD as a whole. Non-significant correlations are displayed in Appendix B.2, page 221.

Variable	r_s
	p
dBP	-0.389
	0.045
nadir dBP	-0.397
	0.04
AUC	0.388
	0.046
Fear of falling	0.454
	0.026

Table 14. NAFLD. Phase 2 correlations with the number of falls.

These correlations demonstrate that increasing numbers of falls are associated with a lower resting dBP and a lower nadir dBP upon standing. Consistent with this BP association is the increasing AUC associating with increasing number of falls. This is the degree to which the sBP drops on standing and the length of time it remains below baseline values. An increasing fear of falls was also associated with an increasing number of falls. Table 15 below displays which variables were included in the binary logistic regression model which aimed to identify which associations were independent associations with the outcome variable fallen or not fallen. Age was included in the model as it was the intention to study older people with NAFLD but because of small numbers all ages were included in analysis.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	0.261	4.161	1.063			0.95
Age	0.006	0.037	1.006	0.936	1.081	0.871
dBP	0.003	0.062	1.003	0.888	1.134	0.956
nadir dBP	-0.042	0.073	0.958	0.831	1.106	0.56
AUC	0.008	0.013	1.009	0.983	1.035	0.517
FES-I	0.061	0.04	1.063	0.983	1.149	0.126

R^2 0.256 (Cox), Hosmer & Lemeshaw χ^2 (8) 8.661, p 0.372

Table 15. NAFLD. Binary logistic regression for Faller or Non-Faller.

The 95% confidence intervals for the odds ratios of the logistic regression model can be seen in Figure 25 below.

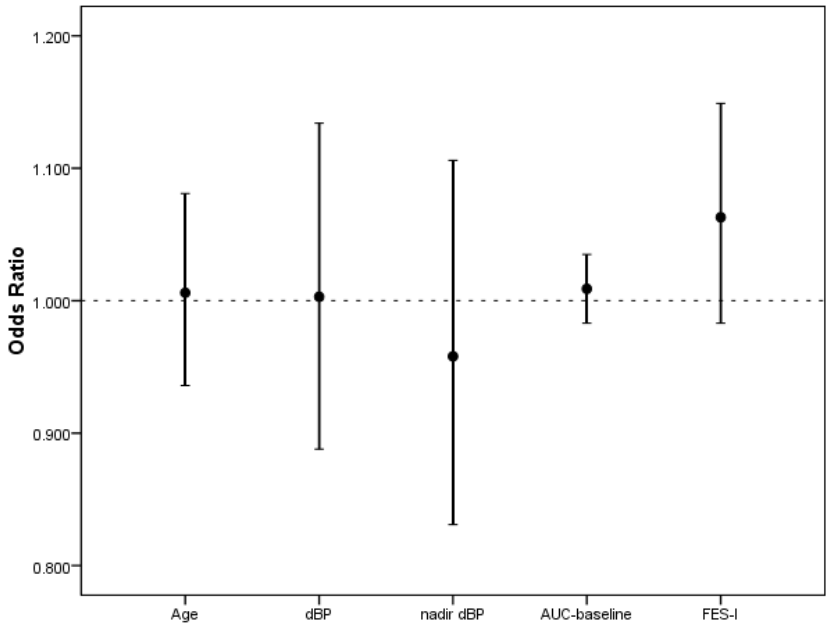


Figure 25. NAFLD. The 95% CI for the ORs derived from the binary logistic regression model.

The regression model described above does not identify variables as being independently associated. This suggests that a single targeted falls intervention may not be appropriate and a multidisciplinary approach may be required. To provide further evidence for possible therapeutic or preventative targets negative binomial regression was performed which explored associations with the number of falls experienced. This model is described below in Table 16.

Variable	***b***	**SE**	**OR**	**95% confidence interval (OR)**		***p***
				Lower bound	**Upper bound**	
Constant	0.778	3.203	2.176	0.004	1159.68	0.808
Age	0.018	0.027	1.018	0.966	1.073	0.502
dBP	-0.002	0.044	0.998	0.915	1.087	0.955
nadir dBP	-0.047	0.058	0.954	0.852	1.069	0.42
AUC	-0.008	0.008	0.992	0.977	1.007	0.279
FES-I	0.064	0.027	1.067	1.011	1.125	0.018

Model likelihood ratio χ^2 (5) 10.345, p 0.066

Table 16. NAFLD. Negative binomial regression model for number of falls.

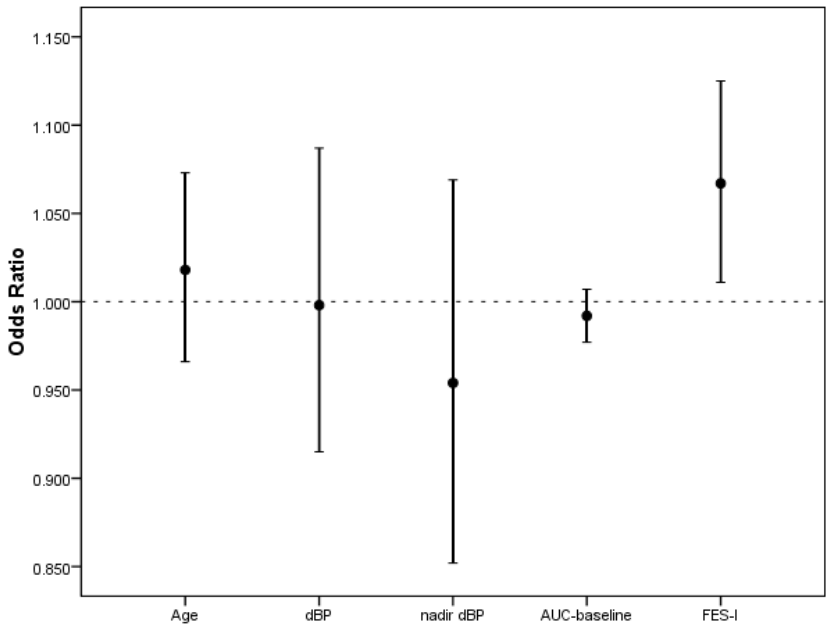


Figure 26. NAFLD. The 95% CI for the ORs derived from the negative binomial regression model.

The regression model above identifies fear of falling as the only variable which is independently associated with the number of falls in the previous year; this may also be seen in Figure 26. This has important clinical implications as fear of falling, a recognised risk factor for falls, is modifiable and represents a possible therapeutic target. This was also seen in the full CLD group and it will be interesting to see in the subsequent chapters whether this will be a consistent finding in each specific CLD.

18.7. INJURY ASSOCIATIONS

The number of participants from Phase 2 when divided into Fallers and Non-Fallers and then subsequently into injured and non injured became too small to identify meaningful associations with injury.

18.8. FALLS AND FUNCTIONAL ABILITY

Returning to the Phase 1 data the association between falling and functional ability was analysed. In order to maximise numbers all ages of NAFLD participants were included in the analysis. There was no significant difference in functional ability across the fall categories from Recurrent-Fallers

[3.75 (0-70)], through Single-Fallers [6.25 (0-51.25)] to Non-Fallers [6.26 (0-61.25), H (2) 0.742, p 0.702)]. In keeping with this, there was no correlation between the number of falls and the PROMIS-HAQ score (r_s -0.139, p 0.442). This is in contrast to the results of the previous chapter and may be suggestive that there is another process which contributes to functional difficulty rather than falls.

18.9. SUMMARY

Falls are common in older people with NAFLD, with 38% of the cohort having had a fall in the previous year. This prevalence was significantly greater than in age- and sex-matched Community Controls. In addition, when Fallers were sub-divided into Single- and Recurrent-Fallers there was also a significant difference between the older NAFLD group and the Community Controls with the prevalence of recurrent falls being twice as high in the older CLD cohort.

Falls were not associated with age, disease severity and interestingly not with diabetes either. MDT assessment found falls to be associated with dBP, nadir dBP on standing, AUC and fear of falling. Regression analysis revealed fear of falling as the only independent association with falls in people with NAFLD.

19.1. CHAPTER AIMS

- To establish the prevalence of falls in older people with PBC
- To define the prevalence of fall related injury in older people with PBC
- To explore factors associated with falling in older people with PBC, particularly dysautonomia

19.2. INTRODUCTION

Given that autonomic dysfunction is particularly prevalent in PBC it was hypothesised that falls would be particularly common in this disease group and would be related to autonomic function. The consequence of autonomic dysfunction could also potentially, lead to significant injury whereby cerebral hypoperfusion causing transient loss of consciousness could prevent protective mechanisms (e.g. grabbing onto supports or sticking out arms to prevent facial injury). Furthermore, the prevalence of osteoporosis is greater in PBC than in several other CLDs [79] and for this reason it may be anticipated that the prevalence of fall related fractures would be greater than in the control group.

19.3. DEMOGRAPHICS

Data concerning sample sizes, demographics and liver disease severity are displayed in Table 17. The community control group was matched for age (±0 years) and sex with the older PBC group with the exception of the oldest PBC participant (95 years) who could only be matched to a younger community control (92 years).

	PBC <65 years (*n* 36)	**PBC ≥65 years (*n* 60)**	**Community controls (*n* 60)**	**Differences**
Age [years]	56 (40-64)	74 (65-95)	74 (65-92)	
Female (%)	32 (89)	57 (95)	57 (95)	FET, *p* 0.456
Diabetic (%)	1 (3)	4 (7)	3 (5)	FET, *p* 0.898
Albumin [g/L]	41 (26-49)	40 (28-45)	44 (39-49)	*H* (2) 20.582, *p* <0.001
Bilirubin [μmol/L]	11 (5-75)	8 (4-21)	7 (4-18)	*H* (2) 6.353, *p* 0.042
ALP [U/L]	235 (48-1033)	149 (61-879)	80 (48-130)	*H* (2) 38.901, *p* <0.001
ALT [U/L]	51 (15-220)	27 (10-181)	18 (10-45)	*H* (2) 35.181, *p* <0.001
Cirrhosis (%)	2 (6)	7 (12)	0	FET, *p* 0.017

Table 17. PBC. Demographic details.

19.4. FALLS PREVALENCE

The prevalence of falls in the previous year in those aged over 65 years with PBC was high at 58%. This prevalence was significantly higher than in the Community Controls [χ^2 (1) 7.552, *p* 0.006]; the high falls prevalence was also present in the younger PBC group, not differing significantly from the older group [χ^2 (1) 1.119, *p* 0.29]. Recurrent falls were also very common in the older PBC group (23%) with significantly more than in the Community Control group [χ^2 (2) 8.062, *p* 0.018]. The proportion of Recurrent Fallers was similar between the PBC age groups [χ^2 (2) 1.125, *p* 0.57]. Figure 27 displays the proportion of Fallers in each cohort.

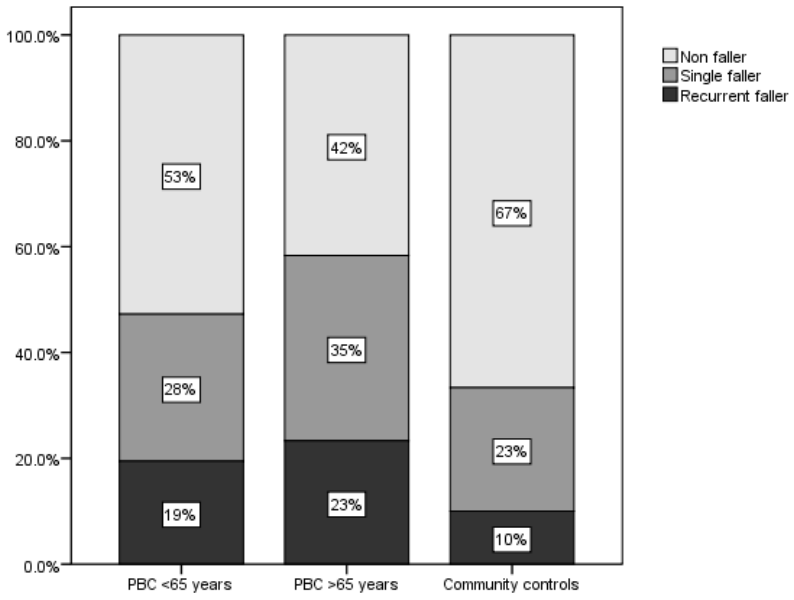


Figure 27. PBC. Falls prevalence.

While the proportion of Recurrent Fallers were significantly greater in the older PBC group than the community controls, the number of falls in those who had fallen were similar through each group and did not differ significantly [PBC <65 years 1 (1-3), PBC >65 years 1 (1-9), community controls 1 (1-6), H (2) 1.148, p 0.568].

19.5. INJURY PREVALENCE

In order to compare injury rates, those older PBC participants who had fallen were age (±1 year) and sex matched to a community control that had fallen. One of the PBC Fallers was 7 years older than the eldest control and as such could not be matched and was excluded from analysis.

Given the high prevalence of autonomic dysfunction and osteoporosis in PBC it was perhaps surprising to note that the prevalence of injury, particularly that of fracture, was not significantly greater than in controls, Table 18. However, given the numbers in each injury category it would be unwise to rely upon the statistical tests. Regardless of the statistics, with such a high proportion of older PBC participants having had a fall the injury rate of 65% must not be ignored. Indeed, in this PBC cohort eight participants had sustained a fall related fracture within the previous year.

	PBC <65 years (*n* 17)	PBC >65 years (*n* 34)	Community controls (*n* 34)	Significance [χ^2 (df), *p*]
Any injury (%)	10 (59)	22 (65)	25 (74)	1.252 (2), 0.523
Soft tissue injury (%)	10 (59)	22 (65)	23 (68)	0.386 (2), 0.877
Accident & Emergency (%)	4 (24)	9 (26)	9 (26)	0.061 (2), 1
Fracture (%)	2 (12)	8 (24)	6 (18)	1.078 (2), 0.592
Hospital admission (%)	2 (12)	5 (15)	5 (15)	FET, p 1

Table 18. PBC. Fall related injury.

19.6. FALL ASSOCIATIONS

With 58% of the older PBC cohort having had a fall in the last year alone, it would appear important to explore factors associated with falling. As with previous chapters age and LFTs could be explored in the larger Phase 1 cohort and the comprehensive MDT assessment in the Phase 2 cohort.

19.6.1. PHASE 1- ASSOCIATION WITH AGE AND DISEASE SEVERITY

There was no demonstrable association between age, albumin, bilirubin, ALP or ALT with the number of falls.

19.6.2. PHASE 2- MDT ASSOCIATIONS

Fall associations were explored in participants of all ages to maximise numbers and power. Forty participants underwent MDT assessment in which associations can be explored, 26 (65%) were aged over 65 years. There were 4 participants with cirrhosis, 2 of which had fallen. Despite the small numbers precluding further statistical analysis it appears from the Phase 1 data that there is no association between disease severity and number of falls. Similarly there were 4 participants with diabetes, 2 of which had fallen. Numbers were greater when analysing normal vision (*n* 24) versus abnormal vision (*n* 16), but as they were still relatively small the Kolmogorov-Smirnov test was used which did not reveal significant differences [0 (0-8) and 0 (0-12) respectively, *z* 0.516, *p* 0.396].

There was also no association with taking anti hypertensive medication (*n* 20) versus not taking it [*n 20*, 0 (0-12) and 0 (0-8) respectively, *z* 0.158, *p* 1]. Nine had a diagnosis of osteoporosis with falls being no more frequent than in those without it [0 (0-1) and 0 (0-12) respectively, *z* 0.558, *p* 0.424].

On autonomic testing the number of falls did not show an association with resting blood pressure. Although there was an association between LFnu and number of falls (r_s -0.42, *p* 0.007) this result was inconsistent with the other HRV results which did not demonstrate significant associations. To explore this possible relationship further, HRV was compared between Fallers and Non-Fallers; the results were consistent with the correlations described above, LFnu was the only HRV variable which demonstrated a significant difference between Fallers and Non-Fallers [37.1 (17.1-66.3), *z* 1.408, *p* 0.024]. The remaining autonomic function results also displayed no association, including valsalva and BRS, and therefore the possibility that the association with LFnu represented a predominantly sympathetic abnormality seems unlikely. Non-significant results are displayed in Appendix B.3, page 222.

The relationship between falling and the OGS was significant in the PBC MDT cohort (r_s 0.342, *p* 0.031). This finding was also present in the whole CLD analysis but not in the NAFLD cohort.

The MDT physiotherapy assessment results revealed several significant correlations with number of falls and these are displayed in Table 19. Each result is consistent in that poorer performance in the test associated with increased numbers of falls.

	r_s *p*
Sit to Stand test	0.526 0.001
Balance	-0.5 0.001
Gait	-0.358 0.023
Fear of falling	0.569 <0.001

Table 19. PBC. Phase 2 correlations with the number of falls.

Binary logistic regression was performed to identify possible independent associations with whether an individual had fallen or not. Age was included in the model as all ages were included in the Phase 2 MDT data exploration to maximise numbers. Including age in the model allows the model to control for factors which may be linked to ageing. The variables included in the model are displayed in Table 20; none violated the assumptions required for logistic regression. One residual case was identified from the regression; on inspecting the data for this case there was no apparent, robust reason why it should be excluded from the model and indeed removing it from the model did not improve the model's fit.

Variable	***b***	**SE**	**OR**	**95% confidence interval (OR)**		***p***
				Lower bound	**Upper bound**	
Constant	-33.766	23.226	0			0.146
Age	0.08	0.86	1.083	0.916	1.281	0.352
OGS	0.171	0.255	1.187	0.719	1.958	0.503
Sit to stand test	0.216	0.181	1.241	0.871	1.77	0.232
Balance	0.328	0.621	1.388	0.411	4.685	0.597
Gait	0.674	0.767	1.962	0.437	8.816	0.379
Fear of falling	0.322	0.167	1.379	0.994	1.915	0.055

R^2 0.465 (Cox), Hosmer & Lemeshaw χ^2 (8) 3.893, p 0.867

Table 20. PBC. Binary logistic regression model for Faller or Non-Faller.

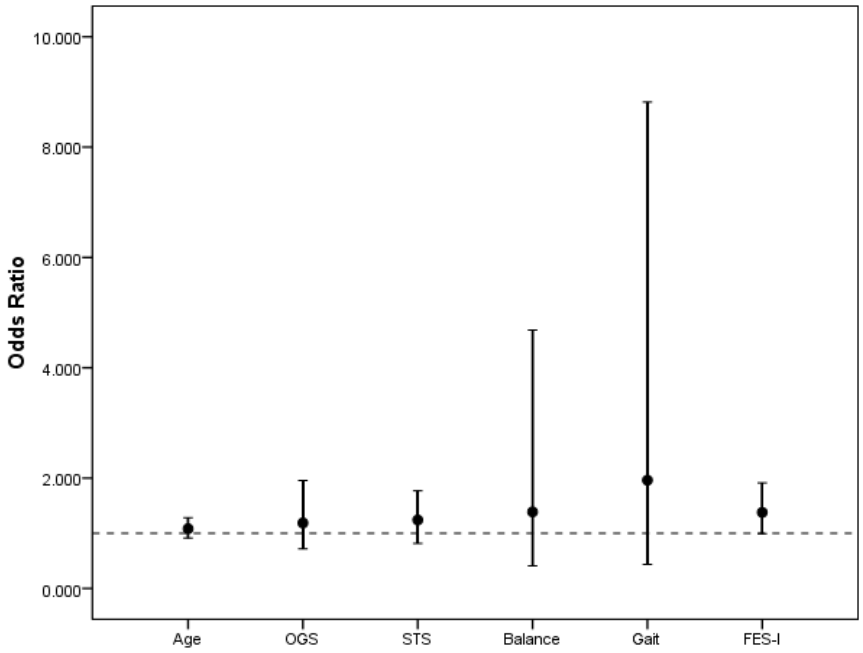


Figure 28. PBC. The 95% CI for the ORs derived from the binary logistic regression model.

The regression model demonstrates that fear of falling approaches the cut off significance level required to be an independent association with being a Faller, this can easily be seen in Figure 28 as the lower bound 95%CI just crosses 1 by only 0.006. This is a particularly important finding given that fear of falling is a modifiable risk factor for falling, but may also support the case that these factors are closely linked and not independent of each other. To explore these associations further, negative binomial regression was performed for the number of falls in the previous year and is displayed below in Table 21 and Figure 29.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-12.182	7.189	5.122	3.891	6.743	0.09
Age	-0.024	0.04	0.976	0.902	1.056	0.545
OGS	0.136	0.126	1.146	0.895	1.466	0.279
Fear of falling	0.115	0.059	1.122	0.999	1.259	0.052
Sit to stand test	0.132	0.045	1.141	1.044	1.246	0.003
Balance	0.056	0.233	1.057	0.669	1.67	0.811
Gait	0.642	0.44	1.901	0.802	4.504	0.145

Model likelihood ratio χ^2 (6) 34.973, p <0.001

Table 21. PBC. Negative binomial regression for the number of falls.

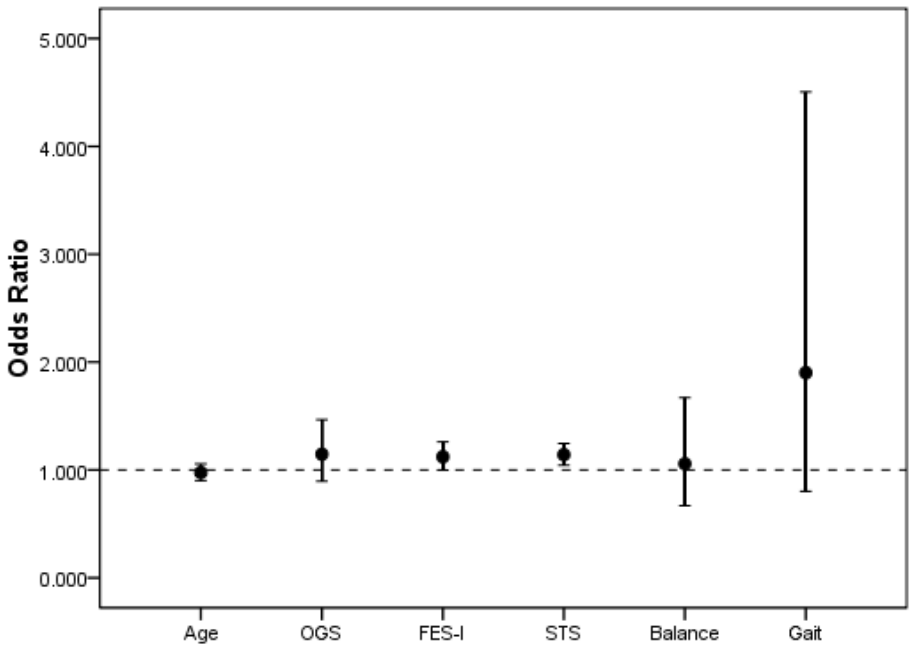


Figure 29. PBC. The 95% CI for the ORs derived from the negative binomial regression model.

The regression model displayed in Table 21 identifies the sit to stand test (STS, predominantly a measure of proximal muscle strength) as an independent association with number of falls. The FES-I was very close to reaching significance with the lower bound 95% CI for FES-I crossing 1 by 0.001. Both of these factors are modifiable and are potential therapeutic/preventative targets for falling in PBC.

19.7. FALLS AND FUNCTIONAL ABILITY

Returning to the Phase 1 data which had greater numbers of participants it was possible to explore the associations between functional ability and falls focussing on the older PBC group (*n* 60). There was a strong, positive correlation between number of falls and the PROMIS-HAQ (increasing scores indicate increasing difficulty) whereby fewer falls associate with less difficulty (r_s 0.407, p 0.003). Figure 30 demonstrates the significant difference in PROMIS-HAQ scores in Recurrent-Fallers [57.5 (0-72.5), Single-Fallers [11.25 (0-43.75)] and Non-Fallers [3.75 (0-75), H (2) 9.83, p 0.007)].

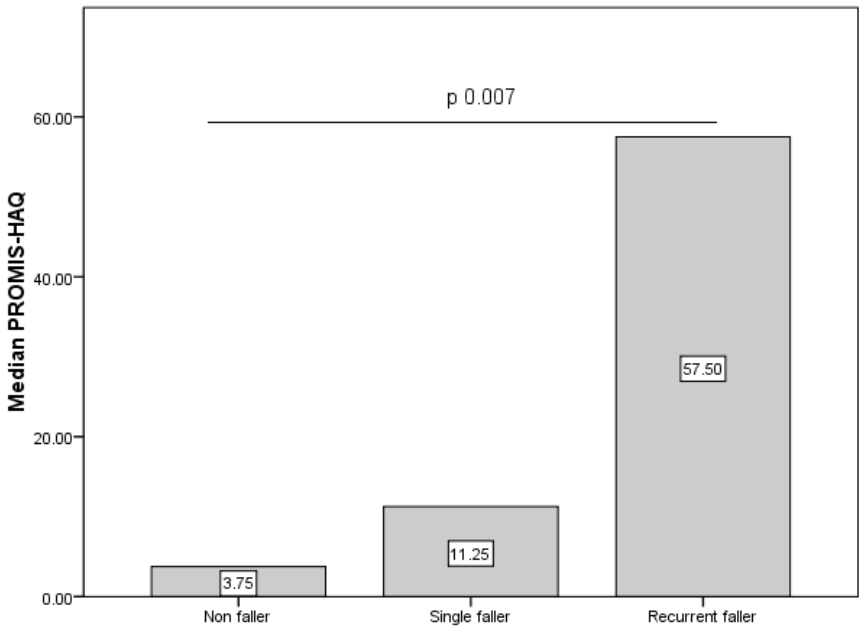


Figure 30. PBC. Functional difficulty and falls.

19.8. SUMMARY

Falls are very common in older people with PBC, with 58% having had a fall in the previous year, significantly more than in the age and sex matched Community Control group. Recurrent falls occurred in 23% of the older PBC cohort which was significantly more than Community Controls. Factors which were associated with falling in PBC were orthostatic dizziness, lower limb strength, balance, gait and fear of falling. Regression analysis revealed lower limb strength as the single factor which is independently associated with falling in PBC.

Injuries were common, with almost two thirds sustaining a fall related injury and almost one quarter suffering a fracture. Important findings, but these fall related injuries were not significantly more common than the control groups, as had been hypothesized.

20.1. CHAPTER AIMS

- To define the prevalence of falls in an ALD population
- To identify modifiable fall associated risk factors
- To establish the rate of fall related injury

20.2. INTRODUCTION

It could be assumed that falls would be a common event in people with ALD for several reasons. Firstly, increased levels of plasma alcohol can lead to poor judgement and slow reaction times both of which could contribute to mechanical falls and injury [236]. Secondly, there are longer lasting consequences of long term excess alcohol consumption such as peripheral neuropathy and cerebellar disease leading to postural and gait abnormalities. Conversely, a fall in an intoxicated individual could go forgotten and unreported, or in those with more severe disease such as vitamin B_1 deficiency or Korsakoff's syndrome, there could be failure to form a memory for the fall. It is possible that clinicians may assume that falls are related to the direct consequences of alcohol and assume that an abstainer who is falling is not being honest about their alcohol intake. It would therefore be particularly important to explore fall associations in the ALD population.

20.3. DEMOGRAPHICS

During Phase 1, 51 individuals with ALD completed the falls and injury tool. Recruitment of ALD participants was slow due to the high 'did not attend' rate to their clinic appointments. Eleven (22%) of the ALD cohort were aged 65 years or more. Each of these was age and sex matched to a community control. Details of these cohorts are displayed in Table 22.

	ALD <65 years (*n* 40)	**ALD ≥65 years (*n* 11)**	**Community controls (*n* 11)**	**Differences**
Age [years]	56 (31-64)	71 (67-83)	71 (67-83)	
Female (%)	12 (30)	3 (27)	3 (27)	FET, *p* 1
Diabetic (%)	0	0	0	
Albumin [g/L]	41 (20-49)	34 (28-47)	45 (41-47)	*H* (2) 8.314, *p* 0.016
Bilirubin [μmol/L]	16 (4-316)	14 (8-72)	9 (6-14)	*H* (2) 11.19, *p* 0.004
ALP [U/L]	97 (40-1969)	95 (72-248)	73 (50-112)	*H* (2) 8.177, *p* 0.017
ALT [U/L]	43 (11-3210)	23 (11-51)	18 (11-35)	*H* (2) 14.856, *p* 0.001
Cirrhosis (%)	26 (65)	9 (82)	0	FET, *p* <0.001

Table 22. ALD. Demographic details.

20.4. FALLS PREVALENCE

The small size of the older ALD group resulted in small numbers in each of the fall categories and interpretation of the statistical comparisons must take this into consideration. In the older ALD group 2 of the 11 individuals had fallen in the previous year. The proportion of Fallers in the older ALD cohort was not statistically greater than in the younger ALD cohort [FET, *p* 0.706], nor than in the Community Controls [FET, *p* 0.476]. The same is true for the proportion of Recurrent Fallers [FET, *p* 1 and FET, *p* 0.476 for younger ALD and Community Controls respectively, Figure 31].

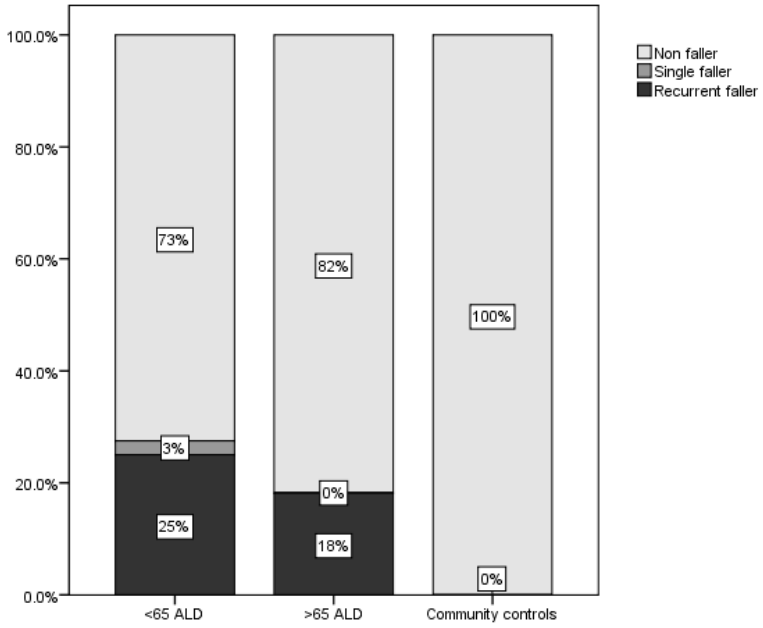


Figure 31. ALD. Falls prevalence.

20.5. INJURY PREVALENCE

Of the 2 Fallers who were aged over 65 years 1 sustained a fall related injury for which they attended Accident and Emergency and were admitted to hospital. As none of the matched community controls had a fall in the previous year it was not possible to compare fall related injury rates.

