Diabetes and tuberculosis: how strong is the association and what is the public health impact?

Fiona Pearson

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Institute of Health and Society
Faculty of Medical Sciences
Newcastle University

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Abstract

Introduction

Recent research has generated discussion upon the historically noted association between tuberculosis (TB) and diabetes mellitus (DM). However, evidence on the direction of the association, its magnitude, specificity and impact remains sparse.

The primary aim of this thesis was to identify whether rates of TB (all sub-types, pulmonary (PTB) and extra pulmonary (EPTB)) are raised amongst those with DM (all sub-types, type 1 (T1DM) and type 2 (T2DM)), or the converse. Further to this, to estimate the magnitude and direction of any such associations.

A secondary aim of the thesis was to investigate whether key TB outcomes differ amongst those with co-morbid DM and TB comparative to those with TB disease alone.

Methods

The Oxford Record Linkage Study (ORLS) is a database containing records of all hospital admissions and all deaths (regardless of where they occurred), in defined populations within the former Oxford National Health Service Region. ORLS1 covers the years 1963 to 1998 and ORLS2 covers the years 1999 to 2008, the two databases are not linkable.

The Health Improvement Network (THIN) is a database containing electronic medical records collected at General Practice clinics throughout the United Kingdom (UK).

Retrospective cohort analyses were carried out using data from ORLS1, ORLS2 and THIN.

All patients in the datasets were classified as exposed to (having had) or unexposed to (not having had) TB (all sub-types, PTB or EPTB) and exposed or unexposed to DM (all sub-types, T1DM or T2DM).

In the ORLS1 and ORLS2 datasets, standardised rate ratios (RR) and corresponding 95% confidence intervals (95% CI) were calculated and compared for DM (all sub-types, T1DM and T2DM) in individuals who have had and have not had TB (all sub-types, PTB or EPTB). Similarly, RR and 95% CI were calculated and compared for TB (all sub-types, PTB or EPTB) in patients with and without DM (all sub-types, T1DM and T2DM).

Within THIN datasets, the incidence rate ratio (IRR) and 95% CI of DM (all sub-types, T1DM and T2DM) were calculated using negative binomial regression, with TB (all sub-types, PTB or EPTB) as an explanatory variable. Similarly, the IRR and 95% CI for

TB (all sub-types, PTB or EPTB) were calculated using negative binomial regression, with DM (all sub-types, T1DM or T2DM) as an explanatory variable.

Systematic searching was performed to identify studies comparing TB outcomes amongst those with and without DM. Data from these studies were utilised to inform meta-analyses that assessed all cause mortality, bacterial clearance rate and TB relapse or recurrence rate amongst individuals with DM and co-morbid TB comparative to those with TB alone.

Results

Significant increases in TB rates (all sub-types) and pulmonary tuberculosis (PTB) rates were identified amongst individuals with DM comparative to those without DM within the Oxford Record Linkage Study datasets.

The RR of TB (all sub-types) was increased amongst individuals with DM (all sub-types) compared to those without in ORLS1 (RR 1.77 (95% CI 1.45-2.15), P-value <0.001) and ORLS2 (RR 2.56 (95% CI 1.78-3.69), P-value <0.001). The RR of PTB was also increased amongst individuals with DM (all sub-types) compared to those without in ORLS1 (RR 1.72 (95% CI 1.22-2.37), P-value <0.001) and ORLS2 (RR 3.33 (95% CI 1.51-6.62), P-value 0.001). There was a statistically significant elevation of risk for TB amongst those with T2DM compared to those without in ORLS1 (RR 1.58 (95%CI1.15-2.14), P-value 0.003) and ORLS2 (RR 3.33 (95% CI 1.51-6.62), P-value 0.001).

There was no significant association between the rates of TB amongst those with T1DM compared to those without in ORLS1. The ORLS 2 dataset was too small to complete this analysis. No significant association was found between the rate of EPTB amongst those with DM comparative to those without in either ORLS1 or ORLS2. There was also no significant association between having had TB (all sub-types, PTB or EPTB) and subsequent risk of DM (all sub-types, T1DM or T2DM) in either ORLS1 or ORLS2.

In THIN dataset the risk of TB (all sub-types) was found to be increased amongst individuals with DM (all sub-types), T1DM and T2DM when compared to those without. Thus, the IRR of TB (all sub-types) were significantly increased amongst individuals with DM (all sub-types) (IRR 1.50 (95%CI 1.27-1.76) P-value <0.001), T1DM (IRR 1.46 (95%CI 1.10-1.92) P-value 0.008) and T2DM (IRR 1.54 (95%CI 1.30-1.82) P-value < 0.001) compared to those without DM.

The rate of PTB amongst individuals with DM (all sub-types), T1DM, or T2DM compared to those without were not significantly raised within THIN.

The rate of EPTB was raised amongst those with T1DM (IRR 2.09 (95%CI 1.19-3.66), P-value 0.010) but was not raised amongst those with DM (all sub-types) (IRR 1.43 (95% CI 0.99-2.07), P-value 0.055) or those with T2DM (IRR 1.39 (95%CI 0.93-2.06), P-value 0.11) when compared to those without DM.

In THIN dataset the rates of DM (all sub-types), T1DM and T2DM were found to be raised amongst individuals who have had TB (all sub-types), PTB and EPTB when compared to those who have not. The rate of DM (all sub-types) was increased amongst those who have had TB (all sub-types) (IRR 5.65 (95% CI 5.19-6.16) P-value <0.001), PTB (IRR 5.74 (95% CI 5.08-6.50) P-value <0.001) and EPTB (IRR 4.66 (95% CI 3.94-5.51) P-value <0.001) when compared to those who have not had TB. The rate of T1DM was increased amongst those who have had TB (all sub-types) (IRR 5.49 (95% CI 5.02-6.02) P-value <0.001), EPTB (IRR 0.84 (95% CI 0.35-2.03) P-value <0.001) but not amongst those who have had PTB (IRR 1.09 (95% CI 0.62-1.93) P-value 0.77) when compared to those who have not had TB. The rate of T2DM was increased amongst those who have had TB (all sub-types) (IRR 2.21 (95% CI 1.68-2.91) P-value <0.001), PTB (IRR 5.38 (95% CI 4.73-6.12) P-value <0.001) and EPTB (IRR 4.36 (95% CI 3.65-5.22) P-value <0.001) when compared to those who have not had TB. However, within THIN dataset these estimates of association were being promoted by a significant age by TB interaction effect.

Utilising systematic review techniques, twenty five studies were identified which reported upon TB outcomes amongst those with compared to without DM. Meta-analyses showed individuals with co-morbid TB and DM had no significant difference in bacterial clearance rate after 2-3 months of treatment (1,675 participants, 6 trials, Relative Risk (*RR*) 1.38 (95% CI 0.97-1.97)), no significant difference in risk of TB recurrence & relapse (1,225 participants, 4 trials *RR* 1.20 (95% CI 0.93-1.54)), but a statistically significant increased risk of all cause mortality (12,128 participants, 18 trials, *RR* 1.97 (95% CI 1.53-2.55)) comparative to those with TB in isolation.

Discussion

TB risk is increased in those with compared to those without DM within a UK setting. However, it remains unclear if risk of PTB and EPTB are raised amongst those with DM comparative to those without. It also remains unclear as to whether risk of DM is

increased amongst those who have had TB comparative to those who have never had TB.

Individuals with co-morbid disease are at a greater risk of mortality during active TB disease than those with TB alone, however risk of TB relapse and recurrence are the same.

Consideration of the association between DM and TB may become more important for improving TB control and TB treatment as DM prevalence rises in the UK and globally. In areas where TB is endemic TB screening amongst those with DM and TB prophylaxis may be needed to reduce or stabilise numbers developing active disease. Also, the increasing numbers suffering from co-morbid TB and DM will need heightened clinical attention in order to improve TB mortality outcomes.

Dedication

To my parents and my husband for their continual support and encouragement.

Acknowledgements

team extracted and provided the data needed by the candidate in order to complete the work.

The candidate reviewed, extracted and synthesised all data for the systematic review upon TB outcomes amongst individuals with DM. In accordance with standard systematic review methods abstract review of all titles returned by the search string and data extraction for included studies was duplicated by a second independent investigator, either JC or NU.

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List of Abbreviations

AFB: acid fast bacilli, 41
AHDF: additional health data file, 71
BMI: body mass index, 41
BP: blood pressure, 27
CD4+: cluster of differentiation 4 positive, 11
CD8+: cluster of differentiation 8 positive, 11
CDC: Centre for disease control and prevention, 41
CI: confidence intervals, ii
CSD-EPIC: Cegedim Strategic Data Epidemiology and Pharmacology Information Core, viii
CW: Clare Wotton, viii
Dec: December, xxi
DM: diabetes mellitus, ii
DNA: Deoxyribonucleic acid, 14
EPTB: extra pulmonary tuberculosis, ii
FBG: fasting blood glucose, 28
FP: Fiona Pearson, 37
GP: general practice/practitioner, 3
HES: Hospital Episode Statistics, 32
HIV: Human Immunodeficiency Virus, 1
HPA: Health Protection Agency, 7
ICD: International Classification of Diseases, 41
IDF: International Diabetes Federation, 27
IFN-γ: interferon gamma, 11
IGT: impaired glucose tolerance, 3
IL: interleukin, 121
IRR: incidence rate ratios, ii
Jan: January, 42
JC: Professor J. Critchley, viii
LRT: lower respiratory tract, 10
M.tuberculosis: Mycobacterium tuberculosis, 7
MESH: medical subject heading, 36
MG: Michael Goldacre, viii
MRF: medical record file, 71
MRR: medical record review, 41
N.Ireland: Northern Ireland, 19
NHS: National Health Services, 61
NICE: National Institute for Clinical Excellence, 15
NU: Professor N. Unwin, viii
OR: odds ratio, 51
ORLS: Oxford Record Linkage Study, ii
PAF: population attributable fractions, 53
PMNs: polymorphonuclear leukocytes, 121
PTB: pulmonary tuberculosis, ii
PVIF: postcode variable indicators file, 71
ROS: reactive oxygen species, 121
RR: rate ratio, ii
RR: relative risk, iv
SES: socio-economic status, 24

T1DM: type 1 diabetes mellitus, ii
T2DM: type 2 diabetes mellitus, ii
TB: tuberculosis, ii
T-Cells: thymocyte cells, 11
Th1: T helper 1, 121
THIN: The Health Improvement Network, ii
TNF-α: tumor necrosis factor alpha, 11
UK: United Kingdom, ii
USA: United States of America, 41
URT: upper respiratory tract, 10
WHO: World Health Organization, 1

Chapter Overviews

Chapter 1

This chapter contains information to contextualise the whole presented body of work; the aims, the chosen methodologies, the results and the critical discussions upon the results.

Section 1.1, the introduction, briefly presents; the main themes of the thesis, the academic motivations behind the work and highlights the recent increase in research output upon the association between DM and TB.

It was not within the remit of this doctoral work to give a review of all published literature upon DM and, or TB. A search of Medline alone for articles with either, or both diseases catalogued as the main focus retrieves over 243,000 citations (December (Dec) 2011). Instead the first two sections of the background, sections 1.2 and 1.3, give a brief narrative overview of each disease. These narrative overviews are intended to give readers an understanding of each disease as it occurs in isolation before any detailed discussion upon their possible association occurs. It is to be noted that parts of these overviews focus upon facets of each disease as is relevant in a UK setting. This is to give specific background to the candidate's work which assesses the magnitude and direction of the association between DM and TB in subsets of the UK population.

Section three of the background, section 1.4, begins with a short synopsis on systematic review methodology which acts as an introduction for a review of evidence to date upon the magnitude and direction of the association between DM and TB. The section ends with a discussion upon further findings from this review; a summary of key publications identified that focus on topics other than the association's directionality and magnitude. The literature review and synopsis of further findings allow the analyses presented in this thesis to be framed within an appropriate body of contemporaneous research.

The final section of the background, section 1.5, outlines the aims, hypotheses and objectives of the research completed by the candidate.

Chapter 2

The second chapter of this thesis outlines the different data sources and methodologies utilised for each set of analyses completed and presented within this body of work.

The first section, section 2.1, outlines in brief the study design and data sources that have been used to test hypotheses 1 to 6 given in full in section 1.5.2. This is in order to give readers an understanding of research possibilities given the available data.

Section 2.2 describes the methods employed whilst interrogating data from a regional UK database (ORLS) to test hypotheses 1 to 6.

Section 2.3 outlines the methods utilised to test hypothesis 1 to 6 using data from a nationally representative UK database (THIN).

The final section of chapter 2, section 2.4, builds upon the brief introduction to systematic review given in the background section 1.4 and describes the specific systematic review and meta-analysis techniques used to test hypothesis 7.

Strengths and weaknesses with the data and the methods applied are not discussed in chapter 2 but are given further thought in chapter 4.

Chapter 3

This chapter outlines individually and gives an overall summary of the results found from work completed as set out in chapter 2.

The first section of chapter 3, section 3.1, details the results found whilst testing hypotheses 1 to 6 using data from the ORLS database.

The second section of chapter 3, section 3.2, details the results identified whilst testing hypotheses 1 to 6 utilising data from THIN database.

The third section of chapter 3, section 3.3, details the results found upon completing a systematic review of TB outcomes amongst individuals with and without DM (testing hypothesis 7).

Chapter 4

The last chapter contains a critical discussion upon the whole body of research completed and presented within the thesis.

The first section of chapter 4 (4.1) summarises the research aims and methods used to achieve these.

The second section of chapter 4 (4.2) contains the discussion upon the research findings of the whole body of work. In section 4.2.1 the principal findings from the work completed utilising the ORLS and THIN database is outlined and discussed in relation to the findings of other published studies (as identified in chapter 1). This puts the results found into context with other contemporary research. A discussion upon the strengths and the weaknesses of these analyses is also completed. In section 4.2.2 the

principal findings from the completed systematic review are outlined and discussed in relation to the findings of other published studies (as identified in chapter 1). The strengths and the weaknesses of the review are then discussed. Section 4.2.3, discusses the plausible biological pathways surrounding the findings of this body of work. With the final section of chapter 4, section 4.2.4, discussing the need for further research.

Chapter 1. Introduction and Background

1.1 Introduction

1.1.1 Why study disease associations?

The World Health Organization (WHO) defines epidemiology as

"the study of the distribution and determinants of health-related states or events, including disease, and the application of this study to the control of diseases and other health problems".[1]

Some diseases co-occur within populations at either an increased or decreased frequency than would be expected due to chance given the background frequency of each disease.[2] Some of these disease associations and dissociations are commonly known for example: sickle cell anaemia and a decreased risk of malarial infection[3]; Infection with human papillomavirus and an increased risk of cervical cancer[4]; Helicobacter pylori infection and an increased risk of stomach ulcers and cancer.[5] However, many disease associations are yet to be identified or fully evidentially validated such as the possible association between Crohn's disease and multiple sclerosis or between DM and herpes virus 8.[6-8]

Disease associations or dissociations may occur due to: a direct causal relationship when the presence of a certain disease causes another disease to be more or less likely to develop, an indirect causal relationship when the presence of a certain disease affects a third variable (perhaps an environmental or genetic factor) causing another disease to be more or less likely to occur, or, a common third variable which increases or decreases the risk of both diseases through separate mechanisms.[2]

It is important to study disease associations as identifying both associations and dissociations can lead to advancement of knowledge upon disease sequalae, aetiology and differences in disease outcome. This in turn can give insights into possible methods for disease prevention, control or management.[2] For example the knowledge that infection with *Human immunodeficiency virus* (HIV) increases risk of active TB led to adaption of TB diagnosis and prevention programmes as well as both TB and HIV management programmes in order to improve disease prevention, identification and treatment.[9 10]

1.1.2 Why investigate a historically noted association between TB & DM?

Reports of diseases which today would be recognised as TB or DM go back to antiquity. Evidence of TB was found in skeletal remains which dated back to 8,000 years before Christ[11] and narrative reports of disease akin to what we now term DM can be found within the works of many of the great physicians from early civilisations.[12 13] That an association exists between these diseases has also been documented throughout history. In Richard Morton's *Phthisiologia: a treatise on consumption* he stated that an association between TB and DM has been known since Roman times[14], Susruta also noted within his works that a relationship exists between the two diseases and Avicenna remarked in his *Canon of Medicine* that 'phthisis' is often complicated by DM.[13 15]

Although an association between TB and DM has been noted historically[12 14] and is cited in key texts[16], until very recently, the association along with its possible effects and implications had become somewhat forgotten in policy and practice. The association was either entirely unmentioned or only briefly mentioned in UK and global guidelines for both TB and DM.[17-22] Perhaps this past omission is unsurprising as although rates of both diseases have been increasing[23 24] high quality, quantitative evidence demonstrating the existence, direction, magnitude and relevance of an association between them was both sparse and difficult to access usually having been reported in publications as a studies minor, or secondary, rather than major, or primary, research findings.[25]

A meta-analysis, published in 2008 as part of a systematic review, found an increased risk of active TB amongst individuals with DM upon statistical pooling of data from three pre-existing cohort studies which assessed the association (*RR* 3.11, 95% CI 2.27-4.26).[25] However, the external validity of this pooled risk estimation is somewhat questionable with two of the three cohort studies contributing to the estimation having been completed amongst populations of individuals with renal failure (renal failure itself being a risk factor for TB).[26 27]

It is important to further the available research upon the existence and magnitude of this association until enough evidence is available to produce robust risk estimates that can be used to inform policy appropriately within differing settings and perhaps lead to information upon disease aetiology and sequelae.

It is conceivable that as well as DM leading to an increased risk of TB that the converse association exists (TB leads to an increased risk of DM) however this phenomenon is much less commonly discussed amidst published literature.[28 29] Perhaps this is because

the biological plausibility of such an association is less coherent.[28] [29] Some studies have shown induced hyperglycaemia and, or, impaired glucose tolerance (IGT) occurring during the early phase of TB.[30-32] This occurrence may be noteworthy as in 20-50% of individuals with IGT progression to overt DM is known to ensue after approximately 3-5 years.[33-36] However interpreting the true importance of observed hyperglycaemia amongst populations of individuals with TB is complicated as hyperglycaemia is often seen to be intermittent or to reverse after the early phase of TB infection.[30] [32] [37] [38] It could be that amongst this population hyperglycaemia is occurring as a side effect of treatment with Rifampicin and Isoniazid[39-41], or, that the hyperglycaemia being observed is 'stress hyperglycaemia'[42] [43] rather than being a true indication of metabolic dysfunction.

Thus, it is also essential to further the available research upon the direction of this association until enough evidence is available to produce confident conclusions that can be used to inform policy appropriately and also perhaps lead to advances in knowledge upon TB and DM aetiology and sequelae.

1.1.3 Investigating the magnitude and effect of an association within the UK

If an association exists between TB and DM it would undoubtedly have the most detrimental public health effect in low to middle income countries, such as India, where the fastest increases in DM are predicted to occur and where the burden of TB is high.[44-46] However, that is not to say that an effect within middle to high income countries such as the UK would be negligible[47] especially amongst population sub-groups already at high risk of each disease such as those of Asian ethnicity.[47-50]

Within the UK, as has occurred elsewhere, there has been an increase in the prevalence of diagnosed DM.[23] Masso-Gonzalez and colleagues calculated, using general practice (GP) data, that between 1996 and 2005 DM prevalence increased by 1.5% (from 2.8% to 4.3%).[23] This rise in DM prevalence was seen to be underlined by an increasing incidence of DM.[23] Modelling projects have shown that there has likely been an increase in the prevalence of undiagnosed DM[51], they estimate that in England in 2010 there were in total (undiagnosed and diagnosed) 3.1 million adults with DM and project that this number will rise to 4.6 million by 2030.[51] [52] Alongside this increasing burden of chronic disease within the UK; TB remains to be a cause of morbidity and mortality. In fact, over the past decade, incidence of TB in the UK has increased from 11.4 to 13.6 per 100,000 population.[24] [53]

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The prevention and treatment of both TB and DM present major public health challenges in all settings across the globe. Given the rising incidence trends of both diseases in the UK it is particularly pertinent to understand the association in detail within this setting so that any relevant information can be utilised to aid local TB and DM prevention and control.

1.1.4 Why investigate the effect of co-morbidity on TB outcomes?

It was estimated that globally between 150 and 171 million people had DM in 2000 and, as is projected for the UK, the global prevalence of DM is projected to dramatically increase by 2030.[46 51 54] Alongside the epidemic proportions of individuals with DM over a third of the global population is latently infected with TB.[55] In 2010 there were 8.8 million active disease episodes and 1.45 million deaths attributable to TB worldwide.[56]

Given these figures, if DM is indeed found in association with TB it is plausible that a substantial proportion of new TB cases will be amongst individuals with DM.[47 57 58] Thus, identifying whether there are any implications for individuals who have these diseases concurrently is important for clinical guidance and practice. In particular it is important to know whether, and if so how, clinically relevant TB outcomes such as sputum clearance rate, and mortality are affected amongst this potentially large sub-group of individuals.[59-62]

1.1.5 A burgeoning area of research

Since the publication of the afore mentioned systematic review[25] upon the magnitude of the association between DM and TB (and the inception of this body of work) there have been approximately 100 articles published discussing or investigating; the existence of any associations, the magnitude of any associations, and the relevance of any such associations within modern times.[47 58 60 63-153] As is perhaps inevitable following these publications there has also been new health policy and guideline papers produced.[129 154] However, it is only the minority of these publications which report new evidence upon the association. Thus even with the influx of recent publications upon the association between TB and DM the investigations as set out in this thesis still add to a relatively small body of research. In particular the analyses presented within this thesis contribute to a highly limited body of work investigating the directionality and specificity by disease sub-type of the association.

At the onset of this doctoral project it was believed that completion of a comprehensive systematic review upon the differences in TB outcomes amongst those with and without DM would be an entirely novel piece of work, there were no existing comprehensive publications of this nature. However, a systematic review reporting upon the differences in TB outcomes amongst those with and without DM has since been published.[121] The differences in methodology and findings between this systematic review and our own have been finitely outlined within the discussion chapter of this thesis.

1.2 & 1.3 A narrative overview of TB and of DM

In order to contextualise further discussion upon the association between TB and DM a brief overview of each disease as it occurs in isolation is now given. The information presented outlines the sub-types, aetiology, diagnostic guidelines, standard treatments and patterning of TB and DM. Information has been assimilated (as for a narrative review) from key research articles, standard texts and publications produced by pertinent organisations and governing bodies. Parts of each overview do give focus to aspects of TB or DM as is relevant in a UK setting. This is to put into context the research presented in this thesis which assesses the magnitude and direction of the association between TB and DM in subsets of the UK population.

1.2 TB: a brief overview

1.2.1 Mycobacterium tuberculosis

TB is a chronic infectious bacterial disease which is caused when the obligate intracellular human parasite *Mycobacterium tuberculosis* (*M.tuberculosis*) colonises a host.[155] The aetiological agent *M.tuberculosis* is an acid fast, gram positive, rod shaped bacterium, 0.5 to 3 micrometres in size which was first isolated by Robert Koch in 1882[156], and is depicted in Figure 1.

Figure 1: Coloured scanning electron micrograph of M.tuberculosis[157]
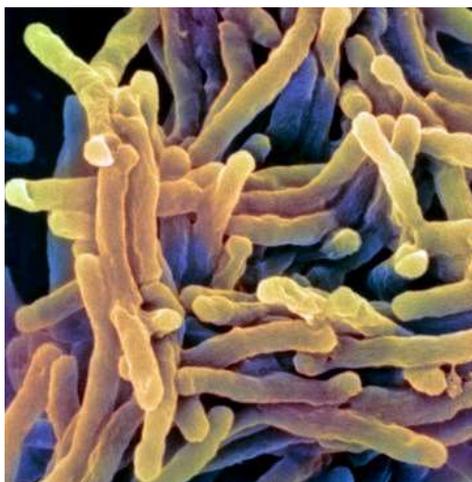
M.tuberculosis is a slow growing, aerobic bacterium with a lipid rich, hydrophobic cell wall and has relatively simple nutritional requirements for growth.[155]

1.2.2 M.tuberculosis transmission and disease outcomes

Host to host transmission of TB occurs when an individual inhales *M.tuberculosis* bacteria that have been expelled into the air in tiny aerosolised droplets of saliva by an individual with active infectious TB whilst coughing or spluttering.[55 155]

There are three main outcomes that can ensue after TB transmission has occurred; bacterial elimination where bacteria are eradicated and no disease state develops, latent TB infection or a form of active TB infection as is portrayed in Figure 2.[158]

Latent TB

The UK's health protection agency (HPA), the body which carries out infectious disease surveillance and provides reference microbiology and microbial epidemiology services within the UK[159], defines latent TB as follows:

"*Latent TB is a disease state where viable bacteria are present in a host but are not causing active disease. These dormant bacteria retain the potential to reactivate,*

replicate and cause active disease. Latent TB may be the result of TB infection which has never progressed to cause active disease or old active TB disease that has become inactive.''[160][161]

After primary infection with *M.tuberculosis* it is estimated that approximately 90% of individuals will go on to develop latent TB, depicted in Figure2.[55][155][162][163] Individuals with latent TB tend to have no signs or symptoms of disease and are not infectious unless disease re-activation occurs.[164]

Active TB

The HPA defines active TB as follows:

"Active TB is a disease state where bacteria are continually replicating and an individual is showing clinical signs of disease, whether or not it is infectious.''[160][161]

Active disease which occurs straight after an individual is infected with TB is known as 'primary progressive TB'.[55][155][162] Some individuals, especially in endemic areas, will develop 'primary progressive TB' after re-infection with the same or an alternate strain of *M.tuberculosis*.[165] Primary progressive TB occurs in approximately 10% of individuals after their primary infection, depicted in Figure 2.[163]

Active disease which occurs due to reactivation of latent TB is known as 'secondary' or 'reactivation TB'.[55][155][162] Reactivation TB occurs in approximately 10% of individuals who develop latent TB, depicted in Figure 2.[158][166]

Figure 2: Percentage expected to develop each TB outcome after exposure and their diagnostic test status[163]
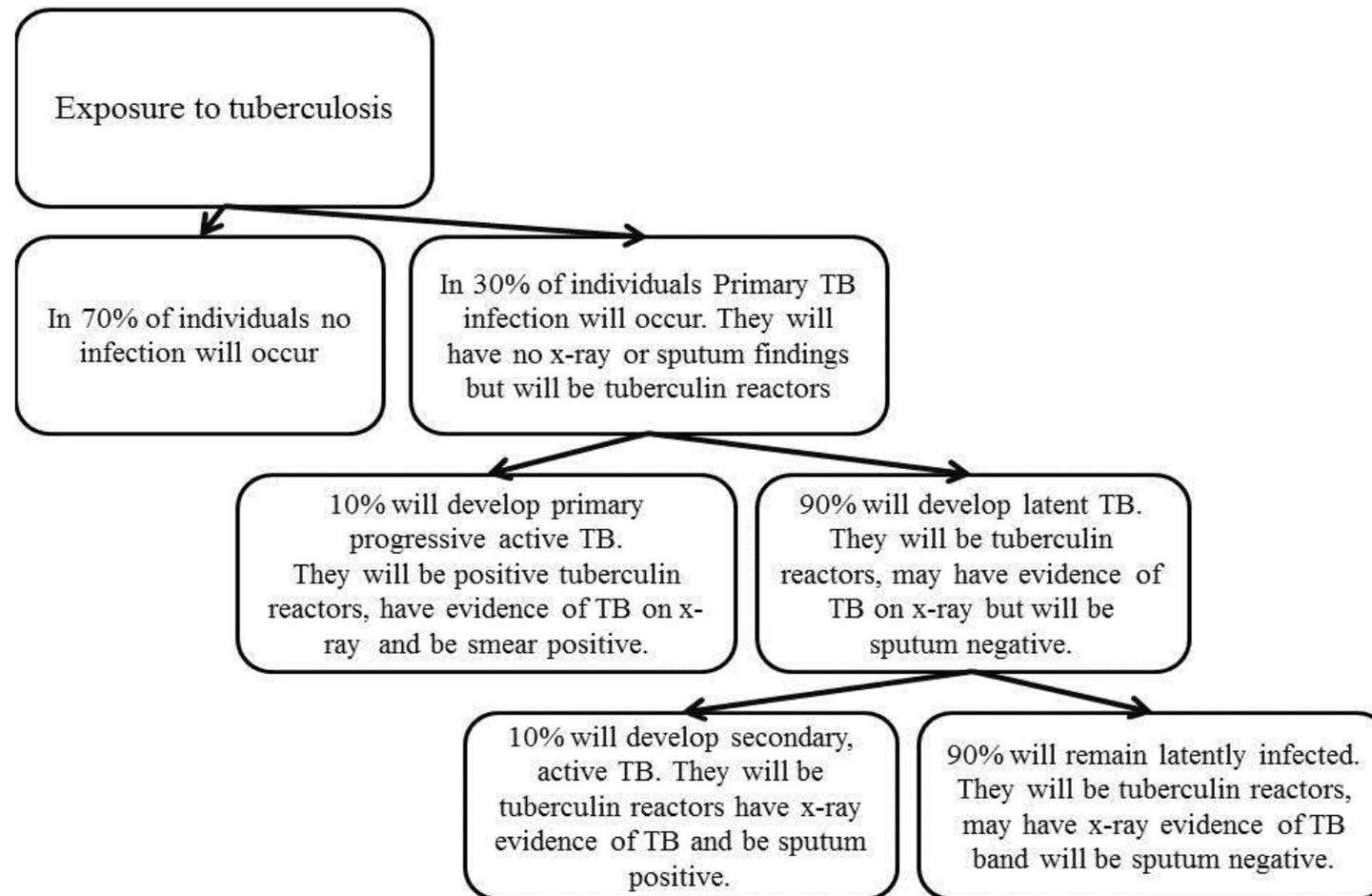
It is very difficult to distinguish previous primary TB infection from re-infection or indeed from reactivation TB.[165]

Dependent upon the situ of the infection active TB can be further categorised as pulmonary or extra pulmonary.[55 155 162] PTB tends to occur more commonly than EPTB although rates are dependent upon a population at risks socio-demographic characteristics and co-morbidities.[160 167]

The signs and symptoms of active TB are non-specific but commonly include; malaise, fatigue, fever with chills and night sweats, chest pain, wasting of lean mass and fat due to anorexia and metabolic disturbances caused by the inflammatory process and immune response to the disease, dyspnoea or orthopnoea in extensive disease and a cough that becomes productive and leads to haemoptysis.[55 155 162 164 168]

1.2.3 Pathogenesis

Whether, and which of these described disease states arises is dependent upon the complex interplay that occurs between the hosts immune system and the bacteria's virulence factors. Current scientific knowledge of which remains incomplete.[160 169]

Innate immune defences

In order to cause an infection and avoid elimination the *M.tuberculosis* bacterium must first pass the physical defences of the upper respiratory tract (URT) including those of the nose, nasal cavity, turbinates, and pharynx.[170] Bacterium must avoid impingement, or expulsion by mucocilliary action or the cough and sneeze reflexes.[155 171] Within the URT many antimicrobial substances are present and active in the clearance of mycobacterium.[172] Antimicrobials of the Cathelicidin and Defensin family in particular have been shown to be active in lysing *M.tuberculosis* bacilli.[172]

If *M.tuberculosis* bacilli pass through the URT they then face the defences of the lower respiratory tract (LRT). Only particles less than 10μm can physically pass into the LRT which is made up of the larynx, trachea, bronchi and the lungs.[155 169 173 174] As in the URT, the LRT employs mucocilliary and antimicrobial action in order to eliminate *M.tuberculosis* bacilli as they pass through the trachea and bronchi.[174] The bronchioles and alveoli are covered in a fluid layer that contains antimicrobial substances,[175] immunoglobulins[176] and molecules of both the alternative and classical complement pathway.[177 178]

Cellular immune response

Once within the LRT *M.tuberculosis* are likely to come into contact with any number of host immune cells all of which can mediate different immune responses after initial interaction with the bacterium.[155][169]

M.tuberculosis may be taken up into host immune cells such as macrophages, dendrites or pneumocytes via phagocytosis as is depicted in Figure 3.[155][169][179] This process can occur via a number of mechanisms as multiple components of the bacterial cell wall act as ligands for alternate host cell receptors which when stimulated all facilitate bacterial uptake.[170][180][181]

When *M.tuberculosis* are engulfed they enter immune cells within a phagosome, an endocytic vacuole, which once in the cell fuses with another type of vacuole known as a lysosome resulting in the formation of a phago-lysosome.[155][182] Within the phago-lysosome the bacteria will encounter a hostile environment, acidic with an abundance of toxic reactive oxygen and nitrogen species, lysosomal enzymes and toxic peptides.[155] Exposure to this environment can destroy *M.tuberculosis*.[182] However some *M.tuberculosis* bacilli are able to survive within phagocytic cells by blocking phago-lysosomal fusion and thus exposure to the hostile environment found within these vacuoles.[155] Scientific understanding upon how *M.tuberculosis* arrests phagolysosomal fusion is at present incomplete. Macrophages that are unable to destroy *M.tuberculosis* become an ideal environment for the bacteria to 'hide' within and replicate within.

Dendritic cells which phagocytose *M.tuberculosis* but are unable to kill the bacilli migrate to the draining lymph nodes where they present bacterial antigens to naïve effector thymocyte cells (T-Cells).[183][184] Presentation of bacterial antigen to naïve effector T-Cells causes T-Cell activation. Active T-Cells can migrate into the circulatory system where they remain until they are attracted to sites of TB infection such as the lung by inflammatory mediators.[184]

Once activated and at the site of TB infection CD8+ T cells (cluster of differentiation 8 positive) and CD4+ T Cells (cluster of differentiation 4 positive) can control TB infection although the mechanisms through which this is achieved again are not fully understood.[185] What is known is that CD4+ T Cells can produce cytokines such as tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) which activate macrophages enabling the killing of *M.tuberculosis* bacteria.[185] Also that CD8+ T Cells can destroy

Figure 3: *M.tuberculosis* **from infection to transmission**[186]
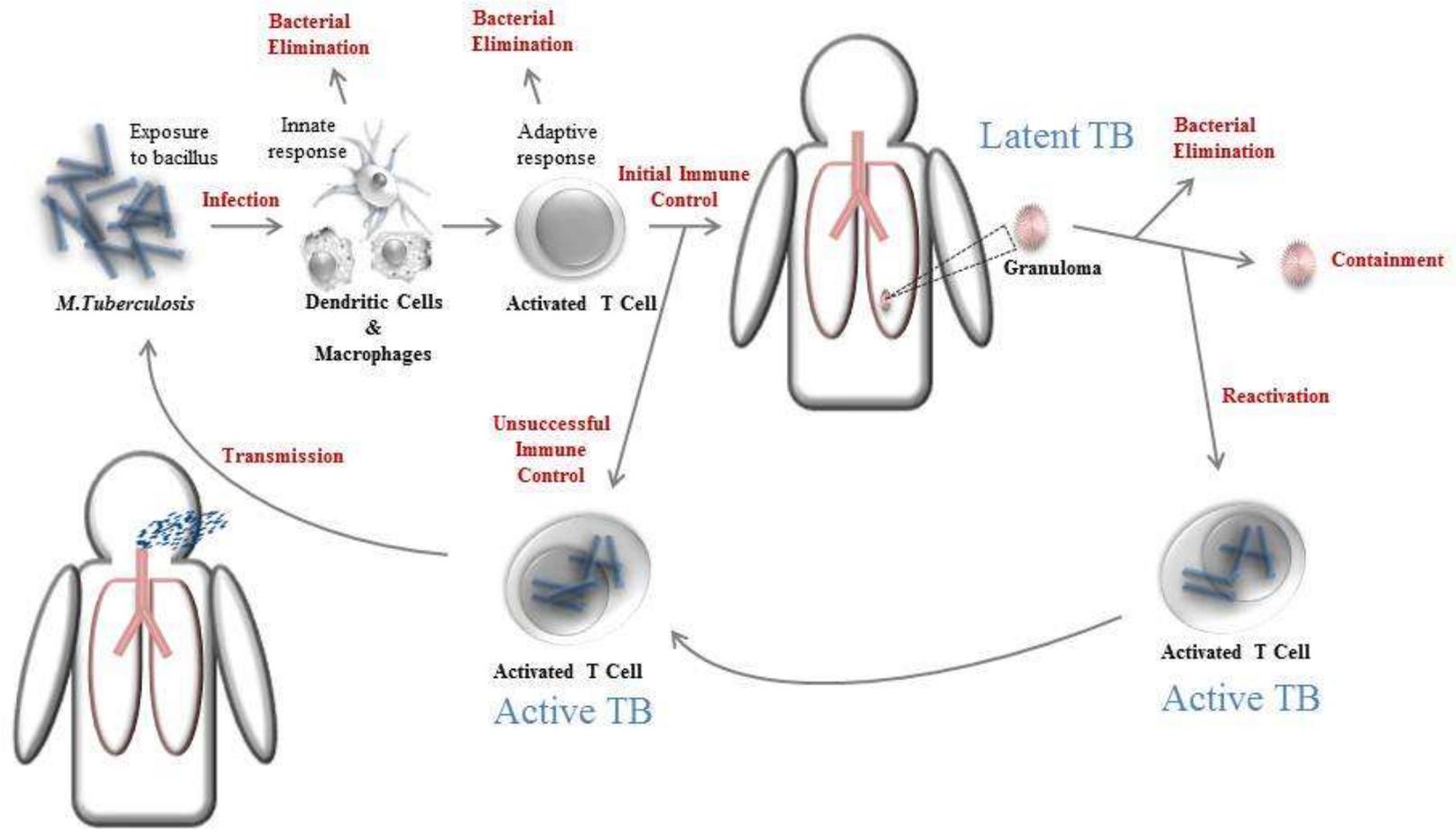
infected macrophages and *M.tuberculosis* bacilli by releasing cytotoxic mediators such as granulysin, perforins and granzymes.[185] Some *M.tuberculosis* bacteria are able to cause persistent infection by subverting the dendritic immune response which brings about T-Cell activation.[187]

Granuloma formation

Whilst T-Cell activation is occurring infected macrophages in the lung are producing chemokines which attract inactivated monocytes, lymphocytes, and neutrophils to the site of TB infection.[171 188] These cells are unable to destroy bacteria but can create fibrous lesions which are able to contain *M.tuberculosis* bacteria halting their spread.[171 188]

Within these granulomatous lesions a caseous necrotic environment, acidic with low oxygen and limited nutrients, develops. This hostile environment restricts replication of the *M.tuberculosis* bacteria but does not necessarily destroy them (latency).[189] Lesions that have undergone fibrosis and calcification can remain dormant for years. However under certain circumstances bacteria can become active again. If bacteria re-activate lesions can become liquid causing their fibrous walls to rupture and bacteria amidst necrotic material to drain back into the bronchi or circulatory system.[189] If bacteria enter and then leave the circulatory system at a different juncture an EPTB infection can ensue.[189] Bacteria that re-enter the bronchus can be coughed into the atmosphere allowing infection of a new host and the infection process to start all over again.[189]

1.2.4 Diagnostic guidelines for TB

Once an individual is infected with TB prompt and accurate diagnosis is key to the effective treatment of the disease and precise disease surveillance. However currently there is no global consensus upon a finite definition of a TB case and thus no standardised diagnostic guidelines. The way in which TB is diagnosed is mainly determined by the setting in which the diagnosis is being made and the resources available.[190 191] There are numerous ways in which to diagnose a case of TB clinically and, or, microbiologically some common methods are outlined within Table 1.

Table 1: Diagnostic tests available to identify a TB case[155]

Diagnostic Test	Clinical Assessment	Chest Radiography	Sputum Smear	Sputum Culture	Polymerase Chain Reaction	Tuberculin skin test	Quantiferon TB test
Mode of detection	Clinician detection of signs, symptoms and history suggestive of TB	Allows detection of signs of TB such as lobar infiltrates or cavitations	Allows identification of acid fast bacilli (*M.tuberculosis*) if present within a sample	Allows identification of *M.tuberculosis* if present within a sample	Allows detection of *M.tuberculosis* Deoxyribonucleic acid (DNA) if present in a sample	Detects immune reactivity indicative of prior exposure to mycobacterium	Detects immune reactivity indicative of prior exposure to mycobacterium
Time to obtain diagnosis	Minutes	Minutes	Up to 24 hours	Up to 6 weeks if using solid media Up to 2 weeks if using high pressure chromatography	Hours	Up to 72 hours	Up to 24 hours

Global case definition and diagnostic criteria

The WHO is the United Nations directing and coordinating health authority for global health. They provide leadership for; the global health research agenda, norms and standards for global health, evidence-based global health policy and monitor and assess global health trends.[192] Their definitions for a TB case and diagnostic guidelines to identify cases are probably the most commonly used worldwide.

