Quantifying the Associations Between Diabetes Mellitus, Glycated Haemoglobin and Incidence of and Mortality from Cancer: Analysis of Longitudinal Data from England and Scotland Linked to Cancer Registry and Mortality Data

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2014

‘ I, Vanessa LZ Gordon-Dseagu confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

I would like to thank my supervisors for supporting me through this research process and enabling me to undertake this PhD to the best of my abilities. I especially thank Jenny and Nicola for being there with me every step of the way. My deepest love and thanks also go to the people of the Fountain and my family, especially Chrissie, without you guys none of this would have been possible.

Word count

Abstract: 292

Thesis: 93,978

Abstract

Background

Studies which have sought to explore the associations between diabetes and cancer have produced heterogeneous results and there is a paucity of evidence related to glycated haemoglobin ($HbA1_C$) and cancer risk.

Methods

Initial analyses utilised data from the Health Survey for England (HSE) and SHeS combined linked to mortality and Cancer Registry data (n=204,533, including 7,199 with diabetes) to explore the associations between diabetes, $HbA1_C$ and cancer incidence and mortality. Additional analyses used linked Whitehall I data (n= 19,019, including 237 with diabetes). Odds Ratios (ORs), Hazard Ratios and 95% Confidence Intervals (CI) were estimated adjusted for a range of confounding factors using logistic, multinomial and Cox regression.

Results

18,310 deaths occurred within the HSE/SHeS follow-up period (4,997 from cancer). The adjusted OR for cancer among those with diabetes was 1.27, CI 1.12-1.43. Raised $HbA1_C$ was associated with an excess risk of dying/developing cancer; diabetes and $HbA1_C$ were associated with a number of site-specific cancers. When analyses were stratified by cardiovascular disease (CVD) baseline status, only those with diabetes who did not report CVD had a statistically significant excess in cancer mortality (adjusted OR: 1.27, 1.08-1.48). There were also sex differences in cancer incidence and mortality risk.

81% of Whitehall I participants died during follow-up (including 4,076 from cancer). These results did not replicate the initial analyses in finding no association between diabetes and cancer mortality - this is likely to relate to the age of the two cohorts and the differences in CVD mortality and incidence.

Conclusion

The association of diabetes and $HbA1_C$ with increased cancer incidence and mortality was not consistent across studies or population groups. Differences in risk by sex and CVD status suggest the need for health professionals to tailor services to take account of the individual circumstances of their diabetic patients.

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1. Chapter 1: Introduction

1.1 Diabetes and cancer: diseases of increasing public health concern

In both developed and developing countries, diabetes is now being viewed as an emerging and serious public health issue. Zimmet concluded that diabetes was a major threat to public health currently and that, for an approach to successfully reduce the morbidity and mortality caused by diabetes, it would need to be focussed upon producing change in behaviour at an individual and societal level.(1)

The financial cost to the NHS of each disease is increasing: 10% of the total NHS budget, and 9% of hospital budgets, are being spent on diabetes, (2,3) In the year 2010/2011 the direct costs of diabetes were £9.8 billion, with this figure expected to increase to 16.9 billion in 2035/2036.(4) The Cancer Reform Strategy (2007) stated that the NHS spent £4.35 billion a year on treating individuals with cancer, and that this amounted to over 5% of NHS spending.(5) In total 15% of the NHS budget is currently spent on treating the two diseases, with this figure expected to rise as incidence of the two diseases increases. A report by Livestrong and the American Cancer Society put the global cost, in terms of the economic value of the Disability Adjusted Life Years (DALY's) lost due to diabetes, at around $204 billion, while for cancer the figure was $895 billion; diabetes ranked fifth while cancer ranked first in terms of their cost in this respect.(6)

Diabetes and cancer are having a growing impact upon both the health of individuals, in terms of mortality and morbidity, and placing an increasing financial burden upon health care systems. If an association were found between diabetes and cancer, then an increased prevalence of the former would impact upon the financial cost of the latter. Supporting this is the growing amount of evidence which suggests a causal relationship between diabetes and cancer incidence and mortality. Because of the number of individuals with diabetes, if diabetes were found to be the cause of only a small percentage increase in the incidence of cancer, this could amount to a large number of cases nationally and internationally. There is also a clear need for a better understanding of the link between the two diseases in order to enable the prevention of cancers attributable to diabetes. If an association were to be found between the two diseases, this would also enable evidence-based public health messages to be developed in order to facilitate increased awareness of the factors related to diabetes which impact upon an individual's risk of developing cancer.

1.2 Diabetes and cancer: background to the current study

There is a growing body of epidemiological evidence which has investigated the associations between diabetes and incidence of and mortality from cancer. Within such studies there is heterogeneity of results related to:

- the methods used within the study,
- the population under investigation,
- the method used to identify the diabetic cohort,
- the end-point under investigation (for example cancer incidence, cancer mortality, all-cancers or site-specific cancers).

There is also a limited amount of evidence related to whether raised glycated haemoglobin, both among those with and without diagnosed diabetes, increases an individual's risk of developing or dying from cancer. The issue of whether or not any associations between glycated haemoglobin and cancer relate to over-all cancer incidence and mortality or particular site-specific cancers also requires further investigation.

A number of the factors related to diabetes (such as adiposity) have also been linked to cancer outcomes; the role that these confounding factors may play within the associations between diabetes and cancer has yet to be conclusively assessed.

1.3 Diabetes Mellitus

Diabetes mellitus is a chronic and progressive condition which currently has no cure. The term is used to describe a number of conditions, which have different clinical outcomes and aetiologies, related to hyperglycaemia (elevated blood glucose)(7). Although the disorder has traditionally been classified into three different forms (type-1, type-2 and gestational) although commentators such Tuomi et al. argue that type-1 and type-2 diabetes are likely to represent only two extreme points along a spectrum of diabetic conditions.(8) Further to this a number of commentators have argued that diabetes mellitus should be regarded as a syndrome rather than a specific disease.(9) Within the following section type-1, type-2, gestational, Maturity Onset Diabetes of the Young and, because of their similarities with diabetes, pre-diabetes and the metabolic, are detailed.

Within this thesis diabetes mellitus will be referred to as 'diabetes'. The term will relate to type-1 and type-2 diabetes; when the discussion includes gestational diabetes this will be made clear. For a lay definition of diabetes please turn to Appendix Two.

1.3.1 Classification and diagnosis of diabetes

In the body of a non-diabetic individual, insulin is created in the β-cells islets of Langerhans within the pancreas and the hormone controls the level of glucose in the blood to within very narrow physiological boundaries. There also occurs a cyclical process within which the β-cells and the insulin sensitive tissue found within the liver, muscles and adipose tissue interact with each other in order to supply the required amount of insulin.(7) Within the body of an individual with diabetes, deficiencies within insulin secretion and reduced responses to insulin, within insulin sensitive tissue, produce hyperglycaemia. Both may occur within the diabetic body and it is often difficult to clearly understand which is the primary cause of the subsequent hyperglycaemia is.(10)

There are a number of different measurements used to test the level of glucose within the blood. Currently the World Health Organization supports the measuring of glycated haemoglobin ($HbA1_C$) as an appropriate method for diagnosing diabetes at an individual level.(11) Glycated haemoglobin is used as a measure of plasma glucose concentration over a two to three month period. An $HbA1_C$ measurements of 48mmol/mol (6.5%) or above is currently considered indicative of the presence of diabetes; measurements below this level have the potential to conceal the condition and could be followed up with further blood tests (such as a fasting plasma glucose or oral glucose tolerance test (GTT)).(12) Impaired Fasting Glucose (IFG), also known as pre-diabetes, occurs when blood glucose level are raised, but not at a level considered indicative of the presence of diabetes. An $HbA1_C$ level between 6.1% and 6.49% is currently used to diagnose IFG (IFG is discussed in more detail below).(13) Among those with diagnosed diabetes the American Diabetes Association suggests an $HbA1_C$ level of 7.0% as optimal for reducing the risk of microvascular and macrovascular complications, although they further suggest that the characteristics of the individual should be considered when agreeing the level.(14) Current NICE recommendations are that, for those with type-2 diabetes and taking one glucose lowering drug, an $HbA1_C$ of 6.5% should be aimed for. While for those taking two or more glucose lowering oral medication or those on insulin the target should be 7.5%.(15)

1.3.2 Type-1 diabetes

Type-1 diabetes (also referred to as insulin-dependent diabetes or juvenile onset-diabetes) usually occurs in childhood and accounts for around 10% of all cases of diabetes.(16) Globally, diagnosed type-1 diabetes in children is increasing by around 3% annually.(17) Although the causes of this are not fully understood, contributing factors may relate to the interplay between genes and the environment, and to better diagnosis of the disease within countries that previously did not undertake service provision.(17,18) Individuals with type-1 diabetes have an excess in mortality at

every age, with some estimates placing it at five to ten times higher.(19) This excess in mortality is related primarily to the metabolic complications caused by type-1 diabetes, which result in increased rates of cardiovascular and renal disease.(20)

In an individual with type-1 diabetes, an autoimmune response destroys the β-cells within the pancreas and leaves the body deficient of insulin.(21) Type-1 diabetes is characterised by a rapid increase in glucose in the blood and severe symptoms which, if left untreated, would almost certainly result in death. Individuals with this form of the disease must therefore take exogenous insulin in order to prevent ketoacidosis, a life threatening complication characterised by acidic ketones and glucose in blood and urine.(22) Within type-1 diabetes, the rate at which β-cells are destroyed can vary, but it usually occurs more rapidly in children with this form of the disease than adults. Adults with this form of the disease may continue to produce limited amounts of insulin for a number of years before levels are reduced enough that they require insulin to prevent ketoacidosis.(10)

Among those who are 10 years old or younger, autoantibody-positive, normal weight and present with ketoacidosis, the diagnosis of type-1 diabetes is often clear-cut, although ketoacidosis is present in nearly 20% of young people with type-2 diabetes.(8) The diagnosis of type-1 diabetes among adults is more complex, as they may still have residual insulin production, although the presence of autoantibodies may assist in this regard.

1.3.3 Type-2 diabetes

Type-2 diabetes accounts for around 90% of all cases of diabetes mellitus.(16) The condition is characterised by either decreased β-cell production of insulin or decreased insulin sensitivity within peripheral tissue.(21) This reduction in insulin sensitivity, otherwise referred to as insulin resistance, is characterised by tissue in the body being less responsive to insulin in terms of uptake of glucose. Within the bodies of those with type-2 diabetes the 'feedback loop' also malfunctions.(7) The result is that the body cannot compensate for reduced insulin sensitivity with increased insulin production. Initial treatment of type-2 diabetes includes changes in lifestyle behaviours followed by the introduction of hypoglycaemic medications. Insulin may be introduced to treat the condition; within the UK, this occurs on average 10-15 years after diagnosis.(23)

Type-2 diabetes was traditionally, almost exclusively, found among adults (hence also being referred to as adult-onset diabetes) but with rising rates of obesity in the young, children are now being diagnosed with the disease in increasing numbers. A report by Diabetes UK in 2005 found that all the

reported cases of type-2 diabetes in the UK among children had been among those who were overweight.(24) Even though there have been observed increases in the incidence of type-2 diabetes in childhood, the disease is still predominantly age related and therefore relatively rare among children. Age is also strongly associated with the risk of developing the disease. Data from the Health Survey for England 2009 showed that prevalence of doctor-diagnosed diabetes increased with age, from a low of <1% within the youngest adults (16-34) to a high of 19.5% of men and 12.7% of women aged 75 years and older.(25) By 2011, up to one in 12 adults overall in England were thought to live with the disease (either diagnosed or undiagnosed); this figure increased to one in four men and one in five women aged 75 and over.(26)

1.3.4 Gestational diabetes

During pregnancy, a woman's body creates a certain amount of insulin resistance in order to enable the delivery of nutrients to the foetus via the placenta.(27) Gestational diabetes develops when the body is unable to produce enough insulin to control glucose levels in the body. Prevalence of gestational diabetes varies by location; a literature review focussed upon developed countries found that prevalence ranged from 1.7-11.6%.(28) Risk factors for gestational diabetes include being overweight or obese, increased age at pregnancy, previous gestational diabetes, a family history of the disease and having given birth to a high weight baby in the past (possibly indicating undiagnosed gestational diabetes).(29,30) Gestational diabetes may also be indicative of previously undiagnosed type-2 diabetes and has been found to increase the risk of type-2 diabetes later in life.(31) Women who have gestational diabetes are at an increased risk of requiring a caesarean section, delivering early or needing to be induced. Further to this, the babies of women with diabetes are at an increased risk of dying before birth and once born, being high weight or having neonatal complications.(32,33)

1.3.5 Maturity Onset Diabetes of the Young

Although the majority of cases of diabetes are currently diagnosed as type-1, type-2 or gestational, there are several forms of diabetes which are related to monogenetic defects within the function of the β-cells. These defects are thought to account for around 1-2% of all cases of diabetes. Referred to as Maturity-Onset Diabetes of the Young (MODY), this form of diabetes is often diagnosed during young adulthood and is characterised by hyperglycaemia caused by deficits within insulin secretion.(34) Differentiating between MODY and type-1 and type-2 diabetes is complicated by the fact that they all share similar characteristics clinically.

1.3.6 Pre-diabetes and the metabolic syndrome

If type-1 and type-2 diabetes are the two extremes along a spectrum of diseases, then pre-diabetes (also referred to as Impaired Fasting Glucose or Impaired Glucose Tolerance) is considered the precursor for type-2 diabetes. It is found within individuals who have increased blood glucose levels that are not at a high enough level to warrant a diagnosis of diabetes, but are raised compared with those who are normoglycaemic.(35) If changes in behaviour and lifestyle are not made, individuals with pre-diabetes are at increased risk of their condition progressing and developing into type-2 diabetes, as well as at an increased risk for cardiovascular complications.(36)

Similarly to pre-diabetes, the metabolic syndrome is a group of factors related to insulin resistance which increase an individual's risk of getting type-2 diabetes; it also increases their risk of other diseases associated with atherosclerosis.(37) Although a single definition of the syndrome is controversial and its clinical utility has not been agreed,(38,39) the World Health Organisation (WHO) define the syndrome as the presence of glucose intolerance, Impaired Glucose Tolerance (IGT) or diabetes mellitus and/or insulin resistance together with at least two of the following:

- Insulin resistance (under hyperinsulinaemic, euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation),
- Raised arterial pressure ≥140/90 mmHg,
- Raised plasma triglycerides (≥1.7 mmol l–1; 150 mg/dl) and/or low HDL–cholesterol (< 0.9 mmol/l, 35 mg/dl men; < 1.0 mmol/l, 39 mg/dl women),
- Central obesity (males: waist to hip ratio > 0.90; females: waist to hip ratio > 0.85) and/or BMI > 30 kg/m^2,
- Microalbuminuria (urinary albumin excretion rate ≥ 20 µg/mg/min or albumin: creatinine ratio³ 30 mg/g).(40)

The National Cholesterol Education Program (NCEP)'s Adult Treatment Panel (ATP) III report also identified six factors related to the metabolic syndrome that increase an individual's risk of developing cardiovascular disease: abdominal adiposity, dyslipidaemia, high blood pressure, insulin resistance and/or glucose intolerance, inflammation and being prothrombotic.(41)

1.3.7 Incidence and prevalence of the metabolic syndrome and diabetes

There is no single definition of the metabolic syndrome and, as discussed in the previous section, a number of different definitions have been used. This has resulted in a wide range of estimates in relation to the prevalence of the syndrome; with some commentators suggesting that a significant

proportion of the population meet the criteria for the condition. For example, eight pooled studies in Europe found that among men and women aged 40-55, 7-36% and 5-22% respectively could be considered to have the condition.(42) Results from NHANES 1999-2006 indicated that, within the US, age-adjusted prevalence of the metabolic syndrome was increasing and stood at 34.2% (± 0.7%).(43)

Globally it is estimated that 347 million individuals are currently living with diabetes mellitus, with this figure expected to rise to 552 million by 2030.(44,45) The World Health Organization estimates that around 3.4 million deaths occur per year as a result of hyperglycaemia,(45) while 2010 study estimated that 3.96 million deaths were caused by diabetes in 2010.(46) The large number of individuals with diabetes means that if the disease contributes even a small percentage increase in mortality, this would result in large numbers of deaths.

Information gathered between April 2011 and March 2012 in England as part of the Quality and Outcomes Framework (QOF) indicated that, among those over 16 years of age, around 2.5 million individuals had diagnosed diabetes, equating to a prevalence of 5.8%.(47) In England around 23% of those with diabetes are thought to be undiagnosed,(48) equating to a further 850,000 individuals in the UK living with diabetes who are either undiagnosed or unregistered.(16) Prevalence of diagnosed diabetes within the other countries of the UK was: 4% within Northern Ireland(49), 4.4% within Scotland(50) and 5.3% within Wales.(51) The APHO Diabetes Projection Model estimated that by 2025 five million individuals will be living with diabetes in the UK.(52) In terms of incidence, the latest estimates suggest that around 145,000 individuals are diagnosed with diabetes each year.(53) Although the prevalence of type-1 and type-2 diabetes is increasing, the pattern and cause of the increase differs. Incidence trends analysis utilising Europe-wide data suggest that the former is increasing by around 3.9% (95% CI 3.5-4.2) each year(54); globally, type-1 diabetes increased by 3.4% (95% CI 2.7-4.3).(17) The cause of these increases remains unclear, although contributing factors are thought to relate to the interaction between the environment and genes, and to improvements in the monitoring and diagnosis of the disease within some countries.(55) The increase in type 2 diabetes is thought to relate to an ageing of the population and rapid increases in overweight/obesity.(56) Hart et al. estimated that around 60% of cases of diabetes could be prevented if the population were to maintain a normal weight.(57)

1.4 Cancer

The causes of cancer are complex, interlinked and include an individual's genetic predisposition to the disease, their age and lifestyle behaviours.(58,59) Analyses by Doll and Peto, carried out in the

1980s, suggested that around half of all cancers could be prevented by changes in lifestyle (particularly in relation to smoking).(60)

There are over 200 different types of cancer, each with its own aetiology, incidence and mortality rate. In England around 275,00 individuals were diagnosed with the disease in 2011.(61) Among men, the three most common incident cancers are prostate, lung and colorectum (accounting for 53% of all cancers diagnosed among men within England).(61) For women the three most commonly diagnosed cancers are those of the breast, lung and colorectum. Within both sexes these three cancers accounted for around 53% of all diagnosed cancers in 2011.

Of the 139,951 recorded cancer deaths in England and Wales in 2011, over half (56%) were from cancers of the lung, colorectum, breast, prostate, pancreas and oesophagus (Table 1-1 details the number of deaths from these site-specific cancers and the total number of cancer deaths in 2011). 2008 data indicates that there were 12.7 million new cases of cancer globally and 7.6 million deaths.(62)

Table 1-1: Six most common causes of site-specific cancer mortality, England and Wales

Cancer Site	**Sex**		
	Male	**Female**	**Total**
Lung	16,881	13,267	30,148
Colorectum	7,578	6,428	14,006
Breast	69	10,328	10,397
Prostate	9,671	0	9,671
Pancreas	3,748	3,686	7,434
Oesophagus	4,488	2,147	6,635
TOTAL	42,435	35,856	78,291
All deaths from cancer	73,709	66,242	139,951

[a] This information is taken from ONS data for 2011.(63)

1.5 A brief overview of the epidemiological evidence related to the associations between diabetes and cancer

The earliest documents to mention either diabetes or cancer came from Egypt around 1600BC. As early as 1885, Freund(64) had begun to document the presence of hyperglycaemia within cancer patients. This was followed by the work of Tuffier(65) which sought to explore a potential correlation between diabetes and cancer. Maynard, who undertook analysis of cancer death rates within the United States, found that a key limitation of research within this area was the inconsistent recording

of deaths caused by cancer or diabetes. Despite this, he reported a correlation between the two diseases.(66)

The discovery of insulin by Banting and Best(67) in the laboratories of JJR Macleod in 1921, and its purification for use as a treatment for type-1 diabetes by James Collip, enabled increases in life expectancy among those with the disease that had been inconceivable in the preceding years; up to this point life expectancy was between one and two years from diagnosis.(68) Cancer being a disease positively correlated with age(69), intuitively it would be expected that an increase in life expectancy would bring about a corresponding increase in cancer incidence and mortality among those with diabetes. The work of Joslin et al. supported this conclusion; they found that in 1900 (before the introduction of insulin) the incidence of cancer among diabetics was 1.5%, while in 1940 (after the introduction of insulin) the figure was 8.9%.(70) However, other researchers found no increase in site-specific cancers among diabetic cohorts(71); such varied conclusions may elicit more about the different methods of research, than the actual rates of cancer among those with diabetes.

An extensive review of the literature relating to the relationship between diabetes and cancer by Kessler(72) in 1971 concluded that studies undertaken using clinical evidence were likely to show a positive relationship between diabetes and cancer, while those that used autopsy data showed a negative relationship. He also found that studies which used a measure of proportionate mortality from cancer (comparing a diabetic sub-group with the general population) supported a negative relationship between diabetes and cancer; this was in all cancers other than pancreatic which was consistently found at higher rates among those with diabetes.

The 1980s began to see studies investigating the link between diabetes and cancer that were methodologically more rigorous than those undertaken previously. It was also at this time that studies began to focus more upon specific cancer sites and their link to diabetes. However, some of these studies still suffered from methodological problems, particularly:

- sample sizes that lacked the power to derive statistically significant conclusions about the association between diabetes and cancer or were dependent on relatively unreliable data sources(73,74),
- a lack of assessment of the role of confounding factors(75),
- a small number of concurrent cases of diabetes and site-specific cancers, and/or
- utilised study populations from homogenous populations (such as patient information from a single hospital).(76)

These weaknesses within the studies may partially explain why, in relation to cancer mortality, some found mortality rates similar to those within the general population,(20,77) while others demonstrated an increase(78–80) or decrease(81,82) among people with diabetes. These studies are discussed in full in the literature review (Chapter 2); the following section gives a brief overview of the key pieces of research (post-1980) that explored the associations between diabetes and cancer.

A study using the American Cancer Society Prevention Study II cohort investigated the risk of cancer mortality among those with diabetes. The study was one of the largest to specifically investigate the risk of cancer mortality among diabetics (the cohort included 467,992 men and 588,321 women).(83) The study found no increased mortality risk for a number of cancers including for men those of the oesophagus (RR=1.20, CI 0.94-1.53), stomach (RR=0.99, CI 0.77-1.27) and kidney (RR=0.82, CI 0.61-1.10) and for women those of the stomach (RR=1.25, CI 0.90-1.73), liver (RR=1.37, CI 0.94-2.0) and kidney (RR=1.12, CI 0.80-1.58). The study also investigated the role BMI might play within the relationship between diabetes and cancer mortality and found that it had little impact.

A 2010 meta-analysis and systematic review undertaken in Japan sought to explore whether those with diabetes had an increased risk of cancer compared with non-diabetics.(84) After adjustment for confounding factors, the meta-analysis of five studies found an increased risk that was significant for diabetic men (RR= 1.25, 95% CI = 1.06-1.46) but not for diabetic women (RR 1.23, 95% CI 0.97-1.56). This point is noteworthy in that a second study undertaken in Japan found the reverse: only women with diabetes were at an increased risk of cancer.(85) Within their systematic review the former researchers found consensus across studies - none of the studies included found a decreased risk of cancer among diabetic patients compared with non-diabetics. Although the meta-analysis utilised a large data-set of just over 250,000 individuals there are a number of issues in terms of extrapolating its findings to a wider population. All the studies were undertaken in Japan and although the aetiology and pathophysiology of diabetes is likely to be the same globally, the population of Japan is very demographically homogenous compared with the UK and so the results may not be the same for these different populations.

The Emerging Risk Factors Collaboration (ERFC) study analysed pooled data from 97 prospective studies (including >800,000 participants) and found increased cancer mortality among those with diabetes (hazard ratio (HR) 1.25, 95% CI 1.19-1.31).(86) A 2008 systematic review and meta-analysis also found an increased risk of cancer mortality among those with diabetes (HR 1.41, 95% CI 1.28-1.55) compared with those without the disease.(87) Studies focussed upon site-specific cancers also demonstrate differences in mortality risk among those with diabetes(78,88,89); the most consistent

results are related to site-specific cancers of the pancreas, but whether this is due to reverse causality is still uncertain.(90) Evidence also demonstrates increased risks for bladder, liver and breast cancer mortality.(83) Analysis of Whitehall I data found significant associations between diabetes and pancreatic and liver cancer, but none of the other 13 cancers analysed.(89) Chia et al. found that women with diabetes subsequently diagnosed with endometrial cancer experienced a 70% increase in all-cause mortality but not mortality from endometrial cancer.(91) There are also mixed findings related to cancer incidence (all-cause and site-specific).(92,93)

Recent investigations related to the biological plausibility between diabetes and cancer have focussed upon hyperglycaemia, hyperinsulinaemia, the use of diabetes related drugs and/or exogenous insulin, although a definitive pathway has yet to be established.(94–97)

The uncertainty surrounding the epidemiological associations between diabetes and cancer incidence and mortality (as well as the impact that confounding factors have upon the associations), in terms of all-cause and site-specific incidence and mortality, suggests the need for further research which utilises nationally representative data to explore the associations further.

Chapter one concludes with an outline of the rest of the thesis.

1.6 Outline of thesis

The thesis consists of 12 chapters, detailed below.

Chapter One

The introduction introduces why diabetes and cancer are increasingly being viewed as diseases of public health concern. Chapter One also gives an overview of the study aims, the background to the study and information concerning the aetiology, diagnosis, prevalence and consequences (in terms of morbidity and mortality) of diabetes and cancer. The chapter concludes with a brief overview of the current epidemiological evidence in relation to an association between diabetes and cancer.

Chapter Two

The focus of the literature review in Chapter Two is to explore the research related to the associations between diabetes and cancer. The review also details previous investigations of the confounding factors within, and biological plausibility of, the potential associations between the two diseases. The chapter also details the gaps in our current knowledge in terms of the associations

between diabetes and cancer and how this information has been used to develop the research questions, hypotheses and aims of the current study.

Chapter Three

The chapter introduces the Health Survey for England, Scottish Health Survey and Whitehall I data. The methods used to ensure variable conformity, link the datasets and identify a number of cohorts within the data are also addressed.

Chapter Four

Chapter Four explores the data issues that were encountered within the analyses and the methods used to analyse the data in relation to diabetes and cancer incidence and mortality.

Chapters Five to Eleven

Within these chapters the results of the analyses are explored. Chapter Five details the associations between diabetes and cancer incidence. Chapter Six includes the results related to $HbA1_C$ and cancer incidence. Chapter Seven is focussed upon diabetes and cause-specific mortality, with a particular focus upon cancer. Chapter Eight details the findings related to diabetes and site-specific cancer mortality. Chapter Nine examines the impact HbA1C has upon mortality. Chapter Ten examines the impact that diabetes and glycated haemoglobin have upon all-cause mortality and Chapter 11 details the results of the analyses of Whitehall I.

Chapter Twelve

A detailed discussion of the results is given in Chapter Twelve. The chapter is divided into sections related to diabetes and $HbA1_C$ and incidence of and mortality from cancer, as well as mortality from other causes. The thesis draws to a close with the conclusions that can be drawn from the research study overall and implications for further research.

2. Chapter 2: Literature review

2.1 Methods

The aim of the literature review was to identify the literature related to the associations between diabetes, $HbA1_C$ and cancer and amalgamate the results. This would enable clarity in relation to the current evidence, and identification of gaps in knowledge, which would then facilitate the formulation of the study's research aims, objectives and hypotheses.

2.1.1 Literature review: research questions

The literature review had a number of overarching questions within it. Primarily, it sought to answer a number of questions related to what evidence exists:

- in relation to the associations between diabetes and cancer mortality
- to support a link between diabetes and overall cancer incidence,
- in terms of a link between diabetes and site-specific cancer incidence and mortality,
- that supports an association between glycated haemoglobin and incidence of and mortality from cancer,
- that indicates the impact that confounding factors (such as obesity and comorbidities) have upon the associations between diabetes and/or glycated haemoglobin and cancer incidence and mortality.

In order to answer these questions the framework for causality proposed by Bradford-Hill(98) was utilised and this elicited further questions:

- Is there homogeneity (consistency and coherence) within epidemiological study results related to diabetes/glycated haemoglobin and cancer incidence and mortality? If so, what is the strength of the association?
- Is diabetes associated with mortality from other causes? Although the evidence related to an association between diabetes and CVD is strong, what evidence exists for diseases of the respiratory system and other causes of death? Within the Bradford-Hill criteria it was suggested that the evidence related to rubella increases the robustness of the results related to the possibility that other viral diseases during pregnancy affect foetal outcomes. In the same way, if diabetes were to impact upon mortality from and incidence of other diseases,

this could be used as evidence with which to support the associations between diabetes and an increased risk of cancer incidence and mortality.

- What does current research advance as the biologically plausible pathways between diabetes and incidence of and mortality from cancer and other causes?
- Is there evidence of reverse-causality within any of the associations?
- Within the associations between glycated haemoglobin and cancer (incidence and mortality), is there a dose-response effect?

An initial broad search within Pubmed (www.ncbi.nlm.nih.gov/pubmed/*)* using the words "cancer" and "diabetes" elicited 15,052 articles. A similar search of Google Scholar produced >2.5 million hits, while a search of the terms 'diabetes and cancer mortality' and 'diabetes and cancer incidence' both generated around 1.5 million hits. In order to check the sensitivity of the Pubmed search strategy, the first twenty pages of each of these were reviewed for relevant literature.

2.1.2 Literature review: inclusion/exclusion criteria

A number of criteria were used to assess a study's suitability for inclusion within the literature review. These were:

- If two studies utilised the same dataset or sample, the earlier study was excluded from the review.
- If a study detailed the excess mortality of a diabetic cohort but did not specifically analyse one of the outcomes of interest for this study (all-cause, cause-specific, site-specific mortality or all-cause cancer or site-specific cancer incidence) compared with the general population, or other specified control group, reports without an appropriate comparison group were excluded.
- A study was excluded if it did not give point estimate information about the association or precision of their measurement, such as 95% Confidence intervals (CI) or p-values.

Analysis of the titles and abstracts of the studies found within the initial search elicited a further question:

- What evidence exists of a relationship between treatments for diabetes and cancer incidence?

Using the inclusion criteria above, studies were then moved into a number of categories depending upon their focus. Studies which sought to explore the biological plausibility of a link between diabetes and cancer, those which investigated diabetes treatments and their link to cancer, and those specifically focussed upon other confounding factors (such as overweight and obesity) were also selected from the initial list. Similarly to the initial search of the broad terms of 'diabetes' and 'cancer', secondary searches of Google Scholar were undertaken. Table 2-1 below gives information about these categories and the number of hits produced by each Pubmed search term and the number of studies that remained after an initial sift of the titles and abstracts. (ordered in descending order). Reference and author searches were also undertaken after each stage of the search process and relevant articles were added to the total number of hits so that their titles and abstracts could be sifted through.

Table 2-1: Search categories within the literature review

Category	No. of total hits	No. after title/abstract sifting
"Diabetes" and "cardiovascular"[a] and "disease"	2,745	84
"Diabetes" and "cancer"	1,141	71
"Diabetes" and "all-cause mortality"	453	65
"Diabetes" and "cancer mortality"	247	57
"Metabolic syndrome"[b] and "cancer"	140	23
"Diabetes" and "cancer incidence"	95	43
"Obesity"[c] and "cancer"	73	41
"Insulin" or "hyperglycaemia" and "cancer"	60	27
"Glycated haemoglobin" and "mortality"	52	21
"Diabetes treatment" and "cancer"	43	27
"Glycated haemoglobin" and "cancer"	36	12
"Diabetes" and "respiratory" and "disease"	27	4

[a] Searches within this category also included the terms "heart disease" "stroke" "CHD" "CVD" and "Ischaemic heart disease".
[b] The results in this section of the table also include those for searches using the terms "metabolism" and "fasting glucose".
[c] The results given also include those for searches utilising the terms "BMI" "overweight" and "adiposity".

Articles within each of these categories were then separated out (using title, abstract and article) into 1) highly relevant, 2) possibly relevant and 3) unlikely to be relevant. Articles within categories one and two were then considered for inclusion within the literature review; they were also moved to category 3, at this stage, if found not to be relevant. This left 57 articles that included information about the associations between diabetes and overall cancer incidence and/or mortality (but not a specific cancer type) which have been used for the literature review section focussed upon

associations between diabetes and cancer in general. There were over 80 articles that included information about diabetes and mortality from all-causes and causes other than cancer and these have also been used to inform the appropriate sections of the literature review.

Articles were also selected, and moved into separate categories, if they focussed upon the associations between diabetes and site-specific cancers. The table below (Table 2-2) lists the cancers for which papers were found (the table is ordered in descending order by the number of studies found). As above, studies were included in the literature review if they met the inclusion criteria and were relevant to the literature review.

Table 2-2: Site-specific search categories within the literature review

Category	Number of studies found	No. after title/abstract sifting
"Diabetes" and "pancreas" and "cancer"	195	22
"Diabetes" and "breast" and "cancer"	138	12
"Diabetes" and ("colorectal" OR "bowel" OR "rectum" OR "colon") and "cancer"	121	19
"Diabetes" and ("endometrial" OR "womb" "uterus") and "cancer"	107	7
"Diabetes" and "prostate" and "cancer"	102	10
"Diabetes" and ("liver" OR "hepatocellular") and "cancer"	77	14
"Diabetes" and ("gastrointestinal" OR "gastric" OR "stomach") and "cancer"	27	9
"Diabetes" and "bladder" "cancer"	25	12
"Diabetes" and ("kidney" OR "renal") and "cancer"	17	9
"Diabetes" and "lung" and "cancer	13	4
"Diabetes" and "non-Hodgkins lymphoma"	11	7
"Diabetes" and "oral" and "cancer"	11	3
"Diabetes" and "ovarian" and "cancer"	7	2
"Diabetes" and ("haematopoietic" OR "leukaemia") and "cancer"	3	3
"Diabetes" and ("skin" OR "melanoma") and "cancer"	1	1

The associations between diabetes and some site-specific cancers were explored within studies looking at a number of site-specific cancers simultaneously, but were not the primary focus of a single study. These cancers, although not included in the table above, were included within the literature review (as long as the studies met the inclusion criteria). In total around 90 studies were used to support the sections of the literature review related to diabetes and site-specific cancer

incidence and mortality. Around 30 studies were also used to garner information about the associations between diabetes treatments and cancer risk.

The literature searches undertaken above highlighted the fact that the majority of studies either did not focus upon type-1 diabetes specifically, or did not differentiate between type-1 diabetes and cancer. Because of this a separate search of the literature in this area was undertaken within PubMed and Google Scholar. Searches utilised the terms “diabetes”, “type 1 diabetes”, “insulin treated diabetes mellitus” “IDDM”, “early onset diabetes”, “juvenile onset”, “young onset”, or “type-1 diabetes mellitus” “T1DM”, and “cancer”, “neoplasm”, “malignancy”, “incidence” or “mortality”. The references cited within each article were then reviewed in order to elicit further relevant articles. Although a meta-analysis was considered, it became apparent that the diversity of endpoints (all-cause and cause-specific incidence and mortality), and the heterogeneity of findings and of study cohorts would make this method inappropriate. Therefore a narrative review was undertaken, plus a visual display of the findings of each included study.

A large number of reports detailed evidence relating to the excess all-cause mortality experienced by those with type-1 diabetes; the references for these reports were also reviewed. Studies were excluded in instances when they did not analyse the two different types of diabetes separately, or when it was unclear which type of diabetes was under analysis. The only instances where studies of this nature have been included in the review is when the focus of the study was upon insulin use and the age group of the cohort was young enough to be composed mainly of those with type-1 diabetes. In total 1,736 hits were produced within the searches, with 43 full-text reviews being undertaken which resulted in 22 studies being included within the review. For a discussion of the results of this literature search see Section 0.

The literature review begins with an exploration of the evidence related to the associations between diabetes, $HbA1_C$ and related factors and cancer incidence and mortality. As mentioned previously, studies were also included in the literature review if they focussed upon diabetes and all-cause and non-cancer cause-specific mortality; epidemiological studies of this nature are discussed at the end of the chapter.

The literature review was updated throughout the PhD to take into consideration new research; the most recent update took place at the end of November, 2013.

2.2 Epidemiological evidence: associations between diabetes and cancer (1880s-present)

The first part of the literature review has been split into three time periods:

- the pre-insulin era,
- the insulin era,
- studies undertaken after 1980.

For the third section, the year 1980 was chosen because it was during this time-period that studies began to utilise methodologically more rigorous techniques than had previously been employed. For example, studies begun to use a range of data sources to confirm the presence of diabetes and incidence of and mortality from cancer.

2.2.1 The pre-insulin era

It was not until the 1920s that Warburg introduced the idea that tumour cells may have higher rates of glucose utilisation than normal cells and that they produce more lactic acid.(99) Even before the first use of insulin to treat diabetes mellitus in 1922, and a clear understanding of the pathologies of diabetes and cancer had been developed, researchers had begun exploring the potential link between diabetes and cancer. In 1885, Freund documented hyperglycaemia in cancer patients and as early as 1888(64), Tuffier begun to explore the correlation between the two diseases.(65) His research devised a framework which sought to address the following three interrelated research questions: 1) how diabetes might affect the incidence of cancer; 2) how diabetes might affect the course of a case of cancer; and 3) how cancer might affect the course of diabetes. Following his study, he further concluded that diabetes was the antecedent, followed by an incident cancer.

In the early part of the twentieth century, large increases in mortality from both cancer and diabetes were reported. Increases in cancer mortality continued throughout the first half of the 20th century, with a consensus being formed that this was due, to a certain extent, to improved diagnosis of cancer as a cause of death and recognition of it within medical records.(66) One of the key limitations of research, undertaken within this period, which sought to explore the link between diabetes and cancer was that the recording of deaths caused by either disease were often inconsistent. Maynard undertook a statistical study reporting cancer death rates using data from the United States and concluded that although he was presenting results, he was aware that the use of death-rates could result in result errors and false conclusions.(66) Despite this, he reported both a

marked increase in cancer and diabetes death rates and a correlation between cancer and diabetes which required further analysis.

2.2.2 The insulin era (1920s-1970s)

Although a number of studies were undertaken between the introduction of insulin and 1980, they were often methodologically flawed, making it difficult for statistically rigorous conclusions to be drawn. This also resulted in inconsistent findings, with some studies finding strong positive correlations between the two diseases and others finding similarly strong negatives ones.

The discovery of insulin in 1921,(67) and its use as a treatment for diabetes, enabled increases in life expectancy among those with diabetes. As was mentioned in chapter one, the increase in life expectancy was associated with a corresponding increase in cancer incidence and mortality among diabetics: the incidence of cancer among this group was 1.5% in 1900 but 8.9% in 1940.(70) Marble used detailed mortality data from the Metropolitan Life Insurance Company, taken from the George F. Baker Clinic in Boston.(100) He found an increased rate of cancer among his diabetic group of 256 cases in 10,000 diabetics. Marble acknowledged that his findings should be treated with caution and that, by only investigating cases among those attending hospital, he may have biased the results.

A 1940 study by Kruger, using 5,844 autopsies between 1934 and 1938, sought to examine the occurrence of cancer and diabetes combined.(101) Within the study population 731 cases of cancer were found, ten within those with concurrent diabetes (n=122). The pathological, anatomical and medical histories of the cases did not allow the researcher to further analyse why the diseases occurred together at this rate. Further to this, he found no links between severity of the metabolic disorder and that of the cancer and concluded that severe diabetes may actually be linked to having a less severe tumour - what he referred to as the 'cancer-inhibiting tendency' of diabetes and the 'diabetes-inhibiting' tendency of cancer. Kruger stated that:

> "an explanation of the infrequent co-occurrence of cancer and diabetes is provided by the metabolic change that takes place when either of these diseases develops, creating unfavourable conditions for the development of the other disease."(101, p12)

Kruger went on to postulate that, although the small sample size did not allow for the drawing of any general conclusions, it did appear that the two conditions together did not lead to increased

morbidity or earlier mortality, and did not increase the chances of metastases. As mentioned previously, the small number of concurrent diabetes and cancer cases makes this research merely indicative of an association between the two diseases.

Jacobson (1948) was cautious about the use of hospital data within this area of research because he believed that diabetics utilising hospital services would not be representative of those within the general population. He postulated this was because:

> "a) these diabetics may be different from others who are not under care by the very fact that they are under care and (b) some of the diabetics found to have cancer may have sought care because the coexistence of the latter condition aggravated the diabetic symptoms."(102, p.91)

Further to this, Berkson in his article *Limitations of the Application of the Fourfold Table Analysis to Hospital Data* illustrated that the use of hospital data to explore correlations between diseases could overemphasise the correlation(103); the crux of his argument was that the more diseases a patient had, the more likely each disease's symptoms would be to be noted by the patient and make the patient attend hospital. The result would be an over-correlation within the hospital population that did not match that found in the general population. Berkson noted that:

> "its effect would be to increase relatively the representation of multiple diagnoses in the hospital, and in general to increase the discrepancy between hospital and parent population" (103, p.50)

Jacobson also concluded that "death certificates are probably not yet sufficiently complete to warrant critical studies of associated causes of death solely on the basis of data from death certificates."(102, p.97) Despite this, the work of Jacobson is of particular note because he undertook a number of studies, using a variety of data sources, in order to explore the link between diabetes and cancer. He was also one of the first researchers to use health survey data (questions were asked of family members in relation to their health and key socioeconomic factors in a way similar to the Health Survey for England and Scottish Health Survey data used within this thesis) to explore the potential link between diabetes and cancer. He also agreed with the earlier work of Tuffier in concluding that an individual's diabetes preceded the development of cancer, and not vice versa. Table 2-3 gives an overview of his key pieces of research and the conclusions that he drew.

Table 2-3: The research of Jacobson in relation to diabetes and cancer

Data Source	Results	Conclusions
Mortality data (1929-1938) from the George F. Baker Clinic Boston. 25 per cent sample of diabetic cohort at the clinic.	83 cancer deaths among the sample, equivalent to 5.3 cancer deaths per 1,000 years of life exposed. The number of expected cancer deaths within the same time-frame was 62.	He believed this study confirmed the hypothesis of a positive association between diabetes and cancer.
U.S census data on causes of death as recorded on death certificates in 1940.	11.6 per cent of non-diabetics are recorded as having died from cancer, compared with 4.0 per cent of diabetics. Cause of death was recorded as diabetes and cancer of the digestive organs and peritoneum (which includes the pancreas) 35 times more than expected.	Negative correlation between diabetes and cancer, but not among diabetes and a specific cancer. Cautious of findings considering that in the U.S. in the 1940s only around half of all death certificates included more than one cause of death.
New York City mortality data from proprietary and municipal hospitals between 1937-1939 and 1941.	Cancer reported as the cause of death among male diabetics as 12.3 and non-diabetics as 18.4 per 100. For women the same figures were 10.3 and 19.8. Further to this, pancreatic cancer was found to constitute a larger percentage of all cancer deaths among diabetics than non-diabetics (6.8 per cent and 3.9 per cent respectively).	The figures indicate a lower rate of cancer among diabetics than non-diabetics, but a similar rate among diabetics as among individuals with diseases associated with cancer (tuberculosis and syphilis). Thus diabetes is still associated with cancer.
U.S population data from 1940 and numbers of deaths from cancer and diabetes in the same period.	Expected number of deaths from both causes was 275. Actual number of deaths from both was 1348.	Positive association between the diabetes and cancer.
New York cause of death data	Actual number of deaths with both causes reported 74 compared with 2.4 expected.	As above.
National Health Survey data; morbidity data taken from 83 cities covering 703,092 families (1,310,051 individuals) over the winter of 1935-1936. U.S. Data was collected on socio-economic factors and general household illness.	2,912 males and 5,278 females were found to have diabetes. Among this group 18 and 37 cases of cancer were reported (0.6 and 0.7 per cent) respectively. Among those under 65 for men and 75 for women diabetics were found to have more cancer. Over these ages they were found to have less than the general population. Within the diabetic group and including all ages the ratio of observed to expected cases of cancer was 1.26 among men and 1.43 among women.	Among women (but not men), and both genders combined, the observed: expected ratio was found to be statistically significant.
Case-control study of individuals with diabetes and those with sinusitis (control group). The study sought to explore whether those who are using health services have higher rates of cancer diagnosed; or whether diabetes specifically is associated with cancer.	The observed to expected ratio among diabetes among both sexes was 1.37 compared with 0.90 for the same figure among those with sinusitis. Cancer of the digestive organs and peritoneum (which includes the pancreas) occurred more than would be expected among female diabetics but not for male diabetics. But neither of these findings were considered statistically significant.	Cancer is more prevalent among diabetics compared with the general population but not among those with sinusitis. Therefore there was found to be a relationship between diabetes and cancer.

[a] The information within this table was adapted from an article by Jacobson.(102)

Tichy analysed autopsy results from 6,571 cases of benign and malignant neoplasm.(104) Among 3,525 men, 85 (2.4%) were found to be diabetic, while among 3,000 women, 126 (4.2%) were. Further to this it was found that there was a lower rate of observed than expected cancers among those with diabetes. For men the figures were 28.8 (expected), 9 (observed) and for women 46.1 (expected), 11 (observed). Tichy concluded that the diabetic cohort had a three to four times reduced risk of developing cancer than those without the disease.