20.6. FALL ASSOCIATIONS

It was possible to explore Phase 1 demographic data for fall associations despite not having Phase 2 data. Including those of all ages with ALD there was no association between age and number of falls (r_s -0.011, p 0.939). There was, however, an association between albumin and number of falls (r_s -0.32, p 0.022) such that a lower level of albumin was associated with an increased number of falls. Dividing the cohort into Fallers and Non-Fallers the levels of albumin did not quite reach statistical significance [median albumin in Non-Fallers 41 (29-49) and in Fallers 33 (20-47), z 1.342, p 0.055 (Figure 32)]. There was no association between falls and the other LFTs [bilirubin (r_s 0.251, p

0.076), ALP (r_s 0.261, p 0.064), ALT (r_s 0.065, p 0.65)] although the p values for bilirubin and ALP did approach significance.

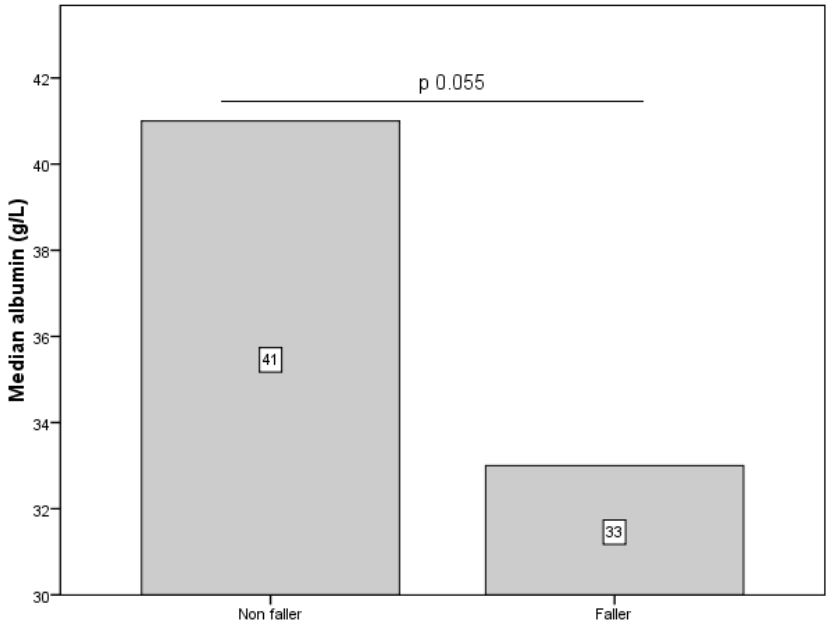


Figure 32. ALD. Albumin and falls.

20.7. SUMMARY

In the older ALD cohort (n 11) 2 individuals reported a fall, these numbers are too small to draw meaningful conclusions. However, the younger ALD group was larger and there was no association between age and falls. As such, looking at all individuals with CLD the prevalence of falls appears to be much less than in the previous results (NAFLD, PBC and CLD).

21.1. CHAPTER AIMS

- To establish the prevalence of falls in a PSC cohort
- To define the prevalence of fall related injury in people with PSC
- To explore factors associated with falling in people with PSC

21.2. INTRODUCTION

It was recognised early in the study that the demographic of the PSC cohort was such that exploring falls and fall related injury would be limited if focussed on older adults and therefore all ages would be included.

21.3. DEMOGRAPHICS

Data concerning sample size, demographics and liver disease severity are displayed in Table 23. Eight (28%) individuals were aged 65 years or over.

	PSC <65 years (*n* 21)	**PSC ≥65 years (*n* 8)**	**Community controls (*n* 8)**	**Differences**
Age [years]	51 (33-64)	73 (66-91)	73 (66-91)	
Female (%)	5 (24)	5 (63)	5 (63)	FET, *p* 0.247
Diabetic (%)	0	0	2 (25)	FET, *p* 0.057
Albumin [g/L]	44 (31-49)	42 (30-45)	42 (38-46)	*H* (2) 2.206, *p* 0.332
Bilirubin [μmol/L]	12 (7-64)	15 (7-67)	6 (5-12)	*H* (2) 10.51, *p* 0.005
ALP [U/L]	138 (60-886)	273 (89-486)	85 (48-113)	*H* (2) 10.433, *p* 0.005
ALT [U/L]	44 (15-118)	30 (19-59)	19 (10-28)	*H* (2) 8.597, *p* 0.014
Cirrhosis (%)	1 (5)	0	0	FET, *p* 1

Table 23. PSC. Demographic details.

21.4. FALLS PREVALENCE

Five (17%) of the whole PSC cohort had fallen in the previous year, of these, 3 (10%) had fallen once and 2 (7%) had fallen recurrently (the 2 Recurrent-Fallers were both aged over 65 years). Figure 33 below demonstrates the proportion of Single-, Recurrent- and Non-Fallers in the older and younger PSC group. An age and sex matched community control group for the older PSC individuals is displayed for interest although statistical analysis was not carried out due to the small numbers.

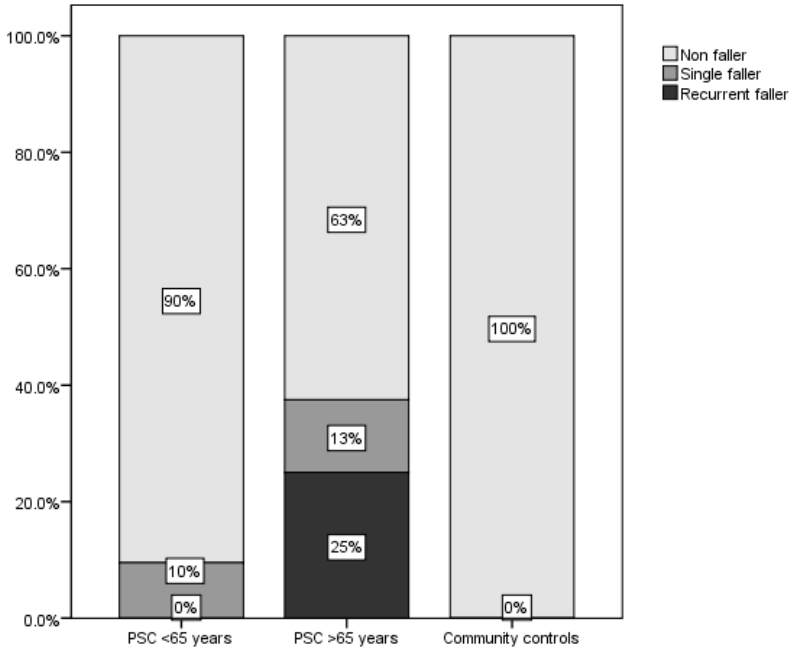


Figure 33. PSC. Falls prevalence.

21.5. INJURY PREVALENCE

Of the 5 individuals with PSC who had fallen in the last year 1 was injured. This individual, in the older group, sustained a fall related fracture and was admitted to hospital, via Accident and Emergency.

21.6. FALL ASSOCIATIONS

21.6.1. PHASE 1- ASSOCIATION WITH AGE AND DISEASE SEVERITY

Analysing the 29 individuals from the Phase 1 cohort revealed no association between number of falls and age, nor with the LFTs (Table 24).

	r_s p
Age	0.22 0.251
Albumin	-0.408 0.054
Bilirubin	0.213 0.33
ALP	0.202 0.354
ALT	-0.193 0.378

Table 24. PSC. Phase 1 correlations with the number of falls.

21.6.2. PHASE 2- MDT ASSOCIATIONS

As PSC is uncommon and affects principally younger males it was more challenging to recruit a PSC MDT cohort. In total, 3 PSC participants were assessed and contributed to the full CLD analysis. Here it is considered that 3 would be too small to draw meaningful conclusions from.

21.7. FALLS AND FUNCTIONAL ABILITY

In the Phase 1 PSC cohort of 29 individuals there was no association between the number of falls and functional ability (PROMIS-HAQ, r_s 0.332, p 0.079). As there were only 5 who had fallen

numbers were too small to explore this association further with a 2 sample Kolmogorov-Smirnov test.

21.8. SUMMARY

In the whole PSC cohort the proportion of individuals who had fallen in the previous year was 17%, but overall numbers were small. Further analyses were redundant due to the small sample size, but in the 29 individuals who responded falls do not appear to be a huge problem.

22.1. CHAPTER AIMS

- To determine if falls prevalence differs between CLDs
- To determine whether CLD type is independently associated with falling
- To identify whether a specific CLD is associated with an increased prevalence of fall related injury

22.2. DEMOGRAPHICS

Demographic data from the previous disease specific chapters are repeated below for ease of comparison, Table 25. Data described relates to Phase 1 participants aged 65 years or more.

	NAFLD (n 32)	**ALD (n 11)**	**PBC (n 60)**	**PSC (n 8)**	**Comparisons**
Age [years]	70 (65-79)	71 (67-83)	74 (65-95)	73 (66-91)	*H* 9.862 (3), *p* 0.02
Female (%)	17 (53)	3 (27)	57 (95)	5 (63)	FET, *p* <0.001
Diabetic (%)	19 (59)	0	4 (7)	0	χ^2 (1) 22.755, *p* <0.001
Albumin [g/L]	44 (35-47)	34 (28-47)	40 (28-45)	42 (30-45)	*H* 14.077 (3), *p* 0.003
Bilirubin [μmol/L]	9 (4-24)	14 (8-72)	8 (4-21)	15 (7-67)	*H* 14.05 (3), *p* 0.003
ALP [U/L]	102 (57-150)	95 (72-248)	149 (61-879)	273 (89-486)	*H* 13.74 (3), *p* 0.003
ALT [U/L]	47 (15-204)	23 (11-51)	27 (10-181)	30 (19-59)	*H* 15.557 (3), *p* 0.001
Cirrhosis (%)	11 (35)	9 (82)	7 (12)	0	FET, *p* <0.001

Table 25. Disease comparisons. Demographic data.

As expected there are obvious differences across the groups. For example PBC would usually affect older females whereas PSC would usually affect younger males, likewise it would be expected that diabetes would be more frequent in NAFLD and that bilirubin and ALP would be higher in the cholestatic diseases.

22.3. FALLS PREVALENCE

It became clear from the previous disease specific result chapters that there were differences in falls prevalence across the disease groups. Figure 34 below demonstrates the proportion of Fallers and Non-Fallers in each disease cohort, aged over 65 years. There was no significant difference identified across the groups when divided into Non-, Single- and Recurrent-Fallers (FET, p 0.079). However, as this result approached significance and numbers are small in each category the Single- and Recurrent-Faller groups were combined to form a Fallers group, which when compared to the proportion of Non-Fallers did reveal a significant difference across the disease specific groups (FET, p 0.041). The figure demonstrates that older people with PBC have the greatest proportion of Fallers, triple that seen in ALD, while NAFLD and PSC groups have similar numbers of Fallers. Post-hoc analyses were not performed; rather the specific CLDs were incorporated into a regression model, results of which are below.

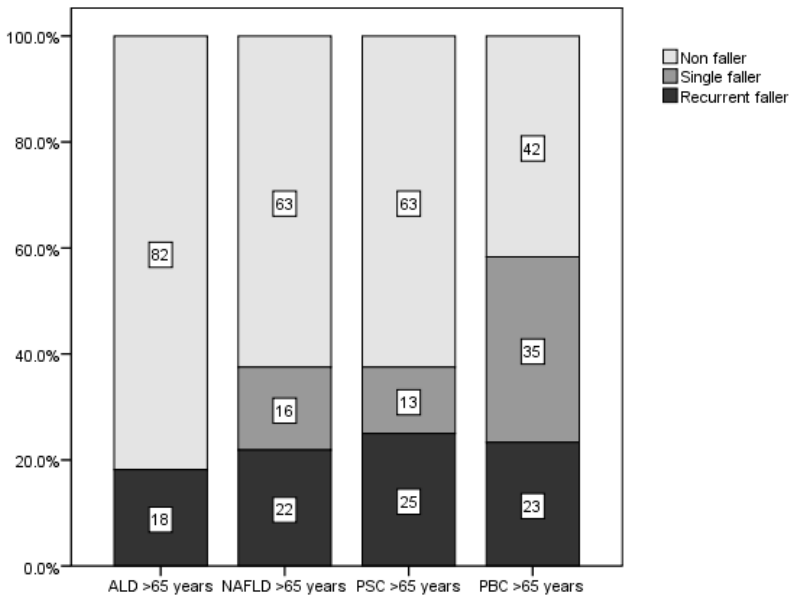


Figure 34. Disease comparisons. Falls prevalence.

Supporting the above results, which suggest that while there is a difference in Fallers across the groups there is not a significant difference in recurrent falls, is the analysis of the number of falls experienced. Figure 35 is useful to demonstrate the highly skewed falls count data with large zero counts and a large number of outlaying (•) and extreme values (*). The median number of falls in each group is 0 with the exception of PBC, in which case the median is 1. This difference does not reach statistical significance however [H 5.208 (3), p 0.157].

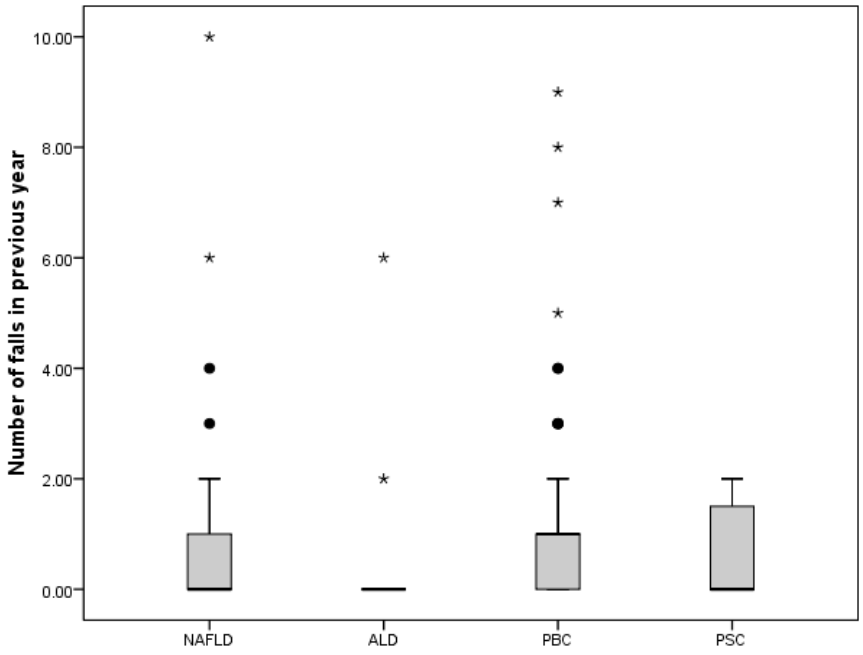


Figure 35. Disease comparisons. The number of falls experienced.

22.4. INJURY PREVALENCE

Within those who had fallen the rates of injury were analysed. Numbers were small and this should be considered when interpreting the results. FET was performed as numbers were small, but this can increase the Type 1 error. Table 26 displays the numbers of Fallers who sustained an injury, and also describes some specific injuries.

	Any injury	Soft tissue injury	Accident & Emergency	Fracture	Hospital admission
NAFLD (*n* 12)	4	3	3	2	2
ALD (*n* 2)	1	0	1	0	1
PBC (*n* 35)	22	22	9	8	5
PSC (*n* 3)	1	1	1	1	1
FET (*p*)	0.269	0.034	0.872	0.914	0.31

Table 26. Disease comparisons. Fall related injury.

Soft tissue injury, demonstrated a significant difference through the disease groups and this is displayed in Figure 36. The proportion of the other injuries did not show a difference through the groups.

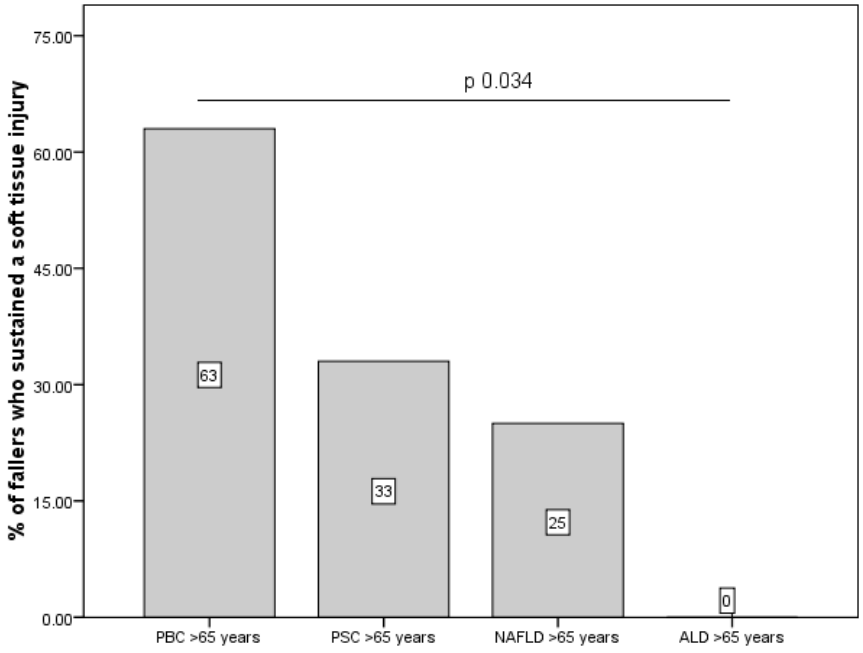


Figure 36. Disease comparisons. Soft tissue injury.

Older individuals with PBC sustained the most soft tissue injuries with ALD having no soft tissue injury (which may be accounted for by the small number of Fallers in the older ALD cohort). Despite this, the results in general would suggest that injuries are important and substantial in all older CLD Fallers.

22.5. FALL ASSOCIATIONS

The results above suggest that falls are more common in older individuals with PBC and least common in older individuals with ALD. However, while a statistical difference was shown across the different CLDs in relation to falls, there were also significant differences seen in the demographic data which ought to be considered. For example, the PBC cohort may have more Fallers because they are an older cohort. In order to investigate this further, regression analyses were performed. All ages were included in the regression models in order to maximise sample size. Age could be built into the model to control for this. A nominal variable for the specific CLDs will be included in order to produce an OR for each specific CLD.

Regression analyses were performed on the Phase 1 data for 2 reasons. Firstly, several significant differences were found between the CLD disease cohort demographic data. The effect of these differences could be explored with a greater sample size using the Phase 1 data. Secondly, as it was not possible to recruit individuals with ALD for a MDT assessment the effects of ALD can not be explored in the Phase 2 regression analyses and the number of individuals in each CLD cohort who underwent was too small to perform regression analyses with disease type as a nominal variable.

Differences in demographic data are displayed in Table 25. Those which showed significant differences across the groups were included in the regression model to see if they accounted for the differences seen in the proportion of Fallers.

Binary logistic regression for the dependent variable Faller or Non-Faller was performed and the model is described below in Table 27 and Figure 37. As PSC was a redundant variable it was not included in the model.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-2.195	2.262	0.111			0.332
Age	0.032	0.015	1.032	1.003	1.063	0.03
Albumin	-.0041	0.041	0.96	0.886	1.039	0.311
Bilirubin	0.001	0.01	1.001	0.982	1.021	0.889
ALP	0	0.001	1	0.998	1.003	0.9
ALT	0.001	0.002	1.001	0.998	1.005	0.5
Cirrhosis	0.493	0.397	1.637	0.752	3.561	0.214
Diabetes	-0.1	0.424	0.905	0.394	2.076	0.813
Male	0.376	0.348	1.456	0.736	2.882	0.28
NAFLD	0.583	0.665	1.791	0.487	6.59	0.381
ALD	0.348	0.717	1.417	0.348	5.773	0.627
PBC	1.289	0.646	3.631	1.024	12.876	0.046

R^2 0.137 (Cox), Hosmer & Lemeshaw χ^2 (8) 3.809, p 0.874

Table 27. Disease comparisons. The binary logistic regression model for Faller or Non-Faller.

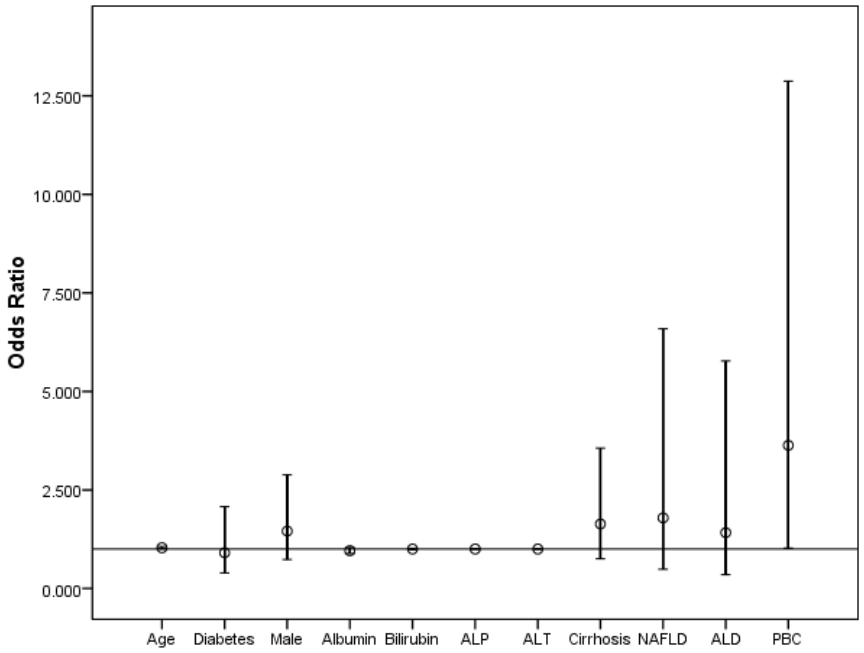


Figure 37. Disease comparisons. The 95% CI for the ORs derived from the binary logistic regression model.

The model described above (based on demographic data, not on fall risk factors) demonstrates that the odds of being a Faller is significantly greater in those with PBC than in those without PBC whereas the other CLDs are not independently associated with being a Faller. In this model, age was also independently associated with being a Faller, although the OR is very slight.

Negative binomial regression was then performed to identify whether specific CLDs were independently associated with the number of falls, PSC was also redundant in this model. The model is described below in the Table 28 and Figure 38.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-0.62	1.5194	0.538	0.027	10.571	0.683
Age	0.007	0.01	1.007	0.988	1.026	0.488
Male	0.376	0.348	1.456	0.736	2.882	0.28
Diabetes	0.823	0.275	2.278	1.328	3.907	0.003
Albumin	-0.035	0.026	0.966	0.918	1.016	0.179
Bilirubin	-0.01	0.007	0.99	0.976	1.004	0.152
ALP	0.001	0.001	1.001	0.999	1.003	0.294
ALT	0	0.001	1	0.999	1.002	0.677
Cirrhosis	-1.034	0.272	0.356	0.209	0.607	<0.001
NAFLD	1.172	0.532	3.229	1.139	9.158	0.028
PBC	1.555	0.525	4.735	1.692	13.245	0.003
ALD	2.29	0.526	9.874	3.52	27.694	<0.001

Model likelihood ratio χ^2 (11) 57.129, p <0.001

Table 28. Disease comparisons. Negative binomial regression model for the number of falls.

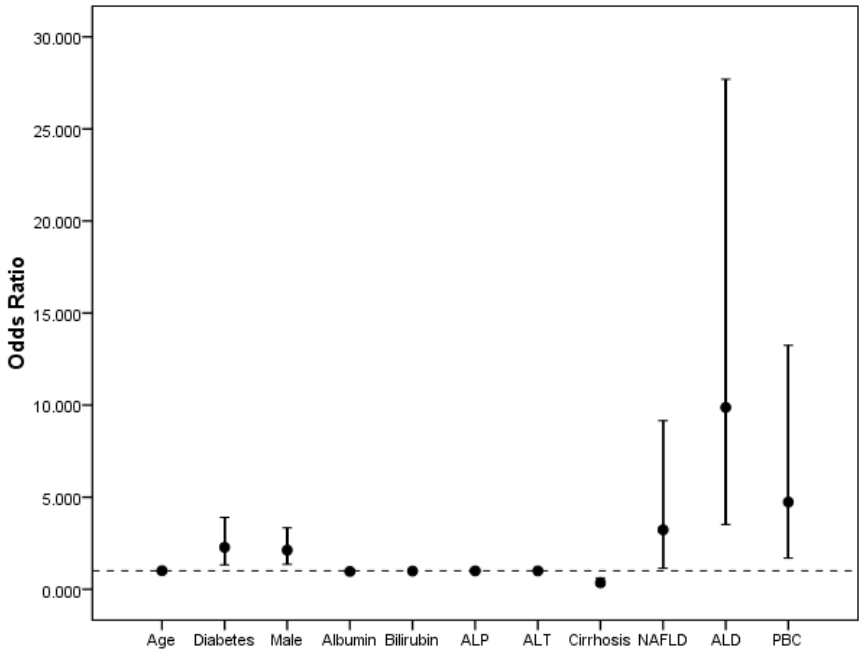


Figure 38. Disease comparisons. The 95% CI for the ORs derived from the negative binomial regression model.

The binomial regression model demonstrates that each specific CLD (with the exception of PSC which could not be calculated in the model because it became redundant) is associated with the number of falls, independent of the demographic data. This model also demonstrates independent associations for diabetes and being male whereas having cirrhosis is independently associated with reduced odds for number of falls.

22.6. SUMMARY

The prevalence of falls varies across the disease-specific older cohorts significantly. The proportion of Fallers is greatest in PBC and declines through NAFLD, PSC and is least in ALD. However, due to small sample sizes, particularly with respect to PSC and ALD, interpretation is tentative. This caution is exaggerated in the injury analysis where it is probably not possible to draw even tentative conclusions.

22.7. DISCUSSION

It is difficult to draw definite conclusions about the differences between the different CLD cohorts because sample size was small in a number of the cohorts, particularly when focussing on the older participants. However, it was possible to include all ages in the regression models and control for

age, revealing that ALD, PBC and NAFLD are independently associated with falls when accounting for disease severity. The draw back here is that the Phase 2 data was lacking for the ALD cohort and could not be included in a regression model.

PBC and NAFLD had larger sample sizes and each of these specific CLDs had significantly greater numbers of Fallers than in age- and sex- matched Community Controls. Interestingly, the associations with falling identified during Phase 2 revealed different associations in PBC and NAFLD. Those associations in NAFLD tended to be related to blood pressure and fear of falling whereas in PBC they were related more to lower limb function (gait, balance, strength) and fear of falling. While it was anticipated that the effects of diabetes, which is common in NAFLD, would cause autonomic dysfunction there was no identifiable association between diabetes and falling in NAFLD. Surprisingly the only autonomic measure which was associated with falling in PBC was the OGS; given the almost universal prevalence of autonomic dysfunction in PBC this was unexpected. Fear of falling, which was identified as an important factor in section 17.5.2, page 72 was also found to be associated with falling in PBC and NAFLD, and independently so in NAFLD. Lower limb muscle strength was identified as the only independent association with falling in PBC and was consistent with the theoretical risk discussed in section 10.2.3, page 22. The lack of a consistently independent association between the liver diseases suggests that either there is a unifying factor which has not been taken into account, that the complexity of falls aetiology precludes the discovery of a unifying factor or that each specific CLD does have differing contributing factors.

The difference in fall associations between the specific CLDs may complicate the suggestions made regarding intervention and prevention programmes in the previous discussion which commented on CLD as a whole. However, the suggested intervention was a multifactorial/multidisciplinary approach and not a single intervention. As the aetiology of falls is complex, using specific falls prevention programmes for specific CLDs may not be appropriate. A multidisciplinary approach enables a thorough assessment with an individualised management plan, regardless of the specific disease. It would be unwise to suggest that those with PBC who have fallen should have leg strength assessed but those with NAFLD should not. And while this leads to the question of how a MDT falls assessment/intervention should be different to a standard programme in the community, it misses the point. The evidence presented here is in favour of further studies to assess the effectiveness of a falls intervention programme in CLD. The dramatic shift in the age of people with CLD and the likely dramatic increase of the 'geriatric syndromes' in the CLD population could

potentially stretch current services available. As the proportion of falls is so great, liver services or geriatric services may need to invest in the skills of a MDT and may require the evidence for such a move in order to secure funding.

Unfortunately commenting on falls in ALD and PSC is limited, but some useful insights may still be drawn. Those with ALD were particularly challenging to recruit. The lack of interest which was seen during clinic recruitment and a lack of interest in undergoing the MDT assessment may suggest that a MDT intervention or prevention programme in ALD may not be worthwhile as individuals would not be willing to participate. It is also important to recognise that those with ALD may not recall falls for reasons described in the introduction but further evidence would be required to support this. It is disappointing that there was insufficient evidence to challenge possible misconceptions about the mechanisms of falls in those with ALD which may be unrelated to the direct effects of alcohol. It was also difficult to recruit PSC participants to the Phase 2 MDT assessments. This was a result of PSC being uncommon but also because the cohort tended to be younger, working males who found it difficult to be assessed during normal working hours. It was not possible to offer an assessment at different times in order to control for the diurnal variation in the autonomic nervous system. However, as the majority of PSC participants who responded to Phase 1 were aged less than 65 years and falls were uncommon in this cohort, it would seem that people with PSC would be unlikely to need the services of a MDT falls assessment/intervention.

22.8. LIMITATIONS

Many of the limitations which were detailed in the whole CLD analysis (section 17.9, page 80) apply here also and will not be repeated. The most obvious limitation is the small sample size in each older specific CLD. However, this study was powered to address its principle aim, CLD, as a whole. The specific disease analyses are secondary analyses only and analysis was always carried out with this in mind. While the falls prevalence figures are interesting, with some specific CLDs such as PBC probably having a large enough sample size to have reasonably powered statistical calculations, interpretation of the fall-related injury prevalence is severely limited and in some cases not possible.

It became clear during the analysis that the binary logistic models were a poor fit of the data. The negative binomial regression models were reliably a good fit of the data with the models being significantly better than the constant alone. The exception to this was seen in NAFLD where

neither regression model was a significant fit of the data which may imply that there are more to falls in NAFLD than can be assessed in a MDT.

The omission of other CLDs such as AIH, viral hepatitis and HCC limits the generalisability of the results, particularly as the majority of people with AIH and HCC are older [25, 34]. However, there are no existing comprehensive, local databases for these conditions and recruitment methods would have been different and less robust, resulting in the same issue of poor generalisibility.

RESULTS - PART THREE

23.1. CHAPTER AIMS

- To determine the prevalence of falls in a post liver transplantation cohort
- To identify the frequency of fall related injury
- To explore modifiable fall associations
- To establish whether falls are less prevalent in a post transplant cohort compared to a non-transplant cohort
- To explore whether transplantation has a beneficial effect on Fallers with CLD
- To identify whether those who fall pre-transplantation will fall sooner after transplant then Non-Fallers

23.2. INTRODUCTION

Those who had undergone LT were analysed separately from the other CLDs as they may be considered to have had definitive treatment. Crudely speaking, LT can be considered as a cure for CLD and as such an improvement in liver disease markers, such as the LFTs, is seen. Despite the laboratory improvements seen it remains controversial as to whether LT improves quality of life [237, 238, 239, 240]. It was unknown whether LT would have a favourable effect on falling but factors which were considered in hypothesis generating were the beneficial effects of transplantation on autonomic dysfunction, the possible negative effect of medications such as prednisolone (muscle weakness) and the possible inactivity of the post-operative period causing inactivity, deconditioning and orthostatic intolerance.