The WHO defines a case of TB as:

"A patient in whom TB has been bacteriologically confirmed or has been diagnosed by a clinician".[193]

The WHO defines an EPTB case simply as an individual with:

"TB of organs other than the lungs".[193]

However these definitions are broad and lead to broad diagnostic guidelines. The WHO suggest basing a TB diagnosis upon either a single positive sputum culture, or strong *"histological or clinical evidence suggestive of TB".*[193] [194]

Definition and diagnostic criteria remain broad as the WHO recognises that many countries still lack microbiological diagnostic capacity.

UK case definition and diagnostic criteria

The National Institute for Clinical Excellence (NICE) is a UK Department of Health 'arms length' body which develops evidence-based guidelines on the most effective ways to diagnose, treat and prevent disease and ill health.[195]

NICE has also outlined definitions and diagnostic guidelines for TB.[21] The diagnostic guidelines for TB as dictated by NICE reflect the UK's capacity to utilise complex laboratory based diagnostic techniques.

In the UK when PTB is suspected due to the presence of some or all of the common TB signs and symptoms NICE suggest that a chest X-Ray should be taken. Then, if results are indicative of TB (evidence of infiltrates, consolidations and or cavitations in upper lobes with or without mediastinal or hilar lymphadenopathy) that three sputum samples should be sent for culture and microscopy.[21]

If EPTB is suspected then NICE suggest a biopsy or needle aspiration be taken and culture or histological examination of either pus or a surgical sample be completed to confirm diagnosis. They also state that upon confirmation of EPTB that a chest X-Ray should also be taken (if not already done) to identify whether there is presence of co-existing respiratory TB.[21]

If latent TB is suspected NICE suggest confirmation by Mantoux testing or, in those for whom Mantoux testing is likely to be unreliable, by IFN-γ testing.[21]

1.2.5 TB Treatment

TB is a curable disease however as with diagnosis, standard treatment regimens for TB differ by setting and resource availability.[196] TB cases, once identified, need to be efficiently and effectively treated in order to reduce transmission, achieve cure and thus reduce preventable morbidity and mortality.[196]

Standard treatment

The standard treatment regimens prescribed for TB are made up of a combination of the following antibiotics; Ethambutol, Isoniazid, Pyrazinamide, Rifampicin and Streptomycin.[21][22]

Antibiotics are given in combination and over a prolonged period of time in order to prevent development of drug resistance.[196]

For PTB both the WHO and NICE advise a daily dose of Rifampicin, Isoniazid, and Ethambutol for two months followed by dosage with Isoniazid and Rifampicin for a further four months.[21][22]

Further treatment standards in the UK

The site of TB infection leads to specific signs and may be associated with specific morbidities and increased mortality. Thus, due to the nature of pericardial, meningeal, spinal and disseminated TB infection NICE also gives specific guidelines for their treatment within the UK.[21]

In the UK, as occurs in other countries, individuals failing to comply with a treatment regimen can be given 'Directly Observed Therapy'. This is when a case worker supplies an individual with their medication and watches whilst they take it.[21][197]

Also, in order to monitor treatment success NICE advocates for microbiological follow up (using sputum smears) of all individuals after treatment for TB.[21] It is recommended that sputum smears are examined two months after an individual starts on treatment (after completion of the initial treatment phase), after five months on treatment, and at the end of treatment.[21]

1.2.6 TB rates and risk factors

The WHO estimates that globally one in 3 people are infected with latent TB and that 5 to 10% of these people will develop active disease at some point over their life-course.[56]

In 2010 there were an estimated 8.8 million prevalent cases of active TB globally and, although TB is a curable infectious disease, it was estimated that it caused 1.45 million deaths.[56] The majority of deaths from TB will occur within middle to low income countries.[56]

In 2010 sub-Saharan Africa saw the largest proportion of new TB cases per population with more than 270 cases occurring per 100,000 individuals.[56] However, due to demographics, the largest number of new TB cases seen in 2010 were within Asia, the world's largest and most highly populated continent.[56] In 2010 60% of the incident global TB cases could be found spread throughout this continent.[56] Figure 4 clearly depicts the areas with the highest incidence of TB.

Looking at Figure 4 it can also clearly be seen that although disproportionately TB affects every part of the world with cases occurring in every single country across the globe.[56]

Prevalence and incidence rates of TB in the UK are relatively low comparative to the rates occurring in other countries globally; however, TB incidence in the UK is similar to the incidence rates across other European countries (see Figure 4).

Figure 4: Estimated incidence rates for TB in 2010 by country[56]
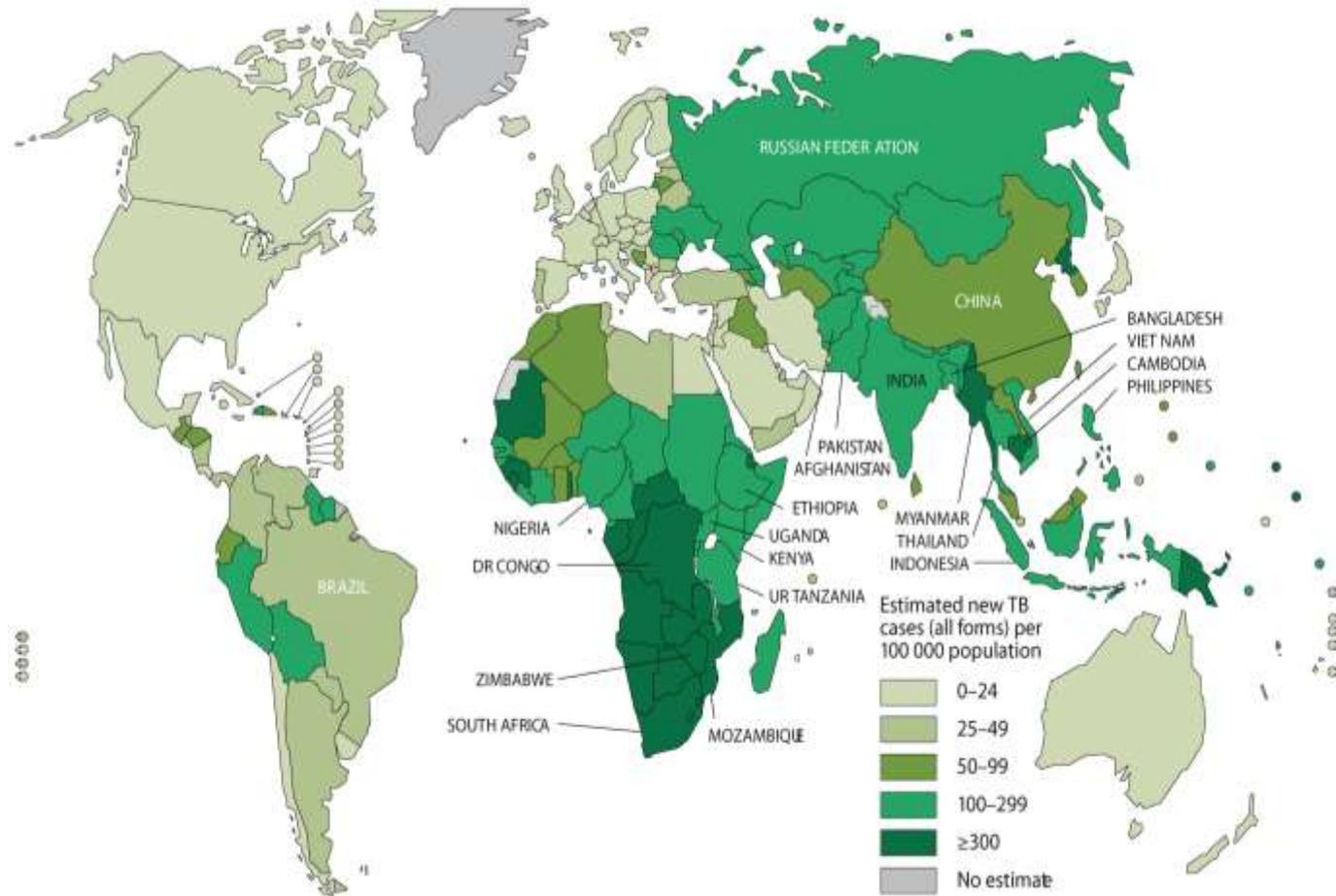
UK TB Rates

In England, Scotland, Northern Ireland (N.Ireland) and Wales TB is a notifiable infectious disease.[198] This means that it is a statutory requirement for registered medical professionals to report cases of TB to the HPA's Centre For Infections as part of their professional duties.[198] Statistics for TB rates within the UK population are thus very accurate and easily identifiable. The HPA collates all data upon TB in the UK through an enhanced reporting system which, because of its accuracy, is where the majority of the data presented below have been assimilated from.[198-200]

Historically the UK had high incident rates of TB and TB was a disease which afflicted the general population. Now however TB mainly affects specific sub-groups of the UK population who are described as being at high risk of active TB.[199]

Although the UK has relatively low rates of TB over recent years these have been seen to be rising. TB incidence for all active TB has seen a slight rise within the UK between 2005 and 2009 from 13.8 per 100,000 to 14.6 per 100,000 as is shown in Table 2.

Within the UK pulmonary TB tends to be slightly more common than EPTB with 4,401 cases (54%) and 3,186 cases (46%) being reported respectively in 2009.[160 198 200 201]

Table 2: TB incidence rates by country and year, 2005-2009[201]

Year	England	N.Ireland	Scotland	Wales	Total
	Rate per 100,000 (95% CI)				
2005	15.2 (14.9-15.6)	4.3 (3.4-5.5)	7.2 (6.4-7.9)	6.4 (5.5-7.3)	13.8 (13.5-14.1)
2006	15.2 (14.9-15.6)	3.5 (2.7-4.5)	7.4 (6.7-8.2)	6.1 (5.3-7.1)	13.8 (13.5-14.1)
2007	14.9 (14.6-15.3)	3.9 (3.1-5.0)	8.0 (7.2-8.8)	6.7 (5.8-7.7)	13.6 (13.3-13.9)
2008	15.4 (15.1-15.8)	3.7 (2.9-4.7)	8.6 (7.8-9.5)	5.6 (4.8-6.5)	14.0 (13.7-14.3)
2009	16.0 (15.7-16.3)	3.1 (2.3-4.0)	9.3 (8.5-10.2)	7.1 (6.2-8.2)	14.6 (14.3-14.9)

Geographic variation

When data is stratified by country a rise in incidence over time can be seen for England, Scotland and Wales but the reverse is seen for N.Ireland, as shown in Table 2.

The decrease in TB incidence within N. Ireland could be due to any number of socio-demographic factors. Perhaps exposure is lower; for example immigration from high risk TB countries to N. Ireland could be decreasing, or perhaps control programmes and contact tracing are becoming more efficient lowering the number of contacts per index case.

The average incidence rate of TB within the UK is 14.6/100,000 however, when stratified by county, incidence rates of TB vary within England by region as shown in Figure 5.[201] The highest incident rates of TB tend to be within urban conurbations such as London where there were 44.4 new cases per 100,000 in 2010 compared to 6.1 new cases per 100,000 in the rural South West of England, see Figure 5.

As well as showing variance between regions, TB incidence shows variance within regions and even within cities. In 2001 in London there was a 30 fold difference between the borough with the highest TB incidence compared to the borough with the lowest TB incidence.[202] The regions covered by the ORLS Database had an average TB incidence rate of 10.5/100,000 population (95% CI 8-13) between 2004 and 2009.

Figure 5: Number and rate of TB cases in England by region, 2010
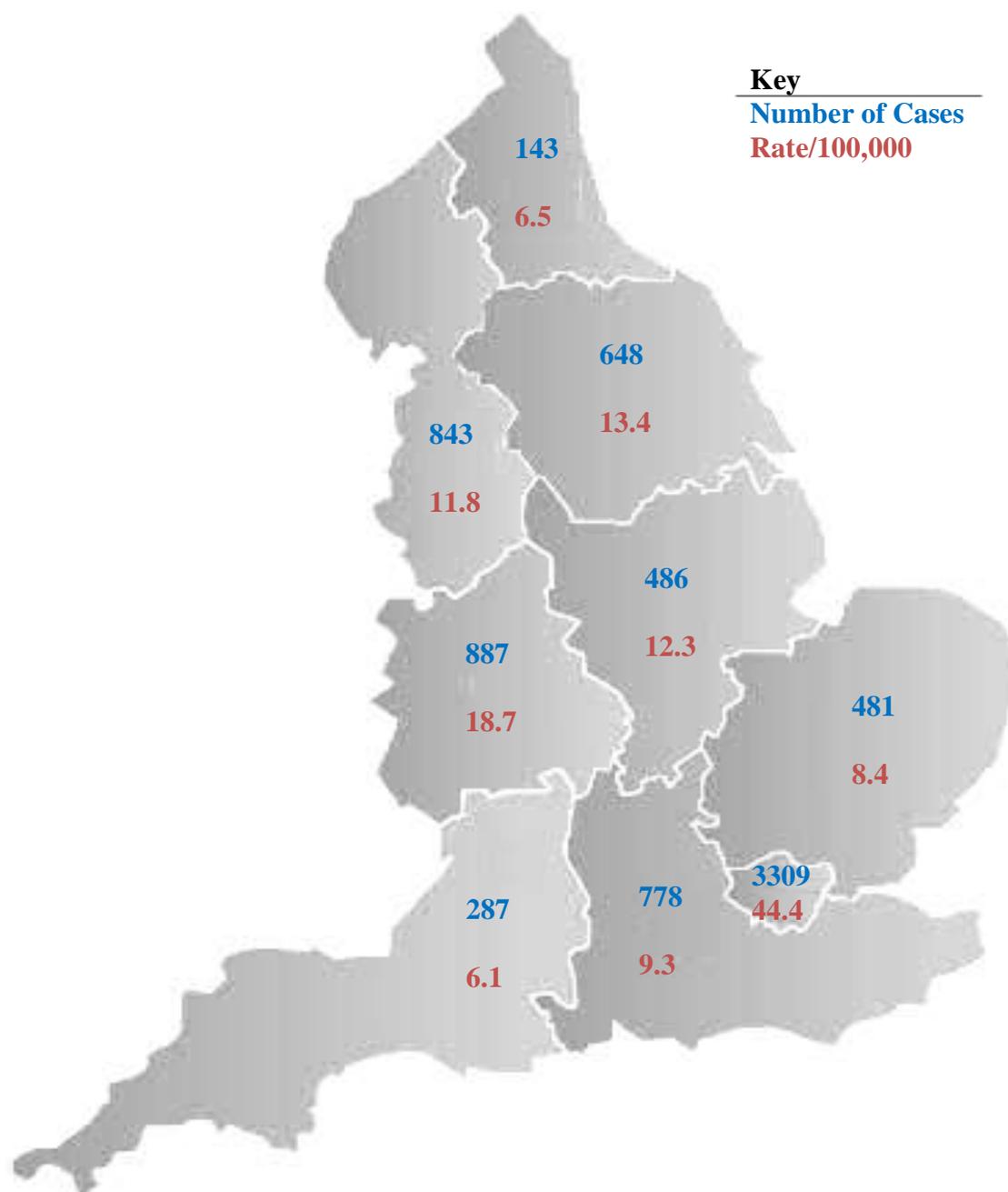
Non modifiable risk factors

Within the UK TB rates are seen to be patterned according to sex. Males are seen to develop active TB more commonly than females. In 2010 4,808 (15.7/100,000) incident TB cases were amongst males comparative to 3,629 (11.5/100,000) amongst females.[201] That is 57% of TB occurred amongst males comparative to 43% amongst females.

TB in childhood is relatively uncommon, see Figure 6. Incidence rates in 2010 peaked for those aged 15 to 40 years and a smaller peak was seen for those aged 70 to 90

Figure 6: Cases of TB reported within UK by age group, 2010
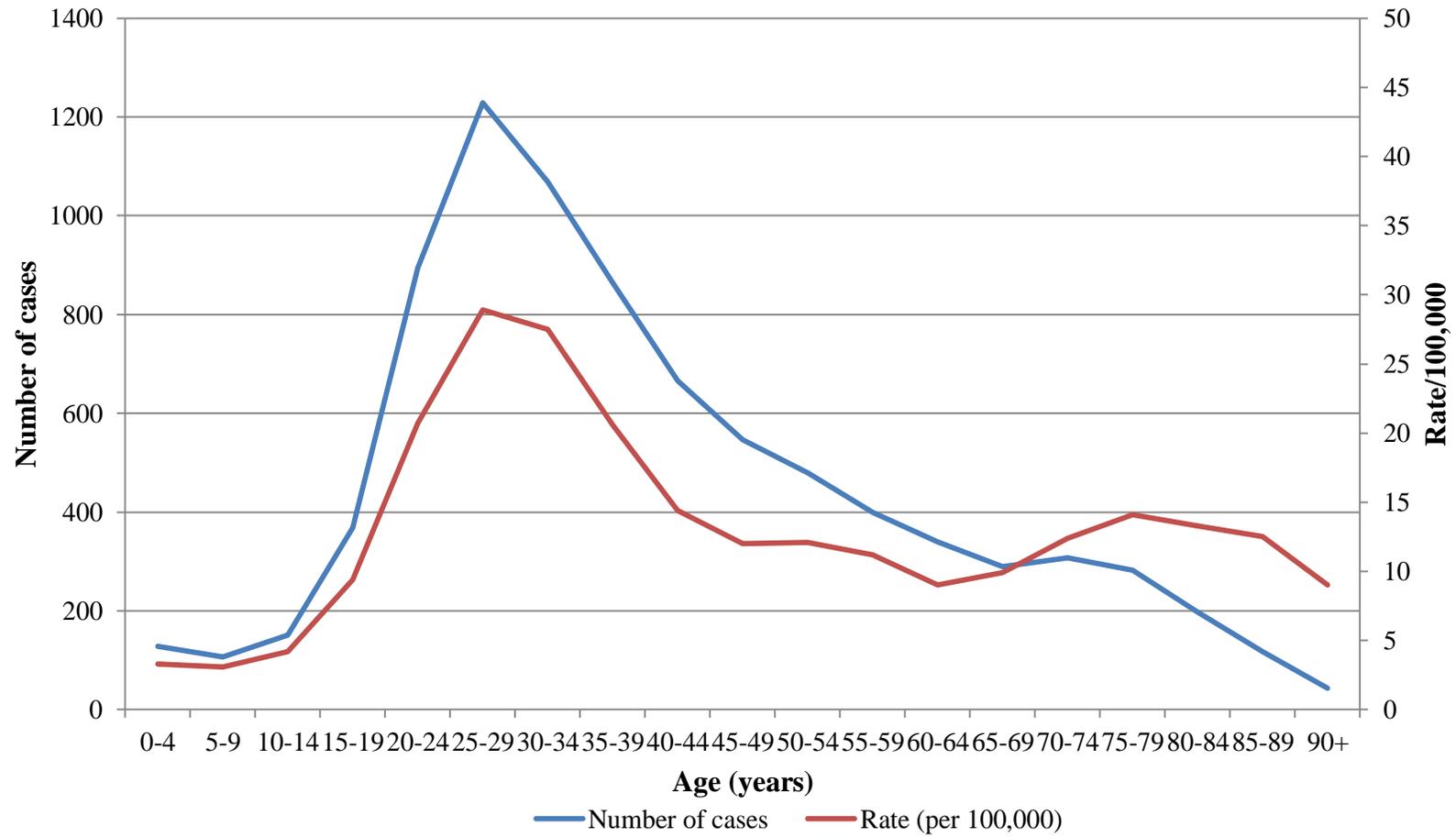
TB rates within the UK population are also ethnically patterned. Figures for incident cases of TB reported in 2009 (as with those reported since 1988) show TB to be much more common amongst individuals of Black African, and Indian Subcontinent ethnic origin.[203][204] Across all ethnicities TB rates are higher amongst migrants i.e. those not born in the UK compared to those born within the UK as is portrayed in Table 3.[201]

Table 3: TB incidence rate for the UK in 2009 stratified by place of birth and ethnic group[201]

Ethnic group	UK-born		Non-UK-born		Total including those of unknown birth place	
	Number of cases	Rate per (100,000)	Number of cases	Rate per (100,000)	Number of cases	Rate per (100,000)
White	1,412	3	241	7	1,881	3
Black - Caribbean	78	21	82	38	173	29
Black – African	130	43	1,574	273	1,749	199
Black – other	26	55	51	218	87	123
Indian	171	30	1,798	235	2,058	154
Pakistani	237	42	1,012	234	1,319	132
Bangladeshi	50	22	252	133	323	78
Chinese	7	11	103	59	119	50
Mixed/other	82	9	758	59	859	39
Total Including those of unknown ethnicity	2,240	4	5,994	86	9,040	15

Amongst non UK born, UK residents the risk of TB increases with time since entry to the UK as shown in Figure 7. However it should be noted that this trend could be a reflection of risk of TB increasing as these individual's age.

Figure 7: Percentage of migrants developing TB by time since entry to the UK

- ■ <2 years
- ■ 2-4 years
- ■ 5-9 years
- ■ >10 years
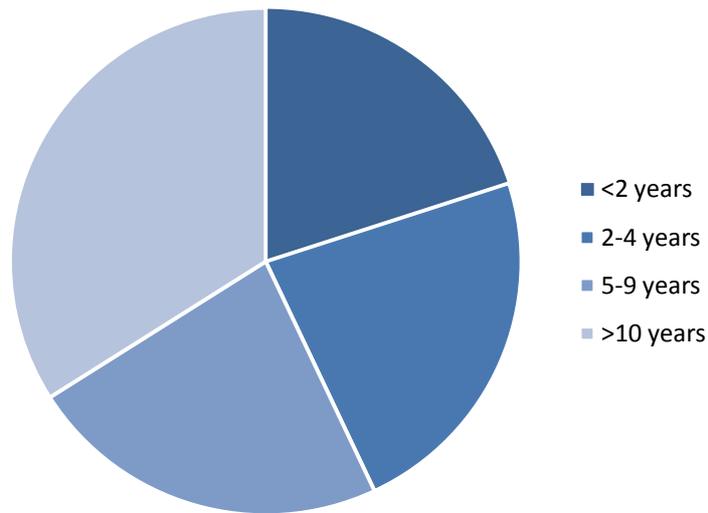
Risk Factors

Commonly cited risk factors for the development of active TB can be broadly grouped into those which increase an individual's likelihood of prolonged exposure to TB bacillus (such as; Socio-economic status (SES), homelessness, working or residing within hospitals, prisons, premises with overcrowding, nursing homes and residential homes)[205][206], or those which increase likelihood of progression to active disease (such as; SES, drug use, alcohol use, smoking status, HIV, silicosis, bronchitis, emphysema, renal failure, carcinoma of the head and neck, transplantation, malnourishment, treatment with corticosteroids, treatment for rheumatoid arthritis or Crohn's disease).[139][205][206]

1.3 DM: a brief overview

1.3.1 Aetiology

Unlike for TB there is no known aetiological agent which causes DM. DM is a chronic condition and has been defined as a group of heterogeneous disorders with a common underlying metabolic dysfunction.[207] The metabolic pathway that is disrupted resulting in DM is shown in Figure 8.[52] [209] [210]

Figure 8: The metabolic pathway disrupted amongst individuals with DM[208]
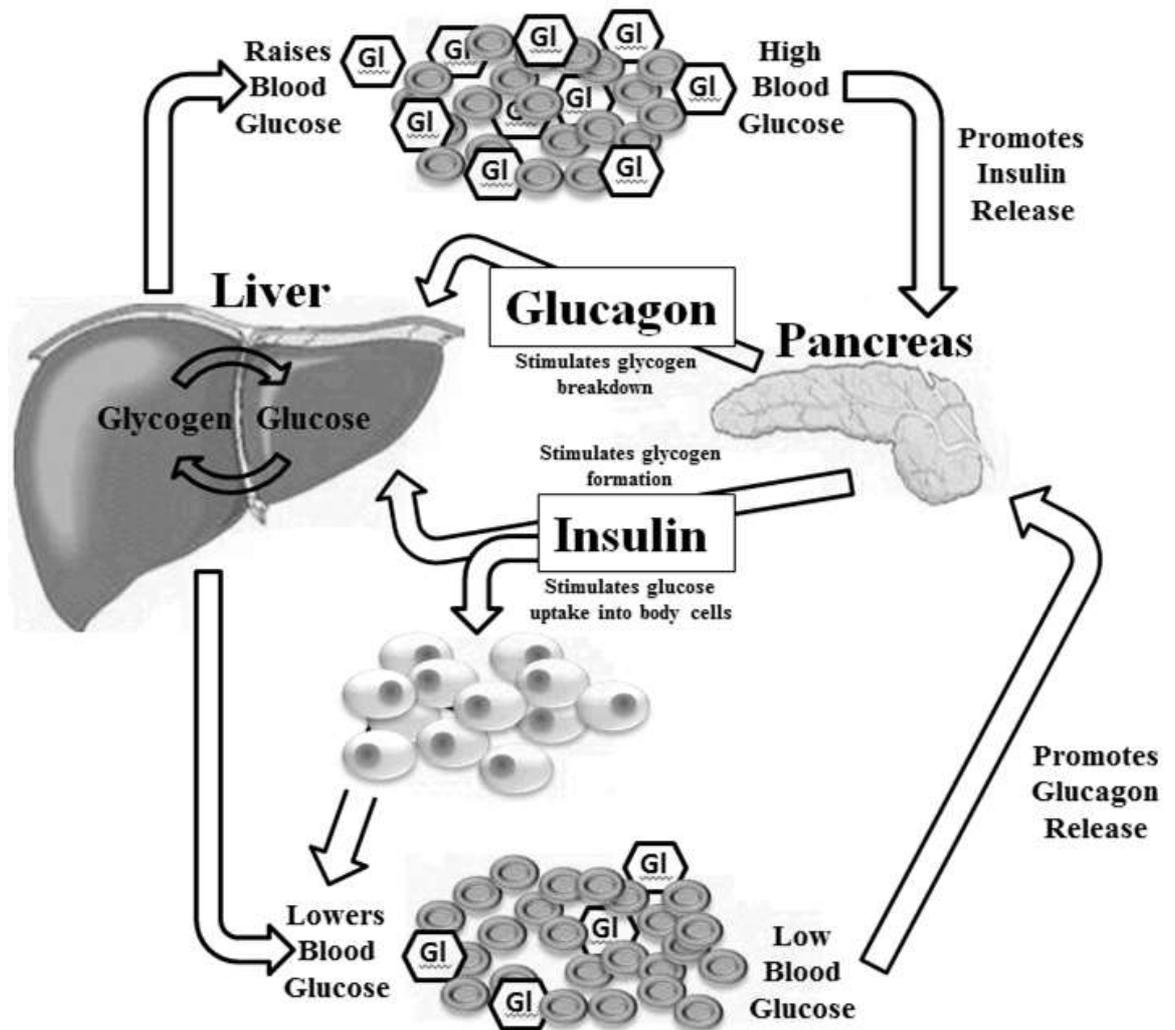
The usual signs of DM are hyperglycaemia and glucose intolerance due to insulin deficiency and, or, impaired insulin action.[207] [209] Insulin is a proteinaceous hormone which is produced within the islets of langerhans β-cells in response to high blood glucose levels.[209] [210] Insulin stimulates; the uptake of blood glucose into body cells where ever it is needed (for example into muscle cells within muscle tissue which use glucose during glycolysis),[209] [210] storage of blood glucose as glycogen,[209] [210] a decrease

in the rate of glycogen breakdown to sugar in the liver and inhibition of the conversion of amino acids and glycerol from fats to sugar[209 210]

There are 3 common sub-types of DM; type 1, type 2 and gestational DM.

Type 1 DM

Individuals with T1DM have evidence of pancreatic β cell destruction which has led to a detrimental decrease in their levels of insulin requiring them to administer insulin in order to prevent ketoacidosis, coma or death. [209 211 212] The inability to produce insulin can be idiopathic or due to an autoimmune response characterised by the presence of insulin auto-antibodies such as Islet Cell Antibodies, anti-glutamic acid decarboxylase antibodies, or protein tyrosine phosphatase-like protein IA-2 antibodies.[209] Signs and symptoms of T1DM are normally a combination of the following: polyuria, malaise, constant thirst and hunger, weight loss, recurrent infections, poor healing, and blurred vision.[209 210] An individual's risk of developing T1DM is influenced by both genetic and environmental risk factors. Genetic risk is predominantly associated with Human leukocyte antigen markers and less strongly with genes from other chromosomes.[213 214] It is thought that environmental triggers such as viral and bacterial infection, or nutritional factors can elicit an autoimmune process in individuals genetically predisposed to developing T1DM.[215] Although the field of literature upon the aetiology of DM is rapidly expanding the precise cause of T1DM is unknown.[213 214]

Type 2 DM

Individuals with T2DM have insulin resistance and, or, a decreased level of insulin secretion the exact aetiology of which is unknown.[209] It is commonly agreed that in individuals with T2DM there is no autoimmune degeneration of the pancreas as is seen in individuals with T1DM and that individuals with T2DM are not ketosis prone.[209] Most often individuals with T2DM can achieve hyperglycaemic control with dietary change and use of oral hypoglycaemic agents. However, if blood glucose control is not achieved by these means, insulin may be used.[209] Weight loss can decrease an individual's risk of developing T2DM and indeed in some individuals with T2DM can stop the need for medication usage or reverse their T2DM disease status.[216] T2DM is commonly asymptomatic, although when signs and symptoms occur they are similar to those of T1DM, thus diagnosis of T2DM is often made incidentally or due to the appearance of its associated complications.[209] The risk of developing T2DM is associated with: older age, ethnicity, dietary intake, a sedentary lifestyle, obesity, and prior history of glucose intolerance or gestational DM. As with T1DM family history of

26

DM (heritable/genetic risk factors) and environmental triggers such as viral or bacterial infection are thought to play a role in susceptibility.[7 209]

Two recent seminal studies have given new and mixed insights into the aetiology of T2DM. A study published by Winer and colleagues has begun to more clearly define a B-cell led auto-immune involvement in the development of T2DM.[217] The study demonstrates that inflammation (which occurs when rapidly growing fat cells apoptose due to an in ability of the blood supply to adapt quickly enough to fulfil their new nutrient demand) causes a B cell, T cell and macrophage response which inhibits the ability of remaining fat cells to respond to insulin and causes fatty acids to be shed into the blood. This release of fatty acids sets in motion a physiological cascade that causes further insulin resistance (as well as high blood pressure (BP) and blood lipids). A recently published intervention study by Lim and colleagues, although undertaken with low participant numbers, has shown that diet is very important in the aetiology of T2DM. This study shows that a reversal in impaired beta cell function and impaired insulin sensitivity can be achieved by major calorific restriction.[216] Further research is needed to corroborate the findings of both of these studies.

1.3.2 Criteria for the classification and diagnosis of DM

Historically there have been many nomenclature and diagnostic criteria used to define DM evolving alongside the evidence base for this disease. However, unlike for TB, there are now universally recognised nomenclature, diagnostic criteria and definitions for DM. In 2006 a revolutionary consensus statement on DM was released by the International Diabetes Federation (IDF, an umbrella organisation of more than 200 national DM associations with the aim of effecting policy, public awareness, health improvement, and knowledge exchange upon DM) and the WHO which gave updated definitions and diagnostic criteria for DM intended for universal use.[212]

In production of this statement the aetiological types and clinical stages of disorders of glycaemia were reviewed. It was concluded that current nomenclature should be maintained keeping the distinctions between T1DM, T2DM and gestational DM, but that the fluidity of the clinical stages should be highlighted, as depicted in Figure 9.[212] It was decided that for notation purposes Arabic numerals should be used universally in favour of Roman numerals.[212]

Figure 9 portrays how some individuals will pass from a stage of normoglycaemia with normal glucose tolerance to IGT with impaired fasting glucose and so forth along the continuum of clinical DM disease stages.

Figure 9: Transient clinical stages of DM[212]
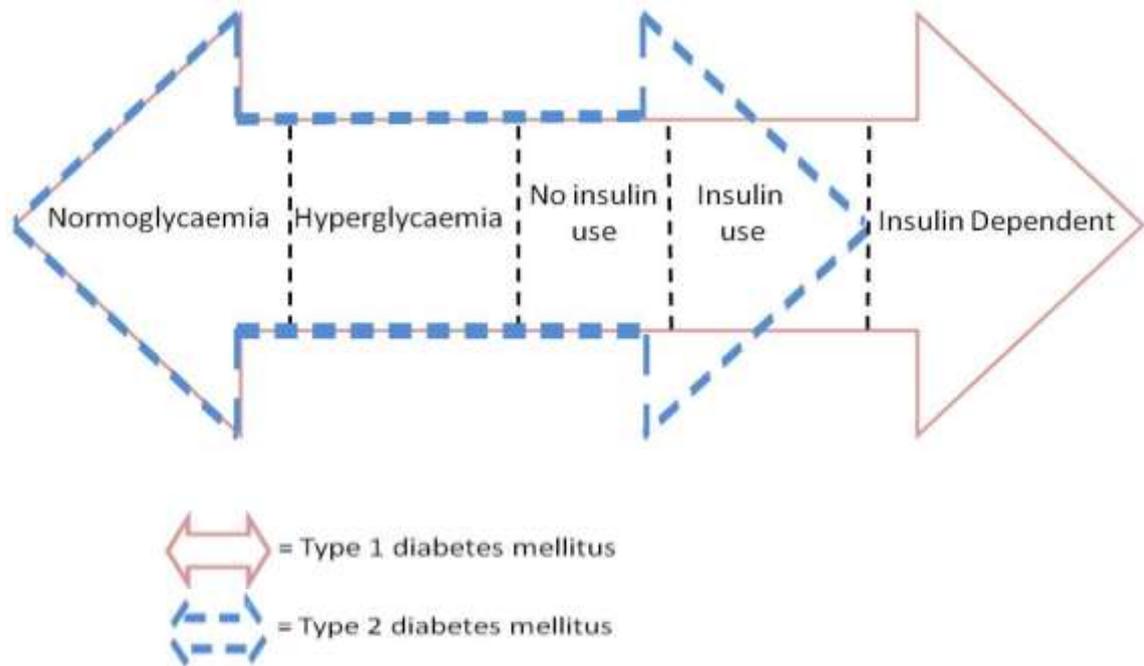
The WHO/IDF consensus statement also gave specific diagnostic guidelines for DM.[212] DM should be diagnosed when clinical signs are present alongside any of the following four measures:

"A random venous plasma glucose concentration of ≥ 11.1mmol/l", or

"A fasting venous plasma glucose concentration of ≥ 7.0mmol/l (whole blood venous ≥ 6.1mmol/l)", or

"A venous plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test", or

"A venous whole blood glucose concentration of ≥ 10.0 two hours after 75g anhydrous glucose in an oral glucose tolerance test."[212]

UK NICE guidelines do differ slightly from this stating that DM should be confirmed by a single diagnostic measurement as given above in presence of classical DM symptoms, or, alongside a secondary diagnostic measure.

The fasting blood glucose (FBG) cut point for a diagnosis of DM (as defined by the WHO) consistently decreased as new evidence and guidance was published from 1980

up until the most recent 2006 diagnostic guidelines were produced. In 1980 guidance was for a positive DM diagnosis if FBG ≥ 8.0mmol/l, in 1985 if FBG ≥ 7.8mmol/l, and in 1999 if FBG was ≥ 7.0mmol/l.[212]

1.3.3 DM Management

The major purpose of DM treatment is to improve health outcomes and reduce associated complications. Unlike for TB there is no 'standard care' for an individual with DM. Treatment differs markedly between settings especially between low to middle income countries and middle to high income countries. A standard global treatment would need to account for the vastly differing healthcare resources and infrastructure found worldwide.

The WHO have begun to set norms for DM care stating that the universal aim of DM treatment should be symptom relief and delay of complications however they are far from giving a treatment standard.[218] For T1DM the WHO highlight that a consistent supply of insulin is essential although acknowledge that even this may not be achievable in many low income countries.[218] They highlight the need for a holistic approach to treat T2DM with use of patient education, and when needed oral hypoglycaemic medications and insulin.[218] The WHO also notes the importance of monitoring treatment effectiveness and those diagnosed for early signs of complication development.[218]

DM management in the UK

Within the UK individuals with T1DM and T2DM for the most part self manage any treatment they have been prescribed in order to normalise their glucose levels. Often their own treatment preferences are integrated into an appropriate care plan in order to create a highly adhered to management regime. Alongside this self managed care a multi-disciplinary team will monitor the effectiveness of blood glucose control in order to facilitate its optimisation and will work to identify and treat as early as possible any diabetic complications or co-morbidities that an individual may develop.[219]

For individuals with T1DM, a form of insulin will almost always be used to regulate blood glucose levels.[220]

Stabilisation of blood glucose amongst individuals with T2DM is usually carried out without pharmacological intervention by implementing lifestyle changes (tackling where appropriate sedentary behaviour and poor nutritional intake).[221][222] However, sometimes this approach to treatment is not possible and individuals will either initially

begin, or progress to, controlling their blood glucose levels using a pharmacological regime which may or may not include insulin.[221 222]

Lowering prevalence of complications

Regardless of sub-type, individuals with DM often have high or cycling glucose levels which lead to many complications either due to the direct toxicity of the high glucose levels or, indirectly, because of elevated BP and lipid levels which occur due to kidney damage or structural and functional anomalies in the microvasculature.[209] Commonly diagnosed complications of DM are cardiovascular disease, nephropathy, neuropathy, retinopathy, hypoglycaemia and hyperosmolar hyperglycaemic state.[209] Large trials have shown that increases in levels of blood glucose, BP and lipid levels correspond to an increase in an individual's risk of developing diabetic complications.[223 224] Conversely healthy lifestyle choices or optimisation of pharmacological therapy leading to low levels of blood glucose, BP and lipid levels can delay or prevent onset of diabetic complications.[225]

NICE gives set guidelines and targets aimed at preventing, improving detection of, or delaying onset of early and late stage DM complications.[220-222] These guidelines are aimed at improving an individual's lifestyle choices, lowering their average blood glucose measure, lowering their average blood lipid levels, lowering their average BP and monitoring their kidney function, visual acuity, presence of neuropathy and psychological wellbeing.[220-222]

1.3.4 DM rates and risk factors

The IDF estimated that in 2011 366 million people worldwide were living with DM, and that 4.6 million people died as a consequence of having DM.[226]

The prevalence of DM in the UK is middling comparative to other countries globally but is similar to that seen in other European countries, see Figure 10.

Figure 10: Relative DM prevalence by country, 2011[226]

DM rates in the UK

Unlike for TB, there is no national surveillance system in place within the UK to monitor incidence and prevalence of DM however there are some regional databases collating this information. This means that although diagnostic criteria for DM are standardised[212], the exact disease prevalence or incidence within the UK population is unknown and only best estimates are available.

Methods used to collate demographic information upon individuals with DM in the UK are as follows; cross sectional surveys (e.g. the Health Survey for England), questionnaires, routine health information (e.g. Hospital Episode Statistics (HES), primary care database records or GP audit data) and specialist local registries.[227] The majority of available DM prevalence and incidence estimates for the UK have been calculated using information from these sources. It is important to note that the use of these sources probably underestimates the number of individuals with DM and in particular of those with T2DM. This is because individuals with T2DM are often asymptomatic with infrequent interaction with healthcare systems meaning that many individuals with T2DM are undiagnosed and unaware of their status.[227]

The following information upon the distribution of DM within the UK population is assimilated from some of the 'best estimates' available.