Glicksmann and Rawson undertook a case-control study with 950 patients to explore the presence of the diabetic glucose curve among those with cancer.(105) Within the study design, diabetic glucose curve was considered present when a patient had one of the following 1) a blood-sugar level above 200 mg per 100cc (11mmol/l) any time during the test; 2) a blood-sugar level of more than 100 mg per 100cc (5.5mmol/l) 2 hours into the test; or 3) a blood sugar level that remained above fasting level for over three hours. They found the presence of this in 36.7% of those with cancer compared with 9.3% of those with benign conditions. Within the study, 13.3% of individuals with cancer had diabetes compared with 4% of the control group. Unfortunately this finding was not explored any further in the research. The diabetic group was also on average 8 years older than the control group; this is likely to increase the incidence of cancer in the former independently of their diabetes status. Confounding factors which may have impacted upon an individual's glucose tolerance, such as liver function, were not considered. Finally, they reported that adjustment for confounding factors such as sex, weight and religion, had occurred but details were not given.
Within this period, other researchers also explored the glucose tolerance of those with cancer; their use of small sample sizes made robust conclusions hard to draw, particularly in terms of understanding the mechanism which created such a decrease in glucose tolerance among those with cancer.(106)

A study using autopsy and morbidity data from Bristol Royal Infirmary found that cancer incidence was lower among those with diabetes compared with non-diabetics; the former had a ratio of 0.50 in the morbidity data and 0.53 in the autopsy data compared with the general population.(107) The study also noted that there were differences between diabetic men and women - men had a cancer occurrence of 87% that of the total autopsy population, with the corresponding figure for women was lower, at 37%. They concluded that the negative association between diabetes and cancer was statistically significant only for women.

Caution should be used when making generalisable conclusions about the association between diabetes and cancer from any study utilising autopsy data for a number of reasons. Within earlier studies, confirmation of primary carcinoma could be imprecise and often only one disease was recorded on an autopsy. This made correlations between diseases liable to statistical error.(72,108) There were also a large number of undetected cases of diabetes within the general population and there was no clear consensus on what constituted a death from diabetes, therefore the disease would often go unreported within autopsy and post mortem records. Mainland also found that there was bias within the selection of cases to undergo autopsy: it was dependent upon the diseases of interest to the individual doctor undertaking the autopsy, the wishes of the family, hospital policies and practices, and wider legal requirements.(108) As with the work of Jacobson mentioned above, the use of hospital data was unlikely to be representative of the wider population.

An extensive review of the literature relating to a correlation between diabetes and cancer undertaken by Kessler in 1971 concluded that studies undertaken using clinical evidence were likely to show a positive relationship between diabetes and cancer, while those that used autopsy data showed a negative relationship.(72) He also found that studies which used a measure of proportionate mortality from cancer (comparing individuals with diabetes with the general population) supported a negative relationship between diabetes and cancer; this was in all cancers other than pancreatic which was consistently found at higher rates among the former (an issue which will be further addressed in a later section of this review). This latter point he also found to be true among studies exploring cancer risk among diabetic cohorts.

A prospective study, tracking mortality among members of the British Diabetic Association (BDA), followed 5,971 individuals and found an excess of deaths relating to diabetes and ischaemic heart disease.(109) The reverse was found to be true for cancer; the expected number of deaths was calculated as 168 while the observed number was 128. The authors concluded that this was due to a lower rate of smoking among BDA members compared with the general population as there were fewer than expected deaths related to this activity, such as lung, pharynx and bladder cancer. When specific tumour sites were investigated they found an excess of death from that of the liver (expected=0.5, observed=4) among both sexes and pancreatic cancer among men (expected=8.1, observed=12) while a lower than expected death rate from cancer of the rectum (observed=4, expected=8.9) was observed.

2.2.3 1980s-present

The 1980s began to see studies investigating the link between diabetes and cancer that were methodologically more rigorous than those undertaken previously, although some studies still used sample sizes that were too small to be able to make statistically significant inferences about the relationship between diabetes and cancer or were dependent on relatively unreliable data sources. It was also at this time that studies began to focus more upon specific cancer sites and their link to diabetes.

The 1982 cohort study by Ragozzino et al. sought to investigate relative cancer risk among individuals with diabetes.(75) Those diagnosed with diabetes within the study were followed for an occurrence of cancer. The study utilised a range of data sources to confirm a diagnosis of cancer (death certificates, autopsies, hospital records, outpatient, clinic visits and nursing home care). Diagnoses of cancer were included in the study only when they were histologically confirmed and occurred after a diagnosis of diabetes; cases were also excluded from the study when both diseases were diagnosed in the same month. Within the study, a total of 1,135 individuals were diagnosed with diabetes and 120 cases of cancer were detected. For all of the cancer sites found, the relative risk was greater than 1.0 (1.2 among men and 1.1 for women), but it only reached statistical significance for women with adenocarcinoma of the pancreas, melanoma and lymphoma. For pancreatic cancer, the study found that around half the cases (four out of nine) were diagnosed in the first year of a diagnosis of diabetes. Although the researchers considered whether the incidence of diabetes occurred before cancer or vice-versa, they concluded that the relationship between the two conditions *"was probably real".* The small number of concurrent cases of diabetes and cancer meant that statistical significance was not reached and no exploration of the effect of confounding factors upon the relationship between diabetes and cancer was undertaken. Overall, the study concluded that the relative risk of cancer among those with diabetes was statistically similar to that of the general population.

O'Mara et al. undertook a multisite case-control study of the relative risk of cancer among diabetics. Using data collected between 1957 and 1965, a total of 8,220 men and 6,690 women between the ages of 30-89 with a diagnosis of cancer were investigated.(76) The study was one of the first to specifically differentiate between type-1 and type-2 diabetes. As with the above study, those whose cancer had been diagnosed within the same year as their diabetes were excluded from the study to reduce the number of cases within which diabetes was merely an outcome of cancer. The study

found the relative risk of cancer was increased among women more than men and gave the following risk ratios:

- 2.0 for uterine cancer among those with adult-onset diabetes; this increased risk remained even after adjustment for obesity and parity, with thinner women being found to have an increased risk compared with overweight and obese women);
- 2.0 for non-melanoma skin cancer among women; and
- 3.0 for kidney cancer among women.

For other cancers, women with diabetes had a lower relative risk than the general population, for example 0.8 for cancer of the cervix. Contradicting the majority of earlier studies, no increased risk was found for diabetes with respect to pancreatic cancer and the study concluded that this type of cancer was likely to induce the occurrence of diabetes. The study further concluded that it was the diabetes, in and of itself, that was increasing the risk of cancer and not the treatment of the disease. A methodological weakness of this research lay in the fact that it only investigated white individuals and the cohort investigated was made up exclusively of individuals attending a single hospital. This would reduce the generalisability of the findings if the hospital was utilised by a homogenous socio-economic/ demographic community. The study did not undertake any analysis of the socio-economic or demographic backgrounds of those involved in the study.

A meta-analysis and systematic review sought to explore whether diabetes conferred an increased risk of cancer.(84) The meta-analysis included five reports (one case-control and four cohort studies) and established an odds ratio of 1.70 (CI 1.38-2.10) among those with diabetes compared with their non-diabetic counterparts. When the analysis adjusted the risk ratio for confounders, the attenuated increased risk was similar in both sexes but was significant only for diabetic men (RR= 1.25, 95% CI = 1.06-1.46) but not for diabetic women (RR 1.23, 95% CI 0.97-1.56). Within the systematic review and meta-analysis, the researchers found consensus across studies - none of the studies included found a decreased risk of cancer among diabetic patients compared with non-diabetics. As mentioned in section 1.8, the meta-analysis was large but was limited to Japanese populations.

In the first decade of the 21st century, researchers began to conclude that in order to understand better any potential relationship between the two diseases it would be necessary to focus either upon 1) type-1 or type-2 diabetes (or measures of blood glucose) or 2) site-specific cancers. A report by the American Diabetes Association and the American Cancer Society in 2010, which aimed to

assess all the evidence relating to diabetes and its link to cancer, stated that *"In view of the variable associations between diabetes and cancer risk at specific sites, we discourage studies exploring links between diabetes and risk of all cancers combined."* (37, p.209) With this in mind the following section of the literature review details the epidemiological evidence pertaining to the associations between diabetes and site-specific cancers.

Two recent studies also found increased all-cause and site-specific cancer mortality among those with diabetes. The Emerging Risk Factors Collaboration utilised data from around 850,000 participants from 97 pooled prospective studies; within the study all-cause cancer mortality among those with diabetes was increased (HR 1.25, 1.19-1.31), while site-specific mortality was only moderately associated with cancers of the colon and rectum, liver, breast, ovary, pancreas, lung and bladder.(86) The second study utilised data from over 1 million participants, with this study allowing for an evaluation of a mortality from a range of site-specific cancers.(110) Table 2-4 details the results.

Table 2-4: Results diabetes and cause-specific mortality in a prospective cohort of one million U.S adults

Site-specific cancer	**Relative Risk, 95% CI**
All-cause mortality	1.90, 1.87-1.93 (women) 1.73, 1.70-1.75 (men)
Liver	1.40, 1.05-1.86 (women) 2.26, 1.89-2.70 (men)
Pancreas	1.31, 1.14-1.51 (women) 1.40, 1.23-1.59 (men)
Endometrium	1.33, 1.08-1.65 (women)
Colon	1.18, 1.04-1.33 (women) 1.15, 1.03-1.29 (men)
Breast	1.16, 1.03-1.29 (women) 4.20, 2.20-8.04 (men)
Oral cavity and pharynx	1.44, 1.07-1.94 (men)
Bladder	1.22, 1.01-1.47 (men)
Prostate	0.88, 0.79-0.97 (men)

2.3 Diabetes and site-specific cancer

The following sections detail the evidence related to the associations between diabetes and site-specific cancers.

2.3.1 Lung cancer

Lung cancer causes the greatest number of cancer deaths within the UK (around one in five cancers among men and women combined).(111) Only a small number of studies have explored the association between diabetes and lung cancer, with heterogeneity within results. The case-control study undertaken by Hall et al. involved 66,848 cases with diabetes and 267,272 controls.(112) They found that, among all those with diabetes, deaths from primary lung cancer were 1.63 per 1000 patient years (95%CI 1.48-1.79) and among those followed after a diabetes diagnosis the corresponding rate was 2.05 (1.76-2.38). For non-diabetics the rate was 2.04 (1.96-2.13). The hazard ratio among diabetics was 0.8 (0.79-0.97) among all diabetics compared with non-diabetics and 1.12 (0.95-1.34) among those with incident diabetes. The study concluded that there was not an increased risk of lung cancer among those with diabetes and that this may be due to a reduction in life expectancy among this group, which prevented the consequences of smoking increasing lung cancer cases. Ehrlich et el. supported this finding: they found an increased risk of diseases such as asthma and pneumonia but not lung cancer.(113) The age, sex and ethnicity-adjusted hazard ratio among diabetics was 1.05 (CI 0.94-1.17) compared with non-diabetics; further adjustment, for factors such as BMI, revealed a non-significantly raised hazard ratio of 1.10 (CI 0.96-1.26). A study of postmenopausal women, comparing risk of lung cancer diagnosis between those with and without diabetes, found that the former were at an increased risk (HR 1.27, 95% CI 1.02-1.59) and that this further increased among women who required exogenous insulin (1.71, 1.15-2.53).(114)

In terms of life expectancy among those who have been diagnosed with lung cancer, Bartling et al. found increased life expectancy at 20 months among those with diabetes (76% survived to this point among diabetics compared with 59% among non-diabetics, p=0.048).(115) When survival was measured at 60 months, there was not a statistically significant difference between the groups (35% and 32%). This study involved a relatively small sample size of 55 cases with diabetes and 111 controls.

A meta-analysis including 34 studies found that diabetes was associated with lung cancer when studies that included adjustment for tobacco consumption were included (Relative Risk (RR)): 1.11, CI 1.02-1.20). There appeared to be no increased risk when studies that did not adjust for smoking

were considered (RR: 0.99, CI 0.88-1.11). When analysis was stratified by gender, only among women was there a statistically significant increased risk (1.14, CI 1.09-1.20).(116)

2.3.2 Colorectal and other gastrointestinal cancers

Colorectal cancer includes those of the colon and rectum and is the second largest site-specific cause of cancer mortality in the UK, killing over 16,000 individuals in 2008.(117) Globally, 1.28 million individuals were diagnosed with the disease in 2008.(118) The majority of studies have found an increased risk of developing colorectal cancer among those with diabetes compared with those without the disease. A case-control study of 14,916 male doctors followed for 13 years found a positive relationship between c-peptide level (a marker of insulin levels within the body) and risk of developing colorectal cancer.(119) Those in the highest quintile of c-peptide level had an increased risk of developing the disease compared with those in the lowest quintile, after adjusting for a number of factors including BMI, alcohol consumption and age (RR=2.7, 95% CI 1.2-6.2). Among patients with colorectal cancer, diabetes was associated with greater all-cause mortality (HR 1.41, CI 1.18-1.70) and mortality from colorectal cancer (1.36, 1.11-1.67).(120)

A meta-analysis utilising a large cohort of over 2.5 million individuals found an increased risk of colorectal cancer among those with diabetes compared with those without the disease (RR=1.30, 95% CI 1.20-1.40).(121) A systematic review and meta-analysis, undertaken up to October 2008, included 15 articles and found that those with concurrent diabetes and colorectal cancer had an increased risk of mortality. Both short-term and long-term mortality was increased among those with diabetes (the latter by around 32%, 95% CI 24-41%).(87) Findings, in terms of increased mortality when both diseases are present, are inconsistent: some studies do not find an increase among those with diabetes compared with those without the disease.

Other gastrointestinal cancers include those of the oesophagus, stomach, liver, biliary system, pancreas, bowel and anus. A number of these cancers are discussed individually in other sections of the literature review. Each year in the UK cancers of the pancreas and oesophagus each cause over 7,000 deaths; while those of the stomach cause over 5000.(117)

2.3.3 Pancreatic cancer

The association between diabetes and pancreatic cancer appears to be the most established of all the site-specific cancers. In an early piece of research, Marble found an increased incidence of the disease among diabetics.(100) He noted that 13% of all tumours among the group were pancreatic,

while U.S data from the same time period showed that, for all cancers diagnosed in the general population, pancreatic cancer accounted for between 3 and 5%. A meta-analysis of 36 cohort and case-control studies found that the odds ratio for developing pancreatic cancer among those with diabetes was 1.8 (95% CI 1.7-1.9) compared with the general population.(122) At the same time, some researchers have argued that this represents reverse causality, that diabetes is merely an indicator of the presence of occult pancreatic cancer: among those who are aged 45-50, lean and have no history of diabetes within the family it is suggested that diabetes should be considered a marker of the presence of pancreatic cancer.(123,124) This finding is supported by an increased incidence of the cancer among those who have had diabetes for the shortest amount of time. For example within the meta-analysis by Huxley et al., those who had had diabetes for less than 4 years were twice as likely to be diagnosed with pancreatic cancer, while those who had the disease for longer had an excess risk of 50% compared with those without diabetes.

2.3.4 Other gastrointestinal cancers

Svacina et al. found no increased risk of developing gastrointestinal cancer among those with type-1 diabetes.(125) A case-control study (311 cases and 10,154 controls) also found no increase in adenocarcinomas of the oesophagus and gastric cardia (OR 1.1, 95% CI 0.8-1.5) among diabetics.(126) Among those with type-2 diabetes, a case-control study utilising 1,172 cases and 496 controls, found an increased odds ratio among diabetics for cancers of the pancreas (OR 3.22, 95% CI 3.03-3.42), biliary system (2.10, CI 1.61-2.53) and gallbladder (2.20, CI 1.56-3.0).(127) A large cohort study (including 113,347 and 131,573 diabetic men and women respectively followed for over 10 years) found an increase in mortality from gastric cancer.(128) For men and women the mortality rate ratio changed with age: among men the figure was 4.49 (95% CI 3.93-5.12) among those aged 25-64, 1.58 (1.40-1.78) among those aged 65-74 and 1.52 (1.31-1.77) among those >74. For women, the same figures were 3.65 (CI 3.11-4.28), 1.95 (1.67-2.27) and 1.58 (1.32-1.90) respectively. A 2013 cohort study supported an increase in gastric cancer among those with diabetes; four years after diabetes diagnosis increased hazard ratio was 1.76, CI 1.06-2.91.(129)

An increased odds ratio was found in relation to oesophageal cancer among those with diabetes (OR 1.59, 95% CI 1.04-2.43).(130) This figure was reduced, to a non-statistically significant level after adjustment for BMI (OR 1.32, CI 0.85-2.05). A cohort study of 469,448 cases found no association between adenocarcinoma of the oesophagus (HR 0.98, CI 0.73-1.31), oesophageal squamous cell carcinoma (HR 1.02, CI 0.60-1.74) and gastric non-cardia adenocarcinoma (HR 0.98, CI 0.70-1.37) but

did find an association with gastric cardia adenocarcinoma (1.89, CI 1.43-2.50).(131) The latter association remained after BMI was taken into account (1.70, CI 1.28-2.26).

2.3.5 Kidney cancer

A Swedish cohort study involving a sample of 153,852 individuals with diabetes and comparing renal cell cancer incidence and mortality among this group with that of the general population found an increase among those with diabetes.(132) A larger than expected number of kidney cancers were diagnosed among the diabetic cohort (267 occurred, while 182 were expected). Standardized Incidence Ratios were also increased among those with diabetes (1.7 (CI 1.4-2.0) among women and 1.3 (1.1-1.6) among men). Mortality from kidney cancer was also found to be higher among this group (1.9 (1.7-2.2) among women and 1.7 (1.4-1.9) among men) compared with the general population. Svacina et al. supported the finding(133), while a non-significant increase in risk was found in a further study (OR 1.3, CI 0.9-1.7).(134) A large cohort study (46,462 men and 64,326 women) found no statistically significant relationship between diabetes and kidney cancer. This appeared to be due to the small number of concurrent cases: in total, there were eight deaths from kidney cancer among those with diabetes.(135)

A 2013 meta-analysis that included data from 24 studies found that diabetes was associated with an increased incidence of kidney cancer (RR 1.40, CI 1.16-1.69); each of the studies included showed an increased risk of developing the cancer among those with diabetes.(136) However the analysis did not indicate a statistically significant association between diabetes and mortality from kidney cancer (RR 1.12, CI 0.99-1.20).

2.3.6 Liver cancer

A case-control study (420 patients with hepatocellular carcinoma and 1,104 healthy controls) found an increased prevalence of diabetes among those with cancer (OR 4.2, CI 3.0-5.9).(137) In the majority of cases (87%), diabetes preceded the onset of cancer (OR 4.4, CI 3.0-6.3). For both men and women, diabetes was found to be associated with an increased risk of liver cancer (men: 1.63, CI 1.06-2.51, women: 1.64, 1.03-2.61); the highest risk occurred during the first five years following the diabetes diagnosis.(138) A systematic review and meta-analysis involving 26 studies found an increased risk of hepatocellular cancer among those with diabetes.(139) Of the 13 case control studies included in the analysis, nine found a significant association, while among 13 cohort studies, seven found a significant association. This equated to a relative risk of 2.5 within both study types (RR=2.5, 95% CI 1.8-3.5 and RR=2.5, 95% CI 1.9-3.2 respectively). A systematic review and meta-

analysis found an odds ratio for hepatocellular cancer of 3.64, 2.61-5.07; when adjusted for confounding factors the OR was only slightly attenuated (2.38, 2.01-2.81). (84)

2.3.7 Haematopoietic cancers

A small number of studies have investigated the relationship between diabetes and haematopoietic cancers (non-Hodgkins lymphoma, leukaemia, and multiple myeloma). A case-control study found that diabetes was a risk factor for incident non-Hodgkins lymphoma (OR 1.88, CI 1.22-2.89).(140) A cohort study of 35,420 participants found an increase in mortality from non-Hodgkins lymphoma among men with a BMI in the highest quartile compared with the lowest (HR 2.57, CI 1.24-5.34) and among men with the highest post-load glucose compared with the lowest (HR 2.86,1.35-6.06).(141) The corresponding figures for leukaemia were HR 1.98, CI 1.07-3.69 for BMI; an association was not found for post-load glucose. Among women, BMI was associated with leukaemia mortality only (HR 2.47, CI 0.96-6.36), while post-load glucose was associated with multiple myeloma only (HR 3.06, CI 1.05-8.93).

A 2008 meta-analysis, focussing upon diabetes and non-Hodgkins lymphoma, included 16 papers (5 detailing a cohort study and 11 a case-control study) and showed a slightly increased risk ratio among diabetics of 1.19 (95% CI 1.04-1.35) compared with non-diabetics.(142) In the same year, a meta-analysis and systematic review found an association between diabetes and non-Hodgkins lymphoma within both case-control studies (OR 1.18, CI 0.99-1.42) and prospective cohort studies (RR 1.79, CI 1.30-2.47). The most recent meta-analysis investigated the association between type-2 diabetes and non-Hodgkins lymphoma, leukaemia and myeloma.(143) In the majority of cases there was a significantly increased odds ratio for incident cancer: non-Hodgkin lymphoma 1.22 (1.07-1.39); leukaemia 1.22 (1.03-1.44); and myeloma 1.22 (0.98-1.53). The authors concluded that future analysis should also consider the impact of confounding factors upon associations between diabetes and these site-specific cancers.

2.3.8 Bladder cancer

Mortality from bladder cancer is the eighth leading cause of cancer death within the UK, equating to around 10,000 deaths each year.(144) A 1988 case-control study found a substantially increased overall relative risk for bladder cancer mortality among those with diabetes of 2.18 (1.75-2.72); among men and women >75 years of age RR=2.18, CI 1.75-2.72 and RR=1.34, CI=0.96-1.89 respectively; while for men and women aged 25-64 the corresponding figures were RR=5.95, CI 4.57-7.74 and RR=7.44, CI 5.46-10.15, respectively. The study further concluded that this excess in risk

was unrelated to diabetes-related medication usage.(145) A case-control study found that diabetes duration was associated with bladder cancer risk (OR for those with diabetes for a duration >16 years was 3.6, CI 1.1-11.2 compared with 2.2, CI 1.3-3.8 overall).(146)

Only one study was focused exclusively upon diabetic women and their risk of bladder cancer. The Iowa Women's Health Study found that diabetic women had, after multivariate adjustments, a relative risk of 2.46, CI=1.32-4.59.(147) A study carried out in an ethnically diverse cohort of 186,000 participants, followed for over 10 years, found an increased risk of urothelial cancer, the majority of which were located in the bladder, among self-reported diabetics (RR=1.25, CI 1.04-1.50).(148) Further analysis suggested that confounding factors such as overweight and obesity did not explain the increased risk. A meta-analysis found an increased risk of bladder cancer among those with diabetes (RR 1.24, 1.08-1.42),(149) while a second, utilising data from 36 studies, resulted in a RR of 1.35, CI 1.17-1.56.(150) These were consistent within results for case-control (RR 1.37, CI 1.04-1.80) and cohort studies (RR=1.43, CI 1.18-1.74).

2.3.9 Breast cancer

Among a cohort of 1,248 Asian-American women, diabetes was found to be associated with a risk of developing breast cancer (OR 1.68, CI 1.15-2.47); the increased risk remained unchanged when factors such as BMI were adjusted for.(151) Of note is the finding that the association was stronger among women with a low BMI (<22.7) (OR 3.50, 1.32-9.24) than in those with a BMI above this threshold (OR 1.39, 0.81-2.36) although this was not statistically significant. Postmenopausal women were found to have an increased, but not statistically significantly raised, risk of incident breast cancer (1.35, CI 0.99-1.85) but not mortality from the cancer.(152)

A meta-analysis of 20 studies found an increased risk of breast cancer among diabetics (RR=1.20, 95% CI 1.12-1.28).(153) Among the case-control studies, the relative risk for incident breast cancer among those with diabetes was 1.18 (CI 1.05-1.32), while for the cohort studies was 1.20 (1.11-1.30). Within the meta-analysis, five cohort studies focussed upon mortality from breast cancer and found a combined RR of 1.24 (CI 0.95-1.62) among those with diabetes compared with those without.

2.3.10 Endometrial cancer

Over 1,900 women each year die of endometrial cancer in the UK, with similar numbers newly diagnosed.(154) A 2013 cohort study found an increased HR of 1.71 (CI 1.48-1.97) of developing endometrial cancer.(155) A meta-analysis, including 16 studies, found an increased risk of

endometrial cancer among women with diabetes (RR=2.10, 95% CI 1.75-2.53) compared with the general population. Further analysis indicated a stronger relationship among women with type-1 diabetes (RR=3.15, 95% CI 1.07-9.29). When analysis utilised data only from studies focussed upon type-1 diabetes, a statistically significant increased risk among those with diabetes remained (RR 3.15, CI 1.07-9.29).(156) An odds ratio of 3.43 (1.53-7.72) was found within a systematic review and meta-analysis exploring incident endometrial cancer; following further adjustment for confounders the OR was 2.71, 1.19-6.19.

2.3.11 Prostate cancer

Prostate cancer is the only site-specific cancer for which research suggests a reduced incidence among those with diabetes. A meta-analysis of 14 studies found a negative relationship between diabetes and the disease (RR=0.91, 95% CI 0.86-0.96).(157) A second meta-analysis, involving a total of 19 studies published between 1971 and 2005, supported this finding. They found an inverse association between diabetes and prostate cancer (RR=0.84, 95% CI 0.76-0.93).(158) Within the case control studies, they found a relative risk of 0.89 (CI 0.72-1.11), while for cohort studies the relative risk was 0.81 (CI 0.71-0.92).

A meta-analysis involving 11 studies focussing specifically upon prostate cancer mortality found a small increase in prostate cancer mortality among those with diabetes; compared with those without diabetes, the pooled hazard ratio was 1.57 (CI 1.12-2.20).(159)

2.3.12 Other cancers and their link to diabetes

As can be seen from the sections above, even when cancers occur relatively frequently it is still difficult to draw firm conclusions in terms of their link to diabetes. This situation is made even more difficult when the cancers occur infrequently and research is therefore restricted in terms of the methods that can be used to explore any potential relationships. There is a limited amount of evidence for a number of other cancers. For example, a 2013 study did not find an association between diabetes and oral cancer, instead the authors called for further research to investigate the associations between the two diseases.(160) An exploration of survival among women with ovarian cancer found that those with diabetes had a shorter survival time compared with those without diabetes (HR 2.04, 1.31-3.17).(161)

2.4 Type-1 diabetes and cancer

The majority of the studies mentioned above either do not differentiate between type-1 and type-2 diabetes or were focussed upon type-2 diabetes. Some commentators have questioned the validity of extrapolating to type-1 diabetes the results of studies focussed upon type-2. (162) Therefore a review which specifically focussed upon research which explored the relationship between type-1 diabetes and cancer was undertaken as part of this thesis. This then formed a paper which was published in the International Journal of Cancer.(163) The following section details the results of this literature review; the published paper is available at the back of this thesis.

As can be seen from Table 2-5, there were mixed results in terms of whether or not those with type-1 diabetes were at greater risk of developing and dying from cancer. Mixed results were found among cohort studies. None of the case-control studies found a statistically significant link between the two diseases, while both of the meta-analyses (which included both study designs) did. There were also mixed findings among research that defined type-1 diabetes in the same way. For example, three studies used diagnosis before the age of 30 as being indicative of the disease: two found no statistically significant relationship, while one did. The rest of this section explores the results of the research found within this review, based upon the method used within the study. Mention has been made of the country in which the study was undertaken as an exploration of the potential geographical differences in the strength of the association between type-1 diabetes and cancer may be beneficial to our understanding of the associations between the two diseases.

Only a small number of cohort studies focussed on type-1 diabetes and overall cancer incidence; only one gave the information required for inclusion in this review. A Swedish study found a 17% increase in cancer among those with type-1 diabetes compared with the general population (RR=1.17 (95% CI 1.04-1.33).(164) At the same time, if analysis excluded specific time periods after diagnosis (based on either one or five years) no significant increase in standardized incidence ratio (SIR) was found. Exclusion of the first year (SIR 1.07, 95% CI 0.94-1.22) was similar to analysis for exclusion of first five years (SIR 1.09, 95% CI 0.96-1.25). This finding may support the reverse causality hypothesis—that diabetes is the result of an undiagnosed cancer rather than the other way round, or it could be the consequence of small numbers within the study. A further cohort study undertaken in Denmark found no overall increase in cancer cases among those with type-1 diabetes compared with the general population; although among men with insulin-treated diabetes, there was an increase in overall cancer incidence (RR= 1.37, 95% CI 1.03-1.83); however, this was not found to be the case for women (RR=1.08, 95% CI 0.77-1.51).(165) Although this study only used

insulin use as a proxy for type-1 diabetes, it has been included within this review because the follow-up years within which the study was undertaken (1973-1981) were such that the majority of those using insulin were likely to have had type-1 diabetes.

A Swedish cohort study found a standardized mortality ratio (SMR) of 1.73 (95% CI 1.45-2.05) among its type-1 diabetic cohort compared with the general population.(166) In support of this, a New Zealand study found an SMR for cancer of 12.96 (95% CI 3.36-22.57) among those diagnosed with type-1 diabetes compared with the general population.(78)The CI is wide and this may be due to there being only seven observed cases of cancer among those diagnosed with diabetes under the age of 30 (the measure used within the study as indicative of type-1 diabetes).

A case-control study (7,713 cases, 38,518 controls) undertaken in the UK explored all-cause and cause-specific mortality among those with type-1 diabetes compared with the general population.(167) They found no statistically significant difference in the hazard ratios (HR) for cancer mortality between the two groups (HR=1.05, 95% CI 0.72-1.52). A second UK study also found no increase in cancer mortality among those with type-1 diabetes. For all-cause cancer mortality the SMR was 0.90 (95% CI 0.75-1.08).(168) A key limitation of this study was that a large proportion of their subjects (20,676 of 28,900) were under the age of 50 at follow-up. This is known to be a period when cancer incidence is lower than in later life; 63% of cancers are diagnosed in those over the age of 65 and only 5.4% of cancer in men, and 8.9% of those in women, occur under the age of 45.(169,170) The US Allegheny County Type-1 Diabetes Registry cohort study investigated cause-specific mortality among its cohort of those with type-1 diabetes (n=1,043). They found no statistically significant association between the two diseases (SMR= 1.2, 95% CI 0.5-2.0) compared with the general population.(171) The lack of statistical significance in this study is likely to be heavily influenced by the small number of cancer deaths and the consequent effect on statistical power.

Table 2-5: Key findings of research exploring the relationship between type-1 diabetes and cancer by outcome measure

Study method	Country	Sample	Case definition (type-1 diabetes)	Outcome measure	Risk of cancer among T1DM participants (95% CI or p-value)	Risk of site-specific cancers (95% CI or p-value)
Cohort(165)	Denmark	1,499 insulin treated individuals	Insulin use	Incidence	Men RR=1.37 (1.03-1.83), Women RR=1.08 (0.77-1.51),	Pancreas RR=2.53 (1.17-5.47); RR=1.69 (p=0.29) once cases excluded where diabetes an indicator of cancer
Cohort (172)	Denmark	109,581 individuals with diabetes	Hospitalised with diabetes <age 50	Incidence	SIR 1.1 (1.0-1.2)	Liver SIR= 4.8 (2.8-7.7), mouth and pharynx SIR=1.8 (1.2-2.6)
Cohort(164)	Sweden	24,052 type-1 diabetic patients	Diagnosis <age 21	Incidence	RR=1.17 (1.04-1.33),	Stomach RR=3.36 (1.44-6.66), skin RR=4.96 (2.83-8.07), leukaemia RR=2.02 (1.15-3.29)
Cohort(173)	Sweden	29,187 diabetes patients	Hospitalisation for diabetes <age 30	Incidence	SIR=1.2 (1.0-1.3)	N/A
Case-control(174)	Italy	752 diabetic women with endometrial cancer and 2,606 admitted to the same hospitals	Diagnosis <age 40	Incidence	OR=1.0 (0.3-3.4)	N/A
Case-control(76)	USA	14,000 participants with diabetes aged 30-89	Diagnosed with diabetes <age 29	Incidence	Not significant (at the p<0.05 level)	N/A
Meta-analysis(156)		I case-control and 2 cohort studies (168,173,175)		Incidence	N/A	Endometrial RR=3.15 (1.07-9.92)
Meta-analysis(176)		3 cohort and 6 case-control studies		Incidence	N/A	Pancreatic RR=2.00 (1.37-3.01)
Cohort(166)	Sweden	144,427 participants with diabetes	Hospitalisation for diabetes <age 40	Mortality	RR=1.73 (1.45-2.05)	N/A
Cohort(78)	New Zealand	966 insulin treated participants including 427 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=12.96 (3.36-22.57)	N/A
Case-control(167)	UK	7,713 cases of type-1 diabetes and 38,518 controls	Those currently on insulin and aged <35 at treatment or <35 years at diagnosis of diabetes	Mortality	HR=1.05 (0.72-1.52)	N/A
Cohort(171)	USA	1,043 type-1 diabetic patients	Diagnosis <age 18	Mortality	SMR=1.2 (0.5-2.0)	N/A
Cohort(168)	UK	28,900 insulin treated diabetics including 23,834 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=0.90 (0.75-1.08),	Ovarian SMR=2.90, (1.45-5.19)

In terms of site-specific cancers the study by Shu et al. found increased SIRs for those of the stomach (3.36, 95% CI 1.44-6.66), squamous cell carcinoma of the skin (4.96, 95% CI 2.83-8.07) and leukaemia (2.02, 95% CI 1.15-3.29).(164) These SIRs were those which excluded the first five years of follow-up after diagnosis of type-1 diabetes, with significance remaining stable across all the three follow-up intervals of all cases, one year follow-up exclusion, and five years' exclusion. Gender was a key factor in excess cancer incidence. After exclusion of the first year following type-1 diabetes diagnosis, SIR remained increased only among women. This statistical significance was also only for cancers of the skin (SIR 9.40, 95% CI 5.12-15.82) and leukaemia (2.55, 95% CI 1.26-4.57). The number of visits an individual made to hospital was also found to be a risk factor for cancer, but the researchers were unsure whether this was due to the increased chance of a cancer being diagnosed within more frequent visits to hospital or because there was an association between type-1 diabetes and cancer. More detailed analysis, undertaken by Green and Jensen, showed that, for site specific cancers, only that of the pancreas had a statistically significant increase (RR=2.53, 95% CI = 1.17-5.47).(165) However, further analysis showed that, once cases were excluded where diabetes was an early indication of the presence of cancer, the relationship was no longer statistically significant (RR= 1.69, p=0.29). In terms of age and gender, only men between the ages of 0-54 had an increased risk of cancer (RR=2.04, 95% CI= 1.11-3.74), although this result may reflect the small numbers within the studies rather than the real effect type-1 diabetes has upon cancer incidence.

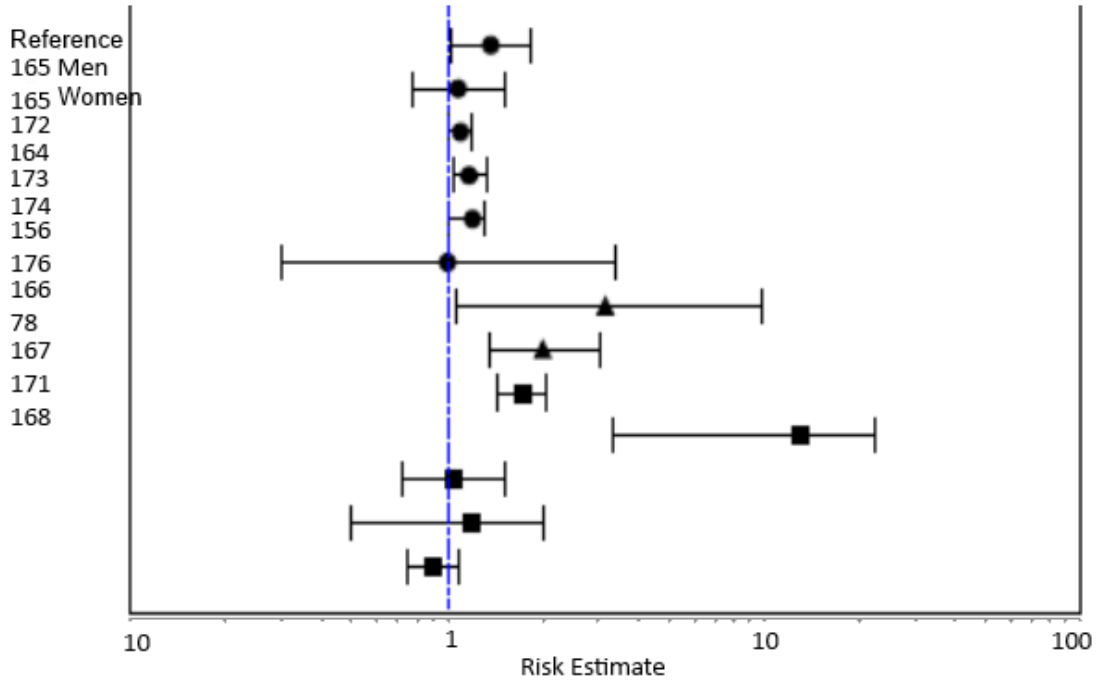
A Danish cohort study found mixed results depending on cancer site.(172) Among those defined as having type-1 diabetes (hospitalised for diabetes within the study period before the age of 50) the SIR for all cancers was 1.1, 95% CI 1.0-1.2; only cancers of the mouth and pharynx (SIR 1.8, 95% CI 1.2-2.6) and liver (SIR 4.8, 95% CI 2.8-7.7) were increased among this group. For cancers of the pancreas, lung and kidney non-statistically significant increases were found (SIR 1.4, 95% CI 0.7-2.3, SIR 1.3, 1.0-1.6 and 1.6, 1.0-2.4, respectively). A third Swedish cohort study found an overall SIR for cancer of 1.2 (95% CI 1.0-1.3) among those with type-1 diabetes compared with the general population.(173) For site-specific cancers significant increases in SIR were found for those of the stomach (2.3, 95% CI 1.1-4.1), cervix (1.6, CI 1.1-2.2), and endometrium (2.7, CI 1.4-4.7).
An Italian case-control study exploring the link between endometrial cancer incidence and diabetes (type-1 diabetes and type-2 diabetes, assessed separately) found no link between type-1 diabetes and the disease (odds ratio (OR)=1.0, 95% CI 0.3-3.4) but only four cases with type-1 diabetes were included in the study.(174) In support of this finding, a second study that included 14,000 individuals aged 30-89 with diabetes, found no statistically significant association (at the 5% level) between a range of site- specific cancers and the disease.(76)

A meta-analysis of the link between diabetes and endometrial cancer found an association between the two diseases (RR=3.15, 95% CI 1.07-9.29).(177) This was based on three studies, one of which was a Swedish case-control study which had few women with type-1 diabetes (<10) and found a relative risk (RR) of 13.3, with a wide CI of 3.1-56.4.(178) The other two studies are those of Swerdlow et al. (UK) and Zendehdel et al. (Sweden), mentioned earlier in this review.(168,173)

A systematic review and meta-analysis focussed upon type-1 diabetes and the incidence of pancreatic cancer.(176) Within the meta-analysis, a RR of 2.00 (95% CI 1.37-3.01) was found for pancreatic cancer among those with type-1 diabetes. The meta-analysis was based on 39 concurrent cases of the two diseases. The researchers themselves reported that the study was limited by the small number of studies published in this area; there were an even smaller number that were published with sufficient concurrent cases of type-1 diabetes and pancreatic cancer: Ekoe et al. found only one case while La Vecchia found three.(179,180) Only two studies had more than five cases among those with type-1 diabetes; the first of these is the Wideroff study mentioned above and the second found an increased RR of pancreatic cancer among those with type-1 diabetes (RR 2.23, 95% CI 1.08-4.58.(181) Three of the studies included in the analysis had no concurrent cases of type-1 diabetes and pancreatic cancer.(76,182,183)

Only a few reports have focussed on cause-specific mortality among those with type-1 diabetes; among these a smaller number still investigated cancer mortality. The reason for this is likely to be the excess of mortality among those with type-1 diabetes caused by complications of the disease itself, such as renal disease and cardiovascular disease.(184) A UK study linked cause of death data to a register of those with diabetes and found that those with type-1 diabetes only accounted for 18 (5%) of all deaths within the study; because of this they did not undertake separate analysis for cause of death among those with this form of diabetes.(185) Other studies were characterised by their inclusion of numbers of concurrent type-1 diabetes and cancer too small to elicit statistically viable results.(186–189) The study mentioned previously by Swerdlow et al. found increased mortality among women with type-1 diabetes for ovarian cancer (SMR 2.90, 95% CI 1.45-5.19); the same was not found to be true for any other cancer sites.(168)

Figure 2-1: Risk estimates for all-cause cancer incidence and mortality among those with diabetes



2.5 Glycated haemoglobin ($HbA1_c$) and cancer

The evidence related to glycated haemoglobin and cancer risk is currently limited and the strength of the association remains unclear. A case control study (cases were those who developed cancer after a diagnosis of diabetes, n=53) found that the incidence of cancer was highest among those with an $HbA1_C$ level ≥8% (OR 3.16, CI 1.34-7.44).(190) The study also found that mean $HbA1_C$ was higher among those who had cancer compared with the control group (7.83 vs 7.30, p=0.02) and that there was a dose-response effect in cancer risk with each step-increase in $HbA1_C$ measurement (OR 1.61, CI 1.09-2.36). This association was accentuated when adjustment was made for a range of confounding factors including overweight/obesity, duration of the presence of diabetes, comorbidities and smoking status (OR 1.67, CI 1.10-2.53). Joshu et al. found that raised glycated haemoglobin was associated with incidence of and mortality from cancer among women, but not men, who were non-diabetic but were not normoglycaemic (HR 1.24, CI 1.07-1.44 and 1.58, CI 1.23-2.05).(191) However, a third study found no association between raised $HbA1_C$ and cause-specific cancer risk (HR 1.02, CI 0.95-1.10) and no association between $HbA1_C$ and a range of site-specific cancers.(192) There also appeared to be no association when $HbA1_C$ was explored as a continuous variable or when quartiles were used. In terms of site-specific cancer incidence, evidence suggests that raised glycated haemoglobin is associated with cancers of the colorectum(193), pancreas(194)

and liver(195). It was also found to be associated with the nature of localised prostate and colorectal cancer; among those with a raised $HbA1_C$ their cancer was more likely to be aggressive in nature.(196,197)

Glycated haemoglobin has also been found to be associated with endpoints related to cardiovascular disease. Elley et al. found that a 1% increase in $HbA1_C$ increased the risk of CVD (HR 1.08, CI 1.06-1.10), myocardial infarction (1.08, 1.04-1.11) and stroke (1.09, 1.04-1.13)(198); an earlier investigation of data from the European Prospective Investigation of Cancer and Nutrition (EPIC)-Norfolk found similar results.(199)

There appears to be heterogeneity within findings related to the association between $HbA1_C$ and all-cause mortality. A 2013 study found that, among those without diabetes, there was a non-significant association (HR 1.21, 95% CI 0.99-1.47) between raised $HbA1_C$ and all-cause mortality; the study found no association among those with diabetes.(200) However a number of studies contradict this result.(201,202) A Danish study found increased all-cause mortality among those with an $HbA1_C$ measurement ≥ 7% HR 1.26 (95% CI 1.15, 1.39) and a U-shaped relationship between increasing $HbA1_C$ and all-cause mortality.(203) A number of studies have highlighted the dangers posed, for example by hypoglycaemia, to the health of individuals with diabetes in seeking to maintain strict control of blood glucose.(204–206)

2.6 The biological pathway between diabetes and cancer

As yet there is no definitive explanation for the possible link between diabetes and cancer and a number of unexplained biochemical factors still elude researchers. Despite this, a number of theories have begun to dominate the research, in both biochemistry and epidemiology, seeking to explain the potential pathway between the two diseases. The two charts below highlight the two overarching hypotheses.

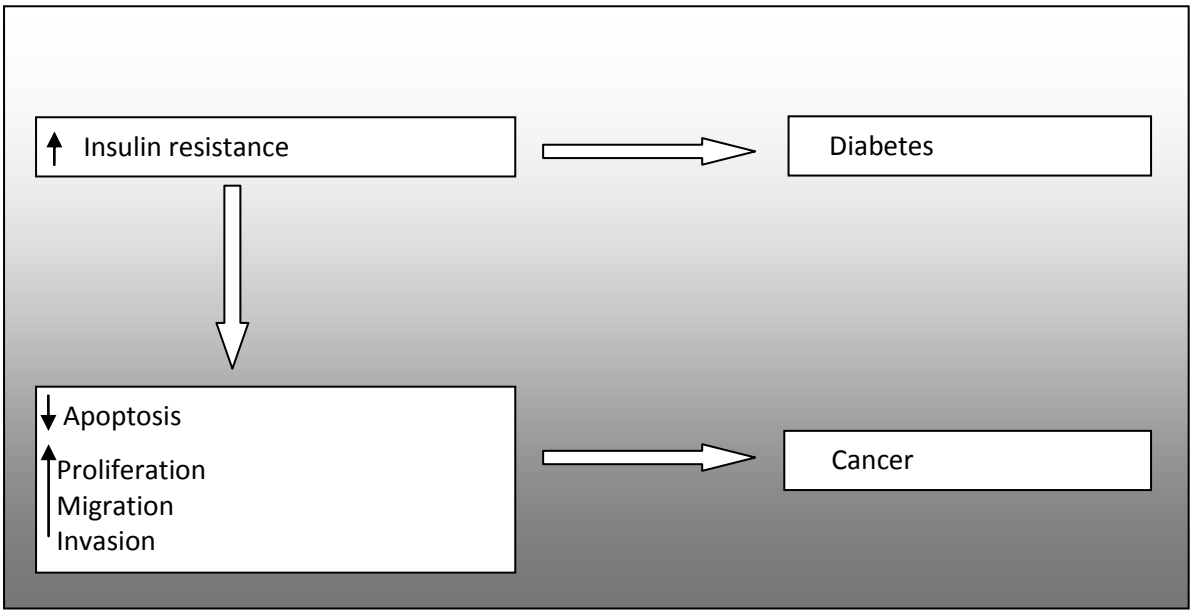
2.6.1 Hypothesis one

Hypothesis one suggests that insulin is the main cause of the relationship between diabetes and cancer. When type-2 diabetes first occurs hyperinsulinaemia occurs in an attempt to overcome the occurrence of insulin resistance in tissue. Insulin and insulin-like growth factor (IGF), along with their receptors, are also known to have both proliferative and mitogenic effects upon normal and cancerous cells.(207,208) Substances that are mitogenic are usually proteins that trigger mitosis via signal transduction and the involvement of mitogen-activated protein kinase. Insulin has also been

found to be anti-apoptotic (a substance that reduces cell suicide).(209) A number of studies have found that high levels of insulin were positively correlated with a range of site-specific cancers.(97,210–212)

IGF-1 is very similar to insulin in being a mitogen and having anti-apoptotic properties. It also shares many of its signalling pathways with the protein. The majority of IGF-1 in circulation is produced by the liver and only a small proportion of it is unbound, the majority of it being bound to IGF-binding proteins (IGFBP). Research has found that high levels of insulin were associated with an increase in risk of cancers of the endometrium; while free IGF-1 levels were associated with a decrease, total IGF-1 and IGFBP were not associated with this type of cancer.(213) IGF-1 and insulin receptors have also been found to be produced, and in some instances over-produced, by cancer cells.(214) Figure 2-2 details the role of insulin within the biologically plausible relationship between diabetes and cancer development.