To determine the effect of LT on falls 3 analyses were performed. Firstly, the prevalence of falls and fall related injury in the previous year were defined and compared to controls in a similar manner to that seen in previous chapters. Secondly, comparisons were made to a matched pre- (non-) transplant cohort; thirdly, falls were compared pre- and post-transplant from retrospective recall of those in the LT cohort; and finally a time to first event analysis was performed comparing those who had fallen and those who had not in the pre-transplant period.

24.1. DEMOGRAPHICS

The demographic details of the transplant recipients which were divided into the younger and older age groups are displayed in Table 29 below. The Community controls were age (±0 years) and sex matched to the older LT cohort. Details of transplant indication, time since transplant and age at transplant are also included.

	LT <65 years (*n* 61)	**LT >65 years (*n* 30)**	**Community controls (*n* 30)**	**Statistical differences**
Age [years]	53 (27-64)	68 (65-79)	68 (65-79)	
Female (%)	27 (44)	10 (33)	10 (33)	χ^2 (2) 1.714, *p* 0.46
Diabetic (%)	0	0	0	
Albumin [g/L]	43 (31-50)	44 (30-49)	43 (39-47)	*H* (2) 0.317, *p* 0.854
Bilirubin [μmol/L]	10 (3-46)	8 (3-30)	8 (4-14)	*H* (2) 1.263, *p* 0.532
ALP [U/L]	113 (50-799)	94 (50-375)	76 (50-113)	*H* (2) 19.014, *p* <0.001
ALT [U/L]	28 (9-235)	23 (8-80)	23 (9-32)	*H* (2) 5.9, *p* 0.052
Reason for LT				
ALD (%)	26 (43)	10 (33)		
PSC	7 (11)	8 (27)		
PBC	10 (16)	2 (7)		
NAFLD	3 (5)	3 (10)		
POD	5 (8)	1 (3)		
HCC	2 (3)	4 (13)		
Viral	2 (3)	1 (3)		
Other	6 (10)	1 (3)		
Months since LT	39 (2-155)	43 (3-121)		*U* 810.5, z -0.883, *p* 0.381
Age at LT	51 (19-61)	65 (59-75)		*U* 14.5 z -7.603, *p* <0.001

POD= Paracetamol overdose

Table 29. LT. Demographic details.

Time since transplant was similar between the older and younger recipients, with the median number of years since transplant being 4 years. Given that there was no difference in time since

transplant there was a difference in age at time of transplantation with the median age in the older group being 65 years with the eldest recipient being 75 years old.

24.2. FALLS PREVALENCE

The prevalence of falls in the previous year in a cohort of older transplant recipients was 20%. The proportion of Recurrent-Fallers within this cohort is displayed in Figure 39 below. Compared to the younger LT control group there were fewer Fallers, but only slightly and this difference was not significant [χ^2 (1) 0.481, p 0.488]. Similarly, the difference in Recurrent-Fallers between the older and younger LT cohorts was not significant [FET, p 0.598]. The age- and sex-matched Community Control cohort, which was matched to the older LT cohort, had no Fallers. While it may be considered that this could have occurred due to chance in the matching process the difference was significant for the proportion of Fallers [FET, p 0.024] and the proportion of Recurrent-Fallers [FET, p 0.024].

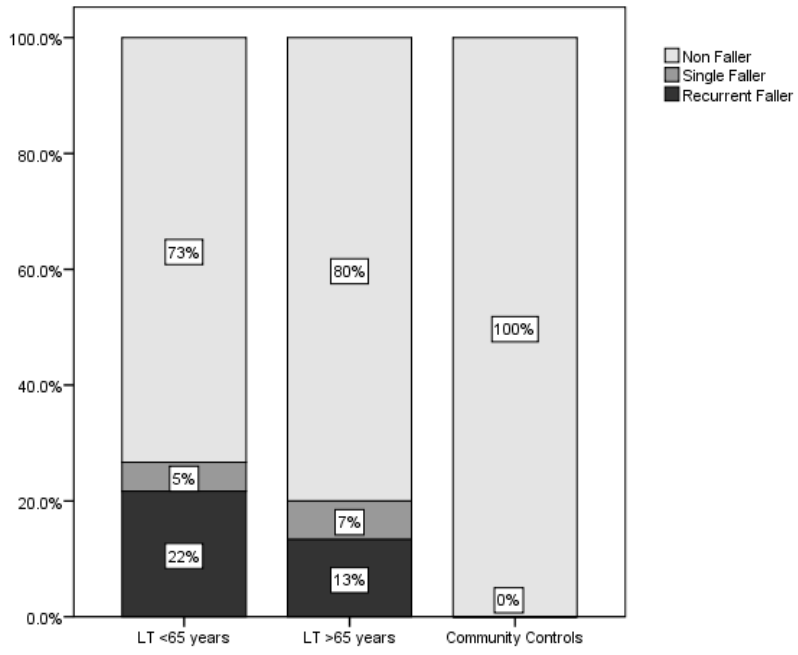


Figure 39. LT. Falls prevalence.

The Figure above demonstrates a larger proportion of Recurrent-Fallers compared to Single-Fallers. This pattern was also seen in several of the specific CLD analyses but not quite to this extent. This would suggest that when a transplanted individual falls, they are likely to do so recurrently. This would be an important finding if injuries are significant in this group. There was a statistically significant difference identified across the 3 cohorts in relation to the median number of falls experienced [LT <65 years 0 (0-23), LT ≥65 years 0 (0-3), Community controls 0, H (2) 9.591, p 0.007]. When considering the falls prevalence in the CLDs in previous chapters, this falls prevalence appears slightly reduced. This will be explored later in the chapter.

24.3. INJURY PREVALENCE

As overall numbers of Fallers was relatively low statistical analyses would not be appropriate. Data is presented below (Table 30) for interest and for consistency but it would be unwise to make comparisons between the groups. Data from the Community control group is from individuals who were matched for age (±1 year) and sex and who had fallen, in order to demonstrate fall related injury.

	LT <65 years (*n* 16)	**LT >65 years (*n* 6)**	**Community controls (*n* 6)**
Any injury	10	3	4
Soft tissue injury	10	3	4
Accident & Emergency	5	1	1
Fracture	4	0	0
Hospital admission	3	0	0

Table 30. LT. Fall-related injury prevalence.

24.4. FALL ASSOCIATIONS

It appears, at first sight, that the falls prevalence is lower in the older LT cohort than seen in previous chapters, although statistical comparison has not yet been made. It may be therefore, that

fall associations will be different in this population. Phase 1 demographic data will be explored first, followed by the comprehensive MDT data. All ages are included in analysis to increase sample size; age will be included in any regression models to account for this.

24.4.1. PHASE 1- ASSOCIATION WITH AGE, DISEASE SEVERITY AND ORTHOSTATIC SYMPTOMS

There was no association demonstrated between number of falls and age nor the LFTs (Appendix B.4, page 223).

One further association could be explored in the LT population which was not explored in the previous CLD chapters. The transplant population data collection occurred after the data collection for the CLD populations because the falls and injury tool required modification. As such, because it appeared that orthostatic symptoms and/or blood pressure were associated with falling in some of the MDT assessments, it was possible to include the OGS tool with the falls and injury postal tool to explore this association further. The result was that orthostatic symptoms associated very strongly with the number of falls in the post-transplant cohort (r_s 0.455, p <0.001). As Spearman rank correlations do not display well on scatter graph this association is displayed in Figure 40 comparing the OGS between the different fall categories, the significance remains on Kruskal-Wallis analysis [H (2) 17.544, p <0.001].

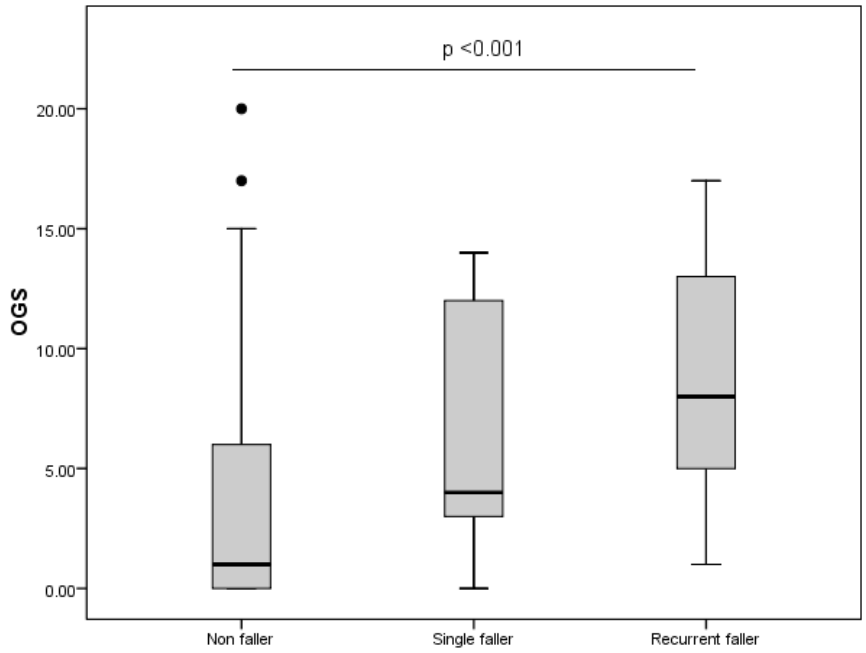


Figure 40. LT. Orthostatic symptoms and falls.

24.4.2. PHASE 2- MDT ASSOCIATIONS

Sixteen post-transplantation individuals underwent MDT assessment. One explanation for the relatively small number compared to the NAFLD and PBC cohort is that the transplant database covers the whole United Kingdom as Newcastle is only 1 of 7 cities (1 of 9 centres) which provide liver transplantation. As a result many of the individuals who responded to the postal tools who did not express an interest in the MDT assessment resided many miles away. All 16 participants are included in analysis to maximise numbers.

Ten (63%) were aged 65 years or more and 9 (56%) were taking anti-hypertensive medication. Five (31%) had abnormal vision and 6 had osteoporosis.

Interestingly, the only measure on MDT which correlated with the number of falls in the previous year was the nadir sBP on standing (r_s -0.499, p 0.049), such that increasing numbers of falls associated with a lower orthostatic blood pressure. This is displayed graphically below with the Kolmogorov-Smirnov non-parametric comparison [z 1.5, p 0.019] of Fallers and Non-Fallers (Figure 41).

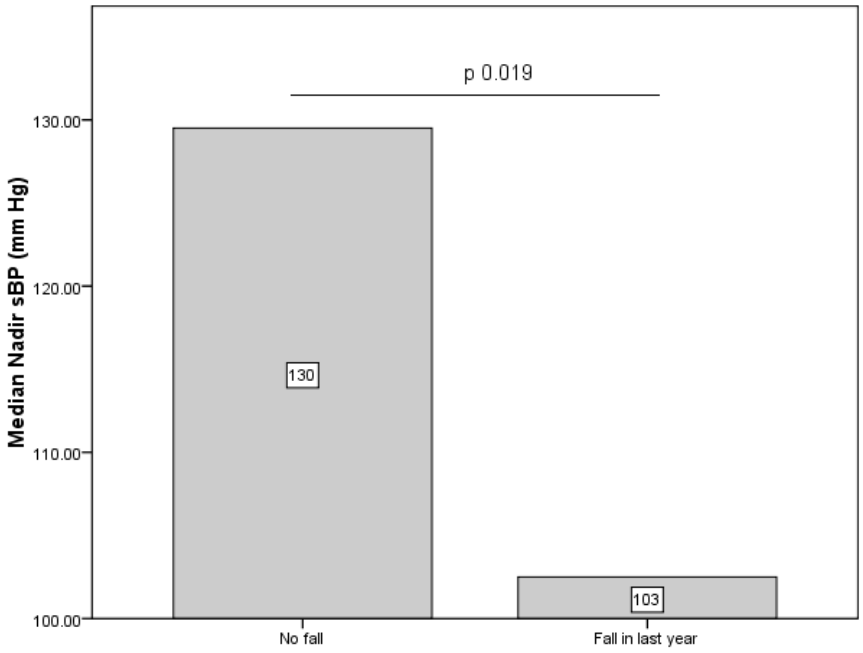


Figure 41. LT. Nadir sBP and falls.

A binary regression model was not attempted due to small numbers in each fall category. A negative binomial regression model was attempted however, to identify whether orthostatic symptoms, nadir sBP on standing were independently associated with being a Faller, while incorporating age into the model to account for all ages being included in the data analyses. The model is displayed below and did not violate the assumptions of regression detailed in the Methods chapter (Table 31 and Figure 42).

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	4.381	4.5215	79.879	0.011	563776	0.333
Age	-0.04	0.051	0.961	0.87	1.062	0.436
Nadir sBP	-0.033	0.248	0.967	0.922	1.015	0.18
OGS	0.399	0.1253	1.49	1.166	1.905	0.001

Model likelihood ratio χ^2 (3) 16.533, *p* 0.001

Table 31. LT. Negative binomial regression model for number of falls.

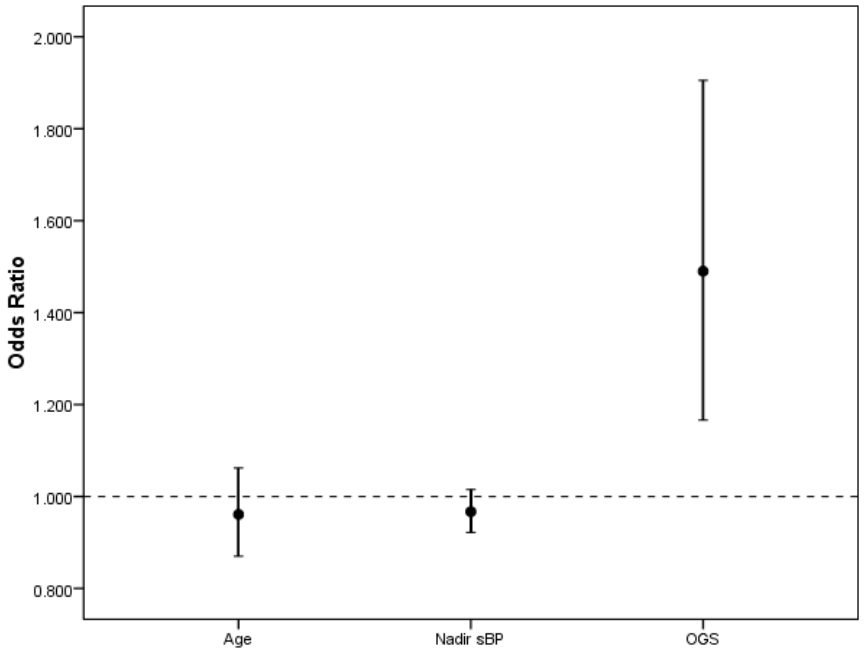


Figure 42. LT. The 95% CI for the ORs derived from the regression model.

The regression model detailed in Table 31 and Figure 42 demonstrates that symptoms of orthostatic dizziness are associated with number of falls independently of age and nadir sBP. This is an important finding for 2 reasons. Firstly, orthostatic symptoms are easy to identify and quantify with the OGS and secondly they are modifiable with conservative measures [241].

24.5. FALLS AND FUNCTIONAL ABILITY

Including all ages of transplant recipients from Phase 1 the associations between the PROMIS-HAQ and falling were explored. Increasing numbers of falls were strongly associated with increasing difficulty with function (r_s 0.469, p <0.001). This association has been displayed graphically using the difference in median PROMIS-HAQ scores below in Figure 43 [Non-Faller 7.5 (0-75), Single Faller 5 (1.25-162.6), Recurrent Faller 46.25 (3.75-80), H (2) 20.357, p <0.001].

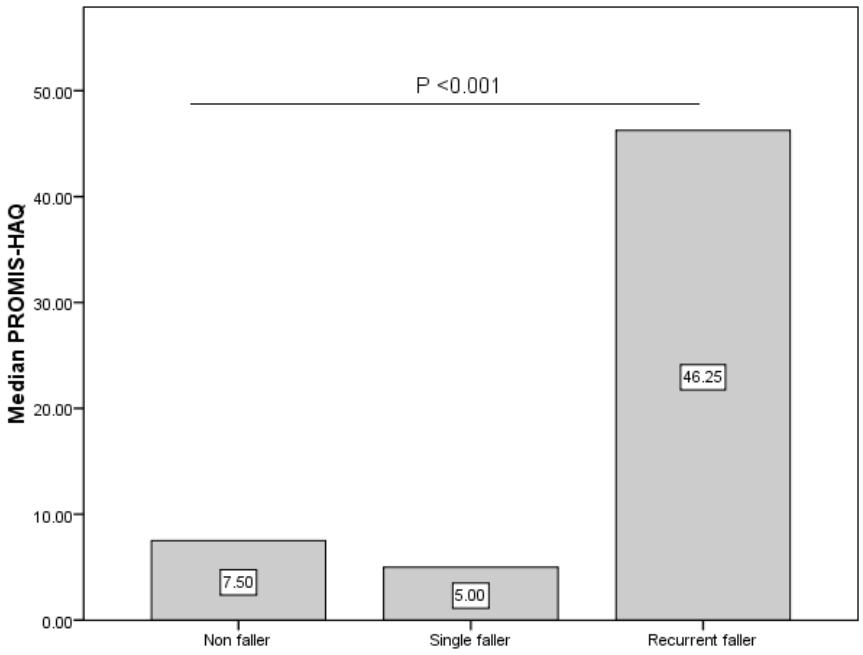


Figure 43. LT. Functional difficulty and falls.

24.6. SUMMARY

The prevalence of falls in an older LT cohort is 20%, significantly more than in matched Community controls. Recurrent falls appeared to be particularly prevalent amongst the Fallers. Falls in people who have undergone LT are unrelated to age and markers of liver disease, but are related to orthostatic symptoms and the degree to which systolic BP drops on standing. Regression revealed that orthostatic symptoms are independently related falls. Functional impairment is particularly severe in those who have fallen recurrently.

25.1. INTRODUCTION

With the results appearing, at first glance, as though falls are less prevalent in the post-transplantation cohort, compared to the CLD cohort, it is important to establish whether this difference exists and whether it is significant. The ideal method to address this question would be to conduct a longitudinal study; however that is beyond the scope of this cross-sectional thesis. Three methods will be used here to attempt to answer this question. The first method will compare a post-transplantation cohort to an age, sex and disease matched non/pre-transplantation cohort. This method has its disadvantages in that it compares 2 matched cohorts without the ability to directly assess the effect of transplantation on falls. The second method is to compare retrospective, self-reported falls in the post-transplant cohort from their memory of before and after the transplant. This has the advantage over the first method in that it controls for many confounding factors and allows for conclusions to be drawn upon the direct effect of transplantation; however it is restricted by the well known limited effect of retrospective recall. It is hoped however, that these methods used alongside each other will provide supportive evidence. A final analysis will study time to event, comparing the time to first post-transplant fall in those who had and those who had not fallen pre-LT.

25.2. COMPARING A POST-TRANSPLANTATION COHORT TO A MATCHED PRE-TRANSPLANT COHORT

The post-transplant cohort was matched for age (±3 years), sex and disease. As falls data were only collected on NAFLD, ALD, PBC and PSC cohorts only those who were transplanted for these reasons were matched and included in this analysis. This allowed controlling for confounding factors such as the effects of diabetes in NAFLD or autonomic dysfunction in PBC. The matched CLD cohort will be referred to as the Non-Transplantation cohort.

25.3. DEMOGRAPHICS

The demographic details for the Non- and the Post-Transplant cohorts are displayed below in Table 32.

	Non-Transplanted (*n* 69)	**Post-Transplant (*n* 69)**	**Differences**
Age [years]	59 (28-80)	59 (28-79)	*U* 2379, *z* -0.006, *p* 0.996
Female (%)	28 (41)	28 (41)	
Diabetic (%)	3 (4)	0	FET, *p* 0.245
Albumin [g/L]	41 (30-49)	43 (31-50)	*U* 1069.5, *z* -2.963, *p* 0.003
Bilirubin [μmol/L]	14 (4-137)	9 (3-43)	*U* 799.5, *z* -4.697, *p* <0.001
ALP [U/L]	122 (40-886)	113 (50-799)	*U* 1381, *z* -1.413, *p* 0.159
ALT [U/L]	42 (12-116)	28 (8-235)	*U* 1220.5, *z* -2.318, *p* 0.02

Table 32. LT. Demographic details (Non- and Post-LT).

As liver transplantation is a treatment, or a cure for some, it is unsurprising to note that the LFTs are, on the whole, significantly 'better' than those with CLD (Table 32). There were surprisingly few diabetics in each cohort, but nevertheless, there were few in each group and the difference was not significant.

25.4. FALLS PREVALENCE

A falls prevalence of 20% was seen in the older post-transplant cohort in the previous result chapter. Here the focus was on determining the effect of transplantation on falls and so individuals of all ages are included. The falls prevalence seen here is slightly different to prevalence described earlier as only those who were matched are included. Figure 44 below displays the proportion of Fallers in the Non- and Post-transplant cohorts. There is no difference between the 2 cohorts when divided into Fallers and Non-Fallers [χ^2 (1) 0.322, *p* 0.706] nor when divided into Single-, Recurrent- and Non-Fallers [χ^2 (2) 1.461, *p* 0.523].

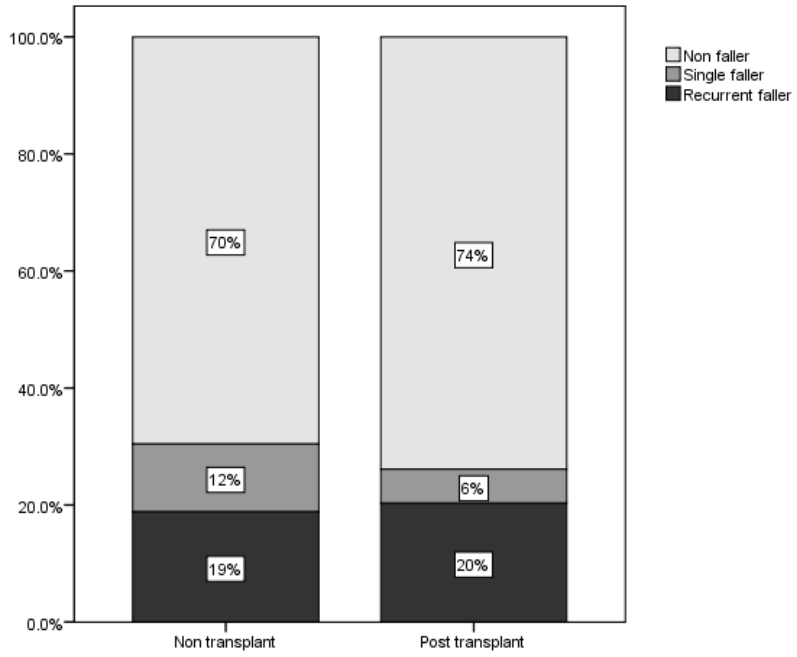


Figure 44. LT. Falls prevalence (Non- and Post-LT).

The graph quite clearly shows that falls are no less common in the Post-Transplant cohort. While this could infer that transplantation would not decrease the number of falls in someone with CLD it does not take into account the fact that often frailer people who may be expected to fall more often may be excluded from undergoing transplantation.

25.5. INJURY PREVALENCE

Those who had fallen from the Post-Transplant group were matched to a Faller from the Non-Transplant CLD group for age (±3 years), sex and CLD. However due to relatively small numbers there were 3 cases which could not be matched for age within 3 years, these were matched within 6, 9 and 11 years. The age difference between the 2 groups did not reach statistical significance (z 0.333, p 0.999). The numbers of injuries sustained in the 2 groups are displayed in Table 33, below.

	Non-Transplant CLD (*n* 18)	**Post-Transplant (*n* 18)**	**Differences**
Any injury	8	12	χ^2 (1) 1.8, *p* 0.315
Soft tissue injury	5	12	χ^2 (1) 5.461, *p* 0.044
Accident & Emergency	6	5	χ^2 (1) 0.131, *p* 1
Fracture	3	3	FET 1
Hospital admission	4	2	FET 0.658

Table 33. LT. Fall related injury (Non- and Post-LT).

The results above suggest that the prevalence of fall related injuries are similar in Non- and Post-Transplanted populations, with the exception of soft tissue injuries which were significantly more common in the Post-Transplant group.

25.6. EFFECT OF TRANSPLANTATION IN REGRESSION

To build the effect of LT into a regression model the Phase 2 data were used. All participants with CLD in Phase 2 were used and the fall associations from this cohort of 87 were explored. Significant associations are displayed in Table 34 below and non-significant associations are included in Appendix B.5, page 224.

	Variable	r_s, p
Active stand	OGS	0.326, 0.003
	sBP	-0.241, 0.026
	nadir sBP	-0.225, 0.037
	RRI 30:15	-0.214, 0.048
HRV	VLF	-0.255, 0.017
	PSD	-0.221, 0.04
MDT	Sit to Stand Test	0.302, 0.006
	Timed Up and Go	0.34, 0.001
	Balance	-0.28, 0.009
	Gait	-0.268, 0.013
	Fear of Falling	0.425, <0.001

Table 34. LT. Phase 2 correlations with the number of falls (all Phase 2 participants).

There was no significant difference in the number of falls between diabetics and non-diabetics [1 (0-12) and 0 (0-30) respectively, U 557.5, z -1.59, p 0.115]. Similarly there was no association with vision [normal 0 (0-30), abnormal 0 (0-12), U 852.5, z -0.589, p 0.559] or cirrhosis [cirrhotic 1 (0-12), non-cirrhotic 0 (0-30), z 0.832, p 0.134].

Significant associations were used to build the regression model with the addition of the new binary, categorical variable, LT or no LT. This would allow for identifying an association between falling and LT while controlling for the identified associations. The binary logistic regression model for fall or no fall is described below in Table 35 and Figure 45.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-4.82	7.252	0.008			0.506
OGS	0.107	0.122	1.113	0.876	1.415	0.38
sBP	-0.03	0.019	0.971	0.396	1.008	0.118
RRI 30:15	-2.356	2.589	0.095	0.001	15.144	0.363
VLF	-0.011	0.006	0.989	0.978	1	0.055
PSD	0.003	0.001	1.003	1.001	1.005	0.009
Sit to Stand	0.116	0.072	1.124	0.976	1.294	0.106
Balance	0.056	0.192	1.057	0.725	1.541	0.773
Gait	0.265	0.385	1.303	0.613	2.772	0.492
FES-I	0.133	0.051	1.142	1.033	1.262	0.009
LT	1.508	1	4.516	0.636	32.063	0.132

R^2 0.451, χ^2 (8) 6.053, p 0.641

Table 35. LT. Binary logistic regression model Faller or Non-Faller, including having had a transplant as a variable.

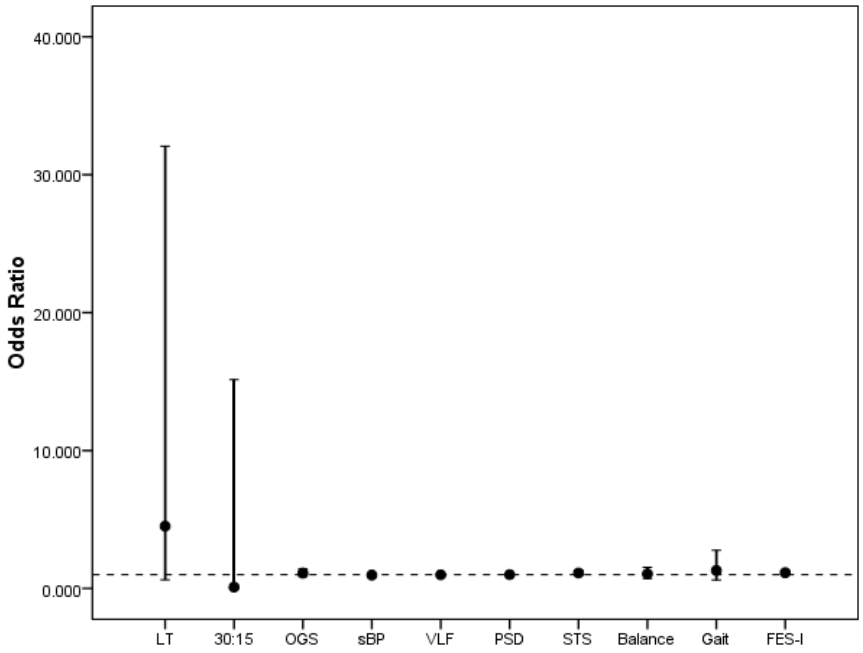


Figure 45. LT. The 95% CI for the ORs derived from the binary logistic regression model.

The binary regression model described above demonstrates that while controlling for fall associations LT is not independently associated with having had a fall. As has been consistent throughout the results chapters the FES-I is strongly, independently associated with falling and here in this model overall HRV (PSD) is also independently associated with having had a fall. This finding was not present in previous results chapter except in the PBC results chapter which found an inconsistent association between HRV and falls. Whether or not these HRV results are important it is not clear and therefore the most appropriate method is to interpret them alongside the other autonomic measures. Furthermore, the aim of this regression analysis was to determine whether LT was associated with falling and as such, here, additional findings are of secondary importance. The negative binomial regression model is displayed below in Table 36 and Figure 46.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Constant	-6.217	4.105	0.002	0.002	6.226	0.13
LT	0.85	0.604	2.339	0.716	7.643	0.16
OGS	0.159	0.07	1.172	1.022	1.345	0.023
sBP	-0.006	0.01	0.994	0.976	1.013	0.556
RRI 30:15	-2.866	2.179	0.057	0.001	4.073	0.188
VLF	-0.002	0.002	0.998	0.995	1.001	0.118
PSD	0.001	<0.001	1.001	1	1.001	0.009
Sit to Stand	0.097	0.029	1.101	1.041	1.165	0.001
Balance	0.102	0.113	1.107	0.887	1.381	0.369
Gait	0.343	0.24	1.409	0.881	2.253	0.153
FES-I	0.063	0.027	1.065	1.01	1.124	0.021

Model likelihood ratio χ^2 (10) 52.555, p <0.001

Table 36. LT. Negative binomial regression model for number of falls, including having had a transplant as a variable.

.

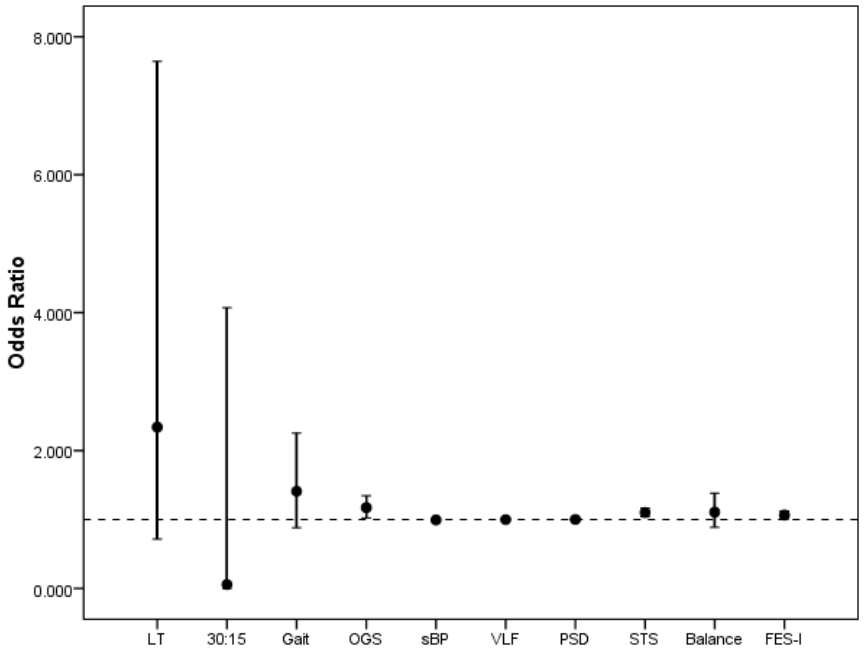


Figure 46. LT. The 95% CI for the ORs derived from the negative binomial regression model.