Rate changes over time

Temporal trends show a dramatic increase in the rates of DM within the UK, between 1996 and 2005 *Gonzalez et al* document an approximate doubling of DM prevalence. They found that in the UK DM prevalence rose from 2.8% in 1996 to 4.3% in 2005 and incidence rose from 2.71 per 1,000 person years in 1996 to 4.42 per 1,000 person years in 2005.[228] When these figures were broken down by sub-type it was noted that the incidence of T2DM had risen most dramatically from 2.60 per 1,000 person years in 1996 to 4.31 per 1,000 person years in 2005.[228]

Geographic variation

Within the UK approximately 4% of adults have a clinical diagnosis of DM, stratified by country the prevalence of diagnosed DM is; 5.1% for England, 4.6% for Wales, 3.9% for Scotland and 4.5% for N.Ireland.[229-235] This equates to their being more than 2.5 million individuals with diagnosed DM in the UK.[229 235] It is estimated that on top of these individuals with diagnosed DM there are up to another 750,000 people with DM in the UK whom remain undiagnosed.[236]

In the areas that are covered by the ORLS database the estimated prevalence of diagnosed DM is 3.47% (95% CI 3.43-3.52) for Oxfordshire, 4.09% (95% CI 4.05-4.14) for Northamptonshire and 3.59% (95% CI 3.50-3.69) for Reading.[235]

Risk factors

As with risk of TB, risk of DM is known to increase with a variety of biological factors such as sex, age and ethnicity.[237]

Throughout the UK DM shows a male preponderance with DM prevalence 1% higher amongst males than females.[229]

Incident rate of DM amongst children and adolescents (those aged 0-19) within the UK are between 10 and 15 cases per 100,000 population per year.[229][235] The majority of these incident cases will be of T1DM as although T1DM can affect all age groups its peak incidence occurs amongst individuals aged 4–5, and 15-20.[238]

In England there are over 22,000 people under the age of 17 with DM. Of these the majority (97%) have T1DM, a small number have early onset T2DM (1.5%) and the same amount again have other uncommon forms of DM (1.5%).[229-235] Unlike those with T2DM, who are mainly asymptomatic, the majority of individuals with T1DM will present to healthcare rapidly due to their need for insulin therapy. Thus, as these individuals make up the majority with childhood DM, most individuals with T1DM are diagnosed and rate estimates are comparatively accurate.[230]

In England, Wales, Scotland and N.Ireland prevalence of DM is highest amongst those aged 65 and above.[232-235] This is because the majority of individuals with DM have T2DM. Incidence of T2DM increases with age, the peak incidence trends occurring amongst those above the age of 40. However, temporal trends show that the age of onset of T2DM is falling especially amongst certain ethnic groups (those of South Asian or African–Caribbean origin).[239]

Of all individuals (adults and children) with prevalent DM it is estimated that 85% have T2DM and 15% have T1DM. Of all adults in the UK with prevalent DM it is estimated that 90% have T2DM and 10% have T1DM.

DM is ethnically patterned with DM prevalence almost double in those of Black Caribbean, Pakistani, Bangladeshi, and Indian origin when compared to the national UK prevalence, see Table 5.[229][235]

Table 4: Prevalence of self reported DM in the UK by ethnic group and sex

Ethnic group	Men	Women
Bangladeshi	8.2%	5.2%
Black African	5%	2.1%
Black Caribbean	10%	8.4%
Chinese	3.8%	3.3%
Indian	10.1%	5.9%
Irish	3.6%	2.3%
Pakistani	7.3%	8.6%
General Population	4.3%	3.4%

The following modifiable risk factors are associated with an increased risk of DM or if already diabetic of developing complications and co-morbidities; poor diet, obesity, physical inactivity, smoking, high alcohol intake and SES.[240][241] The most deprived quintile of the UK population are more likely than the least deprived to have DM at any given age.[242][243]

1.4 A review of available evidence upon the association between TB and DM

To enable the reader to place the analyses carried out by the candidate amidst the body of contemporary research on the magnitude of the association between TB and DM the following section presents a semi-systematic review of evidence published up until March 2012.

This review of available evidence was rigorous and attempted to identify and assimilate published data no matter how disparate whilst applying the main tenets of systematic review methodology. However, as the review of existing evidence was completed by the candidate alone certain standard systematic review conventions could not be adhered to (such as duplicate abstract review by independent investigators) and it is for this reason that this review is referred to as a 'semi-systematic' review.

Systematic Review

Systematic review utilises specific techniques in order to identify and assimilate research evidence upon a specific topic no matter how dissimilar the publications that hold relevant information may be.

Systematic review is a replicable scientific method which begins with a drafted protocol outlining; a research question (hypothesis), how studies that answer this question will be identified and obtained (search strategy), how relevant studies will be summarised (analysis techniques) along with any other information deemed pertinent to the review process.[244 245] Next, pre-outlined search strategies are completed and abstracts of returned citations are reviewed in order to identify relevant literature for full review. Full review of potentially relevant papers is then completed and relevant data is extracted ready for narrative and if appropriate statistical synthesis.[244 245]

The Cochrane Collaboration and the Centre for Review and Research Dissemination based at York University have comprehensively outlined protocols and guidelines to facilitate researchers at each stage of the systematic review process.[244 245] Open access documents giving further detail upon generic systematic review method can be found upon either organisation's website.[244-247]

1.4.1 Semi-systematic review

There have been two previously published systematic reviews of studies upon the magnitude of the association between DM and TB.[25 28] These reviews present a précis and statistical analysis of research published up until the end of March 2007, the review of literature presented here aims to expand upon and update this work.

Search Strategy

The intention of the initial search and abstract review was to identify and systematically critique primary epidemiological publications reporting a risk estimation of the association between TB of any site amongst individuals with any type of DM, or the converse.

The search strategy developed was purposefully broad and sensitive in order to try and identify any relevant, published papers. The search strings outlined in Table 7 were used to comprehensively search literature catalogued within the two largest biomedical databases MEDLINE® and EMBASE® between 1948 and March 2012 utilising the OvidSP search interface (Ovid MEDLINE®1948 to MARCH 2012 and Ovid EMBASE® 1974 to MARCH 2012).

The search strategy used contains both medical subject heading (MESH) terms (terms assigned to studies by a librarian to represent the topics it covers in Major or Minor detail) and text word terms (.tw. which identify studies with any mention of the searched term in the title or abstract) in order to identify all relevant studies whether catalogued under relevant terms or not. Special characters, search functions and Boolean Operators were used to produce a succinct but thorough search strategy.

The "*exp*" and the back slash within search strings 1 and 2 indicate that these strings used the explode command; an exploded search string will select articles indexed with that search term plus articles indexed with related narrower terms. In search strings 3 and 4 the truncation wildcard symbol (*) indicates that articles were returned which contained any elongated derivative of the original search term (for example; diabet* will return articles containing the words diabetes, diabetic, diabetologist etc). Strings 8, 9 and 10 were completed using automated OvidSP limits and ENDNOTEX4 functions.

Due to restricted availability of translation resources only English language papers were reviewed for relevance. Initial search returns were limited to those in English language using the integral OvidSP search interface. Any duplicated references were removed from the listed search results using the integral OvidSP search interface. Duplicated references were also checked for and removed after citations were downloaded in to ENDNOTEX4 using the duplicate function in this programme.

Table 5: Search strategy used to identify papers reporting upon TB and DM

	Search String	MEDLINE Hits	EMBASE Hits
1	Exp diabetes mellitus/	275,732	481,334
2	Exp tuberculosis/	142,480	174,384
3	Diabet*.tw.	329,092	448,985
4	Tuberculo*.tw.	136,781	163,076
5	1 or 3	377,261	560,989
6	2 or 4	173,451	211,137
7	5 and 6	2,173	3,927
8	English Language (OvidSP)	1,148	2,553
9	Remove duplicates preference to keep EMBASE references over MEDLINE (OvidSP)	202	2,523
10	Remove duplicates (ENDNOTE)	2,690	

Abstract review

For this semi-systematic review of background literature abstract review was completed only by Fiona Pearson (FP) and not independently by two investigators.

In order to expand upon as well as update the two prior reviews upon the magnitude of the association the inclusion and exclusion criteria as set out by Jeon *et al* and Stevenson *et al* were not wholly utilised.[25] [28]

Inclusion and exclusion criteria

Publications that cited any analytical estimate of the association between TB and DM (or sub-types of these diseases) with measures of uncertainty surrounding the estimate were included, as well as the converse.[25] [28]

Studies were excluded if they: were case studies or reviews, did not adjust for age, assessed TB, or where relevant DM, differently amongst study population sub-groups, or, were duplicate reports of the same results.[25] [28]

Due to amendments to the inclusion and exclusion criteria of previous systematic reviews searching was completed from the first year of each database rather than simply from March 2007 onwards.[25] [28]

After abstract review 2,639 citations were deemed entirely irrelevant i.e. during abstract sifting were not found to present any quantitative discussion upon the magnitude of the association between TB and DM or the converse and did not fit within the pre-specified inclusion and exclusion criteria.

Forty seven remaining publications were identified as likely to contain risk estimations for an association between active TB amongst individuals with DM, or the converse.[25-28 90 95 205 248-286 295] These publications were retrieved in full in order to verify relevance and allow extraction of data if relevant.

During full review 24 publications were deemed relevant for data extraction, one of which is a paper including work presented in this thesis.[26 27 90 95 205 264-273 276-283 295] The publication of analyses presented in this thesis (Young *et al)* has been included in Table 6 and Figure 11 but findings are not discussed further in this chapter.[283] References of papers identified as being relevant were reviewed in case of further as yet unidentified pertinent publications (grey literature) however no further publications were found.

Case reports and reviews

Amongst the excluded citations there were 44 case reports or small case series (less than 10 cases) describing unusual manifestations of co-morbid TB and DM.[287-331] It is interesting to note the number of case reports published as to a certain extent publication reflects the initial implicit recognition of the importance or at least unusual presenting nature of these co-morbid cases. However, as publication of case reports are spontaneous and contain predominantly anecdotal comment along with minimal descriptive data rather than analytical findings these publications are discussed no further.

Somewhat surprisingly 57 reviews were also identified from the initial search either entirely focussed upon the relationship between DM and TB or that noted the association within an alternately focussed review.[25 28 116 332-363] Again although these publications are not presenting primary data analysis it is interesting to note their number. A large number of reviews would imply that the plausibility of an association is generally accepted by researchers working within the field. It is notable that over 60% of these reviews were published after 2008 (the year this body of work was initiated and the year after 2 systematic reviews of evidence upon the association were published).[25 28 116 351-363] This suggests that it is only very recently that researchers within the field have begun to recognise the importance of a potential association between DM and TB.[25 28 116 351-363] As non-systematic reviews contain anecdotal comment upon a field of research rather than primary analytical findings these publications are also discussed no further.

Five of the identified reviews were full systematic reviews two of which are those that are being updated and expanded upon. These systematic reviews appraised the literature

upon the magnitude of the association between DM and TB up until March 2007.[25 28] A third review which has also been previously mentioned appraises the literature upon TB outcomes amongst individuals with co-morbid TB and DM comparative to those with TB in isolation.[121] A fourth review appraised literature upon bidirectional screening for TB and DM[128], and a fifth reviewed literature upon the epidemiology and public health issues related to DM in sub-Saharan Africa giving only a brief mention of the association.[361]

Amidst the systematic reviews there is some primary analysis of secondary data however most of this is not of relevance to the magnitude and directionality of the association between TB and DM. Thus, only the two systematic reviews being updated that give a synopsis (and one a meta-analysis) of primary publications upon the magnitude of the association between DM and TB are discussed any further.[25 28]

Full review and data extraction

Data extraction was completed for the 24 studies containing relevant information (Alisjahbana 2006[264], Baker 2012[265], Brassard 2006[266], Buskin 1994[267], Chen 2006[27] Coker 2006[268], Dobler 2012[269], Dyck 2007[270], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], Jick 2005[205], John 2001[26], Kim 1995[272], Leegaard 2011[273], Leung 2008[295], Marks 2011[95], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278], Ponce de Leon 2004[279], Rosenman 1996[280], Shetty 2006[281], Wu 2007[282] and Young 2010[283]).

This included nine more studies (Baker 2012[265], Dobler 2012[269], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], Leegaard 2011[273], Leung 2008[295], Marks 2011[95], Wu 2007[282] and Young 2010[283]) than those précised within previous systematic reviews, a study by *Alisjahbana et al*[264] and one completed by *Shetty et al*[281] having been included in the systematic review by *Stevenson et al*[28] but not identified by *Jeon et al*[25] in their review.

Extracted data on the population studied, study design, exposure and outcome definitions (ascertainment method for cases of DM and TB) and confounders that were adjusted for from all of the identified published studies is presented within Table 6.

With no universally accepted standard protocols for quality assessment of observational studies the studies identified were assessed by the following pre-specified 'quality' criteria deemed by the candidate likely to affect study rigour; study design, setting, method of case ascertainment and confounders adjusted for. Based upon these criteria each study was graded as being either of 'high quality', 'unclear quality' or 'low

quality' as would be done within a Cochrane systematic review. However, as only a small number of studies were identified many of which were not specifically designed to look at the association between TB and DM the attributed quality grades seemed somewhat naïve. Whether each study was subjectively deemed of poor or high quality would negate the fact that due to the limited body of knowledge each study is of great importance. It was thus decided that rather than present individual grades an overall evidence grade for quality would be given (see last row of Table 6). This overall evidence grade gives the percentage of all studies graded as 'low quality', 'unclear quality' and 'high quality' in an attempt to outline the shortcomings of the entire body of evidence.

The main risk estimation reported within each paper is presented pictorially within a forest plot (Figure 11).

Table 6: Summary of studies giving a quantitative estimate of the association between DM and TB

First Author	Setting & Study Date	Study Design	Study Population	DM Sub-type & Definition Used	TB Sub-type & Definition Used	Adjustments
Alisjahbana 2006[264]	Indonesia, 2001-05	Case Control	TB patients from a hospital and inpatient clinic. Neighbourhood controls matched for age & sex.	DM: FBG> 126 mg/dl	PTB: Clinical suspicion, chest x-ray and confirmed by acid fast bacilli (AFB) presence in sputum	Age, sex, body mass index (BMI), overcrowding, income, TB contact in family
Baker 2012[265]	Taiwan, 2001-04	Cohort	Participants in the Taiwanese National Health Interview Survey	DM: Self report and medical record review (MRR)	TB: MRR	Age, sex, BMI, overcrowding, smoking, alcohol, household income, employment, receipt of government subsidy, marital status, education residence in an indigenous community, lung disease, hypertension, & heart disease
Brassard 2006[266]	United States of America (USA), 1998-2003	Case Control	Patients with anti-rheumatic prescription on pharmetrics database	DM: Medical records coded using International Classification of Diseases (ICD) 9; 250.0-250.9	TB: Medical records coded as ICD 9; 010-018	Age, sex, silicosis, renal failure, haemodialysis, solid organ transplant, head and neck cancer, Non-steroidal anti-inflammatory medications, steroids, cox-2 inhibitors
Buskin 1994[267]	USA, 1988-90	Case Control	Patients from a Washington TB clinic	DM: Self report	TB: As defined by the Centre for disease control and prevention (CDC)	Age

Chen 2006[27]	Taiwan, 1983-2003	Cohort	Renal transplant patients from Taichung	DM: Medical notes	TB: Positive culture, granuloma presence upon biopsy, or, chest X-ray or clinical findings consistent with TB which clear after treatment	Age, sex, dialysis duration, Hepatitis B or C, immunosuppressive medication, graft rejection>3 months
Coker 2006[268]	Russia, January(Jan)-Dec 2003	Case Control	Residents of Samara	DM: Self report	TB: Diagnosed by culture positivity	Age, sex, smoking, alcohol, illicit drugs, imprisonment, number of co-habiting individuals, assets, employment, financial security, relative with TB, drinking raw milk
Dobler 2012[269]	Australia, 2001-06	Cohort	Patients on the national DM services scheme database and TB notification databases	All DM and T1DM: Self report with clinical confirmation	TB: Notification scheme	Age, sex, indigenous status and TB incidence in country of birth
Dyck 2007[270]	Canada, Jan 1986- Dec 2001		Aboriginals and non-aboriginals from Saskatchewan	DM: Medical records coded as ICD 9; 250	TB: Cases reported to health department	Age, sex, ethnicity
Farhoult-Jepsen 2011[271]	Tanzania, April 2006-Jan 09	Case Control	Residents of Mwanza	DM: FBG >6 mmol/L or a 2hBG>11 mmol/L	PTB: Sputum smear and culture	Age, sex, socio-demography, HIV and AGP
Goldhaber-Fiebert 2011[90]	"Global", 2002-03	Case Control	124,545 adults from 46 countries	DM: Self report	PTB: Self report	Age, sex, BMI, crowding, education, housing quality and health insurance

Jick 2005[205]	UK, 1990-2001	Case Control	GP registered	DM: Primary care data medication record	TB: First diagnosis of TB and 6 months of 3 types of TB medication record	Age, sex, smoking, BMI, index date, amount of history, pulmonary disease, anti-rheumatic, glucocorticoid, immunosuppressive medication
John 2001[26]	India, 1986-99	Cohort	Renal transplant patients	DM: FBG>126 mg/dl or post prandial blood glucose > 200 mg/dL	PTB: X-ray, AFB in gastric juice or culture	Age, chronic liver disease, co-infections, immuno-suppresive medication
Kim 1995[272]	Korea, 1988-90	Cohort	Korean civil servants. 7,705 individuals with & 782,440 without DM.	DM: Screening blood glucose ≥119mg/dl, FBG of ≥150mg/dl or postprandial blood glucose of ≥180mg/dl	PTB: Chest X-ray and 2 positive sputum smears	Age and sex
Leegaard 2011[273]	Denmark, 1980-2008	Case Control	Danish Civil Registration System	T1DM & T2DM: Episode of care and medication use	TB: Hospital diagnosis of TB	Age, sex, place and length of residence in Denmark, and country of emigration alcoholism, immunosuppressive medications, and socioeconomic markers
Leung 2008[295]	Hong Kong, Jan-Dec 2000	Cohort	Population of the elderly (>65)	DM: FBG>7mmol/L	PTB & EPTB: Bacteriologically proven, X-ray, histology or favourable treatment response	Age, sex, BMI, weight loss, smoking, alcohol, SES, marital status, education, housing, employment, language, Cardiovascular disease, hypertension, Chronic Obstructive Pulmonary Disease, asthma, malignancy, hospitalisation, activity and daily living score

Marks 2011[95]	USA, 2000-05	Cohort	US National Health Interview Survey respondents	DM: Self Report	TB: Self Report	Age, sex, ethnicity, foreign birth, high school drop-out, history of homelessness or incarceration, cancer, smoking, alcohol, no health insurance and HIV
Mori 1992[276]	USA, 1986	Case Control	Oglala Sioux Indians from South Dakota	DM: Record of DM medication, Screening Blood Glucose >11.1mmol/L or FBG >7.8mmol/L	TB: Clinical diagnosis	Age, sex, alcohol, Isoniazid therapy, residence
Pablo-Mendez 1997[277]	USA, 1991	Case Control	Residents of California	DM: Medical records coded as ICD 9; 250.0-250.9	TB: Medical records coded as ICD 9; 010-018	Age, sex, ethnicity, alcohol, drug use, education, income, health insurance, HIV related conditions, renal insufficiency, two way interactions
Perez 2006[278]	USA, 1999-2001	Case Control	Residents of Mexico/Texas border countries	DM: Medical records coded as ICD 9; 250.0-250.9	TB: Medical records coded as ICD 9; 010-018	Age, sex, ethnicity, malnutrition, income, education, insurance, renal failure
Ponce de Leon 2004[279]	Mexico, March 1995-2005		Residents of Veracruz	DM: Clinical diagnosis or FBG>126mg/dl or random blood glucose>200mg/dl	TB: DNA fingerprinting	Age, sex
Rosenman 1996[280]	US, 1985-87	Case Control	New Jersey health department reported TB cases	DM: Self Report	PTB: Clinical diagnosis, positive culture or effective treatment	Age, sex, ethnicity

Shetty 2006[281]	India 2001-2003	Case Control	Outpatients from St John's Medical College Hospital in Bangalore	DM: DM diagnosis with or without hypertension or CVD	PTB: Smear positive or chest X-ray	Age sex, alcohol, smoking, overcrowding, income, education, separate kitchen, cooking fuel
Wu 2007[282]	Taiwan, Jan 2002 to Dec 2004	Case Control	TB cases and controls with non TB lower lung infection OR TB contacts	DM: Medical records	PTB: Culture confirmed	Age, sex, pneumoconiosis, prochiectasis, liver cirrhosis, haemodialysis and lung cancer
Young 2010[283]*	UK, 1963-2005	Cohort	Patients from the oxford healthcare region	DM, T1DM and T2DM: MRR using ICD codes	TB, PTB and EPTB: MRR using ICD codes	Age, sex
Overall Quality of Evidence[364]			🟩🟩🟩 🟧 🟥🟥			

*Publication of partial findings from this thesis

Previous reviews of evidence

In a systematic review of evidence on the association between DM and TB by Stevenson and colleagues 9 studies (2 cohort studies and 7 case control studies) were found in which having DM was estimated to increase the risk of TB infection amongst individuals between 1.5 and 7.8 fold.[28] Heterogeneity was deemed too great by the authors to carry out statistical pooling of risk measures identified. Thus narrative synthesis of studies was given.

Jeon and colleagues also completed a systematic review of publications identifying 13 studies (3 cohort studies, 8 Case control and 2 'other') which did not include 2 of the studies identified by *Stevenson et al (*Alisjahbana 2006[264] and Shetty 2006[281]) but reported upon a further 6 (Brassard 2006[266], Buskin 1994[267], Chen 2006[27], John 2001[26] Mori 1992[276] and Rosenman 1996[280]).

The Begg and Egger test were used by *Jeon et al* to show that there was no indication of publication bias amongst the literature they identified.[25]

Jeon et al completed a meta-analysis of identified effect measures which showed having DM was associated with an overall *RR* of 3.11 for contracting TB.[25] However, as previously mentioned, this analysis was heavily weighted by a single study (Kim 1995[272]) and the 2 other studies (John 2001[26] and Chen2006[27])from which results were pooled were completed amongst populations of individuals with renal failure (renal failure itself being a risk factor for TB). Thus, the external validity and improved precision of this pooled estimate is perhaps questionable.

Jeon et al used meta-regression to explore the impact of age upon estimates of the association.[25] They found that as age increased risk estimate decreased this trend was significant in work reported by *Kim et al*[272] and *Ponce de Leon et al*[279] but not of that reported by *Dyck et al*.[270]

Jeon at al also used meta-regression to explore any impact upon the association due to study design, case ascertainment and adjustments made. They identified that studies which; did not establish the temporal order of TB and DM, where DM or TB status was not identified in an empirical manner, that did not adjust for smoking and which did adjust for SES saw an attenuation in the reported effect measure.[25]

Overview of studies identified in the semi-systematic review

Risk of DM amongst individuals with TB

Although the temporal nature of disease is not clear in cross sectional case control studies; no studies were identified by this semi-systematic review that expressly stated measuring the risk of DM amongst individuals who have had TB.

Due to the plausible bi-directional nature of an association between DM and TB and lack of available evidence this is something that will be addressed in the candidate's analyses.

Risk of TB amongst individuals with DM

All 24 studies identified by the semi-systematic review gave an estimation of TB risk amongst individuals with DM adjusted for, at least, by age and sex (inclusion criteria). Risk estimations in the newly identified studies did not affect the overall variance in risk seen within the previous reviews.[25][28] Figure 11 gives a visual overview of the 'main' reported risk estimations published in all of the identified studies.

Study Design

The additional publications identified within this review give a new total of 14 case control studies (Alisjahbana 2006[264], Brassard 2006[266], Buskin 1994[267], Coker 2006[268], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], Jick 2005[205], Leegaard 2011[273], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278], Ponce de Leon 2004[279], Shetty 2006[281] and Wu 2007[282]), seven cohort studies (Baker 2012[265], Chen 2006[27], Dobler 2012[269], Dyck 2007[270], John 2001[26], Kim 1995[272] and Leung 2008[295]) and two further studies (Ponce de Leon 2004[279] and Dyck 2007[270]) which accrued cases prospectively and then determined the distribution of DM during a different time period.

Study design, due to biases inherent with methods used, may affect the measure of a risk estimate either amplifying away from or attenuating towards the null. *Jeon et al* used meta-regression to assess the effect of study design on the measures of association found in their 13 identified studies. They found estimates of TB risk amongst those with DM to be weaker in studies which did not establish the temporal order of TB and DM.[25] Amongst the studies identified by this semi-systematic review the finding of an increase in TB risk amongst those with DM comparative to those without seems robust across study designs (as assessed visually, see Figure 11). Five studies (Buskin 1994[267], Dyck[270], Leegaard 2011[273], Marks 2011[95] and Rosenman 1996[280]) show no significant change in risk of TB amongst those with DM comparative to those without DM, however three of these studies present figures tending towards statistical significance

(Dyck[270], Leegaard 2011[273] and Marks 2011[95]). The remaining 19 identified studies show a statistically significant increase in TB risk for those with DM comparative to those without (Alisjahbana 2006[264], Baker 2012[265], Brassard 2006[266], Chen 2006[27], Coker 2006[268], Dobler 2012[269], Dyck 2007[270], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], Jick 2005[205], John 2001[26], Kim 1995[272], Leung 2008[295], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278], Ponce de Leon 2004[279], Shetty 2006[281] and Wu 2007[282]).

Setting

As was found in the review completed by *Jeon et al* this review finds geographic setting not to affect the increase in TB risk seen amidst those with DM. One study completed by Goldhaber-Fiebert and colleagues looked at the effect of region upon the association finding that stratified risk estimates stayed relatively stable Europe 2.38 (95%CI 1.08-5.24), Africa 1.96 (95%CI 1.23-3.12), Asia 1.74 (95%CI 0.82 3.72) and Latin America 1.99 (95%CI 1.44-2.75).[90]

It is of note that the majority of the studies 17 were completed within high income countries (Baker 2012[265], Brassard 2006[266], Buskin 1994[267], Chen 2006[27], Dobler 2012[269], Dyck 2007[270], Goldhaber-Fiebert 2011[90], Jick 2005[205], John 2001[26], Leegaard 2011[273], Leung 2008[295], Marks 2011[95], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278], Rosenman 1996[280] and Wu 2007[282]), five within middle income countries (Alisjahbana 2006[264], Coker 2006[268], Kim 1995[272], Ponce de Leon 2004[279] and Shetty 2006[281]), only one within a low income country (Farhoult-Jepsen 2011[271]) as specified by the world bank.[413] One study utilised a global dataset (Goldhaber-Fiebert 2011[90]). The impact of any association is likely to be most adverse in low income countries due to inherent issues with healthcare provision.[366] Further research is needed into the magnitude and impact of the association within these settings.

It is also of note that only four studies have assessed the association in areas with high TB incidence two in India (John 2001[26] and Shetty2006[281]), one in Russia (Coker 2006[268]) and one in Tanzania, sub Saharan African (Farhoult-Jepsen 2011[271]), see Figure 4. Given the high background prevalence of TB in these areas[367] and the projected increases in DM[54] even a moderate increase in risk within these regions is likely to have a dramatic public health impact over the coming years.[58] Again further research is needed to identify the magnitude and impact of the association within settings with high TB incidence.

Although undoubtedly impact of an association will be most detrimental in these countries, it is not to say that an effect within middle to high income countries such as the UK would be negligible.[130] Only a single study of those identified gave an estimate of the association within a UK setting (Jick 2005[205]), and this was within a study which was not specifically designed to look at the association.

Figure 11: Pictorial summary of effect estimations with studies ordered alphabetically

Author	Year		Effect Size (95% CI)
Alisjahbana	2006		4.20 (1.50, 11.70)
Brassard	2006		2.09 (1.10, 3.95)
Buskin	1994		1.70 (0.70, 4.30)
Coker	2006		7.83 (2.37, 25.89)
Farhoult-Jepsen	2011		4.23 (1.54, 11.57)
Goldhaber-Fiebert	2011		1.81 (1.37, 2.39)
Jick	2005		3.80 (2.30, 6.10)
Leegarrd	2011		1.18 (0.96, 1.45)
Leung	2008		1.77 (1.41, 2.24)
Marks	2011		1.40 (1.00, 2.00)
Mori	1992		5.20 (1.22, 22.10)
Pablo-Mendez	1997		7.84 (4.71, 13.02)
Perez	2006		1.53 (1.37, 1.70)
Rosenman	1996		1.16 (0.58, 2.32)
Shetty	2006		2.44 (1.17, 5.09)
Wu	2007		3.43 (2.16, 5.46)
Chen	2006		3.07 (1.14, 8.26)
Dobler	2012		1.48 (1.04, 2.10)
Dyck	2007		0.99 (0.80, 1.23)
Kim	1995		3.60 (3.10, 5.20)
Ponce de Leon	2004		6.80 (5.70, 8.20)
Baker	2012		2.09 (1.10, 3.95)
John	2001		2.31 (1.42, 3.76)
Leung	2008		1.77 (1.41, 2.24)
Young	2010		3.11 (1.17, 7.03)

| | .5 | 2 | 8 | 32 |

Methods of case ascertainment utilised in identified studies

Accurate exposure and case identification is fundamental when estimating a measure of association. Misclassification describes the 'mislabeling' of a study subject as; exposed when they are unexposed, as having an outcome of interest when they do not, or, the converse of either of these described situations. Over or underestimation of those exposed or with an outcome of interest can lead to an over or under estimation of effect estimate calculations.[368-370]

The effect that misclassification has upon an effect estimate is dependent upon what variable is misclassified, if it is dichotomous and the type of misclassification that is occurring. Misclassification can be either differential or non-differential (random). Non-differential misclassification can be a random misclassification of an individual's exposure status, outcome status or both that is *independent* of their status for any other of these variables. Differential misclassification is a non-random misclassification of an individual's exposure status, outcome status or both which is *dependent* upon an individual's status for at least one other of these variables.[368-370]

If non differential misclassification exists amongst a study with a dichotomous exposure (DM/no DM) and outcome (has had TB/never had TB), as is the case in most of the studies identified, it will cause an attenuation of the risk estimate towards the null. It is only in rare circumstances that non-differential misclassification will cause an inflation of risk estimates. However, if there is a systematic over estimation of those exposed amongst cases or a systematic underestimate of exposure amongst non-cases i.e. misclassification is dependent upon another variable the subsequently calculated risk estimate will be inflated. A systematic under estimate of cases exposed or a systematic over estimate of exposure in non-cases will give a deflated risk estimate.[368-370]

Within studies of the association between DM and TB the most accurate method of case identification for both diseases (any sub-type) would be utilising the following standard diagnostic techniques; for DM a measure of FBG and for TB through microbiological sputum smear or culture. This is how five of the identified studies ascertained both DM and TB status (Alisjahbana 2006[264], Farhoult-Jepsen 2011[271], Kim 1995[272], Leung 2008[295] and Ponce de Leon 2004[279]).

If diagnostic testing for everyone within an identified population at risk is unfeasible then medical records can be used to identify those who have been clinically diagnosed with either disease. However it should be noted that case ascertainment using medical

records will only identify those diagnosed with TB or DM and would exclude people who have disease but are, as yet, clinically undiagnosed.

The number with undiagnosed TB is likely to be negligible due to the acute nature of the active disease. However, as previously discussed, there are likely to be a number of individuals with DM who are clinically undiagnosed. If individuals with DM are identified in a study as non-cases estimates of an association may be biased towards the null (no association). Seven studies were identified that used medical records to identify cases of DM and TB (Baker 2012[281], Brassard 2006[265], Dobler 2012[269], Dyck 2007[270], Jick 2006[90], Leegaard 2011[273], Pablos-Mendez 1997[276], Perez 2006[277]).

Self report of status through interview or questionnaire could also be used to identify those with either disease although case identification in this manner is likely to be affected by both an individual's ability to identify their own status and whether or not they have been clinically diagnosed (given that status cannot be reported if accurately unknown). In theory, any errors made to recall status should occur non-systematically and equally across those recalling their TB or DM status and thus no attenuation of the measured association should be seen. However, as with using medical records you might expect to miss count a number of individuals with DM as free from disease which would lead to an under estimate of any association seen between DM and TB.

Of the studies identified, only 2 utilised self-report to ascertain cases of DM and cases of TB (Goldhaber-Fiebert 2011[90] and Marks 2011[95]). However seven of the studies used self-report to identify DM status alongside standard diagnostic procedures to identify TB status (Buskin1994[267], Coker 2006[268], Chen 2006[27], John 2001[26], Rosenman 1996[280], Shetty 2006[281] and Wu 2007[282]).

Jeon et al found, for the 13 studies that they identified, that risk of TB amongst those with DM was weaker in studies which did not establish the temporal order of TB and DM and studies where DM or TB status were not identified in an empirical manner.[25] From visual assessment of the studies identified within this review (see Figure 11) no change in direction or significance of effect measure due to study type or method of case ascertainment was seen.

Measures of association between sub-types of TB and DM

Of the studies identified ten did not specify if they were assessing the association between specific sub-types of DM or TB and were assumed to be assessing the association between all types of DM and all types of TB (Baker 2012[265], Brassard

2006[266], Buskin 1994[267], Dyck 2007[270], Jick 2005[205], Marks 2011[95], Pablo-Mendez 1997[277], Perez 2006[278], Ponce de Leon 2004[279] and Rosenman 1996[280]).

Seven studies specified that they were assessing an association between PTB and DM (Alisjahbana 2006[264], Coker 2006[268], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], Shetty 2006[281], Kim 1995[272] and Wu 2007[282]). Two studies assessed the association between post-transplant TB and DM (Chen 2006[27] and John 2001[205]). Two between both T1DM, T2DM and TB (Dobler 2012[269] and Leegaard 2011[273]) and a single study between DM and both PTB and EPTB (Leung 2008[295]). Both papers which included a measure of TB risk amongst individuals with T1DM identified an increase in risk although only one estimate showed significance (*RR* 2.27 (95%CI 1.19-3.66))[269] and (Odds Ratio (OR) 2.59 (95%CI 0.44-15.29)).[273] For T2DM the risk estimates reported were (*RR* 1.48 (95%CI 1.04 – 2.10))[269] and (OR 1.17 (95%CI 0.95-1.44)).[273] Again both studies showed an increase in risk with only one being statistically significant. Both papers showed an increased risk estimate for TB amongst those with T1DM comparative to without T1DM, it has been suggested that this is because the risk is mediated through levels of hyperglycaemia seen amidst people with DM and those with T1DM tend to have poorer hyperglycaemic control.

The only publication to include measures of both PTB and EPTB risk amongst individuals with DM comparative to those without found risk of PTB to be significantly increased amongst individuals with DM and risk of EPTB to be non-significantly increased although numbers for the later sub-analysis were small (*RR* 1.42 (95%CI 1.12-1.80)) and (OR 1.05 (95%CI 0.49-2.31)).

From a public health perspective the association between T2DM and PTB is of most interest as approximately 90% of individuals with DM have T2DM and PTB is the most prevalent infectious form of TB. However in thinking about disease aetiology and the close link between sub-types of DM then it is of interest to explore the relationships between the sub-types of each disease further. This is something that will be addressed within the candidates work.

Risk modification
Few of the studies identified were of sufficient size to give estimates of TB risk amongst individuals with DM by any suspected effect modifiers. Those publications that presented stratified estimates of risk are discussed below.

Only three studies presented stratified risk estimates by gender; two found an increased risk of TB amongst females with DM (Dyck 2007[270] and Leegaard 2011[273]) and one the

converse (Perez 2006[278]). Giving the mixed findings it is fair to say the true impact of gender upon the association between DM and TB is unknown.

This semi-systematic review found only four studies which assessed the impact of age upon the association. Three showed that the estimates of association decrease as age increases (Kim 1995[272], Leegaard 2011[273] and Ponce de Leon 2004[279]), however, one study found no clear effect of age (Dyck 2007[270]). It is possible that the later study was underpowered to detect any effect.

As has already been discussed, *Jeon et al* report that risk estimations for contracting TB amongst individuals with DM vary by age being highest amongst the young and attenuating as age increases.[25]

These findings as with those for gender need further examination. They could be due to a decrease in baseline glucose tolerance amongst those of older age without DM, which would reduce the apparent effect of DM. Or, if we take note of findings upon disease sub-type specificity of the association, trends seen could be due to those of younger age having a more severe form of DM and hyperglycaemia. As most studies did not distinguish between T1DM and T2DM we cannot conclude satisfactorily whether the effect modification by age would have been due to differences in types of DM. *Dyck et al* who found a negative association amongst the elderly suggest that this may be caused by differential mortality occurring amongst those with DM of older age comparative to the elderly without DM.[270]

Evidence for variance in the association from a single study which stratified by specific ethnic groups has shown there to be higher risk amongst 'Whites' and Hispanics with DM for developing TB compared to those without DM than the risk amongst African American's with DM for developing TB compared to those without DM.[277][278] Again, due to the effect of ethnicity on risk of Developing DM and risk of developing TB alone this is something which needs further study.

A single study showed that homelessness and imprisonment is more common amongst those with TB and DM (Perez 1996[278]), and another study found that those with DM and TB were more likely to live in crowded households (Ponce de Leon 2004[279]). Although HIV is an important modifier of TB risk only one study (Farhoult-Jepsen 2011[271]) was able to look at the impact of HIV upon the measure of association between DM and TB finding that the risk of TB amongst those with DM became attenuated amongst individuals who also had HIV. Due to the importance of HIV as a risk factor for TB and thus as a strong competing factor it's affect upon the association between

TB and DM is also in need of further research. It was interesting to note that anti-retroviral use (known to cause metabolic syndrome) seemed to bare no relevance to the association between DM and TB.[271]

Four studies (Alisjahbana 2006[264], Baker 2012[265], Leegaard 2011[273] and Pablos-Mendez 1997[276]) looked at glucose control and how this modified estimates of TB risk amongst individuals with DM. All four studies identified an increase in TB risk for those with poor hyperglycaemic control either as judged by HbA1c measure or by number of existing DM complications although no testing for trend was completed.

1.4.2 Further findings from the semi-systematic review

As the search string for the completed semi-systematic review was purposefully broad many articles were incidentally returned that presented research upon the association between TB and DM but did not focus upon identifying the magnitude or directionality of the association. Further narrative discussion of these publications is given to place the analyses presented within this thesis in to the broader context of published research upon the association between DM and TB.

Numbers presenting with co-morbid TB and DM

The semi-systematic review identified three studies which focused upon estimating the impact of an association between DM and TB upon TB incidence (Ruslami 2010[58], Stevenson 2007[57] and Walker 2010[47]). In order to do this all three studies calculated the population attributable fraction (PAF) of TB due to DM utilising best estimates of; the association size, DM prevalence and TB incidence for specific regions.

Stevenson et al used data from India to make PAF calculations. These showed that up to 20.2% of smear-positive TB can be attributed to DM.[57]

Walker et al calculated PAF for the UK showing that the effects of an association between DM and TB would not be negligible in this setting especially amongst those already at an increased risk of TB due to their ethnicity.[47] Risk estimates for all ages varied showing that from 6.9% of incident TB (amongst white British) to 19.6% of incident TB (amongst those of asian ethnicity) could be attributed to DM.[47]

A publication by *Ruslami et al* outlined the estimated proportion of TB incidence attributable to DM in the ten countries with the highest incidence of TB; India (12.9%), China (7.8%), Indonesia (9.5%), Nigeria (7.6%), South Africa (8.7%), Bangladesh (11.2%), Ethiopia (4%), Pakistan (14.4%), the Philippines (12.9%) and the Democratic

Republic of Congo (5.2%) noting that these estimates would be expected to rise as DM prevalence increases.[58]

The semi-systematic review also identified a number of papers focusing upon the surrounding context of the association between TB and DM; these studies highlight the possible impact of the association given the numbers expected to present co-morbidly with TB and DM.

Unusual radiographic presentation amongst co-morbid individuals

There are a number of studies which have assessed the radiological presentation of TB amongst individuals with DM. As has been discussed, radiographic techniques are normally the initial diagnostic tool and sometimes the only tool used to diagnose active TB disease. If radiographic presentation is atypical amongst this group of individuals (those with co-morbid TB and DM) it is likely that they will go undiagnosed for longer periods of time than those with TB alone and perhaps suffer clinically as a consequence.

PTB is normally found predominantly in the lung apices, however, amongst individuals with DM this is thought not to be the case. There is a review published by *Sosman et al* which found that multilobular cavitary TB is more common in people with DM.[371] The semi-systematic review highlighted numerous studies which suggested that in individuals with co-morbid DM TB occurs predominantly in the lower lobes, with an increased number of multi-lobular cavities and increased prevalence of effusion.[30 253 371-379] However, there were also a number of publications identified that presented evidence contradictory to this. Studies carried out by *Nissapatorn et al* and *Prasad et al* discovered no difference in radiological findings between PTB patients with and without DM.[255 380] A study by *Perez-Guzman et al,* one of the largest studies identified with highest statistical power to detect differences in presentation between patient sub-groups, also finding no differences in the localisation of TB lesions in those with and without DM.[381]

It is of note that the majority of identified studies looking at the difference in radiographic presentation of TB amongst individuals with DM were completed within low to middle income countries where incidence rates of other co-morbidities which may affect presentation of TB are high (such as HIV). Within a westernised setting *Wilcke et al* show that only 8% of individuals with TB have 'unusual radiographic findings'. This perhaps suggests that if there is any impact from co-morbid DM on presentation of TB it is unlikely to be of importance within a setting such as the UK.[382]

As data published on the lung pathology of co-infected DM and TB patients is contradictory any evidence should be considered cautiously.[30] It would perhaps be of merit to consolidate the disparate studies on the presentation of TB amongst individuals with DM using systematic review techniques in order to more confidently assess whether there is a difference in TB presentation amongst those with and without TB.