Figure 2-2: Hypothesis one: a key role for insulin



2.6.2 Hypothesis two

Hypothesis two takes a broader approach to the relationship between diabetes and cancer, suggesting that factors related to diabetes, as well as confounding factors, are involved. Figure 2-3 demonstrates the influence and interaction of all of these factors within the relationship between diabetes and cancer. At around the same time that Tuffier was exploring a potential link between diabetes and cancer, other researchers had begun to observe increased rates of hyperglycaemia

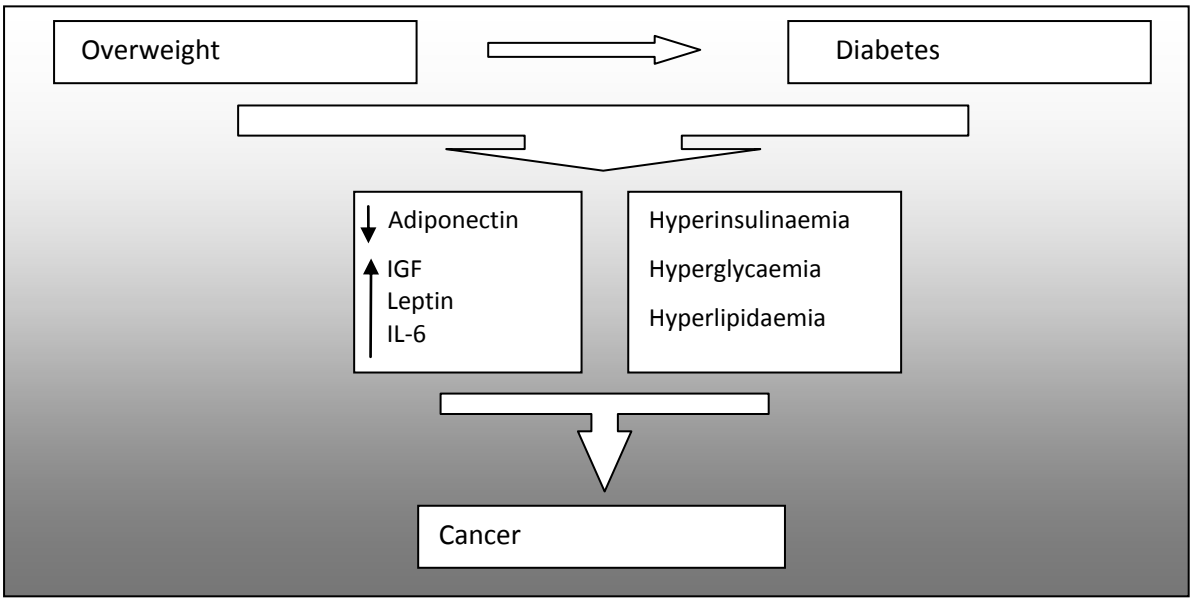
among those with cancer (for a more detailed investigation of the associations between hyperglycaemia and cancer, see section 0 above). Warburg also found that cancer cells could live without oxygen if they were in serum that contained glucose and that tumour cells utilised glucose at higher rates than normal cells.(99) As *in vivo* and *in vitro* research has developed in this field, it has been observed that cancer cells take up glucose independently of the presence of insulin and that they constitutively take up glucose at near full-capacity. Therefore, some commentators have argued that hyperglycaemia is likely to be of less importance, in terms of explaining the relationship between diabetes and cancer, than the role of insulin and IGF-1. Because of the Warburg effect it has been postulated that inducing hypoglycaemia could induce cancer remission, although the research in this area is in its preliminary phase.(215)

During the early part of the 21st century, researchers began to explore the underlying factors that could explain the possible link between diabetes and cancer. This research was predominantly focussed upon attempts to unravel the influence that obesity might have over any potential increased incidence of cancer among diabetics. This was perhaps because, as mentioned previously, being overweight or obese increases an individual's risk of developing type-2 diabetes. Being overweight or obese has also been found to increase the risk of developing cancer and mortality from the disease(216,217); evidence indicates that, in developed countries, around one in 20 deaths from cancer are associated with overweight and obesity,(218) and that its presence may increase the risk of cancers of the gallbladder, bowel, womb, breast, oesophagus, pancreas and kidney.(219) There are a number of interrelated biological factors which may explain the inter-play between overweight and obesity, diabetes and cancer. These are:

- Adipose tissue has been found to be an endocrine organ which releases a range of inflammatory cytokines (such as IL-6 which has been found to reduce cell apoptosis) and can predispose the body to insulin resistance and hyperinsulinaemia.
- Adiposity has been found to be related to cancers such as leukaemia and non-Hodgkin lymphoma.
- Lower levels of adiponectin (an insulin sensitiser) are found among those with type-2 diabetes, obese individuals and those with insulin resistance. Adiponectin is a substance which has been found to regulate insulin sensitivity (reducing an individual's risk of developing typ-2 diabetes), down-regulate TNF-α and increase cell apoptosis.
- Abdominal obesity has been found to reduce the levels of leptin (another cytokine) within the body, a substance which encourages insulin sensitivity and reduces free fatty acid levels.

There is also a small amount of evidence that leptin may have a role in the metastasis of some tumours.(216,220,221)

Figure 2-3: Hypothesis two: the influence of factors related to diabetes and obesity



2.7 Biological pathway between diabetes and site-specific cancers

Because of the diverse aetiologies for individual cancer, a number of factors have been investigated in relation to the association between diabetes and site-specific malignancies. These include:

- the impact that the slower transit time within the colon, found among diabetics, has upon risk of colon cancer(222),
- evidence of increased incidence of bladder and urinary tract infections among diabetics (both factors may increase the risk of these cancers)(147),
- the influence upon prostate cancer of lower levels of testosterone among men with diabetes compared with those without the disease(223), and
- the increased rate of cirrhosis of the liver caused by non-alcoholic steatohepatitis (for which diabetics are at an increased risk).(224) There is also an increased rate of non-alcoholic fatty liver disease among those with type-2 diabetes; around 80% of those with type-2 diabetes are thought to have it, and this may contribute to increased rates of liver cancer among this group.

2.8 Diabetes therapies and their role in the associations between diabetes and cancer

The impact of individual anti-diabetic drugs upon cancer risk is difficult to explore because individuals may change drug regimen over time, may combine drugs or may stop drug use altogether. It may also take a long time for the carcinogenic effect of some drugs to be uncovered, or the carcinogenic effect may disappear with drug cessation. Certain treatments may also be used at different stages of diabetes, for example the use of exogenous insulin is likely to occur at a later stage of type-2 diabetes compared with the use of metformin, with different risks relating to cancer. Finally, different anti-diabetic drugs work differently within the body, in relation to their impact upon hyperglycaemia and hyperinsulinaemia. Because of all these factors, the following section discusses anti-diabetic drugs in relation to their expected impact upon the different elements of the diabetic state.

2.8.1 Sulphonylureas and insulin

In non-diabetic individuals, insulin is produced by the pancreas in the beta-cells. It then travels to the liver via the portal vein where a large proportion is used and degraded; because of this, other organs receive around one-third to one-tenth the amount of insulin received by the liver.(225) In diabetic individuals, who receive their insulin exogeneously, all the organs and tissue receive the same amount of insulin. The issue is therefore whether or not these two different forms of insulin distribution impact upon the proteins influence over cancer incidence and mortality.

Sulphonylureas are a type of secretagogue and work by activating endogenous secretion of insulin. If insulin is the biological mechanism that explains the relationship between diabetes and cancer, then a drug which increases hyperinsulinaemia may, hypothetically, increase the risk of cancer among its users. However, within the research the evidence is mixed; this may relate to the comparison group utilised within the study.(226–228) For example, studies that use individuals taking metformin (as the comparison group) may show an increased cancer risk that is caused more by the putative protective effects of metformin rather than the deleterious effects of sulfonylureas.

2.8.2 Biguanides and thiazolidinediones

These types of drugs increase tissue sensitivity to insulin and therefore reduce hyperinsulinaemia. The most researched of the biguanides, in terms of its anti-carcinogen properties, is metformin. This drug has been found to reduce the risk of cancer among diabetics by around 15%, compared with those with diabetes who are not being treated with metformin.(229–231) Metformin also stimulates

activated protein kinase (AMPK) which stimulates uptake of glucose by muscle, thus lowering hyperglycaemia. A systematic review and meta-analysis found that those being treated with metformin for diabetes did have a lower risk of cancer, but that there was a need for further research which utilised a range of research methods.(232)

The evidence relating to thiazolidinediones is mixed, in terms of cancer risk among users, and commentators have called for further research in this regard.(233–237)

2.9 Evidence from recent studies

In order to ensure that this literature review included information from the most recent studies, a number of searches of PubMed were undertaken throughout the study period (Jan, 2010-November, 2013). The last of these was performed on the 30th of November, 2013. The key results of these, more recent, studies were:

- Those with diabetes were at an increased risk of mortality from all-causes, cardiovascular disease and all-cause cancer after adjusting for a range of confounding factors.(238)
- A consistent association between diabetes and increased risk of developing pancreatic cancer.(239) The evidence also supports the hypothesis that diabetes causes pancreatic cancer, instead of there being 'reverse causality'.(240)
- A reduced risk of developing prostate cancer among men with diabetes, related to a protective effect of hyperglycaemia.(241,242)
- Heterogeneous results related to the associations between diabetes and site-specific cancers other than those of the pancreas.(243–246) Meta-analyses found increased risks, among those with diabetes compared with the general population, for incidence of and mortality from cancers of the stomach, bladder, breast, colorectum, lung, ovary and endometrium.(116,247–251)
- Studies seeking to assess the impact of diabetes treatments upon cancer risk continued to be limited by factors such as short follow-up times and the changing treatment regimens of those with diabetes.(252) Perhaps because of this, such studies produced mixed results when investigating whether specific drugs, such as metformin, had a deleterious or protective effect in relation to cancer incidence and mortality.(253–258) A meta-analysis explored the impact of insulin upon cancer risk and concluded that the use of the drug was associated with increased cancer risk, but that a number of the studies (n=42) included within the analysis had methodological limitations.(259) Thiazolidinediones were also found

not to be associated with overall cancer risk, (260) while a third meta-analysis found that metformin was associated with reduced risk of cancer development and mortality.(261)

- Within studies which explored the associations between diabetes treatments and cancer risk, there were also mixed results depending upon whether cancer in general or site-specific cancers were under investigation.(262)
- Those with diabetes, receiving treatment for cancer, have differing outcomes compared with the general population, although the results of these more recent studies were not conclusive. These differences in cancer outcome were related not only to the presence of diabetes but a number of other factors (such as the use of metformin), and whether the focus of the study was all-cancers combined or site-specific cancers.(263–266)
- The key role that insulin and IGF-1 play in the biological plausibility of an association between diabetes and cancer risk among those with diabetes by encouraging cancer cell proliferation and reducing cell apoptosis (242,267)

In support of the conclusions of earlier studies, the majority of the most recently published papers called for further research to explore the associations between diabetes and cancer incidence and mortality.

2.10 All-cause and cardiovascular disease mortality among those with diabetes

There is strong evidence that diabetes negatively impacts upon rates of all-cause mortality among those with the disease; 3.96 million deaths are estimated to have been caused by diabetes in 2010.(46) The biological impact that the disease has upon the body is also associated with an increased risk of mortality from a range of conditions and diseases, including cardiovascular and renal disease.(268,269) Because of the inter-related nature of the increased all-cause and CVD-specific mortality experienced by those with diabetes, the following section details the causes together in instances where studies produced results for both.

Research exploring the relationship between diabetes and cardiovascular disease has a history dating back to 1965; Ostrander et al. noted that the improving life-span experienced by those with diabetes was accompanied by a sharp increase in death from cardiovascular disease.(270) Since then, the majority of studies exploring cause-specific mortality and diabetes have found that the complications of diabetes and CVD were the main causes of the excess mortality experienced among

those with diabetes; those with diabetes have been found to have up to a fourfold increase risk of dying from cardiovascular disease.

An early study found age-standardised all-cause mortality among those with insulin-treated diabetes to be 50% higher than those without the disease. For women the relative risk (RR) was 1.77 (95% confidence interval (CI) 1.51-2.06) and for men 1.49 (1.29-1.71).(185) They also found excess mortality relating to ischaemic heart disease and cerebrovascular disease but not cancer (women RR for cancer 0.98, 0.61-1.48; men 0.82, 0.55-1.18). A study published in 1998 found increased mortality from all causes after adjusting for age, serum cholesterol, systolic blood pressure, smoking, BMI and coronary disease at baseline among those with diabetes (RR 2.50, 2.11-2.95). The RR for CVD death among men with diabetes was 2.87 (2.31-3.57).(271) Lotufo et al. found an age-adjusted relative risk of all-cause mortality among men with diabetes of 2.3 (2.0-2.6).(272) It is noteworthy that after adjusting for age, BMI, alcohol intake, smoking and exercise status the increased risk did not change significantly (RR 2.1, CI 1.9-2.4) The same study found an increased risk of mortality from coronary heart disease (CHD) among those with diabetes (RR 3.3, CI 2.6-4.1). Guzder et al. found an increased odds ratio for all-cause mortality among those with diabetes compared with the general population (OR 2.47, CI 1.74-3.49).(79) A study of those with Type-2 diabetes found a SMR of all-cause mortality among diabetic women of 1.83, CI 1.51-2.16 and 1.43, CI 1.18-1.67 among men.(273) The majority excess was driven by diseases of the circulatory system (SMR women 1.94, CI 1.52-2.36, men 2.09, CI 1.67-2.51) and not cancer (women 1.09, CI 0.56-1.62, men 0.79, 0.41-1.17) or other causes (women 1.70, CI 1.06-2.34, men 0.99, CI 0.56-1.42).

Barr et al. found that all-cause mortality hazard ratios decreased among those with newly diagnosed diabetes compared with those with known diabetes (HR 1.3, CI 0.9-2.0 and 2.3, CI 1.6-3.2 respectively in comparison with the general population).(269) Panzram et al. also found that age-at-onset of type-1 diabetes was the key factor in determining the excess of all-cause mortality experienced by those with this form of diabetes.(19) Gu et al. found an increase in the relative risk of all-cause mortality among their diabetic cohort, which decreased with age (25-44 RR 3.6, $p<0.05$, 45-64 RR 2.2, $p<0.05$, 65-74 RR 1.5, $p<0.05$).(274) A number of studies supported this finding: Bertoni et al. found that, among those over the age of 65 (receiving Medicare) with diabetes, excess mortality decreased with increasing age but the excess persisted even among the oldest age group (65-69 RR 2.59, CI 2.37-2.82, >85 RR 1.46, CI 1.43-1.49).(73) Swerdlow and Jones also found that all-cause Standardized Mortality Ratios (SMR) were greatest within the youngest age group among those with

diabetes, compared with the general UK population, and decreased significantly as age increased (p< 0.001).(275)

An Italian cohort study found an all-cause SMR of 1.42, CI 1.35-1.50 among those with diabetes compared with those without the disease.(276) For CVD the SMR was 1.34, CI 1.23-1.44. This study found that, although raised, the excess CVD mortality was not as high as that found within American diabetic cohorts. Related to this they noted that this may be due to the severity of the diabetes within different countries, or the differing treatment cultures, for example within the US >25% of those with type-2 diabetes are treated within insulin compared with <10% of those in Italy. However, it was also found that mortality from cancer, respiratory disease and injury and poisoning were not significantly raised. They also found differences in all-cause mortality related to the diabetes treatment being used: those who were treated with diet alone had an increased survival compared with those treated with insulin or oral diabetic drugs (potential confounding factors are discussed in greater detail in later sections of this chapter). The study also proposed that there was a latency period between the onset of type-2 diabetes and its diagnosis of 7-10 years, within which mortality may be higher than once the disease had been diagnosed.

Koskinen et. al. found increased relative mortality among diabetic women of 3.39 (CI 3.30-3.49); for men the corresponding figures were 2.41 (CI 2.34-2.48).(277) Circulatory diseases were found to be driving this excess in mortality, with over half of all deaths being recorded as ischaemic heart disease. Skrivarhaug et al. found an excess in CVD mortality of 4.0, 95% CI 3.2-4.8 among those with type-1 diabetes.(184) The Barr et al. study discussed previously found that those with known diabetes had an increased hazard ratio for CVD mortality, after adjustment for age, sex and other CVD risk factors (HR 2.6, CI 1.4-4.7).(269) They postulated that increased glycaemia may start to impact upon mortality before it reaches a level that would be diagnosed as diabetes. A study focussed upon mortality from CVD among those with diabetes found that those with the disease had the same risk of dying of CVD as those who had already experienced a myocardial infarction (MI) and that once an individual with diabetes experienced a MI they were more likely to die of it than those without diabetes(278); this result was supported by other studies utilising different populations.(279)

The WHO Multinational Study of Vascular Disease in Diabetes found that CVD was the main cause of death among those with type-1 and type-2 diabetes (44% and 52% respectively).(280) They also

found differing SMRs between international study sites; for example women and men in Tokyo who had type-2 diabetes had a very low excess mortality compared with the general population.
A 2009 paper utilised the large sample within The Framingham Heart Study and found that the all-cause and cause-specific mortality excess experienced among their diabetic cohort had begun to decline between the period 1950-1975 and 1976-2001.(281) Despite this, an increase in all-cause mortality persisted among those with diabetes within both time periods (HR, 2.44; P<0.0001 and 1.95; P<0.0001 respectively). Cardiovascular mortality was reduced from fourfold to threefold between the two time periods. This suggests that, within the Framingham study, much of the reduction in excess was caused by lower rates of CVD mortality within the second time period.
In summary, those with diabetes have increased all-cause mortality. Although the majority of this excess mortality appears to relate to the increased risk of cardiovascular disease caused by the consequences of diabetes itself, there is also some evidence of differences in the mortality rate from other causes. Heterogeneity between study results, utilising data from national studies, further suggests that need for research exploring the associations between diabetes and all-cause and cause-specific mortality which utilise data from UK-based, nationally representative samples.

2.10.1 Respiratory disease

Although the evidence related to mortality from respiratory disease among those with diabetes is limited, Dawson et al. found increased SMRs among women and men with type-1 diabetes (SMR 3.31, CI 1.98-4.63 and 2.32, CI 1.41-3.23 respectively).(78) There is a limited amount of evidence relating to the biological plausibility of a relationship between diabetes, obesity and respiratory disease. Zammit et al. postulate that obesity may alter lung physiology, cause inflammation (both systemic and within respiratory organs(282) but this requires further exploration with regard to its potential as a confounding factor between diabetes and such diseases.

2.10.2 Renal disease

One of the key complications of diabetes, which is found at low rates among the general population, is renal disease. A report from the Pittsburgh Epidemiology of Diabetes Complications Study found that, among those with type-1 diabetes who maintained normoalbuminuria (an indicator of kidney function), mortality rates were similar to those for the general population (SMR 1.3, CI 0.2–2.5).(283) Secrest et al. found that the leading cause of death, within the first ten years following diagnosis of diabetes, was complications related to the diabetes itself (renal, CVD, infections); this accounted for 73.6% of all deaths within this time period within their type-1 diabetic cohort.(171) Within the next ten years, mortality was split almost evenly between renal diseases, CVD, acute causes and

infections. After 20 years, the leading cause of death returned to being complications of diabetes; within this, around 40% related to CVD complications. The study also found that women and those from black and minority ethnic (BME) communities had significantly higher diabetes-related mortality compared with men and those from white communities. Of note, the study found that deaths not related to diabetes did not differ between those with diabetes and those without.

2.11 Conclusion

To conclude this chapter the following section discusses the evidence related to the associations and relationships between diabetes and cancer within the context of proving causality.

Diabetes and cancer: assessing causation

In his seminal address on the subject of causality, Bradford Hill listed a number of the components that he considered key to assessing causation.(98) Based on the evidence considered within the above literature review, the following section discusses these components in the context of the potential causal relationship between diabetes and cancer.

Strength

The strength of the evidence relating to the association between diabetes and cancer is mixed. This is dependent upon a number of factors including the research method used, the definition of diabetes within the study and the cancer focussed upon (whether the research explores cancer in general or a site-specific cancer).

Consistency

Similarly to strength, findings within the research relating to the association between diabetes and cancer have been inconsistent. The key areas of inconsistency are related to research method used and cancer site and type of diabetes analysed. For example, within the literature relating to type-1 diabetes, mixed results were found depending upon which method was used. The country within which the study occurred also appears to influence the strength of the association between diabetes and cancer. This suggests that, in order to understand the excess mortality among those with diabetes in a particular country, it is necessary to undertake research within that country.

Specificity

Diabetics have increased mortality across all ages, the majority of which is caused by cardiovascular diseases, as well as neuropathy, nephropathy and retinopathy. Therefore the relationship between

diabetes and cancer is weak in terms of specificity, in that diabetes increases the risk of a number of other diseases.

Temporality

Temporality refers to the order in which diseases occur. The evidence found within this literature review suggests that diabetes precedes cancer in all but one case, that of cancer of the pancreas, where evidenced is mixed as to 'reverse causality' caused by an occult malignancy.

Biological gradient

Again the evidence is mixed as to a dose-response effect within the relationship between diabetes and cancer incidence and/or mortality. There does appear to be some evidence to suggest that cancer risk is increased among those with a raised glycated haemoglobin measurement but that the association may be strongest among those with a measurement between 6 and 7% and tails off above this level.

Plausibility

The biological evidence relating to the association between the two diseases is strong: hyperinsulinaemia and hyperglycaemia appear to be associated with an increased risk of cancer development, both within epidemiological and biological research. Other factors present within diabetes, and overweight and obesity, also contribute to the strength of this evidence.

Coherence, experiment and analogy

Exogenous insulin, insulin sensitivity, Insulin-like Growth Factor-1 (IFG-1) and obesity have all been found to mediate and/or encourage the increased growth of cancer within rat and mouse models.(284–286) Current knowledge relating to cancer suggests that its development is related to factors present within both the metabolic syndrome and diabetes. An analogous example that may relate to the association of diabetes and cancer may be cirrhosis of the liver, found at increased rates among those with diabetes, as well as being a known risk factor for malignancies of the liver. At the same time, as mentioned above, increased hyperinsulinaemia and hyperglycaemia have been found to be related to cancer development.

While a number of interventions have attempted to reduce the rate of diabetes, such as those relating to lifestyle changes and tight glycaemic control, the impact this has upon cancer risk is, as yet, unclear. Thus the experimental evidence relating to a link between the two diseases, and the

prevention of cancer among those with diabetes, is currently mixed. The evidence relating to the use of anti-diabetic drugs which reduce hyperinsulinaemia and hyperglycaemia, specifically metformin, suggests that lowering the occurrence of these factors can reduce the risk of the development of cancer.

A number of diseases have been found to increase the risk of site-specific cancers, but evidence is limited in relation to diseases that have similar characteristics to those of diabetes. Therefore, analogous evidence in this area is limited.

2.12 Literature review: gaps in our current knowledge

A number of issues make it difficult to draw statistically robust conclusions about the relationship between diabetes and cancer, based on current findings. The overarching issue is the heterogeneity of findings. Even though research undertaken post-1980 utilised more rigorous research methods than before, studies continued to draw mixed conclusions. The result is that no clear consensus has been reached regarding the relationship between the two diseases. Up to the present time, research that has focussed upon the relationship between diabetes and cancer has elicited a number of broad, overarching and often contradictory results. The majority of the more recent studies support an association between diabetes and overall cancer mortality, although the magnitude of the effect differs between studies and whether or not there are associations between diabetes and site-specific cancers has yet to be clarified. Previous studies also demonstrate a number of gaps in our knowledge related to:

- the extent to which confounding factors (in particular overweight and obesity) explain the associations between diabetes and cancer,
- how the risk of cancer differs between those with type-1 and type-2 diabetes,
- the impact diabetes has upon the risk of developing and/or dying from site-specific cancers,
- whether or not the impact that diabetes has upon cancer risk differs between the sexes,
- how comorbidities, particularly CVD, impact upon the associations between diabetes and cancer,
- whether or not there is an association between glycated haemoglobin and cancer incidence and mortality,
- how the use of medications impact upon the cancer risk among those with diabetes,
- the biological pathway between diabetes and site-specific cancers.

These findings suggest the need for further research which explores the association between diabetes and cancer incidence and mortality, the role of confounding factors (specifically overweight and obesity) within the associations and the dose effect of glycated haemoglobin upon cancer risk. The next section details the study aims, objectives and hypotheses that were developed after a consideration of the above gaps in our knowledge.

2.13 Hypotheses, aims and objectives

Following on from the literature review, a number of research questions were developed for the study and these were accompanied by specific aims and objectives. The following sections detail how the research questions, and hypotheses, at the heart of the research were developed and informed.

2.13.1 Development of the research question and hypotheses

As discussed above, there is heterogeneity within current results related to the associations between diabetes, glycated haemoglobin and incidence of and mortality from cancer and there are a number of gaps within our current knowledge related to this research area. Through the use of Health Survey for England and Scottish Health Survey linked to Cancer Registry and mortality data it was felt that this study could overcome some of the issues that had hindered previous studies; for example the utilisation of large enough datasets, or datasets with sufficient data related to potential confounders, to appropriately assess any potential associations. At this juncture a number of more detailed objectives were developed, related to an exploration of:

- the relationship between diagnosed diabetes and cancer incidence and death (all-cause and site-specific),
- the impact of glycated haemoglobin upon the risk of cancer incidence and mortality among those with and without diabetes,
- the impact that overweight and obesity have upon the associations between diabetes and cancer,
- the effect of lifestyle and socio-economic/demographic factors upon the above association.

With the data available in the Health Survey for England, Scottish Health Survey and also an occupational cohort, Whitehall I, it was also possible to assess the impact that diabetes had upon mortality from other causes including cardiovascular and respiratory disease and 'other' causes. The review of the literature demonstrated that the extent to which diabetes impacted upon mortality from other causes, particularly within a nationally representative UK-based dataset linked to up-to-

date mortality data, had not been fully explored. Further to this, if diabetes were found to increase mortality from other diseases, this result would complement those which found associations between diabetes and cancer. Because of this, analyses of the associations between diabetes, $HbA1_C$ and all-cause and cause-specific mortality form part of the analyses undertaken within this thesis. The literature review highlighted the strong associations between diabetes and CVD, although there was a limited amount of evidence related to how comorbid CVD might impact upon the associations between diabetes and cancer. The recording of CVD as a longstanding illness within the HSE and SHeS meant that it was possible to include an exploration of this matter within the analyses undertaken in support of this PhD.

Based upon the results of the literature review and a consideration of the aims of the study, a number of research questions and hypotheses were developed.

Research Questions

Does the presence of diabetes, or a raised glycated haemoglobin measurement, alter the risk of incident cancer (both all-cause and site-specific) and/or mortality (all-cause, cause-specific and site-specific cancer mortality) among the general population?

Previous research has found a substantial association between diabetes and cardiovascular disease mortality; does this study support this association? Does the presence of diabetes, or raised glycated haemoglobin, impact upon mortality from other causes (including respiratory disease)?

Null Hypotheses

HØa

Individuals with diabetes do not have an increased risk of developing cancer compared with the general population.
AND
Individuals with diabetes do not have an increased risk of dying from cancer compared with the general population

HØb

A raised glycated haemoglobin measurement is not associated with an increased risk of incident cancer nor mortality from the disease.

The following hypothesis was developed in relation to the impact that diabetes might have upon mortality from diseases other than cancer.

HØc
Diabetes is not associated with mortality from other causes (cardiovascular and respiratory disease and 'other' causes).

Alternative Hypotheses
H1
The specifics of having diabetes directly increase the risk of an individual developing cancer. This increase in cancer incidence is above that caused by related factors such as adiposity.

H2
Individuals with diabetes are more likely to die of cancer than individuals who do not have diabetes.

H3
An increased glycated haemoglobin level is associated with an increased risk of developing cancer and of mortality from the disease.

H4
Diabetes is associated with an increased risk of mortality from other causes (specifically cardiovascular and respiratory disease).

Following an introductory investigation into the variables that were available within the HSE, SHeS and Whitehall I as well as an assessment of the gaps in current research within this area, further hypotheses were added which took into account the presence of cardiovascular disease (CVD) as a comorbidity.

Null Hypothesis
HØd
The presence of comorbid CVD has no impact upon the associations between diabetes and cancer incidence or mortality.

H5
Comorbid CVD alters the strength of the association between diabetes and incidence of and mortality from cancer.

1.1.1 Aims

The key aim of the study was to utilise data from the HSE, SHeS and Whitehall I to assess the associations between diabetes and incidence of and mortality from cancer. The breadth of the nationally representative HSE and SHeS datasets, also enabled an investigation of the effects of confounding factors such as overweight and obesity, the presence of CVD as a comorbidity and socio-economic and demographic factors. The age of the Whitehall I cohort further enabled analyses of a dataset with around 80% mortality and a follow-up period of 40 years.

Among Health Survey for England and Scottish Health Survey participants who had a valid measurement for glycated haemoglobin ($HbA1_c$) level, the study also sought to explore if an association exists between raised $HbA1_c$ level and incidence of and mortality from cancer.

1.1.2 Objectives

The research objectives were to:

- Establish if there are differences in the relative risk of developing cancer between those with and without diabetes.
- Assess how much of this relationship is explained by a range of confounding factors and the extent to which diabetes is an independent risk factor for incidence of and mortality from cancer.
- Investigate the relationship between HbA_{1c} level and cancer incidence and mortality among the general population.
- Assess the impact that comorbid CVD has upon the associations between diabetes and cancer incidence and mortality.
- Establish the strength of the associations between diabetes and mortality from CVD, respiratory disease and 'other' causes.

3. Chapter 3: Data sources

Three different datasets were used within this study to explore the associations between diabetes, glycated haemoglobin and incidence of and mortality from cancer (as well as all-cause and cause-specific mortality) – the Health Survey for England, the Scottish Health Survey, and the Whitehall I cohort. Each of these is detailed below.

3.1 The Health Survey for England

The Health Survey for England (HSE) began in 1991 and is a cross-sectional survey which utilises a large, nationally representative new random sample each year, currently commissioned by the Health and Social Care Information Centre; until 2004, the survey was commissioned by the Department of Health. Since its inception, the survey has covered the adult population living in private households, with children being included from 1995. The survey collects a wealth of socio-economic and demographic information, as well a range of objective health measurements. A number of the stated aims of the survey specifically relate to this research and these are monitoring the nation's health; the prevalence of specific diseases and lifestyle risk factors associated with them (such as overweight and obesity); and the differences in the health of specific populations.(287)

Each year the survey includes core topics related to health and lifestyle behaviours (for example long-standing illnesses, smoking and drinking) as well as physical measurements (blood pressure, height and weight) and biological samples (blood and saliva). Added to this are topics related to specific issues, such as cardiovascular disease (CVD), lung function and physical activity. The health of specific communities or sections of society, such as black and minority ethnic communities or older people, have also been focussed upon.

3.1.1 Design of HSE

Sampling

The survey utilises a two-stage stratified multi-cluster design with random probability sampling. This approach sees the population divided into non-overlapping postcode areas (the Primary Sampling Units); following this, a second stage of sampling occurs to select the addresses to participate in the survey. This results in the survey using a nationally representative sample of all adults (16+) living in private accommodation. The survey utilises a new sample drawn from the general population each year. Through the use of the Postcode Address File, a random sample of postcode sectors are selected; the number selected changes by year. Within these, a further random sample of 'delivery points' (addresses) are selected, which makes up the sample size. For example within the HSE 2005,

the total number of addresses selected was 18,720 made up from 26 addresses within each of the 720 postcode sectors.(288) To ensure that each address in England has an equal probability of being selected (even though the sample is clustered) postcode sectors are in the sampling frame in proportion to the number of addresses they contain. Among adults, a total of 10 can be interviewed within any single household, while for children only two can be included in the core survey, to reduce participant burden on parents.

In some years of the HSE boost samples were used in order to increase the number of individuals from specific groups within the HSE cohort, these were:

- 1999 and 2004 included boosts of individuals from ethnic minority communities.
- 2005 included one boost of those aged 65+ and one of children between the ages of 2-15.

Within the HSE there are certain core questions that are asked each year, there are also boost samples which enable the monitoring of specific areas of interest and comparisons to be drawn across years (for an overview of the focus of each year of the HSE see Appendix Six: Focus of the Health Survey for England 1991-2010). The data used within this research includes only the core sample of adults; children under the age of 16 were excluded from the analyses, primarily because they could not give consent for their data to be linked to mortality and Cancer Registry data. In 2006, because of the length of the survey, only a 50% sub-sample of those aged 65+ were asked to complete the module of the survey related to CVD (which included specific questions related to diabetes).

3.1.2 Data collection

The HSE utilises a two-stage, computer assisted personal interviewing (CAPI) process for data collection. The first of these is a face-to-face interview which consists of the core questions, detailed below, as well as those within the specific issue section.

Core modules within the Health Survey for England interviewer visit:

- household level information,
- demographic and socio-economic information,

- health-related questions, for example the presence of longstanding illnesses, such as diabetes and cancer (for further information about how these variables were used in the current study see section 3.8.1.),
- lifestyle behaviours, such as smoking and alcohol consumption, fruit and vegetable consumption since 2001, and physical activity in some years,
- height and weight measurements.(287)

Within this study, information gathered at this stage of the survey process enabled an exploration of those who indicated doctor-diagnosed diabetes and/or volunteered the disease as a longstanding condition.

If an individual agrees, the interview is then followed by a nurse visit; between 1994 and 2008, 66% of interviewed participants took part in the nurse visit. The following are examples of questions and measurements either asked/collected each survey, or in particular years, of the survey:

- Which prescribed medications are used by the individual, coded to categories of drug; asked within each year of the HSE and SHeS, the information gathered from this question has been used within this thesis to create the variables relating to the use of anti-diabetic drugs (variables medbi1-medbi22).
- Which vitamins are taken by the individual.
- Measurements of the hip and waist circumference and blood pressure.
- Saliva samples to measure cotinine levels (assessment of exposure to tobacco).
- Urine sample which allows for the measurement of creatinine, potassium, sodium and/or albumin.
- Blood sample which allows for the measurement of a number of analytes, which have varied over time. Relating specifically to this study, the taking of blood samples enables measurements of glycated haemoglobin to be taken.(289)

3.2 The Scottish Health Survey

The Scottish Health Survey (SHeS) took place in the years 1995, 1998, 2003, and 2008-2013; the survey is also running for the years 2014-2015. Within this study, data from SHeS 1995, 1998 and 2003 were utilised.

3.2.1 Design of the SHeS

Sampling

All private households within Scotland were eligible to be included in the SHeS; a maximum of three households per address could be included. Similarly to the HSE, the SHeS utilised the Postcode Address File and a random sample approach. For the SHeS 1995, one person aged 16-64 within each household was eligible for inclusion. In 1998 all adults (aged 16-74) were eligible but only one was selected for interview. Within the years 2003 and 2008 onwards all adults and up to two children were eligible; boosts samples were also taken within these years to ensure that sufficient numbers of children were included in the survey.(290,291)

As mentioned previously this study is limited to the adult sample of the HSE and SHeS. Therefore no further mention will be made of child-specific aspects of either dataset. Because this study only included HSE data up to 2008, no mention will be made of the datasets, nor changes to the surveys, from 2008 onwards. See section 3.8 for a discussion of the size of the overall sample, and the method for identifying those with diabetes.

3.2.2 Data collection

The design of the SHeS was similar to that of the HSE in that it is formed of a two-stage process, both of which collect the required information via the use of a CAPI.(292)

The HSE and SHeS are general population health examination surveys combining survey interview data with measurements and biological samples taken from participants. Because the surveys utilise samples of the whole non-institutionalised population, they are better able to produce information related to the prevalence of a specific disease or lifestyle behaviour and the rates of undiagnosed disease, than surveys carried out with self-selecting cohorts such as those undertaken within health care settings. Within this study, data from the HSE to 2008 are used; the 1994, 1998, 2003 and 2006 surveys asked specifically about doctor-diagnosed diabetes within the cardiovascular interview schedule (similar questions were asked in each year of the SHeS). More information about the focus of each year of the HSE is provided in Appendix Six.

3.3 Whitehall I

Whitehall I is a cohort study of male civil servants. Originally the data was used to explore the associations between employment grade and health outcomes and inequalities; early publications focussed upon areas related to cardiovascular disease.(293,294)

3.3.1 Data collection

Collection of baseline data for Whitehall I occurred between the years 1967 and 1970.(295) In total, 19,019 male civil servants working in London and aged 40-69 were surveyed to gather information related to health, socio-demographic information and lifestyle factors related to health. The participants also underwent a clinical examination. Subsequent data collection waves were also undertaken, including a re-survey of participants in 1997-1998 (see section 3.5.1), as well as data linkage to mortality records.

3.4 Amending variables to achieve conformity and appending the datasets

An initial exploration of the 15 datasets within the HSE and three within the SHeS illustrated inconsistencies within variable values and coding, even where they were based on identical questions. These inconsistencies were addressed by the production of syntax for each survey year to recode the variables in a uniform manner. Table 3-1 (below) details each variable, within the minimum dataset used within this research, and when recoding was required.

One of the key issues was lack of uniformity across datasets in relation to the 'Missing values'; these were different both within and across the HSE and SHeS. To remedy this, further syntax was created for each year. For each variable, the missing values were re-coded as follows:

- -9.00 'Not answered'
- -8.00 'Don't know'
- -6.00 'Schedule not obtained'
- -2.00 'Schedule not applicable'
- -1.00 'Item not applicable'

It was also necessary to recode a number of the dichotomous variables included within each year of the HSE and SHeS. This ensured that across all of the survey years '1' indicated the presence of a disease or occurrence of an event (for example diabetes or death) and '0' indicated the absence of disease or that an event had not occurred.

A string variable was then created which included information related to survey (whether HSE or SHeS), survey year and the serial ID for each case: this ensured that each case had a unique identifier when the survey datasets were appended. Cases from each year of the HSE and SHeS were then appended to the 1994 HSE dataset until all survey years were included.

Table 3-1: Recoding of variables within the minimum dataset

Year	Variables													
HSE	**Longill**[a]	**Illsm 1-6**[b]	**diabete2**[c]	**everdi**	**ageinfo1**	**medbi 01-22**[d]	**medcindi**	**advicedi**	**docinfo1**	**insulin**	**age**	**sex**	**height**	**weight**
1994	✓	Ills 1-6	diabdef		ageinfdi	med 1-16	✓	✓	docinfdi	✓	✓	gender	✓	✓
1995	✓	✓	N/A	N/A	N/A	medbi 1-15	N/A	N/A	N/A	N/A	✓	✓	✓	✓
1996	✓	✓	N/A	N/A	N/A	medbi 1-15	N/A	N/A	N/A	N/A	✓	✓	✓	✓
1997	✓	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
1998	✓*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
1999	✓*	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓*	✓	✓
2000	✓	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓*	✓	✓
2001	✓	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
2002	✓	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
2003	✓*	✓	✓	✓*	✓	✓	✓*	✓*	✓*	✓*	✓	✓	✓	✓
2004	✓*	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
2005	✓*	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
2006	✓*	✓	✓*	✓*	✓*	✓	✓*	✓*	✓*	✓*	✓	✓	✓	✓
2007	✓*	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
2008	✓*	✓*	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	✓	✓	✓	✓
SHeS														
1995	✓*	✓	✓*	cvd8*	diage*	medbi 01-16	dimed*	othdi*	diabetes*	✓*	respage	respsex	✓	✓
1998	✓*	✓*	✓*	✓*	✓*	medbia 1-18	✓*	✓*	✓*	✓*	ageyrs	✓	✓	✓
2003	✓*	✓	✓*	✓	✓	Medbi 1-18	✓*	✓*	✓*	✓*	✓	✓*	✓	✓

a longill – Presence of a longstanding illness

b illsm1-6 – Detailed information about the longstanding illness (up to a total of six)

c diabete2, everdi, ageinfo1, medcindi, advicedi, docinfo1 and insulin – Each of these variables gives information related to diabetes

d medbi1-22 – Detailed information about the medications that the participant is taking

Table 3-1: Recoding of variables within the minimum dataset (continued)

Year	Variables									
	Household social class	**Individual social class**	**Age at leaving education**	**Highest qualification**	**Cigarette smoking status**	**BMI**	**Waist: hip ratio**	**Waist circumference**	**Blood sample taken**	**Ethnicity**
HSE	sclasshoh	sclass	educend	edugrouped	cigsta3	Bmi	waisthip	Allwaist	Samptak	ethnic
1994	schhstu1	scallx	✓	topqual	cigsmkng	✓	alwhipra	✓	✓	✓*
1995	scchstx1	✓	✓	quala 1-11	current	✓	N/A	N/A	✓	✓*
1996	schhstx1	✓	✓	quala 1-11	cigsmk2	✓	N/A	N/A	✓	✓*
1997	hsclass	✓	✓	topqual2*	cigst1	✓	whval	Wstval	✓*	✓*
1998	hsclass	scallx	✓	topqual3*	cigst1	✓	whval	Wstval	✓	nethnic
1999	hsclass	scallx	✓	topqual3*	✓	✓	whval	Wstval	Samptakb	ethnich
2000	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	ethnici*
2001	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	ethnici
2002	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	ethnici
2003	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	ethnici
2004	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	dmethn04
2005	schrpg7	scallx	✓	topqual3*	✓	✓	whval	Wstval	✓	ethinda*
2006	schrpg7	scallx*	✓	topqual3*	✓	✓	whval	Wstval	✓	ethinda
2007	schrpg7	scallx*	✓	topqual3*	✓	✓	whval	Wstval	✓	ethinda*
2008	schrpg7	scallx*	✓	topqual3*	✓	✓	whval	Wstval	✓	ethinda*
SHeS										
1994	ciesc	soccls*	✓	topqual*	cigmk2	✓	alwhipra	waistc1 & 2	✓	✓
1998	soc2	sc	✓	topqual*	cigst1	✓	whval	wmeas1, 2 & 3	✓	✓
2003	sccieg7	✓	✓*	hedqual	cigst1	✓	✓	Wstval	✓	ethnicl*

* Denotes that it was necessary to produce syntax to create uniformity across variable values (including missing values).

3.5 Creation of variables within the HSE and SHeS

A number of variables were required that were not available within the baseline survey datasets, but could be created from the variables provided. Table 3-2 below details these variables.

Table 3-2: Variables produced as part of this study

Variable	Variables available within HSE and SHeS
Region (South, Midlands, North, Scotland)	NHS region and GOR[a]
All Diabetes (Diabetes: Yes/No) (see section 3.8.1)	illsm 1-6, medbi 1-22, diabete2
Glycated Haemoglobin (<6.5%/≥6.5%)	Glyhbval
Diabetes and Glycated haemoglobin combined	illsm 1-6, medbi 1-22, diabete2 & glyhbval
Waist-hip ratio all (Waist/Hip raised: Men ≥=0.95, Women ≥0.85)	Waisthip
Waist raised all (Waist raised: Men >102cm, Women> 88cm)	Allwaist
Ethnicity (White/Black/South Asian/Other)	Ethnic
BMI Grouped (<20/20-24.9, 25-29.9, ≥30kg/m^2)	Bmi
All Cancer Mortality (Yes/No/Died of another cause)	CauseDeath
Site-Specific cancer mortality	CauseDeath
Cause-Specific mortality (Cancer, CVD, Respiratory and 'other' causes)	CauseDeath
Age Grouped (16-64/65-75/75+)	Age
Cardiovascular Disease at Baseline	illsm 1-6
Cancer at Baseline	illsm 1-6

[a] Government Offices for the Regions (South West, South East and East Anglia=South, West Midlands and East Midlands=Midlands, North West, Yorkshire and Humberside, and North =North and cases from SHeS = Scotland).