The negative binomial regression model supports the above model in that it also shows that LT is not independently associated with falling. The variables which were identified as being independently associated with falling were different to those in the binary regression model and are more consistent with previous result chapters (fear of falling, lower limb weakness, orthostatic dizziness but also PSD-a measure of overall HRV). This regression model is also more reliable than the binary logistic model.

26.1. INTRODUCTION

Eighty-nine individuals returned the falls and injury data collection tool with complete falls data for both the time Pre- and Post-Transplant (Table 37).

		Post-Transplant	
		No fall	Fall
Pre-Transplant	No fall	37	16[A]
	Fall	15[B]	21

A=group A, B= group B

Table 37. LT. Falls Pre- and Post-LT.

McNemar's test revealed no statistical difference across the contingency table [χ^2 (1) 0, p 1], which provides further support that transplantation has neither a beneficial effect nor detrimental effect on falling.

In an attempt to further identify features which may be associated with falling and the possible effect of LT on falls comparisons were made between group A and group B (only those who had fallen post-LT versus those who had fallen pre-LT but not afterwards). Phase 1 data was available for comparison and did not identify any difference between these 2 groups, Table 38.

	Group A	**Group B**	***z, p***
Age	61 (41-68)	58 (27-68)	0.778, 0.43
OGS	3 (0-17)	3 (0-17)	0.256, 0.99
Albumin	43 (38-50)	44 (30-50)	0.782, 0.355
Bilirubin	8 (4-17)	8 (3-20)	0.487, 0.829
ALP	113 (55-475)	109 (51-256)	0.602, 0.766
ALT	32 (16-235)	25 (15-154)	0.794, 0.433

Table 38. LT. Phase 1 data for those who only fell before LT compared to those who only fell after LT.

26.2. TIME TO FIRST FALL FOLLOWING TRANSPLANT

Of the 37 Post-Transplant Fallers, 35 retrospectively recorded the length of time to their first fall following transplantation. The median length of time to first fall was 182 days (26 weeks) ranging from 0 to 1460 days (0 to 209 weeks). Time to event did not correlate age, OGS or LFTs, see Table 39.

	r_s, p
Age	-0.019, 0.913
OGS	-0.041, 0.814
Albumin	-0.023, 0.9
Bilirubin	-0.025, 0.894
ALP	0.009, 0.959
ALT	0.019, 0.919

Table 39. LT. Phase 1 correlations with time to first fall after LT.

The effect of transplantation on falls was analysed using Cox regression analysis. A fall Post-LT was considered the dependent variable, while controlling for having had a fall pre-transplant, the OGS and age. The Model is displayed below in Table 40, with the resulting hazard ratios (HR) in Figure 47.

	b	SE	HR	95% Confidence intervals (OR)		*p*
				Lower bound	Upper bound	
Fall pre-transplant	0.274	0.366	1.315	0.642	2.694	0.454
OGS	0.02	0.036	1.02	0.95	1.095	0.578
Age	0.021	0.018	1.021	0.986	1.058	0.245

Table 40. LT. Cox regression model for time until first fall following LT.

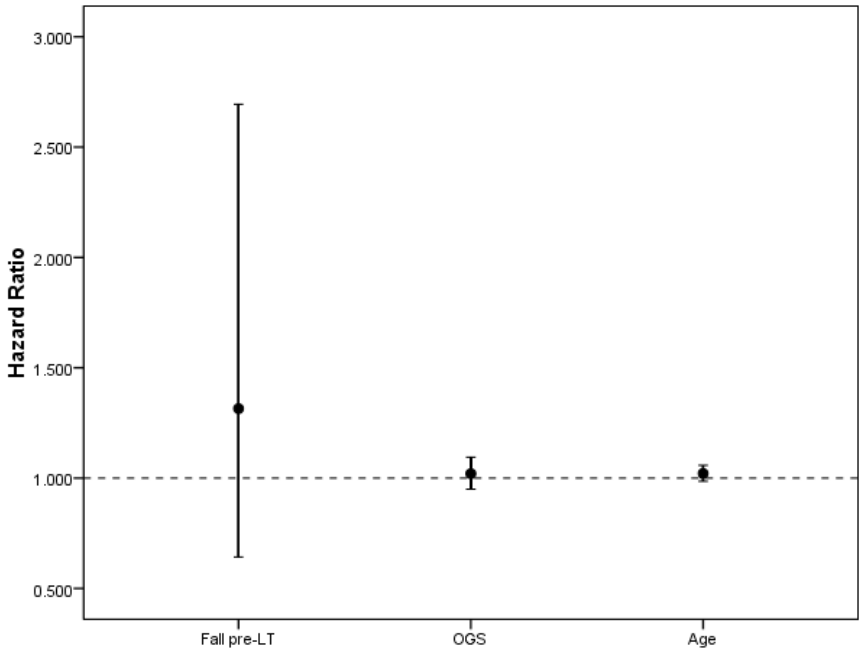


Figure 47. LT. The 95% CI for the HRs derived from the Cox regression model.

The effect of transplant on falls can further be described in Figure 48 below. This displays the time until first fall following transplant for those who had fallen pre-transplant and those who were fall-free pre-transplant. The lines cross several times and demonstrate no difference in time to event.

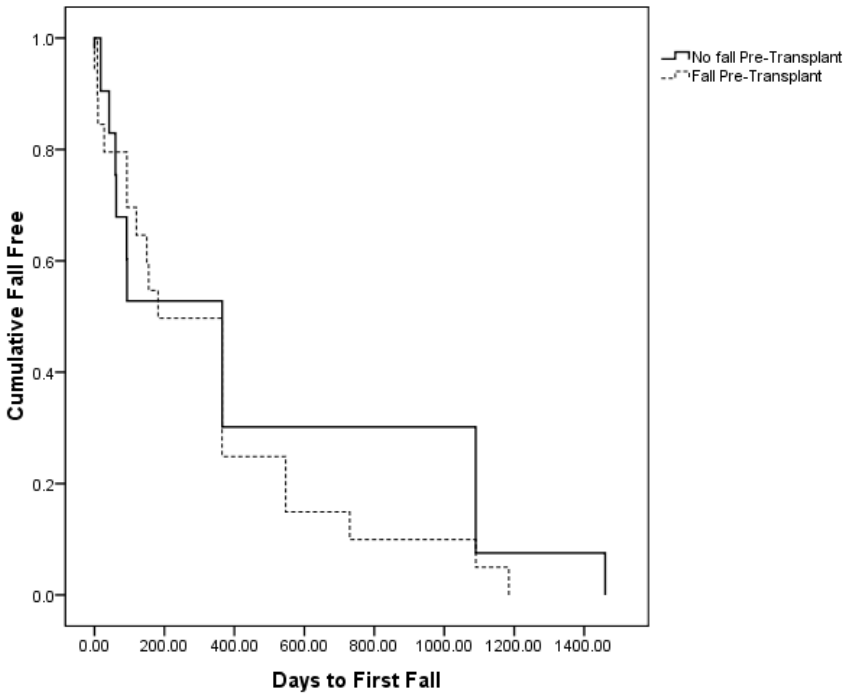


Figure 48. LT. Cumulative frequency of being fall free over time since LT.

Cox regression analysis revealed that having had a fall pre-LT did not increase the risk of having a fall post-LT. As this study was cross-sectional with retrospective recall of falls it was not possible to analyse possible confounding factors which may explain why some individuals fell post-LT but not before. The effect of LT on autonomic dysfunction and falls would be of particular interest but could only be analysed in a longitudinal study.

26.3. SUMMARY

The prevalence of falls and fall related injury are similar in a LT cohort to a non-transplant-CLD cohort but significantly greater than a community control group. Falling is related to the nadir sBP on standing and to symptoms of orthostatic dizziness. LT appears to have neither a beneficial or detrimental effect on falling and does not prevent falls occurring in those who have fallen pre-LT. A small proportion of individuals, who underwent LT and did not fall in the pre-LT period, went on to have a fall following LT. It would be interesting to study this group further, particularly focussing on changes in autonomic function following transplantation.

26.4. DISCUSSION

Falls are significantly more common than in community controls and are similar to those seen in CLD. Indeed, 26% of the younger and 20% of the older LT cohort had fallen in the previous year with 59% of Fallers sustaining an injury. These figures demonstrate that falls are common and must be taken seriously by clinicians who are faced with LT patients. Numbers were relatively small in the injury analysis and as such it is unwise to draw definitive conclusions. However, with the high incidence of bone disease in those who have undergone LT with additional risk factors for the elderly, the potential for devastating injury is high [242, 243]. Although it has become widespread to prescribe bisphosphonates in the LT population there is conflicting data concerning the prevention of fractures [79]. Studies which have focussed on an improvement in bone density have not, in general, assessed the effect on fractures. There are at least 2 studies which have included both bone density and fracture rates which did not demonstrate a reduction in fractures [244, 245]. Other observational studies which have shown a reduction in fracture rates over longer periods of time may be confounded by the fact that the use of tacrolimus is increasing whereas the use of cyclosporine, which is associated with osteoporosis, is decreasing [246]. The importance of these results, alongside the results of this study, stress the importance of preventing falls and thereby preventing possible fall associated fractures and morbidity.

A longitudinal study would be ideal to reveal risk factors for falling post-LT however this cross-sectional study was able to reveal several factors associated with falling which are considered as risk factors in the general population. Those factors which showed no association with falling are also worth considering. Falls are not associated with advancing age which is often the explanation of many patients and clinicians alike. Furthermore, falls were not associated with markers of liver disease severity in the post-LT cohort. The single factor which did associate with falling in Phase 1 was orthostatic dizziness (OGS). As the OGS has previously been shown to correlate strongly with comprehensive laboratory autonomic assessment this result suggests that autonomic dysfunction is associated with falling in post-LT individuals. This association was explored further in the Phase 2 MDT phase of the study. Autonomic assessment was able to demonstrate that the nadir systolic blood pressure was significantly lower in those who had fallen, further evidence for the role of autonomic dysfunction as a cause for falling. Regression analysis revealed that it was the symptoms of orthostatic dizziness rather than the actual sBP which was independently associated with falling. The OGS is a self-completed tool comprising questions which relate to everyday situations in which individuals may experience postural dizziness and therefore reflects real life

situations and symptoms whereas the autonomic assessment performed in Phase 2 is an artificial and isolated single situation. However, there may be an alternative explanation for why symptoms are independently associated with falls regardless of the sBP drop, cerebral auto-regulation. There is evidence that symptoms of postural dizziness can be related to abnormalities of the cerebral circulation in the context of a normal systemic blood pressure [247]. In addition, there is some evidence that cerebral auto-regulation (CA) is impaired in CLD (specifically PBC) [248, 249]. When functioning well, CA maintains cerebral blood flow and perfusion within an acceptable limit even during large changes in systemic blood flow/pressure. Symptomatic OH is thought to occur when the cerebral blood flow/perfusion pressure is unable to respond to a large change in systemic BP, either because the change is too large or because there is impairment of CA. Further research would be required to support this suggestion.

Orthostatic dizziness as a risk factor for falling is important to identify as it is modifiable with simple, conservative measures such as an increased fluid intake, compression stockings and physical manoeuvres [241]. The NICE guidelines recommend performing a cardiovascular examination as part of the multifactorial risk assessment for people at risk of falling and with the evidence presented in section 10.2.1, it would seem essential that assessing for OH should form a standard MDT falls assessment.

A variety of analyses failed to demonstrate a positive or negative effect of LT on falls and while the matched analyses demonstrated significantly better LFTs than those with CLD it is important to remember that laboratory results must not be taken as the sole indicator of an improvement. Quality of life studies have demonstrated that LT does not consistently improve life quality in the long term [250, 251, 252, 253]. Here it has been demonstrated that falls are strongly associated with increased functional difficulty and while it is not possible to determine cause or effect a common sense approach would indicate that falls do reduce quality of life and increase functional impairment. Falls are an important issue and they will occur with increasing frequency in the LT population as the age of people who undergo transplantation and re-transplantation is increasing [27, 254]. Clinicians need to be aware of the challenges which their patients will face and services need to be prepared for these changes.

26.5. LIMITATIONS

A response rate to the postal data collection tool of 57% was reasonable but larger numbers would have increased sample size, power and generalisability. It is well documented in the literature that

a follow up telephone call or sending a second copy of the tool can increase response rates, as can a telephone call prior to sending. None of these methods were undertaken and it must be considered that these individuals, who had given prior consent to be contacted, should not feel under duress or feel hassled to complete the tools. Indeed, at the outset of the study the Caldicott Principles were reviewed and one of these principles was to use patient identifiable data only when absolutely necessary. As the study was designed and powered to calculate falls prevalence in the CLD population it was not considered absolutely necessary to contact the non-responding LT individuals to increase sample size.

The geographical distribution of the LT cohort also appeared to have an impact upon recruitment for the MDT assessment with those residing further away tending to not express an interest in further assessment. As such the sample size for the Phase 2 MDT LT cohort was smaller than anticipated. This small sample size prevented a binary logistic regression from being performed due small numbers in each fall category. However, it was possible to explore falls associations in the negative binomial regression model.

As Newcastle upon Tyne Hospitals NHS Trust receives patients for LT from anywhere within the UK the LT cohort is derived from a different geographical region to both the CLD cohort and the Community Control cohort. The effect of this difference is unknown but it can not be incorporated into analysis and controlled for. It is also worth considering that only those who were transplanted in the previous 5 years were included in the cohort. This could affect the reported prevalence of falls in LT as it is unknown whether the very long term effect of LT will have an impact of falls.

Determining the effect of LT on falls would be limited given the cross-sectional design of this study. However an attempt was made to overcome these limitations by performing different analyses, each of which would provide supportive evidence. The first analysis which compared a post-LT cohort to a matched CLD cohort who had not undergone LT was limited by not directly being able to analyse the effect of transplantation, rather it compared a LT cohort to a non-LT cohort. However, this method had the advantage over the second analysis used (which was dependent on longer term, retrospective recall) as the first analysis compared falls in the previous year. The second analysis was performed using only the LT cohort with recall of falls pre- and post-LT. Retrospective recall is notoriously poor and increasingly so as length of time from event increases. The result could be that the prevalence of falls pre-LT could be under-reported and as such the effect of LT on falls could be underestimated here.

RESULTS – PART FOUR

27. A PILOT STUDY TO EXPLORE THE RELATIONSHIP BETWEEN ORTHOSTATIC SYMPTOMS AND CEREBRAL AUTOREGULATION

27.1. CHAPTER AIMS

- To compare cerebral autoregulation in a liver disease cohort to a control group
- To identify any relationship between orthostatic symptoms and cerebral autoregulation
- To explore whether falls may be associated with cerebral autoregulation

27.2. BACKGROUND

In reviewing the results of the work presented in this thesis and in formulating the discussion and conclusions, an unexpected finding arose. In section 17.5.2, page 72, the negative binomial regression model demonstrates an independent association between the number of falls and symptoms of postural dizziness in people with CLD. The same finding is presented in the post-LT regression model in section 24.4.2, page 132. While this may not appear to be particularly outstanding the association between orthostatic symptoms and falls is unrelated to all measures of BP, including the degree to which it drops on standing.

From clinical experience and from published descriptions of cohorts with OH it is well known that OH causes light-headedness, dizziness and orthostatic intolerance [255, 256, 257]. However, these symptoms can also be caused by other conditions in which OH is not present, such as postural tachycardia syndrome (POTS). Conversely, OH can also be present in the absence of symptoms [257]. The difference between symptomatic and asymptomatic OH is thought to be the result of cerebral autoregulation, whereby an individual with dysfunction of cerebral autoregulation is unable to maintain perfusion pressure in the presence of a decrease in systemic BP [258]. These conclusions, however, are based on a small number of studies composed of small sample sizes, and use novel research methodology to estimate, rather than directly measure, cerebral autoregulation.

27.3. INTRODUCTION

Studies relating to the control of the cerebral circulation are relatively young, principally because of the difficulties in measuring the blood flow of vessels encased within the human skull. However, the concept of cerebral autoregulation (CA) attracted increasing attention over the second half of

the 20th century when it became possible to estimate cerebral blood flow using indicator flow techniques [259]. This method, being time consuming, only allowed for mean values of cerebral blood flow (CBF) over several minutes and could not reflect dynamic, rapid responses to changes in blood pressure [260]. In the 1980s transcranial Doppler (TCD) ultrasound became available and dramatically changed the way CA could be studied. The resulting knowledge allowed for an increase in the understanding of the relationship between arterial pressure, intracranial pressure and cerebrovascular resistance in maintaining CBF; the process being termed CA.

CA is essential to maintain stable and constant blood flow to the brain in the presence of fluctuating systemic BP in order to supply the high and constant demand for metabolic substrates. It is vital to have intact CA in the presence of episodic drops in systemic BP, such as during standing from a supine position, in order to initiate protective mechanisms, preventing cerebral ischaemia and infarction. A normal response to a reduction in BP and hence blood flow arises from a withdrawal of stretch on the cerebral arterialar wall smooth muscle, initiating both a local biochemical response and a global autonomic response, inducing smooth muscle relaxation thereby increasing CBF (Figure 49) [261]. A great deal is unknown about CA, particularly the autonomic reflexes involved; if further understanding is to be achieved it is likely that new techniques will need to be developed alongside an improved understanding of the complex, confounding metabolic factors involved.

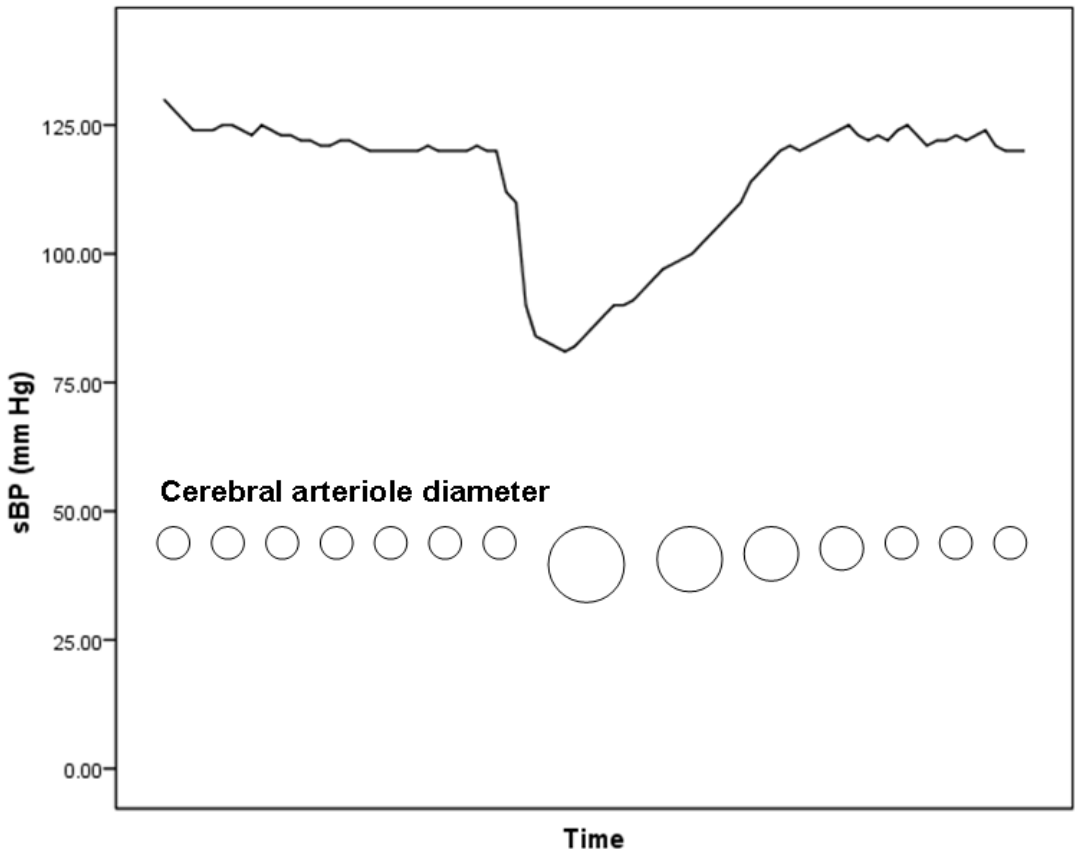


Figure 49. TCD. Normal response of cerebral arteriole diameter during a decline in BP

27.3.1. TRANSCRANIAL DOPPLER

TCD is a highly useful clinical and research tool because it is entirely non-invasive. Furthermore, it is cheap, does not require pharmacological agents and provides real-time, dynamic measurements of CBF. It is preferable to other non-invasive methods such as functional MRI, as it is low cost and is more sensitive to rapid changes in cerebral blood flow velocity (CBFV) [262]. With the contiguous development of non-invasive, beat-to-beat BP measurement techniques it became possible to study dynamic, rapid changes in CBF velocity (CBFV) as changes in BP occurred.

In order to quantify CBFV a cerebral artery must be insonated with a transcranial Doppler probe (Figure 50). The skull poses a significant problem when using ultrasonic radiation as the waves are absorbed or reflected by the bony skull. Fortunately there are four windows through which it can be possible to visualise the arteries. The most commonly used window is the transtemporal window, through which three arteries can be visualised, with the middle cerebral artery (MCA)

being the most commonly used in the literature [263]. CBF is estimated from the blood flow velocity, calculated using Doppler, and the diameter of the vessel, which is thought to remain constant in the MCA [264].

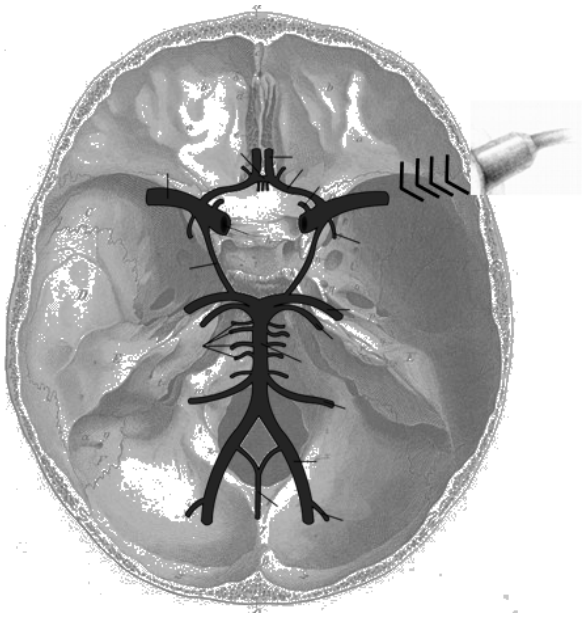


Figure 50. TCD. The TCD probe insonates the right MCA via the right temporal window

27.3.2. INDUCING HAEMODYNAMIC CHANGES

In order to assess CA it is necessary to induce and monitor changes in systemic BP to identify appropriate changes in CBFV. There are several methods which can be employed to induce hypotension. One of the first methods to be used was 'step decreases in blood pressure' which used large, inflated thigh cuffs, which when rapidly deflated induced a drop in systemic BP [265]. This method is uncomfortable for the participant and as there are other more comfortable methods available it would unethical to perform this method.

Lower body negative pressure can be used to induce hypotension [266]. During this procedure the participant's body is encased, from below the diaphragm, in a sealed box, which via a vacuum, has a lower than atmospheric pressure. The negative pressure within the sealed box causes veno-dilatation and hypotension, however these changes may occur slowly and so rapid changes in CBFV can not be measured. The procedure could continue with the aim of inducing a vasovagal

response with a rapid decline in BP; however this would risk inducing syncope and is considered unnecessary when alternative, simpler methods are available. A variation of this method would be the head-up tilt test, but in addition to the risk of syncope there are significant changes in end-tidal carbon dioxide which can influence CBFV [267].

An obvious method to induce rapid, transient hypotension would be active standing from a supine position. This would also have the added advantage of being particularly relevant to the work presented in this thesis. However, in order to induce a transient hypotension the participant would be required to stand relatively quickly which in the case of some participants would be challenging; furthermore the participants would be wearing the beat-to-beat BP monitoring equipment, thereby disabling one arm, and the TCD equipment fixed in place to the head, making the process of standing from a supine position very difficult. It is also essential the TCD probe remains fixed in place throughout as the CBFV is partly based on the diameter of the vessel insonated; any change in the position or angle of the probe would make comparison to the baseline value worthless.

A much more simple, safe and reliable method of inducing BP change is the valsalva manoeuvre. The methods used to perform this have been described in section 15.6.3.4, page 55. Essentially, the valsalva induces hypotension by increasing intrathoracic pressure so that venous return to the right atrium is reduced. The added benefit is that on release of the strain there is a reflex hypertension as venous return is restored and the sympathetic drive is active, this allows for measuring the CBFV response to hypertension. The valsalva is simple and painless for the participant and as it is performed while motionless it reduces movement of the TCD probe. The principle disadvantage of the valsalva is the variability in technique and effort between participants such that a poor haemodynamic response may be induced, however this can be limited using the best-of-three principle and the response can be assessed real-time while it occurs.

27.3.3. MEASURES OF DYNAMIC CA

The measurement of CA is based on cerebral blood flow velocity (CBFV), which is estimated using TCD insonation of the right MCA, alongside the beat-to-beat monitoring of systemic BP. Using these measurements and following equations, CA can be estimated:

Cerebrovascular resistance (CVR) provides an estimate of the resistance of the small cerebral blood vessels based on the following formula (calculated by the Task Force® Monitor programme):

$$CVR = \frac{BP_{mean}}{CBFV_{mean}}$$

Pulsatility Index (PI) is an additional measure of vessel resistance based on the following (calculated by the Task Force® Monitor programme):

$$PI = \frac{CBFV_{systolic} - CBFV_{diastolic}}{CBFV_{mean}}$$

The Autoregulatory Index (AI) is a reflection of the CBFV response to a change in BP. The AI-2 is the response of the CBFV to the change in BP between phase 2a and phase 2b of the valsalva (i.e. How CBFV responds to the partial recovery of BP during the strain phase of valsalva):

$$AI - 2 = \frac{CBFV_{(phase2b-phase2a)} \big/ CBFV_{(phase2a)}}{BP_{(phase2b-phase2a)} \big/ BP_{(phase2a)}}$$

AI-4 is the response of CBFV to the change in BP between phase 1 and phase 4 of the valsalva (i.e. how CBFV responds to the change in BP from just prior to strain to just after releasing the strain):

$$AI - 4 = \frac{CBFV_{(phase4)} \big/ CBFV_{(phase1)}}{BP_{(phase4)} \big/ BP_{(phase1)}}$$

For both AIs it would be expected that normal CA would result in values of greater than 1.00.

The Autoregulatory Slope Index (ASI) reflects the difference in the change of BP and the change in CBFV as a percentage (where phase 2a is the start of the phase 2 slope and +3s is the value 3 seconds following the beginning of phase 2):

$$ASI = \left(\frac{CBFV_{(phase2a+3s)} - CBFV_{(phase2a)}}{CBFV_{(phase2a)}} - \frac{BP_{(phase2a+3s)}}{BP_{(phase2a)}} \right) \times 100$$

The ASI has the advantage over the AI because it allows a small time difference, in effect, to allow the CBFV to respond to the change in BP. The ASI also allows for the decrease in cerebral perfusion pressure (CPP) resulting from the cerebrospinal fluid transmission of intrathoracic pressure. The decrease in CPP results in cerebral vasodilatation just as a decrease in BP during phase 2 of the valsalva would also result in vasodilatation. But as release of strain at phase 4 of the valsalva

results in an immediate increase in CPP, and therefore vasoconstriction, any remaining vasoconstriction 3 seconds after release will be the result of CA.

27.3.4. CEREBRAL AUTOREGULATION IN CLD

As the prevalence of AD is relatively high in people with CLD it could be anticipated that CA is impaired in those with CLD. However, studies assessing CA in people with CLD have generally focussed only on those with severe or cirrhotic disease [268, 269, 270]. Furthermore, these studies have small sample sizes, lack power calculations and in almost all cases study resting CBF rather than dynamic CBF. These studies are summarized in Appendix C where the inconsistency in results can be seen. It is unknown how cirrhosis, or even CLD, causes or contributes to impaired CA. One study noted an impaired sympathetic response of CA during hypotension, on spectral analysis and others have noted in longitudinal studies that CA improves following transplant [271, 272].

When CA is absent or impaired CBF is dependent on adequate levels of systemic BP; however, if systemic BP falls and CA can not respond adequately, CBF will decrease and cerebral ischaemia and infarction could result. It is in this situation that symptoms of orthostatic dizziness occur and why it is hypothesized that CA is present in CLD [258].

27.4. METHODS

27.4.1. RESEARCH DESIGN

A cross-sectional approach was undertaken in this small, pilot study of CA in CLD. Almost all existing studies are limited to participants with cirrhosis; however this pilot study included participants regardless of disease severity. All subjects included underwent TCD during a resting period and during a valsalva manoeuvre in order to assess resting and dynamic CA. Results from the CLD cohort were compared to a non-liver disease, control cohort.

27.4.2. ETHICAL APPROVAL

This small, pilot study was approved by the North Tyneside Local Ethics Committee. All participants were fully informed of the study and provided written consent.

27.4.3. SUBJECTS

Subjects with PBC were enrolled from the Newcastle upon Tyne Hospitals autoimmune liver clinic. The CLD participants were limited to people with PBC. From the MDT assessments described earlier in this thesis, the PBC cohort had significantly greater levels of orthostatic dizziness and therefore represented an ideal group in which to explore the relationship between CA and postural dizziness. In addition, as the prevalence of AD is high in PBC there was a greater chance of impaired CA being found on TCD which was necessary to relate to symptoms on the OGS. Each participant had confirmed PBC, as defined in section 15.5.3, page 46.

Controls were recruited as friends or family of those participants with PBC and had no history of liver disease, cerebro-vascular disease or conditions which could contribute to AD, namely diabetes and Parkinson's disease.

27.4.4. DATA COLLECTION

Autonomic data was collected using identical principles of autonomic assessment as detailed in section 15.6.2, page 47 in order to reduce variation in diurnal autonomic function and circulating catecholamines. To monitor systemic BP participants were monitored with the Task Force® equipment described in section 15.6.2.