Unusual presenting population, with unusual signs and symptoms

The semi-systematic review completed by the candidate also identified a number of studies which assessed the characteristics, signs and symptoms of TB amongst individuals with DM comparative to those without. As with atypical radiographic presentation, atypical presenting signs and symptoms amongst this unusual group of co-morbid individuals would probably mean increased chances of going undiagnosed for longer periods of time than those with TB alone. Again, this could perhaps lead to poor clinical consequences. Late TB diagnosis may also pose a public health problem as it could increase the risk of TB infection for others. As TB disease progresses undiagnosed the index case will have contact with an increased number of new individuals as well as increased repeat contact with a core group of people increasing chance of infection spread.

This semi-systematic review identified published evidence which suggested that the demographic characteristics of those presenting with TB differ significantly for those with and without co-morbidities.[96 109 110 383] Individuals with DM are thought to present with TB at an older age (normal peak incidence is in early adulthood)[30 96], are more likely to be female (TB is normally predominant in males) [30 378 383], have a higher BMI before and after treatment[59 384] and are less likely to present with EPTB.

Another study showed that TB symptoms and signs may differ amongst those with compared to without DM. A retrospective study by *Wang et al* found that patients with TB and DM showed higher frequencies of fever and haemoptysis, although findings were based upon self report of symptoms.[110] *Alladin et al* found symptoms suggestive of DM were not appreciably different between patients with PTB comparative to those without, with the exception of polyuria.[385] There seems to be relatively few studies that look at the symptoms of co-infected DM and TB patients, and with sparse data and contradictory findings further research upon whether TB symptoms and signs differ amongst those with and without DM is needed.

Effect of co-morbidity on TB management

The semi-systematic review also identified studies upon the decreased effectiveness of TB treatment amongst individuals with DM.

DM patients are thought to have impaired gastrointestinal drug absorption due to gastroparesis which may affect uptake and absorption of medication. A study by *Nijland et al* reported that Rifampicin is not absorbed as effectively in individuals with co-morbid TB and DM. Exposure to Rifampicin was 53% lower in Indonesian patients with TB and DM, compared with patients with TB only.[386] This could indeed be due to poor gastrointestinal uptake, or, to differences in metabolism, excretion and body weight amongst those with DM.[386] However it has also been highlighted within one study that individuals with DM and TB are less likely to adhere to their TB medication.[89] However, this finding is inconsistent with other work that demonstrates a lower proportion of co-morbid individuals defaulting on their TB treatment comparative to those with TB alone.[255] Whether these findings are of clinical relevance is debateable with a full evaluation of the efficacy of the Indian category 1 treatment regimen (recommended for all new smear positive TB cases) of the Revised National Tuberculosis Control Programme having been tested for use specifically amongst those with co-morbid DM and being found wholly appropriate.[387]

Effect of co-morbidity on DM management

It is known that certain TB drugs lead to intermittent hyperglycaemia. It is plausible that amongst those being treated for TB hyperglycaemia is occurring as a side effect of treatment with Rifampicin and Isoniazid[39-41], or, that the hyperglycaemia being observed is 'stress hyperglycaemia'[42,43] rather than being a true indication of metabolic dysfunction. Due to the known contra-indications of treatment for TB those with DM being treated for TB may need increased clinical surveillance to ensure tight blood glucose control.

DM and TB outcomes amongst individuals with co-morbid disease

A large number of studies were identified by the semi-systematic review that assessed TB outcomes amongst those with and without DM.

Specifically these studies seemed to have assessed risk of mortality, bacteriological clearance and radiographic clearance amongst co-morbid individuals compared to those with TB alone.[100,109,110,115,388]

Given the plausibility of a large proportion of new TB cases being amongst individuals with DM and of this group of individuals growing as DM incidence increases, any

adverse impact of having DM and TB (comparative to those with no DM) upon TB outcomes would be of serious concern.[57][58] Again however, publications upon this topic were sparse with contradictory findings.

1.5 Aims, hypotheses and objectives

1.5.1 Aims

The aims of this body of work were to:

Further elucidate the association between TB and DM within a UK context.

In particular, given evidence gaps within published literature, to assess the direction of the association and whether there is an association between all sub-types of DM and TB.

Given the incidental findings of the semi-systematic literature review a secondary aim became to assess and analyse available evidence on the potential impact of DM upon TB outcomes in comparison to outcomes amongst those with TB alone.

1.5.2 Hypotheses

Given the aims of this work the following hypotheses were addressed:

1) DM is associated with an increased risk of developing TB, PTB and, or, EPTB

2) T1DM is associated with an increased risk of developing TB, PTB and, or, EPTB

3) T2DM is associated with an increased risk of developing TB, PTB and, or, EPTB

4) TB is associated with an increased risk of developing DM, T1DM and, or, T2DM

5) PTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

6) EPTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

7) It is consistently documented that when TB and DM present concomitantly TB disease outcomes are significantly poorer

1.5.3 Objectives

In order to address these hypotheses the specific objectives of this thesis were to:

Use the ORLS database to elucidate the association between DM and TB within a subset of the UK national population by carrying out a set of retrospective cohort studies.

Use THIN database to elucidate the association between DM and TB within a nationally representative dataset by carrying out a set of retrospective cohort studies.

Produce a systematic review of the outcomes of TB amongst DM patients.

Chapter 2. Methods

2.1 Introduction to study design and data sources (testing hypotheses 1 to 6)

2.1.1 Retrospective (Historical) Cohort Studies

Retrospective (historical) cohort studies are a type of longitudinal research method where historical data upon individuals in a population both exposed and unexposed to a specific variable are followed over time to determine whether and in whom an outcome of interest occurs. Observations from such studies allow for statistical assessment of outcome occurrence in the exposed group compared to the unexposed group and thus measure of an association, if present, between the exposure and outcome.[389][390] The effect of other key variables upon the measure of association can also be accounted for by utilising specific statistical techniques.

Key reasons for choosing to use this study design for the completion of work presented as part of this thesis were the methods ability to demonstrate the temporality and thus direction of an association and to allow for analyses upon relatively rare outcomes with limited resources.[389][390]

2.1.2 Routine health data

The availability of data and adequacy for use testing specific hypotheses is integral to the validity of a retrospective cohort study. Both data sources used for work presented within this thesis are derived from routine health data.

Routine health data are datum derived from established data collection systems and are not normally collected with the aim of answering specific questions.[391] However, routine data can be utilised to produce health information for administrative, statutory, surveillance, or epidemiological purposes if suitable variables of interest have been collated in a non-biased manner.[391]

There is a wealth of routine data sources collated within the UK. The following examples highlight the breadth of data available: census and population registers, cancer registrations, health information systems, medical and hospital records, vital statistics, disease registry data, hospital episode data, primary care data, national immunization records, statutory notifications of infectious diseases, and communicable disease surveillance data.[391][392]

Not all routine data sources would be suitable to test the hypotheses made;

1) DM is associated with an increased risk of developing TB, PTB and, or, EPTB

2) T1DM is associated with an increased risk of developing TB, PTB and, or, EPTB

3) T2DM is associated with an increased risk of developing TB, PTB and, or, EPTB

4) TB is associated with an increased risk of developing DM, T1DM and, or, T2DM

5) PTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

6) EPTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

7) It is consistently documented that when TB and DM present concomitantly TB disease outcomes are significantly poorer

Data sources needed to either individually contain or contain once linked with other data sources longitudinally collated data at an individual level upon TB and DM status as well as information on an individual's demographic details and lifestyle characteristics.

For the retrospective cohort analyses presented in this thesis data from the ORLS database[393] [394] and THIN database,[395] has been utilised. A short overview of the routine data compiled in these databases and of the databases themselves has been given to contextualise the research methods chosen.

2.1.3 HES and the ORLS database

Routinely available data on secondary care in the UK is databased by Northgate Information Services on behalf of the National Health Services (NHS) Information Centre for Health and Social Care. This UK health data is known as Hospital Episode Statistics and came into being in 1987.[396]

HES are collected within all NHS secondary care facilities in England; acute hospitals, primary care trusts and mental health trusts. The HES database includes inpatient data from 1989 onwards and outpatient data from 2003 onwards. Also included is data upon care provided to NHS patients by the independent sector, including that taking place in treatment centres, and data upon care given to private patients in NHS hospitals.[396]

HES data is stored as a large collection of separate records for each period of care (financial year) and can be collated to give individual level longitudinal records of episodic secondary care.[396]

Each record contains information about; an individual patient such as age, gender and ethnicity, any clinical events they have such as diagnoses and operations, administrative information such as time waited and date of admission and geographical information such as treatment area and habiting area.[396]

As is perhaps somewhat obvious individuals often have more than one clinical event occurring upon a single hospital admission. These multiple clinical events are captured upon the single clinical event record by using duplicate fields in which to record event codes. There is a primary 'diagnosis' field in which the main reason for hospitalisation is coded alongside multiple secondary 'diagnoses' fields in which up to 13, six before 2002, other diagnoses relevant to the episode of care can be coded. These records are finalised by coding clerks, rather than the attending clinician, who review patient case notes in order to identify relevant codes for use.[396]

HES data is then centrally collated and undergoes comprehensive processing and validation before its release in order to maintain data quality.[396]

The ORLS Database

The ORLS database contains statistical records of all births, NHS hospital admissions, cancer registrations and all deaths occurring within defined populations in the former Oxford NHS region of England. It comprises two datasets, one for patient admissions between 1963 and 1998 ('ORLS1') and the second for patient admissions between 1999 and 2005 ('ORLS2') these datasets hold information for over 2 million people.[2 397]

Data for each patient was linked together routinely as it accrued within the region's health information systems and historic records are now anonymous and archived.[398]

Unfortunately due to changes in the NHS information system between 1998 and 1999 data in ORLS 1 cannot be linked with data in ORLS 2.[399]

The data within both ORLS databases has been assembled from routine NHS admission statistics (data similar to HES from 1963-87, and the actual HES system from 1988), and includes episodes of both day case and inpatient care. As with HES any individual with a record of hospital attendance has a coded reason for admission which has been assigned by a trained clinical coder utilising a structured hospital case note discharge abstract with diagnoses recorded by clinicians.[398] Relevant birth and death registration data have been linked to the ORLS databases from records in vital statistics registries regardless of where events occurred.[400]

The ORLS database does exclude private sector admissions although for the UK these admissions amount to a negligible proportion of delivered secondary care.[2 397]

Given the information present within the ORLS database (upon exposures, outcomes and basic confounders of interest for this work) and the individual level longitudinal nature of the health records created through data linkage it is suitable to use for

completion of a retrospective cohort study to elucidate the association between TB and DM. Of course the data sources suitability is not withstanding limitations and these are discussed later in this thesis.

2.1.4 GP data and THIN database

Within the UK a GP acts as the major frontline access point for patients to the NHS. They take the initial steps required to provide care for health problems an individual may have irrespective of disease type or personal and social characteristics. If needed, they will refer a patient to a specialist in the prevention, diagnosis, cure, care, and palliation of specific diseases.[401]

In the UK electronic recording of primary care data, information generated when a patient interacts with a GP during an appointment, occurred in the early 1980's long before the computerised recording of secondary care data. GP's maintain a complete longitudinal medical history of their registered patients and it is data from these records that makes up the entries within THIN database.[395]

THIN database

THIN database contains the electronic medical records of 6.9 million patients collated from the clinical systems of over 385 GP practices in the UK, covering approximately 5.7% of the total population in a representative manner.[395]

These routine health data are collected directly and at regular intervals from the management software of GP practices using a modem arrangement which does not interrupt the programmes running and requires no human intervention.[395 402] The data are then processed to provide coded longitudinal records of demographic details, lifestyle characteristics, medical events, prescriptions, specialist referrals, and any diagnostic or laboratory results occurring at an individual patient level. These records also contain information upon socio-economic markers such as Townsend scores, ethnic and environmental variables such as urban classification which have been derived from the 2001 census results and are linked to individuals via their home postcodes to output areas for these measures.[402]

THIN data are organised in relational database files. Data are separated by contributing GP and are shared with researchers arranged in four standardised and one linked file per practice.[402] The coded data are interpreted using ancillary look up tables and dictionaries in which medical events are coded using the Read system and prescriptions are coded using a Multi-lexical code alongside a British National formulary code. The

majority of codes assigned to an individual's records within primary care are done so by the consulting physician or healthcare professional, some data will be input by administrative staff such as GP managers.[402]

The information present in THIN database upon exposures, outcomes and basic confounders of interest for this work and the individual level longitudinal nature of the health records means it is also a suitable data source to use for completion of a retrospective cohort study to elucidate the association between TB and DM. Again however the suitability of THIN is not withstanding limitations and these are discussed later on in this thesis.

2.2 Methods used for analyses utilising ORLS data

This work was completed in collaboration with MG and CW as detailed in the theses acknowledgements section (pages iii-iv). To reiterate work completed was initiated and conceived by the candidate with guidance from MG. Initial analyses were carried out by CW and were re-ran when the candidate visited Oxford Universities Unit of Health Care Epidemiology. Interpretation of results was carried out by the candidate with guidance from MG and CW.

2.2.1 Objectives

Work carried out within the ORLS aimed to establish whether individuals with DM (of any sub-type) have an increased subsequent risk of developing TB (of any sub-type) and the magnitude of any such associations. Analyses were also completed to establish whether the converse of this is true. In doing so analyses completed with datasets from the ORLS database will test hypotheses 1-6 as outlined in section 1.5.2.

2.2.2 Ethical approval

Ethical approval for this work was covered by that granted for the full program of work which has been completed utilising the ORLS database. This was originally provided by the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

2.2.3 Definition of key variables

Within the ORLS database health events are presently and historically coded for using the ICD coding system contemporaneous for the time the health record was made. The ICD is a standard diagnostic classification system used worldwide for epidemiological, health management and clinical purposes. In particular, in the UK, ICD is used for disease classification on vital records including death certificates and health records which as discussed previously are the origin of the linked data within the ORLS database.

Individuals with records in the ORLS database were selected as having an exposure or outcome of interest if they had an event record containing a coding or proximate measure for a key variable as described.

DM: ICD7 260, ICD8 250, ICD9 250, ICD10 E10-E14.

T1DM is not distinguishable from T2DM in the codes presented within ICD7, 8 and 9. In order to be able to select for T1DM and T2DM as outcomes or exposures of interest

throughout the ORLS database age was used as a proximate variable for disease sub-type.

T1DM: People 30 years of age and below at the time of first recorded hospital care for DM (as identified by the pre-outlined DM codes).

T2DM: People over 30 years of age at the time of their first recorded hospital care for DM (as identified by the pre-outlined DM codes).

TB: ICD7 001-019, ICD8 010-019, ICD9 010-018, 137, ICD10 A15-A19, B90

Classification of TB codes by the candidate as either pulmonary or extra pulmonary was validated by a consultant physician in respiratory medicine.

PTB: ICD7 001-002, 003, 005-008, 019.1, ICD8 011-012, 018.1, 019.0, ICD9 011, 012, 018.0, 137.0, ICD10 A15, A16, A19, B90.9.

EPTB: ICD7 004, 010-018, 019.0, 019.2, ICD8 010, 013-017, 018.0, 018.9, 019.1-019.9, ICD9 010, 013-017, 018.8-018.9, 137.1-137.4, ICD10 A17, A18, B90.0-B90.8.

Individuals to be included in the reference cohort (made up of individuals with a diverse range of pre-specified minor disorders) were selected for using the Office of Population, Censuses and Surveys (OPCS) code edition 3 for operations alongside ICD9 codes (again with the equivalent contemporaneous ICD codes used for earlier and later time periods). **Reference Conditions:** OPCS Appendectomy 441, tonsillectomy 230, knee arthroplasty 812, hip arthroplasty 810, 811, ICD squint 378, otitis externa & otitis media 380-382, varicose veins 454, haemorrhoids 455, upper respiratory tract infections 460, deflected septum & nasal polyp 470-471, impacted tooth & other disorders of teeth 520-521, inguinal hernia 550, in growing toenail and other diseases of nail 703, sebaceous cyst 706.2, internal derangement of knee 717, bunion 727.1, selected fractures 810-816, 823-826, dislocations, sprains and strains 830-839, 840-848, superficial injury and contusion 910-919, 920-924.

2.2.4 Cohort construction

The overall study size was fixed by the size of the ORLS population and the number within meeting the inclusion criteria and the number of years for which data were available.

Cohorts were then constructed using the definitions for key variables as outlined in section 2.2.3. A reference cohort and six exposure cohorts (TB, PTB, EPTB, DM, T1DM and T2DM) were created to allow for outcome rate calculation.

Construction methods were comparative for each exposure cohort (DM, T1DM, T2DM, TB, PTB and EPTB). Cohorts were dynamic, with individuals being selected into an exposure cohort from the date of their first record on file for said exposure. First record of an exposure is representative of an individual's first admission, or episode of day care, for the condition in an NHS hospital.

A reference cohort was constructed by identifying the first admission for individuals with a diverse range of minor medical and surgical, conditions (using key variable codes as outlined 2.2.3). The use of a diverse range of conditions rather than a narrow range is standard epidemiological practice when using hospital data in case individuals selected into a non-exposed comparison group, here the reference cohort, are atypical in their risk of any outcome of interest. The reference cohort used is based on a 'reference' group of conditions that has been used in other similar studies of disease associations and dissociations within the ORLS database.[399 400 403]

To validate the use of the selected conditions within the reference cohort for this study the risk of each outcome amongst each reference condition was studied to ensure they did not have atypically high or low rates of studied outcomes.

Individuals who had a record for both an exposure condition and a reference condition were assigned to the exposure cohort and not the reference cohort.

Descriptive statistics were calculated for the main cohorts created although not for subgroups. The age and sex distribution for those with T1DM, due to the proximate measures used to identify them, would be equivalent to those within the DM cohort under the age of 30. For those with T2DM the same would be true although their age and sex distribution would match those within the DM cohort over the age of 30.

2.2.5 Outcome rate and rate ratio calculation

In order to estimate measures of association utilising data from the ORLS database a non-model, stratification based approach was used as has been previously utilised with ORLS data.[399 400 403]

The same methods were used for each set of analyses completed and thus to save repetition are outlined in the remainder of this section in a generic format where the terms outcome and exposure could be substituted with terms as relevant for any of the separate analysis completed in order to obtain the specific methods used. For example for the analyses assessing the risk of subsequent TB amongst those with DM the term outcome could be replaced with TB and the term exposure with DM.

The statistical software package Stata was used for all analyses.

Calculating standardised outcome rates amongst the exposure cohort and the reference cohort (unexposed)

In order to calculate an overall estimate of association using the ORLS data an estimate of outcome rates amongst the exposure cohort members and reference (unexposed) cohort members as they occurred over the study period was first calculated.

To calculate the standardised outcome rate in the exposure and reference cohorts based on person years at risk, entry date into each cohort was taken as the date of first admission for exposure or reference condition and the exit date for each individual was taken as either the date of subsequent admission for outcome, death, or 31st March 1999 (ORLS 1) or 31st March 2005 (ORLS2), whichever occurred first.

Rates were standardised by sex, age (in five year bands), calendar year of first recorded admission (in single years), and district of residence. This was done to ensure that the exposure and reference populations under comparison were equivalent by these variables. The combined exposure and reference cohorts were used as the standard population (internal standardisation).

Where records had missing values for any one of the stratification variables (age, sex, place of residence, or year of admission) they were excluded from the analysis however, data on each variable was missing from less than 1% of the records so less than 1% were excluded.

Standardisation was completed by calculating, within each age, sex, year, and district stratum, the rate of outcome per person years at risk in the standard population; and by applying this rate to the person years at risk in each equivalent stratum in each individual exposure and reference cohort. This gave an expected number of outcome events for each stratum in each cohort.

For each cohort the expected numbers of outcome events across all the strata were then summed and the summed expected figures were compared with the summed observed number. These were then expressed as an overall, standardised rate for each cohort by adjusting the ratio of the observed to the expected outcome event numbers by the crude rate of outcome events in the standard population.

Outcome rates in the reference cohort should approximate those in the general population of the region while allowing for migration in and out of it as data upon actual migration is not available.

Calculating rate ratios and statistical inferences

The ratio of the standardised rate of occurrence of outcome in the exposure cohort relative to that in the reference (unexposed) cohort was then calculated.

Each five year age group of exposed individuals was compared with all of the people within the reference cohort on file for that age group. This was done to increase statistical power and the precision of calculated estimates.

Calculated in this way, the RR provides a measure of relative risk of outcome in the exposure cohort, compared with the reference cohort.

The methods used to calculate RRs and statistical inferences were based upon methods which have been previously used for analyses within the ORLS[400 403] and were first outlined by Breslow and Day.[404] For further information on the Breslow and Day methodology please refer to appendix A.

P-values of less than 0.05 were taken as being statistically significance. However, as multiple comparisons have been made, exact p-values have been given so that the reader may assess the level of significance of each comparison.

Sensitivity analysis

Sensitivity analyses were completed in which people with an outcome within a year of a first admission for exposure were excluded from the dataset. This was done to assess whether Berksonian bias or surveillance bias were unduly affecting calculated risk estimates. Berksonian bias is a type of selection bias; a potential problem in hospital-based studies causing identification of spurious associations between diseases or characteristics due to differing probabilities of admission for those with the exposure, without the exposure and with an outcome of interest.

Sensitivity analyses were also completed to assess whether utilising exposure and outcome admissions recorded only within the primary position on a HES record comparative to those recorded within the secondary position or regardless of where recorded affected any association effects identified.

2.3 Methods used for analyses utilising THIN data

2.3.1 Objectives

Work carried out using data from THIN aimed to establish if individuals with DM (any sub-type) have an increased subsequent risk of developing TB (any sub-type) and the magnitude of any such associations. Analyses were also completed to establish if the converse of this is true. In doing so analyses completed with datasets from THIN database will re-test hypotheses 1-6 as outlined in section 1.5.2.

2.3.2 Ethical approval

Ethical approval for the study carried out using data from THIN database was granted by THIN Scientific Review Committee on the 15/10/2010 (see appendix B).

2.3.3 Definition of key variables

Key Variables for TB, PTB, EPTB, DM, T1DM and T2DM were defined using a combination of Read codes within multiple relevant fields within relational dataset files provided to the candidate by CSD-EPIC. There was a total of 265 codes relevant to a TB diagnosis, 479 codes relevant to a DM diagnosis (see appendices C and F). These codes were then subcategorised into ones which were indicative of disease sub-types. When the candidate was uncertain whether a code was representative of disease of a specific sub-type, or not, they were checked by either a consultant physician in respiratory medicine or by a diabetologist (see appendices D, E, G and H).

2.3.4 Data provision

Datasheets containing study denominator data were provided to the candidates specification and contained the standard THIN denominator data; the numbers of active individuals within THIN (with a patient flag of A or C, meaning their data was adequate for research use as deemed by CSD-EPIC) by each year between 2003 and 2009 aggregated by sex, five year age bands along with additional data upon smoking status (current smoker, previous smoker and non-smoker) and Townsend Quintile. The denominator data provided was essentially equivocal to count data.

As has been stated data upon individuals with DM and, or, TB was provided in relational database files. These were grouped by contributing GP and then arranged in four standardised and one linked file per practice.

2.3.5 Cohort construction

Our study population, the population at risk, was made up of all individuals in THIN database with active records between 2003 and 2009 that met THIN minimum data acceptability standards, that is, those within the database who had a patient flag of A or C showing their data as complete and acceptable for use in research as validated by the CSD-EPIC team.

When generating exposure cohorts for disease sub-types (DM, T1DM, T2DM, TB, PTB, EPTB) the populations were generated to include individuals within the population at risk with an appropriate Read code indicating an exposure event in either one of two medical code fields, within a relational medical record file (MRF) and an additional health data file (AHDF).

Other potential confounders of interest that it was possible to attain data upon and thus adjust for in THIN datasets were; age, sex, Townsend Quintile and smoking status (current smoker, past smoker, non-smoker). Data upon SES for each individual was taken from the appropriate fields within a relational postcode variable indicators file (PVIF). The PVIF records contain a value indicating into which quintile of postcodes with ascending levels of deprivation as measured by Townsend Index an individual's local area falls. Data upon smoking status was, as with exposure and outcome status, identified from Read codes in either of 2 medical code fields within the relational MRF and AHDF. The Read codes used to ascertain status as a current smoker, a past smoker or a non-smoker are outlined in appendix I.

Individuals with missing data for main variables of interest were excluded from datasets as (given the random pattern of missingness) it was deemed that this would not introduce any inherent biases to the analyses. The total number with missing data was negligible (<1%) except foe Townsend score where those with missing data were coded as 9 and included in statistical models.

Multiple recoding and collapsing of the original datasets was completed in order to produce numerator data comparable to the format in which denominator data had been supplied.

Cohort construction methods were comparative for each exposure cohort (DM, T1DM, T2DM, TB, PTB, and EPTB) and are described in a generic manner. Cohorts were dynamic, with individuals being selected into an exposure cohort from the date of their first record on file for said exposure between the years 2003 and 2009 as identified

using Read codes (as listed for each disease in appendices B, C D, E, G and H). In THIN data, first record of an exposure is representative of an individual's first diagnosis of a disease by a GP.

Files were then searched for a subsequent record of an outcome of interest. Unexposed cohorts were constructed from the provided denominator data files.

To account for Berksonian bias and surveillance bias anyone with; less than 1 year of follow up after their first exposure record, with a record of an outcome of interest recorded at the same time as their exposure record, or with a record of an outcome of interest within the first year following their exposure record was excluded in a sensitivity analysis.

Subjects entered the analysis period at their date of diagnosis and exited at the earliest of either date of death, de-registration with their GP or at the end of 31/12/2009 whichever was the last date of available data within the dataset.

The statistical software package Stata was used for all analyses.

Descriptive statistics for each cohort were calculated.

2.3.6 Choosing an appropriate regression technique

In order to estimate measures of association adjusted for multiple variables utilising data from THIN database it was decided that a model based approach to calculate effect estimates would be more appropriate than calculating RRs using a non-model based approach.

The most appropriate regression technique for analysing count data is Poisson regression.[405] However the Poisson model holds a rather strong assumption that the mean and variance are equal.[406] Overdispersion within THIN datasets would be the presence of greater variability (dispersion) than would be expected based on the assumptions of a Poisson model.[406] If overdispersion was present within THIN datasets it would be inappropriate to analyse them using Poisson regression.[406]

Checking for overdispersion
Thus, this assumption was checked by producing a histogram of outcome counts amongst all created THIN datasets, a histogram allows for a visual summary of the skewness and kurtosis of a dataset. The exact figures for each datasets skewness and kurtosis were calculated alongside the mean and variance using the statistical software package Stata and are also given. Skewness is a measure of symmetry which indicates statistically if the variance of a dataset is indeed equivocal to the mean.[407] Kurtosis is a

measure of whether a datasets peak is flat or relative to a normal distribution also assessing whether the dataset fits the expected properties of a normal distribution and whether it would thus be appropriately analysed using Poisson regression.[407] The expected values of skewness and kurtosis for a normally distributed dataset are 0 and 3 respectively.[407]

THIN datasets were identified as being highly skewed with many true zero counts (see section 3.2.3); as being overdispersed.

Given this, the data could undergo transformation in order to try and meet the normality assumption, but it may not be possible to normalise the data in this way and doing so would make the interpretation of any regression coefficients calculated difficult as they would no longer be estimated on their original scale.[408]

The modelling approach that would produce the most conceptually easy to interpret outcomes and be able to accommodate an increased frequency of true zero counts and overdispersion is the negative binomial regression.[409]

Negative binomial regression

Negative binomial regression is a generalisation of Poisson regression that accounts for overdispersion by including a 'disturbance' or 'error term'.[406] The functional form for the negative binomial regression model is given in equation 1.[406] Where λ_i is the expected value of the outcome variable y_i for subject i, x_i are the independent variables with corresponding regression coefficients β_n, and $\sigma\epsilon_i$ is the disturbance term.[406]

Equation 1

$$\text{Log } \lambda_i = \beta_0 + \beta_1\chi_{i1} + \beta_2 \chi_{i2} + \dots + \beta_k\chi_{ik} + \sigma\epsilon_i$$

All univariate and multivariate analyses were carried out using the negative binomial regression function, nbreg.

Univariate analysis was completed to see which of the variables being modelled, age sex, smoking and townsend quintile, were independently associated with TB in the largest dataset with data upon TB as an outcome. Univariate analysis was also completed to see which of the variables being modelled, age, sex, smoking and Townsend quintile, were independently associated with DM within the largest THIN dataset containing data upon DM as an outcome. Results were calculated as IRRs and the following statistical inferences are reported; the 95% CI and the P-value. P-values of less than 0.05 were taken as being statistically significance. However, as multiple

comparisons have been made, exact p-values have been given so that the reader may assess the level of significance of each comparison.

Multivariate analyses were completed to see whether DM and any sub-types of DM were associated with TB and any sub-types of TB, or the converse. The Stata nbreg command was used with relevant counts of disease set as the dependent variable and contributed person years set as the offset. Results were calculated as IRRs and the R^2 was taken as an indicator of model fit. If indicative of the wrong model having been fit the likelihood ratio test that alpha equals zero with its associated chi-squared value were reported (compares the use of the Negative binomial model to a Poisson model). Interaction effects were also tested for in case any of the variables in the multivariate models were representing either or all of the association found between the exposure and outcome variables.

2.4 Methods used for systematic review (testing hypothesis 7)

2.4.1 Overview

This systematic review aimed to exhaustively identify and synthesise data in a quantitative manner (as appropriate) from publications which reported a comparison of clinically relevant TB outcomes amongst individuals with and without co-morbid DM between Jan 1976 and September 2009.

2.4.2 Search strategy

More specifically the objectives of this review were to identify all literature reporting upon the following clinically relevant TB outcomes; culture or sputum conversion after initial treatment phase (2-3 months), sputum or culture conversion after treatment completion (>6 months), TB recurrence or relapse and all cause mortality amongst individuals with DM and TB comparative to those with TB.

Literature was comprehensively searched between 1976 and September 2009 within the 2 largest electronic biomedical databases MEDLINE® and EMBASE®. Searches were completed using the OvidSP search interface (Ovid MEDLINE® 1976- SEPTEMBER 2009 and EMBASE® 1976-SEPTEMBER 2009).

The search strategy used (see Table 7) contains both MESH terms and text word terms, (with the subfix .mp.) which identify studies with any mention of the searched term in the title or abstract or MESH terms, in order to identify all relevant studies whether catalogued under relevant terms or not. Special characters, search functions and Boolean Operators were used as in the semi-systematic review in chapter 1 in order to produce a succinct but thorough search strategy. The exp and the back slash within search strings 1 and 2 indicate that these strings used the explode command. In search strings 3 and 4 the truncation wildcard symbol * was utilised to minimise search strings needed. Strings 8 and 9 were completed using automated OvidSP limits and ENDNOTEXI functions.

Due to limited resources only English language publications were identified and retrieved.

Citations, including abstracts, returned from the completed searches were downloaded into ENDNOTEXI. Duplicated references were removed from the returned citations using the duplicate removal function in the ENDNOTE programme alongside hand search techniques.

Table 7: Equivalent search terms used within Medline and Embase

	Search String
1	Exp diabetes mellitus/
2	Exp tuberculosis/
3	Diabet*.tw.
4	Tuberculo*.tw.
5	1 or 3
6	2 or 4
7	5 and 6
8	Limit to English language (OvidSP)
9	Remove duplicates (ENDNOTE)

In an attempt to identify grey literature of relevance to the review the references lists of pertinent articles identified during abstract and full review were also searched.

2.4.3 Abstract review

Abstract review of all citations returned by the search was completed utilising a pre-specified abstract review form (see appendix J) and was completed by two independent investigators; FP and NU.

2.4.4 Inclusion and exclusion Criteria

The PICO (patient population, intervention, comparator, outcome) framework was used to guide development of inclusion and exclusion criteria which were used to screen articles for inclusion within the review.[410]

Inclusion

All studies reporting upon an outcome of interest as follows amongst those with and without TB, where both the denominator and numerator data was available for data extraction:

1) Sputum or culture clearance at 2-3 months after treatment initiation
2) Sputum or culture clearance more than 6 months after treatment initiation
3) Relapse or recurrence of TB and
4) All cause mortality

Studies including all adult participants (>18 years old) will be included, regardless of other biological and social characteristics.

Exclusion

Studies were excluded if they: were case studies or reviews, if they included individuals with HIV but did not make any adjustment to findings, if they assessed TB differently amongst those with and without DM, or, were re-reports of the same work.

2.4.5 Full review and data extraction

FP obtained full articles published on potentially relevant studies. At least two investigators (JC, NU, or FP) re-assessed study eligibility. Where disagreement on study inclusion occurred this was resolved by discussion between the investigators and where necessary authors were contacted in order to clarify any moot points. FP and either JC or NU extracted relevant data from included papers using a pre-specified data extraction form (appendix K). If data extraction forms for included studies showed disagreements these were resolved by discussion, or by contacting authors for clarification.

Data sections on the extraction form were completed detailing relevant descriptive information upon included studies such as: study date, setting, and design, how DM and TB were defined, numbers with TB and with co-morbid TB and DM included in the analyses. Data sections on the extraction form were also completed in order to assimilate data reported upon any relevant outcomes of interest.

2.4.6 Pre-specified analysis techniques

It was decided that descriptive data upon studies included in the review would be summarised using a standard summary of findings table as was used for the semi-systematic review in chapter 1.

Extracted quantitative outcome data was input into and analysed using the statistical software package Stata. This meant that any between study heterogeneity could be calculated as an I^2 value (where an I^2 of more than 0 indicates the level of heterogeneity present). Heterogeneity is when individual estimates of effect vary more than would be expected by chance alone.[244] Due to the likely disparate nature of the studies being searched for and the likely diversity in study quality it was decided a-priori that all analysis would be completed using a Mantel-Haenszel random effects meta-analysis (with 95% CI) weighting studies more equally relative to one another than a fixed effects analysis would.[244]

As with the semi-systematic review each paper was given a quality grade of 'low quality', 'unclear quality' or high quality' based upon the following criteria; study

design, setting, method of case ascertainment and confounders adjusted for. This grade was then used to produce an overall evidence quality grade, which gives the percentage of all studies graded as 'low quality', 'unclear quality' and 'high quality' to clearly outline the shortcomings of the entire body of evidence (see last row of Table 17).

Chapter 3. Results

3.1 ORLS analyses

3.1.1 Descriptive statistics

In the ORLS1 dataset there were 19,244 patients in the DM cohort, 6,997 in the TB cohort and 572,131 in the reference cohort. The mean age of entry to the DM cohort was 52 years, with an average follow up of 7.1 years. In the TB cohort the mean age at entry was 49 years and the average follow up was 11.2 years. In the reference cohort, the mean age at entry was 31 years, with an average period of follow up of 11.6 years.

In the ORLS2 dataset there were 7,943 patients in the DM cohort, 999 in the TB cohort and 230,085 in the reference cohort. The mean age of entry into the DM cohort was 51 years, with an average follow up of 3.2 years. In the TB cohort the mean age at entry was 46 years and the average follow up was 2.4 years. In the reference cohort, the mean age at entry was 39 years, with an average period of follow up of 3.5 years.

Age distributions for the ORLS1 and ORLS2 cohorts are given in Table 8.

Table 8: Age distributions at entry for the sub-populations in ORLS1 and ORLS2 with DM and TB

Age group distribution (yrs)	ORLS1				ORLS2			
	DM		TB		DM		TB	
	Number	% of total	Number of total	% of total	Number	% of total	Number	% of total
0-4	454	2.4	174	2.5	147	1.9	24	2.4
5-9	707	3.7	106	1.5	311	3.9	11	1.1
10-14	1,038	5.4	129	1.8	543	6.8	12	1.2
15-19	753	3.9	207	3.0	310	3.9	43	4.3
20-24	765	4.0	406	5.8	262	3.3	95	9.5
25-29	687	3.6	516	7.4	308	3.9	145	14.5
30-34	701	3.6	428	6.1	381	4.8	112	11.2
35-39	603	3.1	425	6.1	386	4.9	79	7.9
40-44	674	3.5	442	6.3	393	4.9	59	5.9
45-49	766	4.0	462	6.6	372	4.7	47	4.7
50-54	1,084	5.6	482	6.9	482	6.0	45	4.5
55-59	1,303	6.7	601	8.6	536	6.7	55	5.5
60-64	1,618	8.4	597	8.5	680	8.6	45	4.5
65-69	1,945	10.1	577	8.2	728	9.2	59	5.9
70-74	2,132	11.1	529	7.6	701	8.8	58	5.8
75-79	1,855	9.6	437	6.2	627	7.9	38	3.8
80+	2,159	11.2	479	6.8	776	9.8	72	7.2
Total	19,244		6,997		7,943		999	

The numbers of individuals with DM was much greater in both ORLS datasets for those aged 30 upwards comparative to those under the age of 30.

It can be seen within Table 8 that, for both the ORLS 1 and ORLS 2 dataset, numbers of individuals with TB are lower during childhood than adulthood.

3.1.2 Inferential Statistics

Risk of TB amongst those with DM

The risk of TB (all sub-types) was significantly greater amongst individuals with DM (all sub-types) than amongst those without DM in both the ORLS1 dataset (1963-98) and in the ORLS2 dataset (1999-05). The RRs were, respectively, 1.77 (95% CI 1.45-2.15, P-value <0.001) and 2.56 (95% CI 1.78-3.69, P-value <0.001), refer to Table 9.

The risk of PTB was significantly increased amongst individuals with DM (all sub-types) compared to those without DM (all sub-types) in both the ORLS1 and ORLS2. RRs 1.72 (95% CI 1.22-2.37, P-value <0.001) and 3.33 (95% CI 1.51-6.62, P-value 0.001) respectively, see Table 9.

In ORLS1 and ORLS2 there was no statistically significant association between DM (all sub-types) and subsequent risk of EPTB, refer to Table 9. It should be noted that the numbers in these analysis were very small and therefore may be affected by type II errors.

In ORLS1 there was no statistically significant association between T1DM and subsequent risk of TB, with a RR of 2.24 (95% CI 0.45-6.76, P-value 0.33). However, there was a statistically significant elevation of risk for TB after T2DM compared to no T2DM, with a RR of 1.58 (95%CI1.15-2.14, P-value 0.003).

In ORLS2 it was not possible to compare the rates of TB amongst those with and without T1DM due to the low numbers of individuals within this smaller dataset with T1DM. In the ORLS2, as in the ORLS1, there was a statistically significant increase in the risk of TB after T2DM compared to no T2DM (*RR* 3.60 (95% CI 1.76-6.76, P-value <0.001).

Table 9: RR*s*, 95%CI and P-values for the occurrence of TB amongst people with DM and the converse

Exposure condition	Outcome condition	Observed number in exposure cohort	Expected number in exposure cohort	Adjusted rate ratio (95% CI)[1]	P-value
ORLS1 (1963-1998)					
TB risk amongst individuals with DM					
DM	TB	131	81.0	1.77 (1.45-2.15)	<0.001
T1DM (<30)	TB	3	1.4	2.24 (0.45-6.76)	0.33
T2DM (30+)	TB	48	31.4	1.58 (1.15-2.14)	0.003
DM	PTB	42	25.4	1.72 (1.22-2.37)	0.001
DM	EPTB	10	8	1.27 (0.59-2.39)	0.59
DM risk amongst individuals with TB					
TB	DM	34	30.8	1.11 (0.76-1.55)	0.62
TB	T1DM (<30)	3	3.5	0.86 (0.18-2.54)	0.99
TB	T2DM (30+)	31	27.3	1.14 (0.77-1.63)	0.54
PTB	DM	21	23.3	0.90 (0.55-1.38)	0.70
EPTB	DM	13	8.6	1.51 (0.80-2.60)	0.18
ORLS2 (1999-2005)					
TB risk amongst individuals with DM					
DM	TB	59	32.1	2.56 (1.78-3.69)	<0.001
T1DM (<30)	TB	Numbers too small for meaningful analyses			
T2DM (30+)	TB	12	3.8	3.60 (1.76-6.76)	<0.001
DM	PTB	10	3.4	3.33 (1.51-6.62)	0.001
DM	EPTB	2	0.6	3.68 (0.41-15.4)	0.23
DM risk amongst individuals with TB					
TB	DM	18	13.0	1.39 (0.82-2.19)	0.21
TB	DM (<30)	Numbers too small for meaningful analyses			
TB	DM (30+)	2	0.7	3.00 (0.36-11.0)	0.31
PTB	DM	Numbers too small for analyses			
EPTB	DM				

[1]Adjusted for sex, age in 5-year bands, time-period in single calendar years and district of residence

Risk of DM amongst those with TB

There was no significant association between TB (all sub-types) and subsequent risk of DM (all sub-types), T1DM or T2DM in ORLS1 or ORLS2; see Table 9 for RR*s*, 95% CI, and P-values.