3.5.1 Variables within Whitehall I

Although not as extensive as the HSE and SHeS, in terms of the scope of baseline variables available, Whitehall I included a number of variables related to this study. These were:

- Employment grade
- Date of birth/Age

- Smoking (Current/Ex/Never)
- Diabetes status (+Age at diagnosis + Insulin use)
- Medications
- BMI
- Weight
- Height
- Waist circumference
- Waist to hip ratio
- Fasting blood glucose
- Serum cholesterol
- Cause of death (all-cause, CVD, coronary heart disease (CHD) and cancer (all-cause and site-specific))
- Variables required to undertake survival analysis (date of interview, date of death, length of time within study)

A re-survey of original Whitehall I participants was undertaken in 1997-1998; the sample size within the re-survey totalled 7,033 participants. Those involved completed a postal questionnaire and visited their general practitioner in order to have health-related measurements taken. Variables within the re-survey, related to this study, included:

- Age
- Height (self-reported)
- Weight (self-reported)
- Smoking (Current/Ex/Never)
- Alcohol
- Self-rated health
- Grouped medication
- Grouped longstanding illness
- Grouped cause of death
- Diabetes status
- BMI
- Variables related to survival analysis (date of original survey, date of resurvey, date of death and time within the survey)

3.6 Creation of variables within Whitehall I

The Whitehall I dataset required less manipulation, as the variables mentioned above were already available. In order to be able to compare results of the analyses of the HSE and SHeS with Whitehall I results, categorical variables were produced that matched those within the former dataset in relation to:

- BMI (<20/20-24.9, 25-29.9, ≥30 kg/m^2)
- Age (16-64/65-75/75+)
- The presence of comorbid CVD

3.7 Research ethics

Research ethics approval was gained for each year of the HSE and SHeS from relevant Research Ethics Committees prior to the undertaking of the each year's survey. Approval to link this data to health outcomes data (Cancer Registry and mortality data, via the National Health Service Central Register (NHSCR)) was gained from the NHS Information Centre. From 2003 onwards, each adult participant was asked for their consent to link their HSE data to health outcomes data (the consent form explicitly mentioned the Cancer Registry and mortality data). In the years 1994-2002, participants were asked for consent for data linkage to mortality records but were not asked about data linkage to the Cancer Registry so, for the purposes of the analyses required for this research, the issue arose as to whether it was ethically and legally appropriate to seek the linking of data for years when individuals did not give their consent. Within both time periods around 90% of participants agreed to their data being linked, suggesting that those who agreed to their data being linked to mortality data would also have agreed to their data being linked to the Cancer Registry (if they had been asked). On the 27th of October, 2010, ONS who at that time held both of the outcomes datasets agreed that consent for data linkage for mortality would also cover the Cancer Registry data.

ONS, and those linking the data at Natcen, agreed that the legal basis for the release of mortality data from ONS via MRIS was covered by S42(4) of the Statistics and Registration Service Act 2007, while cancer data was covered by S251 Class Action (pre 2003) and consent (post 2003). Therefore, even though participants had not explicitly given their consent for the linking of their data to the Cancer Registry - it was appropriate to analyse data linked to the Cancer Registry pre-2003.This information has been amended from a correspondence with ONS.

This meant that accessing the linked Cancer Registry data would require a data release request being made to NatCen Social Research in the same way as accessing the linked mortality dataset would.

For Whitehall I, ethical approval had been given for the linking of data with mortality records prior to this study, therefore after agreeing the remit of this study (with PhD supervisors and the Whitehall I data holders at UCL) it was decided that no further ethical approval was required.

3.8 Identifying the diabetic cohort within the data

The following section details the questions within the datasets which enabled the identification of the diabetic cohort.

3.8.1 HSE and SHeS

Within the HSE and SHeS surveys there are three different variables relating to diabetes. Two of them are asked within the initial interview.

Do you have any long-standing illness, disability or infirmity?

Among those who answer yes to this question, the interviewer then asks the participant which illness or illnesses they have. Unlike the diabetes specific question below, this question is open and requires the participant to volunteer the illnesses they have. All of the long-standing illnesses the individual has, up to a maximum of six (variable names illsm1-illsm6), are coded to a high level of disease or group of diseases. Within the longstanding illness code-frame, diabetes is represented by the number 2, cardiovascular disease by 15, 16, 17, 18 and cancer by the number 1. It may be that some cases of diabetes are missed due to six other conditions being volunteered before diabetes, although analysis suggests that a very small number of individuals volunteer six conditions.

Do you now have, or have you ever had diabetes (Variable name 'everdi')?

This closed question was asked in each year of the SHeS but only within the surveys years 1994, 1998, 2003 and 2006. Among those who answered yes to this question, further questions were asked relating to whether or not their diabetes had been diagnosed by a doctor, whether or not they injected insulin or took any other medications or treatments for the disease and whether their diabetes occurred only during pregnancy.(296) For the purposes of this research, the derived variable which includes only those who indicated doctor-diagnosed diabetes (and excludes those with only gestational diabetes) was used.

The third method of identifying those with diabetes occurs within the nurse visit and entails the question:

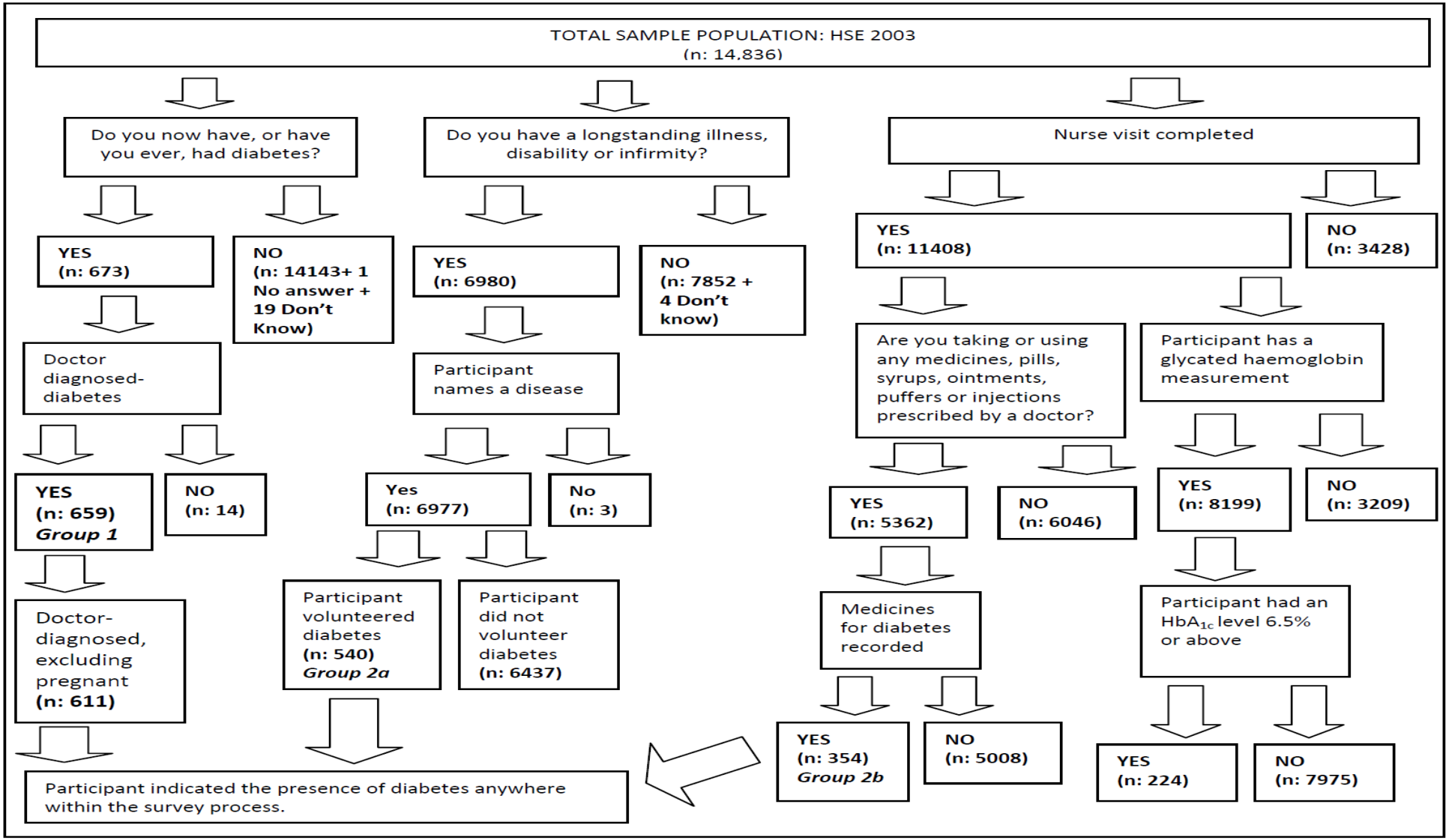
Are you taking or using any medicines, pills, syrups, ointments, puffers or injections prescribed by a doctor? Could I take down the names of the medicines, including pills, syrups, ointments, puffers or injections prescribed by a doctor? (Variable names medbi01-22)

The nurse records all the prescribed medications which the individual is taking. From 1995 onwards, the same six digit codes were used, based on the sub-sections of the British National Formulary (BNF), and for diabetes whether the medication was insulin or orally taken was recorded. For the HSE 1994, only a 2 digit BNF code was used and the survey did not differentiate between the type of diabetic drug being taken. The BNF codes used within the HSE and SHeS enabled the creation of derived variables in order to select individuals who were taking prescribed medication for diabetes. These new variables were:

- Meddiab1- This includes all individuals who were currently taking medications related to diabetes (insulin: BNF Code 060101, Anti-diabetic drugs: BNF Code 060102, Drugs for diabetic ketoacidosis: BNF Code 060103).
- Meddiab2- This includes all individuals who were currently taking insulin (060101).
- Meddiab3- This includes all individuals who were currently taking oral hypoglycaemic drugs (060102).

Figure 3-1 below details the three ways that an individual case could be identified for inclusion in the diabetic cohort within the HSE and SHeS data, as well as the question related to glycated haemoglobin. The numbers included within the figure relate to the 2003 HSE sample.

Figure 3-1: Pathways to identifying those with diabetes within the HSE and SHeS (illustrative example from HSE 2003)



3.8.2 Whitehall I

There were a number of questions related to diabetes within the original Whitehall I survey. The first of these was:

Are you or have you been diabetic? (Answer: Yes/No)

If the participant gave a positive response, they were then asked a series of follow-on questions related to the age at which they were diagnosed with the disease, what their symptoms were, whether they were injecting insulin and if any of their relatives had diabetes. The survey also asked participants:

Are you taking any medications, pills or on a diet? (Answer: Yes/No)

They were then asked to list the medications they were taking and what these medications were for.

A measurement of blood glucose was also taken, but the boundaries for this (in relation to what is considered a raised blood glucose threshold) are inconsistent with those used in more recent studies (this issue is discussed in more detail in Section 3.10).

Within the follow-up resurvey, participants were asked the following yes/no question:

Has a doctor ever told you that you had any of the following conditions?

A number of disease options were then listed, including diabetes and cancer, to which the respondent could answer yes or no. This was followed by:

Please list the names of all medications (tablets, capsules, liquids or injections etc), including over the counter preparations, (such as vitamins and aspirin) that you have taken during the last month?

The key difference between the HSE/SHeS and Whitehall I, related to this second question, was that for the former a nurse would request all the medications being taken and then record them, whereas for Whitehall I the respondent was responsible for documenting their own medication use.

3.9 The use of self-reported survey data

The majority of the information gathered within the HSE and SHeS is self-reported, exceptions to this include height and weight (measured within the interview) and information gathered during the

nurse visit, such as medication use and specific measurements. A study by Okura et al. sought to understand how the use of self-reported data would impact upon the recorded prevalence of a number of diseases, including diabetes, and how much agreement there was between questionnaire data and medical records.(297) The study found strong agreement between the two forms of data for diabetes, with a kappa coefficient of 0.71-0.80. The factors associated with this agreement were being in the younger age group; being female; and increased levels of education.

The study also found sensitivity of 66% for the self-reported questionnaire, which produced a lower prevalence of diabetes compared with medical records, prevalence of 5.2% and 7.4% respectively. Specificity was found to be 99.7% for the self-reported data. This issue will be explored further in the following sections of this thesis.

3.10 Blood glucose within Whitehall I

For glycated haemoglobin ($HbA1_C$) a cut-off point of 6.5% (48mmol/mol) is currently considered indicative of the presence of undiagnosed or uncontrolled diabetes; this was used within the analyses of the association between $HbA1_C$ described within this thesis.(298) Within Whitehall I data participants were recorded as diabetic if, two hours after having drunk a 50g anhydrous dextrose drink, their glucose load was ≥11.1 mmol/l (≥200 mg/100ml).(89) Those with a glucose load of between 5.4 and 11.0 mmol/l (96-199 mg/100ml) were considered to have impaired glucose tolerance. The normoglycaemic group consisted of all those with a measurement below 5.4 mmol/l. As a consequence of this although blood glucose could be adjusted for within the regression models, it would not be possible to directly compare the results of the analyses which explored the association of this variable with all-cause and cause-specific mortality within the Whitehall I data with the results of the HSE and SHeS dataset analyses.

3.11 Sensitivity and specificity analysis

In the first year of the study, and in order to undertake sensitivity analysis, new variables were created which:

- investigated the number of individuals who indicated diabetes in more than one variable (through the use of the logical ‘And’),
- investigated the total number of diabetics (through the use of logical ‘Or’).

The following section details these variables and the initial analyses that were undertaken in order to identify the diabetic cohort. The second of these variables was also required in order to undertake the power calculations detailed in Section 3.15.

The three different methods of identifying the diabetic sub-group within the HSE and SHeS required an investigation of sensitivity and specificity of each variable. Therefore, initial analysis focussed upon the years that included a question related to doctor-diagnosed diabetes, which was deemed to be the 'gold standard' for identifying people with diagnosed diabetes. The data produced was used to create the four sub-groups required for further analysis within this research. The sub-groups were:

- Individuals who could be considered part of the 'gold standard' in terms of identifying diagnosed diabetes (this group comprised those who indicated the presence of doctor-diagnosed diabetes in response to direct questioning).
- Those who only indicated diabetes elsewhere within the survey.
- Those who indicated that they had diabetes at any stage of the survey process (this would include those in group one and group two).
- Those who responded negatively to the diabetes-specific question, did not mention diabetes when asked about the presence of any longstanding illnesses and those who did not appear to be taking diabetes-related medication.

Analysis was undertaken to calculate the total number of people with diagnosed diabetes within the HSE and SHeS, via the different pathways, and the predictive value of each variable. As can be seen from Table 3-3, few participants indicated diabetes in either the longstanding illness or the prescribed medication variables but not within the doctor-diagnosed variable. In total (in the four HSE years), 97 cases were in this group (2.9% of the total number of people with diagnosed diabetes): 31 cases (0.9% of total diabetics) recorded prescribed medications, 43 (1.3%) volunteered diabetes and 23 (0.7%) indicated both. There are a number of factors which explain the occurrence of this group:

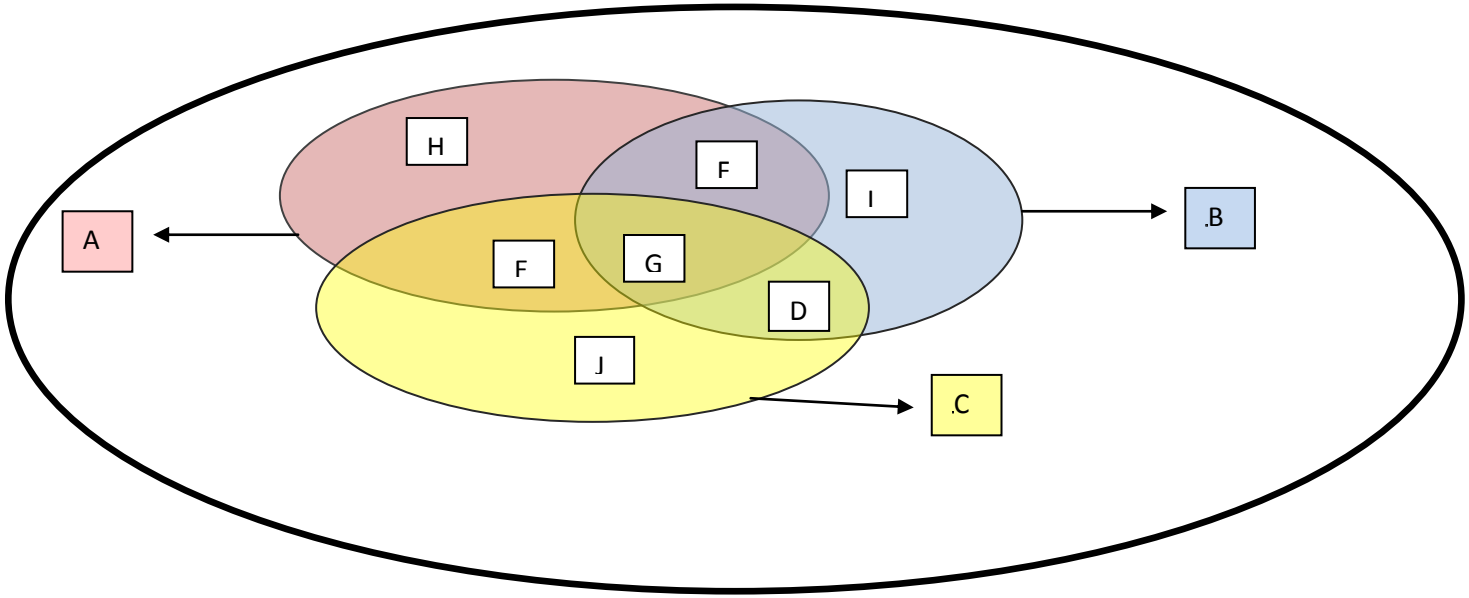
- Cases that had diabetes only during pregnancy and were taking diabetic medication or indicated that their diabetes was longstanding (three women were found within the former and five within the latter group). In total 196 women indicated that they had only gestational diabetes.

- Cases that indicated the presence of diabetes but had not had their disease diagnosed by a doctor (as can be seen from Table 3-3 a total of 95 cases indicated that they had, or previously had, diabetes but that it was not doctor-diagnosed).
- Individuals who were taking prescribed medication for diabetes, but were not aware that they had the disease.

Further to this there were a small number of cases that indicated:

- Diabetes within the longstanding illness variable and were taking prescribed diabetic medication but did not indicate diabetes within the doctor-diagnosed variable (Group D).
- Doctor-diagnosed diabetes and were taking diabetic medication but did not volunteer diabetes as a longstanding illness (Group E).
- Diabetes only within the longstanding illness question (Group I).
- Taking prescribed medication for diabetes only (Group J).

Figure 3-2: Diabetes within the HSE and SHeS



Key 1: The diabetic cohort identified within each area of the Venn diagram

A: Cases who indicated doctor-diagnosed diabetes (=E+F+G+H)
B: Cases who volunteered diabetes within the longstanding illness question (=D+F+G+I)
C: Cases who were recorded as taking diabetic medications (insulin, oral and drugs for diabetic ketoacidosis) (=D+E+G+J)
D: Cases who volunteered diabetes AND were taking diabetic medications but did not indicate doctor-diagnosed diabetes (=BnC not A: where n=intersect or 'AND')
E: Cases who indicated doctor-diagnosed diabetes, AND were taking diabetic medications but did not volunteer diabetes (=AnC not B)
F: Cases who indicated doctor-diagnosed diabetes AND volunteered diabetes but were not recorded as taking diabetic medications (=AnB not C)
G: Cases who indicated doctor-diagnosed diabetes AND volunteered diabetes AND were taking diabetic medications (=AnBnC).
H: Cases who only indicated doctor-diagnosed diabetes (=A-CuB: where u= union or 'AND/OR').
I: Cases who only volunteered diabetes (=B-AuC)
J: Cases who were only taking diabetic medication (=C-AuB)
A, E, F, G and H utilise the doctor-diagnosed (excluding pregnant) variable: diabete2.

Table 3-3: Number of participants within each area of the Venn diagram

YEAR	GROUP													
	A	%	B	%	C	%	D	E	F	G	(%)	H	I	J
HSE														
1994	377	2.4	308	1.9	227	1.4	6	27	103	189	1.2	58	10	5
1998	452	2.8	360	2.3	283	1.8	3	42	109	237	1.5	64	11	1
2003	611	4.1	540	3.6	354	2.4	4	23	206	323	2.2	59	7	4
2006	562	4.5	482	3.8	352	2.8	5	36	168	299	2.4	59	10	12
SHeS														
1995	140	1.8	116	1.5	87	1.1	1	6	36	79	1.0	19	0	1
1998	256	2.8	210	2.3	153	1.7	3	17	72	131	1.4	36	4	2
2003	344	4.2	267	3.3	181	2.2	1	23	114	151	1.9	56	1	6
TOTAL	2,742	N/A	2,283	N/A	1,637	N/A	23	174	808	1,409	N/A	351	43	31

A: Doctor-diagnosed diabetes; B: Diabetes as a longstanding illness; C: On diabetic medication; D: B or C, not A; E: A or C, not B; F: A or B, not C; G: Those reporting diabetes in all three ways; H: Doctor-diagnosed but neither B nor C; I: Diabetes as a longstanding illness but neither A nor C; J: Diabetic medication but neither A nor B.

Around half (46%) of those who indicated diabetes within the doctor-diagnosed variable also indicated diabetes within both of the two derived variables. New variables were created to investigate the number of individuals who indicated diabetes within more than one variable (Table 3-4). Numbers within groups that include the diabetic medication variable are likely to be smaller than groups that exclude it because only a proportion of the entire survey cohort participated in the nurse visit each year.

Table 3-4: Individuals who indicated diabetes within more than one variable

Year	VARIABLE							
	A and B	%	A and C	%	B and C	%	A and B and C	%
HSE								
1994	293	1.9	217	1.4	195	1.2	189	1.2
1998	347	2.2	280	1.8	240	1.5	237	1.5
2003	530	3.6	347	2.3	327	2.2	323	2.2
2006	468	3.7	336	2.7	304	2.4	299	2.4
SHeS								
1995	115	1.4	85	1.1	80	1.0	79	1.0
1998	205	2.3	150	1.7	134	1.5	131	1.4
2003	265	3.3	174	2.1	152	1.9	151	1.9
2008	N/A	N/A	64	1.0	N/A	N/A	N/A	N/A
TOTAL	2,223	2.6	1,653	1.8	1,432	1.7	1,409	1.7

Derived variables were used to investigate the total number of those with diabetes within each year of the survey. This further illustrated the strong sensitivity of the doctor-diagnosed variable for identifying the total number of diabetics within the sample. Using this information it was also possible to calculate the number of individuals who did not indicate the presence of diabetes at any stage of the survey process (see Table 3-5).

Table 3-5: Total number of cases who did/did not indicate diabetes

Year	VARIABLE								
	A or B	%	A or C	%	B or C	%	A or B or C	%	Did not indicate diabetes
HSE									
1994	419	2.7	414	2.6	340	2.2	424	2.7	15,381
1998	508	3.2	498	3.1	403	2.5	509	3.2	15,399
2003	669	4.5	666	4.5	567	3.8	673	4.5	14,163
2006	623	5.0	625	5.0	530	4.2	635	5.1	11,915
SHeS									
1995	150	1.9	151	1.9	123	1.6	151	1.9	7,781
1998	271	3.0	269	3.0	229	2.5	273	3.0	8,774
2003	358	4.4	363	4.5	296	3.6	364	4.5	7,784
2008	N/A	N/A	356	5.5	N/A	N/A	356[a]	N/A	6,109
Total	2,998	3.5	3,342	3.8	2,488	2.9	3,385	3.6	87,306

[a] This number only includes those who responded to the diabetes specific question or were taking prescribed medication for diabetes because at the time of writing the longstanding illness variable was unavailable for SHeS 2008.

Key 2: Total number with/without diagnosed diabetes

A or B: Cases who indicated doctor-diagnosed diabetes OR volunteered diabetes (= (AuB).
A or C: Cases who indicated doctor-diagnosed diabetes OR were taking diabetic medications (= (AuC).
B or C: Cases who volunteered diabetes OR were taking diabetic medications (= (BuC).
A or B or C: Cases who indicated doctor-diagnosed diabetes OR volunteered diabetes OR were taking diabetic medication (=AuBuC).
Did not indicate diabetes: Cases who did not state that they were diabetic when asked the diabetic specific question, did not give diabetes as a longstanding illness and were not recorded as taking any prescribed diabetes medication within the nurse visit.

3.12 Sensitivity of diabetes-related variables

Using this information it was then possible to calculate the sensitivity (what proportion of those with the disease were correctly identified) for each of the diabetes related variables. The total number of those with diabetes within each year was taken to be any case that gave a positive response to any of: the doctor-diagnosed diabetes variable; volunteered the disease within the longstanding illness

variable; or were taking any medication for diabetes, as recorded during the nurse visit. Analysis demonstrated that the doctor-diagnosed diabetes variable had good sensitivity (Table 3-6). Sensitivity for this variable ranged from 89% to 95%; mean sensitivity across all years was 90% (95% CI 89%-91%). Sensitivity for the longstanding illness variable ranged from 71% to 80%, with mean sensitivity across all years of 75% (95% CI 74%-76%). Sensitivity for the diabetic medication variable was lower, in part, because not every individual with diabetes participated in the nurse visit. Sensitivity ranged from 50%-58% (mean sensitivity=55%, 95 CI 52-56). Because of this, sensitivity was also calculated for the prescribed medication variable only among the sub-sample of cases that completed the nurse visit schedule. This increased the sensitivity of this variable to around 70%.

Because the diabetes-specific variable was available only in certain years, sensitivity analysis was undertaken within each year to identify the total number of cases identified as diabetic (either via the longstanding illness derived variable or the prescribed diabetic medication derived variable). This enabled a better understanding of how well these two variables captured the diabetic cohort who might also have positively responded to the doctor-diagnosed variable if they had been asked it. Using a combination of the two derived variables achieved a sensitivity of just over 94% (95% CI 93-94%). This suggested that, in years within which the diabetes-specific variable was not available, around 94% of those with diabetes would be positively identified using the two other variables in combination.

Table 3-6: Sensitivity (%) of diabetes variables

YEAR	Total no. DM[a]	Doc. diagnosed (excl. pregnant)	Sensitivity %	Longstanding illness: DM	Sensitivity %	Prescribed medication for DM	Sensitivity %
HSE							
1994	424	377	89	308	73	227	54
1998	509	452	89	360	71	283	56
2003	673	611	91	540	80	354	53
2006	635	562	89	482	76	352	55
SHeS							
1995	151	140	93	116	77	87	58
1998	273	256	94	210	77	153	56
2003	364	344	95	267	73	181	50
TOTAL	3,029	2,742	91	2,283	75	1,637	55

[a] DM – Diabetes mellitus

Table 3-7 indicates the number of cases with diabetes that were identified within each survey year using either the two variables (column: 'Variables: B or C') or the three diabetes variables, where available (column: 'Variables: A or B or C'). Further analysis of the sensitivity of the two individual variables found that the longstanding illness variable (B) achieved an overall sensitivity of 93% (95% CI 92.6-93.3%). For the prescribed medication variable (C), sensitivity was 63% (95% CI 62-64%).

Table 3-7: Utilising the three diabetes variables to identify those with and without diabetes

Year	Variables: B or C	Variables: A or B or C	Variables: B	Sensitivity: B (%)	Variables: C	Sensitivity: C (%)	Did not indicate DM (n)
HSE							
1994	340	424	308	91	277	81	14,661
1995	364	364	342	94	246	68	15,691
1996	383	383	361	94	265	69	16,060
1997	231	231	217	94	138	60	8,351
1998	403	509	360	89	283	70	15,399
1999	232	232	229	99	26*	11	7,566
2000	476	476	424	89	239	50	10,005
2001	531	531	506	95	322	61	15,116
2002	254	254	240	94	163	64	10,007
2003	567	673	540	95	354	62	14,163
2004	295	295	293	99	25*	8	6,409
2005	331	331	312	95	189	57	7,299
2006	530	635	482	91	461	66	13,507
2007	389	389	351	90	243	62	6,493
2008	786	786	728	93	454	58	14,316
SHeS							
1995	123	151	116	94	87	71	7,781
1998	229	273	210	92	153	67	8,774
2003	296	364	267	90	181	61	7,784
TOTAL	6,760	7,301	6,286	93	4,106	63	199,382

*The 1999 and 2004 HSEs were focussed upon the health of those from Black and Minority Ethnic communities. Within the overall sample from these years a substantially reduced percentage completed a nurse visit, with a corresponding reduction in the number indicating the use of diabetic medication compared with samples from other years.

3.13 Specificity of diabetes variables

Sensitivity analysis enabled a better understanding of how effective the three variables, both independently and combined, were at capturing all cases with diabetes. It was also important to understand how effectively those without the disease were identified, to ensure that the non-diabetic cohort included, as far as possible, only those who did not have diagnosed diabetes. Therefore the specificity of the diabetes variables was also analysed.

Specificity relates to the number of cases without the disease who are correctly identified as such. The diabetes-specific variable utilised within this research considered those who stated that they had diabetes, but that it was not doctor-diagnosed (n=95), as not having diabetes. This group may include those who have had their diabetes diagnosed but made a mistake in responding to the question, were incorrectly coded, or who correctly identified that they had diabetes without the involvement of a doctor. Using the above figure, relating to the total number of cases who did not indicate diabetes, it was possible to calculate a specificity >99.9% for the percentage of diagnosed diabetics included in the non-diabetic cohort. This suggests that the majority of those who indicated diabetes but, within this research, will be identified as non-diabetic are those who had not had their diabetes diagnosed by a doctor.

Within the analyses of Whitehall I, only the variable specifically related to the presence of diabetes was used to identify the diabetic cohort. One of the reasons for this is that it enabled results from the current study to be compared with those previously undertaken. Because of this, no sensitivity or specificity analyses were undertaken.

3.14 Exclusion criteria for cases

Because only those aged 16 and over were able to give consent for their data to be flagged within mortality and Cancer Registry data, children were excluded from the dataset used for this study. To address the issue of the temporality of an association between diabetes and cancer, those reporting cancer at baseline (identified using the longstanding illness questions, Section 3.8) were excluded from further analyses, leaving a sample size of 204,537, including 7,199 with diabetes.

Following advice from NatCen Social Research and discussing the process with members of the Health and Social Surveys Research Group (HSSRG) at UCL, it was decided that certain site-specific

cancer groups were inappropriate for inclusion within the analyses. Skin cancer was excluded as it was not possible with the grouped data provided for this study to distinguish between the different types of skin cancer, while benign tumours were excluded as they are not cancerous (the nature of these types of growth renders them unable to metastasise). Because the specifics of the cancers of uncertain or unknown behaviour could not be ascertained this group was also excluded from becoming a case within the mortality and Cancer Registry variables. Thus once the HSE and SHeS data were linked with mortality and Cancer Registry data, participants with any of the following registered diagnoses were excluded from the analyses:

- Benign growths,
- Cancers of uncertain or unknown behaviours,
- In situ neoplasms,
- Skin.

After cases that matched any of the above criteria had been excluded, the dataset included 204,533 participants. Table 3-8 details the sample and the number of those with diabetes from each survey year.

Table 3-8: Final study sample

Year	Total sample	Participants indicating diabetes (%)	Participants not indicating diabetes (%)
HSE			
1994	15,599	393 (2.5)	15,206 (97.5)
1995	15,807	351 (2.2)	15,456 (97.8)
1996	16,215	382 (2.4)	15,833 (97.6)
1997	8,432	223 (2.6)	8,209 (97.4)
1998	15,686	461 (2.9)	15,225 (97.1)
1999	7,666	223 (2.9)	7,443 (97.1)
2000	10,246	463 (4.5)	9,783 (95.5)
2001	15,359	507 (3.3)	14,852 (96.7)
2002	10,192	243 (2.4)	9,949 (97.6)
2003	14,545	575 (4.0)	13,970 (96)
2004	6,558	286 (4.4)	6,272 (95.6)
2005	10,023	586 (5.8)	9,437 (94.2)
2006	13,847	703 (5.1)	13,144 (94.9)
2007	6,752	373 (5.5)	6,379 (94.5)
2008	14,790	747 (5.1)	14,043 (94.9)
SHeS			
1995	7,300	122 (1.7)	7,178 (98.3)
1998	8,212	241 (2.9)	7,971 (97.1)
2003	7,304	320 (4.4)	6,984 (95.6)

TOTAL	204,533	7,199 (3.5)	197,334 (96.5)

3.15 Power calculations

The three factors of sample size, magnitude of the effect of interest and the statistical significance level used determine statistical power. Traditionally it has been considered unethical to undertake research either with a sample size too small to be able to produce clinically relevant results or so large that the study includes an unnecessary number of participants.(299) In order to decrease the chance of a type II error, that a null hypothesis is not rejected when it is actually false, and to understand the minimum effect size that could be detected within the analysis, a power calculation was undertaken. The power calculation utilised the total number of those with diabetes, found by combining the three diabetes-related variables discussed above. This sample size of 7,199 was inputted into the sample size estimation tool created by Wade and Koutoumanou.(300) The programme 'Sample Size Estimation' includes a '*Spreadsheet for calculation of sample size: Detecting a difference between two rates with specified power and significance*' and this was used to undertake the power calculations. At the significance level of 0.05, the effect size set at 0.2 and the prevalence of cancer within the general population of three percent the power of the study was found to be >95%. Cancer prevalence of three percent was based upon analyses by Maddams et al.(301)

For the analyses utilising measurements of glycated haemoglobin ($HbA1_C$), a sample size of 1,459 was inputted into the sample size estimation tool (this is the number of participants with an $HbA1_C$ measurement ≥6.5%), along with a significance level of 0.05 and the prevalence of cancer set at 3%. Following an assessment of the results of earlier studies which explored the associations between glycated haemoglobin and cancer incidence and mortality, the difference to be detected was set at 0.2. Using all of this information, the power for this particular element of the analyses was found to be >95%.

Cancer incidence was set at 0.5% of the total population based upon the latest figures from the Office for National Statistics (ONS).(61) The diabetic sample of 7,199 was inputted, with a significance level of 0.05, difference to be detected of 0.2. This gave power of > 95% within the analyses of the associations between diabetes and overall cancer incidence. For the analyses of glycated haemoglobin and overall cancer incidence, the power of the study was >90%.

3.16 Identifying longstanding illnesses at baseline (HSE and SHeS)

In order to be able to exclude those with cancer at baseline from the study, the variable 'longcancer' was derived, using data from the variables 'illsm1-6' (codeframe number: 1). Table 3-9 below indicates the number (and percentage) of individuals who indicated that they had the disease.

Similarly to the variable related to cancer at baseline, 'cvdall' was created using data from the longstanding illness variables (illsm 1-6). Any case that mentioned cardiovascular disease (CVD) within these variables (codeframe: 15, 16, 17, 18) was identified as having CVD at baseline. Table 3-9 also details the number within this variable from each year of the HSE and SHeS.

Table 3-9: Cases with cancer and CVD at baseline

Year	Total Sample	Cancer (%)	CVD (%)
HSE			
1994	15,599	206 (1.3)	1,179 (7.6)
1995	15,807	248 (1.5)	1,352 (8.6)
1996	16,215	228 (1.4)	1,484 (9.2)
1997	8,432	150 (1.7)	833 (9.9)
1998	15,686	222 (1.4)	1,450 (9.2)
1999	7,666	132 (1.7)	773 (10.1)
2000	10,246	235 (2.2)	1,454 (14.2)
2001	15,359	288 (1.8)	1,736 (11.3)
2002	10,192	139 (1.3)	790 (7.8)
2003	14,545	291 (2.0)	1,724 (12.5)
2004	6,558	146 (2.2)	822 (12.5)
2005	10,023	280 (2.7)	1,708 (17)
2006	13,847	295 (2.1)	1,727 (12.5)
2007	6,752	130 (1.9)	856 (12.7)
2008	14,790	312 (2.1)	1,940 (13.1)
SHeS			
1995	7,300	63 (0.9)	445 (6.1)
1998	8,212	93 (1.1)	777 (9.5)
2003	7,304	126 (1.2)	842 (11.5)
TOTAL	204,533	3,584 (1.7)	21,892 (10.7)

This CVD at baseline variable was then used to analyse the impact that the presence of the disease, as a comorbidity, had upon the associations between diabetes and cancer mortality and incidence. The results of these analyses are explored in later chapters of this thesis.

3.17 Analysing the impact of diabetes medications upon cancer incidence and mortality

The use of diabetes-related medications was used to identify the diabetic cohort within the HSE and SHeS combined dataset. Within the majority of years within the HSE and SHeS it was not possible to differentiate between those taking insulin and those taking oral medications. At the same time, the often changing treatment regimens of those with diabetes (in terms of the different oral medications available and the introduction of exogeneous insulin as diabetes progresses) makes it difficult for any analyses to unravel the influence of one treatment over another in relation to cancer outcomes. Because of this the decision was made to not include the use of treatments for diabetes within any of the regression models utilised within these analyses. This issue will be addressed within the discussion section.

3.18 Linking the survey datasets with mortality and cancer registry data

In the first instance, the linking of the HSE to mortality data occurred in the secure data enclave at NatCen (see Chapter 4 for further information about the process of accessing the mortality and Cancer Registry data). The following variables were available within the mortality data:

- An anonymised ID for matching with HSE data,
- Consflag (Participant gave consent for mortality data linkage),
- Agedied (Age respondent died),
- doDyr (Year of death),
- QRTdeath (Quarter of year died),
- CauseDeath (Cause of death of interest, in broad categories).

The last of these variables was a broad cause of death variable. Table 3-10 below details the numbers of cases that died of each cause.

Table 3-10: Total number of deaths within the HSE (1994-2008) linked to mortality data

Cause of Death	Number
Ischaemic heart disease	3,032
Stroke	1,468
Other cardiovascular disease	2,433
All cardiovascular disease	6,933
Lung cancer	1,117
Colon cancer	490
Breast cancer	327
Prostate cancer	282
Other cancer	2,781
All cancer	4,997
Respiratory	2,650
Other non-traumatic	3,227
External causes	503
TOTAL	18,310

Once a minimum dataset was created, which included all the required HSE variables but no other variables, both this and the mortality datasets were ordered by the matched ID. The variables from the mortality dataset were then merged with the HSE data. In 2013, access to the site-specific cancer mortality data was granted: this meant that it was also possible to create a more detailed variable based upon deaths from the site-specific cancers shown in Table 3-11 (ordered by descending frequency).

Table 3-11: Site-specific cancer mortality within the HSE (1994-2008)

Site-specific cancer	Number
Trachea, bronchus and lung	1,111
Colorectal	493
Lymphoid, haematopoietic and related tissue	343
Prostate	334
Breast	324
Pancreatic	297
Oesophagus	221
Stomach	188
Bladder	152
Ovarian	149
Kidney	129
Liver	73
Cervix, uterus and endometrium	70
Lip, oral cavity and pharynx	61
Other cancer not specified	936
All cancers	4,881

Because the original site-specific mortality variable was string in nature, the production of the syntax to create this grouped variable was very time-consuming. An example of this syntax is given in Appendix One: Syntax for the creation of the site-specific cancer variables. An advantage of this syntax was that, once it had been written, it (and its corresponding coding framework) could be used to produce variables related to the Cancer Registry, and mortality and incidence variables within the SHeS. This ensured uniformity across the HSE and SHeS and expediency within analyses.

As can be seen from comparing the information in Table 3-11 with that in Table 3-10, there are small differences in the number of deaths from the site-specific cancers; these differences are probably caused by slight differences in the syntax used by NatCen Social Research to produce the original variable compared with the syntax used within this study. The syntax produced for this study was checked by a number of members of the HSSRG at UCL, so it was decided that all site-specific cancer mortality and Cancer Registry variables used within future analyses would be based upon it; while the original variable produced by NatCen Social Research would be used within the all-cause and cause-specific analyses. Table 3-12 details the final number of cause-specific deaths in the HSE data (ordered by number of deaths) within the variable derived by NatCen Social Research. At the time that this data became available it was not possible to check the syntax used to produce this variable.

Table 3-12: Cause-specific mortality in the HSE (1994-2008)

Cause of death	Number
CVD	6,933
Cancer	4,997
Respiratory	2,650
Other	3,730
TOTAL	18,310

The information included in this variable was then used to create a binary variable which indicated whether or not an individual had died (0=Alive, 1=Died) following participation in the HSE. The same variable was created within the SHeS and Whitehall I datasets.

The merging of the HSE Cancer Registry data was a more complex process. As a number of participants had more than one cancer registration, a variable was created that included only a first registration of a cancer of interest (in total there were 10,721 participants in this group). Earlier

studies investigating the associations between diabetes and cancer had considered only the first incidence of cancer and the decision was taken to do the same within this study. This issue will be addressed in more detail in the discussion chapter. Table 3-13 below indicates those cancers included and excluded from this variable (ordered by descending frequency).

Table 3-13: Registrations for cancer included/excluded in the HSE

Included[a]	Number	Excluded	Number
Breast	2,053	Skin	4,112
Prostate	1,299	In situ neoplasms	2,908
Trachea, bronchus and lung	1,203		
Colon	926	Uncertain/unknown behaviour	648
Lymphatic and hematopoietic	822		
Uterus and cervix	553	Benign	170
Bladder	492		
Pancreas	271	Missing	39
Stomach	264		
Kidney	241	Incorrectly coded	34
Oesophagus	235		
Lip	205		
Liver	74		
Other cancers	2,083		
TOTAL	10,721	TOTAL	7,911

[a] After concerns were raised that the small number of cases of incident ovarian cancer might be disclosive, registrations for this cancer were merged into the 'other cancers' group.

Once the linking of the HSE and Cancer Registry data had been completed, it became apparent that either all or some of the Cancer Registry data from HSE 2008 had been incorrectly linked at NatCen Social Research (sex-specific cancers were appearing in the incorrect sex – for example 8 men were found to have cervical cancer and 8 women were found to have prostate cancer). Following discussions with colleagues at UCL and NatCen Social Research, and the time constraints of the study (given the delays in receiving the site-specific Cancer Registry data), it was decided that the most appropriate action would be to exclude cancer registrations from HSE 2008 in the analyses. Therefore the table above excludes those registrations. This issue will be addressed in greater detail in the discussion chapter.

3.19 Identifying cancer within linked SHeS data

The SHeS datasets included the variable 'cause' which detailed cause of death by International Classification of Disease (ICD) 10 code. Using this variable two mortality variables were derived which detailed:

- Cause-specific mortality (cancer, respiratory disease, cardiovascular disease and other causes)
- Site-specific cancer mortality (this variable matched the one produced within the HSE data).

Table 3-14 details the number of cause-specific deaths within the Scottish Health Surveys (survey years: 1993, 1998 and 2003) while Table 3-15 gives the number of site-specific cancer deaths within the dataset (ordered by descending number of deaths by cause).

Table 3-14: Cause-specific mortality in the SHeS

Cause	**Number**
Cancer	574
CVD	556
Other	423
Respiratory	188
TOTAL	1,741

Table 3-15: Site-specific cancer mortality within the SHeS

Site-specific cancer	Number
Trachea, bronchus and lung	186
Colorectal	59
Oesophagus	40
Breast	30
Lymphoid, haematopoetic and related tissue	30
Pancreatic	24
Stomach	23
Bladder	16
Ovarian*	16
Prostate	13
Cervix, uterus and endometrium	11
Kidney	11
Liver and hepatocellular	<10
Lip, oral cavity and pharynx	<10
Other cancer not specified	102
TOTAL	574

*****In order to match the site-specific cancer variable derived within the HSE data, deaths from ovarian cancer were included in the 'other' cancer category in the variable used within the analyses.

Within the linked SHeS datasets, there were a number of variables which garnered information about cancer registration. In order to undertake initial exploratory analysis of this data the variable 'ICD10crshe' was created that matched that produced for the HSE dataset. SHeS participants could be identified as having a registration within Cancer Registry data up to 2008.

Table **3-16** details the incidence of the site-specific cancers of interest within the SHeS cohort.

Table 3-16: Site-Specific cancer incidence in the SHeS

Site-specific cancer	Number
Trachea, bronchus and lung	170
Breast	156
Prostate	63
Colon	63
Lymphatic and hematopoietic	53
Uterus and cervix	32
Stomach	28
Oesophagus	27
Bladder	24
Pancreas	21
Lip, oral cavity and pharynx	20
Kidney	20
Liver	<10
Other cancers	173
TOTAL	857
Excluded	
Skin	268

The cancer incidence variable within the linked SHeS data did not include information about cancers of uncertain or unknown behaviours, in situ or benign neoplasm or those that were incorrectly coded as these were not required for the analyses.

3.20 Cancer variables within Whitehall I

Within the Whitehall I dataset made available for this project, variables related to all-cause, cause-specific and site-specific mortality had already been derived. In order to enable a comparison of the results of this analysis with those of earlier studies, that had utilised shorter follow-up periods, these

variables were used in each of the Whitehall I analyses detailed within this thesis. Information is given in relation to the descriptive analysis of this dataset in the results sections.
As can be seen from the sections above, a considerable amount of time was spent:

- ensuring that sub-groups within the dataset were identified as accurately as possible,
- producing correctly derived variables to enable the analyses required for this study,
- ensuring uniformity across the survey years.

The following chapter details the methods that were used to analyse the associations between diabetes, glycated haemoglobin and all-cause, cause-specific and site-specific (cancer) mortality and incidence of cancer using data from the HSE and SHeS (combined) and Whitehall I datasets.

4. Chapter 4: Methods

4.1 Data issues

A number of factors impacted upon the availability of the linked HSE and mortality/Cancer Registry data and these are described in the following sections.