27.4.5. TRANSCRANIAL DOPPLER

TCD signals were recorded continuously using LabWindows® software which was coupled to the Task Force® Monitor in order to completely synchronise BP and CBFV recordings. While in a supine position a 4 MHz ultrasound probe (Digilite®, RIMED Ltd, Israel) was used to insonate both the common and internal carotid arteries of the participants, in order to exclude those participants with 50% or greater carotid artery stenosis. Following this, a 2 MHz ultrasound probe was used to locate the right MCA through the right temporal window. In those in whom it was not possible to locate the right MCA an attempt to localise the left MCA was made, however in those cases where the right MCA could not be localised, it was also not possible to insolate the MCA on the left. Once the temporal window was located a Muller-Moll probe fixation device was used to hold the probe in place. Continuous systolic, diastolic and mean CBFV was recorded and displayed on the Task Force® Monitor alongside the continuous systolic, diastolic and mean BP.

27.4.6. ASSESSMENT OF AUTOREGULATION

Measures of resting CBF, CVR and PI were taken from the final 2 minutes of supine rest in order to achieve stable cardiovascular values. Following this, participants were assisted into a sitting position where they remained for 2 minutes to achieve stability before beginning the valsalva. The valsalva manoeuvre was performed in an identical manner to that described in section 15.6.3.4, page 55. Continuous TCD and BP recordings were observed and recorded throughout the manoeuvre and assessed for optimal technique. Two valsalvas were performed by each participant with a 2 minute rest between each. If both attempts were judged to be poor then a third was attempted.

End-tidal CO_2 was recorded using a nasal cannula and infrared capnography (Oxipulse® Capnograph system, SIMS-BCI, USA) during the rest period in order to monitor potential confounding from the effects of swings in arterial CO_2 concentrations on cerebral arteriolar diameter; however as the valsalva involved exhaling into a closed system through the mouth the end-tidal CO_2 could not be measured via the nasal cannula during valsalva.

27.4.7. DATA ANALYSIS

Recordings of the continuous TCD and BP measurements were assessed to identify the different phases of the valsalva manoeuvre and the changes which occurred in CBFV during the changes in BP. The results were then used to calculate the indices of CA which are described earlier.

Non-parametrically distributed data are described with the median alongside the minimum and maximum value. Differences in non-parametrically distributed data were analysed using the Kolmogorov-Smirnov *z* test, which has better power than the Mann-Whitney *U* test when assessing small sample sizes. Associations were assessed using the Spearman rho (r_s). Results were considered significant when $p < 0.05$.

27.5. RESULTS

27.5.1. RECRUITMENT

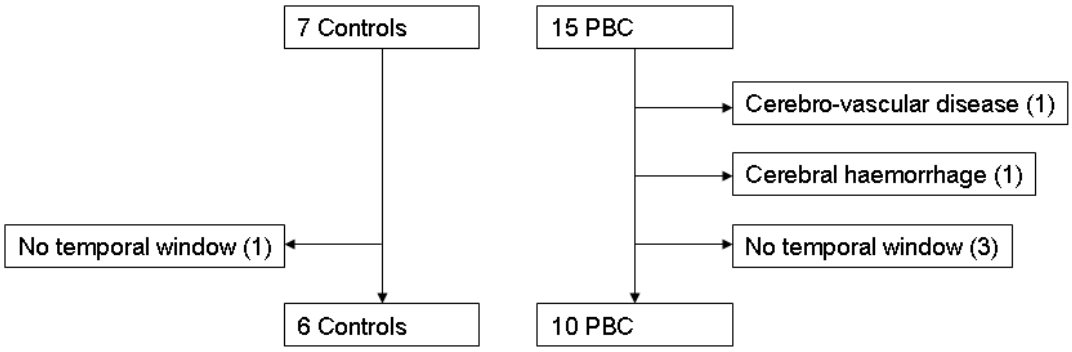


Figure 51. TCD. Recruitment of the TCD cohorts.

Figure 51 above displays the process of recruitment to the study and the resulting cohort size.

27.5.2. DEMOGRAPHICS

Table 41 below describes the PBC participants and the controls. They were similar in terms of age, baseline BP and HR. It also demonstrates that resting levels of CBFV, CVR and PI were similar between the PBC participants and the Controls.

	PBC (*n* 10)	**Controls (*n* 6)**	***z*, *p***
Age (years)	65 (50-77)	52 (28-66)	0.968, 0.176
sBP (mm Hg)	124 (60-149)	123 (110-143)	0.387, 0.992
dBP (mm Hg)	80 (29-100)	84 (64-105)	0.452, 0.96
HR (bpm)	68 (54-83)	61 (58-75)	0.71, 0.577
End tidal CO_2	5.6 (4.4-5.9)	5 (4.9-5.1)	1.162, 0.134
sCBFV (cm/s)	66 (42-75)	65 (38-80)	0.645, 0.713
dCBFV (cm/s)	24 (12-37)	29 (17-48)	0.645, 0.713
CVR	2.3 (1.1-4.5)	2.2 (1.5-3.1)	0.581, 0.835
PI	0.9 (0.7-1.7)	0.8 (0.5-0.9)	1.162, 0.092

Table 41. TCD. Descriptive data of the cohorts.

27.5.3. DYNAMIC CEREBRAL AUTOREGULATION

A normal CA response to a change in BP is to maintain CBFV within a narrow range, ensuring continual supply of nutrients to the brain. During the valsalva the BP is forced to decrease with a reflex increase in BP following release of strain. Figure 52 below displays the sBP and the CBFV for a Control participant with the resting period leading up to the vertical dotted line; after the dotted line the sBP decreases during phase 2a of valsalva and on release of strain, at the dashed vertical line there is an overshoot of sBP. It can be seen that the CBFV, the bottom line, is tightly controlled even during fluctuations in sBP.

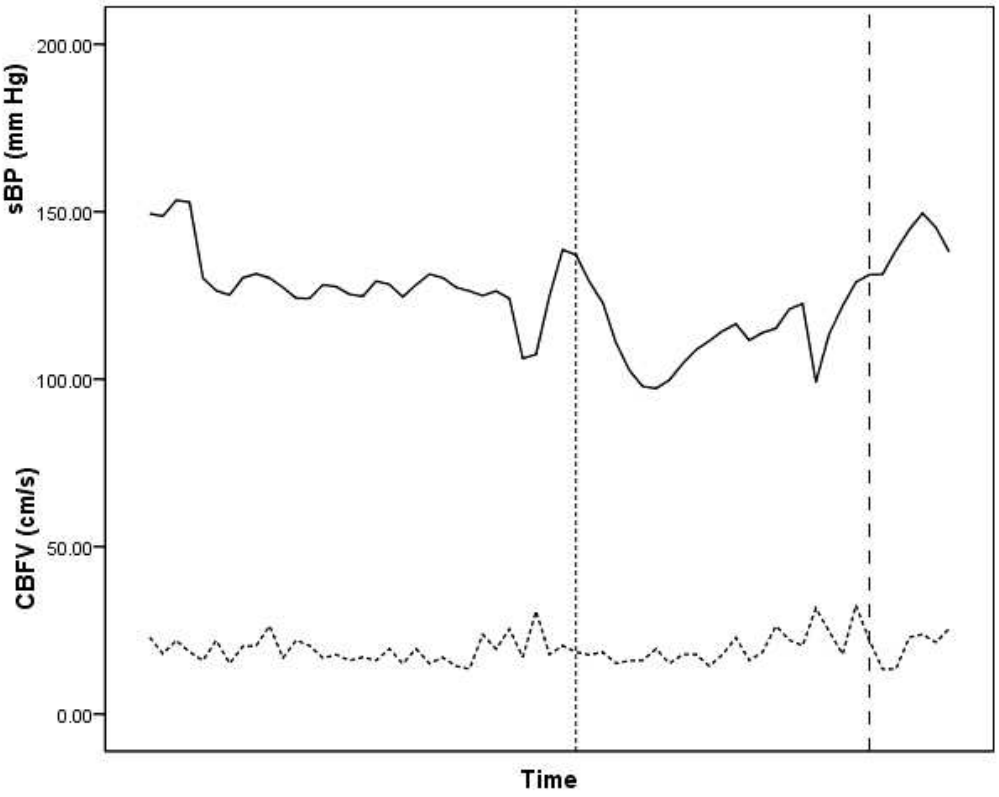


Figure 52. TCD. Normal CBFV response to valsalva in a control subject.

Figure 53 below displays the valsalva and CBFV for one of the PBC participants. The first thing to note is that there is no sympathetic sBP overshoot following the release of strain, vertical dashed line. Perhaps more interesting is the degree to which the CBFV fluctuates in line with the sBP. This shows an absence of CA, such that as sBP decreases there is no cerebral vasodilatation and the CBFV decreases.

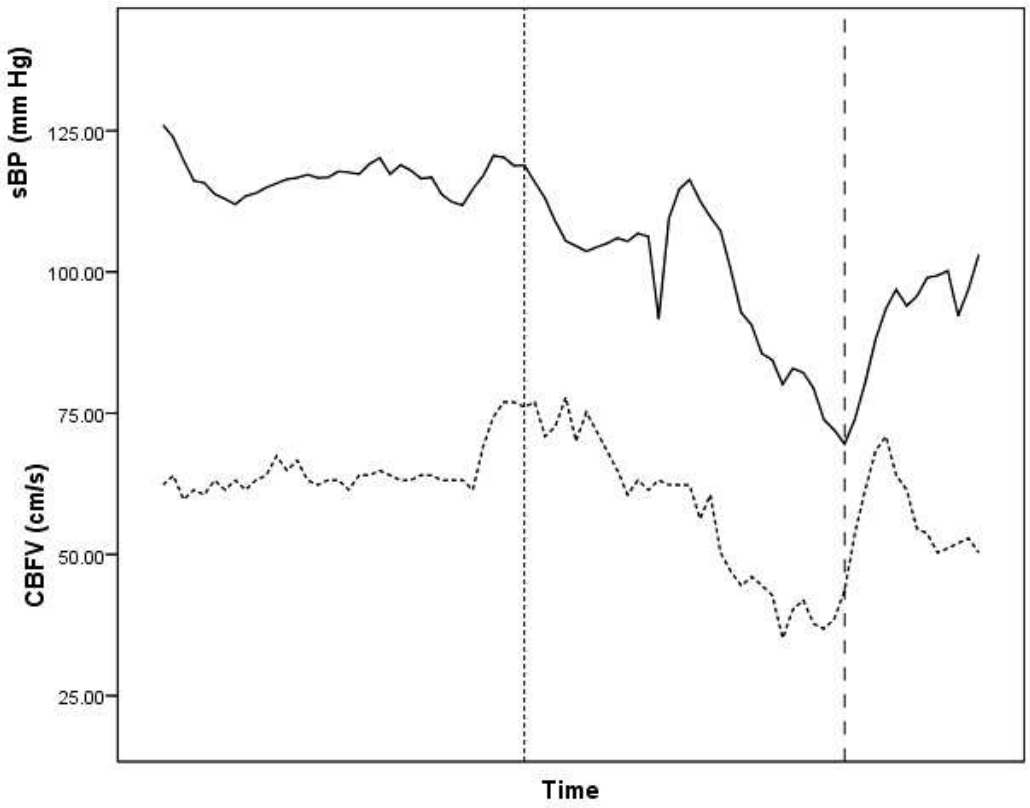


Figure 53. TCD. Abnormal CBFV response to valsalva in a PBC participant.

If the change in CBFV was to be plotted against the change in sBP during the valsalva (from phase 2a to phase 4) the resulting slope should be close to horizontal, indicating a constant CBFV. This normal response can be seen in the Control participants; Figure 54 displays the change in CBFV for each individual in the Control group; each having a reasonably stable CBFV (*y* axis) with a change in BP (*x* axis).

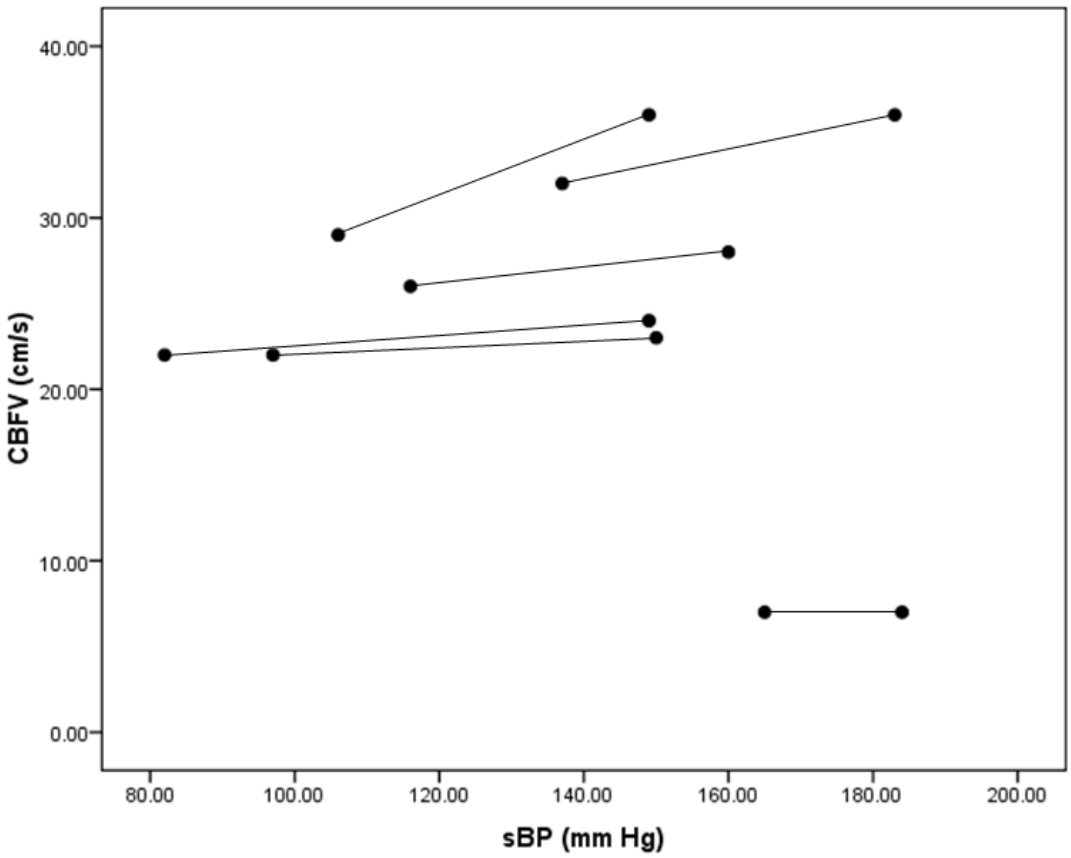


Figure 54. TCD. Change in CBFV per change in sBP in the Controls.

The horizontal lines displayed in Figure 54 are in contrast to those seen in the PBC participants below in Figure 55. Here, almost all individuals display large changes in CBFV during a change in systolic BP. The majority of the individuals display a typical response to changes in BP when there is impairment of CA; as the BP increases the CBFV increases. Four of the PBC participants display a negative slope, which implies abnormal autoregulation, but not in the expected direction. In some populations, namely those with VVS or CSS, there is evidence for an abnormal, paradoxical cerebral arteriolar vasoconstriction in response to hypotension [258, 273, 274, 275]. It could therefore be that those PBC participants with significant negative slopes are having abnormal, paradoxical vasoconstriction, resulting in reduced CBFV.

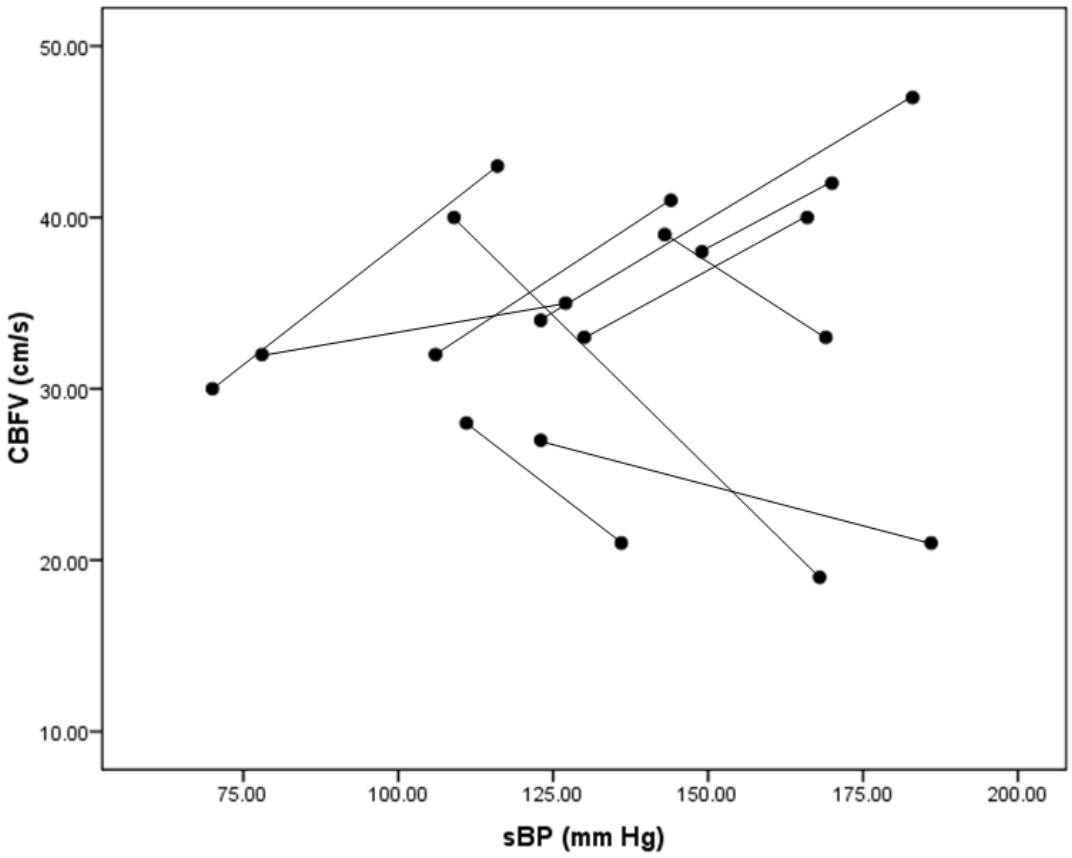


Figure 55. TCD. Change in CBFV per change in sBP in the PBC participants.

The difference in the gradient of these lines is similar to the ASI, which is the change in CBFV standardised by the change in BP from phase 2 to phase 4 of the valsalva. The difference reaches significance and is displayed in Table 42. It also displays the difference in the AI-2 and AI-4 between the cohorts. The results here are slightly conflicting with the difference in the AI-4 reaching significance whereas the results in the AI-2 are similar between the cohorts. This may be because the AI-2 concerns the changes during phase 2 of the valsalva and occurs over a short period of time, as AI-4 occurs from phase 2 to phase 4 there is a longer period of time to detect an abnormal response.

	PBC	Control	*z*, *p*
AI-2	-0.19 (-5.05-1.83)	0.92 (0.36-2.27)	1.095, 0.166
AI-4	0.71 (0.1-1.22)	0.97 (0.93-1.24)	1.356, 0.031
ASI	-6.42 (-28.96-8.56)	11.8 (-1.99-13.38)	1.461, 0.019

Table 42. TCD. Indices of CA in PBC and Control participants.

27.5.4. CEREBRAL AUTOREGULATION AND ORTHOSTATIC SYMPTOMS

As falls were associated with orthostatic symptoms but not measures of BP it was hypothesized that orthostatic symptoms would be related to impaired CA. However, measures of resting and dynamic CA did not correlate with symptoms of orthostatic dizziness (OGS, Table 43).

	r_s, *p*
sCBFV	0.333, 0.347
dCBFV	0.241, 0.503
CVR	0.56, 0.879
PI	-0.235, 0.514
AI-2	0.13, 0.721
AI-4	0.111, 0.76
ASI	-0.469, 0.171

Table 43. TCD. Associations between CA and the OGS.

27.5.5. CEREBRAL AUTOREGULATION AND FALLS

The relationship between falls and CA was analysed to establish whether there was an association. Table 44 displays the measures of CA in the Fallers and the Non-Fallers. There was one measure which demonstrated a significant difference between the groups, the AI-2. However, the relationship was the opposite of what would have been anticipated; the poorest AI-2 values were seen in the Non-Fallers compared to the Fallers. However the numbers in the analysis were very small and the results displayed are for interest; conclusions should be heavily tempered.

	Fallers	Non-Fallers	*z*, *p*
CBFV	67.6 (42.2-75.4)	62.5 (52.5-73.1)	0.516, 0.924
CVR	2 (1.1-3.6)	2.8 (1.9-4.5)	0.904, 0.295
PI	1 (0.8-1.1)	1.1 (0.7-1.7)	0.775, 0.552
AI-2	0.8 (-5-1.8)	-1.4 (-5.1-0.0)	1.291, 0.048
AI-4	0.8 (0.5-1.2)	0.2 (0.1-1.2)	1.162, 0.095
ASI	-6.4 (-29-15.2)	-3.3 (-11.7-6.6)	0.904, 0.295

Table 44. TCD. Association between CA and falls.

27.6. SUMMARY

In this small, pilot study there is evidence that dynamic, but not resting, CA is impaired in people with PBC, including those with early stage disease. The original hypothesis that orthostatic symptoms in PBC are related to impaired CA could not be confirmed, nor was it possible to demonstrate an association between falls and CA.

27.7. DISCUSSION

This study is one of the first to describe CA in a cohort of non-cirrhhotic CLD patients, each with PBC. The results demonstrate a normal, resting CA which becomes impaired during dynamic changes in BP. Dynamic changes in BP occur frequently throughout the day, for example, during standing from sitting, while coughing or sneezing, while defecating and while lifting heavy loads. As AD is common in CLD, particularly in PBC, these dynamic changes can be exaggerated, as displayed in Figure 52, where there is a large phase 2 decrease in BP. With such exaggerated changes in BP it is essential that the brain can maintain constant blood flow in order to prevent ischaemia and infarction. However, as is described here, in PBC the response to episodes of induced hypotension during strain is impaired and results in substantial reductions in cerebral blood flow.

The valsalva manoeuvre proved to be an effective method of inducing dynamic BP changes in all participants, despite concerns about its validity. For the purposes of this small study it was an ideal

method as it is non-invasive, comfortable for participants to perform and limited the movement of the TCD probes. However, it has been suggested that the valsalva is not appropriate to assess CA because of the changes it induces in intracranial pressure and therefore in cerebral perfusion pressure [276]. However, the changes in intracranial pressure can be considered as instantaneous and as constant during phase 2 of the valsalva so that any changes in CBFV during phase 2 are occurring as a result of changes in BP (i.e. CA) and are occurring regardless of the ICP [277]. There is also a suggestion that a raised end-tidal CO_2 at the end of the valsalva would contribute to an increase in cerebral vasodilatation, however this is not supported by published evidence; indeed, evidence suggests negligible to no change occurs in end-tidal CO_2 following valsalva [278, 279]. This is fortunate as changes in end-tidal CO_2 could not be measured during valsalva in the equipment used here, and therefore could not be controlled for when analysing changes in CBFV.

The AI-2, AI-4 and the ASI have all been validated in healthy controls and in cohorts with impaired CA [277, 278]. The ASI has the advantage over the AIs because it allows for changes in CBFV to occur following changes in BP, rather than at the same time, before CA may have responded, particularly in the AI-2 where changes must be noted over a short period and is particularly sensitive to the effort invested into the valsalva. New indices continue to be developed, and as yet there is no consensus in the measurement or analysis of CA. This leads to the absence of a gold standard, conflicting results and lack of clinical utility.

This study is not longitudinal and can not directly assess the implications of such impairments in CA. There is surprisingly little published data concerning the clinical consequences of impaired CA. However, there is data to suggest that syncope, falls and dizziness result from hypotensive episodes when CA is impaired [258, 280]. There is also a risk of hepatic encephalopathy being precipitated during episodes of hypotension and impaired CA [268, 269, 281]. Although this study was unable to confirm the hypothesis that impaired CA is associated with falling as has been demonstrated in other studies, it may be limited by its small sample size. However, it does demonstrate that the methods used here are simple and effective and could easily be performed in a cohort of a pre-determined sample size and power. In such a study it would be interesting to fully consider the relationship between CA, orthostatic symptoms and falls.

It is worth considering here that the association between falls and orthostatic dizziness, independent of BP, could be related to the methodology used in measuring BP. Despite OH being a well described, well known and common condition there remain several uncertainties relating to its diagnosis and investigation. Firstly, it is universal practise to rest a patient supine, prior to

standing, in order to achieve stable, baseline values. However, there is great heterogeneity in the length of time used to achieve baseline values. Times vary from 5 to 20 minutes in published research methodologies, but lack referenced evidence-base [257, 282, 283, 284]. The Consensus statement of the definition of OH, authored by the American Autonomic Society and the American Academy of Neurology is a widely cited article concerning methods of diagnosing OH; however it makes no recommendations concerning baseline values [179]. Conversely, the European Federation of Neurological Sciences' guideline on the diagnosis of OH states 'the patient should rest whilst supine for ideally 5 min…' but no evidence is cited for this recommendation [285]. Potentially the baseline values used when assessing postural BP could make a significant difference to the degree of BP drop which is noted as the patient stands. Whether this could be enough to explain the association between falls and dizziness, independently of BP drop is unknown and the question remains unanswered. In addition to the lack of recommendation regarding baseline values, guidelines have not progressed alongside the advances in technology, leading to a lack of certainty in particular situations. For example, advances in continuous beat-to-beat BP monitoring have enabled the detection of single, or very short lived drops in BP which meet the criteria for a diagnosis of OH but which have unknown clinical significance.

27.8. LIMITATIONS

As has been mentioned previously there is great heterogeneity in the data collection and analysis of CBF with no current, accepted gold standard. In addition, a great deal is unknown about CA and many undiscovered factors which contribute to CBF, independently of CA could exaggerate results. In relation to TCD there is controversy regarding the possible changes in diameter of the MCA; in order for CBFV recordings to be accurate it is essential that the MCA diameter is constant. Animal studies have demonstrated changes in MCA diameter under direct sympathetic stimulation [286]; this has not been confirmed in humans. Indeed, direct visualisation of the MCA using angiography and during neurosurgery has demonstrated little to no change in diameter during sympathetic stimulation [264, 287].

An obvious limitation is the small sample size of the cohorts. This seriously limits the generalisability of the results, even more so as the CLD cohort consisted of only PBC participants. However, the sample size is in keeping with many other studies relating to CA (see Appendix C) and can be used to inform future larger studies. Undertaking TCD can be time consuming due to the variability in the location of the temporal window, the size of the window and the angle

required to visualise the MCA. Once located, it is challenging to fix the probe in place without inadvertently moving the probe slightly, in which case the signal will be lost. For this reason, limited numbers of participants can be booked into one session.

RESULTS - PART FIVE

28. POTENTIAL BARRIERS TO EFFECTIVE FALLS PREVENTION/ INTERVENTION PROGRAMMES

28.1. CHAPTER AIMS

- Identify independent factors which could be targeted to increase the uptake or adherence to physical therapy
- Understand whether people with CLD appreciate the benefits of exercise
- Determine whether there is a lack of confidence to exercise in people with CLD
- Identify modifiable factors associated with having difficulty performing activity

28.2. INTRODUCTION

As the primary aims and objectives of this thesis were being met it became clear that one of the potential strategies which would be required for a targeted falls intervention/prevention program would be a multidisciplinary approach. Results presented earlier in this thesis demonstrated that falls were associated with both fear of falling, muscle weakness and orthostatic symptoms. While medical assessment and intervention may be required to address diabetes, blood pressure and perhaps leg weakness, physiotherapy intervention would be essential to address fear of falling and treat muscle weakness. Intervention which addresses fear of falling typically takes the form of physical therapy/exercise [228, 288]. Therefore it is essential if clinicians are to promote physical therapy, to understand what factors could prevent individuals from taking up and adhering to prescribed activity.

The NICE falls guidelines recommend that individualised, multidisciplinary fall intervention is offered to people who sustain a fall related injury in order to promote physical independence. As part of the recommended intervention the guidelines suggest addressing potential barriers to fall prevention programmes such as fear of falling and self-efficacy. Furthermore, The ProFaNE Consensus recommends using physical activity as an outcome in falls intervention programmes to improve an individual's autonomy and independence [227].

There are several known factors which can influence an individual's likelihood of engaging in physical therapy. Self-efficacy expectations are an individual's judgement of confidence to carry

out specific behaviours [289]. It determines whether an individual chooses to perform exercise, the effort they invest and the length of time that they will continue to exercise [290]. Self-efficacy has previously been identified as one of the most important strategies to engage individuals with NAFLD in lifestyle modification, including physical activity [291] and as such represents a potentially important barrier to falls intervention and prevention programmes in people with CLD.

Outcome expectations are beliefs that beneficial results will be produced by performing physical activity [292]. An understanding of the benefits of exercise is associated with physical function in other chronic diseases such as coronary heart disease and cancer survivors [293, 294] and so it may be expected that an appreciation of the benefits of physical activity in people with CLD would be associated with increased levels of physical function.

Paradoxically, although the treatment for fear of falling is physical therapy, fear of falling strongly influences engagement in physical activity, with greater levels of fear of falling correlating with lower levels of activity performed, worsening gait and balance and a poorer quality of life [113, 295]. It would seem important therefore that fear of falling should be recognised and targeted early to prevent a vicious cycle of fear and inactivity.

An additional factor which may influence engagement with physical activity in CLD is fatigue. Fatigue is common in CLD [120, 167] and may be associated with poorer levels of physical activity [296]. Given these multiple factors which could act as barriers to physical activity, particularly in a falls intervention/prevention programme, it is important to explore these factors further.

28.3. METHODS

28.3.1. STUDY DESIGN

A cross sectional approach was undertaken, using self-complete, postal data collection tools. All participants were mailed a letter detailing the purpose of the study, the data collection tools and a pre-paid return envelope. The ethical considerations to this study are covered by the ethical permissions discussed in section 15.3, page 44.

28.3.2. STUDY POPULATIONS

Three CLD populations were targeted for data collection. PBC, NAFLD and ALD were chosen as they had the greatest proportion of fallers (54%, 29% and 26% respectively); these cohorts also

represent the most common CLDs who have a database of individuals who have consented to be contacted. The PBC database population has been described previously in Chapter 2 Methods. An alternative approach was taken to data collection from the NAFLD and ALD populations. It was felt that the data collection method employed in the previous falls and injury chapters was sub-optimal due to the high non-attendance rate to clinic appointments. In addition, participants were being asked to complete several tools which may have been too lengthy for the clinic waiting room setting. For these reasons the data collection tools were mailed out in the same manner as the PBC cohort above. Although in the previous chapters it was felt that response rates to postal tools in NAFLD and ALD would be too low it was considered preferable to the clinic data collection.

28.3.3. DATA COLLECTION TOOLS

28.3.3.1 Outcome Expectation for Exercise Scale (OEES)

The OEES consists of nine questions relating to the subjective benefits of exercise [297]. Participants indicate whether they strongly agree through to strongly disagree with the statements concerning exercise. This gives an overall score out of 45 which is divided by 9 to give the OEES score; lower scores showing greater expectations of exercise. This scale has undergone reliability and validity testing with strong evidence for both [297].