There was no statistically significant association between PTB or EPTB and subsequent DM risk in ORLS1 (see Table 9 for detail). Numbers in ORLS2 only allowed for meaningful analysis of risk of DM and risk of T2DM after TB, refer to Table 9.

Sensitivity Analyses

Conditions selected into the reference cohorts were checked in case they themselves had atypical risk of TB or DM. As grouped by condition, no individuals selected into the referent population upon examination had an atypical risk of TB, PTB, EPTB, DM, T1DM or T2DM.

Cases were also excluded dependent on the position of exposure health events on their HES records in order to ascertain whether having an exposure as a primary or secondary diagnosis changed the risk of developing an outcome of interest. No difference in effect estimates was found.

To account for potential Berksonian or surveillance biases cases with a diagnosis of an exposure of interest within a year of diagnosis of any outcome of interest were excluded. This did not affect most trends seen (see table 10), but did effect risk estimates calculated due to decreases in the overall numbers included in analyses.

Table 10: RR*s*, 95% CI and P-values for occurrence of TB in people with DM and the converse after excluding people who present with both diseases within a year

Exposure condition	Outcome condition	Observed number in exposure cohort	Expected number in exposure cohort	Adjusted rate ratio (95% CI)[3]	P-value
ORLS1 (1963-1998)					
TB risk amongst individuals with DM					
DM	TB	81	46.3	1.91 (1.48-2.44)	<0.001
T1DM (<30)	TB	Numbers too small for meaningful analyses			
T2DM (30+)	TB				
DM	PTB	27	15.6	1.80 (1.16-2.67)	0.005
DM	EPTB	9	4.8	1.98 (0.88-3.92)	0.008
DM risk amongst individuals with TB					
TB	DM	105	140.7	1.00 (0.82-1.22)	0.99
TB	T1DM (<30)	Numbers too small for meaningful analyses			
TB	T2DM (30+)				
PTB	DM	19	20.7	0.92 (0.55-1.43)	0.79
EPTB	DM	12	8.1	1.49 (0.77-2.60)	0.23
ORLS2 (1999-2005)					
TB risk amongst individuals with DM					
DM	TB	25	15.9	1.93 (1.12-3.27)	0.013
DM (<30)	TB	Numbers too small for meaningful analyses			
DM (30+)	TB				
DM	PTB	6	2.5	2.63 (0.91-6.30)	0.05
DM	EPTB	Numbers too small for analyses			
DM risk amongst individuals with TB					
TB	DM	9	5.10	1.77 (0.81-3.37)	0.13
TB	DM (<30)	Numbers too small for meaningful analyses			
TB	DM (30+)				
PTB	DM				
EPTB	DM				

[1]Adjusted for sex, age in 5-year bands, time-period in single calendar years and district of residence

After excluding cases that had an outcome of interest within a year of being diagnosed with an exposure of interest within both the ORLS1 and ORLS 2 datasets statistically significant increases in risk of TB and PTB after DM in ORLS1 and ORLS2 still remained although point estimates were reduced, see Table 10. However, now a statistically significant increase in the risk of EPTB compared to no EPTB after DM was seen within ORLS 1 (RRs 1.98 (95% CI 0.88-3.92, P-value 0.008)). It should be noted that due to the exclusion of cases this sensitivity analysis contained very small numbers and therefore may show type I errors. Risk of DM after TB compared to no TB in both ORLS1 and ORLS2 remained to show no statistically significant association as did risk of DM after PTB and EPTB within ORLS1.

3.2 THIN analyses

3.2.1 Descriptive statistics

Within THIN dataset there were 224,508 individuals in the DM cohort, in the T1DM cohort 44,874, in the T2DM cohort 193,929, in the TB cohort 5,470, in the PTB cohort 1,589 and in the EPTB cohort 1,006. The mean age of entry into the DM cohort was 60 years, T1DM cohort 51 years, T2DM cohort 62 years, TB cohort 48 years, PTB cohort 53 years and EPTB cohort 47 years respectively. Average follow up for each cohort was 4.1 years, 4.8 years, 4.2 years, 3.7 years, 3.7 years, and 4 years respectively.

Sex, age, SES and Smoking distribution for the DM cohorts are given in Table 11 and for the TB cohorts are given in Table 12.

Table 11: Sex, Age, SES and Smoking distribution within the DM, T1DM and T2DM cohort

Cohort		DM		T1DM		T2DM	
Variable	**Categories**	**N (224,508)**	**% of total**	**N (44,874)**	**% of total**	**N (193,929)**	**% of total**
Sex	**Male**	123,264	54.9	24,771	55.2	106,760	55.1
	Female	101,244	45.1	20,103	44.8	87,169	44.9
Age Group	**0-15**	3,045	1.3	2,739	6.1	201	0.1
	16-30	8,696	3.9	5,686	12.6	2,975	1.5
	31-45	29,576	13.1	9,027	20.1	22,241	11.5
	46-60	63,977	28.5	10,716	23.9	57,921	29.9
	61-75	80,235	35.7	11,995	26.7	74,999	38.7
	76+	38,979	17.4	4,751	10.6	35,592	18.3
Towensend Quintile	**1**	45,608	20.3	9,150	20.4	39,012	20.1
	2	44,518	19.8	8,697	19.4	38,553	19.9
	3	45,121	20.1	9,095	20.3	39,120	20.2
	4	43,283	19.3	8,724	19.4	37,702	19.4
	5	32,502	14.5	6,500	14.5	28,238	14.6
Smoker	**Yes**	62,288	27.7	13,231	29.5	54,514	28.1
	Past	119,619	53.3	21,430	47.8	106,377	54.9
	No	42,601	19.0	10,213	22.8	33,038	17.0

The prevalence of DM in THIN dataset is highest amongst males. The prevalence of TB and of DM increases with age, however, there is no spike in DM prevalence at age 14 years within THIN dataset as there is in the ORLS dataset.

Table 12: Sex, Age, SES and Smoking distribution within the TB, PTB and EPTB cohort

Cohort		TB		PTB		EPTB	
Variable	Categories	N (5,470)	% of total	N (1,589)	% of total	N (1,006)	% of total
Sex	Male	2,698	49.3	856	53.9	440	43.7
	Female	2,772	50.7	733	46.1	566	56.3
Age Group	0-15	394	7.2	68	4.2	67	6.7
	16-30	1,035	19	236	14.9	174	17.4
	31-45	375	19.3	78	16.4	239	23.8
	46-60	1,109	20.3	328	20.7	211	21.1
	61-75	1,268	23.2	473	29.8	226	22.6
	76+	584	10.7	219	13.8	85	8.5
Towensend Quintile	1	774	14.1	210	13.2	152	15.1
	2	800	14.6	234	14.7	136	13.5
	3	1,017	18.6	280	17.6	216	21.5
	4	1,193	21.8	376	23.7	221	22.0
	5	1,252	22.9	364	22.9	212	21.1
Smoker	Yes	1,449	26.5	420	26.4	254	25.2
	Past	2,236	40.9	781	49.2	410	40.8
	No	1,785	32.6	388	24.4	342	34.0

3.2.3 Testing for over-dispersion

Poisson models are the standard regression method used to model count response data however as previously discussed they have a very strong theoretical assumption; that the conditional variance of the outcome variable is equal to the conditional mean. Due to the nature of the data being analysed over-dispersion was suspected amongst every single compiled dataset from THIN database; testing to see if this Poisson assumption held was completed. For all analyses graphing of outcome counts showed that data was skewed and does not approximate a normal distribution as outlined by a plotted normal distribution curve (see Appendix L). Summary statistics for each analyses completed showed that the mean was not equivalent to the variance with Skewness figures far from zero and Kurtosis figures far from 3 indicative of over-dispersion within each dataset (see Table 13).

Table 13: Tests for over-dispersion within THIN cohorts

Exposure	Outcome	Mean	Variance	Skewness	Kurtosis	Over-dispersion Present
DM	TB	1.047	9.66	4.9	33.91	Yes
T2DM	TB	0.61	3.71	5.96	54.05	Yes
T1DM	TB	0.59	3.66	6.01	55.08	Yes
DM	PTB	0.15	0.31	6.11	61.30	Yes
T2DM	PTB	0.16	0.33	5.95	58.13	Yes
T1DM	PTB	0.15	0.32	6.16	61.25	Yes
DM	EPTB	0.10	0.20	6.25	55.08	Yes
T2DM	EPTB	0.10	0.20	6.25	55.08	Yes
T1DM	EPTB	0.11	0.21	6.23	54.34	Yes
TB	DM	28.18	7,005.99	6.05	51.11	Yes
PTB	DM	32.14	7,919.02	5.65	44.90	Yes
EPTB	DM	33.71	8,273.25	5.51	42.86	Yes
TB	T1DM	13.18	1,049.72	4.06	23.48	Yes
PTB	T1DM	15.06	1,172.09	3.77	20.69	Yes
EPTB	T1DM	5.34	172.461	4.56	30.44	Yes
TB	T2DM	26.21	6,635.80	6.12	51.80	Yes
PTB	T2DM	29.86	7,501.93	5.71	45.49	Yes
EPTB	T2DM	31.30	7,835.97	5.58	43.43	Yes

3.2.2 Inferential Statistics

Univariate analyses were completed using negative binomial regression to ascertain which of the independent variables had a direct relationship with the dependent variable amongst the datasets created within THIN database.

There were no significant associations between TB risk and sex.

Risk of TB was significantly higher amongst those aged 21-40 years comparative to those under the age of 20 years (IRR 1.38 (95% CI 1.12-1.69, P-value 0.002)), see Table 14.

TB risk decreased with Townsend score i.e. was lowest for those of highest SES. Comparative to a Townsend score of 1 a Townsend score of 2 (IRR 0.29 (95% CI 0.24-0.36, P-value <0.001)), 3 (IRR 0.35 (95% CI 0.29-0.43, P-value <0.001)), 4 (IRR 0.44 (95% CI 0.36-0.52, P-value <0.001) and 5 (IRR 0.58 (95% CI 0.48-0.69, P-value <0.001)) was significantly associated with lower risk of developing TB, see Table 14.

Risk of TB was also significantly increased for past smokers (IRR 2.37 (95% CI 2.06-2.72, P-value <0.001)) and current smokers (IRR 1.70 (95% CI 1.47-1.98, P-value <0.001)) in comparison to non-smokers.

Table 14: Baseline characteristics associated with TB risk within THIN

Individual's baseline characteristics	Categories	Outcome	IRR (95% CI)[1]	P-value
Risk of TB following DM				
Sex	Male	TB	1	
	Female		0.95 (0.84-1.08)	0.445
Age	0-20	TB	1	
	21-40		1.38 (1.12-1.69)	0.002
	41-60		0.96 (0.78-1.18)	0.685
	61-80		1.18 (0.96-1.46)	0.114
	81+		0.95 (0.68-1.32)	0.741
Townsend	1 (Most Deprivation)	TB	1	
	2		0.29 (0.24-0.36)	<0.001
	3		0.35 (0.29-0.43)	<0.001
	4		0.44 (0.36-0.52)	<0.001
	5 (Least Deprivation)		0.58 (0.48-0.69)	<0.001
Smoking	Non-Smoker	TB	1	
	Past Smoker		2.37 (2.06-2.72)	<0.001
	Current Smoker		1.70 (1.47-1.98)	<0.001

There was a significant decrease in DM risk amongst women compared to men (IRR 0.87 (95% CI 0.77-0.98, P-value 0.024)), see Table 15.

DM risk increased with age. Comparative to those under the age of 20 years those aged 41-60 years (IRR 4.77 (95% CI 3.92-5.80, P-value <0.01)), 61-80 years (IRR 8.06 (95% CI 6.63-9.80, P-value <0.01)) and 81 years and over (IRR 3.94 (95% CI 3.03-5.13, P-value <0.01)) were at a significantly higher risk of developing DM, see Table 15.

DM risk was not significantly associated with Townsend score, all IRRs reported were near to 1 and P-values were above 5%.

Risk of DM significantly increased for past smokers (IRR 4.47 (95% CI 4.00-5.00, P-value <0.001) and current smokers (IRR 8.59 (95% CI 7.70-9.57, P-value <0.001)) in comparison to non-smokers.

Table 15: Baseline characteristics associated with DM risk within THIN

Individual's baseline characteristics	Categories	Outcome	IRR (95% CI)[1]	P-value
		Risk of DM following TB		
Sex	Male	DM	1	
	Female		0.87 (0.77-0.98)	0.024
Age	0-20	DM	1	
	21-40		0.98 (0.80-1.20)	0.873
	41-60		4.77 (3.92-5.80)	<0.01
	61-80		8.06 (6.63-9.80)	<0.01
	81+		3.94 (3.03-5.13)	<0.01
Townsend	1 (Most Deprivation)	DM	1	
	2		1.01(0.82-1.25)	0.900
	3		1.10 (0. 90-1.36)	0.360
	4		1.15 (0.93-1.42)	0.190
	5 (Least Deprivation)		1.09 (0.89-1.35)	0.370
Smoker	Non Smoker	DM	1	
	Past Smoker		4.47 (4.00-5.00)	<0.001
	Current Smoker		8.59 (7.70-9.57)	<0.001

In order to sufficiently model the association between TB and DM, and the converse, multivariate analysis was performed to take into account the effect of multiple predictor variables simultaneously upon outcomes of interest. Specifically, multivariate negative binomial regression was conducted.

In THIN dataset the risk of TB (all sub-types) was found to be significantly increased amongst individuals with DM (all sub-types), T1DM and T2DM when compared to those without. The IRR of TB (all sub-types) was significantly increased amongst individuals with DM (all sub-types) (IRR 1.50 (95%CI 1.27-1.76) P-value <0.001), T1DM (IRR 1.46 (95%CI 1.10-1.92) P-value 0.008) and T2DM (IRR 1.54 (95%CI 1.30-1.82) P-value < 0.001) compared to those without DM.

The rate of PTB amongst individuals with DM (all sub-types) (IRR 1.237 (95%CI 0.93-1.64), P-value = 0.137), T1DM (IRR 1.30 (95% CI 0.79-2.16), P-value = 0.303), or T2DM (IRR 1.24 (95% CI 0.92-1.67), P-value = 0.152), compared to those without DM were not significantly raised.

The rate of EPTB was raised significantly amongst those with T1DM (IRR 2.09 (95%CI 1.19-3.66), P-value 0.010) but was not significantly raised amongst those with DM (all sub-types) (IRR 1.43 (95% CI 0.99-2.07), P-value 0.055) or those with T2DM (IRR 1.39 (95%CI 0.93-2.06), P-value 0.11) when compared to those without DM.

However, it should be noted that the P-value for EPTB amongst those with DM tended towards significance and may be being affected by type II errors.

Table 16: IRRs, 95%CI and P-values for the occurrence of TB amongst people with DM

Exposure condition	Outcome condition	Unadjusted IRR (95% CI)	P-value	Adjusted IRR (95% CI)[1]	P-value	PseudoR^2
Risk of TB following DM						
DM	**TB**	1.619 (1.367-1.917)	< 0.001	1.50 (1.27-1.76)	<0.001	0.08
T1DM	**TB**	1.692 (1.275-2.245)	<0.001	1.455 (1.104-1.917)	0.008	0.09
T2DM	**TB**	1.654 (1.384-1.975)	<0.001	1.536 (1.296-1.822)	<0.001	0.08
DM	**PTB**	1.735 (1.299-2.316)	<0.001	1.237 (0.934-1.638)	0.137	0.10
T1DM	**PTB**	1.844 (1.106-3.074)	0.019	1.304 (0.787-2.160)	0.303	0.11
T2DM	**PTB**	1.747 (1.288-2.368)	<0.001	1.243 (0.923-1.673)	0.152	0.10
DM	**EPTB**	1.561 (1.088-2.240)	0.016	1.434 (0.993-2.071)	0.055	0.05
T1DM	**EPTB**	2.428 (1.385-4.256)	0.002	2.088 (1.190-3.664)	0.010	0.06
T2DM	**EPTB**	1.514 (1.028-2.230)	0.036	1.388 (0.934-2.062)	0.105	0.05

[1]Adjusted for age, sex, region, Townsend score and smoking status

In THIN dataset the rates of DM (all sub-types), T1DM and T2DM were found to be significantly raised amongst those who have had TB (all sub-types), PTB and EPTB when compared to those who have not had TB (all sub-types), PTB and EPTB.

The rate of DM (all sub-types) was significantly increased amongst those who had had TB (all sub-types) (IRR 5.65 (95% CI 5.19-6.16) P-value <0.001), amongst those who had had PTB (IRR 5.74 (95% CI 5.08-6.50) P-value <0.001) and amongst those who had had EPTB (IRR 4.66 (95% CI 3.94-5.51) P-value <0.001) when compared to those who had not had TB.

The rate of T1DM was significantly increased amongst those who had had TB (all sub-types) (IRR 5.49 (95% CI 5.02-6.02) P-value <0.001), amongst those who had had EPTB (IRR 0.84 (95% CI 0.35-2.03) P-value <0.001) but was not significantly raised amongst those who had had PTB (IRR 1.09 (95% CI 0.62-1.93) P-value 0.77) when compared to those who had not had TB.

The rate of T2DM was significantly increased amongst those who had had TB (all sub-types) (IRR 2.21 (95% CI 1.68-2.91) P-value <0.001), amongst those who had had PTB

(IRR 5.38 (95% CI 4.73-6.12) P-value <0.001) and amongst those who have had EPTB (IRR 4.36 (95% CI 3.65-5.22) P-value <0.001) when compared to those who have not had EPTB.

Table 17: IRRs, 95%CI and P-values for the occurrence of DM amongst people with TB

		Risk of DM following TB				
Exposure condition	Outcome condition	Unadjusted IRR (CI)	P-value	Adjusted IRR (CI)[1]	P-value	PseudoR^2
TB	DM	6.384 (5.693-7.159)	<0.001	5.651 (5.185-6.159)	<0.001	0.16
TB	T1DM	6.668 (5.876-7.566)	<0.001	5.491(5.019-6.020)	<0.001	0.19
TB	T2DM	2.103 (1.582-2.797)	<0.001	2.212 (1.684-2.906)	<0.001	0.12
PTB	DM	8.026 (6.896-9.342)	<0.001	5.740 (5.077-6.490)	<0.001	0.16
PTB	T1DM	1.591 (0.893-2.835)	0.115	1.088 (0.616-1.930)	0.772	0.13
PTB	T2DM	8.130 (6.880-9.608)	<0.001	5.382 (4.730-6.124)	<0.001	0.19
EPTB	DM	5.416 (4.460-6.577)	<0.001	4.659 (3.940-5.509)	<0.001	0.15
EPTB	T1DM	1.025 (0.423-2.483)	0.956	0.843 (0.349-2.034)	<0.001	0.13
EPTB	T2DM	5.427 (4.385-6.716)	<0.001	4.364 (3.649-5.218)	<0.001	0.18

[1]Adjusted for age, sex, region, Townsend score and smoking status
Adjusted results

Testing for interaction effects: TB to DM

Upon testing for interaction effects whilst exploring the relationship seen between risk of DM following TB a large, statistically significant interaction was seen between age and TB as displayed within Table 18.

Table 18: Test of the interaction effect between age and TB, IRR (95% CI) and P-values

Exposure	Outcome	Interaction Effect		IRR (95% CI)	P-value
TB	DM	Age	0-20	1	
			21-40	11.54 (1.58-84.17)	0.016
			41-60	20.27 (2.82-145.49)	0.003
			61-80	21.14 (2.95-151.57)	0.002
			80+	17.89 (2.43-131.59)	0.005
R^2				0.17	

3.3 Systematic review findings

3.3.1 Summary of studies identified and included in full review

Table 19 displays the number of citations returned by each search string carried out as part of the full search strategy.

Table 19: Search strategy used to identify papers reporting upon TB and DM with a view to identifying papers including data on TB outcomes

Search	MEDLINE Hits	EMBASE Hits
Exp diabetes mellitus/	229,502	379,224
Exp tuberculosis/	129,184	165,413
Diabet*.mp.	308,584	402,511
Tuberculo*.mp.	134,652	143,762
1 or 3	368,086	502,113
2 or 4	164,236	198,365
5 and 6	985	2,101
English Language (OvidSP)	879	1,986
Remove duplicates (ENDNOTE)	1, 868	

After abstract review 116 papers were identified as likely to contain data upon TB outcomes amongst those with and without DM. These papers were retrieved in full by the candidate and searched for relevance with a decision being made on inclusion in the full review by 2 independent investigators (FP and either NU or JC).

Upon full review twenty five studies were identified as including relevant data for extraction. These were then searched for specific information using a pre-specified data extraction form (Appendix L).

Specifically data on the following was extracted:

1) All cause mortality
2) Bacterial clearance at 2-3 months (culture results included preferentially to sputum smear)
3) Bacterial clearance at >6 months (again with culture results included preferentially to sputum smear)
4) Re-occurrence of TB

Table 20 summarises the detail of the 25 studies including most notably the study design, the way in which case ascertainment was made and the outcomes of interest upon which each paper reported.

In this review 7 studies described as prospective cohort studies (Alisjahbana 2007[59], Ambrosetti 1999 (1995)[411], Ambrosetti 1999 (1996)[412], Ambrosetti 1999 (1997)[413], Centis 2000[414], Centis 2002[415] and Ponce de Leon 2004[279]) were identified, 16 described as retrospective cohort studies (Banu-Rekha 2007[416], Chiang 2009[115], Dooley 2009[60], Fielder 2002[417], Fischer Hoch 2008[252], Guler 2007[418], Hasibi 2008[419], Matthew 2006[420], Oursler 2002[421], Singla 2003[62], Singla 2006[422], Subhash 2003[423], Tatar 2009[111], Vasankari 2009[424], Wang 2001[425] and Wang 2009[110]) and two (Bashar 2001[251] and Kourbatova 2006[426]) as retrospective case control studies.

Only three studies identified both TB and DM status using standard diagnostic testing (Alisjahbana 2007[59], Singla 2003[62] and Singla 2006[422]), the rest utilised a mix of self report or MRR.

The majority of the studies were completed within high income countries (13; Ambrosetti 1999 (1995)[411], Ambrosetti 1999 (1996)[412], Ambrosetti 1999 (1997)[413], Bashar 2001[251], Centis 2000[414], Centis 2002[415], Chiang 2009[115], Dooley 2009[60], Fielder 2002[417], Fischer Hoch 2008[252], Oursler 2002[421], Singla 2003[62], Singla 2006[422], Vasankari 2009[424], Wang 2001[425] and Wang 2009[110]) with 9 completed in middle to low income countries (Alisjahbana 2007[59], Banu-Rekha 2007[416], Guler 2007[418], Hasibi 2008[419], Kourbatova 2006[426] Matthew 2006[420], Ponce de Leon 2004[279], Subhash 2003[423] and Tatar 2009[111]).

Only four of the studies were completed in countries with a high incidence of TB (Banu-Rekha 2007[416], Kourbatova 2006[426], Subhash 2003[423] and Matthew 2006[420]). Twenty of the studies reported upon all cause mortality, six gave numbers with sputum conversion at 2-3 months, only 1 at 6 months and four studies reported upon recurrence or relapse of TB, as indicated in Table 20. The majority of the studies identified, as graded by the pre-specified criteria, were of a 'poor' quality (see Table 20).

Table 20: Summary of findings table showing the characteristics of identified studies

First Author & Year Published	Setting & Study Date	Study Design	DM Definition Used	TB Definition Used	Outcomes of Interest Reported
Alishjahbana 2007[59]	Indonesia, 1998-2002	Prospective cohort	FBG>126 mg/dl at 2 different time points	PTB: Clinical & radiological symptoms & a positive smear	1, 2 and 3
Ambrosetti 1999 (1995)[411]	Italy, 1995	Prospective cohort	MRR	TB: histological findings of AFB, or positive culture or smear	1
Ambrosetti 1999 (1996)[412]	Italy, 1996	Prospective cohort	MRR	TB: histological findings of AFB, or positive culture or smear	1
Ambrosetti 1999 (1997)[413]	Italy, 1997	Prospective cohort	MRR	TB: histological findings of AFB, or positive culture or smear	1
Banu-Rekha 2007[416]	India, 1998-2002	Retrospective analyses	MRR and FBG	PTB: Radiological symptoms and positive culture or smear	2
Bashar 2001[251]	USA, 1987-1997	Retrospective case control	Previously diagnosed DM, MRR	TB: Record review for culture results	1
Centis 2000[414]	Italy, 1998	Prospective cohort	MRR	TB: Positive culture or smear	1
Centis 2002[415]	Italy, 1999	Prospective cohort	MRR	TB: Positive culture or smear	1
Chiang 2009[115]	Taiwan, 2003	Retrospective cohort	MRR	PTB: Positive culture or smear	1
Dooley 2009[60]	USA, 2004-2005	Retrospective cohort	MRR & taking DM medication or non-FBG> 200g/dl	TB: Positive culture	1 and 2
Fielder 2002[417]	USA, 1993-1998	Retrospective cohort	MRR	PTB: Positive smear	1
Fischer Hoch 2008[252]	USA-Mexico border, 1996-2002	Retrospective cohort	Self Report	TB: Positive culture or smear	1 and 4
Guler 2007[418]	Turkey, 2000-2005	Retrospective cohort	MRR	PTB: Positive smear	2

Hasibi 2008[419]	Iran, 1999-2006	Retrospective cohort	MRR	Disseminated TB, clinically & microbiologically diagnosed	1
Kourbatova 2006[426]	Russia, 1995-2001	Retrospective case control	MRR	TB: clinical symptoms, chest x-ray or positive culture or smear	1
Matthew 2006[420]	Russia, 2002-2003	Retrospective cohort	MRR	PTB: clinical, radiological or microbiological evidence	1
Oursler 2002[421]	USA 1994-1996	Retrospective cohort	MRR	TB: Fingerprinting with Restriction Fragment Length Polymorphism	1
Ponce de Leon 2004[279]	Mexico, 1995-2003	Cohort	MRR Non-FBG> 200g/dl or FBG>126 mg/dl	TB: Positive culture or fingerprinting with Restriction Fragment Length Polymorphism	1
Singla 2003[62]	Saudi Arabia, 1998-1999	Retrospective cohort	Fasting Plasma Glucose >140mg/dl at 2 time points	PTB: Positive smear or culture	2[*]
Singla 2006[422]	Saudi Arabia, 1998-1999	Retrospective cohort	Fasting Plasma Glucose >140mg/dl at 2 time points	PTB: Positive smear or culture	1, 2 and 4
Subhash 2003[423]	India, 1997-1999	Retrospective chort	MRR and medication review or Non-FBG> 140mg/dl	TB: Positive culture	4
Tatar 2009[111]	Turkey, 1997-2003	Retrospective cohort	MRR	TB: Positive Smear or Culture	1 and 2
Vasankari 2009[424]	Finland, 1995-1996	Retrospective cohort	DM medication use	PTB: Positive culture	1
Wang 2001[425]	Taiwan, 1996-1999	Retrospective cohort	MRR	PTB: Radiological findings, clinical suspicion or microbiological evidence	4
Wang 2009[110]	Taiwan, 2003-2006	Retrospective cohort	Medical history and treatment	PTB: Culture or smear positive	1
Overall Quality of Evidence[364]					

[*]Findings re-published alongside further data in Singla 2006[422]

3.3.2 Statistical synthesis of extracted data

Data upon mortality, bacterial clearance at 2-3 months, 6 months and relapse or recurrence was extracted from each paper in its most basic format; as numbers with an outcome of interest amongst the non-exposed (TB alone) and the exposed (Co-morbid TB and DM). This information is given below in Table 21.

Table 21: Data extracted from identified studies upon TB outcomes of interest

First Author & Year Published	All Cause Mortality		No Bacterial Clearance at				Relapse or Recurrence	
			2-3 months		> 6months			
	TB	TB & DM	TB	TB & DM	TB	TB & DM	TB	TB & DM
Alishjahbana 2007[59]	0/540	2/94	68/372	7/41	32/333	6/27	-	-
Ambrosetti 1999 (1995)[411]	29/737	3/32	-	-	-	-	-	-
Ambrosetti 1999 (1996)[412]	19/773	4/50	-	-	-	-	-	-
Ambrosetti 1999 (1997)[413]	1/40	43/667	-	-	-	-	-	-
Banu-Rekha 2007[416]	-	-	10/68	8/69	-	-	-	-
Bashar 2001[251]	1/105	7/50	-	-	-	-	-	-
Centis 2000[414]	49/1059	5/41	-	-	-	-	-	-
Centis 2002[415]	26/852	2/40	-	-	-	-	-	-
Chiang 2009[115]	137/886	52/241	-	-	-	-	-	-
Dooley 2009[60]	20/255	6/42	9/30	50/163	-	-	-	-
Fielder 2002[417]	29/152	13/22	-	-	-	-	-	-
Fischer Hoch 2008[252]	112/1022	46/391	-	-	-	-	20/115	14/47
Guler 2007[418]	-	-	88/262	32/44	-	-	-	-
Hasibi 2008[419]	3/6	6/44	-	-	-	-	-	-
Kourbatova 2006[426]	87/440	5/20	-	-	-	-	-	-
Matthew 2006[420]	75/1872	8/44	-	-	-	-	-	-
Oursler 2002[421]	14/108	8/18	-	-	-	-	-	-
Ponce de Leon 2004[279]	61/409	34/172	-	-	-	-	-	-
Singla 2006[422]	3/505	1/187	45/486	30/185	-	-	3/505	2/187
Subhash 2003[423]	-	-	-	-	-	-	106/145	20/28
Tatar 2009[111]	0/78	2/78	8/53	11/55	-	-	-	-
Vasankari 2009[424]	86/537	22/92	-	-	-	-	-	-
Wang 2001[425]	-	-	-	-	-	-	3/25	27/173
Wang 2009[110]	11/143	13/74	-	-	-	-	-	-

All Cause Mortality

Data extracted from all studies reporting upon all cause mortality was pooled using a random effects analysis due to the high statistical heterogeneity present (I-squared 59.9%). Of the studies pooled, 9 showed no statistically significant findings, the

remainder showed a significant increase in risk of death amongst individuals with co-morbid disease compared to those with TB alone.

The pooled results showed a statistically significant increase in all cause mortality amongst those with concomitant TB and DM compared to those with TB alone (12,128 participants, 18 trials, *RR* 1.97 (95% CI 1.53-2.55)).

Figure 12: Forest plot showing the individual and pooled risk of mortality amongst those with TB compared to those with concomitant TB and DM

Author	Year	DataCollection	RR (95% CI)	Weight %
Ambrosetti	1999	1997	0.39 (0.05, 2.74)	1.50
Ambrosetti	1999	1996	3.25 (1.15, 9.20)	4.02
Ambrosetti	1999	1995	2.38 (0.77, 7.41)	3.57
Bashar	2001		14.70 (1.86, 116.27)	1.36
Centis	2002	1998	2.64 (1.11, 6.26)	5.05
Centis	2000	1999	1.64 (0.40, 6.66)	2.60
Chiang	2000		1.40 (1.05, 1.86)	10.40
Dooley	2009		1.82 (0.78, 4.27)	5.14
Fielder	2002		3.10 (1.92, 4.99)	8.44
Fischer Hoch	2008		1.07 (0.78, 1.48)	10.04
Hasibi	2008		3.67 (1.23, 10.93)	3.76
Kourbatova	2006		1.26 (0.58, 2.76)	5.65
Matthew	2006		4.54 (2.33, 8.82)	6.62
Oursler	2002		3.43 (1.68, 6.98)	6.22
Ponce de Leon	2004		1.33 (0.91, 1.94)	9.46
Singla	2006		0.90 (0.09, 8.60)	1.16
Vasankari	2009		1.49 (0.99, 2.26)	9.12
Wang	2009		2.28 (1.08, 4.85)	5.88
Overall (I-squared = 59.9%, p = 0.001)			1.97 (1.53, 2.55)	100.00

NOTE: Weights are from random effects analysis

.05 .1 .5 1 2 8 16 32

Higher amongst unexposed (TB)   Higher amongst exposed (TB DM)

Sputum and culture clearance at 2-3 months an over

Data extracted from all studies reporting upon sputum clearance at 2-3 months was pooled using a random effects analysis due to the high statistical heterogeneity present (I-squared 60.3%). Four of the studies pooled showed no statistically significant findings, the remainder showed an increased risk of remaining sputum or culture positive amongst individuals with co-morbid disease at 2-3 months after treatment initiation when compared to those with TB alone.

The pooled results showed no statistically significant findings (1,675 participants, 6 trials *RR* 1.38 (95% CI 0.97-1.97)), although the results tended towards significance meaning type II statistical error may be occurring.

Figure 13: Forest plot showing the individual and pooled risk of failure to clear bacteria amongst those with TB compared to those with concomitant TB and DM

Author	Year		RR (95% CI)	Weight %
Alisjahbana	1999 (1997)		0.93 (0.46, 1.90)	13.72
Banu-Rekha	2007		0.79 (0.33, 1.88)	10.75
Dooley	2009		1.02 (0.56, 1.85)	16.43
Guler	2007		2.17 (1.69, 2.78)	26.63
Singla	2006		1.75 (1.14, 2.69)	21.08
Tatar	2009		1.33 (0.58, 3.04)	11.39
Overall (I-squared = 60.3%, p = 0.028)			1.38 (0.97, 1.97)	100.00

NOTE: Weights are from random effects analysis

.3 .5 1 2 4

Higher amongst unexposed (TB)   Higher amongst exposed (TB DM)
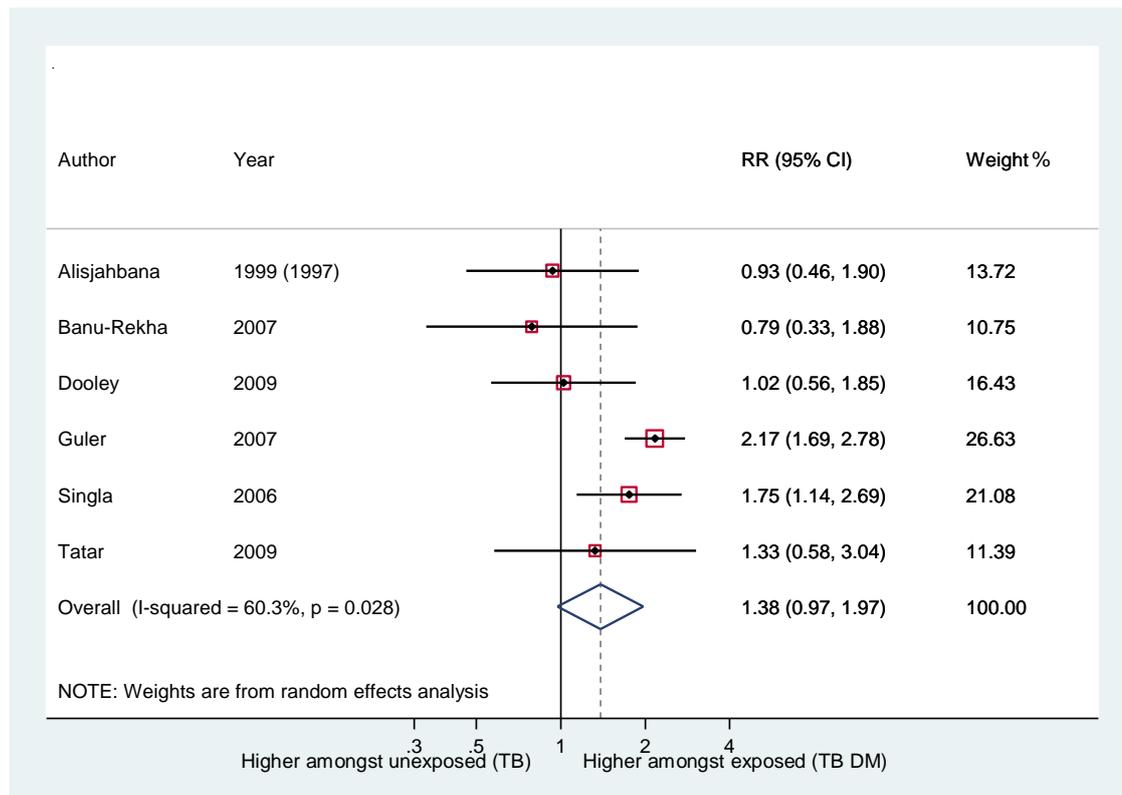
Sputum and culture clearance at 6 months

Only a single study by *Alisjahbana et al* measured failure to clear bacteria by 6 months (treatment completion) they found 28% with DM had not achieved cure at 6 months compared to 11% with TB alone not achieving cure.

Recurrence or relapse

Data extracted from all studies reporting upon TB recurrence or relapse was pooled using a fixed effects analysis as statistical heterogeneity was low (I-squared = 26.2%). Of the studies pooled, none identified any statistically significant findings.

The pooled results also showed no statistically significant findings (1,225 participants, 4 trials *RR* 1.20 (95% CI 0.93-1.54)), although the results tended towards significance meaning type II statistical error may be occurring.

Figure 14: Forest plot showing the individual and pooled risk of TB relapse or recurrence amongst those with TB compared to those with concomitant TB and DM

Author	Year	RR (95% CI)	Weight %
Fisher Hoch	2008	1.71 (0.95, 3.10)	21.99
Subhash	2003	1.80 (0.30, 10.69)	3.07
Singla	2006	0.98 (0.76, 1.26)	65.01
Wang	2001	1.30 (0.43, 3.97)	9.93
Overall (I-squared = 26.2%, p = 0.254)		1.20 (0.93, 1.54)	100.00

.2 .3 .4 .6 1 2 4 8 16

Higher amongst unexposed (TB)   Higher amongst exposed (TB DM)
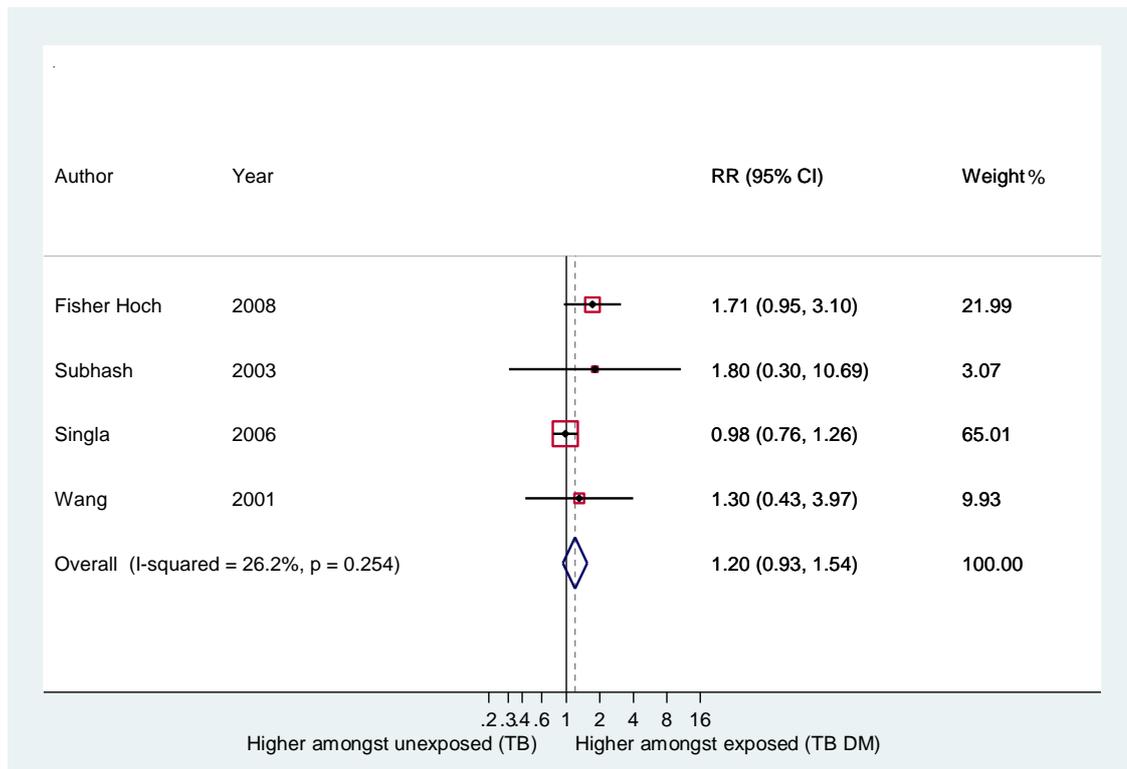
Chapter 4. Discussion

4.1 Brief synopsis of research aims and methods

Diseases can co-occur within populations at either an increased or decreased rate than would be expected due to chance given the background frequency of each disease.[2]

Identifying disease associations and dissociations is important as it may lead to the advancement of knowledge upon disease sequalae, aetiology and upon differences in disease outcome. This in turn can give insights into methods for disease prevention, control or management.[2]

This body of work was initiated to elucidate the association between DM and TB. The presence, direction, specificity, and magnitude of any such associations were investigated as well as the impact of having co-morbid DM and TB upon TB outcomes.