4.1.1 NatCen Social Research data release requests

In order to access the mortality and Cancer Registry data it was necessary to submit a Data Release Request to NatCen. This request was then discussed by a panel and a decision made as to whether or not data would be made available for the purposes of this research, and whether or not access would be granted outside the NatCen offices. NatCen makes data available to researchers within the data enclave (a computer not connected to a network). Any output from the analyses is then sent to the researcher, reducing the potential for data leaving NatCen that is disclosive. An initial Data Release Request, for linked HSE and cancer mortality and registry data was submitted on the 23rd of September 2010, with the Data Release Panel (DRP) meeting on the 10th of October 2010. Following this, access was granted to data already held by UCL, which included a broad perspective mortality variable (mortality data for HSE participants were updated to the first quarter of 2011) which included information related to the following causes of death:

- Non-traumatic, not including other sub-groups of interest
- Cardiovascular
- Stroke
- Ischaemic heart disease
- Respiratory
- Cancer, not including other sub-groups of interest
- Lung cancer
- Colon cancer
- Breast cancer
- Prostate cancer
- Other cause of death.

Concurrently the panel concluded that allowing access to more detailed data (in relation to site-specific cancer mortality and cancer registrations) would be inappropriate without an initial descriptive exploration of the data, in order to assess whether or not the small number of deaths (or incidents of cancer) from these detailed causes would make the data disclosive. As the data became

available a number of Data Release Requests (related to cancer incidence and mortality) were submitted that related to the following site-specific cancers (ICD 9 and 10 Codes):

- oral cavity and pharynx (ICD-9 140-149 ICD-10C00-C149)
- Oesophagus (ICD-9 150, ICD-10 C15)
- Stomach (ICD-9 151, ICD-10 C16)
- Colorectal (ICD-9 153-154, ICD-10 C18-C21)
- Bladder (ICD-9 188, ICD-10 C67)
- Breast (ICD-9 174, ICD-10 C50)
- Cervix/Uterus/Endometrium (ICD-9 179, 180, 182, ICD-10 C53 C54-C55)
- Liver (ICD-9 155, ICD-10 C22)
- Trachea, bronchus and lung (ICD-9 162, ICD-10 C33-C34)
- Kidney/Renal (ICD-9 189, ICD-10 C64-C66)
- Lymphoid, haematopoietic and related tissue: includes non-Hodgkins Lymphoma, Leukaemia and Hematopoietic (ICD-9 200-208, ICD-10 C81-C96)
- Prostate (ICD-9 185, ICD-10 C61)
- Other cancers (this group is made up of all those cancers not included in the above).

It was decided that these cancers should be focussed upon because previous research suggested an association with diabetes (based upon results from the literature review) and they occurred at high enough rates that including them in a linked dataset would not negatively impact upon the disclosivity of the study dataset.

4.1.2 Delays in data acquisition

There were significant delays in accessing the mortality (detailed site-specific cancer mortality variables) and Cancer Registry data linked to the HSE. The key cause of the delay related to concerns NatCen had in relation to the disclosive nature of the linked data; it was felt that linking detailed mortality data to the variables within the HSE would enable the identification of individual participants. In relation to the mortality data there were also considerable delays in the provision of the data to NatCen initially from the ONS and subsequently from the Health and Social Care Information Centre. This was followed by further delays caused by a lack of staff available to undertake the data linkage. Following the submission of a Data Release Request, the panel meeting at NatCen decided that the most appropriate course of action was for the data to be made available, for linking and analyses, only within the NatCen enclave. Availability of the enclave was restricted

both by renovations to the building and its use by NatCen staff. Because of these delays, initial linking and analyses of the detailed mortality data took place in December 2012, with a minimum dataset being made available outside of the enclave on the 18th of December 2012.

There were longer delays in gaining access to the Cancer Registry data, caused by delays in NatCen receiving the data and the availability of staff to link the data. A dichotomous Cancer Registry variable (cancer registration: yes or no) was made available at the start of 2013. Following this an initial exploration of the site-specific Cancer Registry data was possible, within the enclave, at the start of 2013; this data was then made available outside of the enclave on the 17th of April 2013.

In order to reduce the disclosive nature of the HSE linked data (mortality and cancer incidence) it was agreed that two of the continuous variables would be replaced with categorical grouped variables. These were:

- Age (replaced with grouped: 16-64, 65-75, 75+)
- BMI (grouped: <20, 20-24.99, 25-<30, ≥30kg/m^2).

4.2 SHeS

Accessing the linked SHeS data was unproblematic; the data was already available to members of the HSSRG team at UCL and informing the Health Information Group within the NHS National Services Scotland of the nature of the research and any publications that would result from it enabled access to the data for the purposes of this research. Access to the linked SHeS data (for SHeS years 1995, 1998 and 2003) was granted on the 21st of April 2011.

4.3 Whitehall I

Held within the Department of Epidemiology and Public Health at UCL, the data became available (in September 2012) following a discussion of the aims and potential outcomes of the current study with Dr David Batty and Dr Martin Shipley. Through the analyses of Whitehall I data, it was possible to further test the hypotheses of this current study using a dataset with exceptionally long follow-up and within which around 80% of the study population had died within the 40 year follow-up period.

4.4 Analyses

To assess the associations between diabetes and cancer incidence and mortality a range of statistical methods were utilised; the following sections details the analyses that were undertaken.

4.5 HSE and SHeS

4.5.1 All-cause mortality: logistic regression

Using the binary variables related to the presence of diabetes and all-cause mortality, a logistic regression was undertaken in order to explore the risk of an individual with diabetes dying of any cause compared with those without the disease and produce Odds Ratios (ORs)and 95% Confidence Intervals (CI) for the association. Within all of the analyses undertaken the reference group consisted of those who had not indicated the presence of diabetes or who had a glycated haemoglobin measurement of <6.5% (48mmol/mol). In order to assess the impact of confounding factors upon the associations between diabetes and all-cause mortality a number of variables were entered into the regression model. Age and sex were included in every regression model, with the following variables added at consecutive steps of the regression model:

- Basic model: age and sex plus Smoking status (Current, Ex-regular, Never-regular)
- Advanced model: Basic model plus BMI (<20, 20-24.9, 25-29.9, 30+)
- CVD model: Advanced model plus CVD status (CVD at baseline: Yes/No).

To explore the impact of socio-economic/demographic factors upon the association between diabetes and all-cause mortality further adjustment included the advanced model plus:

- Education: degree/other/none (educend)
- Social class: I-VII (sclass)
- Region: south/midlands/north/Scotland (region)
- $HbA1_C$: Normal/Raised (≥6.5%) and continuous (glyhbval2 and glyhbval respectively)

To establish how measurements of overweight and obesity impact upon the association between diabetes and all-cause mortality, the following variables were also added to the basic model:

- Waist-hip ratio (Normal/raised)
  + CVD status
- Waist circumference (Normal/raised)
  + CVD status
- Education
- Social Class
- Region

- $HbA1_C$

Progressive adjustment then took into account a number of these variables:

- Advanced model + Social class, region and CVD
  + $HbA1_C$
- Advanced model + Education, region and CVD
  + $HbA1_C$
- Basic model + Waist-hip ratio, social class, region and CVD
  +$HbA1_C$
- Basic model + Waist-hip ratio, education, region and CVD
  + $HbA1_C$
- Basic model + Waist circumference, social class, region and CVD
  + $HbA1_C$
- Basic model + Waist circumference, education, region and CVD
  + $HbA1_C$

CVD status was then removed from the above models and the syntax re-run. Initially analyses utilised the whole sample. Following this, the above analyses were re-run with the data stratified by CVD status and then by sex; sensitivity analysis, among those who indicated that they had never been a regular smoker, was then undertaken using the models above.

The analyses described below follows the schedule detailed within this section, unless otherwise stated.

4.5.2 Cause-specific and site-specific cancer mortality: multinomial logistic regression

Both the cause-specific and site-specific cancer mortality variables were categorical; because of this, initial analyses of these variables utilised multinomial logistic regression to produce ORs and CIs. Within the analyses the reference category was 'alive' and the association of diabetes with the specific causes of death was estimated. The regression model framework followed the same pathway as that undertaken for the all-cause mortality analyses mentioned above.

In order to perform the multinomial logistic regression within SPSS, dummy variables were produced for the following variables:

- Smoking status (current smoker/everyone else, ex-smoker/everyone else)
- Grouped BMI (<20kg/m^2/everyone else, 25-29.9 kg/m^2/everyone else, 30+ kg/m^2/everyone else)
- Region (midlands/everyone else, north/everyone else, Scotland/everyone else)
- Education (other qualification/everyone else, no qualifications/everyone else)
- Social class (II/everyone else, NMIII/everyone else, MIII/everyone else, IV/everyone else, V/everyone else, other/everyone else).

The syntax required to undertake the multinomial logistic regression was then written, for both the cause-specific and site-specific cancer mortality variables, this followed the analyses schedule detailed within the all-cause mortality methods section above.

Survival analysis and Cox regression were undertaken to further explore the associations between diabetes and cancer mortality by adding a time to event element to the analyses. It was necessary to create a number of variables in order to undertake this method of analysis. This included:

- A binary 'cancer/everyone else' variable.

All cases who were alive at the end of the follow-up period and those who died of a cause, other than cancer, were included in the latter group.

- An interview date and censor date variable.

The interview date variable was computed within SPSS by combining the three date variables within the HSE and SHeS datasets (dintb = day of interview, mintb = month of interview, yintb = year of interview). The censor date refers either to the date that the event of interest (in this instance mortality from cancer) or when an observation is right censored (the follow-up period ended and the observation had not experienced the event). This variable was produced using either death date variables (doDyr = year of death, QRTdeath = Quarter of year of death) for cases who were flagged within the mortality data or a censor date (this was set as the end of the first quarter of 2011 – the last available date a case could be flagged within mortality data) for those who had not died within the study time-period. These variables enabled the computation of a variable that included information about the duration of time cases had spent in the study, this variable was then used within the survival analysis and Cox regression. Because of the issue of disclosivity a day of death

variable was unavailable within the HSE and SHES data. The day of death was therefore set to 16 for all cases that died of cancer (the middle of the month).

Following survival analysis and a Cox regression which analysed all-cause cancer mortality, variables were then computed for each site-specific cancer mortality category. For example a binary variable (cases who died of pancreatic cancer/died of another cause or were alive). The syntax utilised within the initial survival analysis and Cox regression was then adapted to assess the associations between diabetes and these site-specific cancers.

4.5.3 Cancer incidence

A binary variable (participant experienced an incident cancer: yes/no) was created within the dataset. This enabled a logistic regression to be undertaken which would detailed whether or not those with diabetes had an increased risk of incident cancer compared with those without diabetes (through the generation of ORs and CIs).

The primary approach to assessing the associations between diabetes and site-specific cancer incidence utilised multinomial logistic regression. The estimates, within these analyses, were ORs and 95% CI. The dummy variables required to perform these analyses had already been computed for the cause-specific mortality analyses. The syntax produced for the latter were therefore adapted to undertake the site-specific incidence analyses. Further to this, survival analyses and Cox regression were undertaken, to explore whether or not those with diabetes had differing risks of developing incident cancer. The date variables computed for the all-cause mortality survival analyses were also utilised in this section. The analyses described above were then re-run utilising three diabetes-related variables:

- Glycated haemoglobin (normal/raised ≥ 6.5%)
- Glycated haemoglobin (continuous)

The analyses of HSE and SHeS were performed using SPSS version 20.

4.6 Whitehall I: logistic regression and survival analysis

4.6.1 All-cause mortality

Initial analyses of Whitehall I data utilised logistic regression to estimate the increased risk of all-cause mortality among those with diabetes compared with the general population. The analyses

schedule matched the one developed for analysing the HSE and SHeS datasets, where corresponding variables were available. The Whitehall I data included only men who worked in London, so sex and region were not adjusted for.

Whitehall I data were analysed using STATA 11. Within STATA dummy variables are produced by the programme as part of the analyses, therefore it was not necessary to produce them for the categorical independent variables.

The following logistic regression models were developed:

- Age
- Basic model: Age and smoking status (current, ex-regular, never-regular)
- Advanced model: Age, smoking status and BMI (grouped the same as the HSE and SHeS variable or continuous)

Cardiovascular disease status was only available within the resurvey dataset as a question related to the presence of the disease was not asked within the original dataset. Therefore it was only possible to produce a model which included this variable within the analyses of the resurvey data.

The 'basic model' within these analyses referred to adjustment for age and smoking status, while the 'advanced model' included BMI (grouped). Additional adjustment was made for variables related to:

- Position within the civil service (social class)
- Blood glucose measurement

All cause-specific, survival analysis and Cox regression follows this schedule.

4.6.2 Cause-specific mortality

Within the Whitehall I data, binary variables had been computed for cause-specific mortality prior to the current study. In order to compare the results of the current analyses, which included 40 years of follow-up, with those of an earlier study with 27 years of follow-up logistic, rather than multinomial, regression for the following causes of death was performed:

- Cancer
- CVD

- CHD
- Stroke
- Other causes

Survival analysis and Cox regression were performed to explore the association between diabetes and mortality from all-causes and cancer overall. This utilised a 'time in study' variable that was already available in the dataset. Analyses of the associations between diabetes and the following site-specific cancers were also undertaken:

- Pancreas
- Liver
- Colon
- Lung
- Melanoma
- Skin
- Oesophagus
- Bladder
- Brain
- Leukaemia
- Myeloid leukaemia
- Prostate
- Stomach

Although analyses of some of the site-specific cancers above were not undertaken using the HSE and SHeS datasets, it was agreed that analysing them within Whitehall I data would enable comparison with earlier results which utilised a shorter follow-up time. Regression analysis was not performed for the following site-specific cancers because descriptive analysis indicated that there were no cases among those who reported diabetes.

- Rectum
- Lymphoma
- Lymphoid leukaemia
- Kidney
- Other skin

The following chapters detail the results of the above analyses.

5. Chapter 5: Results – diabetes and cancer incidence

Chapter five begins with an exploration of the study sample by detailing the descriptive analysis undertaken using data from the whole sample as well as the diabetic and non-diabetic cohorts. The following section then details the results related to the association between diabetes and cancer incidence.

All of the results chapters are focused upon assessing the associations between diabetes and/or glycated haemoglobin and cancer incidence and mortality; as well as all-cause and mortality from respiratory and cardiovascular disease and 'other' causes. In instances where a statistically significant association was found these will be discussed. Further to this, and to enable a better understanding of results that may be indicative of an association, when point estimates are consistently raised or reduced (but the results are not statistically significant) these will also be discussed.

Each chapter includes tables of results and within these the Odds Ratios and Hazard Ratios given refer to the risk or excess among those with either diabetes or raised glycated haemoglobin compared to those who did not indicate the presence of either.

5.1 Models used within the analyses

As discussed in the previous chapter, a number of models were consistently used within the study analyses. Each of these included the following covariates:

- Basic model: Age, sex and smoking
- Advanced model: Age, sex, smoking and BMI (categorical)
- CVD model: Age, sex, smoking, BMI and Cardiovascular disease at baseline.

When analyses were stratified by either sex or CVD status these variables were removed from the regression model.

Further analyses included variables related to educational attainment; the region the participant lived in; socioeconomic status; and whether the participant had a raised glycated haemoglobin ($HbA1_C$) measurement (≥6.5%). These models were used within the analyses related to the combined Health Survey for England and Scottish Health Survey dataset.

The following models were used within the analyses of Whitehall I data:

- Basic model: Age and smoking (all the participants of Whitehall I were male so the sex variable was redundant).
- Advanced model: Age, smoking and BMI (categorical).

Further models were developed which adjusted for grade of employment (used as a proxy for socioeconomic status) and blood glucose measurement (used as a proxy for glycated haemoglobin) but no variable related to CVD at baseline was available.

5.2 Descriptive analysis

Table 5-1 gives an overview of the HSE/SHeS study sample. Within the dataset there were 7,199 cases with diabetes (3.5% of the total) and 197,334 controls without known diabetes. Those with diabetes were considerably older (mean age 63 years old (SD±15.1) p-value <0.01) than those without the disease (mean 47 years old (SD±19.1)) and within the former group a larger percentage were aged ≥75 years old (23% vs 9%). In relation to lifestyle factors, a smaller percentage of those with diabetes indicated that they were current smokers compared with those without diabetes (p-value <0.01). Measurements related to overweight and obesity were raised among those with diabetes compared with those who did not have the disease. The p-values for the differences in BMI, waist circumference and waist-to-hip ratio means between the two groups were <0.01 (independent two-sample T-tests were performed).

There were no significant statistical differences in the region in which they lived between the diabetic and non-diabetic groups (south (England), midlands (England), north (England), and Scotland). Social class was separated into seven groups based upon the Registrar-General's Social Class Occupation bandings (I: Professional occupations, II: Managerial and technical, IIINM: Skilled non-manual, IIIM: Skilled manual, IV: Partly-skilled, V: Unskilled and other); there were no differences between those with and without diabetes in terms of the distribution between the classes. A higher percentage of those without diabetes had a degree or other qualification, while 50% of those with diabetes were found to have no qualifications (compared with 28% of those who did not indicate the presence of the disease). 38% of those with diabetes indicated that they had comorbid cardiovascular disease, compared with 10% of those without diabetes.

Table 5-1: Characteristics of HSE/SHeS study cohort (by diabetes status)

Characteristics	Diabetes	Did not indicate diabetes	Total
Demographic factors			
Total sample (%)	7,199 (3.5)	197,334 (96.5)	204,533
Age-groups no. (%)			
16-64	3,448 (48)	156,816 (80)	160,264 (78)
65-74	2,127 (30)	22,376 (11)	24,503 (12)
75+	1,624 (23)	18,142 (9)	19,766 (10)
Sex - no. (%)			
Male	3,762 (52)	87,648 (45)	91,410 (45)
Female	3,437 (48)	109,511 (55)	112,948 (55)
Missing	36	139	175 (1)
Lifestyle factors			
Smoking status-no. (%)			
Never	3,023 (43)	95,084 (48)	98,827 (48)
Ex-regular smoker	2,828 (39)	47,515 (24)	50,343 (25)
Current smoker	1,226 (17)	52,719 (27)	53,945 (26)
Missing	122 (2)	2016 (1)	2,138 (1)
Anthropometric measures			
BMI			
No. with data (%)	5,986 (84)	176,670 (90)	182,656 (89)
Mean – kg/m^2 (SD)	29.79 (5.5)	26.47 (4.8)	28.13 (5.4)
BMI: <20 kg/m^2	83 (1)	9,836 (6)	9,919 (5)
BMI: 20-<25 kg/m^2	1,019 (17)	64,310 (36)	65,329 (32)
BMI: 25-<30 kg/m^2	2,287 (38)	66,888 (38)	69,175 (34)
BMI: ≥30 kg/m^2	2,597 (43)	35,607 (20)	38,204 (19)
BMI: Missing	1,213 (16)	20,693 (10)	21,906 (11)
Waist circumference			
No. With data (%)	4,302 (59)	111,935 (57)	116,237 (57)
Above threshold (Men: 102cm, Women: 88cm)	2,877 (67)	42,716 (38)	45,593 (39)
Mean-cm (SD)	101.85 (14.4)	89.45 (13.7)	95.65 (14.1)

Waist-to-hip ratio			
No. with data (%)	4,291 (59)	111,785 (57)	116,076 (57)
Above threshold (Men: 0.949, Women: 0.849) (%)	2,804 (65)	31,503 (28)	34,307 (30)
Mean (SD)	0.93 (0.09)	0.86 (0.09)	0.90 (0.09)
Socio-demographic			
Region (%)			
South	3,067 (43)	86,611 (44)	89,678 (44)
Midlands	1,341 (19)	35,389 (18)	36,730 (18)
North	1,889 (26)	50,910(26)	52,799 (26)
Scotland	683 (10)	22,133 (11)	22,816 (11)
Education (%)			
Degree	595 (8)	28,361 (14)	28,956 (14)
Other	2,886 (40)	111,443 (57)	114,329 (56)
No qualifications	3,587 (50)	55,829 (28)	59,416 (29)
Missing	131 (2)	1,701 (1)	1832 (1)
Socio-economic class (%)			
I: Professional	222 (3)	8,591 (4)	8813 (4)
II: Managerial	1,614 (22)	50,767 (26)	52,381 (26)
III: Skilled Non-manual	1,319 (18)	45,614 (23)	46,933 (23)
III: Skilled Manual	1,667 (23)	35,150 (18)	36,817 (18)
IV: Semi-skilled Manual	1,363 (19)	32,779 (17)	34,142 (17)
V: Unskilled manual	553 (8)	11,491 (6)	12,044 (6)
Other	313 (4)	10,054 (5)	10,367 (5)
Missing	148 (2)	2,888 (2)	3,036 (1)
Comorbidity			
CVD reported at baseline (%)	2,722 (38)	19,170 (10)	21,892 (10)

5.3 Descriptive statistics: cancer incidence

Within the Health Survey for England (HSE) and Scottish Health Survey (SHeS) data linked to the Cancer Registry a string variable gave the three digit International Classification of Disease (ICD) code

(either from ICD 9 or 10). This chapter details the analyses related to the associations between diabetes and incidence of all-cancers combined and incidence of site-specific cancers.

As mentioned previously, the inconsistencies within the Cancer Registry linked data for HSE 2008 meant that participants from that year of the survey were excluded from the dataset used for this section of the thesis. This produced a reduced dataset including 189,743 cases, of which 6,488 (3.4%) indicated the presence of diabetes at baseline. Table 5-2 details the number of incident cancers that were flagged among those within the HSE and SHeS appended dataset. 11% of those with diabetes had an incident cancer compared within 6% of those without diabetes.

Table 5-2: Cancer Registrations (HSE and SHeS)

Cancer Registration	Diabetic (%)	Did not indicate diabetes (%)	Total
Yes	679 (11)	10,899 (6)	11,578 (6)
No	5,442 (89)	164,544 (94)	169,986 (94)

Table 5-3 demonstrates the number of incident site-specific cancers registered during the follow-up period.

Table 5-3: Site-specific cancer registrations (HSE and SHeS)

Site-specific cancer registrations	Diabetic	Did not indicate diabetes	Total
Breast	100	2,109	2,209
Lung	96	1,277	1,373
Prostate	75	1,287	1,362
Colorectal	68	921	989
Lymphatic[a]	39	836	875
Cervix[b]	38	547	585
Bladder	46	470	516
Pancreatic	25	267	292
Stomach	18	274	292
Oesophagus	16	246	262
Kidney/Renal	22	239	261
Lip[c]	6	219	225

Liver	<5	77	81
Other cancer[d]	126	2,130	2,256

[a] Lymphatic group also includes haematopoietic and related tissue cancers.
[c] Cervix also includes cancers of the uterus and endometrium.
[b] Lip cancer group also contains those of the oral cavity and pharynx.
[d] 'Other cancer' category contains those cancers not specified in other groups.

Information was available for other cancers (skin, n=4,380) and types of neoplasms (benign, n=170; uncertain/unknown origin, n=648; in situ, n=2,908; incorrectly coded, n=34) that were excluded from the analyses as their type, site of origin and/or malignant nature could not be clarified.

5.4 Overall cancer incidence

Using the derived binary variable for cancer incidence, regression models were developed to assess the association between diabetes and any registration of cancer. The results given in Table 5-4 demonstrate that, when analyses were focused upon the whole sample, within both the basic (OR 1.13, CI 1.04-1.23) and advanced models (1.11, CI 1.01-1.21) those with diabetes were at a statistically significant increased risk of cancer incidence. This increase remained, but became non-significant, when adjustment included CVD at baseline, education or glycated haemoglobin. When analyses were stratified by CVD status at baseline, those with diabetes but without comorbid CVD were found to have increased odds ratios in relation to cancer incidence while those with CVD did not. Within the sex-stratified analyses, women with diabetes were found to have a statistically significant increased risk of developing cancer, while for men only the point estimate was increased. Sensitivity analysis was performed (using cases who indicated that they had never been a regular smoker): among this group there were non-significant increases within each model, including those used within the additional adjustment, which appeared to be non-significant.

Table 5-4: Cancer incidence ORs among those with diabetes compared with the general population

Progressive adjustment	Whole sample	Stratified by CVD status		Stratified by sex		Never smokers Only
		NO	YES	WOMEN	MEN	
Age & sex	1.15 (1.05-1.25)	1.21 (1.09-1.35)	0.92 (0.80-1.06)	1.22 (1.08-1.38)	1.06 (0.94-1.19)	1.20 (1.04-1.38)
& Smoking	1.13 (1.04-1.23)	1.20 (1.08-1.34)	0.92 (0.80-1.06)	1.22 (1.08-1.38	1.04 (0.93-1.17)	N/A
& BMI	1.11 (1.01-1.21)	1.17 (1.04-1.32)	0.94 (0.81-1.09)	1.16 (1.02-1.33)	1.03 (0.91-1.17)	1.13 (0.97-1.32)
Basic & CVD Status	1.10 (1.00-1.20)	N/A	N/A	1.19 (1.05-1.34)	1.01 (0.90-1.14)	1.17 (1.01-1.35)
Additional adjustment (Advanced model + the following variables in turn)						
+ CVD	1.08 (0.98-1.19)	N/A	N/A	1.14 (0.99-1.31)	1.00 (0.88-1.14)	1.11 (0.95-1.29)
+ Education	1.08 (0.98-1.18)	1.14 (1.02-1.28)	0.94 (0.81-1.09)	1.12 (0.98-1.29)	1.01 (0.89-1.15)	1.11 (0.95-1.30)
+ Social Class	1.11 (1.01-1.22)	1.18 (1.05-1.32)	0.94 (0.81-1.09)	1.18 (1.03-1.35)	1.03 (0.91-1.17)	1.15 (0.98-1.34)
+ Region	1.11 (1.01-1.22)	1.18 (1.05-1.32)	0.94 (0.81-1.09)	1.17 (1.02-1.34)	1.03 (0.91-1.17)	1.13 (0.96-1.32)
+$HbA1_c$	1.16 (0.86-1.58)	1.20 (0.82-1.75)	1.07 (0.63-1.82)	1.98 (1.30-3.03)	0.68 (0.43-1.06)	1.38 (0.84-2.29)

Models were then developed which included alternative measurements for overweight and obesity. As can be seen from the advanced model and the results given in Table 5-5 and Table 5-6, including a measurement of BMI, waist-to-hip ratio (WHR) or waist circumference (WC) did little to alter the excess risk of developing cancer among those with diabetes compared with those without diabetes. Further to this, when a combination of covariates were included in the models, and when analyses were stratified by either sex or baseline CVD status, this excess in risk of cancer incidence remained among those with diabetes compared with the general population.

Table 5-5: Cancer incidence ORs among those with diabetes (alternative measures of overweight and obesity)

Further adjustment	Whole sample	Stratified by CVD status		Stratified by sex		Never smokers Only
		NO	YES	WOMEN	MEN	
& BMI	1.11 (1.01-1.21)	1.17 (1.04-1.32)	0.94 (0.81-1.09)	1.16 (1.02-1.33)	1.03 (0.91-1.17)	1.13 (0.97-1.32)
Basic & WHR	1.14 (1.03-1.28)	1.23 (1.07-1.41)	0.96 (0.81-1.15)	1.26 (1.08-1.48)	1.04 (0.89-1.20)	1.14 (0.95-1.37)
Basic & WC	1.15 (1.03-1.28)	1.23 (1.07-1.41)	0.97 (0.81-1.16)	1.23 (1.05-1.45)	1.06 (0.91-1.24)	1.13 (0.94-1.36)
Basic + WHR & CVD	1.12 (1.00-1.25)	N/A	N/A	1.22 (1.04-1.44)	1.02 (0.88-1.19)	1.13 (0.93-1.36)
Basic + WC & CVD	1.12 (1.00-1.26)	N/A	N/A	1.20 (1.02-1.41)	1.05 (0.90-1.22)	1.12 (0.93-1.35)

Table 5-6: Cancer incidence ORs (measures of overweight and obesity removed)

Further adjustment	Whole sample	Stratified by CVD status		Stratified by sex		Never smokers Only
		NO	YES	WOMEN	MEN	
Basic + Education	1.10 (1.01-1.20)	1.16 (1.04-1.30)	0.92 (0.80-1.06)	1.17 (1.03-1.32)	1.02 (0.91-1.15)	1.17 (1.02-1.35)
Basic + Social Class	1.13 (1.04-1.24)	1.21 (1.08-1.35)	0.93 (0.81-1.07)	1.23 (1.09-1.40)	1.04 (0.92-1.17)	1.21 (1.05-1.40)
Basic + Region	1.15 (1.05-1.25)	1.22 (1.10-1.36)	0.93 (0.80-1.07)	1.24 (1.09-1.41)	1.05 (0.93-1.18)	1.19 (1.03-1.38)
Basic + $HbA1_c$	1.16 (0.87-1.55)	1.22 (0.86-1.74)	1.04 (0.63-1.72)	1.86 (1.25-2.77)	0.71 (0.47-1.08)	1.43 (0.90-2.27)

5.5 Site-specific cancer incidence (HSE and SHeS)

Using the categorical variable related to site-specific cancer incidence, multinomial logistic regression models were then developed to investigate whether those with diabetes had an increased risk of a range of incident site-specific cancers (information about the number of site-specific cancers among those with and without diabetes is given in Table 5-3 above). Only for incident pancreatic cancer were those with diabetes at an increased risk within both the basic (1.58, CI 1.04-2.40) and advanced (1.60, 1.02-2.50) models compared with those without diabetes. For cancers of the kidney and lung there were statistically significant increases within the basic, but not advanced models, while for cancers that were sex-specific and those of the oesophagus, colorectum, bladder and other sites there were point estimates increases in risk among the former (Table 5-7).

Diabetes appeared to lower the risk of incident lip cancer, although this was a non-statistically significant reduction. These results remained when alternate measurements of overweight and obesity were included in further models and when adjustment was made for socio-demographic and economic factors (data not shown).

The models developed above were then repeated stratified by baseline CVD status. The number of cancers within each of these groups can be found within Table 5-8. Among those with diabetes and comorbid CVD there were point estimate increases in risk for cancers of the oesophagus, liver, pancreas, lung and kidney (although none of these were statistically significant, Table 5-9). The results suggest that those with diabetes but without CVD had a statistically significant increase in the risk of developing 'other' cancers (Table 5-10), and there were point estimate increases for cancers of the oesophagus, stomach, colorectum, pancreas, lung, bladder, kidney, lymphatic system and sex-specific sites (cervix, prostate and breast).

Analyses were then performed stratified by sex. Table 5-11 details the number of site-specific cancers among men and women. Among men with diabetes, the results suggested a statistically significant risk for pancreatic and bladder cancer that remained consistent within each of the models. Further to this, within the BMI and CVD regression models the ORs were increased for cancers of the stomach, colorectum, lung, lymphatic, prostate and 'other' sites. Women with diabetes were found to have an increased risk of developing cancers of the lung (statistically significant increased risk in the basic and CVD models), breast and cervix (statistically significant increases for cervical cancer were found within the basic, but not advanced, models). There were also point estimate increases for cancers of the oesophagus, colorectum, pancreas and kidney among women with diabetes.

Table 5-7: Site-specific cancer incidence ORs among those with diabetes

Progressive adjustment	Lip	Oesophagus	Stomach	Colorectal	Liver	Pancreas	Lung	Sex-specific cancer	Bladder	Kidney	Lymphatic	Other cancers
Age & sex	0.63 (0.28-1.42)	1.10 (0.66-1.84)	0.98 (0.60-1.61)	1.14 (0.88-1.46)	0.94 (0.34-2.60)	1.59 (1.05-2.42)	1.24 (1.00-1.53)	1.12 (0.97-1.29)	1.30 (0.95-1.77)	1.64 (1.05-2.55)	0.90 (0.85-1.25)	1.13 (0.94-1.35)
& Smoking	0.64 (0.28-1.45)	1.10 (0.66-1.83)	0.97 (0.59-1.59)	1.12 (0.87-1.44)	0.93 (0.34-2.56)	1.58 (1.04-2.40)	1.29 (1.04-1.60)	1.09 (0.94-1.26)	1.29 (0.95-1.75)	1.64 (1.05-2.56)	0.90 (0.65-1.24)	1.12 (0.93-1.34)
& BMI	0.84 (0.37-1.92)	1.10 (0.63-1.91)	0.93 (0.55-1.59)	1.12 (0.86-1.46)	0.92 (0.33-2.57)	1.60 (1.02-2.50)	1.25 (0.99-1.58)	1.05 (0.90-1.22)	1.19 (0.84-1.68)	1.55 (0.97-2.49)	0.88 (0.62-1.24)	1.11 (0.91-1.35)
& CVD	0.82 (0.36-1.87)	1.12 (0.64-1.94)	0.92 (0.53-1.60)	1.10 (0.84-1.43)	0.87 (0.31-2.45)	1.48 (0.93-2.35)	1.20 (0.94-1.52)	1.05 (0.90-1.23)	1.10 (0.77-1.58)	1.47 (0.91-2.37)	0.87 (0.61-1.24)	1.06 (0.86-1.29)

Table 5-8: Site-specific cancer incidence by CVD status

Comorbid CVD	Pancreas	Colorectal	Bladder	Stomach	Lip	Liver	Lung	Lymphatic	Kidney	Oesophagus	Other	Sex-specific[a]
Yes	66	232	118	58	31	19	293	136	63	50	400	684
No	226	757	398	232	194	61	1,078	738	198	212	1,854	3,469

[a] This category includes cancers that only occur in one gender (prostate and cervical) and those that are rarely found within a specific sex (breast). In the sex-stratified analyses the results are given for these cancers.

Table 5-9: Site-specific cancer incidence ORs among those with diabetes and comorbid CVD

Progressive adjustment	CVD indicated at baseline											
	Lip	Oesophagus	Stomach	Colorectal	Liver	Pancreas	Lung	Sex-spec cancer	Bladder	Kidney	Lymphatic	Other cancers
Age, sex	0.72 (0.22-2.38)	1.09 (0.49-2.42)	0.50 (0.18-1.38)	0.91 (0.61-1.36)	1.29 (0.37-4.43)	1.62 (0.88-2.99)	1.14 (0.82-1.58)	0.93 (0.73-1.18)	0.83 (0.47-1.45)	1.22 (0.62-2.40)	0.72 (0.55-1.27)	0.76 (0.55-1.06)
& Smoking	0.73 (0.22-2.39)	1.08 (0.48-2.40)	0.50 (0.18-1.37)	0.91 (0.61-1.36)	1.34 (0.39-4.62)	1.59 (0.86-2.93)	1.18 (0.85-1.64)	0.92 (0.72-1.17)	0.82 (0.47-1.44)	1.21 (0.61-2.38)	0.71 (0.40-1.26)	0.77 (0.55-1.07)
& BMI	0.94 (0.28-3.16)	1.02 (0.40-2.63)	0.60 (0.22-1.69)	0.90 (0.59-1.37)	1.49 (0.42-5.29)	1.65 (0.85-3.21)	1.20 (0.83-1.72)	0.96 (0.75-1.24)	0.89 (0.49-1.60)	1.13 (0.55-2.32)	0.68 (0.36-1.28)	0.75 (0.53-1.07)

Table 5-10: Site-specific cancer incidence ORs among those with diabetes and without comorbid CVD

Progressive adjustment	CVD not indicated at baseline											
	Lip	Oesophagus	Stomach	Colorectal	Liver	Pancreas	Lung	Sex-spec cancer	Bladder	Kidney	Lymphatic	Other cancers
Age, sex	0.51 (0.16-1.61)	1.05 (0.54-2.07)	1.27 (0.72-2.24)	1.18 (0.85-1.63)	0.42 (0.06-3.03)	1.36 (0.75-2.45)	1.17 (0.88-1.55)	1.18 (0.99-1.41)	1.58 (1.10-2.29)	1.63 (0.90-2.95)	1.01 (0.68-1.49)	1.30 (1.04-1.62)
& Smoking	0.53 (0.17-1.66)	1.05 (0.54-2.10)	1.26 (0.71-2.22)	1.17 (0.85-1.62)	0.41 (0.06-2.95)	1.36 (0.76-2.46)	1.22 (0.92-1.63)	1.15 (0.96-1.38)	1.58 (1.09-2.29)	1.65 (0.91-2.99)	1.00 (0.67-1.49)	1.29 (1.03-1.61)
& BMI	0.69 (0.21-2.18)	1.17 (0.59-2.30)	1.14 (0.61-2.11)	1.20 (0.86-1.69)	0.40 (0.06-2.94)	1.42 (0.77-2.64)	1.19 (0.88-1.63)	1.07 (0.88-1.31)	1.36 (0.89-2.08)	1.64 (0.88-3.05)	1.01 (0.67-1.53)	1.31 (1.04-1.65)

Table 5-11: Site-specific cancer incidence by sex

Sex	Pancreas	Colorectal	Bladder	Breast	Cervical	Stomach	Lip	Liver	Lung	Lymphatic	Kidney	Oesophagus	Prostate	Other
Male	140	491	377	0	0	185	141	43	787	479	169	159	1,361	1,114
Female	152	498	139	2,196	585	105	84	37	584	395	92	103	0	1,140

Table 5-12: Site-specific cancer incidence ORs among men with diabetes

Progressive adjustment	Lip etc	Oesophagus	Stomach	Colorectal	Liver	Pancreas	Lung	Bladder	Kidney	Lymphatic	Prostate	Other cancers
Age & sex	0.84 (0.34-2.08)	1.09 (0.57-2.09)	1.03 (0.57-1.87)	1.13 (0.81-1.57)	1.13 (0.34-3.70)	1.74 (1.01-3.02)	1.16 (0.88-1.51)	1.43 (1.02-2.00)	1.67 (0.99-2.83)	0.96 (0.64-1.44)	0.80 (0.63-1.02)	1.07 (0.83-1.38)
& Smoking	0.86 (0.35-2.13)	1.07 (0.56-2.05)	1.01 (0.56-1.83)	1.11 (0.79-1.54)	1.09 (0.33-3.57)	1.69 (0.98-2.93)	1.19 (0.91-1.56)	1.41 (1.01-1.97)	1.66 (0.98-2.81)	0.94 (0.63-1.41)	0.78 (0.61-0.99)	1.06 (0.82-1.36)
& BMI	1.03 (0.96-1.10)	1.06 (1.02-1.11)	1.07 (1.02-1.12)	1.05 (1.02-1.09)	1.05 (0.97-1.14)	1.11 (1.05-1.16)	1.10 (1.08-1.13)	1.11 (1.04-1.18)	1.00 (0.95-1.06)	1.05 (1.01-1.09)	1.05 (1.02-1.09)	1.07 (1.05-1.10)
& CVD	1.03 (0.95-1.11)	1.07 (1.02-1.11)	1.06 (1.01-1.12)	1.05 (1.01-1.08)	1.03 (0.95-1.13)	1.10 (1.04-1.16)	1.09 (1.07-1.12)	1.09 (1.02-1.16)	1.00 (0.94-1.06)	1.05 (1.01-1.09)	1.06 (1.03-1.09)	1.07 (1.05-1.10)

Table 5-13: ORs site-specific cancer incidence among women with diabetes

Progressive adjustment	Lip	Oeso-phagus	Stomach	Colo-rectal	Liver	Pancreas	Lung	Breast	Cervix	Bladder	Kidney	Ovarian	Lymphatic	Other cancers
Age & sex	0.29 (0.04-2.09)	1.17 (0.51-2.68)	0.90 (0.37-2.23)	1.15 (0.78-1.68)	0.62 (0.08-4.59)	1.42 (0.74-2.71)	1.37 (0.97-1.94)	1.26 (1.03-1.56)	1.70 (1.21-2.38)	0.80 (0.35-1.81)	1.54 (0.67-3.56)	1.07 (1.02-1.12)	(0.80 (0.46-1.40)	1.18 (0.90-1.55)
& Smoking	0.30 (0.04-2.14)	1.18 (0.51-2.71)	0.91 (0.37-2.25)	1.14 (0.78-1.66)	0.63 (0.09-4.64)	1.43 (0.75-2.73)	1.49 (1.05-2.12)	1.25 (1.02-1.54)	1.64 (1.17-2.30)	0.81 (0.36-1.85)	1.56 (0.67-3.60)	1.07 (1.02-1.12)	0.80 (0.46-1.40)	1.19 (0.91-1.56)
& BMI	0.37 (0.05-2.67)	1.28 (0.51-3.20)	0.81 (0.30-2.24)	1.18 (0.80-1.76)	0.52 (0.07-3.87)	1.29 (0.62-2.67)	1.38 (0.93-2.05)	1.22 (0.97-1.53)	1.35 (0.93-1.95)	0.78 (0.31-1.91)	1.70 (0.73-3.98)	1.06 (1.02-1.11	0.68 (0.36-1.29)	1.15 (0.86-1.53)
& CVD	0.96 (0.84-1.09)	1.07 (1.00-1.14)	1.06 (0.99-1.13)	1.06 (1.02-1.10)	1.09 (0.97-1.23)	1.07 (1.01-1.12)	1.07 (1.04-1.10)	1.04 (1.00-1.07)	0.99 (0.93-1.05)	1.03 (0.96-1.12)	1.13 (1.02-1.26)	1.06 (1.02-1.11	1.03 (0.99-1.08)	1.04 (1.01-1.07)

The results detailed within this chapter suggest that those with diabetes may be at an increased risk of cancer incidence, when all cancers are considered, compared with the general population. Concurrently, such risk appears dependent upon a number of factors related to the presence of CVD as a comorbidity, sex and smoking status. In terms of site-specific cancers, the presence or not of CVD as a comorbidity appears to alter an individual's risk of incident cancer. Both men and women with diabetes appear to have an increased risk of lung cancer; at the same time the risk of developing a number of other site-specific cancers appears to differ between the sexes.

The following chapter detail the association between glycated haemoglobin and cancer incidence.

6. Chapter 6: Results – glycated haemoglobin and cancer incidence

6.1 Descriptive statistics: glycated haemoglobin

In total, 28,754 participants had a valid glycated haemoglobin ($HbA1_C$) measurement (14% of the total sample) at baseline. The mean $HbA1_C$ was 5.50 (SD 0.74), with 5% of the sample having a measurement of 6.5% (48mmol/mol) or above; this threshold indicates uncontrolled or undiagnosed diabetes (Table 6-1). The majority of the sample were in the 16-64 age group (75%), with slightly more women than men (15,541 and 13,213, respectively). 50% of the sample indicated that they had never been a regular smoker. In relation to the anthropometric measures, the mean BMI was 27.01 (SD 4.85), 41% had a waist circumference above the threshold (102cm for men and 88cm for women) and 34% had a raised measurement for waist-to-hip ratio (WHR: 0.95 or above for men and 0.85 or above for women). 42% of the sample lived in the South. A majority (42%) indicated that they had qualifications other than a degree (29% indicated no qualifications) and 5% were from the 'professional' socioeconomic class. 3,539 (12%) indicated the presence of cardiovascular disease as a comorbidity: 32% of those with $HbA1_C$ ≥6.5% compared with 11% of those with a measurement below this. Among those with raised $HbA1_C$, 57% indicated the presence of diabetes, compared with 2% with a normal measurement. When $HbA1_C$ was divided into tertiles, the majority of those with diabetes (90%) were in the top tertile (indicating the highest measurements) compared with 34% of those who did not indicate the presence of diabetes.

Table 6-1: Descriptive statistics – valid glycated haemoglobin sample

Characteristics	**$HbA1_C$ sample**		
Total sample (%)	**Raised**	**Normal**	**All**
	n=1,459	**n=27,295**	**n=28,754**
Glycated haemoglobin			
Mean (SD)	7.81 (1.46)	5.37 (0.40)	5.50 (0.74)
$HbA1_c$ Tertiles			
1 (lowest)	0 (0)	10,335 (38)	10,335 (35)
2	0 (0)	7,956 (29)	7,956 (28)
3 (highest)	1,459 (100)	9,004 (33)	10,463 (36)
Age-groups no. (%)			
16-64	714 (49)	20,910 (77)	21,624 (75)

65-74	451 (31)	3,832 (14)	4,283 (15)
75+	294 (20)	2,553 (9)	2,847 (10)
Sex - no. (%)			
Male	791 (54)	12,422 (46)	13,213 (46)
Female	668 (46)	14,873 (55)	15,541 (54)
Lifestyle factors			
Smoking status-no. (%)			
Never	620 (43)	13,713 (50)	14,333 (50)
Ex-regular smoker	555 (38)	7,242 (27)	7,797 (27)
Current smoker	283 (19)	6,291 (23)	6,574 (23)
Missing	1 (<1)	49 (<1)	50 (<1)
Anthropometric measures			
BMI			
No. with data (%)	1,316 (90)	25,795 (95)	27,111 (94)
Mean – kg/m^2 (SD)	29.88 (5.36)	26.87 (4.78)	27.01 (4.85)
BMI: <20 kg/m^2	12 (<1)	1,112 (4)	1,124 (4)
BMI: 20-24.99 kg/m^2	233 (17)	8,658 (33)	8,891 (31)
BMI: 25-29.99 kg/m^2	484 (36)	10, 318 (40)	10,802 (38)
BMI: ≥30 kg/m^2	587 (44)	5,707 (22)	6,294 (22)
BMI: Missing	143 (10)	1,500 (6)	1,643 (6)
Waist circumference			
No. With data (%)	1,388 (95)	26,429 (97)	27,817 (97)
Above threshold (Men: 102cm, Women: 88cm)	953 (69)	10,875 (41)	11,828 (41)
Mean-cm (SD)	102.74 (14.66)	90.87 (13.53)	91.46 (13.84)
Waist-to-hip ratio			
No. with data (%)	1,385 (95)	26,402 (97)	27,787 (97)
Above threshold (Men: ≥0.95, Women: ≥0.85) (%)	942 (68)	8,830 (33)	9,772 (34)
Mean (SD)	0.93 (0.07)	0.82 (0.07)	0.87 (0.09)
Region			
South	625 (43)	11,349 (42)	11,974 (42)
Midlands	283 (19)	4,678 (17)	4,961 (17)

North	387 (27)	7,444 (27)	7,831 (27)
Scotland	164 (11)	3,824 (14)	3,988 (14)
Education			
Degree	159 (11)	5,005 (18)	5,164 (18)
Other	584 (40)	14,641 (54)	15,225 (53)
No qualifications	714 (49)	7,624 (28)	8,338 (29)
Missing	2 (<1)	25 (<1)	27 (<1)
Socio-economic status			
I: Professional	59 (4)	1,439 (5)	1,498 (5)
II: Managerial	371 (26)	8,109 (30)	8,480 (30)
III: Skilled Non-manual	251 (17)	6,092 (23)	6,343 (22)
III: Skilled Manual	329 (23)	4,805 (18)	5,134 (18)
IV: Semi-skilled Manual	288 (20)	4,249 (16)	4,537 (16)
V: Unskilled manual	106 (7)	1,417 (5)	1,523 (5)
Other	44 (3)	941 (4)	985 (3)
Missing	11 (<1)	243 (<1)	254 (<1)
Morbidity and mortality			
Diabetes	827 (57)	415 (2)	1,242 (4)
CVD reported at baseline (%)	462 (32)	3,077 (11)	3,539 (12)
Vital status			
Alive	1,291 (89)	26,101 (96)	27,392 (95)
Dead	168 (12)	1,194 (4)	1,362 (5)
Cause of death			
Cancer	47 (28)	402 (34)	449 (33)
Respiratory	19 (11)	154 (13)	173 (13)
CVD	73 (43)	398 (33)	471 (35)
Other	29 (17)	240 (20)	269 (20)

The following chapter details the results related to glycated haemoglobin ($HbA1_C$) and cancer incidence (all-cancers and site-specific) when analyses were undertaken using the combined HSE and SHeS dataset. Amongst those with a valid $HbA1_C$ measurement there were 1,137 recorded incident cancers within the follow-up period, including 103 among those with an $HbA1_C$ of ≥6.5%. The next section assesses the associations between raised $HbA1_C$ and overall cancer incidence.