28.3.3.2 Self Efficacy for Exercise Scale (SEES)

The SEES is a tool used to assess an individual's confidence to perform exercise [290]. Participants indicate with a score out of 10 (1 for not confident, through to 10 for very confident) how confident they feel to perform the nine activities which are listed. A value between 9 and 90 is reached and divided by 9 to give the SEES score. Reliability and validity have been confirmed for this tool [290].

28.3.3.3 Falls Efficacy Scale International (FES-I)

This tool is described in section 15.6.2.5, page 50.

28.3.3.4 Fatigue Impact Scale (FIS)

The FIS allows for quantification of an individuals level of fatigue and the impact this has upon their daily functions [298]. There are 40 items which are scored as 0 (no problem) through to 4 (extreme problem). It has previously been validated in CLD populations [299].

28.3.3.5 PROMIS-HAQ

Activity was analysed from a functional perspective using the PROMIS-HAQ [300]. This tool is described in section 15.6.2.5, page 50. One specific question concerning physical activity is included in the PROMIS-HAQ and this question was used here to quantify an individuals ability to perform activity (from completely, mostly or moderately through to a little or not at all). Reliability and validity have been confirmed [301].

28.3.4. DATA ANALYSIS

All continuous data were non-parametric and are summarised with the median and range. Spearman rank correlation was performed to explore associations between the dependent variable, which was ordinal, and the continuous variables. The Mann-Whitney U test was used to identify statistical differences between 2 data sets and is described in section 15.7, page 56. Ordinal logistic regression was the most appropriate form of regression for the ordinal, dependent variable. It is preferred to linear regression because of the non-standardised distance between each category and allows more outcome categories for the dependent variable than binary logistic regression. The model is displayed in an identical manner to the binary logistic regression models described in section 15.7, page 56.

28.4. RESULTS

28.4.1. RECRUITMENT

The combined databases provided a population size of 819 individuals. Each of these was contacted and 441 (54%) returned the data collection tools. The final cohort consisted of NAFLD 52%, ALD 26% and PBC 22%.

28.4.2. DEMOGRAPHICS

Details concerning age, sex and LFTs are displayed below in Table 45.

	Cohort (*n* 441)
Age (years)	62 (19-95)
Female (%)	225 (51)
Albumin [g/L]	42 (26-49)
Bilirubin [μmol/L]	8 (4-107)
ALP [U/L]	117 (48-864)
ALT [U/L]	34 (15-187)
Cirrhosis (%)	110 (25)

Table 45. Barriers. Demographic details.

28.4.3. ACTIVITY

Level of activity ranged from 0 (completely able to perform) to 4 (unable to perform) with a median of 1 (mostly able to perform activities). The proportions of individuals experiencing the different levels of difficulty are described below in Figure 56 (0 no difficulty, 1 a little difficulty, 2 some difficulty, 3 much difficulty, 4 unable to do). Forty per cent experienced at least some difficulty and 21% were able to perform only a little or no activity.

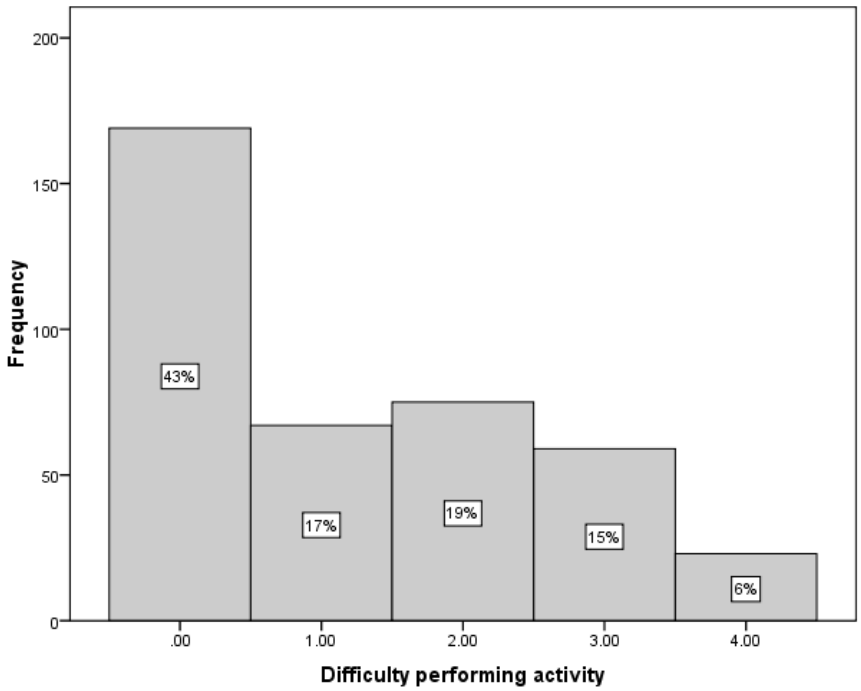


Figure 56. Barriers. The proportion of individuals for each degree of difficulty with activity.

28.4.4. BARRIERS TO ACTIVITY

The possible barriers to activity measured in the CLD population are displayed in Table 46 with their descriptive statistics.

	Median (range)
SEES (confidence to exercise)	4 (1-10)
OEES (expectations of exercise)	2.38 (1-5)
FES-I (fear of falling)	27 (16-64)
FIS (fatigue)	60 (0-160)

Table 46. Barriers. The potential barriers to activity.

Unfortunately there are no 'cut off' values to determine what proportions of individuals have abnormal levels of those variables in the table. However, the results suggest that on the whole, individuals have relatively low confidence to exercise; indeed, 24% scored the lowest score possible, indicating that a quarter of people with CLD are not confident to perform physical activity. They also suggest that in general, people with CLD need informing of the benefits of activity, with only 13% scoring the highest score possible for appreciating the benefits and 3% not appreciating any benefit of exercise at all. Ninety-six percent of the participants had at least some fear of falling (although there is no control group to compare this to) and 94% had at least some level of fatigue, meaning that most of the individuals have potential barriers to physical activity. Given these results it is important to explore their associations with levels of activity to identify whether they represent barriers in the CLD population.

28.4.5. ASSOCIATIONS WITH ACTIVITY

Demographic associations with the degree of difficulty experienced during activity are displayed in Table 47. An increasing age is associated with increasing levels of difficulty whereas decreasing levels of both albumin and bilirubin are associated with increasing difficulty. Activity was similar between those with cirrhosis [1 (0-4)] and those without cirrhosis [1 (0-4) U 2858, z -0.145, p 0.678]. One possible explanation for the association between albumin and activity is the influence of advancing age which associates with lower levels of albumin [302]. This can be explored further in the regression analysis below.

	r_s, p
Age	0.126, 0.013
Albumin	-0.212, <0.001
Bilirubin	-0.2, 0.001
ALP	0.025, 0.671
ALT	-0.079, 0.188

Table 47. Barriers. The associations between activity and demographic details.

Figure 57 below displays the median values for OEES, SEES, FIS and FES-I for each grade of difficulty with activity. Each measure demonstrated a significant association with the degree of difficulty performing activity Table 48. Low confidence to perform exercise was associated with increasing difficulty with activity, appreciating the benefits of exercise was associated with significantly less difficulty and increasing levels of fatigue and of fear of falling was associated with more difficulty with activity.

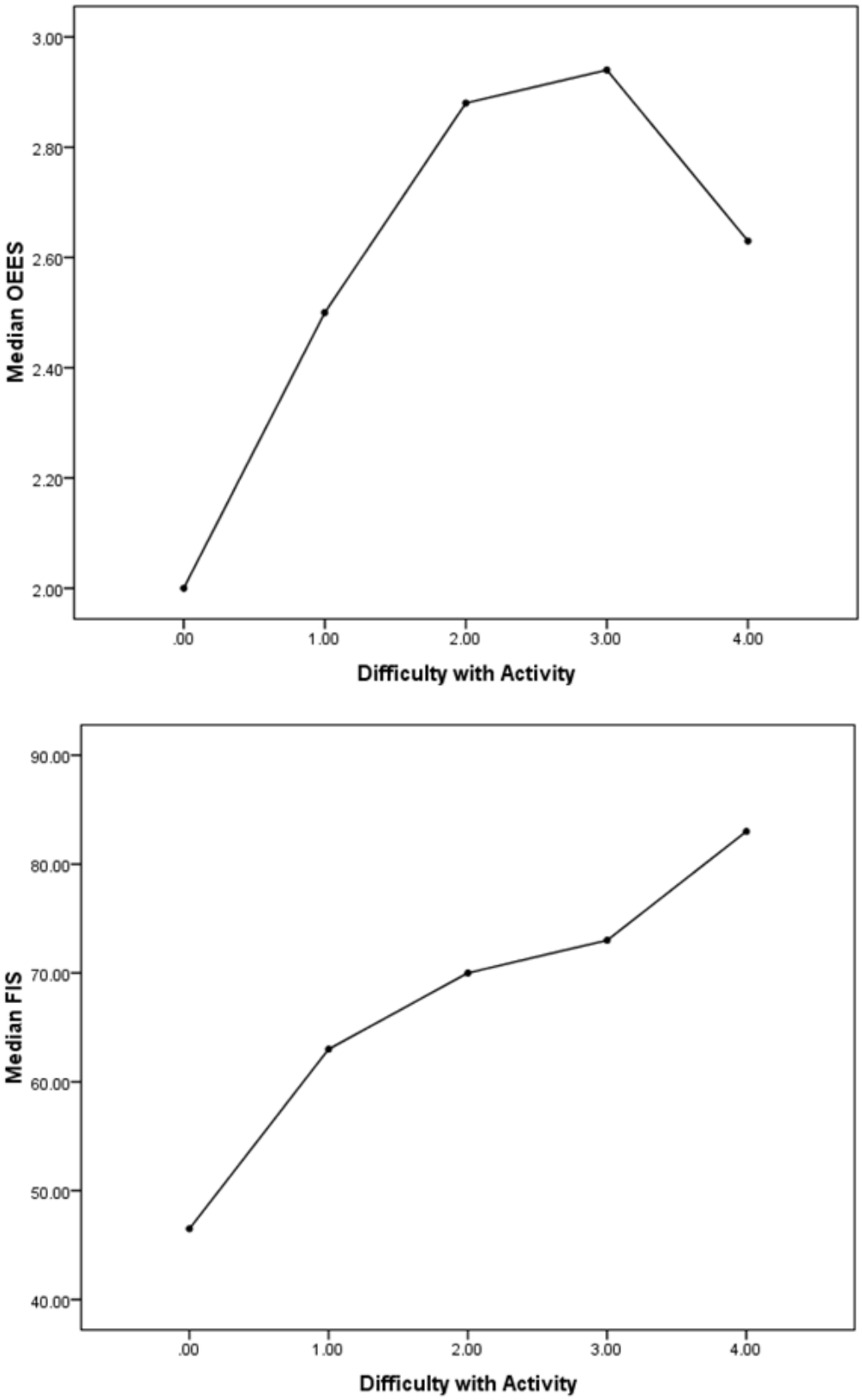
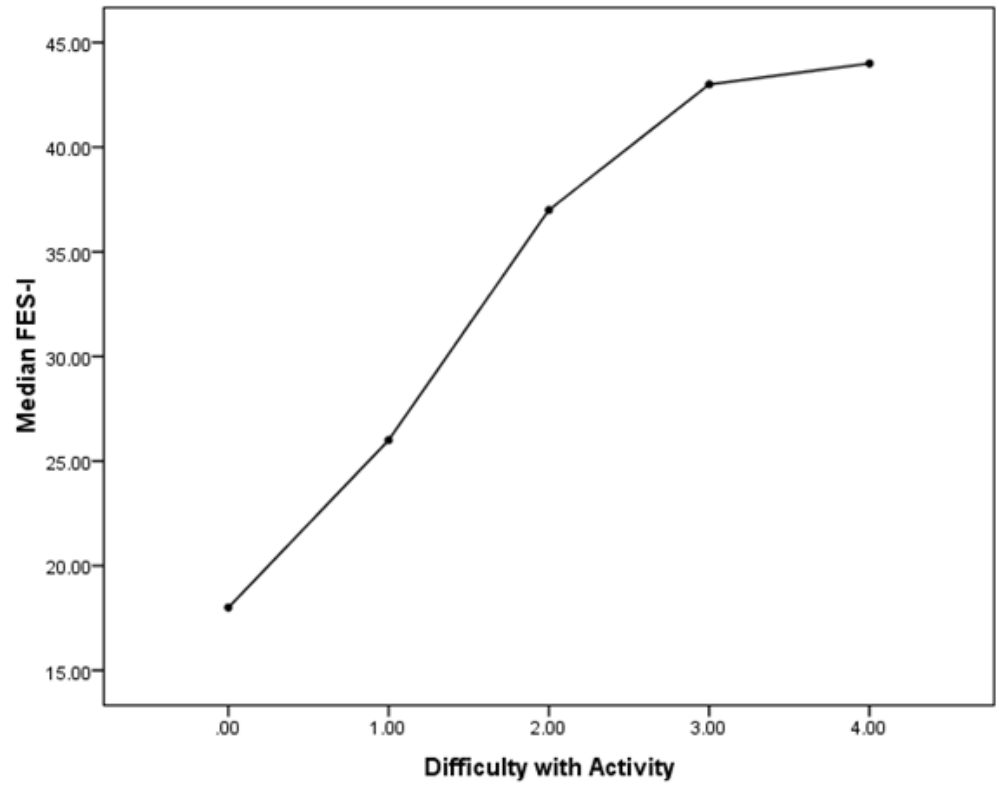


Figure 57. Barriers. Associations between activity and potential barriers to it.



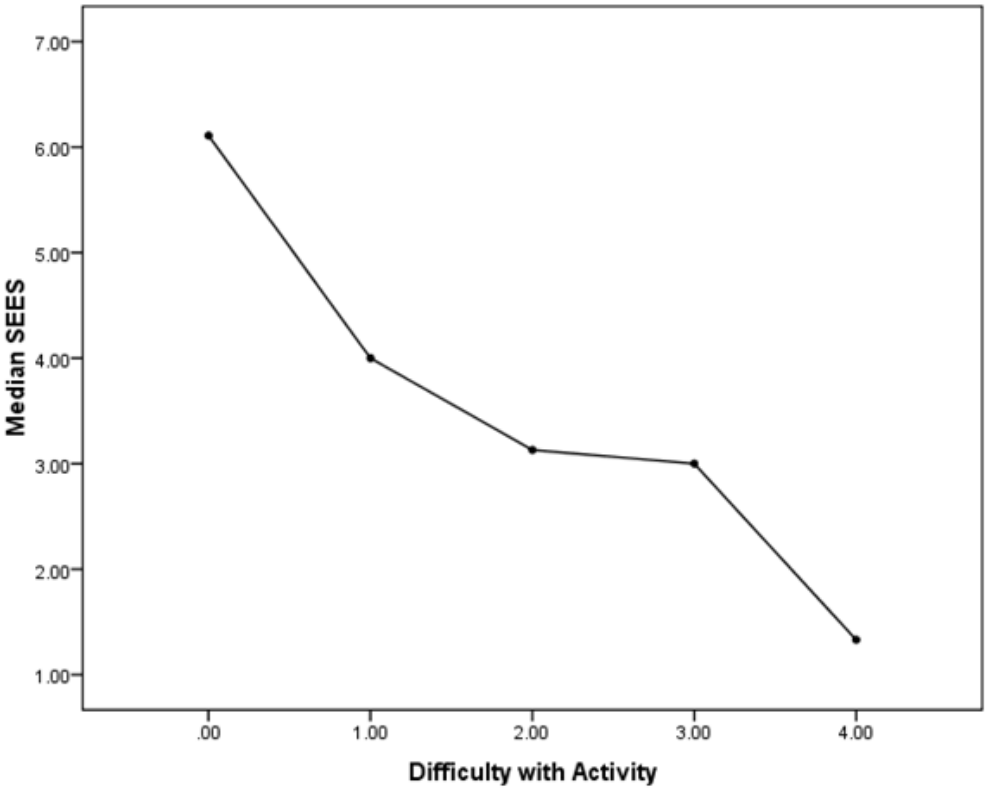


Figure 57. Barriers. Associations between activity and potential barriers to it.

Potential barrier	r_s, p
SEES	-0.403, <0.001
OEES	0.371, <0.001
FIS	0.381, <0.001
FES-I	0.673, <0.001

Table 48. Barriers. Associations between difficulty with activity and potential barriers to activity.

28.4.6. EXPLORING INDEPENDENT ASSOCIATIONS

Incorporating the aforementioned significant associations into an ordinal logistic regression model revealed an increasing fear of falling as the sole independent association with the degree of difficulty experienced with activity. The model is displayed in Table 49 and Figure 58 below.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Age	0.04	0.032	1.04	0.977	1.107	0.214
Albumin	0.02	0.069	1.02	0.891	1.169	0.771
Bilirubin	0.008	0.016	1.008	0.977	1.04	0.617
SEES	-0.208	0.119	0.812	0.643	1.026	0.081
FES-I	0.087	0.039	1.091	1.011	1.177	0.026
OEES	0.185	0.359	1.203	0.595	2.432	0.606
FIS	0.001	0.012	1.001	0.978	1.025	0.937

Model χ^2 (7) 47.136, p <0.001

Table 49. Barriers. The ordinal logistic regression model for difficulty with activity.

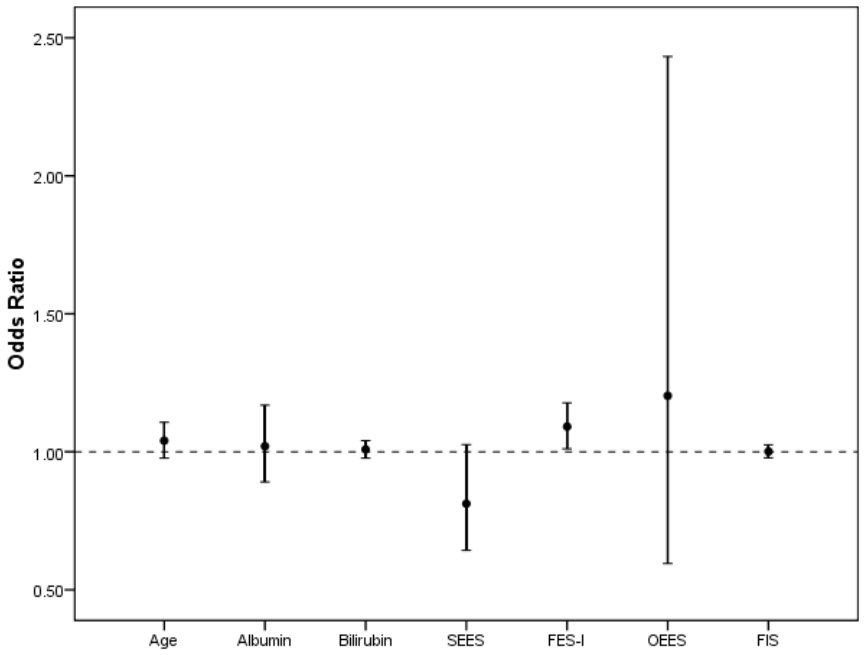


Figure 58. Barriers. The 95% CI for the ORs derived from the ordinal logistic regression model.

28.4.7. DISEASE SPECIFIC BARRIERS

Further analysis was performed to explore whether these barriers were consistent in each specific CLD or whether differing CLD, experience different barriers to activity. Ordinal logistic regression was performed for each cohort including only those associations with activity which were present in that specific cohort; age was also included in each model to allow conclusions to be drawn irrespective of age.

28.4.7.1 NAFLD

Fatigue was excluded from the regression model due to multicollinearity.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Age	-0.003	0.033	0.997	0.935	1.064	0.94
Albumin	-0.03	0.091	0.97	0.812	1.159	0.739
Bilirubin	0.016	0.016	1.016	0.985	1.048	0.313
SEES	-0.215	0.125	0.807	0.632	1.03	0.085
FES-I	0.108	0.027	1.114	1.058	1.174	<0.001
OEES	-0.089	0.305	0.915	0.503	1.662	0.77
Model χ^2 (6) 33.812, p <0.001						

Table 50. Barriers NAFLD. The ordinal logistic regression model for difficulty with activity.

The results in Table 50 demonstrate that fear of falling is the single independent association with difficulty with activity, and is so, regardless of age.

28.4.7.2 ALD

The SEES was excluded from the regression model because of multicollinearity.

Variable	*b*	SE	OR	95% confidence interval (OR)		*p*
				Lower bound	Upper bound	
Age	0.02	0.029	1.021	0.964	1.08	0.483
FES-I	0.077	0.026	1.08	1.026	1.136	0.003
OEES	0.983	0.318	2.672	1.434	4.98	0.002
FIS	0.002	0.008	1.002	0.986	1.019	0.776
Model χ^2 (4) 26.603, p <0.001						

Table 51. Barriers ALD. The ordinal logistic regression model for difficulty with activity.

The results of the regression model (Table 51) for the ALD cohort demonstrates that fear of falling is independently associated with difficulty with activity, consistent with the NAFLD cohort. In addition, an understanding of the benefits of exercise was independently associated with less difficulty with activity, which suggests that in ALD educating people who require physical therapy is an important consideration.

28.4.7.3 PBC

No variable suffered multicollinearity and as such, all significant associations in the PBC cohort were included in the model below.

Variable	***b***	**SE**	**OR**	**95% confidence interval (OR)**		***p***
				Lower bound	Upper bound	
Age	0.029	0.037	1.029	0.957	1.107	0.441
SEES	-0.114	0.112	0.892	0.717	1.11	0.305
FES-I	0.128	0.035	1.137	1.062	1.217	<0.001
OEES	0.545	0.36	1.724	0.851	3.493	0.13
FIS	0.022	0.013	1.022	0.996	1.05	0.098

Model χ^2 (5) 52.354, p <0.001

Table 52. Barriers PBC. The ordinal logistic regression model for difficulty with activity.

28.5. SUMMARY

Several barriers have been identified as having strong associations with physical difficulty. Fortunately each of these barriers (with the exception of age) is potentially modifiable and if targeted could increase engagement in physical activity and increase uptake and adherence to falls intervention/prevention programmes. Regression analysis revealed that an increasing fear of falling is independently associated with more difficulty in performing activity. The difficulty here is that physical activity is the treatment for fear of falling which in itself is a barrier to physical activity.

28.6. DISCUSSION

Previous results chapters have demonstrated that fear or falling and lower limb muscle weakness are independently associated with falling. Potential intervention for both of these fall risk factors includes physiotherapy, which would typically take the form of physical therapy/exercise. However, physical therapy and exercise may be difficult to 'prescribe' as several potential barriers have been demonstrated here. While each of these barriers is known to affect uptake and continued adherence to physical exercise programmes they are probably not well understood in the clinical setting, particularly in the context of CLD.

This exploratory study revealed that the amount of difficulty experienced while performing physical activity was strongly associated with an understanding of the benefits of exercise. This is hugely important because it demonstrates a lack of knowledge concerning exercise in the CLD population which has the potential to be improved. Although there is a lack of evidence to suggest that outcome expectations are modifiable it is a logical assumption that counselling a patient about the benefits of exercise could improve their understanding. Unfortunately, there is also a lack of evidence to suggest that improving outcome expectations will be beneficial. However, it would be reasonable to assume that it would, given the strong association between the OEES and physical activity. Regardless of this lack of evidence, clinicians must be responsible for educating their patients about health promotion strategies [303]; with particular relevance to the NAFLD population in whom lifestyle modification has become standard advice [291, 304].

Confidence to perform activity was strongly associated with the degree of difficulty experienced during physical activity. This seems obvious but the point is that clinicians need to be aware of these factors when promoting physical therapy, such as in a falls intervention programme. Improving an individual's confidence to exercise improves adherence to exercise programmes [290] and has been shown to be an important consideration for those with NAFLD [291]. However, more evidence base is required to suggest the most appropriate strategies to improve self-efficacy; at present, evidence is at best, vague [305].

It was unsurprising to demonstrate that greater levels of fatigue were associated with increased difficulty with activity. Fatigue can be a debilitating symptom, is common in CLD, has complex aetiology and is challenging to treat [167, 306, 307]. It represents a particularly difficult barrier to physical exercise programmes given the lack of effective treatments available. However, on

regression analysis fatigue was not independently associated with physical activity and although it is important, it is not as amenable to intervention as other factors which were identified.

As with previous results chapters, fear of falling emerges as an important and independent association. Here, it is independently associated with increased difficulty with activity [OR 1.085 (1.043-1.128)]. Although this is problematic because fear of falling is a barrier to its own intervention, physical activity, it is potentially modifiable. It represents a real, potential opportunity to dramatically improve the quality of life of people with CLD. Fear of falling intervention strategies have the potential, in CLD, to prevent falls, improve functional ability, increase physical activity and to prevent social isolation, depression and institutionalisation [308].

The associations identified in the demographic data revealed strong relationships between age, albumin and bilirubin with the amount of difficulty experienced during activity; however an increasing age was not associated with more difficulty in the regression model. Older people with CLD may represent a challenging group in whom to offer physical activity as a therapeutic strategy for reasons not covered here, e.g. arthritis. However, this challenge should not preclude this group from physiotherapy but should alert the clinician to the increased difficulties experienced by this group. The relationship between albumin and physical activity did not remain significant in the regression model. The most likely explanation for this is the confounding relationship between age and albumin, in which albumin is known to reduce with age (albeit within the normal range) [302].

28.7. LIMITATIONS

It would have been preferable to have included a broader range of CLDs to improve generalisabilty of the results. However, the number of individuals included was relatively large and does provide important considerations for future studies.

It is necessary to point out that the dependent variable, difficulty with activity, is not a measure of activity performed. While the measure used is useful pragmatically and provides an understanding of an individual's ability/difficulty with activity it does not provide a quantifiable level of activity performed. This may be misleading if an individual has rated themselves as having difficulty with activity but still engages in it, or an individual who never performs any activity may have described themselves as having no difficulty.

Both the OEES and the SEES were designed for and validated in the elderly and have not been validated, as yet, in the younger general population or in a CLD population. It must be recognised

therefore, that the results may not be wholly accurate in the younger individuals who participated. The same is true for the FES-I which has been discussed previously in section 15.6.2.5, page 50. The OEES and SEES have however, been validated in other younger disease groups and are therefore not exclusive to older people [309, 310]. Furthermore, the original development and validation studies do not specify an age at which they used to include their participants, referring to them only as 'older adults''. In this study 57% were aged over 60 years and 38% were aged over 65 years and so it could be argued that the majority of participants were older adults.

A significant omission from the analysis is the inclusion of a measure of autonomic dysfunction. Given that orthostatic dizziness was associated with falling in the previous results chapters it would have been interesting to have assessed its association with activity. However, at the time of investigating the factors associated with activity it had not become apparent that OGS scores were higher in the Fallers. A more robust model may have been possible by including further details such as arthritis, angina and breathing difficulties, each of which could potentially be a barrier to physical therapy. But while the regression model above may not have included all potential barriers to activity it displays some very strong associations which are clinically relevant and previously unknown in the CLD population. This exploratory work may help inform future studies concerning physical activity in people with CLD.

SUMMING UP AND FUTURE CONSIDERATIONS

As hypothesised, falls are extremely common in older people with CLD. This unique, cross-sectional study has demonstrated a significantly greater proportion of older people having a fall in the previous year than in age- and sex-matched Community Controls. Despite the high prevalence of falls, fall-related injury was no more common in the older CLD cohort; this was an unexpected finding, negating one of the prospective, original hypotheses. Through multidisciplinary assessment of a sub-group of people with CLD, fall associations were explored. Statistical analysis revealed that orthostatic dizziness, lower limb strength and fear of falling were each independently associated with falling. The significance here is that each of these fall associations is modifiable. The importance of falling in CLD was further highlighted by the strong association between falling and increased functional difficulty.

On exploring disease-specific falls prevalence, both NAFLD and PBC had significantly greater proportions of people who fell and who fell recurrently than in age- and sex-matched Community Controls. Statistical comparisons were limited for the PSC and ALD cohorts due to relatively small numbers responding to recruitment. Phase 2 revealed that fear of falling was independently associated with falling in the NAFLD cohort; in the PBC cohort lower limb strength was independently associated with falling. Once again, these independent associations are potentially modifiable and offer evidence to support future prevention/intervention studies employing the skills of a multidisciplinary team.

The post-LT cohort was analysed with a number of different methods. Firstly the cohort was compared to an age- and sex- matched Community Control cohort, demonstrating a significantly greater prevalence of falls in the post-LT cohort. Comparison was then made to a matched CLD cohort who had not undergone LT. Rates of falling were similar in the two cohorts; furthermore the rates of falling were similar in the post-LT cohort to the rate of falling retrospectively recalled from a time before the cohort underwent LT. Fall associations during Phase 2 of the study revealed that orthostatic symptoms, heart rate variability, lower limb weakness and, once again, fear of falling were independently associated with falling.

The results suggest that in designing a falls treatment or prevention programme for older people with CLD a multidisciplinary approach will most likely be required, with a particular focus on the treatment of fear of falling. Fortunately fear of falling is amenable to treatment with physical

therapy in the form of exercises. Further analysis of the CLD cohort revealed several associations with difficulty performing activity and represent potential barriers to the uptake and/or adherence to a physical therapy programme. Fear of falling was identified as the sole independent association with difficulty performing activity. Fear of falling is therefore a barrier to the treatment of fear of falling and represents a significant therapeutic target to prevent falls and increase uptake of physical therapy.

The association between postural dizziness and falls, independently of BP, remains unexplained. A small, pilot study undertaken to explore CA as the unifying factor, demonstrated that impairment of CA was significant in PBC but was unrelated to orthostatic symptoms. This suggests that there may be an underlying process which we do not yet understand or that the methods used to assess BP, falls or postural dizziness are inadequate.

As is the case with much evidence base, studies including or relating specifically to older people are few, although the need for such evidence is certainly not lacking. This need will only increase dramatically over the next decade as the older population expands. One sub group of this expanding population is the older CLD population, which may arguably expand at a greater rate than other older populations. The work presented in this thesis provides evidence to contextualise the problem of falls in the older CLD population, a process recommended by the MRC in the development of complex intervention studies. However, this work goes further and provides exploratory data to inform the design of the complex intervention which would be required to investigate the benefit of a multifaceted falls prevention/intervention programme.

If the results above were to be used to inform a falls intervention or prevention trial it would appear appropriate to address those risk factors identified. Whether the intervention would focus on all associations or only those which were independently associated with falling (postural dizziness, lower limb strength and fear of falling) a MDT approach would be required, utilising the skills of a physician, nurse, physiotherapist and arguably an OT and cognitive therapist.

There is great heterogeneity in the literature concerning multidisciplinary/ multifactorial fall interventions. This heterogeneity results from wide variations in falls research. The first major problem is the lack of a standard definition of a fall [233], although with groups such as the Prevention of Falls Network Europe (ProFaNE) it is hoped that one definition will become standard. Though the majority of publications do not define what they consider to be a fall, the most common definition used (amongst those who do define a fall) is 'unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure'. However, this definition would not include those who fall as a result of syncope, for example as a result of syncopal OH. The definition suggested by ProFaNE is much more encompassing 'an unexpected event in which the participants come to rest on the ground, floor or other lower level' [227]. Heterogeneity is further created by differing inclusion criteria in fall intervention studies, for example including or excluding those with cognitive impairment or including only recurrent fallers. But perhaps one of the most important issues which has contributed to conflicting results regarding multifactorial falls intervention is the differences in the multifactorial component.