The following hypotheses, as previously listed in section 1.5, were addressed utilising a quantitative approach:

1) DM is associated with an increased risk of developing TB, PTB and, or, EPTB

2) T1DM is associated with an increased risk of developing TB, PTB and, or, EPTB

3) T2DM is associated with an increased risk of developing TB, PTB and, or, EPTB

4) TB is associated with an increased risk of developing DM, T1DM and, or, T2DM

5) PTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

6) EPTB is associated with an increased risk of developing DM, T1DM and, or, T2DM

7) It is consistently documented that when TB and DM present concomitantly TB disease outcomes are significantly poorer

Secondary data from the ORLS, a regional dataset, and THIN, a national dataset, were used to inform retrospective cohort studies which addressed hypotheses 1 to 6. Quantitative systematic review techniques were used to address hypothesis 7.

The Oxford Record Linkage Study (ORLS) is a database containing records of all hospital admissions and all deaths (regardless of where they occurred), in defined populations within the former Oxford National Health Service Region. It consists of 2 separate datasets which are not linkable; ORLS1 which covers the years 1963 to 1998 and ORLS2 which covers the years 1999 to 2008. The Health Improvement Network (THIN) is a database containing electronic medical records collected at GP clinics throughout the UK. Data was used from the years 2003-2009.

Within both databases all patients were classified as exposed to (having had) or unexposed to (not having had) TB (all sub-types, PTB or EPTB) and exposed or unexposed to DM (all sub-types, T1DM or T2DM).

In the ORLS1 and ORLS2 datasets, standardised RRs and corresponding 95% CIs were calculated and compared for DM (all sub-types, T1DM and T2DM) in individuals who have had and have not had TB (all sub-types, PTB or EPTB). Also, the converse, RR and 95% CIs were calculated and compared for TB (all sub-types, PTB or EPTB) in patients with and without DM (all sub-types, T1DM and T2DM).

Within THIN datasets, IRRs and 95% CIs of DM (all sub-types, T1DM and T2DM) were calculated using negative binomial regression, with TB (all sub-types, PTB or EPTB) as an explanatory variable. Also, the converse, IRRs and 95% CIs for TB (all sub-types, PTB or EPTB) were calculated using negative binomial regression with DM (all sub-types, T1DM or T2DM) as an explanatory variable.

Systematic searches were completed within Medline and Embase to identify studies comparing TB outcomes amongst those with and without DM. Data from these studies were utilised to inform meta-analyses that assessed all cause mortality, bacterial clearance rate and TB relapse or recurrence rate amongst individuals with DM and co-morbid TB comparative to those with TB alone.

4.2 Discussion of findings

4.2.1 Analysis of ORLS and THIN data

Summary of descriptive and univariate statistics

ORLS1 and ORLS2

The mean patient age at entry into the exposed cohorts generated in ORLS1 and ORLS2 was greater than the mean patient age at entry into the unexposed cohorts. Mean age at entry into the: DM cohorts was 52 years (ORLS1) and 51 years (ORLS2), TB cohorts was 49 years (ORLS1) and 46 years (ORLS2) and into the unexposed, reference cohorts was 31 years (ORLS1) and 39 years (ORLS2). As the analyses were standardised by age this will have had no bearing upon any of the RR's calculated however it does highlight the association between both the exposure and outcome diseases under study and older age.

In both ORLS datasets the follow-up time in the exposed and unexposed cohorts was similar; however, it was much shorter for all cohorts generated within ORLS2 when compared to all cohorts generated within ORLS 1. This is due to the substantially shorter time period covered by ORLS2 (9 years, 1999 to 2008) compared to that covered by ORLS1 (35 years, 1963 to 1998). If the lag time between our exposure and outcomes of interest is long, this could potentially affect estimates of risk within the ORLS 2 dataset biasing towards the null.

The number of individuals within the DM cohorts (all subtypes) generated in ORLS1 and ORLS2 identified as having T2DM (over 30 years old) were much greater than the numbers identified as having T1DM (under 30 years old). This is reflective of the rates of T1DM comparative to T2DM within the background population. In the UK the prevalence of T1DM is 15% whereas the prevalence of T2DM is much higher at 85%.[229-235] Within both the ORLS 1 and ORLS 2 datasets, TB prevalence was greatest amongst those over 25 years old and was lowest during childhood. This is again reflective of the background population rates of TB. In the UK TB incidence is very low during childhood with only around 4 cases per 100,000 individuals under the age of 15 years old being diagnosed each year.[200]

THIN

The mean patient ages at entry into the exposed, TB and DM, cohorts generated within THIN dataset were comparable to those for the exposed cohorts generated in ORLS1 and ORLS2. Mean age at entry into the DM cohort was 60 years old and into the TB

cohort was 48 years old. Due to the aggregated format of the referent data it was not possible to calculate the mean age at entry into the unexposed cohorts generated within THIN.

Mean follow up time for all cohorts generated within THIN database were similar ranging from 3.7 to 4.1 years. THIN database covers a 6 year time period from 2003 to 2009. The mean follow up times in cohorts generated in THIN were similar to those for cohorts generated in ORLS2 which covers a comparable time period (9 years, from 1999 to 2008) but were much shorter than the mean follow up times for cohorts generated in ORLS1 which covers a much longer, and more historic time period (35 years, 1963 to 1998).

The number of individuals within the constructed THIN T1DM cohort (n=44,874) was much smaller than the number of individuals within the T2DM cohort (n=193,929). This is most likely due to the higher prevalence of T2DM (85%) comparative to T1DM (15%) in the background population and is as would be expected within a sample population representative of the UK. The prevalence of DM amongst those under the age of 14 years old in THIN dataset (1%) is also representative of the prevalence of DM in the UK which is 1% amongst those under the age of 16 years old.[229]

Within THIN datasets it was found that risk of DM is significantly raised amongst males comparative to females, amongst current or past smokers comparative to non-smokers, and amongst those above the age of 20 years comparative to those aged 20 years and below. This is representative of DM rates in the general UK population which show a male preponderance[229] and have been found to be associated with older age and smoking.[240 241]

Within THIN datasets it was found that the risk of TB is significantly increased amongst current or past smokers comparative to non-smokers and those aged 21-40 years comparative to those under the age of 20 years old. This is again representative of TB rates in the general UK population. In the UK the incidence rates of TB peak amongst those aged 20 to 40 years[201] and the risk of TB is increased amongst individuals who are current or past smokers.[139 205 206] In the THIN dataset, as elsewhere, it was found that the risk of TB is greater amongst those of low SES when compared to those of high SES.[229]

Discussion of risk estimates calculated

DM risk amongst individuals with TB

The analyses completed in ORLS1 and ORLS2 found no statistically significant increases in risk of developing DM (any sub-type, T1DM or T2DM) amongst individuals who have had TB (any sub-type, PTB or EPTB) when compared to those who have not. This, alongside results for the converse analyses, suggests that the association between TB and DM is uni-directional.

However, within THIN risk of DM was found to be significantly increased amongst individuals who have had; TB (IRR 5.651 (95% CI 5.185-6.159, P-value <0.001)), PTB (IRR 5.740 (95% CI 5.077-6.490, P-value <0.001)) and EPTB (IRR 4.659 (95% CI 3.940-5.509, P-value <0.001)) compared to those who have not. Risk of T1DM was found to be significantly increased amongst individuals who have had TB (IRR 5.491 (95% CI 5.019-6.020, P-value <0.001)) and EPTB (IRR 0.843 (95% CI 0.349-2.034, P-value <0.001)) compared to those who have not. And, risk of T2DM was found to be significantly increased amongst individuals who have had; TB (IRR 2.212 (95% CI 1.684-2.906, P-value <0.001)), PTB (IRR 5.382 (95% CI 4.730-6.124), P-value <0.001)) and EPTB (IRR 4.364 (95% CI 3.649-5.218, P-value <0.001)) when compared to those who have not.

No other studies identified in the semi-systematic review have specifically assessed the risk of DM amongst those with TB comparative to those without so it is not possible to compare findings presented in this thesis directly with the work of others. To put these findings in context; it is biologically plausible that the risk of developing DM is increased amongst those who have had TB when compared to those who have not. As discussed in chapter 1, there are numerous cross sectional studies which have found a high prevalence of glucose intolerance amongst individuals with TB.[32 427] Studies have shown induced hyperglycaemia and, or, impaired glucose tolerance occurring during the early phases of active TB disease[29-32] and these metabolic states themselves are linked with progression to overt DM amongst 20-50% of individuals after 3 to 5 years.[33-36] However, these findings do need to be interpreted cautiously as some studies have noted that the hyperglycaemia observed amongst populations of individuals with TB is intermittent reversing after the early, acute phase of TB infection.[30 32 37 38] It could be that these observations of hyperglycaemia are due to short term side effects of treatment with Rifampicin and Isoniazid[39-41], or, to stress hyperglycaemia[42 43] rather than being signs of true metabolic dysfunction and DM.

As has been previously outlined Berksonian bias is a type of selection bias; a potential problem particularly in hospital-based studies causing identification of spurious associations or inflation of risk estimates between diseases or characteristics due to differing probabilities of admission for those with the exposure, without the exposure and with an outcome of interest. In the work presented within this thesis, to account for Berksonian bias and surveillance bias, sensitivity analyses were completed in which anyone with; less than 1 year of follow up after their first exposure record, with a record of an outcome of interest recorded at the same time as their exposure record, or with a record of an outcome of interest within the first year following their exposure record was excluded in a case-wise fashion. In THIN these analyses attenuated risk estimates slightly but did not alter the statistical significance of the findings. This primarily indicates that the increase in risk identified is not an artefact due to different probabilities of attendance at a GP's for those with the outcome, without the outcome and with the exposure of interest. However, it also suggests that the cause of the DM seen amongst those with TB is unlikely to be due to TB treatment as there would have been enough time for treatment 'wash out' within the first year of diagnosis. If the DM diagnosed amongst those who have had TB was due to a side effect of treatment the case exclusion analyses would be expected to show dramatically attenuated risk estimates.

Further exclusion analyses were also completed within the ORLS datasets to assess whether utilising exposure and outcome admissions recorded only within the primary position on a HES record comparative to those recorded within the secondary position or regardless of where recorded had an impact upon effect estimates identified. No significant changes were found.

It is of importance to note that Pseudo R^2 figures for the models fitted to assess the risk of DM amongst those with TB comparative to those without in THIN dataset were very low. This suggests that the variables modelled accounted only for a minimal amount of the association seen between the variables. This could mean that the increased risk of DM amongst those with TB comparative to those without is not truly positive and rather is due to unmeasured confounding. If this were the case it would mean that the apparent TB to DM association was being overestimated when in truth the exposure has no causal effect on the outcome.

In order to try and further understand these risk estimates, tests for interaction between variables included within the THIN models were carried out. The interaction between

TB and age was seen to be highly significant. An interaction shows that the combined effect of two risk factors in increasing the risk of an outcome of interest is higher than the effect of either single factor. An interaction between TB and age could be amplifying the effect estimates calculated. Those who have TB and are of an older age could be at an increased risk of DM comparative to those with TB and of a younger age. This could be because baseline DM risk being higher amongst individuals of an older age or because those of an older age have a higher overall risk of developing DM due to their greater additive life time risk.

TB risk amongst individuals with DM

Within ORLS 1, ORLS2 and THIN a significant increase in TB risk was found amongst individuals with DM comparative to those without; (ORLS1 RR 1.77 (95% CI 1.45-2.15, P-value <0.001)), (ORLS2 RR 2.56 (95% CI 1.78-3.69, P-value <0.001)) and (THIN IRR 1.50 (95% CI 1.27-1.76, P-value <0.001)). Effect estimates calculated in ORLS1 and THIN are comparable, however, the effect estimate calculated in ORLS2 is almost double those.

Positive findings are in line with the majority of results presented amongst other studies which have assessed this association and that were identified in the semi-systematic literature review (see section 1.4). An increase in risk of TB amongst those with DM comparative to those without was identified in 11 studies (Baker 2012[265], Brassard 2006[266], Chen 2006[27], Coker 2006[268], Dobler 2012[269], Jick 2005[205], Leung 2008[295], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278] and Ponce de Leon 2004[279]). Five of the studies identified by the semi-systematic review (Buskin 1994[267], Dyck[270], Leegaard 2011[273], Marks 2011[95] and Rosenman 1996[280]) showed no significant change in risk of TB amongst those with DM. It is of interest that three of these five studies presented positive effect estimates tending towards statistical significance (Dyck[270], Leegaard 2011[273] and Marks 2011[95]), perhaps these studies are suffering from type II statistical error. However, all five studies are fairly heterogeneous and it is thus unlikely that they are all showing null effect estimates due to a specific anomaly in study design causing statistical error and bias.

Seven studies (Alisjahbana 2006[264], Farhoult-Jepsen 2011[271], Goldhaber-Fiebert 2011[90], John 2001[26], Kim 1995[272], Shetty 2006[281] and Wu 2007[282]) found an increase in PTB risk amongst those with DM when compared to those without. A significant increase in PTB risk amongst those with DM compared to those without was also found in analyses within ORLS1 (RR 1.72 (95% CI 1.22-2.37, P-value = 0.001) and ORLS2 (RR 3.33

(95% CI 1.51-6.62, P-value = 0.001). This finding was not replicated within the analyses completed in THIN dataset. It should be noted that again the effect estimate calculated in ORLS2 is almost double that in ORLS1.

In ORLS1 the RR of acquiring TB (any sub-type) and PTB amongst individuals with DM (any sub-type) compared to those without DM is very similar, (TB RR 1.77 (95%CI 1.45-2.15, P-value <0.001)) and (PTB RR 1.72 (95% CI 1.22-2.37, P-value = 0.001)). This is perhaps unsurprising as the majority of TB cases within the UK (over 80%) will be of PTB[201] and thus make up the vast majority of people amongst the 'all' TB group with 'their' risk heavily affecting that of the whole group.

The only study (Leung 2008[295]) identified during semi-systematic review to assess risk of EPTB following DM found an increase in risk of EPTB amongst those with comparative to those without DM. No significant association between DM status and EPTB was found in ORLS1, ORLS2, or THIN. However, in THIN the risk of EPTB amongst those with DM comparative to those without tended towards statistical significance (IRR 1.434 (95% CI 0.993-2.071, P-value = 0.055)). It should be noted that the numbers for these analyses in all datasets were small and thus null findings could conceivably be due to bias or type II statistical error.

Just two studies identified within the semi-systematic literature review specifically looked at risk of TB amongst individuals with Type 1 DM comparative to those with no DM (Dobler 2012[269] and Leegaard 2011[273]). These studies showed an increased risk of TB amongst those with T1DM comparative to those without, as was found in THIN (IRR 1.455 (95% CI 1.104-1.917, P-value = 0.008)). However, in ORLS1 risk of TB was not found to be raised amongst those with T1DM comparative to those without. The ORLS2 dataset was too small to complete these analyses. Again, it should be noted that the numbers for these analyses were very small and null findings could conceivably be due to type II statistical error.

The risk of TB amongst those with T2DM compared to those without was raised in ORLS1 (RR 1.58 (95% CI 1.15-2.14, P-value = 0.003)), ORLS2 (RR 3.60 (95% CI 1.76-6.76, P-value <0.001)) and THIN (IRR 1.536 (95% CI 1.296-1.822, P-value <0.001)). Again, the risk estimates in THIN and ORLS1 were comparable whereas the estimates calculated in ORLS2 were almost double those.

Four studies (Alisjahbana 2006[264], Baker 2012[265], Leegaard 2011[273] and Pablos-Mendez 1997[276]) identified in the semi-systematic review looked at glucose control and how this modified estimates of TB risk amongst individuals with DM. All four studies identified

an increase in TB risk for those with poor hyperglycaemic control, as judged by HbA1c measure or by the number of DM complications an individual had, although no tests for trend were completed. Analyses completed within ORLS1, ORLS2 and THIN did not directly address this. However, if somewhat naively subtype of DM is taken as a proxy for glycaemic control, findings in this thesis do not support the hypotheses that TB is more common amongst those with poorer control given that risk estimates for TB are fairly stable amongst those with T1DM and T2DM.

From a public health perspective the association between T2DM and PTB is of most interest as approximately 80% of individuals with DM have T2DM and PTB is the most prevalent infectious form of TB. In THIN risk of PTB was not raised amongst those with T1DM or T2DM when compared to those without. This is to be expected given that risk of PTB was not raised amongst those with DM (any sub-type). These analyses could not be completed in ORLS1 or ORLS2 due to the datasets relatively small sizes.

In THIN risk of EPTB was raised amongst those with T1DM comparative to those without DM (IRR 2.088 (95% CI 1.190-3.664, P-value = 0.010)) but not amongst those with T2DM comparative to without DM. These analyses could not be completed in ORLS1 or ORLS2 due to the datasets relatively small sizes.

Case exclusion, sensitivity analyses were again completed to assess whether effect estimates were being altered by either Berksonian or surveillance bias. There was no alteration in overall trends identified; however, the exact effect estimates calculated did alter slightly. Further exclusion analyses were again completed in the ORLS datasets to assess whether utilising exposure and outcome admissions recorded only within the primary position on a HES record comparative to those recorded within the secondary position or regardless of where recorded had an impact upon effect estimates identified. No significant changes were found. Again, due to the exclusion of cases these sensitivity analyses contained very small numbers and therefore may be prone to type II statistical errors.

The R-squared values indicative of the relative predictive power of estimating TB risk following DM were low for all models constructed in both ORLS and THIN datasets. This is likely to be due to the inability to control for potential confounders of the association between DM and TB, such as ethnicity, in these analyses.

Further comments

It is interesting to note that the risk of developing TB amongst individuals with DM compared to those without was increased both within a 'historic' era when TB incidence in the UK was high (ORLS1) and within recent times when TB incidence has been relatively low (ORLS2 and THIN). This suggests that other risk factors for TB, historically present in the UK, do not mask the effect of DM on TB risk.

Seventeen previously published studies looking at the association between DM and TB were completed in high income countries (Baker 2012[265], Brassard 2006[266], Buskin 1994[267], Chen 2006[27], Dobler 2012[269], Dyck 2007[270], Goldhaber-Fiebert 2011[90], Jick 2005[205], John 2001[26], Leegaard 2011[273], Leung 2008[295], Marks 2011[95], Mori 1992[276], Pablo-Mendez 1997[277], Perez 2006[278], Rosenman 1996[280] and Wu 2007[282]), five within middle income countries (Alisjahbana 2006[264], Coker 2006[268], Kim 1995[272], Ponce de Leon 2004[279] and Shetty 2006[281]), and only one within a low income country (Farhoult-Jepsen 2011[271]); as specified by the world bank.[413] Estimations of increased TB risk amongst those with comparative to without DM were not systematically effected by a countries wealth. However, the impact of the association between DM and TB is likely to be most adverse in low income countries due to inherent issues with healthcare provision.[366] Only four of these 23 studies assessed the association between DM and TB in areas with high TB incidence and high TB transmission rates; two in India (John 2001[26] and Shetty2006[281]), one in Russia (Coker 2006[268]) and one in Tanzania, sub Saharan African (Farhoult-Jepsen 2011[271]). These four studies also found an increase in TB rate amongst individuals with DM. Given the high TB transmission rates in these areas and the projected increases in DM[54] even a moderate increase in risk of TB amongst those with DM compared to those without will have a dramatic public health impact over the coming years.[58] In areas where TB is endemic, TB screening amongst those with DM and, or, TB prophylaxis may be needed to reduce or stabilise numbers developing active TB.

HIV, a well-known risk factor for TB, attenuated but did not mask the effect of DM on TB risk.[271] This means that in areas like Tanzania where the prevalence of active TB infection is already high in part due to a high HIV prevalence; rising DM rates will further exacerbate TB prevalence.[90] The effects of the association between DM and TB will also undoubtedly be further impacted upon in low and middle income countries by intertwining risk factors such as high internal migration rates and rapidly increasing chronic disease rates whilst some countries still undergo epidemiological transition.

Internal migration from rural to urban areas can lead to an increase in DM risk[428] and bring people from an area where TB transmission rates are relatively low to an area where they are high, this may confound the association seen between DM and TB.[429] The increases in TB rates are likely to be especially pronounced amidst specific population sub-groups whose baseline risk of TB and, or, DM is already high such as those of Asian ethnicity.[430][431] Those who have a high baseline risk of both diseases may confound the association between DM and TB.

Strengths and limitations

Research is often a more pragmatic, iterative process than perhaps would be wished for with all bodies of work having inherent strengths and limitations. Some limitations may cause undue bias and affect study findings whilst some will have a much more modest impact. The key strengths, limitations and plausible affects upon results presented in this thesis calculated in analyses utilising ORLS and THIN datasets are now discussed.

A key strength of the analyses completed using the ORLS and THIN datasets was the cohort design which allowed a temporal order between the exposures of interest and the outcomes to be established.[389] This allowed for assessment of the direction of the association between TB and DM something which semi-systematic review revealed had not been carried out explicitly in prior studies.

The availability of data and adequacy for use testing specific hypotheses is integral to the validity of a retrospective cohort study. Data sources used for work presented within this thesis are derived from routine health-care data. Health-care datum are derived from established data collection systems and are not normally collected with the aim of answering specific questions.[391] However, this data can be utilised to produce health information for administrative, statutory, surveillance, or epidemiological purposes if suitable variables of interest have been collated in a non-biased manner.[391]

Due to the dataset size, and the combination of data available in THIN and the ORLS it was possible to investigate the risk associations between DM and TB and, in cases, between the sub-types of each disease. As study populations were fixed by the population size of each database and the numbers within meeting inclusion criteria analysis of the risk associations between the different subtypes of DM and TB was not always possible in the smaller ORLS datasets.

As has been discussed in section 1.4.1 the accurate identification of those who have an exposure or outcome of interest is fundamental to making a valid effect size calculation.

To re-iterate misclassification is when a study subject is identified as; exposed when they are unexposed, as having an outcome of interest when they do not, or, the converse of either of these situations.[368-370] Over or underestimation of those exposed or with an outcome of interest can lead to an over or under estimation of effect size dependent upon the variable that is misclassified, whether it is dichotomous and the type of misclassification that is occurring.[368-370] Non-differential misclassification is a random misclassification of an individual's exposure status, outcome status or both that is *independent* of their status for any other of these variables. Differential misclassification is a non-random misclassification of an individual's exposure status, outcome status or both which is *dependent* upon an individual's status for at least one other of these variables.[368-370]

In THIN, key variables for TB, PTB, EPTB, DM, T1DM and T2DM were defined using a combination of Read codes that were input in to specific fields within relational dataset files by GP staff. Inaccuracies in these codes allocated by GP staff due to human error may lead to incorrect identification of an individual's exposure or outcome status within the presented analyses. In the ORLS database key variables for TB, PTB, EPTB, DM, T1DM and T2DM were defined using ICD codes. In a similar fashion, inaccuracies in codes allocated by hospital staff due to human error may lead to issues in correctly identifying an individual's exposure or outcome status within ORLS. However, human error whilst coding is likely to occur randomly across all records for both exposures and outcomes of interest in a way which does not impact upon calculated risk estimates.

Within THIN, a primary care database, the number of individual's with a record for DM is likely to be accurate due to these individual's increased interaction with primary healthcare. However, it is suspected that codes for TB in THIN may slightly underestimate the true incidence of TB as care will mainly be instigated and completed by secondary providers and relevant information may not be fed back to primary care bodies. This 'misclassification' is likely to be occurring in a non-differential manner; that is, randomly and irrespective of DM status. If this is the case whether TB is being examined as the exposure of interest or the outcome of interest risk estimates may be biased towards the null. The 'worst case scenario' of this being that findings presented in this thesis could have been attenuated so far from the 'true' effect size that true positive associations have become negative, non-significant and gone undetected.

However, rates of TB identified in THIN are comparative to UK rates meaning it is unlikely that misclassification is occurring to a great extent.

Within ORLS, a secondary care database, the number of individual's with a record for TB is likely to be accurate due to the acute nature of the disease and thus their likely presentation to secondary care. However, it is suspected that codes for DM may slightly underestimate the true incidence. Care for DM will mainly be instigated and completed by primary care providers and relevant information on an individual's health status may not be recorded on their secondary care records. This 'misclassification' is likely to be occurring in a non-differential manner; randomly and irrespective of TB status. If this is the case whether DM is being examined as the exposure of interest or the outcome of interest risk estimates may be biased towards the null. Findings presented in this thesis could have been attenuated so far from the 'true' effect size that true positive associations have gone undetected. However, rates of DM identified in both ORLS databases are comparative to those for the UK population meaning it is unlikely that misclassification is occurring to a great extent. Also, no matter where on an individual's health record DM was listed (primary diagnosis code or secondary diagnosis code) calculated risk estimates remained fairly stable.

As previously discussed in section 1.4.1 the ideal way to assess DM and TB status amongst study participants would be through the utilisation of standard diagnostic tests such as a sputum smear for TB and a FBG measure for DM. Within the ORLS and THIN datasets medical records are compiled to give longitudinal data on the health events of individuals within specific populations. These longitudinal health event records are used in the analyses presented within this thesis to identify those who have been clinically diagnosed with either TB or DM. The use of medical records only allows for the identification of individuals with disease who have been actively diagnosed and will exclude those who have the disease but are, as yet, clinically undiagnosed. Those with active TB are unlikely to be undiagnosed due to the acute nature of the disease. However, there are likely to be a number of individuals with DM who have the disease but are clinically undiagnosed. These individuals are also likely to be misclassified in the analyses completed using ORLS and THIN data in a non-differential fashion; unlinked to their TB status. In analyses where DM is the exposure of interest, if individuals with DM have been misclassified and identified as non-exposed when they are indeed exposed the calculated risk estimates may be biased towards the null. In analyses where DM is the outcome of interest, if individuals with DM have been

misclassified and identified as not having developed the outcome of interest when they actually have, as long as misclassification is truly occurring in a non-differential manner, risk estimates will also be biased towards the null. In the worst case scenario risk estimates may have been attenuated so far that true positive associations are now negative or non-significant and go undetected. It is impossible to identify those who are undiagnosed but have DM without carrying out prospective diagnostic tests.

Over time the standard diagnostic guidelines for DM have become more sensitive.[212] In 1980 WHO guidance was for a positive DM diagnosis if FBG was equal to or above 8.0mmol/l, in 1985 if FBG was equal to or over 7.8mmol/l, and in 1999 if FBG was equal to or above 7.0mmol/l.[212] THIN and the ORLS2 datasets only hold health records documented after the most recent change (in 1999) to clinical diagnostic cut-points for DM. However, ORLS1 contains health records documented throughout a period (January 1st 1963 to December 31st 1999) during which clinical diagnostic cut-points for the identification of individuals with DM changed twice. This means that the incidence of DM codes in the ORLS1 database from 1963 to 1980 and from 1981 to 1998, which were allocated using diagnostic criteria contemporary at the time, will be an underestimate of incidence as would be calculated using todays diagnostic criteria. This will be the case to a lesser extent for each time period as diagnostic criteria became increasingly sensitive. This may have caused some misclassification of those who are exposed as unexposed in the earlier time periods covered by ORLS1. However, this will be occurring in a non-differential manner, irrespective of TB status. In analyses completed using data from ORLS1 with DM as the outcome or the exposure of interest risk estimates may have been biased towards the null. This means that risk estimates presented in this thesis may be underestimating associations, in a 'worst case scenario' to a point at which a true association becomes negative, non-significant and goes undetected.

It is not possible to distinguish individuals who have T1DM from those who have T2DM using codes in ICD 7, 8 or 9; these ICD versions were used within the ORLS1 and ORLS2 databases when they were contemporary to classify health events as they occurred. It is thus not possible to identify those with T1DM or T2DM prior to the use of ICD 10 (1994) without the use of a proxy variable. In order to be able to select for T1DM and T2DM as outcomes or exposures of interest in the analyses completed utilising data from the ORLS databases age was used as an approximate variable for disease sub-type. In westernised countries in particular the mean age at onset of T2DM

is decreasing. It is thus plausible that a number of individuals with T2DM have been misclassified as having T1DM. This misclassification is unlikely to have occurred in a differential manner (in association with TB status). In analyses where T1DM and T2DM are exposures of interest misclassification of individuals as unexposed when they are actually exposed will lead to an attenuation of calculated risk estimates as will misclassification of individuals as exposed when they are unexposed. If this misclassification is occurring, within completed analyses, in a worst case scenario positive associations may have been falsely identified as null findings. However, as T1DM and T2DM rates in ORLS1 and ORLS2 are representative of rates for the UK it is unlikely misclassification is occurring to a great extent.

Alongside bias due to misclassification another potential source of bias in all cohort studies is disproportionate losses to follow-up amongst the exposed and unexposed groups.[389] In the studies completed within this thesis individual's in open cohorts constructed in ORLS1, ORLS2 or THIN were; at risk of death, able to migrate into or out of the study population, and were able to refuse to allow continued use of their health data. If losses to follow-up were related to the exposure, outcome or both then calculated effect estimates would potentially have been biased.[389] However, if the loss to follow up was random, meaning that the average characteristics of those 'lost' in either the exposed or unexposed group were similar to those who remained in either group, no bias would have been introduced.[389] There are no losses to follow up thought to have occurred in any of the datasets in a systematic fashion which would have affected risk estimates presented. As with all healthcare datasets, changes in geographical boundaries may contribute to fluctuations in data within THIN and the ORLS databases. Within THIN this should be accounted for by comparative changes in the denominator population. For the ORLS there is no true denominator population however the use of a referent cohort as a comparator should compensate for any migration into or out of the ORLS datasets or fluctuations in geographic boundaries. Both the ORLS databases and, to a lesser extent, THIN database lacked information upon possible confounding factors for the association between DM and TB. Confounders are variables which are not causal themselves but distort the effect or association between an exposure and outcome either away from or towards the null.[389] Although age, sex and district of residence are controlled for in ORLS analyses and age, sex, SES and smoking status within THIN analyses it was not possible to account for; alcohol intake, BMI, ethnicity, and sedentary behaviour.

Individuals with specific characteristics will have an increased baseline risk of TB and, or, DM and when not controlled for could potentially confound risk estimates. Those of Asian or African ethnic background have an increased risk of developing TB[430] and of developing DM.[430 431] Heavy alcohol intake increases an individual's risk of TB by almost 3 fold and increases DM incidence by 43%.[432 433]

Increasing BMI and sedentary behaviour are associated with an increase in DM risk that can be reversed if risk factors are reversed.[434] Due to the acute nature of active TB individuals will often become sedentary and, once on treatment, will see a rapid increase in weight.

It could be argued that SES and ethnicity are accounted for within the ORLS analyses due to the population covered who live mainly in market towns, rural areas or relatively small conurbations like Oxford, Reading and Northampton which are affluent and healthy, compared with the English national average. Of the people in the ORLS1 dataset, 55% were born in the Oxford Region itself and 94% in the British Isles (equivalent data not available for ORLS2) leaving small scope for confounding by ethnicity. Also, other work has found this risk factor to have little effect upon estimates of the association.[435]

Data upon ethnicity could have been imputed into THIN datasets however methods used for similar datasets (Q-Research) have been somewhat arbitrary assuming that all of those with missing data are of 'white British' origin.[436] There was no a-priori data on the pattern of missing-ness for ethnicity data within THIN dataset which would have allowed for improved imputation and creation of a proxy ethnicity variable. As such, imputation was not completed as it was deemed unlikely to significantly increase the validity of risk estimates.

Completing the analyses of interest within both a national UK (THIN) and regional database (ORLS) allowed for a validation of analyses in a geographically and temporally different, but related study population. Results that have been validated within this way are considered to provide stronger evidence upon the hypotheses tested if consistency between results is identified. Confidence that an exposure of interest is causing a specific outcome is strengthened when several studies give the same result, in particular when the same results are seen across studies that are heterogeneous in design and setting.[389] Some, but not all of the results found within ORLS and THIN analyses showed consistency. A lack of consistency does not rule out the presence of an association between an exposure and outcome as within different studies different

exposure levels and other unknown conditions may reduce the impact of the causal factor under investigation.[389]

Analyses within THIN and the ORLS add to a relatively small evidence base, with which our finding that DM leads to an increased risk of TB is consistent. This is only the second study upon the association to addresses its magnitude within a predominantly 'white British' population. Work completed within the ORLS and THIN is novel in that it assesse the direction of the association and interactions between disease sub-types. Further work needs to be completed in order to clarify these findings.

Conclusions

It remains unclear if having had TB disease increases an individual's risk of developing DM. Results presented within this thesis are inconsistent and further research is needed in order to validate or refute the findings.

There is now a growing body of research to show that having DM leads to an increased risk of developing TB. Although it remains unclear if this association is specific to certain TB and DM sub-types, initial evidence suggests that the association is not sub-type specific.

4.2.2 Addressing hypotheses 7; Systematic review of TB outcomes

It was estimated that globally between 150 and 171 million people had DM in 2000 and, as is projected for the UK, the global prevalence of DM is expected to dramatically increase by 2030.[46 51 54] Alongside the epidemic proportions of individuals with DM over a third of the global population are latently infected with TB.[55] In 2010 there were 8.8 million active disease episodes and 1.45 million deaths attributable to TB worldwide.[56] Given these figures, and the findings within this thesis which show that DM causes an increase in risk of developing TB, it is plausible that a substantial proportion of new TB cases will be amongst individuals with DM.[47 57 58] It has been estimated that up to 20.2% of incident TB will be attributable to DM.[57 58 130]

Identifying whether there are any implications for individuals who have these diseases concurrently is important for clinical guidance and practice. In particular, it is important to know whether and if so how clinically relevant TB outcomes such as sputum clearance rate and mortality are affected.[59-62] These questions were addressed utilising systematic review techniques.

A search strategy identified 1,868 papers for title and abstract review. Once reviewed by two independent investigators 116 publications were identified for full review. After

full review by at least 2 of 3 independent investigators 25 studies were identified as including relevant data for extraction and analysis.

The majority of these 25 studies were retrospective cohort studies undertaken utilising data from high income countries with DM cases ascertained utilising MRR and TB status ascertained using microbiological diagnostic techniques.

Risk estimates

Using quantitative systematic review techniques it was found that failure to become sputum or culture negative after 3 months was not increased amongst individuals with DM and TB comparative to those with TB alone, although the results bordered upon statistical significance (OR 1.38 (95%CI 0.97-1.97)). There was also no statistically significant increase in the risk of TB relapse or recurrence amongst those with co-morbid DM and TB when compared to those with TB alone (OR 1.20 (95%CI 0.93-1.54)). Again the results bordered upon statistical significance. However, risk of death (OR 1.97 (95%CI 1.53-2.55)) was significantly increased almost 2 fold amongst individuals with co-morbid DM and TB comparative to those with TB alone. As this pooled effect estimate is for all cause mortality it is not known if the increased risk of death is from TB disease or other causes. It could simply be indicative of the poorer underlying health of individuals who present with co-morbid disease or of the increased age of individuals in this group.

There is another systematic review that addresses similar research questions to our own.[121] This review identified a further 8 studies, all non-English language. Data extracted upon TB outcomes differed somewhat in the review by Baker et al compared to the one presented within this thesis and as such, so did the data that was pooled in the meta-analyses.[121] Data in the review by *Baker et al* was extracted on; sputum conversion rates at 2-3 months after treatment initiation, relapse, failure and death during TB treatment, death during TB treatment and drug resistant, recurrent disease.[121]

The data extracted on sputum conversion was not pooled in the review by *Baker et al* meaning there is no figure for comparison with the results in this thesis.[121]

In the review by *Baker et al* no association was found between DM status and drug resistant, recurrent disease. This was not explored by the review completed for this thesis.[121]

Baker et al found TB relapse was significantly increased amongst those with DM comparative to those without DM, (RR 3.89 (95% CI 2.43-6.23)).[121] However, results from the review presented in this thesis found no significant association between DM

status and TB relapse. Pooled risk estimates in this thesis contained data from a smaller number of studies, and thus had a smaller number of overall participants in each 'study arm'. This could be causing type II statistical error and might explain the difference in results between the two reviews, especially as pooled estimates presented in this thesis tend towards statistical significance (OR 1.20 (95%CI 0.93-1.54)).

Baker et al identified a significant increase in failure and death amongst those with comparative to without DM (RR 1.69 (95% CI 1.36-2.12)).[121] Within this thesis TB failure was not assessed, only relapse and recurrence. Baker et al also found an increase in death during TB treatment amongst those with DM comparative to without (RR 1.89 (95% CI 2.43-6.23)).[121] An increase in all cause mortality throughout study follow up was found by the review presented within this thesis (OR 1.97 (95%CI 1.53-2.55)). It is surprising to note, that although the outcome definitions utilised for 'death' between the two reviews are very different, the pooled effect estimates are very similar.[121]

Further comments, strengths and limitations

To carry out primary analysis assessing the outcomes of TB amongst those with and without DM would require significant research resources. A review of literature is relatively cheap and allows for the objective assessment of the effect of DM upon TB outcomes through the appraisal of secondary data through the utilisation of quantitative systematic review and meta-analytic techniques.

Although it is believed that a robust, sensitive search strategy was employed to identify relevant studies for inclusion within the systematic review it is plausible, due to the disparate nature of the studies being reviewed, that articles containing pertinent data were missed. Relevant data upon TB outcomes amongst those with DM in published papers was often incidental to the main focus of the study meaning that DM went unmentioned within the abstract or title. Thus, these articles are unidentifiable from a database search utilising a strategy developed to identify studies on DM. However, comparing search results for the candidates review to that by *Baker et al* it can be seen that use of an alternative search strategy did not initially identify a greater number of papers.[121]

Inherent to the method, findings of a systematic review are only as robust as those of the individual studies from which data is extracted. Given this, it is important to note that many of the publications contributing to this review would be classed as 'low' or 'poor quality' and as such interpretation of findings and conclusions drawn from the review should be adequately tempered. Of particular note is the fact that the majority of studies

included in the review identified cases using non-standard diagnostic measures. This may lead to an underestimation of exposure levels in studies giving attenuated risk measures and as such an attenuated pooled risk estimate.

The review presented within this thesis, as has been mentioned, included 8 less papers in final full review than the systematic review by Baker et al. The missing papers were all non -English language papers excluded due to the two reviews differing exclusion criteria. Within the citations returned for the systematic review, as for the semi-systematic review, there were a large number of Japanese publications which when reviewing titles looked likely to be of relevance. If exclusion criteria leads to the exclusion of pertinent data a reviews findings can be seriously affected. However, it is interesting to note that although the exclusion of non-English language papers had a large effect upon the number of identified studies the effect upon the overall pooled risk estimates for death was actually quite minimal; *Baker et al* (RR 1.89 (95% CI 2.43-6.23))[121] comparative to thesis results (OR 1.97 (95%CI 1.53-2.55)).

Pooled risk estimates for all cause mortality are likely to be effected by loss to follow up bias within the cohort studies contributing data to the meta-analysis. Of the studies found only one used statistical survival analyses techniques which are able to account for variant follow up time in their risk estimations. However this study did show an increased risk of mortality amongst those with DM and TB comparative to those with TB alone.[421]

As all cause mortality rather than TB specific mortality was assessed (the latter being uncommonly reported amongst the identified literature) the increase in risk estimate may be reflective of the higher baseline risk of death amongst those with DM, or, the older age of those with DM associated TB.

The increased number of papers identified by *Baker et al*[121] for final review yielded a larger sample size allowing analysis upon an increased number of outcomes comparative to the review in this thesis and allowed further sub-group analysis for validation of their meta-analytic findings.

It is difficult to identify the difference between TB recurrence events and TB relapse events as although they are biologically different, they are clinically similar. In the studies identified by systematic review individual measures presented are probably a combination of both events. Thus, TB recurrence and relapse were combined into a single outcome when calculating pooled risk estimates. This should be noted when

interpreting this data as findings cannot necessarily be inferred to each separate event (recurrence or relapse).