6.2 Overall cancer incidence

A binary variable was produced which included those with and without an incident cancer (0=no cancer, 1=cancer registration). This dependent variable was then used to assess the associations between $HbA1_C$ and cancer incidence. Within the whole sample, there were statistically significant increased ORs among those with a raised measurement within the basic (1.33, CI 1.07-1.66) but not advanced model, although within the latter there was a point estimate increase (1.22, 0.96-1.55). This point estimate increase remained when additional variables, related to socio-economic and demographic covariates, were added to the regression model. The analyses were then re-run with the data stratified by CVD status. As can be seen from Table 6-2, those without comorbid CVD but with a raised $HbA1_C$ measurement were at an increased risk of developing cancer within both the basic (1.44, 1.10-1.89) and advanced (1.34, 1.00-1.79) models, while those with CVD did not appear to have a statistically significant increased risk. When the data were stratified by sex, women with a raised $HbA1_C$ measurement had an increased risk at the point estimate, while men had statistically significant increased odds within the basic (1.44, 1.08-1.93) but not advanced models. Among those who indicated that they had never been a regular smoker, there were point estimate increases in the risk of incident cancer, but these were non-significant.

Further analyses were undertaken which explored the impact of alternative measurements of overweight and obesity upon the association between raised $HbA1_C$ and overall cancer incidence. As can be seen from Table 6-3, the inclusion of these covariates had little impact upon the increased risk in odds found among those with raised $HbA1_C$ compared with those with a lower measurement. The exclusion of all the adiposity related variables, as well as the inclusion of a number of socio-economic and demographic covariates, had little impact upon the results given below (results not shown).

Table 6-2: Cancer incidence ORs among those with $HbA1_C$ ≥6.5%

Progressive adjustment	**WHOLE SAMPLE**	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		NO	**YES**	**WOMEN**	**MEN**	
Age & sex	1.34 (1.08-1.67)	1.45 (1.11-1.90)	1.12 (0.76-1.65)	1.20 (0.85-1.68)	1.45 (1.09-1.95)	1.31 (0.91-1.87)
& Smoking	1.33 (1.07-1.66)	1.44 (1.10-1.89)	1.10 (0.75-1.63)	1.20 (0.85-1.69)	1.44 (1.08-1.93)	N/A
& BMI	1.22	1.34	0.99	1.10	1.31	1.13

	(0.96-1.55)	(1.00-1.79)	(0.65-1.50)	(0.77-1.59)	(0.95-1.79)	(0.76-1.69)
Basic + CVD status	1.32 (1.06-1.65)	N/A	N/A	1.19 (0.84-1.67)	1.44 (1.07-1.93)	1.31 (0.91-1.89)
Additional adjustment (Advanced model + the following variables)						
+ CVD	1.21 (0.95-1.54)	N/A	N/A	1.10 (0.76-1.58)	1.30 (0.94-1.78)	1.14 (0.76-1.69)
+ Education	1.19 (0.94-1.52)	1.30 (0.97-1.74)	1.03 (0.68-1.60)	1.08 (0.75-1.56)	1.27 (0.93-1.75)	1.12 (0.75-1.67)
+ Social Class	1.20 (0.95-1.53)	1.30 (0.97-1.74)	1.01 (0.67-1.54)	1.06 (0.73-1.54)	1.30 (0.95-1.78)	1.09 (0.73-1.64)
+ Region	1.22 (0.96-1.55)	1.32 (0.99-1.77)	0.99 (0.65-1.51)	1.10 (0.77-1.59)	1.31 (0.96-1.80)	1.13 (0.76-1.69)
+ Diabetes	1.12 (0.84-1.51)	1.22 (0.86-1.73)	0.95 (0.55-1.61)	0.75 (0.48-1.18)	1.61 (1.09-2.39)	0.94 (0.56-1.55)

Table 6-3: Cancer incidence ORs among those with raised $HbA1_C$ (including alternative measures of overweight and obesity)

Additional adjustment	**WHOLE SAMPLE**	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		NO	YES	WOMEN	MEN	
Basic + WHR	1.23 (0.98-1.55)	1.28 (0.96-1.69)	1.16 (0.78-1.72)	1.09 (0.76-1.55)	1.35 (0.99-1.82)	1.15 (0.79-1.68)
Basic + WC	1.26 (1.00-1.58)	1.32 (1.00-1.74)	1.14 (0.77-1.70)	1.11 (0.78-1.58)	1.38 (1.02-1.86)	1.16 (0.79-1.69)
Basic + WHR & CVD	1.23 0.98-1.55)	N/A	N/A	1.08 (0.76-1.55)	1.35 (1.00-1.83)	1.16 (0.79-1.69)
Basic + WC & CVD	1.26 (1.00-1.58)	N/A	N/A	1.10 (0.77-1.57)	1.38 (1.02-1.86)	1.17 (0.80-1.71)

6.3 Site-specific cancer incidence

Using the derived site-specific Cancer Registry variable (produced for the analyses related to diabetes and cancer incidence) it was possible to explore the associations between raised $HbA1_C$ and the risk of developing specific cancers. As can be seen from Table 6-4, for some of the site-specific incident cancers there was a small number registered among those with raised glycated haemoglobin during the follow-up period. This prevented the undertaking of analyses which stratified the sample by either sex or comorbid CVD; therefore the results given below are those for analyses of the whole $HbA1_C$ sample.

Table 6-4: Site-specific cancer registrations among those with a valid $HbA1_C$ sample

Site-specific cancer	Normoglycaemic	Raised
Lip	16	<5
Oesophagus	25	<5
Stomach	20	8
Colon	93	11
Liver	5	<5
Pancreas	13	<5
Lung	109	16
Breast	227	12
Cervix	66	6
Bladder	47	<5
Kidney	47	<5
Lymphatic	77	<5
Prostate	131	16
Other	181	17
TOTAL	1,034	103

The only incident cancers that appeared to have a consistent, statistically significant, association with raised $HbA1_C$ were those of the stomach and lung; $HbA1_C$ was associated with a statistically significant increased odds of developing pancreatic cancer within the basic (3.40, 1.08-10.66) but not the advanced (2.95, 0.79-10.97) model. Other site-specific cancers (lip, colon, 'other' and sex-specific cancers) produced increases at the point estimate which were non-significant. The addition of variables related to region, socio-economic status and education level did not significantly alter the results given in Table 6-5. The analyses then explored the associations between $HbA1_C$ and sex-specific cancer incidence.

Table 6-5: Site-specific cancer incidence ORs among those with raised $HbA1_c$

Progressive adjustment	Site-specific cancer											
	Lip	**Oesophagus**	**Stomach**	**Colon**	**Liver**	**Pancreas**	**Lung**	**Bladder**	**Kidney**	**Lymphatic**	**Other cancers**	**Sex-specific**
Age, sex	1.19 (0.15-9.20)	0.48 (0.06-3.56)	4.44 1.91-10.33)	1.41 (0.75-2.67)	2.70 (0.30-24.26)	3.42 (1.09-10.71)	1.92 (1.12-3.30)	0.85 (0.30-2.38)	1.12 (0.26-4.83)	0.75 (0.27-2.07)	1.35 (0.81-2.25)	1.14 (0.79-1.64)
& Smoking	1.17 (0.15-9.05)	0.47 (0.06-3.52)	4.36 (1.87-10.14)	1.43 (0.76-2.71)	2.57 (0.29-23.19)	3.40 (1.08-10.66)	1.83 (1.06-3.15)	0.83 (0.30-2.33)	1.15 (0.27-4.96)	0.74 (0.27-2.04)	1.35 (0.81-2.24)	1.15 (0.80-1.65)
& BMI	1.67 (0.21-13.30)	0.55 (0.07-4.13)	4.07 (1.54-10.76)	1.21 (0.60-2.45)	N/A	2.95 (0.79-10.97)	1.99 (1.12-3.53)	0.67 (0.20-2.18)	0.99 (0.23-4.29)	0.73 (0.26-2.03)	1.32 (0.77-2.28)	1.03 (0.70-1.51)
& CVD	1.79 (0.22-14.36)	0.58 (0.08-4.41)	4.80 (1.81-12.73)	1.11 (0.55-2.24)	N/A	2.76 (0.74-10.36)	2.00 (1.12-3.56)	0.65 (0.20-2.11)	0.96 (0.22-4.18)	0.71 (0.26-1.99)	1.34 (0.77-2.31)	1.03 (0.70-1.52)

Among men there were 16 cases of prostate cancer among those with a measurement of $HbA1_C$ ≥6.5%. The ORs within the basic, advanced and CVD models indicated a non-significant increased odds and were: 1.30, 0.76-2.22; 1.29, 0.76-2.22; 1.03, 0.57-1.87, respectively. Among women there appeared to be no increased risk of incident breast cancer for those with raised $HbA1_C$ and a point estimate increase for cervical cancer (ORs 1.38, 0.59-3.25; 1.18, 0.46-3.01 and 1.24, 0.48-3.20, respectively).

This chapter indicates that those with a raised glycated haemoglobin measurement appear to be at an increased risk of developing incident cancer. Concurrently, only those without comorbid CVD had a statistically significant increased risk of incident cancer. The risk also differed between the sexes, although only within the basic model were men found to have a statistically significant increased risk of developing cancer if they had an $HbA1_C$ measurement of 6.5% or above. Turning to site-specific cancer incidence, although the small number of cases prevented further analyses there appears to be a statistically significant association between $HbA1_C$ and cancers of the stomach and lung, as well as point estimate increases for a number of other site-specific cancers. The next chapter discusses the results of the analyses which were focussed upon the associations between diabetes and cause-specific mortality.

7. Chapter 7: Results – diabetes and cause-specific mortality

The following chapter details the results related to diabetes and mortality from cancer, CVD, respiratory disease and 'other' causes when analyses utilised data from the HSE and SheS combined dataset.

7.1 Cause-specific mortality (with a particular focus upon cancer)

As discussed in the literature review, the association between diabetes and cardiovascular disease is well established, although there are differences in the strength of the association dependent upon a number of factors - including the population being investigated and the covariates adjusted for. At the same time, there is a paucity of evidence related to the association between diabetes and respiratory disease. Therefore, in order to support the main aims of this research, to explore the associations between diabetes and cancer incidence and mortality, analyses were undertaken which explored the association between diabetes and four broad causes of mortality (including cancer). Within the linked HSE dataset, provided by NatCen Social Research, a variable was available that gave information about four broad, primary causes of death. These were:

- cancer (ICD 10 C00-C97)
- respiratory diseases (J00-J99)
- CVD (ICD10 codes I00-I99)
- 'Other' causes included all deaths not included in the three categories above.

Because this variable was not available within the SHeS dataset it was necessary to create one that matched it. This was produced using the string mortality variable, which contained the ICD 10 codes related to cause of death, included within the linked SHeS dataset. Once this had been derived it was then possible to combine the two datasets and analyse the associations of diabetes with these broad causes of mortality. Table 7-1 details the number of cases that had died during the study follow-up period (up to the first quarter of 2011 for the HSE and 2008 for the SHeS). Among those with and without diabetes, cardiovascular disease (CVD) accounted for the largest number of deaths (45% among those with diabetes and 37% among those without). A higher percentage of those without diabetes died of cancer compared with those with diabetes (29% vs. 20%, respectively). Similar percentages within each group were recorded as having died of respiratory disease (12% among those with diabetes and 14% among those without diabetes).

Table 7-1: Cause-specific mortality among those with and without diabetes

Cause of death (% of total deaths)[a]	Diabetes	Did not indicate diabetes	Whole sample
CVD	819 (45)	6,670 (37)	7,489 (37)
Cancer	355 (20)	5,216 (29)	5,571 (28)
Respiratory	212 (12)	2,626 (14)	2,838 (14)
Other	428 (24)	3,725 (20)	4,153 (21)
TOTAL	1,814	18,237	20,051

[a] Percentages have been rounded so summed percentages may not add up to 100%.

Initial analyses explored the associations between diabetes and cause-specific mortality using data from the whole sample. Table 7-2 details the excess mortality experienced by the diabetic cohort. The odds ratios (ORs) were increased among those with diabetes for each specific cause of death. The largest excess in mortality among those with diabetes was for cardiovascular disease (CVD); within the 'basic model' (age, sex and smoking) the OR for mortality from CVD was 1.96 (CI 1.80-2.14). This increase remained unchanged after further adjustment for BMI (1.94, CI 1.76-2.13) and was attenuated at the point estimate following adjustment for CVD status (1.69, CI 1.54-1.86), although this decrease was not statistically significant.

For cancer, the ORs for those with diabetes, compared with the general population, were also increased. Within the 'basic model' the OR was 1.26 (CI 1.13-1.42); this remained unchanged after further adjustment for BMI (1.27, CI 1.12-1.43) and CVD (1.21, CI 1.06-1.36). The corresponding estimates for respiratory disease were also increased (1.25, CI 1.08-1.46; 1.39, CI 1.18-1.64 and 1.34, CI 1.13-1.58, respectively. The ORs for 'other' causes were also increased within each model.

Table 7-2: Cause-specific mortality odds ratios (and 95% CI) among those with diabetes

Progressive adjustment				
	Cancer	**Respiratory**	**CVD**	**Other**
Age, sex	1.23 (1.09-1.38)	1.18 (1.02-1.37)	1.89 (1.73-2.05)	1.97 (1.77-2.20)
& Smoking	1.26 (1.13-1.42)	1.25 (1.08-1.46)	1.96 (1.80-2.14)	2.06 (1.84-2.30)
& BMI	1.27 (1.12-1.43)	1.39 (1.18-1.64)	1.94 (1.76-2.13)	2.09 (1.85-2.37)
Basic + CVD status	1.20 (1.07-1.35)	1.22 (1.05-1.41)	1.71 (1.57-1.87)	2.00 (1.79-2.24)
Additional adjustment (Advanced model + the following variables)				
+ CVD	1.21 (1.06-1.36)	1.34 (1.13-1.58)	1.69 (1.54-1.86)	2.01 (1.78-2.28)
+ Education	1.22 (1.08-1.38)	1.34 (1.14-1.59)	1.89 (1.72-2.08)	2.03 (1.79-2.30)
+ Social Class	1.26 (1.11-1.42)	1.37 (1.16-1.62)	1.92 (1.75-2.11)	2.07 (1.83-2.34)
+ Region	1.26 (1.11-1.43)	1.40 (1.18-1.66)	1.93 (1.75-2.12)	2.09 (1.85-2.37)
+ $HbA1_c$	1.19 (0.74-1.89)	1.46 (0.72-2.95)	2.22 (1.52-3.25)	3.39 (2.07-5.55)

Additional covariates were added to the advanced model. Within each of these models the excess in mortality remained for CVD; those with diabetes had over double to the odds of dying of CVD, when the model included adjustment for glycated haemoglobin ($HbA1_C$) (OR 2.22, CI 1.52-3.25), compared with those without diabetes. The increased ORs were also unchanged within the analyses of 'other' cause of mortality. For cancer the increased odds of cancer-specific mortality remained statistically significant after adjustment for education (1.22, CI 1.08-1.38), social class (1.26, CI 1.11-1.42), region (1.26, CI 1.11-1.43) but not $HbA1_C$ (1.19, CI 0.74-1.89). The same outcome was found for respiratory disease (education: 1.34, CI 1.14-1.59; social class: 1.37, CI 1.16-1.62; region: 1.40, CI 1.18-1.66 and $HbA1_C$: 1.46, CI 0.72-2.95, respectively).

Table 7-3: Cause-specific mortality ORs (adjusting for alternative measures of overweight and obesity)

Additional adjustment				
	Cancer	**Respiratory**	**CVD**	**Other**
Basic + BMI	1.27 (1.12-1.43)	1.39 (1.18-1.64)	1.94 (1.76-2.13)	2.09 (1.85-2.37)
Basic + WHR[a]	1.22 (1.05-1.42)	1.28 (1.04-1.56)	1.78 (1.58-1.99)	1.87 (1.60-2.19)
Basic + WC[b]	1.22 (1.05-1.42)	1.32 (1.08-1.61)	1.81 (1.62-2.04)	1.93 (1.65-2.26)
Basic + WHR & CVD	1.18 (1.02-1.38)	1.24 (1.01-1.52)	1.56 (1.39-1.76)	1.82 (1.55-2.13)
Basic + WC & CVD	1.19 (1.02-1.38)	1.28 (1.05-1.57)	1.59 (1.42-1.79)	1.87 (1.6-2.19)

[a] WHR – Waist-to-hip ratio
[b] WC – Waist circumference

In order to assess the impact of adjusting for different measurements of overweight and obesity, further models were developed which, in the first instance, excluded any measurement of adiposity then included either waist-to-hip ratio or waist circumference. Within these models the increased odds ratios for each cause of death, among those with diabetes, remained statistically significant. For cancer those with diabetes were consistently found to have around a 20% increased odds of mortality from this cause. For respiratory and cardiovascular disease there was a wider range in the ORs, which appeared to be dependent upon whether cardiovascular disease at baseline had been adjusted for.

Table 7-4: Cause-specific mortality ORs among diabetic cases (without adjustment for overweight and obesity)

Additional adjustment				
	Cancer	**Respiratory**	**CVD**	**Other**
Basic + Education	1.21 (1.08-1.36)	1.21 (1.04-1.40)	1.91 (1.75-2.08)	1.99 (1.78-2.22)
Basic + Social Class	1.25 (1.11-1.40)	1.23 (1.06-1.43)	1.93 (1.78-2.11)	2.03 (1.81-2.26)
Basic + Region	1.27 (1.13-1.43)	1.30 (1.11-1.51)	1.98 (1.82-2.16)	2.03 (1.81-2.27)
Basic + $HbA1_c$	1.20 (0.78-1.85)	1.25 (0.66-2.40)	2.33 (1.64-3.31)	3.31 (2.1-5.23)

Models were then developed which included the variables related to socioeconomic/ demographic information and $HbA1_C$, but excluded measurements of overweight and obesity. As can be seen by comparing the results in Tables 7-3 and 7-4 which indicate that the inclusion or exclusion of measurements of overweight and obesity had little impact upon the excess in cause-specific mortality experienced by those with diabetes compared with those without diabetes. Similarly to the model that included BMI, the increase in cancer-specific mortality was not statistically significant when $HbA1_C$ was included in the model (1.20, CI 0.78-1.85) and the same was true for respiratory disease (1.25, CI 0.66-2.40). Further models were developed which took into account a number of the covariates of interest. As can be seen from tables 7-5 and 7-6, the diabetic cohort remained at an increased risk of cause-specific mortality within a variety of models; unless $HbA1_C$ was included (cancer and respiratory disease). For cardiovascular disease and mortality from 'other' causes the excess remained for those with diabetes within all of the models.

Table 7-5: Cause-specific mortality ORs among cases with diabetes (further adjustment)

Further adjustment	Cancer	Respiratory	CVD	Other
Advanced Model + Sclass, Region & CVD	1.19 (1.05-1.35)	1.33 (1.12-1.58)	1.67 (1.51-1.84)	1.99 (1.75-2.25)
Advanced Model + Sclass, Region, CVD & $HbA1_c$	1.17 (0.75-1.83)	1.41 (0.71-2.77)	1.93 (1.34-2.77)	2.84 (1.79-4.52)
Advanced Model + Education, Region & CVD	1.16 (1.03-1.32)	1.31 (1.11-1.56)	1.65 (1.50-1.81)	1.96 (1.72-2.22)
Advanced Model + Education, Region, CVD & $HbA1_c$	1.16 (0.75-1.82)	1.31 (0.65-2.61)	1.90 (1.32-2.74)	2.77 (1.74-4.40)
Basic Model + Waist/Hip, Sclass, Region & CVD	1.17 (1.01-1.37)	1.21 (0.99-1.48)	1.55 (1.37-1.74)	1.79 (1.53-2.10)
Basic Model + Waist/Hip, Sclass, Region, CVD & $HbA1_c$	1.20 (0.78-1.83)	1.15 (0.59-2.23)	1.87 (1.31-2.66)	2.34 (1.44-3.80)
Basic Model + Waist/Hip, Education, Region & CVD	1.16 (1.00-1.35)	1.21 (0.99-1.48)	1.56 (1.39-1.75)	1.79 (1.53-2.10)
Basic Model + Waist/Hip, Education, Region, CVD & $HbA1_c$	1.20 (0.78-1.84)	1.07 (0.54-2.10)	1.86 (1.31-2.64)	2.28 (1.41-3.69)
Basic Model + Waist Circ, Sclass, Region & CVD	1.17 (1.01-1.36)	1.24 (1.02-1.52)	1.57 (1.39-1.76)	1.84 (1.57-2.16)
Basic Model + Waist Circ, Sclass, Region, CVD & $HbA1_c$	1.17 (0.76-1.79)	1.17 (0.60-2.28)	1.87 (1.32-2.66)	2.32 (1.43-3.77)
Basic Model + Waist Circ, Education, Region & CVD	1.16 (1.0-1.35)	1.24 (1.01-1.52)	1.58 (1.40-1.78)	1.84 (1.57-2.15)
Basic Model + Waist Circ, Education, Region, CVD & $HbA1_c$	1.17 (0.76-1.80)	1.09 (0.55-2.14)	1.85 (1.30-2.63)	2.25 (1.39-3.65)

Table 7-6: Cause-specific mortality ORs (no adjustment for CVD at baseline)

Additional adjustment				
	Cancer	**Respiratory**	**CVD**	**Other**
Advanced model + Sclass & Region	1.25 (1.10-1.42)	1.39 (1.17-1.64)	1.91 (1.74-2.04)	2.07 (1.83-2.35)
Advanced model + Sclass, Region & $HbA1_c$	1.22 (0.78-1.90)	1.49 (0.76-2.95)	2.19 (1.52-3.16)	3.15 (1.98-5.00)
Advanced model + Education, Region	1.22 (1.07-1.38)	1.36 (1.15-1.61)	1.88 (1.71-2.07)	2.03 (1.79-2.31)
Advanced model + Education, Region & $HbA1_c$	1.21 (0.78-1.88)	1.38 (0.69-2.76)	2.17 (1.51-3.11)	3.05 (1.93-4.84)
Basic model + WHR, Sclass & Region	1.21 (1.04-1.40)	1.24 (1.02-1.52)	1.75 (1.56-1.97)	1.85 (1.58-2.16)
Basic model + WHR, Sclass, Region & $HbA1_c$	1.23 (0.80-1.88)	1.19 (0.61-2.31)	2.10 (1.48-2.99)	2.52 (1.55-4.08)
Basic model + WHR, Education & Region	1.20 (1.03-1.39)	1.24 (1.01-1.52)	1.76 (1.57-1.98)	1.84 (1.57-2.16)
Basic model + WHR, Education, Region & $HbA1_c$	1.23 (0.80-1.88)	1.10 (0.56-2.17)	2.09 (1.47-2.97)	2.45 (1.51-3.95)
Basic model + WC, Sclass, Region	1.21 (1.04-1.40)	1.28 (1.05-1.57)	1.78 (1.59-2.00)	1.90 (1.62-2.22)
Basic model + WC, Sclass, Region & $HbA1_c$	1.20 (0.78-1.84)	1.22 (0.63-2.37)	2.11 (1.49-3.00)	2.50 (1.55-4.05)
Basic model + WC, Education & Region	1.19 (1.03-1.39)	1.28 (1.04-1.56)	1.79 (1.6-2.01)	1.89 (1.62-2.21)
Basic model + WC, Education, Region & $HbA1_c$	1.20 (0.79-1.84)	1.13 (0.57-2.21)	2.09 (1.48-2.97)	2.43 (1.50-3.91)

In order to explore potential differences in cause-specific mortality risk between the sexes, the above analyses were re-run stratified by sex. Within each of the models, women with diabetes had an excess in cancer-related mortality compared with women without diabetes (of particular note is that this increase remained even after adjustment for raised $HbA1_c$: 2.45, CI 1.24-4.86). For men the increase in odds of dying from cancer persisted within each of the models (apart from the one which included adjustment for $HbA1_C$). Among women with diabetes, an increased odds of dying of respiratory disease was found; within the model that adjusted for $HbA1_C$ there was an increase at the point estimate, but this was not statistically significant (1.58, CI 0.59-4.22). As can be seen from Table 7-7, for both men and women with diabetes the odds of mortality from CVD were substantially increased and close to doubled. For men the association between diabetes and mortality from

respiratory disease was increased within the vast majority of models; although within the basic, advanced and $HbA1_C$ models the increase was not statistically significant. The excess in mortality among those with diabetes from 'other' causes remained within each of the models for both men and women.

Analyses then explored the impact that utilising different measurement of overweight and obesity (waist-to-hip ratio and waist circumference) would have upon the association. Table 7-7 illustrates that for women with diabetes, only within one of these models was the association with cancer mortality statistically significant (basic + CVD: OR 1.28, CI 1.07-1.53). However, for the other causes of mortality among women with diabetes, the excess remained within each of these models. Among men there was a point estimate increased odds of mortality from cancer and respiratory disease, but these were not statistically significant within any of these advanced models. The ORs for CVD and 'other' causes remained substantially increased following adjustment for alternative measurements of overweight and obesity. Table 7-9 gives information pertaining to stratified analyses that excluded adjustment for measurements of overweight and obesity. For women the increased odds of cause-specific mortality remained within each of these models, only for respiratory disease (and when the model included adjustment for $HbA1_C$) was there an increased OR that appeared to be non-significant. Among men there was an excess of mortality from cancer, although the confidence interval suggested that this was not statistically significant when adjustment included $HbA1_C$. Further to this, there were point estimate increases for respiratory disease and statistically significant increased odds for mortality from cardiovascular disease and 'other' causes.

Adjustment was then made which included a number of covariates within each model. As can be seen from Table 7-10 and Table 7-11, the increase in cancer-specific mortality differed between men and women with diabetes (as with the earlier models). For example, for women the ORs were increased within each of the models that adjusted for $HbA1_C$, while for men with diabetes the majority of the models (that did or did not include comorbid CVD) found an increase at the point estimate that was not statistically significant. For the other causes of death, including a number of covariates had little impact upon the ORs that had been produced within the earlier models.

Table 7-7: Cause-specific mortality odds ratios (and 95% CI) among those with diabetes (stratified by sex)

PROGRESSIVE ADJUSTMENT	Women				Men			
	Cancer	**Respiratory**	**CVD**	**Other**	**Cancer**	**Respiratory**	**CVD**	**Other**
Age, sex	1.27 (1.07-1.51)	1.29 (1.05-1.60)	1.83 (1.61-2.07)	1.71 (1.46-2.00)	1.19 (1.02-1.38)	1.09 (0.89-1.34)	1.94 (1.73-2.17)	2.30 (1.98-2.68)
& Smoking	1.33 (1.12-1.59)	1.38 (1.12-1.71)	1.92 (1.69-2.18)	1.80 (1.54-2.11)	1.21 (1.03-1.40)	1.14 (0.93-1.41)	1.99 (1.78-2.24)	2.36 (2.03-2.75)
& BMI	1.27 (1.05-1.54)	1.41 (1.09-1.82)	1.92 (1.67-2.22)	1.72 (1.43-2.08)	1.25 (1.10-1.47)	1.37 (1.10-1.71)	1.95 (1.72-2.22)	2.51 (2.13-2.96)
Basic + CVD status	1.28 (1.07-1.53)	1.36 (1.09-1.68)	1.72 (1.51-1.95)	1.78 (1.52-2.09)	1.14 (0.98-1.33)	1.10 (0.89-1.35)	1.70 (1.51-1.91)	2.26 (1.94-2.64)
Additional adjustment (Advanced model + the following variables)								
+ CVD	1.22 (1.00-1.48)	1.36 (1.05-1.76)	1.72 (1.49-1.99)	1.68 (1.39-2.03)	1.18 (1.01-1.39)	1.31 (1.05-1.64)	1.67 (1.47-1.90)	2.39 (2.02-2.82)
+ Education	1.22 (1.00-1.48)	1.37 (1.06-1.77)	1.88 (1.63-2.16)	1.68 (1.39-2.02)	1.21 (1.03-1.43)	1.32 (1.06-1.65)	1.91 (1.68-2.16)	2.43 (2.05-2.86)
+ Social Class	1.26 (1.04-1.52)	1.37 (1.06-1.77)	1.88 (1.63-2.18)	1.69 (1.40-2.04)	1.25 (1.06-1.47)	1.37 (1.09-1.70)	1.94 (1.71-2.20)	2.49 (2.11-2.94)
+ Region	1.25 (1.03-1.52)	1.41 (1.09-1.83)	1.91 (1.65-2.21)	1.74 (1.44-2.11)	1.25 (1.06-1.47)	1.39 (1.11-1.73)	1.95 (1.72-2.21)	2.49 (2.11-2.95)
+ $HbA1_c$	2.45 (1.24-4.86)	1.58 (0.59-4.22)	1.94 (1.08-3.50)	2.56 (1.13-5.80)	0.73 (0.39-1.35)	1.44 (0.53-3.94)	2.55 (1.56-4.17)	4.07 (2.20-7.52)

Table 7-8: Cause-specific mortality ORs (adjusting for alternative measures of overweight and obesity) stratified by sex

Additional adjustment	Women				Men			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Basic + BMI	1.27 (1.05-1.54)	1.41 (1.09-1.82)	1.92 (1.67-2.22)	1.72 (1.43-2.08)	1.25 (1.10-1.47)	1.37 (1.10-1.71)	1.95 (1.72-2.22)	2.51 (2.13-2.96)
Basic + WHR	1.25 (0.99-1.58)	1.50 (1.12-2.01)	1.81 (1.52-2.16)	1.73 (1.37-2.19)	1.18 (0.97-1.44)	1.11 (0.84-1.46)	1.75 (1.50-2.05)	2.03 (1.64-2.51)
Basic + WC	1.25 (0.99-1.58)	1.50 (1.12-2.02)	1.83 (1.53-2.18)	1.76 (1.39-2.22)	1.20 (0.99-1.46)	1.15 (0.88-1.52)	1.81 (1.55-2.10)	2.10 (1.70-2.59)
Basic + WHR & CVD	1.21 (0.96-1.54)	1.46 (1.09-1.97)	1.62 (1.36-1.94)	1.70 (1.35-2.15)	1.15 (0.94-1.40)	1.07 (0.81-1.42)	1.53 (1.31-1.78)	1.95 (1.57-2.41)
Basic + WC & CVD	1.21 (0.96-1.53)	1.47 (1.09-1.98)	1.64 (1.37-1.96)	1.73 (1.37-2.19)	1.16 (0.95-1.41	1.11 (0.84-1.47)	1.56 (1.33-1.82)	2.00 (1.62-2.48)

Table 7-9: Cause-specific mortality ORs among diabetic cases (without adjustment for overweight and obesity) stratified by sex

Additional adjustment	Women				Men			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Basic + Education	1.27 (1.06-1.51)	1.34 (1.08-1.66)	1.87 (1.65-2.12)	1.75 (1.49-2.05)	1.16 (1.00-1.35)	1.10 (0.89-1.35)	1.94 (1.73-2.18)	2.27 (1.95-2.65)
Basic + Social Class	1.31 (1.10-1.57)	1.33 (1.07-1.65)	1.86 (1.64-2.12)	1.75 (1.50-2.06)	1.20 (1.03-1.39)	1.13 (0.92-1.39)	1.98 (1.76-2.22)	2.34 (2.01-2.72)
Basic + Region	1.34 (1.12-1.60)	1.44 (1.15-1.79)	1.96 (1.72-2.23)	1.78 (1.51-2.11)	1.21 (1.04-1.41)	1.18 (0.96-1.45)	2.00 (1.78-2.24)	2.32 (1.98-2.71)
Basic + $HbA1_c$	2.14 (1.12-4.07)	1.27 (0.52-3.09)	1.96 (1.15-3.35)	2.96 (1.48-5.91)	0.79 (0.44-1.40)	1.31 (0.51-3.33)	2.76 (1.74-4.36)	3.70 (2.02-6.77)

Table 7-10: Cause-specific mortality ORs among cases with diabetes (further adjustment) stratified by sex

Additional adjustment	Women				Men			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Advanced Model + Sclass, Region & CVD	1.20 (0.99-1.46)	1.32 (1.02-1.72)	1.67 (1.44-1.94)	1.66 (1.37-2.01)	1.17 (1.00-1.38)	1.32 (1.06-1.65)	1.65 (1.45-1.88)	2.35 (1.98-2.78)
Advanced Model + Sclass, Region, CVD & $HbA1_c$	2.29 (1.19-4.41)	1.69 (0.66-4.33)	1.95 (1.11-3.44)	2.49 (1.15-5.39)	0.73 (0.40-1.33)	1.30 (0.48-3.47)	1.98 (1.23-3.20)	3.02 (1.69-5.41)
Advanced Model + Education, Region & CVD	1.17 (0.96-1.42)	1.33 (1.03-1.73)	1.67 (1.45-1.94)	1.65 (1.36-2.00)	1.14 (0.97-1.35)	1.29 (1.03-1.61)	1.63 (1.43-1.85)	2.30 (1.94-2.72)
Advanced Model + Education, Region, CVD & $HbA1_c$	2.27 (1.18-4.36)	1.64 (0.64-4.19)	1.94 (1.10-3.42)	2.49 (1.15-5.38)	0.73 (0.40-1.33)	1.17 (0.42-3.29)	1.95 (1.21-3.14)	2.91 (1.63-5.20)
Basic Model + Waist/Hip, Sclass, Region & CVD	1.19 (0.94-1.51)	1.38 (1.03-1.86)	1.58 (1.32-1.89)	1.66 (1.31-2.10)	1.15 (0.94-1.40)	1.07 (0.81-1.42)	1.52 (1.30-1.77)	1.96 (1.58-2.42)
Basic Model + Waist/Hip, Sclass, Region, CVD & $HbA1_c$	1.91 (1.01-3.60)	1.24 (0.50-3.08)	1.78 (1.03-3.08)	2.17 (1.02-4.61)	0.84 (0.47-1.49)	1.13 (0.43-2.96)	2.01 (1.27-3.20)	2.49 (1.32-4.69)
Basic Model + Waist/Hip, Education, Region & CVD	1.19 (0.94-1.51)	1.43 (1.06-1.93)	1.62 (1.36-1.94)	1.68 (1.33-2.12)	1.13 (0.93-1.38)	1.05 (0.79-1.38)	1.52 (1.30-1.77)	1.94 (1.57-2.40)
Basic Model + Waist/Hip, Education, Region, CVD & $HbA1_c$	1.93 1.02-3.63)	1.23 (0.50-3.05)	1.77 (1.03-3.06)	2.16 (1.02-4.56)	0.84 (0.47-1.49)	1.01 (0.37-2.77)	1.99 (1.25-3.15)	2.39 (1.28-4.49)
Basic Model + Waist Circ, Sclass, Region & CVD	1.18 (0.93-1.50)	1.39 (1.03-1.88)	1.59 (1.33-1.90)	1.69 (1.33-2.13)	1.16 (0.95-1.41)	1.10 (0.84-1.46)	1.54 (1.32-1.80)	2.00 (1.62-2.48)
Basic Model + Waist Circ, Sclass, Region, CVD & $HbA1_c$	1.92 (1.02-3.63)	1.29 (0.52-3.20)	1.78 (1.03-3.08)	2.14 (1.01-4.54)	0.81 (0.46-1.43)	1.15 (0.44-3.00)	2.01 (1.27-3.19)	2.47 (1.32-4.64)
Basic Model + Waist Circ, Education, Region & CVD	1.18 (0.93-1.50)	1.43 (1.06-1.93)	1.63 (1.37-1.96)	1.70 (1.34-2.15)	1.14 (0.93-1.39)	1.08 (0.82-1.42)	1.54 (1.32-1.80)	1.98 (1.60-2.46)
Basic Model + Waist Circ, Education, Region, CVD & $HbA1_c$	1.94 (1.03-3.67)	1.28 (0.51-3.17)	1.77 (1.03-3.05)	2.12 (1.00-4.48)	0.81 (0.46-1.43)	1.02 (0.37-2.81)	1.98 (1.25-3.14)	2.37 (1.27-4.44)

Table 7-11: ORs cause-specific mortality (no adjustment for CVD at baseline) stratified by sex

Additional adjustment	Women				Men			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Advanced model + Sclass & Region	1.24 (1.02-1.51)	1.37 (1.05-1.77)	1.87 (1.62-2.17)	1.71 (1.42-2.07)	1.25 (1.06-1.47)	1.39 (1.11-1.73)	1.94 (1.71-2.20)	2.48 (2.09-2.93)
Advanced model + Sclass, Region & $HbA1_c$	2.31 (1.21-4.44)	1.77 (0.69-4.53)	2.09 (1.18-3.69)	2.58 (1.19-5.60)	0.78 (0.43-1.42)	1.40 (0.52-3.73)	2.34 (1.46-3.76)	3.51 (1.97-6.25)
Advanced model + Education, Region	1.21 (0.99-1.46)	1.37 (1.06-1.78)	1.87 (1.61-2.16)	1.70 (1.41-2.05)	1.21 (1.03-1.42)	1.34 (1.07-1.67)	1.90 (1.68-2.16)	2.41 (2.04-2.86)
Advanced model + Education, Region & $HbA1_c$	2.29 (1.20-4.39)	1.72 (0.67-4.38)	2.07 (1.18-3.65)	2.58 (1.19-5.58)	0.78 (0.43-1.41)	1.25 (0.45-3.50)	2.30 (1.44-3.69)	3.36 (1.89-5.97)
Basic model + WHR, Sclass & Region	1.22 (0.97-1.55)	1.41 (1.05-1.90)	1.75 (1.47-2.10)	1.69 (1.34-2.13)	1.18 (0.97-1.44)	1.11 (0.84-1.47)	1.75 (1.50-2.04)	2.04 (1.65-2.52)
Basic model + WHR, Sclass, Region & $HbA1_c$	1.93 (1.03-3.63)	1.27 (0.51-3.14)	1.91 (1.11-3.30)	2.23 (1.05-4.72)	0.87 (0.49-1.54)	1.19 (0.45-3.09)	2.34 (1.48-3.70)	2.82 (1.51-5.28)
Basic model + WHR, Education & Region	1.22 (0.97-1.54)	1.46 (1.08-1.96)	1.80 (1.51-2.16)	1.70 (1.35-2.15)	1.16 (0.96-1.42)	1.08 (0.82-1.43)	1.74 (1.49-2.03)	2.01 (1.63-2.50)
Basic model + WHR, Education, Region & $HbA1_c$	1.95 (1.04-3.67)	1.26 (0.51-3.11)	1.89 (1.10-3.26)	2.21 (1.05-4.66)	0.87 (0.49-1.54)	1.05 (0.39-2.87)	2.31 (1.46-3.65)	2.71 (1.45-5.06)
Basic model + WC, Sclass, Region	1.21 (0.96-1.54)	1.42 (1.06-1.91)	1.77 (1.48-2.11)	1.71 (1.36-2.16)	1.19 (0.98-1.45)	1.15 (0.87-1.51)	1.79 (1.54-2.09)	2.10 (1.70-2.60)
Basic model + WC, Sclass, Region & $HbA1_c$	1.95 (1.03-3.68)	1.32 (0.53-3.28)	1.91 (1.11-3.30)	2.19 (1.03-4.66)	0.84 (0.47-1.48)	1.20 (0.46-3.15)	2.34 (1.48-3.70)	2.81 (1.50-5.24)
Basic model + WC, Education & Region	1.21 (0.96-1.53)	1.46 (1.08-1.96)	1.81 (1.52-2.17)	1.73 (1.37-2.18)	1.17 (0.96-1.43)	1.12 (0.85-1.48)	1.78 (1.53-2.08)	2.07 (1.68-2.56)
Basic model + WC, Education, Region & $HbA1_c$	1.97 (1.05-3.71)	1.31 (0.53-3.25)	1.89 (1.10-3.27)	2.17 (1.03-4.58)	0.84 (0.48-1.48)	1.07 (0.39-2.92)	2.31 (1.46-3.64)	2.69 (1.44-5.00)

Analyses then explored whether or not those with diabetes and comorbid CVD had differences in cause-specific mortality risk compared to those without the former, but without the latter. As can be seen from Table 7-12, those with diabetes but not comorbid CVD had an excess risk of cancer mortality compared with those without diabetes. This increase remained statistically significant until $HbA1_C$ was adjusted for. The same was found for mortality from respiratory disease, while for CVD and 'other' causes of mortality the excess remained significant within each of the models. For those with diabetes and comorbid CVD there were point estimate increases in ORs for cancer and respiratory disease and statistically significant increases, within each of the models, for mortality from CVD and 'other' causes. When adjustment included different measurement of overweight and obesity (waist-to-hip ratio and waist circumference) the excess in mortality from cancer was raised at the point estimate, but appeared not to be significant. The excess mortality from respiratory disease remained when adjustment was made for waist circumference but not waist-to-hip ratio. For CVD and mortality from 'other' causes the ORs remained raised among those with diabetes and comorbid CVD compared with those with diabetes only. Among diabetics with comorbid CVD there were statistically significant increases for mortality from CVD and 'other' causes within each of the initial models.

Covariates related to socioeconomic and demographic information were then adjusted for. The results are given in Table 7-14 and indicate that those with diabetes and comorbid CVD were found to have an excess in each of the specific causes of mortality; only within the model that adjusted for $HbA1_C$ did the ORs and/or confidence intervals suggest that the association was not statistically significant. Among those with diabetes, who also indicated comorbid CVD there were increased ORs for each cause but the association only appeared statistically significant for CVD and 'other' causes. Because the analyses were stratified by CVD, adjustment was not made for this variable within this section. Further analyses included a range of covariates within each model. As can be seen from Table 7-15, among those without comorbid CVD there was a point estimate increase for mortality from cancer and respiratory disease and statistically significant increases for CVD and 'other' causes. Among those with CVD, there were mixed results for each cause of mortality.