However, it is not just the multifactorial intervention which is important, the process in which it is delivered is equally as crucial [311].

In forming a Phase 2 exploratory trial (based on the MRC linear research framework) the aforementioned considerations must be taken into account. In support of a multifactorial intervention in the older CLD cohort is the results seen in the general population. Here the aetiology of falls are complex and trials which have compared single intervention to multifaceted interventions have demonstrated benefits in having a multidisciplinary approach [312] whereas interventions lead by a single health professional have not shown reductions in falls [313, 314]. Furthermore, one meta-analysis of 5 high-quality multifactorial intervention studies (in older, falling, community dwelling adults) demonstrated a pooled risk ratio of 0.86 (95% CI 0.76, 0.98) for preventing a further fall. As falls in CLD appear to have complex aetiology it would seem appropriate to adopt this multidisciplinary approach; including the assessment and management of orthostatic dizziness, limb weakness and fear of falling.

In designing the data collection for such a falls prevention/treatment programme consideration would have to be given to the method used for prospectively collecting falls data. At present, there is no single, fully reliable method with a tendency for most methods to be based, at least in part, on retrospective recall, and therefore under-reporting incidence. Secondly, the length of follow-up may be crucial as the effect of an intervention programme may be underestimated if it is too short. The study presented here supports the use of negative binomial regression to model falls data in future studies as the falls data was highly skewed with high zero frequencies; furthermore the binomial regression models were a better fit of the data than the categorical binary logistic regression models.

The final results chapter demonstrated several potential barriers to intervention with physical therapy. These are important considerations in the design of a multifaceted falls prevention programme and represent difficulties which may lead to poor adherence and high drop out rates if not addressed.

REFERENCES

1 Schmucker DL. Hepatocyte fine structure during maturation and senescence. *J Electron Microsc Tech* 1990;**14**:106-25.

2 Sabaretnam T, Kritharides L, O'Reilly JN, *et al.* The effect of aging on the response of isolated hepatocytes to hydrogen peroxide and tert-butyl hydroperoxide. *Toxicology in Vitro* 2010;**24**:123-8.

3 Schmucker DL, Sachs H. Quantifying dense bodies and lipofuscin during aging: a morphologist's perspective. *Arch Gerontol Geriatr* 1994;**34**:249-61.

4 Le Couteur DG, Warren A, Cogger VC, *et al.* Old age and the hepatic sinusoid. *Anat Rec* 2008;**291**:672-83.

5 Sato K, Kawamura T, Wakusawa R. Hepatic blood flow and function in elderly patients undergoing laparoscopic cholecystectomy. *Anesth Analg* 2000;**90**:1198-202.

6 Wynne HA, Cope LH, Mutch E, *et al.* The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* 1989;**9**:297-301.

7 Ito Y, Sørensen KK, Bethea NW, *et al.* Age-related changes in the hepatic microcirculation in mice. *Exp Gerontol* 2007;**42**:789-97.

8 Woodhouse KW, James OF. Hepatic drug metabolism and ageing. *Br Med Bull* 1990;**46**:22-35.

9 Vestal RE. Aging and determinants of hepatic drug clearance. *Hepatology* 1989;**9**:331-4.

10 Sotaniemi EA, Arranto AJ, Pelkonen O, *et al.* Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathologic conditions[ast]. *Clin Pharmacol Ther* 1997;**61**:331-9.

11 Schmucker DL, Woodhouse KW, Wang RK, *et al.* Effects of age and gender on in vitro properties of human liver microsomal monooxygenases. *Clin Pharmacol Ther* 1990;**48**:365-74.

12 Wynne H, Wood P, Herd B, *et al.* The association of age with the activity of alcohol dehydrogenase in human liver. *Age Ageing* 1992;**21**:417-20.

13 Seitz H, Egerer G, Simanowski U, *et al.* Human gastric alcohol dehydrogenase activity: Effect of age, sex, and alcoholism. *Gut* 1993;**34**:1433-7.

14 Gambert SR. Alcohol abuse: medical effects of heavy drinking in late life. *Geriatrics* 1997;**52**:30-7.

15 Giorgadze S, Gujabidze N, Tevzadze N, *et al.* Apoptosis and proliferative activity of hepatocytes of white rats during aging. *Georgian Medical News* 2009:88-91.

16 Jin J, Wang G-L, Shi X, *et al.* The age-associated decline of glycogen synthase kinase 3beta plays a critical role in the inhibition of liver regeneration. *Mol Cell Biol* 2009;**29**:3867-80.

17 Bloomer SA, Zhang HJ, Brown KE, *et al.* Differential regulation of hepatic heme oxygenase-1 protein with aging and heat stress. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences* 2009;**64**:419-25.

18 Tauchi H, Sato T, Ito Y. Morphological aspects of aging liver: half a century of progress in Japan. *Arch Gerontol Geriatr* 1994;**19**:135-44.

19 Wei G, Bergquist A, Broome U, *et al.* Acute liver failure in Sweden: etiology and outcome. *J Intern Med* 2007;**262**:393-401.

20 O'Grady JG. Acute liver failure. *Postgrad Med J* 2005;**81**:148-54.

21 Forbes A, Williams R. Increasing age - an important adverse prognostic factor in hepatitis A virus infection. *J R Coll Physicians Lond* 1988;**22**:237-9.

22 Schmidt LE. Age and paracetamol self-poisoning. *Gut* 2005;**54**:686-90.

23 Potter J, James O. Clinical features and prognosis of alcoholic liver disease in respect of advancing age. *Gerontology* 1987;**33**:380-7.

24 Frith J, Day C, Henderson E, *et al.* Non-alcoholic fatty liver disease in older people. *Gerontology* 2009;**55**:607-13.

25 Parker D, Kingham J. Type 1 autoimmune hepatitis is primarily a disease of later life. *QJM* 1997;**90**:289-96.

26 Andrade RJ, Lucena MI, Fernandez MC, *et al.* Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period.[erratum appears in Gastroenterology. 2005 Nov;129(5):1808]. *Gastroenterology* 2005;**129**:512-21.

27 Garcia C, Garcia R, Mayer A, *et al.* Liver transplantation in patients over sixty years of age. *Transplantation* 2001;**72**:679-84.

28 Quoilin S, Hutse V, Vandenberghe H, *et al.* A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. *Eur J Epidemiol* 2007;**22**:195-202.

29 Braconier J, Nordenfelt E. Serum hepatitis at a home for the aged. *Scand J Infect Dis* 1972;**4**:72-82.

30 Chiaramante M, Floreani A, Naccarato R. Hepatitis B virus infection in homes for the aged. *J Med Virol* 1982;**9**:247-55.

31 Wright R. Hepatitis B and the HBsAg carrier: an outbreak related to sexual contact. *JAMA* 1975;**232**:717-21.

32 Cook J, Gualde N, Hessel L, *et al.* Alterations in the human immune response to the hepatitis B vaccine among the elderly. *Cell Immunol* 1987;**109**:89-96.

33 Schramm C, Kanzler S, Meyer zum Buschenfelde K, *et al.* Autoimmune hepatitis in the elderly. *Am J Gastroenterol* 2001;**96**:1587-91.

34 Collier J, Curless R, Bassendine M, *et al.* Clinical Features and prognosis of hepatocellular carcinoma in Britain in relation to age. *Age Ageing* 1994;**23**:22-7.

35 Newton J, Jones D, Metcalf J, *et al.* Presentation and mortality of primary biliary cirrhosis in older patients. *Age Ageing* 2000;**29**:305-9.

36 Newton J, Burt A, Park J, *et al.* Autoimmune hepatitis in older patients. *Age Ageing* 1997;**26**:441-4.

37 Kondo Y, Tsukada K, Takeuchi T, *et al.* High carrier rate after hepatitis B virus infection in the elderly. *Hepatology* 1993;**18**:768-74.

38 Brind A, Watson J, James O, *et al.* Hepatitis C virus infection in the elderly. *Q J Med* 1996;**89**:291-6.

39 James O. Parenchymal liver disease in the elderly.[see comment]. *Gut* 1997;**41**:430-2.

40 Gilmore I, Burroughs A, Murray-Lyon I, *et al.* Indications, methods and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;**36**:437-41.

41 Woodhouse K, James O. Alcoholic liver disease in the elderly: Presentation and outcome. *Age Ageing* 1985;**14**:113-8.

42 Breslow R, Smothers B. Drinking patterns of older Americans: National Health Interview Surveys, 1997-2001. *J Stud Alcohol* 2004;**65**:232-40.

43 Mangion D, Platt J, Syam V. Alcohol and acute medical admission of elderly people. *Age Ageing* 1992;**21**:362-7.

44 Foster KJ, Dewbury KC, Griffith AH, *et al.* The accuracy of ultrasound in the detection of fatty infiltration of the liver. *Br J Radiol* 1980;**53**:440-2.

45 Al-Chalabi T, Boccato S, Portmann B, *et al.* Autoimmune hepatitis (AIH) in the elderly: A systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. *J Hepatol* 2006;**45**:575-83.

46 Czaja A, Freese D. Diagnosis and treatment of autoimmune hepatitis. *Hepatology* 2002;**36**:479-97.

47 Zein CO, McCullough AJ. Association between fatigue and decreased survival in primary biliary cirrhosis.[comment]. *Gut* 2007;**56**:1165-6; author reply 6.

48 Tischdorf J, Hecker H, Kruger M, *et al.* Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study. *Am J Gastroenterol* 2007;**102**:107-14.

49 Vind I, Riis L, Jess T, *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database.[see comment]. *Am J Gastroenterol* 2006;**101**:1274-82.

50 Jess T, Loftus EV, Jr., Harmsen WS, *et al.* Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. *Gut* 2006;**55**:1248-54.

51 McMahon B, Alwrd W, Hall D, *et al.* Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *The Journnal of Infectious Diseases* 1985;**151**:599-603.

52 Rudin D, Shah S, Kiss A, *et al.* Interferon and lamivudine vs. interferon for hepatitis B e antigen positive hepatitis B treatment: meta-analysis of randomized controlled trials. *Liver International* 2007;**24**:784-95.

53 Kawaoka T, Suzuki F, Akuta N, *et al.* Efficacy of lamivudine therapy in elderly patients with chronic hepatitis B infection. *J of Gastroenterology* 2007;**42**:395-401.

54 Bresci G, Del Corso L, Romanelli A, *et al.* The use of recombinant interferon alfa-2b in elderly patients with anti-HCV-positive chronic active hepatitis. *J Am Geriatr Soc* 1993;**41**:857-62.

55 Honda T, Katano Y, Urano F, *et al.* Efficacy of ribavirin plus interferon-alpha in patients aged >/= 60 years with chronic hepatitis C. *Hepatology* 2007;**22**:989-95.

56 El-Serag H, Siegel A, Davila J, *et al.* Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: A population based study. *J Hepatol* 2006;**44**:158-66.

57 Niederau C, Fischer R, Purschel A, *et al.* Long-term survival in patients with hereditary hemochromatosis.[see comment]. *Gastroenterology* 1996;**110**:1107-19.

58 Willis G, Wimperis JZ, Smith KC, *et al.* Haemochromatosis gene C282Y homozygotes in an elderly male population. *Lancet* 1999;**354**:221-2.

59 Moirand R, Adams PC, Bicheler V, *et al.* Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 1997;**127**:105-10.

60 Demarquay G, Setiey A, Morel Y, *et al.* Clinical report of three patients with hereditary hemochromatosis and movement disorders. *Mov Disord* 2000;**15**:1204-9.

61 Roggli VL, Hausner RJ, Askew JB, Jr. Alpha-1-antitrypsin globules in hepatocytes of elderly persons with liver disease. *Am J Clin Pathol* 1981;**75**:538-42.

62 Janus ED, Phillips NT, Carrell RW. Smoking, lung function, and alpha 1-antitrypsin deficiency. *Lancet* 1985;**1**:152-4.

63 Stremmel W, Meyerrose KW, Niederau C, *et al.* Wilson disease: clinical presentation, treatment, and survival.[see comment]. *Ann Intern Med* 1991;**115**:720-6.

64 Ross ME, Jacobson IM, Dienstag JL, *et al.* Late-onset Wilson's disease with neurological involvement in the absence of Kayser-Fleischer rings. *Ann Neurol* 1985;**17**:411-3.

65 Danks DM, Metz G, Sewell R, *et al.* Wilson's disease in adults with cirrhosis but no neurological abnormalities. *BMJ* 1990;**301**:331-2.

66 Hefter H, Weiss P, Wesch H, *et al.* Late diagnosis of Wilson's disease in a case without onset of symptoms.[see comment]. *Acta Neurol Scand* 1995;**91**:302-5.

67 Kumagi T, Horiike N, Michitaka K, *et al.* Recent clinical features of Wilson's disease with hepatic presentation. *J Gastroenterol* 2004;**39**:1165-9.

68 Frith J, Newton J. Autonomic dysfunction in chronic liver disease. *Liver International* 2009;**29**:483-9.

69 Kruse WH. Problems and pitfalls in the use of benzodiazepines in the elderly. *Drug Saf* 1990;**5**:328-44.

70 Solerio E, Isaia G, Innarella R, *et al.* Osteoporosis: still a typical complication of primary biliary cirrhosis? *Digestive & Liver Disease* 2003;**35**:339-46.

71 Prasad S, Dhiman RK, Duseja A, *et al.* Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy.[see comment]. *Hepatology* 2007;**45**:549-59.

72 Morgan MY, Blei A, Grungreiff K, *et al.* The treatment of hepatic encephalopathy. *Metab Brain Dis* 2007;**22**:389-405.

73 Romero Y, Evans JM, Fleming KC, *et al.* Constipation and fecal incontinence in the elderly population. *Mayo Clin Proc* 1996;**71**:81-92.

74 Deschenes M, Dufresne MP, Bui B, *et al.* Predictors of clinical response to transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients with refractory ascites. *Am J Gastroenterol* 1999;**94**:1361-5.

75 Ochs A, Rossle M, Haag K, *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites.[see comment][erratum appears in N Engl J Med 1995 Jun 8;332(23):1587]. *N Engl J Med* 1995;**332**:1192-7.

76 Sanyal AJ, Freedman AM, Shiffman ML, *et al.* Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology* 1994;**20**:46-55.

77 Bullimore DW, Miloszewski KJ, Losowsky MS. The prognosis of elderly subjects with oesophageal varices. *Age Ageing* 1989;**18**:35-8.

78 Roberts CM, Carey B, Faizallah R, *et al.* Injection sclerotherapy for oesophageal varices in the elderly. *Age Ageing* 1983;**12**:139-43.

79 Collier J. Bone disorders in chronic liver disease. *Hepatology* 2007;**46**:1271-8.

80 Leslie WD, Bernstein CN, Leboff MS, *et al.* AGA technical review on osteoporosis in hepatic disorders.[see comment]. *Gastroenterology* 2003;**125**:941-66.

81 Cooper BT, Neumann CS. Upper gastrointestinal endoscopy in patients aged 80 years or more. *Age Ageing* 1986;**15**:343-9.

82 Garcia-Tsao G, Sanyal A, Grace N, *et al.* Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;**46**:922-38.

83 Fong Y, Blumgart L, Fortner J, *et al.* Pancreatic or liver resection for malignancy is safe and effective for the elderly. *Ann Surg* 1995;**222**:426-37.

84 Bruix J, Sherman M. Management of Hepatocellular Carcinoma. *Hepatology* 2005;**42**:1208-36.

85 Collins B, Pirsch J, Becker Y, *et al.* Long-term results of liver transplantation in patients 60 years of age and older. *Transplantation* 2000;**70**:780-3.

86 Levy M, Somasundar P, Jennings L, *et al.* The elderly liver transplant recipient: a call for caution. *Ann Surg* 2001;**233**:107-13.

87 Larson AM, Curtis JR. Integrating palliative care for liver transplant candidates: "too well for transplant, too sick for life".[see comment]. *JAMA* 2006;**295**:2168-76.

88 Sanchez W, Talwalkar JA. Palliative care for patients with end-stage liver disease ineligible for liver transplantation. *Gastroenterol Clin North Am* 2006;**35**:201-19.

89 Rhee C, Broadbent AM. Palliation and liver failure: palliative medications dosage guidelines. *Journal of Palliative Medicine* 2007;**10**:677-85.

90 Watson J, Brind A, Chapman C. Hepatitis C virus: epidemiolgy and genotypes in the North East of England. *Gut* 1996;**38**:269-76.

91 Adams L, Lymp J, St Sauver J, *et al.* The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;**126**:113-21.

92 Beasly R. HBV: the major etiology of HCC. *Cancer* 1988;**61**:1942-56.

93 Hollingsworth KG, Newton JL, Taylor R, *et al.* Pilot study of peripheral muscle function in primary biliary cirrhosis: potential implications for fatigue pathogenesis. *Clinical Gastroenterology & Hepatology* 2008;**6**:1041-8.

94 Jones D, Hollingsworth K, Fattakhova G, *et al.* Impaired cardiovascular function in Primary Biliary Cirrhosis. *American Journal of Physiology - Gastrointestinal & Liver Physiology* 2010;**298**:In press.

95 Trevisani F, Sica G, Bernardi M. Autonomic neuropathy in advanced liver disease. *Hepatology* 1996;**24**:1549.

96 Hendrickse MT, Triger DR. Peripheral and cardiovascular autonomic impairment in chronic liver disease: prevalence and relation to hepatic function. *J Hepatol* 1992;**16**:177-83.

97 Szalay F, Marton A, Keresztes K, *et al.* Neuropathy as an extrahepatic manifestation of chronic liver diseases. *Scandinavian Journal of Gastroenterology - Supplement* 1998;**228**:130-2.

98 Solfrizzi V, D'Introno A, Colacicco A, *et al.* Alcohol consumption, mild cognitive impairment, and progression to dememtia. *Neurology* 2007;**68**:1791-9.

99 Newton JL, Hollingsworth KG, Taylor R, *et al.* Cognitive impairment in primary biliary cirrhosis: symptom impact and potential etiology. *Hepatology* 2008;**48**:541-9.

100 O'Carroll RE, Hayes PC, Ebmeier KP, *et al.* Regional cerebral blood flow and cognitive function in patients with chronic liver disease. *Lancet* 1991;**337**:1250-3.

101 Yilmaz Y, Ozdogan O. Liver disease as a risk factor for cognitive decline and dementia: an under-recognized issue. *Hepatology* 2009;**49**:698; author reply

102 Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health* 2003;**57**:740-4.

103 Kannus P, Parkkari J, Koskinen S, *et al.* Fall-induced injuries and deaths among older adults.[see comment]. *JAMA* 1999;**281**:1895-9.

104 Grisso JA, Kelsey JL, Strom BL, *et al.* Risk factors for falls as a cause of hip fracture in women. The Northeast Hip Fracture Study Group. *N Engl J Med* 1991;**324**:1326-31.

105 Salkeld G, Cameron ID, Cumming RG, *et al.* Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ* 2000;**320**:341-6.

106 Donald IP, Bulpitt CJ. The prognosis of falls in elderly people living at home. *Age Ageing* 1999;**28**:121-5.

107 Vellas B, Cayla F, Bocquet H, *et al.* Prospective study of restriction of activity in old people after falls. *Age Ageing* 1987;**16**:189-93.

108 Cwikel J, Fried AV. The social epidemiology of falls among community-dwelling elderly: guidelines for prevention. *Disabil Rehabil* 1992;**14**:113-21.

109 Delbaere K, Crombez G, Vanderstraeten G, *et al.* Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. *Age Ageing* 2004;**33**:368-73.

110 Tinetti ME, Liu WL, Claus EB. Predictors and prognosis of inability to get up after falls among elderly persons. *JAMA* 1993;**269**:65-70.

111 Murphy J, Isaacs B. The post-fall syndrome. A study of 36 elderly patients. *Gerontology* 1982;**28**:265-70.

112 Tinetti ME, Mendes de Leon CF, Doucette JT, *et al.* Fear of falling and fall-related efficacy in relationship to functioning among community-living elders. *J Gerontol* 1994;**49**:M140-7.

113 Cumming R, Salkeld G, Thomas M, *et al.* Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores and nursing home admission. *Journal of Gerontology: Medical Sciences* 2000;**55**:299-305.

114 Oakley A, Dawson MF, Holland J, *et al.* Preventing falls and subsequent injury in older people. *Qual Health Care* 1996;**5**:243-9.

115 National Institute of Clinical Excellence. Clinical practice guideline for the assessment and prevention of falls in older people. Clinical Guideline 21. London 2004.

116 Davies AJ, Kenny RA. Falls presenting to the accident and emergency department: types of presentation and risk factor profile. *Age Ageing* 1996;**25**:362-6.

117 Shaw FE, Kenny RA. The overlap between syncope and falls in the elderly. *Postgrad Med J* 1997;**73**:635-9.

118 Kenny RA, Richardson DA, Steen N, *et al.* Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J Am Coll Cardiol* 2001;**38**:1491-6.

119 Tinetti ME, Baker DI, McAvay G, *et al.* A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 1994;**331**:821-7.

120 Newton JL, Hudson M, Tachtatzis P, *et al.* Population prevalence and symptom associations of autonomic dysfunction in primary biliary cirrhosis. *Hepatology* 2007;**45**:1496-505.

121 Lindgren S, Lilja B, Verbaan H, *et al.* Alcohol abuse exaggerates autonomic dysfunction in chronic liver disease. *Scand J Gastroenterol* 1996;**31**:1120-4.

122 Chaudhry V, Corse AM, O'Brian R, *et al.* Autonomic and peripheral (sensorimotor) neuropathy in chronic liver disease: a clinical and electrophysiologic study. *Hepatology* 1999;**29**:1698-703.

123 Thuluvath PJ, Triger DR. Autonomic neuropathy and chronic liver disease. *Q J Med* 1989;**72**:737-47.

124 Carey EJ, Gautam M, Ingall T, *et al.* The effect of liver transplantation on autonomic dysfunction in patients with end-stage liver disease. *Liver Transplantation* 2008;**14**:235-9.

125 Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988;**319**:1701-7.

126 Lord SR, Sambrook PN, Gilbert C, *et al.* Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. *Med J Aust*;**160**:684-5.

127 Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;**80**:896-903.

128 Alameri HF, Sanai FM, Al Dukhayil M, *et al.* Six Minute Walk Test to assess functional capacity in chronic liver disease patients. *World Journal of Gastroenterology* 2007;**13**:3996-4001.

129 Lorincz MT. Neurologic Wilson's disease. *Ann N Y Acad Sci*;**1184**:173-87.

130 Garcia-Valdecasas-Campelo E, Gonzalez-Reimers E, Santolaria-Fernandez F, *et al.* Brain atrophy in alcoholics: relationship with alcohol intake; liver disease; nutritional status, and inflammation. *Alcohol Alcohol* 2007;**42**:533-8.

131 Cordeiro RC, Jardim JR, Perracini MR, *et al.* Factors associated with functional balance and mobility among elderly diabetic outpatients. *Arq Bras Endocrinol Metabol* 2009;**53**:834-43.

132 Moreland JD, Richardson JA, Goldsmith CH, *et al.* Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2004;**52**:1121-9.

133 Krasnoff JB, Painter PL, Wallace JP, *et al.* Health-related fitness and physical activity in patients with nonalcoholic fatty liver disease.[see comment]. *Hepatology* 2008;**47**:1158-66.

134 Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol* 2004;**16**:1095-105.

135 Nevitt MC, Cummings SR, Kidd S, *et al.* Risk factors for recurrent nonsyncopal falls. A prospective study. *JAMA* 1989;**261**:2663-8.

136 Lord SR, Ward JA, Williams P, *et al.* Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc* 1994;**42**:1110-7.

137 Davison J, Marrinan S. Falls. *Reviews in Clinical Gerontology* 2007;**17**:93-107.

138 Harwood RH. Visual problems and falls. *Age Ageing* 2001;**30 Suppl 4**:13-8.

139 Haran MJ, Cameron ID, Ivers RQ, *et al.* Effect on falls of providing single lens distance vision glasses to multifocal glasses wearers: VISIBLE randomised controlled trial. *BMJ*;**340**:c2265.

140 Day L, Fildes B, Gordon I, *et al.* Randomised factorial trial of falls prevention among older people living in their own homes. *BMJ* 2002;**325**:128.

141 Cumming RG, Ivers R, Clemson L, *et al.* Improving vision to prevent falls in frail older people: a randomized trial. *J Am Geriatr Soc* 2007;**55**:175-81.

142 Giovannini A, Ballardini G, Amatetti S, *et al.* Patterns of lacrimal dysfunction in primary biliary cirrhosis. *Br J Ophthalmol* 1985;**69**:832-5.

143 Tsolakos A, Zalatimo N. Hepatitis C: a review of diagnosis, management, and ocular complications from treatment. *Optometry*;**74**:517-23.

144 Roncone DP. Xerophthalmia secondary to alcohol-induced malnutrition. *Optometry* 2006;**77**:124-33.

145 Abe T, Nakajima A, Satoh N, *et al.* Clinical characteristics of hepatitis C virus-associated retinopathy. *Jpn J Ophthalmol* 1995;**39**:411-9.

146 Severn PS, Fraser SG. Bilateral cataracts and glaucoma induced by long-term use of oral prednisolone bought over the internet. *Lancet* 2006;**368**:618.

147 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952-60.

148 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;**47**:40-50.

149 Schlatter C, Egger SS, Tchambaz L, *et al.* Pharmacokinetic changes of psychotropic drugs in patients with liver disease: implications for dose adaptation. *Drug Saf* 2009;**32**:561-78.

150 Lyons R. Modification of the home environment for the reduction of injuries (Cochrane review). Oxford: Update software 2006.

151 Sattin RW, Rodriguez JG, DeVito CA, *et al.* Home environmental hazards and the risk of fall injury events among community-dwelling older persons. Study to Assess Falls Among the Elderly (SAFE) Group. *J Am Geriatr Soc* 1998;**46**:669-76.

152 O'Mahony JF. Cognitive performance and liver function among recently abstinent alcohol abusers. *Addict Behav* 2005;**30**:369-73.

153 Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: a review. *Dig Dis Sci* 2008;**53**:307-21.

154 Fleckenstein JF, Frank S, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996;**23**:471-5.

155 Abraldes JG, Iwakiri Y, Loureiro-Silva M, *et al.* Mild increases in portal pressure upregulate vascular endothelial growth factor and endothelial nitric oxide synthase in the intestinal microcirculatory bed, leading to a hyperdynamic state. *American Journal of Physiology - Gastrointestinal & Liver Physiology* 2006;**290**:G980-7.

156 Arroyo V, Planas R, Gaya J, *et al.* Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis. Relationship to functional renal failure and sodium and water excretion. *Eur J Clin Invest* 1983;**13**:271-8.

157 Dillon JF, Nolan J, Thomas H, *et al.* The correction of autonomic dysfunction in cirrhosis by captopril. *J Hepatol* 1997;**26**:331-5.

158 Ferlitsch A, Pleiner J, Mittermayer F, *et al.* Vasoconstrictor hyporeactivity can be reversed by antioxidants in patients with advanced alcoholic cirrhosis of the liver and ascites. *Crit Care Med* 2005;**33**:2028-33.

159 Miyaaki H, Ichikawa T, Nakao K, *et al.* Clinicopathological study of nonalcoholic fatty liver disease in Japan: the risk factors for fibrosis. *Liver International* 2008;**28**:519-24.

160 Kingston ME, Ali MA, Atiyeh M, *et al.* Diabetes mellitus in chronic active hepatitis and cirrhosis. *Gastroenterology* 1984;**87**:688-94.

161 Cryer PE. Hypoglycemia in diabetes: pathophysiological mechanisms and diurnal variation. *Prog Brain Res* 2006;**153**:361-5.

162 Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;**350**:2272-9.

163 Lhuillier F, Dalmas ED, Gratadour PM, *et al.* Spontaneous baroreflex cardiac sensitivity in end-stage liver disease: effect of liver transplantation. *Eur J Anaesthesiol* 2006;**23**:426-32.

164 Newton JL, Gibson GJ, Tomlinson M, *et al.* Fatigue in primary biliary cirrhosis is associated with excessive daytime somnolence. *Hepatology* 2006;**44**:91-8.

165 Monforte R, Estruch R, Valls-Sole J, *et al.* Autonomic and peripheral neuropathies in patients with chronic alcoholism. A dose-related toxic effect of alcohol. *Arch Neurol* 1995;**52**:45-51.

166 Kempler P, Szalay F, Varadi A, *et al.* Prolongation of the QTc-interval reflects the severity of autonomic neuropathy in primary biliary cirrhosis and in other non-alcoholic liver diseases. *Z Gastroenterol* 1993;**31 Suppl 2**:96-8.

167 Newton JL, Jones DE, Henderson E, *et al.* Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 2008;**57**:807-13.

168 Cauch-Dudek K, Abbey S, Stewart DE, *et al.* Fatigue in primary biliary cirrhosis. *Gut* 1998;**43**:705-10.

169 Newton JL, Davidson A, Kerr S, *et al.* Autonomic dysfunction in primary biliary cirrhosis correlates with fatigue severity. *Eur J Gastroenterol Hepatol* 2007;**19**:125-32.

170 Bottini P, Tantucci C, Scionti L, *et al.* Cardiovascular response to exercise in diabetic patients: influence of autonomic neuropathy of different severity.[see comment]. *Diabetologia* 1995;**38**:244-50.

171 Gomez-Lobo V, Burgansky A, Kim-Schluger L, *et al.* Gynecologic symptoms and sexual function before and after liver transplantation. *J Reprod Med* 2006;**51**:457-62.

172 Haensch CA, Jorg J. Autonomic dysfunction in multiple sclerosis. *J Neurol* 2006;**253 Suppl 1**:I3-9.

173 Galati JS, Holdeman KP, Dalrymple GV, *et al.* Delayed gastric emptying of both the liquid and solid components of a meal in chronic liver disease. *Am J Gastroenterol* 1994;**89**:708-11.

174 Galati JS, Holdeman KP, Bottjen PL, *et al.* Gastric emptying and orocecal transit in portal hypertension and end-stage chronic liver disease. *Liver Transpl Surg* 1997;**3**:34-8.

175 Ohlsson B, Melander O, Thorsson O, *et al.* Oesophageal dysmotility, delayed gastric emptying and autonomic neuropathy correlate to disturbed glucose homeostasis. *Diabetologia* 2006;**49**:2010-4.

176 Earle CM, Stuckey BG. Biochemical screening in the assessment of erectile dysfunction: what tests decide future therapy? *Urology* 2003;**62**:727-31.

177 Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. *Liver Transplantation* 2006;**12**:1473-7.

178 Marchesini G, Bianchi G, Amodio P, *et al.* Factors associated with poor health-related quality of life of patients with cirrhosis.[see comment]. *Gastroenterology* 2001;**120**:170-8.

179 Anonymous. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996;**46**:1470.

180 Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab* 1986;**15**:855-88.