Conclusions

Risk of death is increased amongst individuals with co-morbid DM and TB almost two fold comparative to those with TB disease alone. However, there are no statistically significant associations between the risk of TB treatment failure or TB relapse amongst individuals with co-morbid TB and DM comparative to those with TB disease alone.

4.2.3 Plausible immunological pathways

Given the findings presented from work in both THIN and ORLS it is interesting to think about the plausible biological pathways that may cause an individual with DM to be at an increased risk of developing TB comparative to an individual without DM.

DM is known to cause immune dysfunction and moderate suppression of the immune system.[437][438] There is research to suggest that DM affects innate immune function such as the production of antimicrobial peptides which are known to be active in the URT in stopping initial TB infection.[439]

More specifically DM is known to hinder cell mediated immunity and has been associated with decreased levels of leucocytes, polymorphonuclear neutrophils (PMNs) and a decreased T-helper 1 (Th1) cytokine response in reaction to TB.[438][440][441] PMNs produce cytokines and carry out phagocytosis.[442]

Th1 type cytokines are vital in the control and inhibition of TB, for example, IFN-γ is important for combating microbial infection and both IFN-γ and TNFα, another Th1 cytokine attack TB via the activation of macrophages.[155][440-442] Activated macrophages release reactive oxygen species (ROS) and free radicals such as Nitric Oxide which are essential for the control of infection, including TB infection.[441][442] Not only are macrophages the primary site of TB infection but they also instigate the main immune response to TB.[28][155] Individuals with DM show strongly reduced non-specific IFN-γ production.[443] With a lower production of IFN-γ and interleukin (IL) 12 being seen in diabetic animal models during early TB infection when compared to levels during early infection in non-diabetic models.[444][445]

Also individuals with DM have inhibited macrophage function, with decreased production of ROS and decreased phagocytic and chemotactic functions.[252][440][441] Specifically alveloar macrophages in active TB patients with co-morbid DM have been identified as being less active.[446] All of which as stated are important for TB clearance.

In human plasma studies, high levels of insulin have been shown to promote a decrease in Th1 immunity through a reduction in the number of Th1 cells and the levels of IFN-y and IL 4. These studies suggest immune modulation in individuals with DM as a highly plausible mechanism for the association seen between DM and TB.[443][447]

Results from work completed within THIN showed that an individual who has had TB may have a higher risk of developing DM comparative to an individual who has not had TB. The inflammation caused by IL 6, and TNFα whilst modulating a response to TB infection could cause a decrease in insulin production by raising levels of beta cell destruction thus causing an increase in blood glucose.[448] Also, as has already been discussed TB medications such as Isoniazid have been shown to have hyperglycaemic effects.[40]

4.2.4 Further work

Further research is still needed to clarify the specificity and direction of the association between TB and DM. Further research is needed into whether risk of developing DM is increased amongst those who have had an active TB infection comparative to those who have not in order to validate evidence presented and inform upon the complexity of the association and its aetiological importance.

It is thought that environmental triggers such as viral and bacterial infection, or nutritional factors can elicit an autoimmune process in individuals genetically predisposed to developing T1DM.[215] This may also hold true for T2DM, however associations between infection and DM are not well understood and findings from this work do not make this clearer. Further investigation of TB as an infectious risk factor for DM is needed alongside current work upon the role of viruses such as; the herpesvirus8 and the entero-viruses.

The effect of key confounders upon the association remains poorly understood. Although newer studies have begun to look at the role of variables such as; BMI, ethnicity, smoking status and HIV, further work is necessary to build a clear picture of the competing factors involved in both TB and DM risk.

With a plausibly large number of individuals presenting with both DM and TB, and this number likely to increase as DM prevalence rises the implications of co-morbidity need to be addressed.[47][57][58] There is a need for appropriate clinical guidance for this specific group of individuals allowing for good clinical practice and better disease outcomes.

As rates of DM increase[23] the incidence of TB may also increase. Publication by *Goldhaber-Fiebert et al* showed that this has already begun to occur in numerous countries.[90] The prevention of DM associated TB will become increasingly important and presents a major public health challenge both in the UK and globally.

Appendices

Appendix A: Breslow and Day Methodology for the Calculation of Rate Ratio's

For comparison between two levels of exposure, exposed (k = 2) and unexposed (k = 1) utilising these pre-programmed methods. Where 0_1 was regarded as a Poisson variable with mean $\theta_1 E_1^*$ and 0_2 as Poisson variable with mean $\theta_2 E_2^*$. With θ set equal to θ_1, $\Psi = \Psi_2 = \theta_2/\theta_1$, and $\theta\Psi = \theta_2$, the parameter of interest is the rate ratio Ψ, with θ playing the role of a nuisance parameter that interferes with our inferences concerning Ψ. Thus if the maximum likelihood estimate of π is $\hat{\pi}=0_2/0_+$ it follows that the maximum likelihood estimate of Ψ is as depicted in equation 1.

Equation 2

$$\widehat{\Psi} = \frac{\hat{\pi}\widehat{E}_1^*}{(1-\hat{\pi})\widehat{E}_2^*} = \frac{0_2 E_1^*}{0_1 E_2^*}$$

Taken from equation 3.8 from Statistical methods in cancer research volume II: The design and analysis of cohort studies, Breslow and Day[404]

Exact $100(1-\alpha)\%$ confidence limits for may be calculated using the binomial parameters π_L and π_U calculated from equation 2 and 3 where $F_{\alpha/2}$ (μ_1, μ_2) denotes the upper $100\alpha/2$ percentile of the F distribution with μ_1 and μ_2 degrees of freedom.

Equation 3 and 4

$$\pi_L = \frac{0_2}{0_2 + (0_1+1)F_{\alpha/2}(20_1+2, 20_2)}$$

and

$$\pi_U = \frac{(0_2+1)F_{\alpha/2}(20_2+2, 20_1)}{0_1 + (0_2+1)F_{\alpha/2}(20_2+2, 20_1)}$$

Taken from equation 3.9 from Statistical methods in cancer research volume II: The design and analysis of cohort studies, Breslow and Day[404]

Then substitute π_L and π_U into equation 4 to calculate the CIs for the rate ratio.

Equation 5

$$\Psi = \frac{\pi E_1^*}{(1 - \pi)E_2^*}$$

Taken from equation 3.6 from Statistical methods in cancer research volume II: The design and analysis of cohort studies, Breslow and Day[404]

Then equation 5 can be used to approximate chi-square statistic based on the observed deviation of 0_2 from its expected where we have used the fact that Var (0_2) is as defined in equation 6.

Equation 6

$$\chi^2 = \frac{\left\{|0_2 - E(0_2)| - \frac{1}{2}\right\}^2}{Var\ (0_2)} = \frac{\left\{|0_1 - \hat{E}_1^*(0_2)| - \frac{1}{2}\right\}^2}{\hat{E}_1^*} + \frac{\left\{|0_2 - \hat{E}_2^*(0_2)| - \frac{1}{2}\right\}^2}{\hat{E}_2^*}$$

Taken from text of Statistical methods in cancer research volume II: The design and analysis of cohort studies, Breslow and Day[404]

Equation 7

$$\text{Var}\ (0_2) = 0 + \pi 0(1 - \pi 0) = \hat{E}_1^* \hat{E}_2^* / (\hat{E}_1^* + \hat{E}_2^*) \text{ and } 01 - \hat{E}_1^* = -(02 - \hat{E}_2^*)$$

Taken from equation 3.7 from Statistical methods in cancer research volume II: The design and analysis of cohort studies, Breslow and Day[466]

Then using the appropriate software function (probchi(…)) the p value can be calculated.

Appendix B: Ethics Approval Form

SRC Feedback

Researcher Name: Fiona Young
Organisation: Institute of Health and Society, Newcastle University
SRC Reference Number: 10-030
Date: 15/11/2010
Study title: Diabetes and the risk of tuberculosis: elucidating the association and its public health impact in the UK
Committee opinion: Approved

_____

The following feedback has been supplied by the SRC.

Advice
(General advice for the researchers as information only – no response is required)
This was well written and well justified. I found the description of the unexposed groups, and the precise nature of the data that would be provided on them rather unclear. Presumably this includes disease status though that isn't specifically stated, for example. For this reason, it wasn't completely clear where and why logistic regression analysis would be used rather than rates analysis and indeed the power calculations seem to refer to hazards and odds somewhat interchangeably - but this is a point for the researchers to address rather than a fundamental issue.

_____

We are pleased to inform that you can proceed with the study as this is now approved.

Once the study has been completed and published, you must let EPIC know in order for your reference number to be closed.

EPIC will let the relevant Ethics committee know this study has been approved by the SRC and will inform them of study completion (when known) on your behalf.

I wish you and your team all the best with the study progression.

Kind Regards,

Mustafa Dungarwalla
Researcher Assistant

SRC
Scientific Review Committee

Appendix C: DM Read Codes

Read Code	Description
C100000	Diabetes mellitus, juvenile type, no mention of complication
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complications
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma

C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E211	Type I diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complications
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma

C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EG11	Type I diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C107300	IDDM with peripheral circulatory disorder
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C10EG12	Insulin dependent diab mell with peripheral angiopathy
C10EJ12	Insulin dependent diab mell with neuropathic arthropathy
L180500	Pre-existing diabetes mellitus, insulin-dependent
ZRbH.00	Perceived control of insulin-dependent diabetes
ZC2C900	Dietary advice for type I diabetes
ZC2C911	Diet advice for insulin-dependent diabetes
66Ag.00	Insulin needles changed daily
66Ah.00	Insulin needles changed for each injection
66AH000	Conversion to insulin
66Aj.00	Insulin needles changed less than once a day
66Am.00	Insulin dose changed
66Ap.00	Insulin treatment initiated
7L10000	Continuous subcutaneous infusion of insulin
7L19800	Subcutaneous injection of insulin
66A5.00	Diabetic on insulin
66AA.11	Injection sites - diabetic
66An.00	Diabetes type 1 review
C100011	Insulin dependent diabetes mellitus
C100100	Diabetes mellitus, adult onset, no mention of complication
C100112	Non-insulin dependent diabetes mellitus
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C104100	Diabetes mellitus, adult onset, with renal manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps

C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications

C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FQ11	Type II diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C107400	NIDDM with peripheral circulatory disorder
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109H00	Non-insulin dependent d m with neuropathic arthropathy
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
ZC2CA00	Dietary advice for type II diabetes
ZC2CA11	Dietary advice non-insulin-dependent diabetes
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
66Ao.00	Diabetes type 2 review
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis

C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104y00	Other specified diabetes mellitus with renal complications
C104z00	Diabetes mellitis with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107y00	Other specified diabetes mellitus with periph circ comps
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C10y.00	Diabetes mellitus with other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec comps
C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication
Cyu2.00	XDiabetes mellitus
Cyu2000	XOther specified diabetes mellitus
Cyu2300	XUnspecified diabetes mellitus with renal complications
C110.00	Hypoglycaemic coma
C110z00	Hypoglycaemic coma NOS
C110.11	Insulin coma
C10ER00	Latent autoimmune diabetes mellitus in adult
C10M.00	Lipoatrophic diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication
66AJ100	Brittle diabetes
F171100	Autonomic neuropathy due to diabetes
F345000	Diabetic mononeuritis multiplex
F35z000	Diabetic mononeuritis NOS
F372.00	Polyneuropathy in diabetes
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F381300	Myasthenic syndrome due to diabetic amyotrophy
F381311	Diabetic amyotrophy
F3y0.00	Diabetic mononeuropathy
F420.00	Diabetic retinopathy
F420000	Background diabetic retinopathy
F420100	Proliferative diabetic retinopathy
F420200	Preproliferative diabetic retinopathy
F420300	Advanced diabetic maculopathy

F420400	Diabetic maculopathy
F420500	Advanced diabetic retinal disease
F420600	Non proliferative diabetic retinopathy
F420700	High risk proliferative diabetic retinopathy
F420800	High risk non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F440700	Diabetic iritis
F464000	Diabetic cataract
G73y000	Diabetic peripheral angiopathy
K01x100	Nephrotic syndrome in diabetes mellitus
Kyu0300	XGlomerular disorders in diabetes mellitus
L180X00	Pre-existing diabetes mellitus, unspecified
Lyu2900	XPre-existing diabetes mellitus, unspecified
M037200	Cellulitis in diabetic foot
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
N030000	Diabetic cheiroarthropathy
N030011	Diabetic cheiropathy
N030100	Diabetic Charcot arthropathy
R054200	DGangrene of toe in diabetic
R054300	DWidespread diabetic foot gangrene
ZC2C800	Dietary advice for diabetes mellitus
ZV65312	VDietary counselling in diabetes mellitus
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
2BBF.00	Retinal abnormality - diabetes related
2BBJ.00	O/E - no right diabetic retinopathy
2BBK.00	O/E - no left diabetic retinopathy
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
2BBL.00	O/E - diabetic maculopathy present both eyes
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
2BBM.00	O/E - diabetic maculopathy absent both eyes
2BBo.00	O/E - sight threatening diabetic retinopathy
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2BBT.00	O/E - right eye proliferative diabetic retinopathy
2BBV.00	O/E - left eye proliferative diabetic retinopathy
2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2G51000	Foot abnormality - diabetes related
2G5A.00	O/E - Right diabetic foot at risk
2G5B.00	O/E - Left diabetic foot at risk
2G5C.00	Foot abnormality - diabetes related
2G5D.00	Foot abnormality - non-diabetes
2G5E.00	O/E - Right diabetic foot at low risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5G.00	O/E - Right diabetic foot at high risk
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5I.00	O/E - Left diabetic foot at low risk
2G5J.00	O/E - Left diabetic foot at moderate risk
2G5K.00	O/E - Left diabetic foot at high risk
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
66A..00	Diabetic monitoring
66A1.00	Initial diabetic assessment

66A2.00	Follow-up diabetic assessment
66A8.00	Has seen dietician - diabetes
66A9.00	Understands diet - diabetes
66Aa.00	Diabetic diet - poor compliance
66Ab.00	Diabetic foot examination
66Ac.00	Diabetic peripheral neuropathy screening
66AD.00	Fundoscopy - diabetic check
66Af.00	Patient diabetes education review
66AG.00	Diabetic drug side effects
66AH.00	Diabetic treatment changed
66AI.00	Diabetic - good control
66Ai.00	Diabetic 6 month review
66AJ.00	Diabetic - poor control
66AJ.11	Unstable diabetes
66AJz00	Diabetic - poor control NOS
66Ak.00	Diabetic monitoring - lower risk albumin excretion
66AK.00	Diabetic - cooperative patient
66Al.00	Diabetic monitoring - higher risk albumin excretion
66AL.00	Diabetic-uncooperative patient
66AM.00	Diabetic - follow-up default
66AN.00	Date diabetic treatment start
66AO.00	Date diabetic treatment stopped
66AP.00	Diabetes: practice programme
66Aq.00	Diabetic foot screen
66AQ.00	Diabetes: shared care programme
66AR.00	Diabetes management plan given
66AS.00	Diabetic annual review
66AT.00	Annual diabetic blood test
66AU.00	Diabetes care by hospital only
66AV.00	Diabetic on insulin and oral treatment
66AW.00	Diabetic foot risk assessment
66AX.00	Diabetes: shared care in pregnancy - diabetologist and obstetrician
66AY.00	Diabetic diet - good compliance
66AZ.00	Diabetic monitoring NOS
66b1.00	Diabetic monitoring not required
6761.00	Diabetic pre-pregnancy counselling
68A7.00	Diabetic retinopathy screening
68A9.00	Diabetic retinopathy screening offered
68AB.00	Diabetic digital retinopathy screening offered
7276.00	Pan retinal photocoagulation for diabetes
8A12.00	Diabetic crisis monitoring
8A13.00	Diabetic stabilisation
8B3l.00	Diabetes medication review
8BL2.00	Patient on maximal tolerated therapy for diabetes
8CA4100	Pt advised re diabetic diet
8CP2.00	Transition of diabetes care options discussed
8CR2.00	Diabetes clinical management plan
8CS0.00	Diabetes care plan agreed
8H2J.00	Admit diabetic emergency
8H3O.00	Non-urgent diabetic admission
8HBG.00	Diabetic retinopathy 12 month review
8HBH.00	Diabetic retinopathy 6 month review
8Hg4.00	Discharged from care of diabetes specialist nurse
8HKE.00	Diabetology D.V. requested
66A6.00	Last hypo. attack
66A7.00	Frequency of hypo. attacks
66A7000	Frequency of hospital treated hypoglycaemia
66A7100	Frequency of GP or paramedic treated hypoglycaemia
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance

66AJ200	Loss of hypoglycaemic warning
66AJ300	Recurrent severe hypos
8HLE.00	Diabetology D.V. done
8HME.00	Listed for Diabetology admissn
8I3W.00	Diabetic foot examination declined
8I3X.00	Diabetic retinopathy screening refused
8I57.00	Patient held diabetic record declined
8I6F.00	Diabetic retinopathy screening not indicated
8I6G.00	Diabetic foot examination not indicated

Appendix D:T1DM Read Codes

Read Code	Description
C100000	Diabetes mellitus, juvenile type, no mention of complication
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma

C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E211	Type I diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma

C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EG11	Type I diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C107300	IDDM with peripheral circulatory disorder
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C10EG12	Insulin dependent diab mell with peripheral angiopathy
C10EJ12	Insulin dependent diab mell with neuropathic arthropathy
L180500	Pre-existing diabetes mellitus, insulin-dependent
ZRbH.00	Perceived control of insulin-dependent diabetes
ZC2C900	Dietary advice for type I diabetes
ZC2C911	Diet advice for insulin-dependent diabetes
66Ag.00	Insulin needles changed daily
66Ah.00	Insulin needles changed for each injection
66AH000	Conversion to insulin
66Aj.00	Insulin needles changed less than once a day
66Am.00	Insulin dose changed
66Ap.00	Insulin treatment initiated
7L10000	Continuous subcutaneous infusion of insulin
7L19800	Subcutaneous injection of insulin
66A5.00	Diabetic on insulin
66AA.11	Injection sites - diabetic
66An.00	Diabetes type 1 review
C100011	Insulin dependent diabetes mellitus

Appendix E: T2DM Read Codes

Read Code	Description
C100100	Diabetes mellitus, adult onset, no mention of complication
C100112	Non-insulin dependent diabetes mellitus
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C104100	Diabetes mellitus, adult onset, with renal manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract

C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy

C10FQ11	Type II diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C107400	NIDDM with peripheral circulatory disorder
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109H00	Non-insulin dependent d m with neuropathic arthropathy
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
ZC2CA00	Dietary advice for type II diabetes
ZC2CA11	Dietary advice non-insulin-dependent diabetes
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
66Ao.00	Diabetes type 2 review

Appendix F: TB Read Codes

Read Code	Description
4E38.00	Sputum: tubercle on Z-N stain
65V9.00	Notification of tuberculosis
65V9.11	TB - tuberculosis notification
65Y0.00	Tuberculosis index case
65Y1.00	On tuberculosis chemoprophylaxis
65Y2.00	Streptomycin resistant tuberculosis
65Y3.00	Rifampicin resistant tuberculosis
65Y4.00	Pyrazinamide resistant tuberculosis
65Y5.00	Isoniazid resistant tuberculosis
65Y6.00	Ethionamide resistant tuberculosis
65Y7.00	Ethambutol resistant tuberculosis
65Y8.00	Ciprofloxacin resistant tuberculosis
65Y9.00	Inactive tuberculosis
65Y9.11	Latent tuberculosis
745F.00	Tuberculosis support
745Fy00	Other specified tuberculosis support
745Fz00	Tuberculosis support NOS
A1...00	Tuberculosis
A10..00	Primary tuberculous infection
A100.00	Primary tuberculous complex
A101.00	Tuberculous pleurisy in primary progressive tuberculosis
A10y.00	Other primary progressive tuberculosis
A10z.00	Primary tuberculous infection NOS
A11..00	Pulmonary tuberculosis
A11..11	Lung tuberculosis
A110.00	Infiltrative lung tuberculosis
A111.00	Nodular lung tuberculosis
A112.00	Tuberculosis of lung with cavitation
A113.00	Tuberculosis of bronchus
A114.00	Tuberculous fibrosis of lung
A115.00	Tuberculous bronchiectasis
A116.00	Tuberculous pneumonia
A117.00	Tuberculous pneumothorax
A11y.00	Other specified pulmonary tuberculosis
A11z.00	Pulmonary tuberculosis NOS
A12..00	Other respiratory tuberculosis
A120.00	Tuberculous pleurisy
A120000	Tuberculosis of pleura
A120100	Tuberculous empyema
A120200	Tuberculous hydrothorax
A120z00	Tuberculous pleurisy NOS
A121.00	Tuberculosis of intrathoracic lymph nodes
A121000	Tuberculosis of hilar lymph nodes
A121100	Tuberculosis of mediastinal lymph nodes
A121200	Tuberculosis of tracheobronchial lymph nodes
A121z00	Tuberculosis of intrathoracic lymph nodes NOS
A122.00	Isolated tracheal or bronchial tuberculosis
A122000	Isolated tracheal tuberculosis
A122100	Isolated bronchial tuberculosis
A122z00	Isolated tracheal or bronchial tuberculosis NOS
A123.00	Tuberculous laryngitis
A124100	Tuberculosis of lung, confirmed by culture only
A124200	Tuberculosis of lung, confirmed histologically
A124300	Tuberculosis of lung, confirmed by unspecified means
A124500	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
A124600	Tuberculous pleurisy, conf bacteriologically/histologically

A125000	Tuberculosis of lung, bacteriologically & histolog'y neg
A125100	Tuberculosis lung bact and histological examin not done
A12y.00	Other specified respiratory tuberculosis
A12y000	Tuberculosis of mediastinum
A12y100	Tuberculosis of nasopharynx
A12y200	Tuberculosis of nasal septum
A12y300	Tuberculosis of nasal sinus
A12yz00	Other specified respiratory tuberculosis NOS
A13..00	Tuberculosis of meninges and central nervous system
A130.00	Tuberculous meningitis
A130000	Tuberculosis of cerebral meninges
A130100	Tuberculosis of spinal meninges
A130200	Tuberculous leptomeningitis
A130300	Tuberculous meningoencephalitis
A130z00	Tuberculous meningitis NOS
A131.00	Tuberculoma of meninges
A132.00	Tuberculoma of brain
A133.00	Tuberculous abscess of brain
A134.00	Tuberculoma of spinal cord
A135.00	Tuberculous abscess of spinal cord
A136.00	Tuberculous encephalitis or myelitis
A136000	Tuberculous encephalitis
A136100	Tuberculous myelitis
A136z00	Tuberculous encephalitis or myelitis NOS
A13y.00	Other specified tuberculosis of central nervous system
A13z.00	Tuberculosis of central nervous system NOS
A14..00	Tuberculosis of intestines, peritoneum and mesenteric glands
A140.00	Tuberculous peritonitis
A14y.00	Other gastrointestinal tract tuberculosis
A14y000	Tuberculosis of anus
A14y100	Tuberculosis of large intestine
A14y200	Tuberculosis of small intestine
A14y300	Tuberculosis of mesenteric lymph glands
A14y400	Tuberculosis of rectum
A14y500	Tuberculosis of retroperitoneal lymph nodes
A14yz00	Other gastrointestinal tract tuberculosis NOS
A14z.00	Tuberculosis of gastrointestinal tract NOS
A15..00	Tuberculosis of bones and joints
A15..11	Tuberculous osteomylelytis
A15..12	Tuberculous arthritis
A15..13	Tuberculous synovitis
A150.00	Tuberculosis of vertebral column - Pott's
A151.00	Tuberculosis of hip
A152.00	Tuberculosis of knee
A153.00	Tuberculosis limb bones - Tuberculous dactylitis
A154.00	Tuberculous mastoiditis
A15x.00	Tuberculosis of other specified bones
A15y.00	Tuberculosis of other specified joint
A15z.00	Tuberculosis of bones or joints NOS
A16..00	Tuberculosis of genitourinary system
A160.00	Tuberculosis of kidney
A160.11	Renal tuberculosis
A160000	Tuberculous nephropathy
A160100	Tuberculous pyelitis
A160200	Tuberculous pyelonephritis
A160z00	Tuberculosis of kidney NOS
A161.00	Tuberculosis of bladder
A162.00	Tuberculosis of ureter
A163.00	Tuberculosis of other urinary organs

A164.00	Tuberculosis of epididymis
A165.00	Tuberculosis of other male genital organs
A165000	Tuberculosis of prostate
A165100	Tuberculosis seminal vesicle
A165200	Tuberculosis of testis
A165z00	Tuberculosis of other male genital organs NOS
A166.00	Tuberculous oophoritis or salpingitis
A166000	Tuberculous oophoritis
A166100	Tuberculous salpingitis
A166111	Fallopian tube tuberculosis
A166z00	Tuberculous oophoritis or salpingitis NOS
A167.00	Tuberculosis of other female genital organs
A167000	Tuberculous cervicitis
A167100	Tuberculous endometritis
A167z00	Tuberculosis of other female genital organs NOS
A168.00	Tuberculosis of urinary tract
A16z.00	Genitourinary tuberculosis NOS
A17..00	Tuberculosis of other organs
A170.00	Tuberculosis of skin and subcutaneous tissue
A170.11	Lupus - tuberculous
A170000	Tuberculosis - lupus exedens
A170100	Tuberculosis - lupus vulgaris
A170200	Tuberculosis - scrofuloderma
A170300	Tuberculosis - lupus NOS
A170400	Tuberculosis colliquativa
A170500	Tuberculosis cutis
A170600	Tuberculosis lichenoides
A170700	Tuberculosis papulonecrotica
A170800	Tuberculosis verrucosa cutis
A170z00	Tuberculosis of skin and subcutaneous tissue NOS
A171.00	Tuberculosis with erythema nodosum hypersensitivity reaction
A171100	Tuberculous erythema nodosum
A171z00	Erythema nodosum with tuberculosis NOS
A172.00	Tuberculosis of peripheral lymph nodes
A172000	Tuberculous - cervical lymphadenitis
A172011	Scrofula - tuberculous cervical lymph nodes
A172100	Scrofulous tuberculous abscess
A172200	Tuberculous adenitis
A172z00	Tuberculosis of peripheral lymph nodes NOS
A173.00	Tuberculosis of eye
A173000	Tuberculous chorioretinitis
A173100	Tuberculous episcleritis
A173200	Tuberculous interstitial keratitis
A173300	Tuberculous chronic iridocyclitis
A173400	Tuberculous keratoconjunctivitis
A173z00	Tuberculosis of eye NOS
A174.00	Tuberculosis of ear
A175.00	Tuberculosis of thyroid gland
A176.00	Tuberculosis of adrenal glands - Addison's disease
A177.00	Tuberculosis spleen
A178.00	Tuberculosis oesophagus
A17y.00	Tuberculosis of other specified organs
A17y000	Tuberculosis endocardium
A17y100	Tuberculosis myocardium
A17y200	Tuberculosis pericardium
A17y300	Tuberculosis of stomach
A17y400	Tuberculosis of liver
A17yz00	Tuberculosis of other specified organs NOS
A17z.00	Tuberculosis of other organs NOS

A18..00	Miliary tuberculosis
A180.00	Acute miliary tuberculosis
A180000	Acute miliary tuberculosis of a single specified site
A180100	Acute miliary tuberculosis of multiple sites
A18y.00	Other specified miliary tuberculosis
A18z.00	Miliary tuberculosis NOS
A1y..00	Other specified tuberculosis
A1z..00	Tuberculosis NOS
AE0..00	Late effects of tuberculosis
AE00.00	Late effects of respiratory tuberculosis
AE01.00	Late effects of central nervous system tuberculosis
AE02.00	Late effects of genitourinary system tuberculosis
AE03.00	Late effects of tuberculosis of bones and joints
AE04.00	Late effects of tuberculosis of other specified organs
AE0z.00	Late effects of tuberculosis NOS
Ayu1.00	XTuberculosis
Ayu1000	XOther resp tubercul,confirmd bacteriologicly+histologicly
Ayu1100	XResp tuberculos unspcfd,confirmd bacteriolog+histologicly
Ayu1200	XOth resp tubercul, w'out m/bacteriol or histol confirmatn
Ayu1400	XOther tuberculosis of nervous system
Ayu1500	XTuberculosis of nervous system, unspecified
Ayu1600	XTuberculosis of other specified organs
Ayu1700	XAcute miliary tuberculosis, unspecified
Ayu1800	XOther miliary tuberculosis
Ayu1900	XMiliary tuberculosis, unspecified
AyuJ000	XSequelae of central nervous system tuberculosis
AyuJ100	XSequelae of genitourinary tuberculosis
AyuJ200	XSequelae of tuberculosis of bones and joints
AyuJ300	XSequelae of tuberculosis of other organs
AyuJ400	XSequelae of respiratory and unspecified tuberculosis
F004.00	Meningitis - tuberculous
F033300	Encephalitis due to tuberculosis
F033311	Tuberculous encephalitis
F040600	Tuberculous intracranial abscess
F041300	Tuberculous intraspinal abscess
F4A5500	Keratitis due to tuberculosis
G500300	Acute pericarditis - tuberculous
G520600	Acute myocarditis - tuberculous
H450.00	Pneumoconiosis associated with tuberculosis
J550200	Peritonitis - tuberculous
J615E00	Cardituberculous cirrhosis
Jyu9300	XTuberculous disorders of intestine and mesentery
K154800	Cystitis in tuberculosis
K214300	Prostatitis in tuberculosis
K43..00	Female tuberculous pelvic inflammatory disease
L173.00	Maternal tuberculosis in pregnancy/childbirth/puerperium
L173000	Maternal tuberculosis,unspec whether in pregnancy/puerperium
L173100	Maternal tuberculosis during pregnancy - baby delivered
L173200	Maternal tuberculosis in puerperium - baby delivered
L173300	Maternal tuberculosis in pregnancy - baby not yet delivered
L173400	Maternal tuberculosis in puerperium - baby previously deliv.
L173z00	Maternal tuberculosis in pregnancy/childbirth/puerperium NOS
M151400	Erythema tuberculatum
N018.00	Tuberculous arthritis
N22yD00	Tuberculous infection of tendon sheath
N304.00	Tuberculosis of spine (Pott's)
N304.11	Tuberculosis of spine
N304000	Tuberculosis of cervical spine
N304100	Tuberculosis of thoracic spine

N304200	Tuberculosis of lumbar spine
N304300	Tuberculosis of sacrum/coccyx
N305.00	Tuberculosis of limb bones
N305000	Tuberculosis of unspecified limb bone
N305100	Tuberculosis of the upper arm bone
N305200	Tuberculosis of the forearm bone
N305300	Tuberculosis of the pelvic and thigh bones
N305400	Tuberculosis of the lower leg bone
N305500	Tuberculosis of other limb bones
N305600	Tuberculosis of multiple limb bones
N305z00	Tuberculosis of limb bones NOS
N306.00	Tuberculosis of other bones
N306000	Tuberculosis of bone, site unspecified
N306100	Tuberculosis of the bones of the shoulder region
N306200	Tuberculosis of the bones of the hand
N306300	Tuberculosis of the bones of the ankle and foot
N306400	Tuberculosis of the bones of other sites
N306500	Tuberculosis of the bones of multiple sites
N306z00	Tuberculosis of bone NOS
Q402400	Congenital tuberculosis
65V9.11	TB - tuberculosis notification
8BAD100	TB chemotherapy
A124.00	Resp TB bacteriologically and histologically confirmed
A124000	TB lung confirm sputum microscopy with or without culture
A124400	TB intrathoracic lymph nodes confirm bact histologically
A124700	Primary respiratory TB confirm bact and histologically
A125.00	Respiratory TB not confirmed bact or histologically
A125200	Prim respiratory TB without mention of bact or hist confirm
A125X00	Resp TB unspcf,w'out mention/bacterial or histol confrmtn
Ayu1300	XResp TB unspcf,w'out mention/bacterial or histol confrmtn
G500311	TB - acute pericarditis

Appendix G: PTB Read Codes

Read Code	Description
A11y.00	Other specified pulmonary tuberculosis
A11z.00	Pulmonary tuberculosis NOS
A122.00	Isolated tracheal or bronchial tuberculosis
A124300	Tuberculosis of lung, confirmed by unspecified means
A125000	Tuberculosis of lung, bacteriologically & histolog'y neg
A125100	Tuberculosis lung bact and histological examin not done
A124000	TB lung confirm sputum microscopy with or without culture

Appendix H: EPTB Read Codes

Read Code	Description
A120.00	Tuberculous pleurisy
A120000	Tuberculosis of pleura
A120100	Tuberculous empyema
A120200	Tuberculous hydrothorax
A120z00	Tuberculous pleurisy NOS
A121.00	Tuberculosis of intrathoracic lymph nodes
A121000	Tuberculosis of hilar lymph nodes
A121100	Tuberculosis of mediastinal lymph nodes
A121200	Tuberculosis of tracheobronchial lymph nodes
A121z00	Tuberculosis of intrathoracic lymph nodes NOS
A123.00	Tuberculous laryngitis
A124500	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
A124600	Tuberculous pleurisy, conf bacteriologically/histologically
A12y000	Tuberculosis of mediastinum
A12y100	Tuberculosis of nasopharynx
A12y200	Tuberculosis of nasal septum
A12y300	Tuberculosis of nasal sinus
A13..00	Tuberculosis of meninges and central nervous system
A130.00	Tuberculous meningitis
A130000	Tuberculosis of cerebral meninges
A130100	Tuberculosis of spinal meninges
A130200	Tuberculous leptomeningitis
A130300	Tuberculous meningoencephalitis
A130z00	Tuberculous meningitis NOS
A131.00	Tuberculoma of meninges
A132.00	Tuberculoma of brain
A133.00	Tuberculous abscess of brain
A134.00	Tuberculoma of spinal cord
A135.00	Tuberculous abscess of spinal cord
A136.00	Tuberculous encephalitis or myelitis
A136000	Tuberculous encephalitis
A136100	Tuberculous myelitis
A136z00	Tuberculous encephalitis or myelitis NOS
A13y.00	Other specified tuberculosis of central nervous system
A13z.00	Tuberculosis of central nervous system NOS
A14..00	Tuberculosis of intestines, peritoneum and mesenteric glands
A140.00	Tuberculous peritonitis
A14y.00	Other gastrointestinal tract tuberculosis
A14y000	Tuberculosis of anus
A14y100	Tuberculosis of large intestine
A14y200	Tuberculosis of small intestine
A14y300	Tuberculosis of mesenteric lymph glands
A14y400	Tuberculosis of rectum
A14y500	Tuberculosis of retroperitoneal lymph nodes
A14yz00	Other gastrointestinal tract tuberculosis NOS
A14z.00	Tuberculosis of gastrointestinal tract NOS
A15..00	Tuberculosis of bones and joints
A15..11	Tuberculous osteomylelytis
A15..12	Tuberculous arthritis
A15..13	Tuberculous synovitis
A150.00	Tuberculosis of vertebral column - Pott's
A151.00	Tuberculosis of hip
A152.00	Tuberculosis of knee
A153.00	Tuberculosis limb bones - Tuberculous dactylitis
A154.00	Tuberculous mastoiditis
A15x.00	Tuberculosis of other specified bones

A15y.00	Tuberculosis of other specified joint
A15z.00	Tuberculosis of bones or joints NOS
A16..00	Tuberculosis of genitourinary system
A160.00	Tuberculosis of kidney
A160.11	Renal tuberculosis
A160000	Tuberculous nephropathy
A160100	Tuberculous pyelitis
A160200	Tuberculous pyelonephritis
A160z00	Tuberculosis of kidney NOS
A161.00	Tuberculosis of bladder
A162.00	Tuberculosis of ureter
A163.00	Tuberculosis of other urinary organs
A164.00	Tuberculosis of epididymis
A165.00	Tuberculosis of other male genital organs
A165000	Tuberculosis of prostate
A165100	Tuberculosis seminal vesicle
A165200	Tuberculosis of testis
A165z00	Tuberculosis of other male genital organs NOS
A166.00	Tuberculous oophoritis or salpingitis
A166000	Tuberculous oophoritis
A166100	Tuberculous salpingitis
A166111	Fallopian tube tuberculosis
A166z00	Tuberculous oophoritis or salpingitis NOS
A167.00	Tuberculosis of other female genital organs
A167000	Tuberculous cervicitis
A167100	Tuberculous endometritis
A167z00	Tuberculosis of other female genital organs NOS
A168.00	Tuberculosis of urinary tract
A16z.00	Genitourinary tuberculosis NOS
A17..00	Tuberculosis of other organs
A170.00	Tuberculosis of skin and subcutaneous tissue
A170.11	Lupus - tuberculous
A170000	Tuberculosis - lupus exedens
A170100	Tuberculosis - lupus vulgaris
A170200	Tuberculosis - scrofuloderma
A170300	Tuberculosis - lupus NOS
A170400	Tuberculosis colliquativa
A170500	Tuberculosis cutis
A170600	Tuberculosis lichenoides
A170700	Tuberculosis papulonecrotica
A170800	Tuberculosis verrucosa cutis
A170z00	Tuberculosis of skin and subcutaneous tissue NOS
A171.00	Tuberculosis with erythema nodosum hypersensitivity reaction
A171100	Tuberculous erythema nodosum
A171z00	Erythema nodosum with tuberculosis NOS
A172.00	Tuberculosis of peripheral lymph nodes
A172000	Tuberculous - cervical lymphadenitis
A172011	Scrofula - tuberculous cervical lymph nodes
A172100	Scrofulous tuberculous abscess
A172200	Tuberculous adenitis
A172z00	Tuberculosis of peripheral lymph nodes NOS
A173.00	Tuberculosis of eye
A173000	Tuberculous chorioretinitis
A173100	Tuberculous episcleritis
A173200	Tuberculous interstitial keratitis
A173300	Tuberculous chronic iridocyclitis
A173400	Tuberculous keratoconjunctivitis
A173z00	Tuberculosis of eye NOS
A174.00	Tuberculosis of ear

A175.00	Tuberculosis of thyroid gland
A176.00	Tuberculosis of adrenal glands - Addison's disease
A177.00	Tuberculosis spleen
A178.00	Tuberculosis oesophagus
A17y.00	Tuberculosis of other specified organs
A17y000	Tuberculosis endocardium
A17y100	Tuberculosis myocardium
A17y200	Tuberculosis pericardium
A17y300	Tuberculosis of stomach
A17y400	Tuberculosis of liver
A17yz00	Tuberculosis of other specified organs NOS
A17z.00	Tuberculosis of other organs NOS
A18..00	Miliary tuberculosis
A180.00	Acute miliary tuberculosis
A180000	Acute miliary tuberculosis of a single specified site
A180100	Acute miliary tuberculosis of multiple sites
A18y.00	Other specified miliary tuberculosis
A18z.00	Miliary tuberculosis NOS
A1y..00	Other specified tuberculosis
AE01.00	Late effects of central nervous system tuberculosis
AE02.00	Late effects of genitourinary system tuberculosis
AE03.00	Late effects of tuberculosis of bones and joints
AE04.00	Late effects of tuberculosis of other specified organs
AE0z.00	XOther tuberculosis of nervous system
Ayu1.00	XTuberculosis of nervous system, unspecified
Ayu1000	XTuberculosis of other specified organs
Ayu1100	XAcute miliary tuberculosis, unspecified
Ayu1200	XOther miliary tuberculosis
Ayu1400	XMiliary tuberculosis, unspecified
Ayu1500	XSequelae of central nervous system tuberculosis
Ayu1600	XSequelae of genitourinary tuberculosis
Ayu1700	XSequelae of tuberculosis of bones and joints
Ayu1800	XSequelae of tuberculosis of other organs
Ayu1900	XSequelae of respiratory and unspecified tuberculosis
AyuJ000	Meningitis - tuberculous
AyuJ100	Encephalitis due to tuberculosis
AyuJ200	Tuberculous encephalitis
AyuJ300	Tuberculous intracranial abscess
AyuJ400	Tuberculous intraspinal abscess
F004.00	Keratitis due to tuberculosis
F033300	Acute pericarditis - tuberculous
F033311	Acute myocarditis - tuberculous
F040600	Pneumoconiosis associated with tuberculosis
F041300	Peritonitis - tuberculous
F4A5500	Cardituberculous cirrhosis
G500300	XTuberculous disorders of intestine and mesentery
G520600	Cystitis in tuberculosis
H450.00	Prostatitis in tuberculosis
J550200	Female tuberculous pelvic inflammatory disease
L173100	Erythema tuberculatum
L173200	Tuberculous arthritis
L173300	Tuberculous infection of tendon sheath
L173400	Tuberculosis of spine (Pott's)
L173z00	Tuberculosis of spine
M151400	Tuberculosis of cervical spine
N018.00	Tuberculosis of thoracic spine
N22yD00	Tuberculosis of lumbar spine
N304.00	Tuberculosis of sacrum/coccyx
N304.11	Tuberculosis of limb bones

N304000	Tuberculosis of unspecified limb bone
N304100	Tuberculosis of the upper arm bone
N304200	Tuberculosis of the forearm bone
N304300	Tuberculosis of the pelvic and thigh bones
N305.00	Tuberculosis of the lower leg bone
N305000	Tuberculosis of other limb bones
N305100	Tuberculosis of multiple limb bones
N305200	Tuberculosis of limb bones NOS
N305300	Tuberculosis of other bones
N305400	Tuberculosis of bone, site unspecified
N305500	Tuberculosis of the bones of the shoulder region
N305600	Tuberculosis of the bones of the hand
N305z00	Tuberculosis of the bones of the ankle and foot
N306.00	Tuberculosis of the bones of other sites
N306000	Tuberculosis of the bones of multiple sites
N306100	Tuberculosis of bone NOS
N306200	Congenital tuberculosis
A124700	TB - acute pericarditis

Appendix I: Smoking Status

Current Smoker	Past Smoker	Non Smoker
	Read Codes	
137..11	1377.00	1371.00
137f.00	137N.00	1371.11
67H1.00	745H400	9kn..00
H310100	9OO..11	1371.00
137Y.00	9OOA.00	**AHD Code/V Code**
E251100	1378.00	1003040000/3
Eu17y00	137O.00	
1372.00	745Hy00	
137G.00	9OO..12	
8HkQ.00	9OOZ.00	
ZG23300	1379.00	
SMC..00	137S.00	
E251200	745Hz00	
Eu17z00	9OO1.00	
1372.11	38DH.00	
137H.00	137B.00	
8HTK.00	13p..00	
ZRaM.00	8CAL.00	
137..00	9OO3.00	
E251z00	745H100	
J036400	137A.00	
1373.00	137T.00	
137J.00	8CAg.00	
8I6H.00	9OO2.00	
ZRaM.11	745H000	
137a.00	137l.00	
Eu17.00	745H.00	
SMC..00	9OO..00	
137C.00	137L.00	
137R.00	13p3.00	
9kf1.11	9kc0.00	
137a.00	9OO7.00	
6893.00	8B3f.00	
Eu17400	67H6.00	
137c.00	13p2.00	
137V.00	9kc..00	
9kf2.00	9OO6.00	
137g.00	8B2B.00	
68T..00	8I39.00	
Eu17500	9km..00	
137d.00	13p1.00	
6791.00	8HBM.00	
9kf2.11	9OO5.00	
137M.00	745H300	
E251.00	137F.00	
Eu17600	13p0.00	
137e.00	8H7i.00	
67A3.00	9OO4.00	
9ko..00	745H200	
137X.00	8I2I.00	
E251000	E251300	
Eu17700	137j.00	
1375.00	13p5.00	
137P.11	9N4M.00	
9hG0.00	9OO9.00	

ZRao.11	8BP3.00	
137h.00	137K.00	
Eu17100	13p4.00	
ZV4K000	9N2k.00	
1374.00	9OO8.00	
137P.00	8B3Y.00	
9hG..00	E023.00	
ZRao.00	**AHDCode/VCode**	
137D.00	1003040000/2	
Eu17000		
ZV11600		
137b.00		
137Q.11		
9kf1.00		
ZRh4.11		
63C5.00		
Eu17300		
1376.00		
137Q.00		
9hG1.00		
ZRh4.00		
137Z.00		
Eu17200		
ZV6D800		
AHDCode/VCode		
1003040000/1		

Appendix J: Systematic review study Inclusion form (abstract review)

Paper Review- Study Inclusion Form

Paper Details

Data Extractor: FY ☐ NU ☒
Paper number: ☐

First Author: ☐

Year of publication: ☐

Inclusion criteria	Exclusion criteria
Assesses and reports upon at least one of the following outcomes in a population of individuals with concomitant **TB and DM** or **Hyperglycaemia** **Mortality,** ○ Rate or number with **MDR-TB,** ○ Time to **sputum negativity** or related outcomes assessing time to cure (smear negative, bacteriologic cure, smear conversion, sputum conversion), ○ **Treatment failure** rate (or number) ○ **Cure rate** (or number) ○ **Relapse rate** (or number)	Should already be removed from systematic review if: ○ **Non-English Language** ○ **Single Case Report** ○ Not an Original Research Article (review) ○ Irrelevant (does not look at TB outcomes in patients with concomitant DM or hyperglycaemia)

Excluded / Unclear because &
if Unclear what action taken: ☐

Investigator(s) contacted
for more information: ☐

Address: ☐

Telephone: ☐

E-mail: ☐

Comments: ☐

To be included in full review? Yes ☐ No ☐
To be included in discussion? Yes ☐ No ☐

1

Appendix K: Systematic review data extraction form

Data Extraction Form

Publication Details

Data Extractor: FY ☒ NU ☐ JC ☐

Paper Number:

First Author:

Year of publication:

Title:

Study & Participant details

Type of study/design:Cross Sectional

Other/more detail:

Background and Objectives: (explain rationale and objectives/hypotheses)

Time period of study:

Target Population:

Geographical area of study:

Sample Size:

Σ study population	TB DM patients			

Median ☐ or mean ☒ age of:

Σ study population	TB DM patients			

Age range of:

Σ study population	TB DM patients			

Gender ratio of (M:F):

Σ study population	TB DM patients			

Ethnicity of participants:

What/were anthropometric measures were taken?