Table 7-12: Cause-specific mortality odds ratios (and 95% CI) among those with diabetes (stratified by CVD status)

PROGRESSIVE ADJUSTMENT	**Did not indicate CVD at baseline**				**Indicated CVD at baseline**			
	Cancer	**Respiratory**	**CVD**	**Other**	**Cancer**	**Respiratory**	**CVD**	**Other**
Age, sex	1.22 (1.05-1.41)	1.18 (0.97-1.42)	1.81 (1.61-2.03)	2.04 (1.77-2.34)	1.03 (0.86-1.24)	1.05 (0.83-1.33)	1.37 (1.22-1.55)	1.63 (1.36-1.96)
& Smoking	1.26 (1.09-1.46)	1.26 (1.04-1.52)	1.90 (1.69-2.14)	2.13 (1.86-2.45)	1.06 (0.88-1.27)	1.09 (0.86-1.38)	1.40 (1.24-1.59)	1.67 (1.39-2.00)
& BMI	1.27 (1.08-1.48)	1.40 (1.13-1.73)	1.91 (1.67-2.17)	2.18 (1.86-2.55)	1.11 (0.91-1.35)	1.23 (0.95-1.61)	1.45 (1.26-1.66)	1.71 (1.40-2.10)
Additional adjustment (Advanced model + the following variables)								
+ Education	1.22 (1.04-1.44)	1.36 (1.10-1.69)	1.86 (1.63-2.12)	2.12 (1.81-2.49)	1.09 (0.89-1.33)	1.20 (0.92-1.57)	1.43 (1.25-1.64)	1.67 (1.37-2.05)
+ Social Class	1.26 (1.07-1.48)	1.37 (1.11-1.71)	1.89 (1.66-2.15)	2.16 (1.84-2.52)	1.10 (0.90-1.34)	1.22 (0.94-1.60)	1.44 (1.26-1.65)	1.70 (1.39-2.08)
+ Region	1.25 (1.07-1.47)	1.42 (1.15-1.77)	1.92 (1.68-2.19)	2.18 (1.86-2.56)	1.11 (0.91-1.35)	1.23 (0.94-1.61)	1.42 (1.24-1.63)	1.70 1.39-2.09)
+ $HbA1_c$	1.02 (0.55-1.90)	2.09 (0.86-5.07)	2.70 (1.62-4.5)	2.75 (1.39-5.42)	1.33 (0.64-2.76)	0.74 (0.24-2.27)	1.42 (0.81-2.47)	3.51 (1.71-7.2)

Table 7-13: Cause-specific mortality ORs (adjusting for alternative measures of overweight and obesity) stratified by CVD status

Additional adjustment	Did not indicate CVD at baseline				Indicated CVD at baseline			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Basic + WHR	1.21 (0.99-1.47)	1.28 (0.98-1.66)	1.70 (1.45-2.01)	1.79 (1.46-2.20)	1.12 (0.88-1.42)	1.16 (0.84-1.58)	1.38 (1.17-1.62)	1.78 (1.39-2.28)
Basic + WC	1.21 (0.99-1.47)	1.33 (1.03-1.73)	1.76 (1.49-2.07)	1.86 (1.51-2.28)	1.13 (0.89-1.43)	1.15 (0.84-1.58)	1.38 (1.17-1.62)	1.81 (1.41-2.32)

Table 7-14: Cause-specific mortality ORs among diabetic cases (without adjustment for overweight and obesity) stratified by CVD status

Additional adjustment	Did not indicate CVD at baseline				Indicated CVD at baseline			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Basic + Education	1.21 (1.04-1.41)	1.22 (1.01-1.48)	1.85 (1.64-2.09)	2.08 (1.81-2.38)	1.04 (0.87-1.25)	1.06 (0.84-1.35)	1.39 (1.23-1.57)	1.63 (1.36-1.95)
Basic + Social Class	1.25 (1.08-1.45)	1.23 (1.01-1.49)	1.87 (1.66-2.11)	2.10 (1.83-2.42)	1.05 (0.87-1.26)	1.08 (0.85-1.37)	1.39 (1.23-1.57)	1.65 (1.38-1.98)
Basic + Region	1.27 (1.09-1.47)	1.34 (1.10-1.63)	1.95 (1.73-2.20)	2.07 (1.79-2.39)	1.07 (0.89-1.28)	1.07 (0.84-1.36)	1.39 (1.23-1.57)	1.68 (1.39-2.01)
Basic + $HbA1_c$	0.99 (0.58-1.77)	1.74 (0.79-3.87)	2.85 (1.78-4.57)	2.78 (1.51-5.13)	1.45 (0.74-2.83)	0.65 (0.22-1.92)	1.44 (0.86-2.41)	3.47 (1.75-6.88)

Table 7-15: ORs cause-specific mortality (no adjustment for CVD at baseline) stratified by CVD status

Additional adjustment	Did not indicate CVD at baseline				Indicated CVD at baseline			
	Cancer	**Respiratory**	**CVD**	**Other**	**Cancer**	**Respiratory**	**CVD**	**Other**
Advanced model + Sclass & Region	1.25 (1.06-1.47)	1.40 (1.13-1.74)	1.90 (1.66-2.17)	2.16 (1.84-2.53)	1.10 (0.90-1.34)	1.22 (0.93-1.60)	1.41 (1.23-1.62)	1.69 (1.38-2.07)
Advanced model + Sclass, Region & $HbA1_c$	1.07 (0.59-1.93)	2.03 (0.87-4.73)	2.63 (1.62-4.27)	2.68 (1.44-4.99)	1.23 (0.61-2.49)	0.76 (0.25-2.34)	1.28 (0.75-2.20)	2.96 (1.46-6.01)
Advanced model + Education, Region	1.21 (1.03-1.43)	1.39 (1.12-1.73)	1.88 (1.64-2.14)	2.12 (1.81-2.49)	1.09 (0.90-1.33)	1.20 (0.92-1.57)	1.41 (1.23-1.61)	1.67 (1.36-2.05)
Advanced model + Education, Region & $HbA1_c$	1.07 (0.59-1.93)	2.03 (0.87-4.71)	2.57 (1.59-4.18)	2.63 (1.42-4.88)	1.23 (0.61-2.48)	0.64 (0.20-2.06)	1.29 (0.75-2.22)	2.88 (1.43-5.81)
Basic model + WHR, Sclass & Region	1.20 (0.98-1.45)	1.25 (0.96-1.62)	1.68 (1.42-1.98)	1.76 (1.43-2.16)	1.11 (0.87-1.41)	1.13 (0.82-1.56)	1.38 (1.17-1.62)	1.77 (1.38-2.27)
Basic model + WHR, Sclass, Region & $HbA1_c$	1.06 (0.60-1.87)	1.66 (0.74-3.73)	2.49 (1.56-3.99)	2.10 (1.10-4.02)	1.38 (0.70-2.72)	0.59 (0.19-1.85)	1.29 (0.77-2.19)	2.68 (1.28-5.62)
Basic model + WHR, Education & Region	1.18 (0.97-1.44)	1.26 (0.97-1.64)	1.69 (1.44-1.99)	1.77 (1.44-2.17)	1.11 (0.88-1.41)	1.12 (0.81-1.54)	1.40 (1.19-1.65)	1.75 (1.37-2.25)
Basic model + WHR, Education, Region & $HbA1_c$	1.07 (0.61-1.89)	1.66 (0.75-3.70)	2.49 (1.56-3.98)	2.07 (1.09-3.94)	1.38 (0.70-2.69)	0.46 (0.14-1.59)	1.31 (0.78-2.20)	2.56 (1.23-5.35)
Basic model + WC, Sclass, Region	1.19 (0.98-1.45)	1.30 (1.00-1.69)	1.72 (1.47-2.03)	1.82 (1.48-2.23)	1.12 (0.88-1.42)	1.12 (0.81-1.54)	1.37 (1.17-1.62)	1.79 (1.40-2.30)
Basic model + WC, Sclass, Region & $HbA1_c$	1.03 (0.58-1.81)	1.69 (0.75-3.79)	2.49 (1.56-3.99)	2.10 (1.10-4.00)	1.37 (0.70-2.69)	0.60 (0.19-1.92)	1.29 (0.76-2.17)	2.63 (1.26-5.51)
Basic model + WC, Education & Region	1.18 (0.97-1.43)	1.31 (1.01-1.70)	1.74 (1.48-2.04)	1.83 (1.49-2.24)	1.12 (0.88-1.42)	1.11 (0.80-1.53)	1.39 (1.18-1.64)	1.77 (1.38-2.27)
Basic model + WC, Education, Region & $HbA1_c$	1.04 (0.59-1.83)	1.69 (0.76-3.77)	2.48 (1.55-3.96)	2.06 (1.08-3.91)	1.36 (0.70-2.65)	0.78 (0.14-1.6)	1.30 (0.77-2.19)	2.51 (1.21-5.23)

To remove the impact of further confounding caused by smoking, sensitivity analysis was carried out which included only those cases who indicated they had never been a regular smoker (n=98,107). For cancer the OR was increased for those with diabetes within the 'basic' model (1.27, CI 1.02-1.59), but not when CVD was added (1.24, CI 0.99-1.55). The 'advanced' model was not utilised within the sensitivity analysis as it included adjustment for smoking status. The ORs for respiratory disease, CVD and 'other' causes, among those with diabetes, were significantly increased compared with those without the disease.

Within the models that included education, socioeconomic class and region, those with diabetes had an increased risk for every cause of mortality. The multinomial logistic regression model, which included adjustment for $HbA1_C$, resulted in mortality only from 'other' causes having a statistically significant increased OR (3.47, CI 1.50-8.02); although for respiratory disease and CVD there was an increase at the point estimate.

Table 7-16: Cause-specific mortality odds ratios (and 95% CI) among those with diabetes (sensitivity analysis)

PROGRESSIVE ADJUSTMENT	**Indicated never regular-smoker**			
	Cancer	**Respiratory**	**CVD**	**Other**
Age, sex	1.31 (1.07-1.61)	1.46 (1.12-1.90)	1.96 (1.70-2.26)	1.88 (1.58-2.25)
& Smoking[a]	N/A	N/A	N/A	N/A
& BMI	1.27 (1.02-1.59)	1.54 (1.14-2.08)	1.93 (1.65-2.26)	1.91 (1.57-2.33)
Basic + CVD status	1.28 (1.04-1.57)	1.46 (1.12-1.90)	1.78 (1.54-2.05)	1.90 (1.59-2.27)
Additional adjustment (Advanced model + the following variables)				
+ CVD	1.24 (0.99-1.55)	1.53 (1.13-2.08)	1.76 (1.50-2.06)	1.90 (1.56-2.22)
+ Education	1.25 (1.00-1.57)	1.51 (1.11-2.04)	1.90 (1.62-2.22)	1.86 (1.52-2.27)
+ Social Class	1.26 (1.01-1.58)	1.50 (1.11-2.03)	1.90 (1.62-2.22)	1.87 (1.53-2.28)
+ Region	1.28 (1.02-1.60)	1.51 (1.11-2.06)	1.92 (1.64-2.25)	1.90 (1.55-2.33)
+ $HbA1_c$	0.83 (0.33-2.10)	1.13 (0.29-4.47)	1.42 (0.75-2.71)	3.47 (1.50-8.02)

[a] Because the sensitivity analyses only included those who indicated never regular-smoking this variable was excluded from the analyses.

The analyses then included the alternative measurements for overweight and obesity. Although the OR among diabetic never regular-smokers was raised compared with those without diabetes when the model included BMI, as can be seen from Table 7-17 this was not the case when either waist-to-hip ratio or waist circumference were included. For each of the other causes of mortality the ORs were increased within each step of the additional adjustment.

Table 7-17: Cause-specific mortality ORs (adjusting for alternative measures of overweight and obesity)

Additional adjustment	**Indicated never regular-smoker**			
	Cancer	**Respiratory**	**CVD**	**Other**
Basic + BMI	1.27 (1.02-1.59)	1.54 (1.14-2.08)	1.93 (1.65-2.26)	1.91 (1.57-2.33)
Basic + Waist-Hip Ratio	1.23 (0.94-1.62)	1.58 (1.11-2.25)	1.78 (1.46-2.16)	1.91 (1.48-2.46)
Basic + WHR & CVD	1.21 (0.92-1.60)	1.55 (1.08-2.20)	1.63 (1.34-1.98)	1.89 (1.47-2.44)
Basic + Waist Circumference	1.19 (0.90-1.57)	1.57 (1.10-2.23)	1.78 (1.46-2.16)	1.91 (1.49-2.46)
Basic + WC & CVD	1.17 (0.89-1.55)	1.54 (1.08-2.20)	1.63 (1.34-1.98)	1.90 (1.47-2.45)

As with the previous analyses undertaken, models were then utilised that took into account a range of socioeconomic/demographic covariates in order to understand whether they had an impact upon the association between diabetes and cause-specific mortality. Within Table 7-18 it can be seen that those with diabetes had a statistically significant excess in mortality from cancer when education, social class and region were added to the basic model. This excess disappeared when $HbA1_C$ was adjusted for. For the other causes of death there were point estimates increase, which within the majority of models were statistically significant; only the inclusion of $HbA1_C$ removed the significance.

Table 7-18: Cause-specific mortality ORs among diabetic cases (without adjustment for overweight and obesity) sensitivity analysis

Additional adjustment	Indicated never regular-smoker			
	Cancer	Respiratory	CVD	Other
Basic + Education	1.28 (1.04-1.57)	1.43 (1.10-1.86)	1.92 (1.67-2.21)	1.83 (1.54-2.19)
Basic + Social Class	1.29 (1.05-1.59)	1.42 (1.09-1.85)	1.91 (1.66-2.21)	1.84 (1.54-2.19)
Basic + Region	1.32 (1.07-1.63)	1.48 (1.12-1.94)	1.99 (1.73-2.30)	1.88 (1.56-2.26)
Basic + $HbA1_c$	0.92 (0.39-2.17)	1.00 (0.27-3.78)	1.59 (0.87-2.88)	3.86 (1.84-8.10)

Table 7-19: Cause-specific mortality ORs among cases with diabetes (further adjustment) sensitivity analysis

Additional adjustment	**Indicated never regular-smoker**			
	Cancer	**Respiratory**	**CVD**	**Other**
Advanced Model + Sclass, Region & CVD	1.23 (0.98-1.55)	1.46 (1.07-2.00)	1.72 (1.46-2.02)	1.84 (1.49-2.26)
Advanced Model + Sclass, Region, CVD & $HbA1_c$	0.82 (0.33-2.02)	1.19 (0.31-4.61)	1.40 (0.75-2.63)	3.14 (1.40-7.06)
Advanced Model + Education, Region & CVD	1.22 (0.98-1.53)	1.48 (1.08-2.03)	1.72 (1.47-2.02)	1.83 (1.49-2.25)
Advanced Model + Education, Region, CVD & $HbA1_c$	0.82 (0.33-2.03)	1.09 (0.29-4.15)	1.34 (0.71-2.52)	3.18 (1.43-7.04)
Basic Model + Waist/Hip, Sclass, Region & CVD	1.20 (0.91-1.58)	1.46 (1.01-2.09)	1.58 (1.30-1.93)	1.84 (1.43-2.38)
Basic Model + Waist/Hip, Sclass, Region, CVD & $HbA1_c$	0.92 (0.40-2.12)	1.14 (0.30-4.29)	1.49 (0.81-2.75)	2.97 (1.34-6.60)
Basic Model + Waist/Hip, Education, Region & CVD	1.22 (0.93-1.61)	1.51 (1.06-2.17)	1.62 (1.33-1.97)	1.88 (1.46-2.42)
Basic Model + Waist/Hip, Education, Region, CVD & $HbA1_c$	0.95 (0.42-2.19)	1.05 (0.28-3.94)	1.46 (0.79-2.70)	2.99 (1.37-6.53)
Basic Model + Waist Circ, Sclass, Region & CVD	1.16 (0.88-1.53)	1.45 (1.01-2.08)	1.58 (1.29-1.92)	11.84 (1.43-2.38)
Basic Model + Waist Circ, Sclass, Region, CVD & $HbA1_c$	0.87 (0.38-2.02)	1.12 (0.30-4.21)	1.48 (0.81-2.72)	2.93 (1.32-6.50)
Basic Model + Waist Circ, Education, Region & CVD	1.18 (0.89-1.56)	1.51 (1.05-2.16)	1.61 (1.33-1.97)	1.88 (1.46-2.42)
Basic Model + Waist Circ, Education, Region, CVD & $HbA1_c$	0.91 (0.40-2.10)	1.04 (0.28-3.90)	1.44 (0.78-2.66)	2.92 (1.34-6.39)

Table 7-20: Cause-specific mortality ORs (no adjustment for comorbid CVD) sensitivity analysis

Additional adjustment	Indicated never regular-smoker			
	Cancer	**Respiratory**	**CVD**	**Respiratory**
Advanced model + Sclass & Region	1.27 (1.01-1.59)	1.47 (1.07-2.00)	1.89 (1.61-2.22)	1.86 (1.52-2.28)
Advanced model + Sclass, Region & $HbA1_c$	0.86 (0.35-2.13)	1.24 (0.32-4.80)	1.53 (0.82-2.86)	3.27 (1.46-7.32)
Advanced model + Education, Region	1.26 (1.00-1.57)	1.48 (1.09-2.02)	1.89 (1.61-2.22)	1.85 (1.51-2.27)
Advanced model + Education, Region & $HbA1_c$	0.87 (0.35-2.14)	1.12 (0.29-4.31)	1.46 (0.78-2.74)	3.30 (1.49-7.31)
Basic model + WHR, Sclass & Region	1.22 (0.92-1.61)	1.48 (1.03-2.12)	1.73 (1.42-2.10)	1.85 (1.44-2.39)
Basic model + WHR, Sclass, Region & $HbA1_c$	0.96 (0.42-2.20)	1.17 (0.31-4.42)	1.60 (0.87-2.92)	3.06 (1.38-6.77)
Basic model + WHR, Education & Region	1.24 (0.94-1.64)	1.54 (1.07-2.20)	1.77 (1.45-2.15)	1.89 (1.47-2.43)
Basic model + WHR, Education, Region & $HbA1_c$	0.99 (0.43-2.27)	1.08 (0.29-4.06)	1.57 (0.85-2.88)	3.08 (1.41-6.72)
Basic model + WC, Sclass, Region	1.17 (0.89-1.55)	1.48 (1.03-2.11)	1.72 (1.42-2.10)	1.85 (1.44-2.39)
Basic model + WC, Sclass, Region & $HbA1_c$	0.91 (0.39-2.09)	1.17 (0.31-4.37)	1.59 (0.87-2.90)	3.02 (1.36-6.68)
Basic model + WC, Education & Region	1.20 (0.91-1.58)	1.53 (1.07-2.19)	1.76 (1.45-2.14)	1.89 (1.46-2.43)
Basic model + WC, Education, Region & $HbA1_c$	0.95 (0.41-2.17)	1.09 (0.29-4.05)	1.55 (0.85-2.85)	3.12 (1.38-6.57)

When analyses included a number of covariates within a single model it appeared that those with diabetes did not have a statistically significant increased excess in cancer mortality, with $HbA1_C$ producing substantial attenuation within each of the models. For respiratory disease and CVD the excess in mortality remained within each of the models that did not include $HbA1_C$, although when $HbA1_C$ was included, the point estimates remained raised. Within each of the additional adjustment models, the ORs for 'other' causes of mortality remained increased. As can be seen from Table 7-20, removing CVD at baseline from the models had little impact upon the ORs for mortality from each of the specific causes.

7.2 Diabetes and cancer-specific mortality (Cox regression and survival analysis)

7.2.1 HSE and SHeS

Binary variables were derived within the Health Survey for England and Scottish Health Survey dataset which included the following information:

- Cancer mortality/Everyone else.

These variables were then used to create survival analysis models in order to explore the associations between diabetes and mortality and produce the Hazard Ratios related to it. The variables required for survival analysis were also derived and these included:

- A censor date variable (this either contained information about date of death or the end of the follow-up period).
- A duration of time in study variable (derived from the baseline interview date and censor date).

Table 7-21 indicates that, within all of the Cox regression models which used date from the HSE and SHeS appended dataset, those with diabetes were at an increased risk of mortality from cancer. The HRs for cancer were increased at the point estimate within each model, only when $HbA1_C$ was adjusted for did the association became statistically non-significant (HR 1.36, CI 0.95-1.94).

Table 7-21: cancer-specific mortality HRs

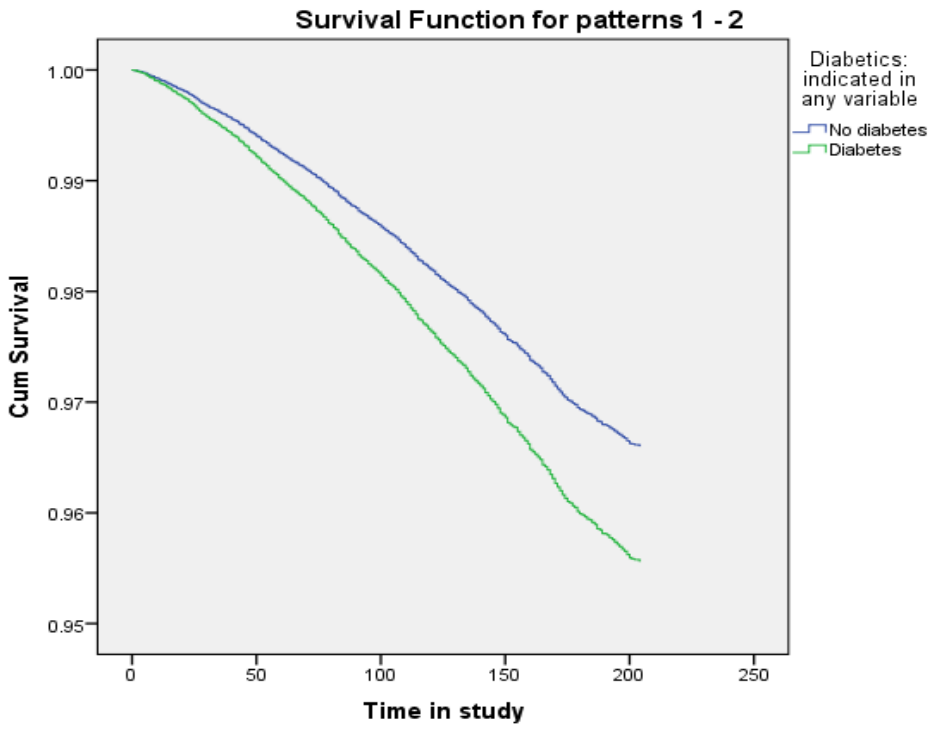
Progressive adjustment	**Cancer**
Age & sex	1.31 (1.18-1.47)
Age, sex & smoking	1.35 (1.21-1.50)
Age, sex, smoking & BMI	1.34 (1.19-1.50)
Age, sex, smoking, BMI & CVD	1.28 (1.14-1.44)
Further adjustment	
Age, sex, smoking, BMI & Education group	1.30 (1.16-1.47)

Age, sex, smoking, BMI & social class	1.34 (1.19-1.50)
Age, sex, smoking, BMI & Region	1.34 (1.19-1.50)
Age, sex, smoking, BMI & $Hba1_c$	1.36 (0.95-1.94)
Age, sex, smoking & waist raised	1.31 (1.14-1.51)
Age, sex, smoking & waist-hip-ratio	1.30 (1.13-1.50)

7.2.2 Survival curve (cancer mortality)

Survival curves were produced for cancer mortality. The HRs and survival curves developed for these analyses further suggest that the association between diabetes and cancer-specific mortality is not significantly altered by a range of confounding factors related to overweight/obesity, socio-demographic and economic confounding factors; although adjusting for $HbA1_C$ does appear to attenuate the association. Survival curves were produced for each of the above models: as the inclusion of other covariates did little to alter the associations between diabetes and all-cause mortality, only those showing the models adjusted for age and sex are shown below

Figure 7-1: Cancer mortality: HSE/SHeS (age and sex)



The results presented within this chapter suggest that, even after adjustment for a range of factors, those with diabetes are at an increased risk of mortality from various different causes and, specifically, from cancer. Further to this, there are differences in the excess mortality experienced by the diabetic cohort dependent upon gender, the presence of comorbid CVD and smoking status. Within the basic and advanced models, those with diabetes were at an increased risk of cancer mortality when analyses included the whole sample, was stratified by either sex or CVD status and within the sensitivity analysis. The odds ratios produced for respiratory disease also suggest that those with diabetes are at an increased risk of mortality from respiratory causes. The results of this study further confirm the substantial increase in mortality from CVD among those with diabetes compared with the general population.

The next section explores the associations between diabetes and site-specific cancer mortality.

8. Chapter 8: Results – diabetes and site-specific cancer mortality

This chapter details the exploration of the associations between diabetes and mortality from site-specific cancer. Utilising the string variable within the HSE and SHeS datasets which gave detailed information about cause of death, the ICD9 and 10 codes for each cause to three digits, it was possible to derive a variable that gave information about mortality from a range of site-specific cancers.

8.1 Diabetes and site-specific cancers: HSE and SHeS

Table 8-1 details the number of deaths from each cancer of interest (by descending order of number of deaths by cause). In total, of the 5,571 cancer deaths within the original all-cause and cause-specific dataset, information about the cancer site was available for 5,455 cases (98% of the total cancer deaths).

Table 8-1: Site-specific cancer mortality (HSE and SHeS)

Site-specific cancer mortality	Diabetic	Did not indicate diabetes	Total
Lung	88	1,209	1,297
Colorectal	34	518	552
Lymphatic[a]	19	354	373
Breast	22	332	354
Prostate	20	327	347
Pancreatic	26	295	321
Oesophagus	15	246	261
Stomach	19	192	211
Bladder	12	156	168
Ovarian	6	159	165
Kidney	11	129	140
Liver	3	79	82
Cervix[b]	3	78	81
Lip	3	62	65
Other cancer	65	973	1,038
TOTAL	346	5,109	5,455

[a] Lymphatic includes haematopoietic cancers and leukaemia.
[b] Cervix includes cancers of the endometrium.
[C] Lip includes cancers of the oral cavity and pharynx.

Initial analyses were performed using multinomial logistic regression with the alive cases comprising the reference category. As can be seen from Table 8-2 those with diabetes had a substantial increase

in odds of dying of pancreatic cancer compared with those without diabetes. This increase remained after adjusting for a range of covariates. There were also point estimate increases for cancers of the colorectum, bladder, stomach, lymphoid, lung, kidney, oesophagus, lip and other cancers. There were also reduced point estimates among those with diabetes for cancers of the liver. Because of the small number of site-specific cancer deaths among those with a measurement of glycated haemoglobin there was insufficient power to detect the effect that diagnosed diabetes had upon mortality, when adjustment included $HbA1_C$, and therefore glycated haemoglobin was not included within the regression models. Further analyses were undertaken which included waist circumference and waist-to-hip ratio as alternative measurements of overweight and obesity. Their inclusion had little impact upon the results (not shown).

Analyses were then stratified by sex, to allow for an exploration of sex-specific associations between diabetes and cancer, as well as associations with sex-specific cancers. For men there was a substantial excess in the odds of dying of pancreatic cancer among those with diabetes; this increase was maintained within each of the regression models. There were also substantial increases in odds of dying of stomach cancer among men with diabetes, which became statistically significant within the advanced model. There were also raised point estimates for a number of other site-specific cancers, while those for liver, lymphoid and prostate cancer were indicative of a reduced risk of mortality from these causes among men with diabetes, although the results were statistically non-significant. Women with diabetes were found to have an increased risk of mortality from breast cancer, which remained statistically significant within both the basic and advanced models. There were also raised point estimates for mortality from a number of other site-specific cancers among women with diabetes. The analysis detailed below includes only the basic and advanced models; further analyses were undertaken but had little impact upon the excess in site-specific cancer mortality found among men and women with diabetes compared with those without the disease.

To assess the impact that comorbid CVD had upon the association between diabetes and site-specific cancers the above analyses were repeated stratified by baseline CVD status. The point estimates for site-specific cancers among those with diabetes but without CVD were consistently increased, although the confidence intervals suggested that none of the associations were statistically significant. This was in contrast to those with diabetes who also had comorbid CVD: this group had a substantial increase in pancreatic cancer within the advanced model (1.88, 1.02-3.49), while there were point estimate increases for colorectal, oesophagus, stomach, lung and lip. Further

analyses were undertaken, but did not significantly affect the results in relation to the excess in site-specific mortality experienced by those with diabetes and with and without comorbid CVD.

Table 8-2: Site-specific cancer mortality ORs among those with diabetes

Progressive Adjustment	Pancreas	Colorectal	Bladder	Gender-Specific	Stomach	Liver	Lung	Lymphatic	Kidney	Oesophagus	Lip	Other cancer
Age & sex	1.62 (1.08-2.44)	1.14 (0.80-1.62)	1.20 (0.66-2.16)	1.09 (0.82-1.45)	1.54 (0.95-2.52	0.70 (0.22-2.23)	1.29 (1.04-1.61)	0.93 (0.58-1.48)	1.44 (0.77-2.68	1.11 (0.65-1.88)	1.12 (0.35-3.60)	1.23 (0.95-1.59)
+ Smoking	1.58 (1.05-2.38)	1.11 (0.78-1.58)	1.16 (0.64-2.09)	1.06 (0.80-1.42)	1.50 (0.92-2.44)	0.67 (0.21-2.14)	1.23 (0.98-1.53)	0.91 (0.57-1.45)	1.41 (0.76-2.64)	1.07 (0.64-1.82)	1.08 (0.34-3.48)	1.21 (0.94-1.56)
+ BMI	1.76 (1.14-2.70)	1.18 (0.82-1.70)	1.19 (0.62-2.29)	1.05 (0.77-1.44)	1.57 (0.94-2.60)	0.70 (0.22-2.28)	1.26 (0.99-1.62)	1.01 (0.62-1.64)	1.39 (0.72-2.67)	1.11 (0.63-1.95)	1.86 (0.57-6.11)	1.27 (0.97-1.67)
Addition adjustment (Advanced model + the following variables)												
+ CVD	1.62 (1.06-2.50)	1.11 (0.77-1.61)	1.10 (0.57-2.12)	1.03 (0.75-1.41)	1.48 (0.89-2.46)	0.61 (0.19-1.97)	1.18 (0.92-1.52)	1.01 (0.62-1.64)	1.32 (0.68-2.57)	1.10 (0.62-1.95)	1.91 (0.58-6.33)	1.22 (0.93-1.61)
+ Education	1.71 (1.12-2.62)	1.14 (0.79-1.64)	1.15 (0.60-2.19)	1.02 (0.75-1.40)	1.40 (0.83-2.35)	0.70 (0.22-2.24)	1.19 (0.93-1.52)	0.97 (0.60-1.58)	1.36 (0.70-2.62)	1.07 (0.60-1.86)	1.68 (0.51-5.51)	1.23 (0.94-1.61)
+Social class	1.76 (1.15-2.70)	1.18 (0.82-1.70)	1.18 (0.62-2.26)	1.05 (0.77-1.44)	1.53 (0.92-2.54)	0.71 (0.22-2.28)	1.24 (0.97-1.59)	1.01 (0.62-1.63)	1.38 (0.72-2.66)	1.10 (0.62-1.95)	1.80 (0.55-5.93)	1.27 (0.97-1.66)
+ Region	1.76 (1.15-2.70	1.19 (0.82-1.71)	1.20 (0.63-2.29)	1.04 (0.76-1.42)	1.58 (0.95-2.62)	0.73 (0.23-2.35)	1.27 (0.99-1.62)	1.01 (0.63-1.64)	1.39 (0.72-2.68)	1.02 (0.56-1.83)	1.23 (0.29-5.14)	1.28 (0.97-1.68)

Table 8-3: Site-specific cancer deaths by sex, HSE and SHeS

		No Diabetes	Diabetes	Total
Male	Alive	78,816	2,768	81,584
	Pancreatic	138	15	153
	Colorectal	264	20	284
	Bladder	102	12	114
	Stomach	114	13	127
	Liver	43	2	45
	Lung	691	57	748
	Lymphoid	198	10	208
	Kidney	79	7	86
	Prostate	326	20	346
	Oesophagus	150	10	160
	Lip	46	1	47
	Other cancer	498	33	531
	Total cancers	2,649	200	2,849
Female	Alive	100,247	2,648	102,895
	Pancreatic	157	11	168
	Colorectal	254	14	268
	Bladder	54	0	54
	Breast	331	22	353
	Cervix	78	3	81
	Stomach	78	5	83
	Liver	36	1	37
	Lung	516	31	547
	Lymphoid	155	9	164
	Ovarian	159	6	165
	Kidney	50	4	54
	Oesophagus	96	5	101
	Lip	16	2	18
	Other cancer	472	32	504
	Total cancers	2,452	145	2,597

Table 8-4: Site-specific cancer mortality ORs (men)

Progressive adjustment	Pancreatic	Colorectal	Bladder	Stomach	Liver	Lung	Lymphatic	Kidney	Prostate	Oesophagus	Lip	Other Cancer
Age	1.69 (0.99-2.91)	1.16 (0.73-1.84)	1.67 (0.91-3.06)	1.74 (0.97-3.11)	0.74 (0.18-3.08)	1.26 (0.95-1.66)	0.76 (0.40-1.43)	1.32 (0.60-2.89)	0.80 (0.51-1.27)	1.18 (0.62-2.26)	0.56 (0.08-4.13)	1.09 (0.76-1.56)
+ Smoking	1.64 (0.95-2.82)	1.12 (0.71-1.78)	1.59 (0.87-2.92)	1.69 (0.94-3.02)	0.69 (0.17-2.88)	1.20 (0.91-1.59)	0.74 (0.39-1.40)	1.29 (0.59-2.82)	0.79 (0.50-1.24)	1.14 (0.60-2.18)	0.52 (0.07-3.82)	1.06 (0.74-1.52)
+ BMI	1.97 (1.14-3.42)	1.19 (0.74-1.92)	1.67 (0.86-3.25)	1.82 (1.01-3.28)	0.77 (0.18-3.23)	1.25 (0.93-1.70)	0.85 (0.44-1.61)	1.25 (0.54-2.91)	0.85 (0.52-1.37)	1.16 (0.58-2.30)	1.10 (0.15-8.18)	1.12 (0.76-1.65)
+ CVD	1.81 (1.04-3.51)	1.10 (0.68-1.78)	1.48 (0.76-2.88)	1.72 (0.95-3.11)	0.68 (0.16-2.86)	1.15 (0.85-1.57)	0.86 (0.45-1.64)	1.22 (0.52-2.86)	0.84 (0.52-1.36)	1.14 (0.57-2.28)	1.09 (0.15-8.15)	1.35 (1.07-1.71)

Table 8-5: Site-specific cancer mortality ORs (women)[a]

Progressive adjustment	Pancreas	Colorectal	Breast	Cervix etc	Stomach	Liver	Lung	Lymphatic	Ovarian	Kidney	Oesophagus	Lip	Other cancer
Age	1.52 (0.82-2.82)	1.11 (0.65-1.91)	1.59 (1.02-2.46)	0.98 (0.31-3.14)	1.21 (0.49-3.01)	0.63 (0.09-4.60)	1.34 (0.92-1.93)	1.21 (0.62-2.39)	0.94 (0.41-2.13)	1.68 (0.60-4.69)	1.01 (0.41-2.50)	2.42 (0.55-10.69)	1.42 (0.98-2.04)
+ Smoking	1.50 (0.81-2.78)	1.09 (0.63-1.88)	1.56 (1.01-2.42)	0.97 (0.30-3.10)	1.18 (0.48-2.94)	0.61 (0.08-4.52)	1.28 (0.89-1.86)	1.20 (0.61-2.37)	0.94 (0.41-2.13)	1.66 (0.60-4.66)	0.99 (0.40-2.45)	2.41 (0.55-10.66)	1.41 (0.98-2.02)
+ BMI	1.47 (0.74-2.92)	1.17 (0.66-2.07)	1.62 (1.01-2.61)	1.08 (0.33-3.48)	1.13 (0.41-3.12)	0.61 (0.08-4.49)	1.29 (0.85-1.97)	1.30 (0.63-2.69)	0.49 (0.16-1.55)	1.64 (0.58-4.64)	1.06 (0.38-2.92)	3.13 (0.67-14.55)	1.46 (1.00-2.13)
+ CVD	1.37 (0.68-2.73)	1.12 (0.64-2.00)	1.57 (0.97-2.53)	1.05 (0.32-3.42)	1.06 (0.38-2.95)	0.51 (0.07-3.80)	1.24 (0.81-1.90)	1.27 (0.61-2.63)	0.48 (0.15-1.51)	1.49 (0.52-4.25)	1.07 (0.39-2.98)	3.41 (0.73-16.04)	1.43 (0.97-2.09)

[a] There were no cases of bladder cancer among women with diabetes

Table 8-6: Site-specific cancer mortality by CVD status

		No Diabetes	Diabetes	All
No CVD reported at baseline	Alive	164,573	3,498	168,071
	Pancreas	235	11	246
	Colorectal	408	16	424
	Bladder	117	8	125
	Gender-specific cancers	743	29	772
	Stomach	147	13	160
	Liver	57	<5	58
	Lung	959	47	1,006
	Lymphatic	292	15	307
	Kidney	101	8	109
	Oesophagus	205	8	213
	Lip	57	<5	59
	Other cancer	794	43	837
	Total cancers	4,115	201	4,316
CVD reported at baseline	Alive	14,595	1,921	16,516
	Pancreas	60	15	75
	Colorectal	110	18	128
	Bladder	39	<5	43
	Gender-specific cancers	153	22	175
	Stomach	45	6	51
	Liver	22	<5	24
	Lung	250	41	291
	Lymphatic	62	<5	66
	Kidney	28	<5	31
	Oesophagus	41	7	48
	Lip	5	<5	6
	Other cancer	179	22	201
	Total cancers	994	145	1,139

Table 8-7: Site-specific cancer mortality ORs among those without comorbid CVD

Progressive adjustment	Pancreas	Colorectal	Bladder	Sex-specific	Stomach	Liver	Lung	Lymphatic	Kidney	Oesophagus	Lip	Other cancers
Age & sex	1.20 (0.65-2.22)	0.93 (0.56-1.53)	1.43 (0.70-2.96)	1.02 (0.70-1.49)	1.79 (0.99-3.25)	0.46 (0.06-3.31)	1.18 (0.87-1.59)	1.19 (0.70-2.01)	1.76 (0.85-3.65)	0.96 (0.47-1.95)	1.06 (0.26-4.38)	1.35 (0.99-1.85)
+ Smoking	1.19 (0.64-2.18)	0.91 (0.55-1.50)	1.39 (0.67-2,86)	1.00 (0.69-1.46)	1.75 (0.96-3.17)	0.43 (0.06-3.14)	1.16 (0.69-1.97)	1.17 (0.69-1.97)	1.75 (0.84-3.62)	0.93 (0.46-1.91)	1.03 (0.25-4.26)	1.34 (0.98-1.83)
+ BMI	1.42 (0.77-2.63)	0.98 (0.58-1.65)	1.55 (0.71-3.37)	0.92 (0.61-1.41)	1.76 (0.94-3.29)	0.47 (0.06-3.40)	1.14 (0.82-1.60)	1.28 (0.74-2.21)	1.71 (0.78-3.74)	1.10 (0.54-2.26)	1.83 (0.44-7.70)	1.42 (1.02-1.98)

Table 8-8: ORs site-specific cancer among those with comorbid CVD

Progressive adjustment	Pancreas	Colorectal	Bladder	Sex-specific	Stomach	Liver	Lung	Lymphatic	Kidney	Oesophagus	Lip	Other cancers
Age & sex	1.77 (1.00-3.13)	1.18 (0.71-1.94)	0.69 (0.24-1.92)	1.08 (0.69-1.70)	0.95 (0.40-2.23)	0.67 (0.16-2.85)	1.15 (0.82-1.60)	0.47 (0.17-1.30)	0.77 (0.23-2.52)	1.22 (0.55-2.73)	1.50 (0.17-12.86)	0.88 (0.57-1.38)
+ Smoking	1.74 (0.98-3.07)	1.16 (0.70-1.91)	0.68 (0.24-1.91)	1.07 (0.68-1.69)	0.93 (0.40-2.19)	0.66 (0.16-2.83)	1.10 (0.79-1.54)	0.46 (0.17-1.28)	0.75 (0.23-2.46)	1.20 (0.54-2.69)	1.46 (0.17-12.57)	0.88 (0.56-1.37)
+ BMI	1.88 (1.02-3.49)	1.23 (0.73-2.08)	0.6 (0.19-1.97)	1.25 (0.77-2.02)	1.13 (0.47-2.69)	0.75 (0.17-3.23)	1.23 (0.85-1.79)	0.57 (0.21-1.59)	0.79 (0.24-2.65)	1.09 (0.42-2.82)	1.84 (0.20-16.90)	0.95 (0.59-1.52)

Analyses were then performed using Cox regression. Unlike the multinomial regression above, this compared those who had died from the site-specific cancer of interest with the rest of the study population (those still alive at the end of the follow-up period, plus those who died of another cause). Table 8-9 gives the results of these analyses. Those with diabetes had a consistently increased risk of mortality from pancreatic cancer; this increase remained after adjustment for the full range of covariates, apart from $HbA1_C$. Women with diabetes were found to have an increased risk of mortality from breast cancer; this remained statistically significant within the advanced model (1.61, CI 1.01-2.59), but not within the further analyses. The Hazard Ratios (HRs) were increased at the point estimate for mortality from cancers of the colorectum, bladder, lip, stomach, kidney, and 'other' cancers but the increase was not statistically significant. The results suggest that those with diabetes do not have an increased risk of mortality from ovarian, prostate and liver cancer, while the results were inconsistent for cancers of the cervix and oesophagus. For lung cancer mortality there was a statistically significant increased risk of mortality among those with diabetes within the basic but not advanced models.

Table 8-9: HRs for site-specific cancers among those with diabetes compared with those without diabetes

Progressive Adjustment	Pancreatic	Colorectal	Bladder	Breast	Cervix	Ovarian	Stomach	Lymphatic
Age & sex	1.59 (1.06-2.38)	1.09 (0.77-1.55)	1.12 (0.62-2.03)	1.58 (1.02-2.45)	1.02 (0.32-3.26)	0.96 (0.42-2.19)	1.47 (0.90-2.39)	0.90 (0.57-1.43)
+ smoking	1.58 (1.06-2.38)	1.08 (0.76-1.53)	1.12 (0.62-2.03)	1.59 (1.03-2.46)	1.02 (0.32-3.27)	0.96 (0.42-2.19)	1.47 (0.90-2.40)	0.90 (0.56-1.43)
+ BMI	1.67 (1.09-2.55)	1.11 (0.77-1.59)	1.08 (0.57-2.07)	1.61 (1.01-2.59)	1.13 (0.35-3.66)	0.50 (0.16-1.58)	1.47 (0.88-2.43)	0.96 (0.60-1.55)
+ CVD	1.56 (1.02-2.40)	1.06 (0.74-1.53)	1.02 (0.53-1.95)	1.57 (0.98-2.53)	1.11 (0.34-3.61)	0.49 (0.16-1.56)	1.40 (0.84-2.34)	0.98 (0.60-1.58)
Advanced + Education	1.65 (1.08-2.53)	1.08 (0.75-1.55)	1.05 (0.55-2.01)	1.57 (0.98-2.52)	1.11 (0.35-3.60)	0.49 (0.16-1.56)	1.32 (0.78-2.21)	0.94 (0.58-1.52)
Advanced + Social class	1.68 (1.10-2.57)	1.11 (0.77-1.60)	1.07 (0.56-2.05)	1.69 (1.05-2.72)	1.12 (0.35-3.62)	0.53 (0.17-1.69)	1.44 (0.87-2.38)	0.94 (0.58-1.52)
Advanced + Region	1.68 (1.10-2.57)	1.12 (0.78-1.61)	1.09 (0.57-2.08)	1.55 (0.96-2.52)	1.16 (0.36-3.75)	0.50 (0.16-1.59)	1.49 (0.90-2.47)	0.94 (0.58-1.52)
Advanced + $HbA1_c$	0.85 (0.13-5.53)	2.79 (0.91-8.65)	1.12 (0.99-12.83)	2.74 (0.45-16.57)	N/A	2.33 (0.13-41.14)	0.26 (0.03-2.52)	0.69 (0.07-6.62)
Basic + WC	1.79 (1.05-3.01)	1.23 (0.79-1.91)	0.89 (0.36-2.22)	1.36 (0.73-2.54)	0.35 (0.05-2.58)	0.42 (0.10-1.73)	1.80 (1.02-3.18)	1.25 (0.72-2.17)
Basic + WHR	1.81 (1.07-3.07)	1.23 (0.79-1.91)	0.87 (0.35-2.16)	1.42 (0.76-2.64)	0.40 (0.06-2.97)	0.44 (0.11-1.82)	1.73 (0.98-3.05)	1.26 (0.72-2.19)

Table 8-9: continued

Progressive Adjustment	Prostate	Lung	Liver	Kidney	Oesophagus	Lip	Other
Age & sex	0.74 (0.45-1.16)	1.25 (1.00-1.55)	0.70 (0.22-2.23)	1.42 (0.76-2.65)	1.06 (0.63-1.80)	1.10 (0.34-3.55)	1.17 (0.91-1.51)
+ smoking	0.73 (0.46-1.15)	1.31 (1.05-1.64)	0.70 (0.21-2.17)	1.42 (0.76-2.65)	1.06 (0.63-1.80)	1.16 (0.36-3.75)	1.18 (0.92-1.52)
+ BMI	0.75 (0.46-1.20)	1.22 (0.96-1.56)	0.69 (0.22-2.22)	1.34 (0.69-2.57)	1.05 (0.59-1.85)	1.83 (0.56-6.04)	1.18 (0.91-1.55)
+ CVD	0.76 (0.47-1.23)	1.15 (0.90-1.47)	0.60 (0.19-1.94)	1.29 (0.67-2.50)	1.06 (0.60-1.88)	1.89 (0.57-6.28)	1.15 (0.89-1.51)
Advanced + Education	0.74 (0.46-1.20)	1.17 (0.92-1.50)	0.70 (0.22-2.25)	1.33 (0.69-2.57)	1.01 (0.57-1.79)	1.68 (0.51-5.53)	1.16 (0.89-1.51)
Advanced + Social class	0.75 (0.46-1.21)	1.21 (0.95-1.55)	0.70 (0.22-2.24)	1.33 (0.69-2.56)	0.96 (0.53-1.74)	1.80 (0.55-5.94)	1.18 (0.91-1.55)
Advanced + Region	0.76 (0.47-1.23)	1.23 (0.97-1.57)	0.72 (0.22-2.30)	1.35 (0.70-2.60)	0.96 (0.53-1.73)	1.23 (0.29-5.17)	1.20 (0.91-1.57)
Advanced + $HbA1_c$	0.69 (0.15-3.23)	1.40 (0.63-3.10)	N/A	5.03 (0.60-42.12)	1.25 (0.22-7.26)	N/A	0.30 (0.06-1.42)
Basic + WC	0.82 (0.47-1.45)	1.17 (0.88-1.57)	0.33 (0.05-2.43)	0.90 (0.33-2.51)	0.80 (0.37-1.72)	0.88 (0.12-6.64)	1.32 (0.97-1.81)
Basic + WHR	0.82 (0.47-1.45)	1.14 (0.85-1.52)	0.34 (0.05-2.48)	1.00 (0.36-2.79)	0.76 (0.35-1.65)	0.90 (0.12-6.81)	1.34 (0.98-1.84)

The above analyses were then re-run excluding deaths within the first year following participation in the HSE and SHeS. This enabled an assessment of the issue of reverse causality for the association of diabetes with mortality from pancreatic, as well as the other, cancer mortality. Specifically for mortality from cancer of the pancreas, within all of the models the HRs were not significantly attenuated (Basic: 1.57, 1.04-2.38; Advanced: 1.66, 1.07-2.56; CVD 1.54, 1.00-2.39).The results for mortality from other site-specific cancers also remained unchanged (results not shown).