181 Gines P, Guevara M, De Las Heras D, *et al.* Review article: albumin for circulatory support in patients with cirrhosis. *Aliment Pharmacol Ther* 2002;**16 Suppl 5**:24-31.

182 Sola-Vera J, Minana J, Ricart E, *et al.* Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology* 2003;**37**:1147-53.

183 Jones DE, Newton JL. An open study of modafinil for the treatment of daytime somnolence and fatigue in primary biliary cirrhosis. *Aliment Pharmacol Ther* 2007;**25**:471-6.

184 Ko DT, Hebert PR, Coffey CS, *et al.* Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction.[see comment]. *JAMA* 2002;**288**:351-7.

185 Bloomgarden ZT. Diabetic neuropathy. *Diabetes Care* 2008;**31**:616-21.

186 Lacy BE, Crowell MD, Schettler-Duncan A, *et al.* The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care* 2004;**27**:2341-7.

187 Abell T, McCallum R, Hocking M, *et al.* Gastric electrical stimulation for medically refractory gastroparesis.[see comment]. *Gastroenterology* 2003;**125**:421-8.

188 Lehur PA, Glemain P, Bruley des Varannes S, *et al.* Outcome of patients with an implanted artificial anal sphincter for severe faecal incontinence. A single institution report. *Int J Colorectal Dis* 1998;**13**:88-92.

189 Kamm MA, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. *Gut* 1988;**29**:969-73.

190 Apostolidis AN, Fowler CJ. Evaluation and treatment of autonomic disorders of the urogenital system. *Semin Neurol* 2003;**23**:443-52.

191 Chew ML, Mulsant BH, Pollock BG, *et al.* Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 2008;**56**:1333-41.

192 Shamliyan TA, Kane RL, Wyman J, *et al.* Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med* 2008;**148**:459-73.

193 Gluud C, Wantzin P, Eriksen J. No effect of oral testosterone treatment on sexual dysfunction in alcoholic cirrhotic men. *Gastroenterology* 1988;**95**:1582-7.

194 Van Thiel DH, Gavaler JS, Sanghvi A. Recovery of sexual function in abstinent alcoholic men. *Gastroenterology* 1983;**84**:677-82.

195 Nolte W, Schindler CG, Figulla HR, *et al.* Increase of serum estradiol in cirrhotic men treated by transjugular intrahepatic portosystemic stent shunt. *J Hepatol* 2001;**34**:818-24.

196 Forgue ST, Phillips DL, Bedding AW, *et al.* Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007;**63**:24-35.

197 Daghfous R, El Aidli S, Zaiem A, *et al.* Sildenafil-associated hepatotoxicity. *Am J Gastroenterol* 2005;**100**:1895-6.

198 Naumann M, So Y, Argoff CE, *et al.* Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and

Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;**70**:1707-14.

199 McDougall AJ, Davies L, McCaughan GW. Autonomic and peripheral neuropathy in endstage liver disease and following liver transplantation. *Muscle Nerve* 2003;**28**:595-600.

200 Lhuillier F, Dalmas ED, Gratadour PM, *et al.* Spontaneous baroreflex cardiac sensitivity in end-stage liver disease: effect of liver transplantation. *Eur J Anaesthesiol* 2006;**23**:426-32.

201 Oliver MI, Miralles R, Rubies-Prat J, *et al.* Autonomic dysfunction in patients with non-alcoholic chronic liver disease. *J Hepatol* 1997;**26**:1242-8.

202 Hendrickse MT, Thuluvath PJ, Triger DR. Natural history of autonomic neuropathy in chronic liver disease.[see comment]. *Lancet* 1992;**339**:1462-4.

203 Jones DE, Bhala N, Burt J, *et al.* Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort.[see comment]. *Gut* 2006;**55**:536-41.

204 Jones DEJ, Sutcliffe K, Pairman J, *et al.* An integrated care pathway improves quality of life in Primary Biliary Cirrhosis. *QJM* 2008;**101**:535-43.

205 Craig P, Dieppe P, Macintyre S, *et al.* Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;**337**:a1655.

206 Campbell M, Fitzpatrick R, Haines A, *et al.* Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;**321**:694-6.

207 Campbell NC, Murray E, Darbyshire J, *et al.* Designing and evaluating complex interventions to improve health care. *BMJ* 2007;**334**:455-9.

208 Matthews D, Hosker J, Rudenski A, *et al.* Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;**28**:412-9.

209 Prince MI, James OF, Holland NP, *et al.* Validation of a fatigue impact score in primary biliary cirrhosis: towards a standard for clinical and trial use. *J Hepatol* 2000;**32**:368-73.

210 Goldblatt J, Taylor PJ, Lipman T, *et al.* The true impact of fatigue in primary biliary cirrhosis: a population study.[see comment]. *Gastroenterology* 2002;**122**:1235-41.

211 Robertson D, Johnson GA, Robertson RM, *et al.* Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. *Circulation* 1979;**59**:637-43.

212 Hudson M, Newton J, Walters R, *et al.* An evidence-based model for the targeting of varices screening in PBC. *Hepatology* 2005;**42**:469A.

213 Roth M, Tym E, Mountjoy CQ, *et al.* CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* 1986;**149**:698-709.

214 Schrezenmaier C, Gehrking JA, Hines SM, *et al.* Evaluation of orthostatic hypotension: relationship of a new self-report instrument to laboratory-based measures. *Mayo Clin Proc* 2005;**80**:330-4.

215 Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology* 2004;**19**:203-14.

216 Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;**39**:142-8.

217 Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc* 1986;**34**:119-26.

218 Faber MJ, Bosscher RJ, van Wieringen PCW. Clinimetric Properties of the Performance-Oriented Mobility Assessment. 2006:944-54.

219 Yardley L, Beyer N, Hauer K, *et al.* Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age Ageing* 2005;**34**:614-9.

220 ProFaNE. 2007. Falls Efficacy Scale International. October 2007. http://www.profane.eu.org/fesi.php

221 Cella D, Yount S, Rothrock N, *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care* 2007;**45**:S3-S11.

222 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health & Quality of Life Outcomes* 2003;**1**:20.

223 Anonymous. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[see comment]. *Circulation* 1996;**93**:1043-65.

224 Di Rienzo M, Parati G, Castiglioni P, *et al.* Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life.[see comment]. *American Journal of Physiology - Regulatory Integrative & Comparative Physiology* 2001;**280**:R744-51.

225 Ullah S, Finch C, Day L. Statistical modelling for falls count data. *Accid Anal Prev* 2010;**42**:384-92.

226 Stevens JA, Corso PS, Finkelstein EA, *et al.* The costs of fatal and non-fatal falls among older adults. *Inj Prev* 2006;**12**:290-5.

227 Lamb SE, Jorstad-Stein EC, Hauer K, *et al.* Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc* 2005;**53**:1618-22.

228 Zijlstra GAR, van Haastregt JCM, van Rossum E, *et al.* Interventions to reduce fear of falling in community-living older people: a systematic review. *J Am Geriatr Soc* 2007;**55**:603-15.

229 Newton JL. Fatigue in primary biliary cirrhosis. *Clinics in Liver Disease* 2008;**12**:367-83; ix.

230 Zijlstra GAR, van Haastregt JCM, Ambergen T, *et al.* Effects of a multicomponent cognitive behavioral group intervention on fear of falling and activity avoidance in community-dwelling older adults: results of a randomized controlled trial. *J Am Geriatr Soc* 2009;**57**:2020-8.

231 Tennstedt S, Howland J, Lachman M, *et al.* A randomized, controlled trial of a group intervention to reduce fear of falling and associated activity restriction in older adults. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences* 1998;**53**:P384-92.

232 Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc* 1988;**36**:613-6.

233 Hauer K, Lamb SE, Jorstad EC, *et al.* Systematic review of definitions and methods of measuring falls in randomised controlled fall prevention trials. *Age Ageing* 2006;**35**:5-10.

234 Skelly M, James P, Ryder S. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *J Hepatol* 2001;**35**:195-9.

235 Bedogni G, Miglioli L, Masutti F, *et al.* Prevalence of and risk factors for non-alcoholic fatty liver disease: The Dionysos nutrition and liver study. *Hepatology* 2005;**42**:44-52.

236 Tiplady B, Franklin N, Scholey A. Effects of ethanol on judgements of performance. *Br J Psychol* 2004;**95**:105-18.

237 Santos Junior R, Miyazaki MCOS, Domingos NAM, *et al.* Patients undergoing liver transplantation: psychosocial characteristics, depressive symptoms, and quality of life. *Transplant Proc* 2008;**40**:802-4.

238 Aberg F, Rissanen AM, Sintonen H, *et al.* Health-related quality of life and employment status of liver transplant patients. *Liver Transplantation* 2009;**15**:64-72.

239 van den Berg-Emons R, Kazemier G, van Ginneken B, *et al.* Fatigue, level of everyday physical activity and quality of life after liver transplantation. *Journal of Rehabilitation Medicine* 2006;**38**:124-9.

240 Tome S, Wells JT, Said A, *et al.* Quality of life after liver transplantation. A systematic review. *J Hepatol* 2008;**48**:567-77.

241 Grubb B, Kanjwal Y, Karabin B, *et al.* Orthostatic hypotension and autonomic failure: a concise guide to diagnosis and management. *Clinical Medicine: Cardiology* 2008;**2**:289-91.

242 Crosbie OM, Freaney R, McKenna MJ, *et al.* Predicting bone loss following orthotopic liver transplantation. *Gut* 1999;**44**:430-4.

243 Trautwein C, Possienke M, Schlitt HJ, *et al.* Bone density and metabolism in patients with viral hepatitis and cholestatic liver diseases before and after liver transplantation. *Am J Gastroenterol* 2000;**95**:2343-51.

244 Monegal A, Navasa M, Suaraz M, *et al.* Effects of intravenous pamidronate on bone loss after liver transplantation. *Calcif Tissue Int* 2006;**78**:S148.

245 Crawford BA, Kam C, Pavlovic J, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial.[see comment][summary for patients in Ann Intern Med. 2006 Feb 21;144(4):I37; PMID: 16490906]. *Ann Intern Med* 2006;**144**:239-48.

246 Smallwood GA, Wickman JM, Martinez E, *et al.* Osteoporosis screening in an outpatient liver transplant clinic: impact of primary immunosuppression. *Transplant Proc* 2002;**34**:1569-70.

247 Claassen J. Cerebral perfusion in neurogenic orthostatic hypotension. *The Lancet Neurology* 2008;**7**:573.

248 Frith J, Jones D, Newton J. Regulation of cerebral blood flow is significantly impaired in primary biliary cirrhosis. *J Hepatol* 2009;**50**:S246.

249 Hollingsworth KG, Jones D, Taylor R, *et al.* Impaired cerebral autoregulation in primary biliary cirrhosis: implications for the pathogenesis of cognitive decline. *Liver International* 2010;**30**:878-85.

250 Kousoulas L, Neipp M, Barg-Hock H, *et al.* Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation. *Transpl Int* 2008;**21**:1052-8.

251 de Kroon L, Drent G, van den Berg AP, *et al.* Current health status of patients who have survived for more than 15 years after liver transplantation. *Neth J Med* 2007;**65**:252-8.

252 Lewis MB, Howdle PD. Cognitive dysfunction and health-related quality of life in long-term liver transplant survivors. *Liver Transplantation* 2003;**9**:1145-8.

253 Karam VH, Gasquet I, Delvart V, *et al.* Quality of life in adult survivors beyond 10 years after liver, kidney, and heart transplantation. *Transplantation* 2003;**76**:1699-704.

254 Frith J, Newton J. Liver transplantation in more elderly age. *Transpl Int* 2009;**22**:599-600.

255 Tilvis RS, Hakala SM, Valvanne J, *et al.* Postural hypotension and dizziness in a general aged population: a four-year follow-up of the Helsinki Aging Study. *J Am Geriatr Soc* 1996;**44**:809-14.

256 Robertson D, Kincaid DW, Haile V, *et al.* The head and neck discomfort of autonomic failure: an unrecognized aetiology of headache. *Clin Auton Res* 1994;**4**:99-103.

257 Low PA, Opfer-Gehrking TL, McPhee BR, *et al.* Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin Proc* 1995;**70**:617-22.

258 Novak V, Novak P, Spies JM, *et al.* Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke* 1998;**29**:104-11.

259 Lassen NA. Autoregulation of Cerebral Blood Flow. *Circ Res* 1964;**15**:SUPPL:201-4.

260 Tiecks FP, Lam AM, Aaslid R, *et al.* Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;**26**:1014-9.

261 Harder DR, Roman RJ, Gebremedhin D, *et al.* A common pathway for regulation of nutritive blood flow to the brain: arterial muscle membrane potential and cytochrome P450 metabolites. *Acta Physiol Scand* 1998;**164**:527-32.

262 Van Lieshout JJ, Wieling W, Karemaker JM, *et al.* Syncope, cerebral perfusion, and oxygenation. *J Appl Physiol* 2003;**94**:833-48.

263 Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auton Res* 2009;**19**:197-211.

264 Giller CA, Bowman G, Dyer H, *et al.* Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993;**32**:737-41; discussion 41-2.

265 Aaslid R, Lindegaard KF, Sorteberg W, *et al.* Cerebral autoregulation dynamics in humans. *Stroke* 1989;**20**:45-52.

266 Schmidt JF, Waldemar G, Vorstrup S, *et al.* Computerized analysis of cerebral blood flow autoregulation in humans: validation of a method for pharmacologic studies. *J Cardiovasc Pharmacol* 1990;**15**:983-8.

267 Cencetti S, Bandinelli G, Lagi A. Effect of PCO2 changes induced by head-upright tilt on transcranial Doppler recordings. *Stroke* 1997;**28**:1195-7.

268 Frokjaer VG, Strauss GI, Mehlsen J, *et al.* Autonomic dysfunction and impaired cerebral autoregulation in cirrhosis. *Clin Auton Res* 2006;**16**:208-16.

269 Kawakami M, Koda M, Murawaki Y, *et al.* Cerebral vascular resistance assessed by transcranial color Doppler ultrasonography in patients with chronic liver diseases. *J Gastroenterol Hepatol* 2001;**16**:890-7.

270 Lagi A, La Villa G, Barletta G, *et al.* Cerebral autoregulation in patients with cirrhosis and ascites. A transcranial Doppler study. *J Hepatol* 1997;**27**:114-20.

271 Lagi A, Laffi G, Cencetti S, *et al.* Impaired sympathetic regulation of cerebral blood flow in patients with cirrhosis of the liver. *Clin Sci* 2002;**103**:43-51.

272 Dam M, Burra P, Tedeschi U, *et al.* Regional cerebral blood flow changes in patients with cirrhosis assessed with 99mTc-HM-PAO single-photon emission computed tomography: effect of liver transplantation. *J Hepatol* 1998;**29**:78-84.

273 Lagi A, Cencetti S, Corsoni V, *et al.* Cerebral vasoconstriction in vasovagal syncope: any link with symptoms? A transcranial Doppler study. *Circulation* 2001;**104**:2694-8.

274 Carey BJ, Eames PJ, Panerai RB, *et al.* Carbon dioxide, critical closing pressure and cerebral haemodynamics prior to vasovagal syncope in humans. *Clin Sci* 2001;**101**:351-8.

275 Parry SW, Steen N, Baptist M, *et al.* Cerebral autoregulation is impaired in cardioinhibitory carotid sinus syndrome. *Heart* 2006;**92**:792-7.

276 Williams B. Simultaneous cerebral and spinal fluid pressure recordings. I. Technique, physiology, and normal results. *Acta Neurochir (Wien)* 1981;**58**:167-85.

277 Tiecks FP, Douville C, Byrd S, *et al.* Evaluation of impaired cerebral autoregulation by the Valsalva maneuver. *Stroke* 1996;**27**:1177-82.

278 Tiecks FP, Lam AM, Matta BF, *et al.* Effects of the valsalva maneuver on cerebral circulation in healthy adults. A transcranial Doppler Study. *Stroke* 1995;**26**:1386-92.

279 Meyer JS, Gotoh F, Takagi Y, *et al.* Cerebral hemodynamics, blood gases, and electrolytes during breath-holding and the Valsalva maneuver. *Circulation* 1966;**33**:II35-48.

280 Krajewski A, Freeman R, Ruthazer R, *et al.* Transcranial Doppler assessment of the cerebral circulation during postprandial hypotension in the elderly. *J Am Geriatr Soc* 1993;**41**:19-24.

281 Almdal T, Schroeder T, Ranek L. Cerebral blood flow and liver function in patients with encephalopathy due to acute and chronic liver diseases. *Scand J Gastroenterol* 1989;**24**:299-303.

282 Braam EAJE, Verbakel D, Adiyaman A, *et al.* Orthostatic hypotension: revision of the definition is needed. *J Hypertens* 2009;**27**:2119-20; author reply 20.

283 van der Velde N, van den Meiracker AH, Stricker BHC, *et al.* Measuring orthostatic hypotension with the Finometer device: is a blood pressure drop of one heartbeat clinically relevant? *Blood Press Monit* 2007;**12**:167-71.

284 Fedorowski A, Burri P, Melander O. Orthostatic hypotension in genetically related hypertensive and normotensive individuals. *J Hypertens* 2009;**27**:976-82.

285 Lahrmann H, Cortelli P, Hilz M, *et al.* EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurol* 2006;**13**:930-6.

286 Van Riper DA, Bevan JA. Evidence that neuropeptide Y and norepinephrine mediate electrical field-stimulated vasoconstriction of rabbit middle cerebral artery. *Circ Res* 1991;**68**:568-77.

287 Oleson J. The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. *Neurology* 1972;**22**:978-87.

288 Barnett A, Smith B, Lord SR, *et al.* Community-based group exercise improves balance and reduces falls in at-risk older people: a randomised controlled trial. *Age Ageing* 2003;**32**:407-14.

289 Bandura A. *Social foundations of thought and action: A social cognitive theory*. Englewood Cliffs, NJ: Prentice-Hall 1986.

290 Resnick B, Jenkins LS. Testing the reliability and validity of the Self-Efficacy for Exercise scale. *Nurs Res* 2000;**49**:154-9.

291 Bellentani S, Dalle Grave R, Suppini A, *et al.* Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. *Hepatology* 2008;**47**:746-54.

292 Jette AM, Rooks D, Lachman M, *et al.* Home-based resistance training: predictors of participation and adherence. *Gerontologist* 1998;**38**:412-21.

293 Lapier T, Cleary K, Kidd J. Exercise self efficacy, habitual physical activity and fear of falling in patients with coronary heart disease. *Journal of Cardiopulmonary Physical Therapy* 2009;**20**:5-11.

294 Perkins H, Waters A, Baum G, *et al.* Outcome expectations, expectancy accessibility and exercise in endometrial cancer survivors. *Journal of Sport and Exercise Psychology* 2009;**31**:776-85.

295 Delbaere K, Crombez G, Vanderstraeten G, *et al.* Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. *Age Ageing* 2004;**33**:368-73.

296 Newton J, Elliott C, Frith J, *et al.* Appreciation of the benefits of exercise programmes in non-alcoholic fatty liver disease- implications of fatigue and impact upon activities of daily living. *Hepatology* 2008;**48**:1136.

297 Resnick B, Zimmerman S, Orwig D, *et al.* Model testing for reliability and validity of the Outcome Expectations for Exercise Scale. *Nurs Res* 2001;**50**:293-9.

298 Fisk JD, Ritvo PG, Ross L, *et al.* Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994;**18 Suppl 1**:S79-83.

299 Frith J, Newton J. Fatigue Impact Scale. *Occup Med* 2010;**60**:159.

300 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003;**30**:167-78.

301 Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005;**23**:S14-8.

302 Campion EW, deLabry LO, Glynn RJ. The effect of age on serum albumin in healthy males: report from the Normative Aging Study. *J Gerontol* 1988;**43**:M18-20.

303 GMC. Good Medical Practice. 2006.

304 Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. *Gut* 2007;**56**:1760-9.

305 Lee L-L, Arthur A, Avis M. Using self-efficacy theory to develop interventions that help older people overcome psychological barriers to physical activity: A discussion paper. *Int J Nurs Stud* 2008;**45**:1690-9.

306 Newton JL, Gibson GJ, Tomlinson M, *et al.* Fatigue in primary biliary cirrhosis is associated with excessive daytime somnolence. *Hepatology* 2006;**44**:91-8.

307 Kramer L, Hofer H, Bauer E, *et al.* Relative impact of fatigue and subclinical cognitive brain dysfunction on health-related quality of life in chronic hepatitis C infection. *AIDS* 2005;**19 Suppl 3**:S85-92.

308 Scheffer AC, Schuurmans MJ, van Dijk N, *et al.* Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing* 2008;**37**:19-24.

309 Shaughnessy M, Resnick BM, Macko RF. Reliability and validity testing of the short self-efficacy and outcome expectation for exercise scales in stroke survivors. *Journal of Stroke and Cerebrovascular Diseases* 2004;**13**:214-9.

310 McAuley E, Motl RW, White SM, *et al.* Validation of the Multidimensional Outcome Expectations for Exercise Scale in Ambulatory, Symptom-Free Persons With Multiple Sclerosis. *Arch Phys Med Rehabil* 2009;**91**:100-5.

311 Mahoney J. Why multifactorial fall-prevention interventions may not work (commentary). *Arch Intern Med* 2010;**170**:1117-9.

312 Close J, Ellis M, Hooper R, *et al.* Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet* 1999;**353**:93-7.

313 Lightbody E, Watkins C, Leathley M, *et al.* Evaluation of a nurse-led falls prevention programme versus usual care: a randomized controlled trial. *Age Ageing* 2002;**31**:203-10.

314 Kingston P, Jones M, Lally F, *et al.* Older people and falls: a randomised controlled trial of a health visitor (HV) intervention. *Reviews in Clinical Gerontology* 2001;**11**:209-14.

315 Burra P, Senzolo M, Pizzolato G, *et al.* Does liver-disease aetiology have a role in cerebral blood-flow alterations in liver cirrhosis? *Eur J Gastroenterol Hepatol* 2004;**16**:885-90.

316 Dillon JF, Plevris JN, Wong FC, *et al.* Middle cerebral artery blood flow velocity in patients with cirrhosis. *Eur J Gastroenterol Hepatol* 1995;**7**:1087-91.

317 Iversen P, Sorensen M, Bak LK, *et al.* Low cerebral oxygen consumption and blood flow in patients with cirrhosis and an acute episode of hepatic encephalopathy. *Gastroenterology* 2009;**136**:863-71.

318 Iwasa M, Matsumura K, Kaito M, *et al.* Decrease of regional cerebral blood flow in liver cirrhosis. *Eur J Gastroenterol Hepatol* 2000;**12**:1001-6.

319 Iwasa M, Matsumura K, Watanabe Y, *et al.* Improvement of regional cerebral blood flow after treatment with branched-chain amino acid solutions in patients with cirrhosis. *Eur J Gastroenterol Hepatol* 2003;**15**:733-7.

320 Larsen FS, Olsen KS, Ejlersen E, *et al.* Cerebral blood flow autoregulation and transcranial Doppler sonography in patients with cirrhosis. *Hepatology* 1995;**22**:730-6.

321 Yamamoto M, Iwasa M, Matsumura K, *et al.* Improvement of regional cerebral blood flow after oral intake of branched-chain amino acids in patients with cirrhosis. *World Journal of Gastroenterology* 2005;**11**:6792-9.

322 Yazgan Y, Narin Y, Demirturk L, *et al.* Value of regional cerebral blood flow in the evaluation of chronic liver disease and subclinical hepatic encephalopathy. *J Gastroenterol Hepatol* 2003;**18**:1162-7.

APPENDICES

APPENDIX A. FALLS AND INJURY POSTAL TOOL

Please place a tick in the Yes or No box.

		Yes		No	
1	Have you had any falls?		If yes complete all questions		If no go to question 9
2	Have you fallen in the last year?				
3	If so, how many falls have you had in the last year?				
4	Did you blackout or lose consciousness when you fell?				
5	Did you go to Accident & Emergency following your fall?				
6	Did you fracture any bones from your fall?				
7	Did you need any stitches or medical attention for any injuries other than fractured bones?				
8	Were you admitted to hospital as a result of your fall?				
9	Would you be happy for us to contact you again about developing services for people who attend the liver clinic?				

APPENDIX B. NON-STATISTICALLY SIGNIFICANT RESULTS

Appendix B.1. CLD.

Non significant correlations with number of falls, section 17.5, page 71.

	Variable	r_s	p
Demographics	Albumin	-0.106	0.106
	Bilirubin	-0.027	0.683
	ALP	0.062	0.347
	ALT	-0.054	0.409
	BMI	0.024	0.024
Active stand	sBP	-0.152	0.209
	dBP	-0.046	0.707
	nadir sBP	-0.127	0.295
	nadir dBP	-0.015	0.903
	RRI 30:15	-0.147	0.225
	AUC	0.085	0.485
HRV	LFnu	-0.216	0.071
	HFnu	0.119	0.322
	VLF	-0.216	0.071
	LF	-0.158	0.189
	HF	-0.114	0.346
	PSD	-0.186	0.121
	LFnu:HFnu	-0.164	0.173
BRS	Slope mean	0.019	0.875
	BEI	-0.209	0.081
Valsalva	Valsalva RRI ratio	0.079	0.547
	Overshoot	0.087	0.508
MDT	Cognition	-0.055	0.648
	Hand grip	-0.135	0.262

Appendix B.2. NAFLD.

Non significant correlations with number of falls, section 18.6, page 88.

	Variable	r_s	p
Demographics	Age	0.125	0.207
	Albumin	0.044	0.662
	Bilirubin	-0.035	0.728
	ALP	0.011	0.911
	ALT	-0.037	0.711
	BMI	0.033	0.881
	IR	-0.279	0.467
Active stand	OGS	0.089	0.679
	sBP	-0.354	0.07
	nadir sBP	-0.34	0.083
	RRI 30:15	-0.378	0.052
HRV	LFnu	0.017	0.932
	HFnu	-0.017	0.932
	VLF	-0.174	0.375
	LF	0.039	0.845
	HF	-0.149	0.449
	PSD	-0.18	0.359
	LFnu:HFnu	0.017	0.932
BRS	Slope mean	-0.134	0.504
	BEI	-0.241	0.217
Valsalva	Valsalva RRI ratio	0.081	0.712
	Overshoot	0.123	0.577
MDT	Cognition	-0.125	0.527
	Hand grip	-0.156	0.428
	Sit to Stand Test	0.159	0.439
	Timed Up and Go	0.318	0.099
	Balance	0.055	0.781
	Gait	-0.161	0.413

Appendix B.3. PBC.

Non significant correlations with number of falls, section 19.6, page 98.

	Variable	r_s	p
Demographics	Age	0.065	0.529
	Albumin	0.114	0.394
	Bilirubin	-0.147	0.281
	ALP	-0.197	0.137
	ALT	-0.073	0.585
	BMI	-0.106	0.514
Active stand	sBP	-0.1	0.951
	dBP	0.198	0.222
	nadir sBP	0.025	0.88
	nadir dBP	0.243	0.13
	AUC	-0.046	0.78
	RRI 30:15	-0.012	0.943
HRV	HFnu	0.233	0.148
	VLF	-0.202	0.212
	LF	-0.185	0.253
	HF	-0.054	0.739
	PSD	-0.16	0.324
BRS	Slope mean	0.163	0.315
	BEI	-0.045	0.784
Valsalva	Valsalva RRI ratio	0.215	0.223
	Overshoot	0.095	0.591
MDT	Cognition	0.126	0.444
	Hand grip	-0.159	0.326
	Timed Up and Go	0.261	0.103

Appendix B.4. LT.

Non significant correlations with number of falls, section 24.4, page 130.

	Variables	r_s	p
Demographics	Age	-0.134	0.204
	Albumin	-0.027	0.805
	Bilirubin	0.025	0.823
	ALP	0.203	0.063
	ALT	0.1	0.364
	BMI	-0.333	0.244
Active stand	sBP	-0.43	0.097
	dBP	-0.009	0.972
	nadir dBP	-0.058	0.83
	AUC	0.126	0.641
	RRI 30:15	-0.353	0.18
HRV	LFnu	-0.387	0.138
	HFnu	0.38	0.147
	VLF	-0.274	0.304
	LF	-0.054	0.844
	HF	0.361	0.17
	LFnu:HFnu	-0.387	0.138
	PSD	-0.062	0.819
BRS	Slope mean	0.093	0.743
	BEI	0.153	0.586
Valsalva	Valsalva RRI ratio	-0.087	0.767
	Overshoot	-0.156	0.595
MDT	Cognition	0.079	0.773
	Hand grip	0.104	0.702
	Sit to Stand Test	0.234	0.421
	Timed Up and Go	0.39	0.136
	Balance	-0.434	0.093
	Gait	-0.246	0.376
	FES-I	0.13	0.631

Appendix B.5. CLD and LT.

Non significant correlations with number of falls in the combined cohort, section 25.6, page 139.

		r_s	p
Demographics	Age	0.024	0.823
	Albumin	-0.142	0.212
	Bilirubin	-0.044	0.703
	ALP	0.072	0.528
	ALT	-0.047	0.682
	BMI	-0.052	0.651
Active stand	dBP	-0.055	0.617
	nadir dBP	-0.052	0.638
	AUC	0.116	0.29
HRV	LFnu	-0.174	0.107
	HFnu	0.099	0.363
	LF	-0.185	0.086
	HF	-0.12	0.27
	LFnu:HFnu	-0.136	0.21
BRS	Slope mean	-0.028	0.801
	BEI	-0.141	0.196
Valsalva	Valsalva RRI ratio	0.033	0.781
	Overshoot	0.013	0.911
MDT	Cognition	-0.012	0.911
	Hand grip	-0.094	0.385

APPENDIX C. STUDIES OF CEREBRAL AUTOREGULATION IN CLD

Study	Sample size	Method	Result
Almdal 1989 [281]	28	Indicator flow	↓ CBF in cirrhosis + HE. No association between CBF and liver function
Burra 2004 [315]	50	SPECT	↓ regional CBF. All controls were under investigation for headache
Dam 1998 [272]	23	SPECT	↓ CBF in cirrhosis which resolved post-LT, except in those with ALD
Dillon 1995 [316]	37	TCD	↓ CBFV in cirrhosis (Child's B & C but not in Child's A), 65% had ALD
Frokjaer 2006 [268]	14	TCD	Reports impaired CA in cirrhosis but no different to controls on testing with FET
Iverson 2009 [317]	12	PET	↓ CBF in cirrhosis + HE but normal if HE is absent
Iwasa 2000 [318]	28	SPECT	↓ regional CBF in cirrhosis which associated with increasing disease severity
Iwasa 2003 [319]	14	SPECT	↓ regional CBF in cirrhosis
Lagi 1997 [270]	15	TCD	↓ recovery of CBF to ↓ BP in cirrhosis but normal resting CBF
Lagi 2002 [271]	10	TCD	↓ response to ↑ BP in cirrhosis
Larsen 1995 [320]	10	TCD	CBF and CA similar in cirrhosis to controls
Yamamoto 2005 [321]	43	SPECT	↓ regional CBF in cirrhosis
Yazgan 2003 [322]	31	SPECT	↑ & ↓ regional CBF in cirrhosis. No association with liver disease severity