Participant inclusion/exclusion criteria:

Controls used (if used):

Comments:

Study Quality (based on NOS)

Case/Control

Is the case definition adequate?
Yes, with independent validation ☐
Yes, eg record linkage or based on self reports ☐
No description ☐
Details:

Are cases representative?
Consecutive or obviously representative series of cases ☐
Potential for selection biases or method of case ascertainment not stated ☐
Details:

Definition of Controls if used
No history of disease with an endpoint ☐
No description of source ☐
Details:
Is rationale for choice of controls listed?
Community controls ☐
Hospital ☐
No description ☐
Other ☐
Comment:

Same method of ascertainment for cases and controls? Yes ☐ No ☐

Are cases/control groups comparable? Yes ☐ No ☐
Comment:

Cohort
Are the following identified: outcomes Yes ☐   No ☐
                                exposures Yes ☐   No ☐
Ascertainment of exposure:
Secure record (eg surgical records) ☐
Structured interview where blind to case/control status ☐
Interview not blinded to case/control status ☐
Written self report or medical record only ☐
No description ☐
Other ☐
Details/Comments:

Representativeness of the exposed cohort:
    Truly representative of the average patient ☐
    Somewhat representative of the patient ☐
    Not representative of the average patient ☐
    No description of the derivation of the cohort ☐

    Details:

Selection of the non exposed cohort:

    Drawn from the same community as the exposed cohort ☐
    Drawn from a different source ☐
    No description of the derivation of the non exposed cohort ☐

    Details:
Assessment of outcome
    Were methods of outcome assessment reported and appropriate? Yes ☐ No ☐
    Independent blind assessment ☐
    Record linkage ☐
    Self report ☐
    No description ☐
    Other ☐
    Details/Comments:

    Was follow-up long enough for outcomes to occur? Yes (6 months) ☐ No ☐
    Details/Comments:

Adequacy of follow up of cohorts:
    Complete follow up - all subjects accounted for ☐
    Subjects lost to follow up unlikely to introduce bias - small number lost ☐
    Follow up rate poor and no description of those lost ☐
    No statement ☐

All studies

Were samples representative of target population? Yes ☐ No ☐

Was there any loss to follow up? Yes ☐   No ☐
Numbers/% given?
Non-Response rate:
    Same response rate for all groups ☐
    Non respondents described ☐
    Rate different and no designation ☐
    Comment:

Were study limitations discussed? Yes ☐   No ☐
Comments:

Were potential major confounders taken into consideration in study design or analysis?
Age ☐ Sex ☐ BMI ☐ SES ☐ Ethnicity ☐ HIV status ☐ Smoking status ☐
Homelessness ☐ Alcoholism ☐ History of Imprisonment ☐
Other ☐ Please Describe/comments:

Can study findings be generalised to the population from which the study subjects are
derived? Yes ☐   No ☐

Was there any evidence of bias e.g. selection, detection, attrition? Yes ☐ No ☐
Details:
Were any possible conflicts of interest identified? Yes ☐   No ☐

Was the precision of the final risk values given? Yes ☐   No ☐

Comments:

Definition and type of TB

Type of TB:PTB Further explanation:

Was TB diagnosis defined: clinically ☐ and / or microbiologically ☐

Were any of the following taken? Sputum Smear

Further Explanation:

Was/how was primary, latent & re-activated (secondary) TB differentiated?

What TB Regimen was used?

Comments:

Definition of diabetes/ Hyperglycaemia

Was DM already diagnosed: Yes ☐   No ☐

If yes was this diagnosis confirmed? Yes ☐   No ☐

How was: diabetes ☐ and/or hyperglycaemia ☐

Newly diagnosed?

Was a differentiation between type 1 and type 2 DM given? Yes ☐   No ☐

How was: diabetes ☐ and/or hyperglycaemia ☐

defined, any cut points used?

Was a fasting plasma glucose or 2hr plasma glucose test used for definition in accordance
with IDF guidelines? Yes ☐ No ☐

How was: diabetes ☐ and/or hyperglycaemia ☐

treated?

Comments:

AFFECT OF CO-MORBIDITY ON TB OUTCOMES

Point at which surveillance began: eg immediately after TB infection

Duration of surveillance:

When was TB treatment initiated:

When was (if) DM treatment initiated:

Time to symptom improvement

Was fever improvement measured? Yes☐ No☐
If so list either number with or time to improvement:

Was cough improvement measured? Yes☐ No☐
If so list either number with or time to improvement:

Were any measures of physical functioning, quality of life, or ability to return to work taken if so list below:

Comments:

Affect on time to cure/cure rate

Were sputum-smear, or sputum-culture taken and if so at what time points?

Were any other measures indicative of cure taken?

Time to cure, any estimate of time in weeks or months needed to achieve cure in population subgroups?

Was any affect on cure rate seen, give details:

Comments:

Affect on rate of treatment completion

Was any measure of treatment completion given for TB infected individuals and individuals with co-morbid TB and DM? (please specify measure taken and give full figures reported)

Comments:

Affect on rate of treatment failure

Number of eligible patients who failed to respond to chemotherapy and who had persistent evidence of active disease (positive culture) at the end of the treatment:

Were there any differences in numbers with treatment failure between population sub-groups?

Comments:

Affect on bacterial load/ rate of MDR-TB (linked with poorer outcomes)

Was bacterial load measured? Yes☐ No☐

If yes please list measurements taken and n/%:

Were any TB cases reported as MDR? Yes☐ No☐

If Yes please list n/%:

Affect on rate of relapse

Was number of patients that relapsed recorded Yes ☐ No ☐

Was any difference seen between population sub groups in the rate of relapse?

Comments:

Affect on mortality rate

What was the all cause incidence of death in individuals with TB & DM compared to the rest of the study population or controls (etc)?   (give both numerator and denominator for each group and time frame of data collection)

What was the cause specific incidence of death in individuals with TB & DM compared to the rest of the study population or controls (etc)?   (give both numerator and denominator for each group and time frame of data collection)

What was the median interval to death?

Any other relevant measure taken?

Comments:

Adverse events

Number of fatalities from adverse reactions in each population subgroup:

Number of individuals who developed life threatening conditions in each population subgroup:

Number of individuals requiring hospitalization, or change of treatment regimen in each population subgroup (including those who develop MDRTB):

Total number of adverse events in each population subgroup:

Any other measure of adverse reaction recorded?

Any affect of co-morbidity on DM outcomes reported?

Any additional comments or appropriate information?

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Appendix L:Plots of outcome counts against a normal curve

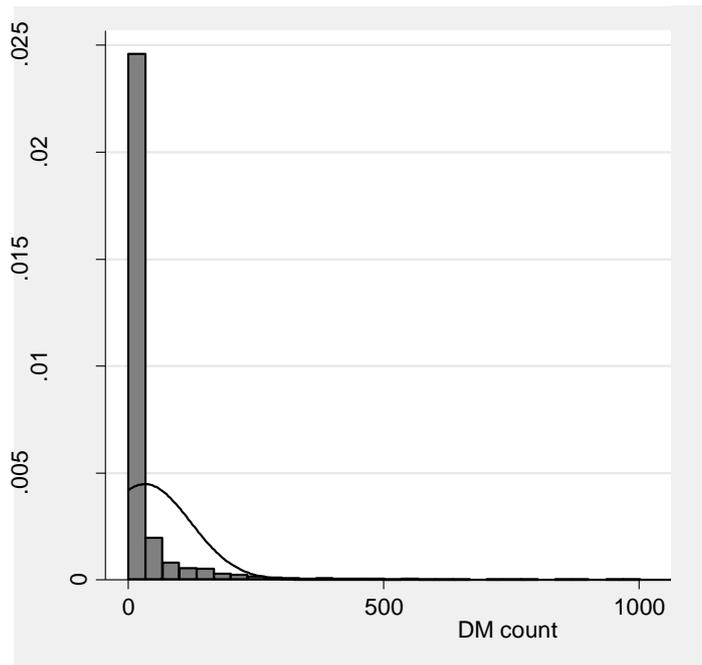**Figure 15: A plot of TB counts alongside a normal curve (DM as a risk factor for TB)**
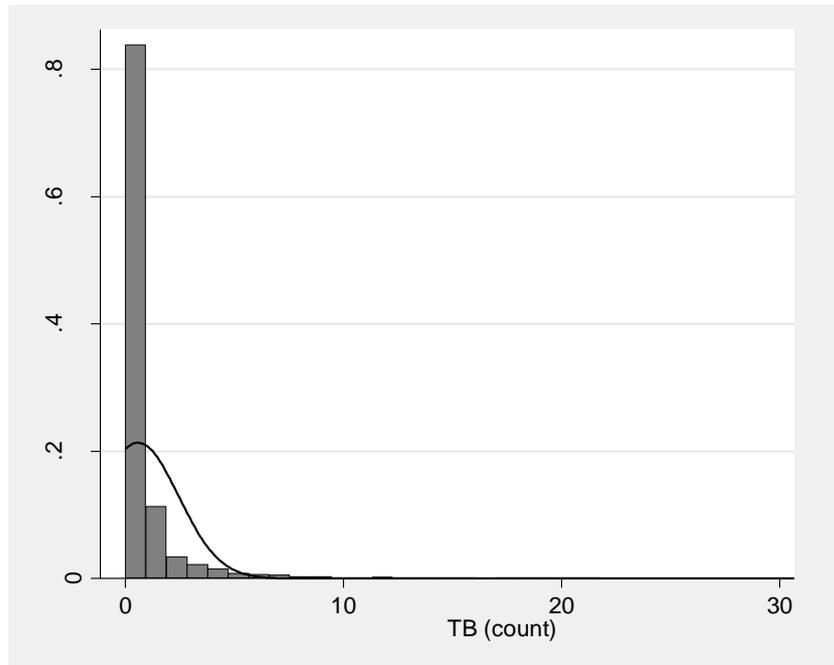
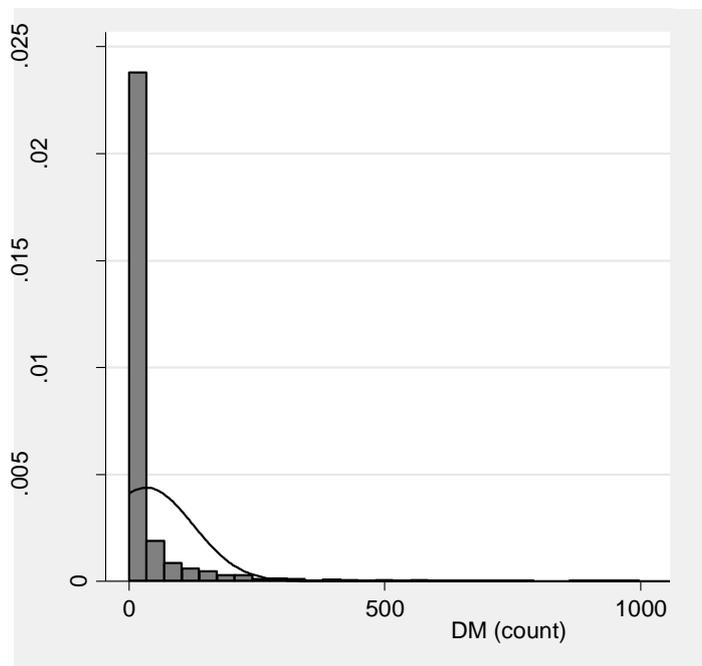**Figure 16: A plot of TB counts alongside a normal curve (T1DM as a risk factor for TB)**
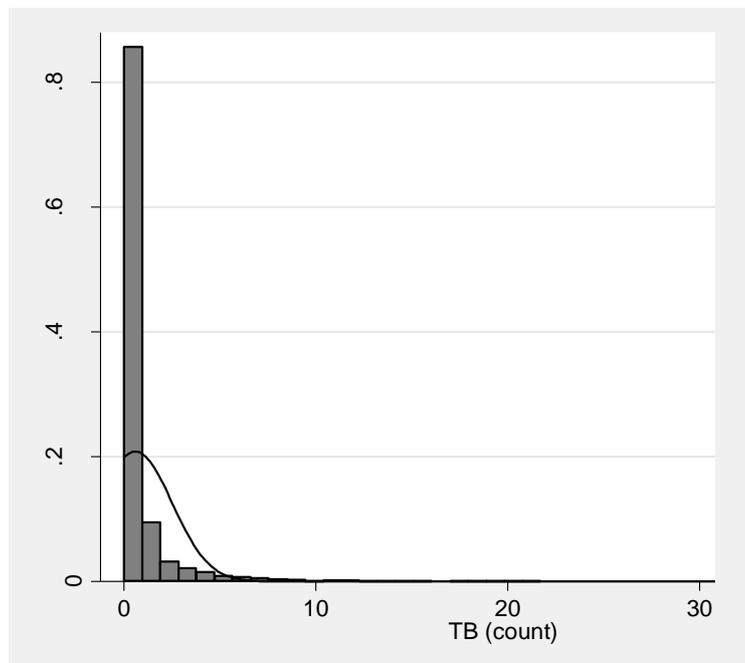
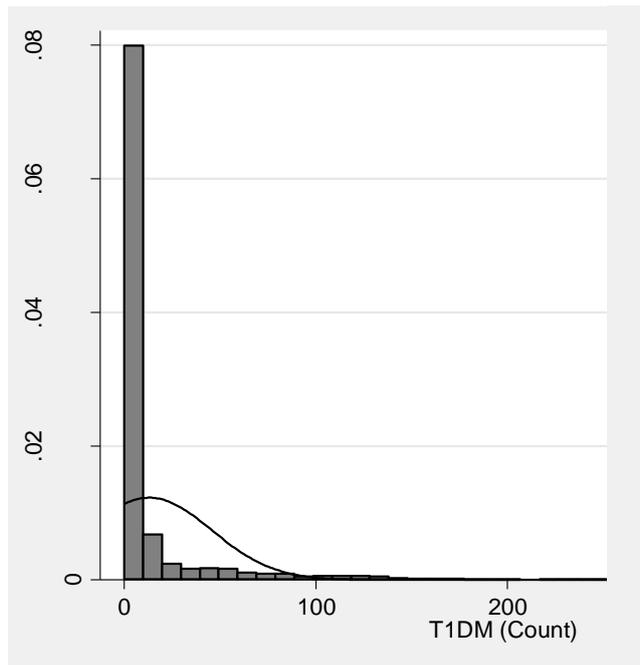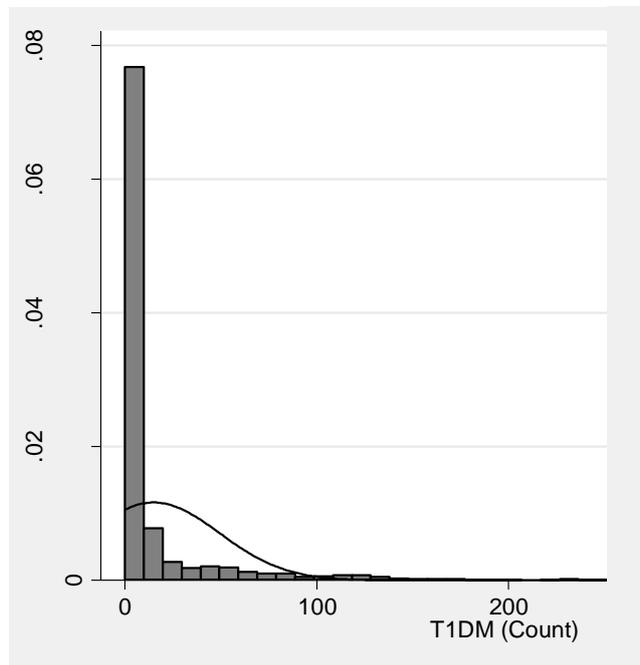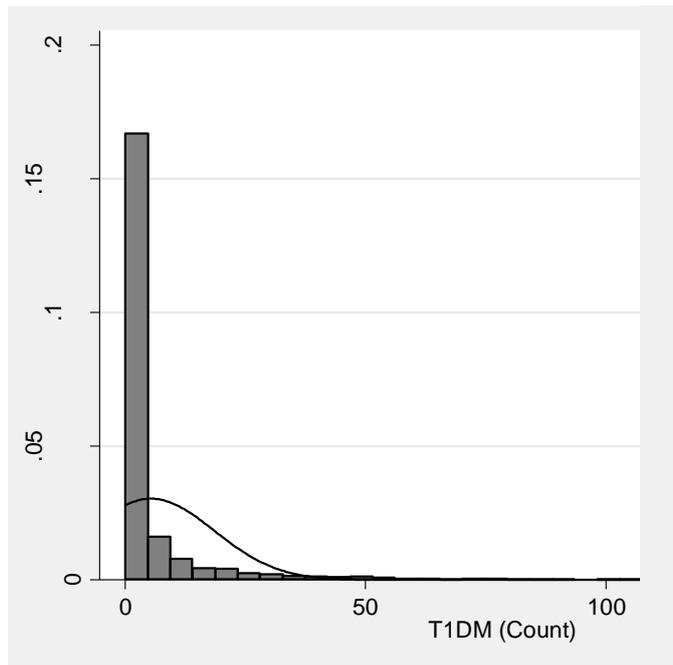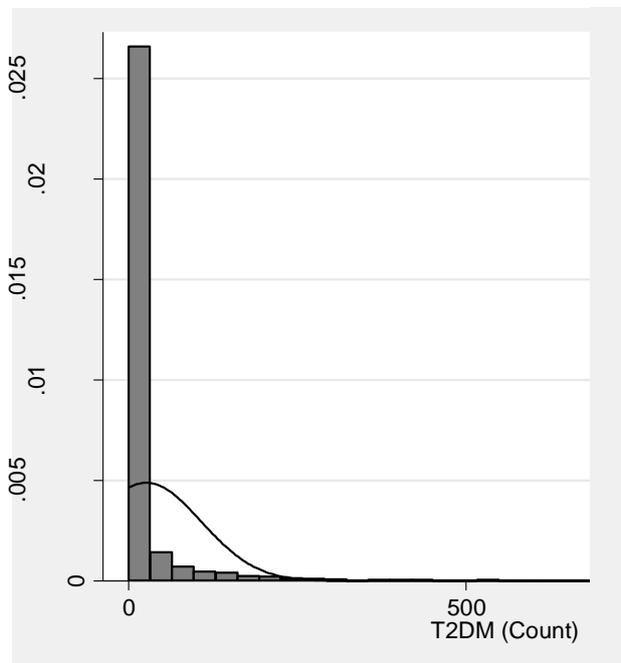**Figure 17: A plot of TB counts alongside a normal curve (T2DM as a risk factor for TB)**
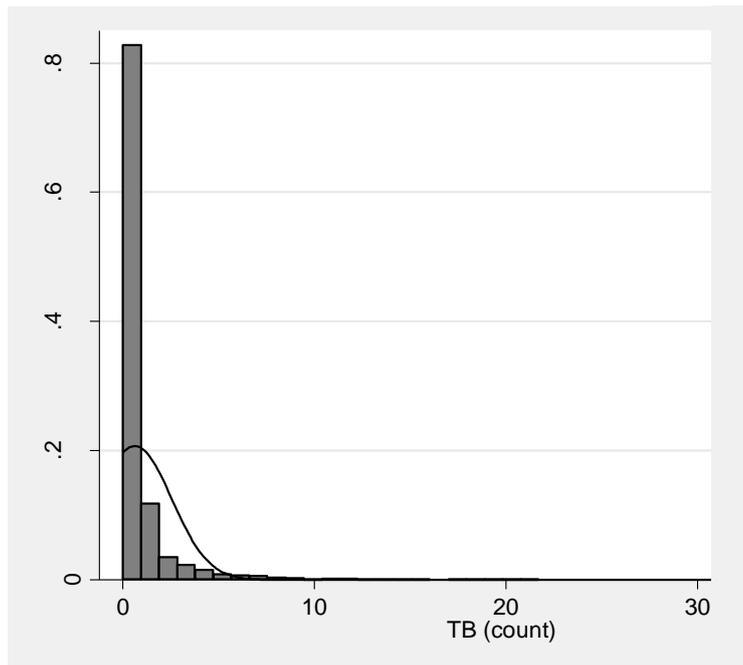
Figure 18: A plot of PTB counts alongside a normal curve (DM as a risk factor for PTB)
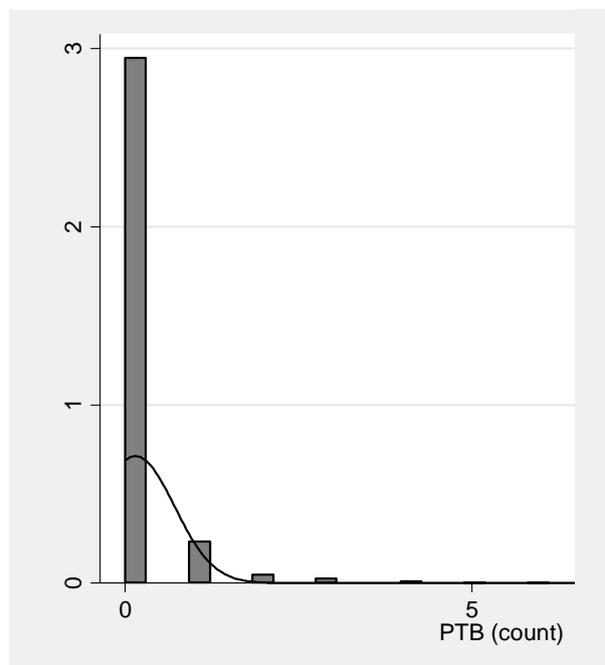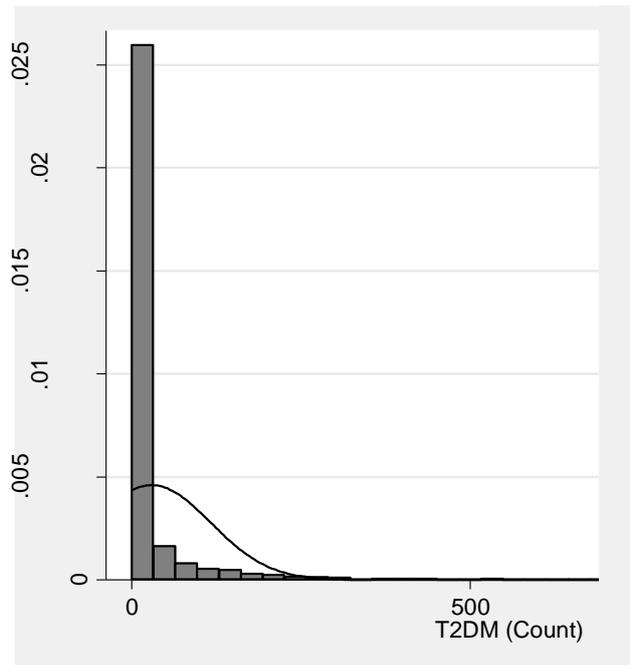
Figure 19: A plot of PTB counts alongside a normal curve (T1DM as a risk factor for PTB)
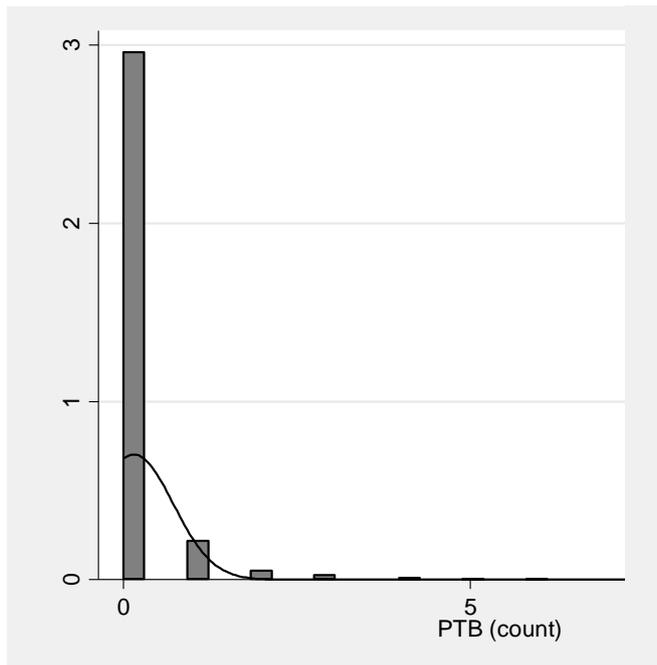
Figure 20: A plot of PTB counts alongside a normal curve (T2DM as a risk factor for PTB)
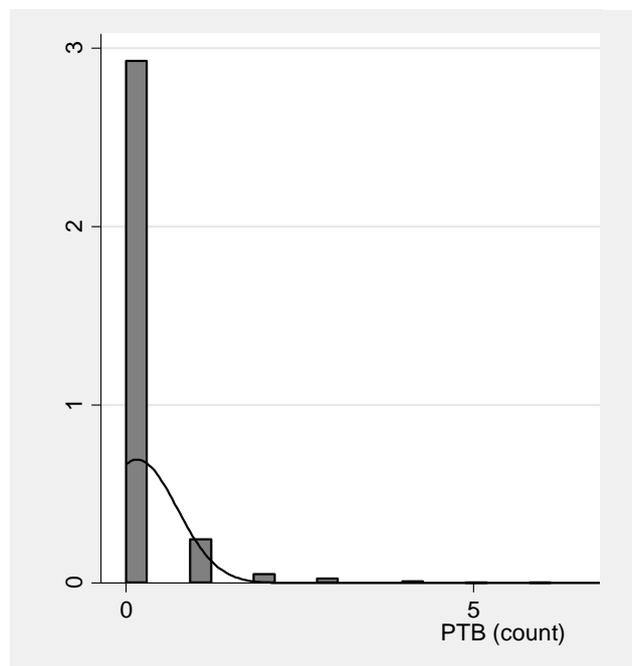
Figure 21: A plot of EPTB counts alongside a normal curve (DM as a risk factor for EPTB)
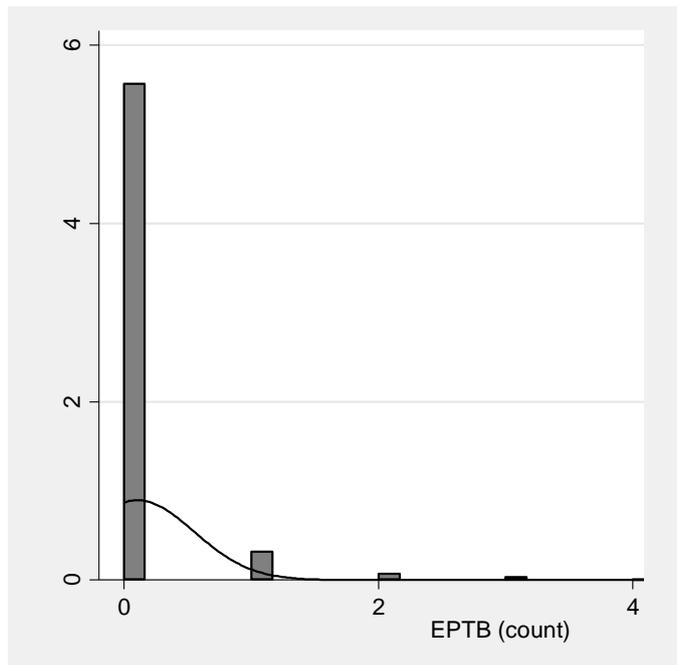
Figure 22: A plot of EPTB counts alongside a normal curve (T1DM as a risk factor for EPTB)
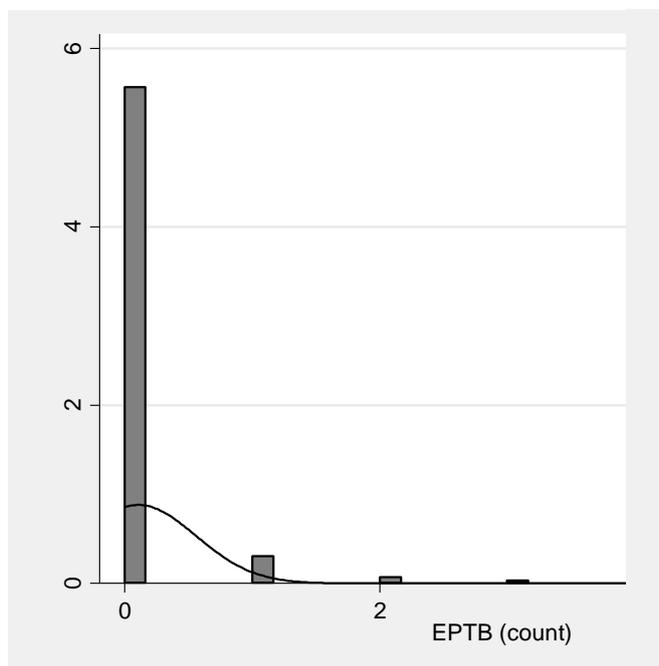
Figure 23: A plot of EPTB counts alongside a normal curve (T2DM as a risk factor for PTB)
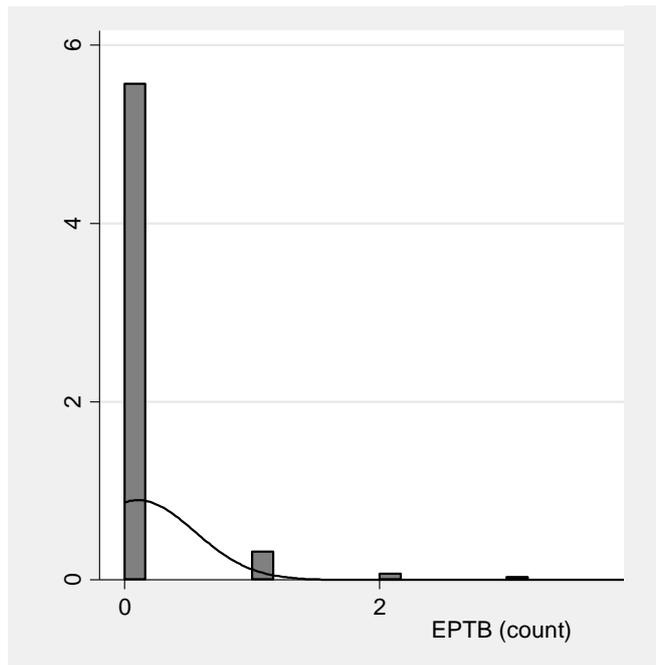
Figure 24: A plot of DM counts alongside a normal curve (TB as a risk factor for DM)
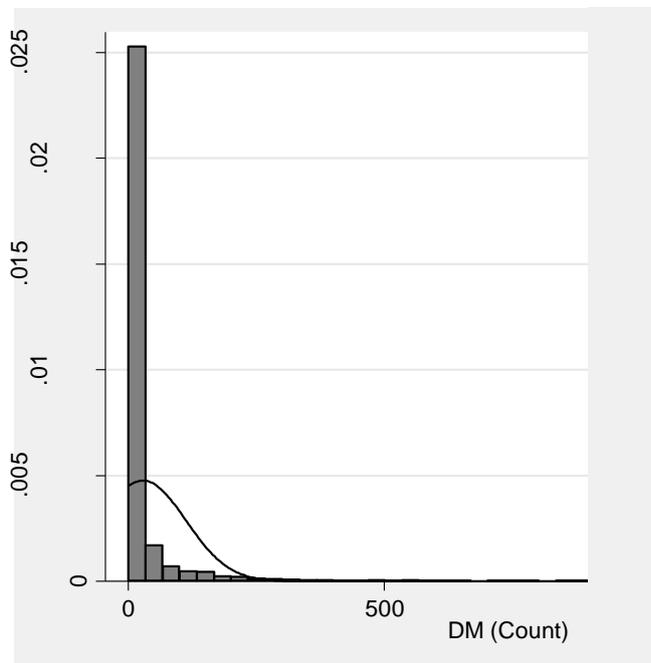
Figure 25: A plot of DM counts alongside a normal curve (PTB as a risk factor for DM)

Figure 26: A plot of DM counts alongside a normal curve (EPTB as a risk factor for DM)

Figure 27: A plot of T1DM counts alongside a normal curve (TB as a risk factor for T1DM)

Figure 28: A plot of T1DM counts alongside a normal curve (PTB as a risk factor for T1DM)

Figure 29: A plot of T1DM counts alongside a normal curve (EPTB as a risk factor for T1DM)

Figure 30: A plot of T2DM counts alongside a normal curve (TB as a risk factor for T2DM)

Figure 31: A plot of T2DM counts alongside a normal curve (PTB as a risk factor for T2DM)

Figure 32: A plot of T2DM counts alongside a normal curve (EPTB as a risk factor for T2DM)
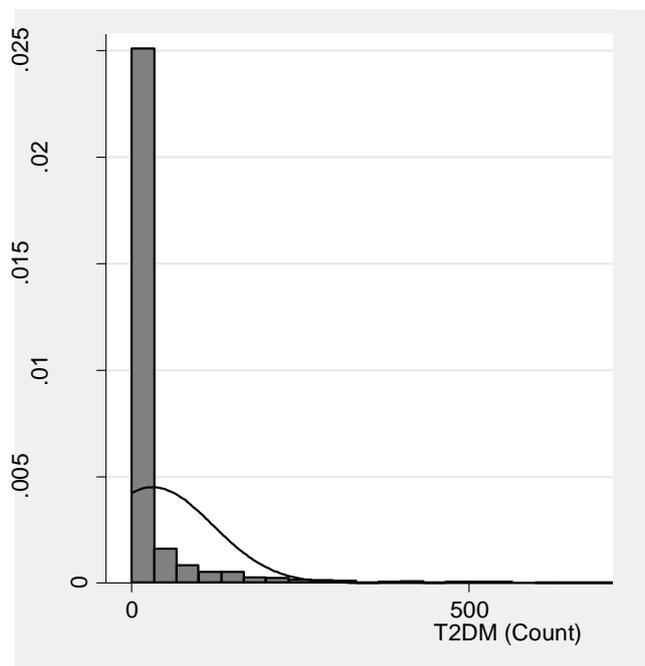
Appendix M: Invited Presentations and Peer Reviewed Publications

Presentations

A review of co-morbidity between infectious and chronic disease. The Annual Society for Social Medicine Conference (9/9/2009 Newcastle)

Publications from this thesis

1.   Young, F. et al. *Diabetes & tuberculosis: a dangerous liaison & no white tiger.* Indian Journal of Medical Research, 2009. **130**: p. 1-4.

2.   Young, F. et al. Increased risk of tuberculosis disease in people with diabetes mellitus: record-linkage study in a UK population. Journal of Epidemiology and Community Health, doi:10.1136/jech.2010.114595

Publications produced throughout candidates time as an integrated MRes PhD student at Newcastle University

1.   Young, F. et al. Coronary Mortality Declines in the U.S. Between 1980 and 2000: Quantifying the Contributions from Primary and Secondary Prevention. American Journal of Preventive Medicine. **39**(3): p. 228-234.

2.   Young, F. et al. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization. Globalization and Health, 2009. **5**(1): p. 9.

3.   Young, F et al. Globalization and the dual disease burden in Sub-Saharan Africa. Diabetes Voice, 2010. **55**(1).

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