The next chapter details the results of the analyses related to the association between glycated haemoglobin and mortality.

9. Chapter 9: Results – glycated haemoglobin and mortality within the HSE and SHeS

Within the HSE and SHeS, some participants had a measurement of glycated haemoglobin, a measurement of longer term blood glucose levels that can be used to detect uncontrolled or undiagnosed diabetes. This allowed analyses to be performed which assessed the strength of the association between this variable and all-cause and cause-specific mortality.

9.1 Glycated haemoglobin: descriptive analysis

9.2 $HbA1_C$ and cause-specific mortality

Within the $HbA1_C$ sample there were a total of 1,362 deaths, of which 449 were caused by cancer, 471 by cardiovascular disease (CVD), 173 by respiratory disease, and 269 by other causes. Within the CVD category, 84 were from stroke and 263 from ischaemic heart disease (IHD). Multinomial regression was used to investigate whether $HbA1_C$ was associated with specific causes of death.

Those with an $HbA1_C$ measurement ≥6.5% had statistically significant increased odds of cancer mortality within the basic model (1.44, CI 1.05-1.97) but not in the advanced or CVD models, although there were point estimate increases within each model, including the one which contained diabetes (Table 9-1). Among those with a raised $HbA1_C$ measurement there were point estimate increases in risk of mortality from respiratory disease and statistically significant increases for other causes within each model. The risk of mortality from CVD was close to doubled among those with a raised $HbA1_C$ measurement compared with those with a lower measurement.

Table 9-1: Raised glycated haemoglobin and cause-specific mortality (ORs and 95% CI)

Progressive adjustment	Cancer	Respiratory	CVD	Other
Age, sex	1.47 (1.07-2.01)	1.35 (0.83-2.19)	2.02 (1.55-2.64)	1.59 (1.07-2.36)
& Smoking	1.44 (1.05-1.97)	1.33 (0.81-2.16)	2.02 (1.54-2.63)	1.57 (1.06-2.34)
& BMI	1.38 (0.98-1.95)	1.52 (0.89-2.61)	1.94 (1.45-2.60)	1.70 (1.11-2.60)
Additional adjustment (Advanced model + the following variables				
+ CVD	1.34 (0.95-1.90)	1.44 (0.84-2.48)	1.73 (1.29-2.33)	1.56 (1.02-2.39)
+ Education	1.31	1.34	1.85	1.58

	(0.93-1.85)	(0.77-2.33)	(1.38-2.48)	(1.03-2.42)
+ Social Class	1.36 (0.96-1.91)	1.45 (0.85-2.50)	1.92 (1.43-2.57)	1.65 (1.07-2.52)
+ Region	1.40 (0.99-1.97)	1.53 (0.89-2.62)	2.00 (1.49-2.67)	1.66 (1.09-2.53)
+ Diabetes	1.26 (0.82-1.94)	1.23 (0.62-2.44)	1.19 (0.81-1.75)	0.79 (0.45-1.37)

When the multinomial logistic regression models included alternate measures of adiposity the odds ratios were found to be similar to those found when adjustment included BMI. For cancer the ORs were: BMI 1.38, CI 0.98-1.95; WHR 1.35, 0.97-1.88 and WC 1.42, 1.02-1.97. The ORs also remained consistent for respiratory disease, CVD and other causes of mortality (Table 9-2). Further to this, removing all of the measurement of overweight and obesity did little to alter the ORs for each cause of mortality (Table 9-3). The same results were found when a number of additional independent variables were included within the model (results not shown).

Table 9-2: Raised $HbA1_c$ and cause-specific mortality adjusting for alternative measures of overweight and obesity)

Further adjustment	**Cancer**	**Respiratory**	**CVD**	**Other**
Basic & BMI	1.38 (0.98-1.95)	1.52 (0.89-2.61)	1.94 (1.45-2.60)	1.70 (1.11-2.60)
Basic &WHR	1.35 (0.97-1.88)	1.26 (0.75-2.13)	2.04 (1.55-2.70)	1.64 (1.07-2.52)
Basic & WC	1.42 (1.02-1.97)	1.33 (0.79-2.24)	2.08 (1.57-2.74)	1.65 (1.08-2.52)
Additional adjustment for baseline CVD status				
Basic + WHR & CVD	1.32 (0.95-1.84)	1.23 (0.73-2.07)	1.86 (1.40-2.46)	1.55 (1.01-2.38)
Basic + WC & CVD	1.39 (1.00-1.93)	1.29 (0.77-2.18)	1.88 (1.42-2.49)	1.55 (1.02-2.38)

Table 9-3: All-cause mortality ORs among diabetic cases (without adjustment for overweight and obesity) $HbA1_C$ ≥6.5%

Further adjustment	Cancer	Respiratory	CVD	Other
Basic & Education	1.35 (0.99-1.85)	1.18 (0.71-1.95)	1.91 (1.46-2.49)	1.46 (0.98-2.17)
Basic & Social Class	1.41 (1.03-1.93)	1.28 (0.79-2.10)	2.00 (1.53-2.61)	1.52 (1.02-2.27)
Basic & Region	1.48 (1.08-2.03)	1.37 (0.84-2.23)	2.12 (1.62-2.77)	1.60 (1.08-2.38)
Basic & Diabetes	1.30 (0.87-1.95)	1.17 (0.63-2.16)	1.19 (0.83-1.70)	0.73 (0.44-1.23)

The data were then stratified by CVD status and the above analyses re-run. As can be seen from Table 9-4, there were point estimate increases for all of the causes under investigation; only for mortality from CVD were the increases consistently statistically significant among those with and without comorbid CVD. The addition of other covariates did not impact upon these results. Table 9-5 details the results of the analyses stratified by sex. For women raised $HbA1_C$ appeared to be associated with an increased risk of mortality from cancer at the point estimate and statistically significant increases for respiratory disease, CVD and other causes within each of the models. Somewhat contradicting this result, men were found to have statistically significant increased ORs for cancer (basic: 1.55, CI 1.05-2.27 and advanced: 1.55, 1.04-2.39), but not for respiratory disease, CVD or other causes. The results remained statistically unchanged when a range of covariates were added to the regression model. Among those who indicated that they had never been a regular smoker, those with a raised measurement for HbA1c there were point estimate increases in risk for all of the causes of mortality under investigation; although these were only statistically significant for mortality from CVD (advanced: 2.38, 1.50-3.79). Results of these analyses are given in Table 9-6.

Table 9-4: Cause-specific mortality odds ratios (and 95% CI) among those with raised $HbA1_C$ stratified by CVD status

Progressive adjustment	CVD as a comorbidity (CVD removed from the model)							
	NO				YES			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Age & sex	1.48 (1.00-2.20)	1.32 (0.70-2.48)	2.11 (1.47-3.03)	1.68 (1.02-2.77)	1.34 (0.79-2.26)	1.23 (0.57-2.66)	1.51 (1.02-2.23)	1.21 (0.63-2.33)
& Smoking	1.45 (0.98-2.15)	1.30 (0.70-2.46)	2.12 (1.46-3.01)	1.67 (1.01-2.75)	1.30 (0.77-2.21)	1.21 (0.56-2.62)	1.49 (1.00-2.20)	1.17 (0.61-2.27)
& BMI	1.35 (0.88-2.09)	1.33 (0.63-2.81)	1.94 (1.30-2.90)	1.73 (1.00-3.00)	1.34 (0.76-2.36)	1.58 (0.72-3.50)	1.52 (0.99-2.34)	1.34 (0.68-2.63)
Advanced adjustment (Advanced model + the following variables)								
+ Education	1.30 (0.84-2.00)	1.28 (0.60-2.70)	1.87 (1.25-2.79)	1.63 (0.94-2.82)	1.31 (0.74-2.30)	1.26 (0.54-2.91)	1.50 (0.98-2.31)	1.27 (0.65-2.50)
+ Social Class	1.34 (0.86-2.07)	1.25 (0.59-2.64)	1.92 (1.29-2.87)	1.67 (0.96-2.90)	1.31 (0.74-2.31)	1.54 (0.70-3.42)	1.53 (0.99-2.35)	1.31 (0.67-2.57)
+ Region	1.31 (0.85-2.01)	1.28 (0.61-2.69)	1.91 (1.28-2.85)	1.58 (0.92-2.73)	1.67 (0.94-2.97)	1.74 (0.78-3.87)	1.91 (1.23-2.98)	1.55 (0.78-3.10)
+ Diabetes	1.34 (0.79-2.27)	0.88 (0.35-2.23)	1.08 (0.64-1.83)	0.97 (0.47-1.97)	1.11 (0.53-2.35)	1.88 (0.69-5.16)	1.22 (0.69-2.15)	0.57 (0.24-1.32)

Table 9-5: Cause-specific mortality odds ratios (and 95% CI) among those with raised $HbA1_C$ stratified by sex

Progressive adjustment	Sex (sex removed from the models)							
	WOMEN				MEN			
	Cancer	Respiratory	CVD	Other	Cancer	Respiratory	CVD	Other
Age & sex	1.24 (0.71-2.16)	2.17 (1.16-4.06)	2.93 (1.99-4.31)	1.96 (1.10-3.48)	1.57 (1.07-2.30)	0.80 (0.36-1.75)	1.53 (1.06-2.20)	1.35 (0.78-2.34)
& Smoking	1.23 (0.70-2.15)	2.11 (1.12-3.96)	2.91 (1.97-4.30)	1.93 (1.09-3.44)	1.55 (1.05-2.27)	0.81 (0.37-1.78)	1.52 (1.06-2.20)	1.35 (0.78-2.34)
& BMI	1.04 (0.56-1.96)	2.62 (1.29-5.30)	3.02 (1.97-4.62)	2.09 (1.08-4.04)	1.58 (1.04-2.39)	0.88 (0.37-2.07)	1.40 (0.93-2.10)	1.50 (0.86-2.62)
& CVD	1.02 (0.54-1.93)	2.45 (1.20-4.99)	2.70 (1.76-4.16)	1.98 (1.02-3.84)	1.52 (1.00-2.31)	0.84 (0.36-1.98)	1.25 (0.83-1.88)	1.34 (0.77-2.36)
Further adjustment (Advanced model + the following variables)								
+ Education	0.95 (0.51-1.79)	2.35 (1.16-4.75)	2.85 (1.86-4.36)	1.93 (1.00-3.72)	1.53 (1.01-2.31)	0.69 (0.27-1.76)	1.34 (0.89-2.01)	1.40 (0.80-2.45)
+ Social Class	1.01 (0.53-1.89)	2.38 (1.17-4.83)	2.97 (1.94-4.56)	2.01 (1.04-3.89)	1.56 (1.03-2.36)	0.86 (0.37-2.03)	1.39 (0.93-2.09)	1.47 (0.84-2.57)
+ Region	1.02 (0.55-1.92)	2.58 (1.28-5.20)	3.01 (1.97-4.60)	1.93 (1.00-3.71)	1.64 (1.09-2.48)	0.88 (0.37-2.07)	1.47 (0.98-2.20)	1.51 (0.87-2.64)
+ Diabetes	0.61 (0.28-1.33)	2.04 (0.83-5.02)	2.07 (1.18-3.62)	1.22 (0.52-2.84)	1.88 (1.12-3.16)	0.71 (0.24-2.06)	0.76 (0.44-1.30)	0.59 (0.29-1.22)

Table 9-6: Cause-specific mortality odds ratios (and 95% CI) among those with raised $HbA1_C$ among never smokers

Progressive adjustment	Cause of mortality			
	Cancer	**Respiratory**	**CVD**	**Other**
Age & sex	1.52 (0.84-2.74)	1.49 (0.58-3.87)	2.34 (1.53-3.57)	1.76 (0.92-3.38)
& BMI	1.44 (0.75-2.74)	2.13 (0.79-5.75)	2.38 (1.50-3.79)	2.06 (1.02-4.15)
& CVD	1.39 (0.73-2.66)	1.97 (0.73-5.32)	2.22 (1.39-3.53)	2.00 (0.99-4.03)
Further adjustment (Advanced model + the following variables)				
+ Education	1.38 (0.73-2.64)	2.05 (0.76-5.53)	2.32 (1.46-3.68)	1.96 (0.97-3.94)
+ Social Class	1.40 (0.73-2.69)	2.09 (0.78-5.64)	2.39 (1.50-3.80)	1.97 (0.98-3.99)
+ Region	1.42 (0.75-2.70)	2.13 (0.79-5.74)	2.39 (1.51-3.79)	1.97 (0.98-3.95)
+ Diabetes	1.59 (0.71-3.58)	1.99 (0.56-7.12)	1.93 (1.05-3.56)	0.91 (0.36-2.31)

The continuous $HbA1_C$ variable was then used within the regression models. For cancer and respiratory disease, there were small point estimate increases in odds ratios, while for CVD the increase was statistically significant. There appeared to be no association between the continuous $HbA1_C$ variable and the combined 'other' causes of mortality. Each of these results remained unchanged following the inclusion of further covariates (results not shown). Further analyses were then performed using tertiles of $HbA1_C$ (using data from the whole sample as well as stratified by CVD status and sex); none of these analyses showed an association between this variable and cause-specific mortality (results not shown).

Table 9-7: Cause-specific mortality odds ratios (and 95% CI) continuous $HbA1_C$ variable

Progressive adjustment	Cause of mortality			
	Cancer	**Respiratory**	**CVD**	**Other**
Age, sex	1.05 (0.94-1.18)	1.07 (0.89-1.28)	1.21 (1.10-1.33)	0.96 (0.81-1.14)
& Smoking	1.03 (0.92-1.16)	1.05 (0.87-1.26)	1.20 (1.09-1.31)	0.94 (0.79-1.12)
& BMI	1.02 (0.89-1.16)	1.17 (0.97-1.40)	1.17 (1.05-1.30)	0.99 (0.82-1.18)
Additional adjustment (advanced model + the following variables)				
+ CVD	1.01 (0.88-1.15)	1.14 (0.95-1.38	1.12 (1.00-1.25)	0.95 (0.79-1.14)
+ Education	0.99 (0.87-1.13)	1.08 (0.89-1.32)	1.14 (1.02-1.27)	0.95 (0.79-1.14)
+ Social Class	1.01 0.88-1.15)	1.14 (0.95-1.38)	1.16 (1.04-1.29)	0.97 (0.81-1.16)
+ Region	1.07 (0.94-1.21)	1.2 (1.00-1.43)	1.21 (1.10-1.34)	1.04 (0.88-1.23)
+ Diabetes	0.95 (0.82-1.11)	1.1 (0.88-1.37)	0.97 (0.85-1.12)	0.72 (0.58-0.90)

9.3 Site-specific cancer mortality and $HbA1_C$

There was found to be a relatively small number of site-specific cancer deaths within the sample with a valid glycated haemoglobin measurement, with an even smaller number of deaths among those with raised $HbA1_C$. Table 9-8 demonstrates the number of cases within the sample; as can be seen, there were no deaths among those with raised $HbA1_C$ from cancers of the cervix, kidney and lip. Therefore analyses of the association between $HbA1_C$ and these cancers were not performed. The ORs were raised at the point estimate for cancers of the pancreas, liver, colorectum, stomach, oesophagus, lung and other cancers; while for mortality from sex-specific cancers there appeared to

be a statistically significant increase in risk among those with a raised $HbA1_C$. Because of the small number of cancer cases, no further covariates were added to the model.

Table 9-8: Site-specific cancer mortality among the $HbA1_C$ sample

Site-specific cancer deaths	Glycated haemoglobin level		
	Normal	Raised	Total
Alive	26,117	1,291	27,408
Lung	111	12	123
Colorectal	41	<5	44
Oesophagus	25	<5	28
Lymphatic	27	<5	28
Prostate	16	5	21
Stomach	16	<5	20
Pancreatic	15	<5	19
Breast	16	<5	19
Bladder	14	<5	15
Liver	10	<5	11
Ovarian	10	<5	11
Kidney	8	0	8
Cervix	<5	0	<5
Lip	<5	0	<5
Other cancer	72	8	80
Death unrelated to cancer	789	122	911
TOTAL	27,295	1,459	28,754

The data were then stratified by sex, in order to explore whether or not there were differences in risk between men and women. This also enabled an exploration of the sex-specific cancers and their associations with raised $HbA1_C$. In the instances when there were not deaths from a specific cancer among those with a raised glycated haemoglobin measurement, analyses were not performed. Among men there was a significant association between $HbA1_C$ and mortality from stomach cancer, as well as point estimate increases for cancers of the liver, lung, prostate, oesophagus, pancreas, colorectum, bladder and 'other' cancers. There were point estimate increases in risk of mortality from cancers of the pancreas, lung, lymphatic system, breast and ovary among women, none of these were statistically significant. As above, the small number of site-specific cancer deaths prevented the inclusion of further variables within the regression model. Table 9-10 details the number of site-specific cancers by sex and $HbA1_C$ (normal/≥6.5%).

Table 9-9: Site-specific cancer mortality ORs among those with $HbA1_C$ ≥6.5%

Progressive adjustment	Site-specific cancers									
	Pancreas	**Colorectal**	**Bladder**	**Gender-specific**	**Stomach**	**Liver**	**Lung**	**Lymphatic**	**Oesophagus**	**Other cancer**
Age & sex	2.94 (0.96-9.01)	1.00 (0.31-3.28)	0.83 (0.11-6.43)	2.52 (1.21-5.22)	2.38 (0.79-7.19)	1.36 (0.17-10.87)	1.41 (0.77-2.59)	0.46 (0.06-3.44)	1.50 (0.45-5.06)	1.31 (0.62-2.74)
& Smoking	2.87 (0.94-8.82)	1.00 (0.31-3.27)	0.82 (0.11-6.31)	2.50 (1.20-5.19)	2.32 (0.77-7.03)	1.27 (0.16-10.17)	1.36 (0.74-2.50)	0.45 (0.06-3.36)	1.47 (0.44-4.96)	1.29 (0.62-2.72)
& BMI	2.37 (0.66-8.57)	1.10 (0.33-3.64)	0.96 (0.12-7.56)	2.85 (1.35-6.02)	2.05 (0.57-7.36)	N/A	1.74 (0.94-3.23)	0.51 (0.07-3.81)	1.18 (0.27-5.19)	0.96 (0.38-2.42)
& CVD	0.90 (0.11-7.25)	1.17 (0.35-3.96)	1.21 (0.14-10.08)	1.54 (0.52-4.54)	2.69 (0.52-13.90)	N/A	1.68 (0.84-3.33)	0.71 (0.09-5.52)	1.47 (0.33-6.60)	1.16 (0.45-2.97)

Table 9-10: Site-specific cancer mortality by sex and $HbA1_C$

Sex	Pancreas	Colorectal	Bladder	Cervix	Stomach	Liver	Lung	Lymphatic	Ovarian	Kidney	Prostate	Oesophagus	Lip	Other cancer
Male														
Normal	8	25	8	N/A	9	5	61	17	N/A	<5	16	17	<5	40
Raised	<5	<5	<5	N/A	<5	<5	8	0	N/A	0	5	<5	0	5
Female														
Normal	7	16	6	<5	7	5	50	10	10	5	N/A	8	<5	32
Raised	<5	0	0	0	0	0	<5	<5	<5	0	N/A	0	0	<5

Table 9-11: ORs for site-specific cancer mortality among men with raised $HbA1_C$

PROGRESSIVE ADJUSTMENT	Site-specific cancers[a]								
	Pancreas	**Colorectal**	**Bladder**	**Stomach**	**Liver**	**Lung**	**Prostate**	**Oesophagus**	**Other cancers**
Age	2.10 (0.44-10.01)	1.43 (0.42-4.85)	1.13 (0.14-9.16)	3.85 (1.16-12.77	2.06 (0.23-18.24)	1.43 (0.67-3.03)	2.75 (0.99-7.62)	2.02 (0.58-7.08)	1.26 (0.49-3.24)
& Smoking	2.13 (0.45-10.17)	1.43 (0.42-4.84)	1.09 (0.13-8.86)	3.95 (1.19-13.13)	1.92 (0.22-17.06)	1.39 (0.65-2.95)	2.72 (0.98-7.55)	2.02 (0.58-7.10)	1.25 (0.49-3.23)
& BMI	2.20 (0.44-11.03)	1.56 (0.45-5.38)	1.58 (0.19-13.36)	4.94 (1.21-20.20)	N/A	1.74 (0.80-3.75)	3.02 (1.06-8.58)	1.65 (0.36-7.50)	1.31 (0.45-3.79)
& CVD	1.20 (0.14-10.59)	1.70 (0.48-6.05)	2.18 (0.23-21.04)	6.88 (1.05-45.07)	N/A	1.64 (0.72-3.77)	1.47 (0.32-6.87)	2.25 (0.47-10.71)	1.47 (0.50-4.34)

[a] There were no deaths from kidney, lymphatic or lip cancers found among men with a raised $HbA1_C$ measurement.

Table 9-12: Site-specific cancer mortality ORs among women with raised $HbA1_c$

Progressive adjustment	Site-specific cancers[a]					
	Pancreas	**Lung**	**Lymphatic**	**Breast**	**Ovarian**	**Other cancers**
Age	4.38 (0.88-21.82)	1.34 (0.48-3.76)	1.55 (0.20-12.39)	3.12 (0.89-10.97)	1.68 (0.21-13.48)	1.36 (0.41-4.49)
& Smoking	6.58 (1.78-24-25)	1.18 (0.39-3.56)	1.38 (0.14-13.37)	3.33 (0.94-11.80)	1.51 (0.97-2.35)	1.22 (0.35-4.31)
& BMI	2.28 (0.23-22.43)	1.43 (0.45-4.52)	1.85 (0.17-20.31)	4.11 (1.15-14.66)	2.44 (1.70-3.49)	0.59 (0.10-3.50)
& CVD	0.67 (0.01-49.37)	1.24 (0.30-5.05)	1.50 (0.10-23.26)	1.15 (0.09-14.37)	2.19 (0.89-5.39)	0.83 (0.12-5.71)

[a] There were no deaths from cancers of the colorectum, bladder, cervix, stomach, liver, kidney, oesophagus or lip among women with raised $HbA1_c$.

Within the current study $HbA1_C$ was found to be significantly associated with mortality from CVD and the group of 'other' causes, as well as being associated with mortality from cancer and respiratory disease at the point estimate. For cause-specific mortality there appeared to be differences in risk when the analyses were stratified either by sex or the presence of comorbid CVD.

Although limited by the number of deaths from site-specific cancers, the results above are also indicative of an association between $HbA1_C$ and some site-specific cancers as well as the potential for there being differences in risk between the sexes.

10. Chapter 10: Diabetes and all-cause mortality

As with the analyses which explored the associations between diabetes, raised $HbA1_C$ and mortality from CVD, respiratory disease and other causes, the following analyses sought to examine the strength of the association between diabetes and all-cause mortality within a recent, general population cohort. Through the use of data from the HSE/SHeS and Whitehall I it was also possible to compare results from analyses of two different datasets – one of which had relatively recently collected baseline data and the other having a 40 year follow-up period.

10.1 All-cause mortality: HSE and SHeS

Within the analyses of the appended HSE/SHeS dataset, the all-cause mortality variable (deadalive) was binary (0=alive and 1=died) and those whose death had been registered within UK mortality records during the follow-up period were included in the 'died' category.

In total, 20,051 cases were identified as having died during the follow-up period, with 1,814 deaths among those with diagnosed diabetes. Table 10-1

Table 10-1 details the results related to the increased risk of all-cause mortality among those with diabetes compared with the general study population. Among the whole sample, those with diabetes had an increased odds for all-cause mortality that ranged from 1.68 (95% CI 1.57-1.79) within the basic model (adjusted for age-group, sex and smoking status) which was attenuated to 1.56 (CI 1.45-1.68) when adjustment included age-group, sex, smoking status, BMI (categorical) and CVD as a baseline comorbidity. When the analyses were stratified by baseline CVD status, those with diabetes and either with or without comorbid CVD had increased odds of all-cause mortality compared with those without diabetes. These increases remained statistically significant after adjustment for a range of confounding factors.

When the analyses were stratified by sex, and analyses compared the risk of all-cause mortality among those with and without diabetes, both men and women with diabetes appeared to be at increased risk. Men with diabetes had an increased risk at the point estimate compared with women with diabetes, but this was not statistically significant. Sensitivity analysis, which included only those who indicated that they had never been a regular smoker, was then performed. This indicated that never smokers with diabetes had increased odds of all-cause mortality of 1.63 (CI 1.44-1.83) within the CVD model which was similar to the raised odds among diabetics in the whole study population.

Table 10-1: All-cause mortality odds ratios (and 95% CI) among those with diabetes

PROGRESSIVE ADJUSTMENT	WHOLE SAMPLE	STRATIFIED BY CVD[a]		STRATIFIED BY GENDER[b]		NEVER SMOKERS ONLY
						n=98,107
		NO	YES	WOMEN	MEN	
Age, sex	1.61 (1.51-1.72)	1.58 (1.45-1.72)	1.29 (1.18-1.42)	1.58 (1.44-1.73)	1.64 (1.50-1.79)	1.72 (1.55-1.92)
& Smoking[c]	1.68 (1.57-1.79)	1.66 (1.52-1.81)	1.33 (1.20-1.46)	1.67 (1.51-1.83)	1.69 (1.54-1.84)	N/A
& BMI[d]	1.69 (1.57-1.82)	1.68 (1.53-1.85)	1.38 (1.24-1.54)	1.63 (1.46-1.81)	1.74 (1.58-1.92)	1.71 (1.51-1.92)
Basic + CVD status	1.55 (1.46-1.66)	N/A	N/A	1.57 (1.43-1.73)	1.54 (1.41-1.68)	1.65 (1.48-1.84)
Additional adjustment (Advanced model + the following variables)						
+ CVD[e]	1.56 (1.45-1.68)	N/A	N/A	1.52 (1.37-1.70)	1.59 (1.44-1.75)	1.63 (1.44-1.83)
+ Education	1.64 (1.53-1.76)	1.64 (1.49-1.80)	1.36 (1.22-1.51)	1.58 (1.42-1.76)	1.69 (1.54-1.86)	1.67 (1.48-1.88)
+ Social Class	1.66 (1.54-1.78)	1.65 (1.50-1.82)	1.35 (1.22-1.51)	1.57 (1.41-1.75)	1.73 (1.57-1.90)	1.65 (1.47-1.86)
+ Region	1.69 (1.57-1.81)	1.68 (1.53-1.85)	1.37 (1.23-1.52)	1.62 (1.45-1.80)	1.74 (1.58-1.91)	1.70 (1.51-1.92)
+ $HbA1_c$	1.93 (1.49-2.49)	1.95 (1.39-2.74)	1.57 (1.06-2.31)	2.12 (1.43-3.14)	1.84 (1.31-2.58)	1.49 (0.95-2.35)

a CVD removed from the model when analyses stratified by baseline CVD.
b Sex removed from the model when analyses stratified by sex.
c Referred to as the 'basic' model.
d Referred to as the 'advanced' model.
e Referred to as the 'CVD' model.

Additional adjustment was made which included the variables related to education, social class, region and glycated haemoglobin ($HbA1_C$). Within all of these models, participant with diabetes remained at an increased risk for all-cause mortality (at the point estimate). The lack of statistical significance found within the sensitivity analysis which adjusted for $HbA1_C$ may relate to the small number of participants within this group who also had a valid measurement for this variable.

As can be seen from Table 10-2, an excess risk of all-cause mortality remained among those with diabetes compared with the reference group after adjustment for either waist-to-hip ratio (WHR) or

waist circumference (WC). These increases were statistically similar to those found within the advanced model (which adjusted for BMI).

Table 10-2: All-cause mortality ORs (adjusting for alternative measures of overweight and obesity)

Additional adjustment	**WHOLE SAMPLE**	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		(CVD removed from model)		(Sex removed from model)		n=98,107
		NO	YES	WOMEN	MEN	
Basic + BMI	1.69 (1.57-1.82)	1.68 (1.53-1.85)	1.38 (1.24-1.54)	1.63 (1.46-1.81)	1.74 (1.58-1.92)	1.71 (1.51-1.92)
Basic + WHR[a]	1.56 (1.43-1.70)	1.50 (1.34-1.68)	1.35 (1.19-1.53)	1.59 (1.40-1.81)	1.53 (1.36-1.72)	1.64 (1.41-1.89)
Basic + WC[b]	1.59 (1.46-1.73)	1.54 (1.37-1.72)	1.35 (1.19-1.54)	1.60 (1.41-1.83)	1.57 (1.40-1.76)	1.62 (1.40-1.87)
Basic + WHR[a] & CVD[c]	1.45 (1.33-1.58)	N/A	N/A	1.50 (1.32-1.71)	1.42 (1.26-1.59)	1.56 (1.35-1.81)
Basic + WC[b] & CVD[c]	1.48 (1.36-1.61)	N/A	N/A	1.51 (1.33-1.72)	1.44 (1.29-1.62)	1.55 (1.34-1.79)

[a] WHR – Waist-to-hip ratio
[b] WC – Waist circumference
[c] CVD – Cardiovascular disease

Table 10-2 and Table 10-3 demonstrate that the ORs for all-cause mortality remained statistically similar among those with diabetes whether or not the model included a measurement related to overweight and obesity. For example, analyses of the whole sample found a raised OR among those with diabetes of 1.93 (CI 1.52-2.45) when adjustment did not include BMI compared with 1.93 (CI 1.49-2.49) when it did.

Table 10-3: All-cause mortality ORs among diabetic cases (without adjustment for overweight and obesity)

Additional adjustment	**WHOLE SAMPLE**	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		(CVD removed from the model)		**(Sex removed from the model)**		**n=98,107**
		NO	**YES**	**WOMEN**	**MEN**	
Basic + Education	1.62 (1.52-1.73)	1.61 (1.47-1.75)	1.31 (1.19-1.44)	1.61 (1.46-1.77)	1.63 (1.49-1.78)	1.68 (1.51-1.87)
Basic + Social Class	1.64 (1.54-1.75)	1.63 (1.49-1.77)	1.30 (1.18-1.43)	1.60 (1.45-1.76)	1.67 (1.53-1.82)	1.66 (1.49-1.85)
Basic +	1.69	1.70	1.32	1.68	1.69	1.74

Region	(1.58-1.80)	(1.53-1.82)	(1.20-1.45)	(1.53-1.85)	(1.54-1.84)	(1.56-1.94)
Basic + $HbA1_c$	1.93 (1.52-2.45)	1.95 (1.43-2.67)	1.58 (1.10-2.27)	2.05 (1.43-2.93)	1.87 (1.36-2.58)	1.65 (1.09-2.51)

Further analyses included a combination of the above variables. Table 10-5 demonstrates that the increased risk of all-cause mortality remained among those with diabetes, even after adjusting for combination of a number of confounding factors. Only within the sensitivity analysis, and when $HbA1_C$ was adjusted for, did the association between diabetes and all-cause mortality become non-significant (1.47, CI 0.96-2.24). A power calculation undertaken for this group suggested that the analysis was underpowered; among those who had indicated that they had never been a regular smoker there were only 3,023 cases with diabetes and among this group only 532 had a valid measurement for $HbA1_C$. Within this additional adjustment, the majority of the excess in all-cause mortality remained. When the analyses were stratified by CVD status, only those without CVD at baseline had consistently statistically significant increased ORs; for those with comorbid CVD the inclusion of $HbA1_C$ produced point estimate increased ORs that were not statistically significant. These analyses were then repeated, without adjustment for CVD (Table 10-6): as can be seen, the removal of this variable had very little impact upon the increased risk of all-cause mortality found among those with diabetes compared with the general population.

10.1.1 Diabetes and all-cause mortality: further analyses

Similarly for the cox regression undertaken to explore the associations between diabetes and cancer mortality, variables were derived within the Health Survey for England and Scottish Health Survey dataset which included the following information:

- All-cause mortality/Everyone else.
- A censor date variable (this either contained information about date of death or the end of the follow-up period).
- A duration of time in study variable (derived from the baseline interview date and censor date).

As can been seen from the table below, those with diabetes had a substantially increased HRs compared with those in the general population. This remained unchanged after adjustment for a range of covariates.

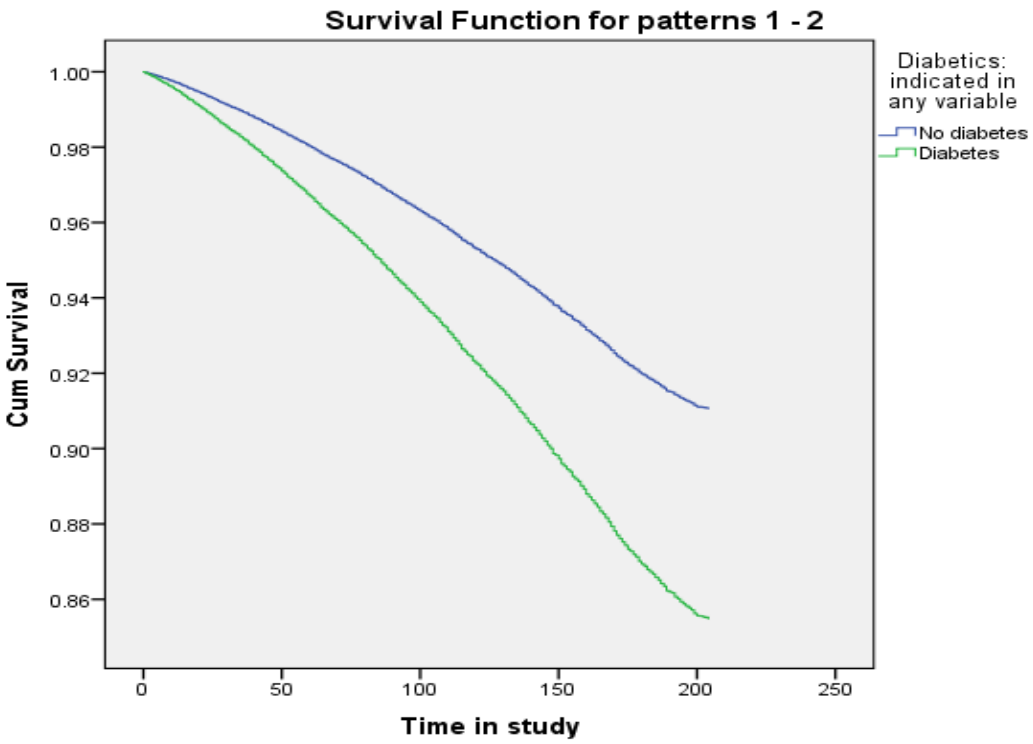
Table 10-4: HRs all-cause mortality among those with diabetes

Progressive adjustment	All cause
Age & sex	1.68 (1.60-1.76)
Age, sex & smoking	1.74 (1.66-1.83)
Age, sex, smoking & BMI	1.76 (1.67-1.86)
Age, sex, smoking, BMI & CVD	1.64 (1.55-1.73)
Further adjustment	
Further adjustment Age, sex, smoking, BMI & Education group	1.73 (1.64-1.82)
Age, sex, smoking, BMI & social class	1.74 (1.65-1.83)
Age, sex, smoking, BMI & Region	1.77 (1.67-1.87)
Age, sex, smoking, BMI & $Hba1_c$	1.84 (1.47-2.30)
Age, sex, smoking & waist raised	1.70 (1.59-1.82)
Age, sex, smoking & waist-hip-ratio	1.66 (1.55-1.78)

10.1.2 Survival curves (all-cause mortality)

Survival curves were also produced for mortality from all-causes and, as can be seen below, they indicate that the diabetic cohort were found to have substantially increased all-cause mortality compared with those without diabetes.

Figure 10-1: All-cause mortality: HSE/SHeS (age and sex)



These analyses suggest that the diabetic cohort has an increased risk of all-cause mortality even after adjustment for a range of factors. Further to this, after adjusting for measurements of overweight and obesity (BMI, waist-to-hip ratio and waist circumference) this increased risk remains. One issue of particular note is that after adjusting for glycated haemoglobin the excess in all-cause mortality remains amongst those with diabetes. The next section explores the associations between $HbA1_C$ and all-cause mortality.

Table 10-5: All-cause mortality ORs among cases with diabetes (further adjustment)

Further adjustment	WHOLE SAMPLE	STRATIFIED BY GENDER		NEVER SMOKERS ONLY
		WOMEN	MEN	n=98,107
Advanced Model + Sclass, Region & CVD	1.52 (1.42-1.64)	1.47 (1.31-1.64)	1.57 (1.42-1.73)	1.56 (1.39-1.77)
Advanced Model + Sclass, Region, CVD & $HbA1_c$	1.76 (1.37-2.26)	2.13 (1.46-3.11)	1.57 (1.13-2.18)	1.45 (0.93-2.25)
Advanced Model + Education, Region & CVD	1.51 (1.41-1.63)	1.48 (1.33-1.65)	1.54 (1.39-1.69)	1.59 (1.41-1.79)
Advanced Model + Education, Region, CVD & $HbA1_c$	1.72 (1.34-2.20)	2.07 (1.42-3.02)	1.54 (1.11-2.13)	1.42 (0.92-2.21)
Basic Model + Waist/Hip, Sclass, Region & CVD	1.42 (1.30-1.55)	1.44 (1.26-1.64)	1.41 (1.26-1.59)	1.49 (1.28-1.73)
Basic Model + Waist/Hip, Sclass, Region, CVD & $HbA1_c$	1.63 (1.28-2.08)	1.81 (1.26-2.61)	1.53 (1.10-2.11)	1.49 (0.98-2.29)
Basic Model + Waist/Hip, Education, Region & CVD	1.44 (1.32-1.57)	1.48 (1.30-1.69)	1.40 (1.25-1.58)	1.56 (1.34-1.80)
Basic Model + Waist/Hip, Education, Region, CVD & $HbA1_c$	1.60 (1.25-2.04)	1.78 (1.24-2.56)	1.50 (1.08-2.07)	1.49 (0.98-2.29)
Basic Model + Waist Circ, Sclass, Region & CVD	1.44 (1.32-1.57)	1.45 (1.27-1.65)	1.43 (1.27-1.61)	1.47 (1.27-1.71)
Basic Model + Waist Circ, Sclass, Region, CVD & $HbA1_c$	1.62 (1.27-2.07)	1.82 (1.26-2.63)	1.51 (1.09-2.09)	1.47 (0.96-2.25)
Basic Model + Waist Circ, Education, Region & CVD	1.45 (1.33-1.59)	1.49 (1.31-1.70)	1.42 (1.27-1.60)	1.54 (1.33-1.78)
Basic Model + Waist Circ, Education, Region, CVD & $HbA1_c$	1.59 (1.25-2.03)	1.79 (1.24-2.58	1.48 (1.07-2.05)	1.47 (0.96-2.24)

Table 10-6: All-cause mortality ORs (no adjustment for CVD at baseline)

Additional adjustment	WHOLE SAMPLE	STRATIFIED BY CVD		STRATIFIED BY GENDER		NEVER SMOKERS ONLY
		NO	YES	WOMEN	MEN	
Advanced model + Sclass & Region	1.65 (1.54-1.78)	1.66 (1.50-1.82)	1.34 (1.20-1.49)	1.57 (1.40-1.75)	1.72 (1.57-1.90)	1.65 1.46-1.86)
Advanced model + Sclass, Region & $HbA1_c$	1.92 (1.50-2.46)	1.97 (1.42-2.72)	1.43 (0.97-2.09)	2.24 (1.53-3.27)	1.77 (1.28-2.45)	1.54 (0.99-2.40)
Advanced model + Education, Region	1.64 (1.52-1.76)	1.64 (1.49-1.80)	1.35 (1.21-1.50)	1.58 (1.41-1.76)	1.69 (1.53-1.86)	1.67 (1.48-1.88)
Advanced model + Education, Region & $HbA1_c$	1.88 (1.47-2.40)	1.93 (1.39-2.67)	1.41 (0.96-2.06)	2.17 (1.49-3.17)	1.73 (1.25-2.39)	1.52 (0.98-2.35)
Basic model + WHR, Sclass & Region	1.52 (1.40-1.66)	1.48 (1.31-1.66)	1.32 (1.16-1.50)	1.52 (1.34-1.74)	1.52 (1.36-1.71)	1.56 (1.35-1.8)
Basic model + WHR, Sclass, Region & $HbA1_c$	1.75 (1.37-2.23)	1.78 (1.30-2.45)	1.39 (0.95-2.02)	1.89 (1.31-2.73)	1.68 (1.22-2.32)	1.56 (1.03-2.4)
Basic model + WHR, Education & Region	1.53 (1.41-1.67)	1.48 (1.32-1.66)	1.35 (1.19-1.53)	1.57 (1.38-1.79)	1.51 (1.35-1.70)	1.63 (1.41-1.88)
Basic model + WHR, Education, Region & $HbA1_c$	1.72 (1.35-2.19)	1.77 (1.29-2.43)	1.36 (0.94-1.98)	1.86 (1.29-2.68)	1.65 (1.19-2.27)	1.57 (1.03-2.40)
Basic model + WC, Sclass, Region	1.55 (1.42-1.69)	1.50 (1.34-1.69)	1.32 (1.16-1.50)	1.53 (1.34-1.75)	1.55 (1.38-1.74)	1.54 (1.33-1.78)
Basic model + WC, Sclass, Region & $HbA1_c$	1.75 (1.37-2.22)	1.77 (1.29-2.43)	1.39 0.95-2.02)	1.90 (1.32-2.75)	1.67 (1.21-2.30)	1.55 (1.01-2.36)
Basic model + WC, Education & Region	1.56 (1.43-1.70)	1.51 (1.34-1.69)	1.35 (1.19-1.53)	1.57 (1.38-1.79)	1.54 (1.37-1.73)	1.61 (1.39-1.86)
Basic model + WC, Education, Region & $HbA1_c$	1.71 (1.34-2.18)	1.75 (1.28-2.41)	1.36 (0.93-1.97)	1.87 (1.30-2.69)	1.63 (1.18-2.25)	1.54 (1.01-2.36)

10.2 $HbA1_C$ and all-cause mortality

There were a total of 1,362 deaths among those with a valid $HbA1_C$ measurement (5% of those with $HbA1_C$ data); this compared with 1,814 deaths among the diabetic sample within the whole combined HSE and SHeS dataset. Among those with raised $HbA1_C$, 28% of deaths were caused by cancer, 11% by respiratory and 43% by cardiovascular disease. This compared with 34%, 13% and 33% among those with an $HbA1_C$ <6.5%.

The results given in Table 10-7 demonstrate that, those with a raised $HbA1_C$ measurement, had an increased odds ratio (OR) in relation to all-cause mortality within the basic (OR 1.65, CI 1.38-1.98), advanced (1.66, CI 1.36-2.02) and CVD models (1.54, CI 1.26-1.88). When the data were stratified by CVD status, the increased risk for those with raised $HbA1_C$ for all-cause mortality remained. The increased risk appeared greater among those without comorbid CVD compared with those with CVD, at the point estimate, although was not statistically significant. There was a statistically significant increased risk of all-cause mortality in both men and women with a raised glycated haemoglobin measurement. The odds were doubled amongst women, with this increase remaining within each of the models, while for men the OR was around 1.42. Finally, the ORs were also doubled among those who indicated that they had never been a regular smoker. These increases remained when covariates related to education, social class and region were added to the models. The only variable to impact upon the statistical significance of the association was the presence of diabetes; only among the 'never smokers' group did the increased risk of all-cause mortality among those with a raised $HbA1_C$ remain statistically significant after adjustment for this variable.

Table 10-7: Mortality odds ratios (and 95% CI) among those with a raised $HbA1_C$ measurement (≥6.5%)

Progressive adjustment	WHOLE SAMPLE	STRATIFIED BY CVD[a]		STRATIFIED BY GENDER[b]		NEVER SMOKERS ONLY
		NO	YES	WOMEN	MEN	
Age, sex	1.67 (1.39-2.00)	1.69 (1.34-2.14)	1.38 (1.03-1.83)	2.07 (1.58-2.72)	1.42 (1.11-1.81)	1.90 (1.40-2.58)
& Smoking	1.65 (1.38-1.98)	1.67 (1.32-2.12)	1.35 (1.01-1.80)	2.05 (1.56-2.70)	1.41 (1.10-1.80)	N/A
& BMI	1.66 (1.36-2.02)	1.61 (1.24-2.09)	1.45 (1.07-1.97)	2.08 (1.54-2.81)	1.42 (1.09-1.84)	2.00 (1.44-2.79)
Additional adjustment (Advanced model + the following variables)						
+ CVD	1.54 (1.26-1.88)	N/A	N/A	1.94 (1.43-2.63)	1.31 (1.00-1.71)	1.90 (1.36-2.65)

+ Education	1.56 (1.27-1.90)	1.54 (1.19-2.01)	1.38 (1.01-1.88)	1.92 (1.42-2.60)	1.34 (1.02-1.75)	1.93 (1.39-2.70)
+ Social Class	1.62 (1.32-1.98)	1.56 (1.20-2.03)	1.44 (1.10-1.96)	1.98 (1.46-2.69)	1.40 (1.08-1.83)	2.00 (1.43-2.79)
+ Region	1.67 (1.37-2.04)	1.55 (1.20-2.01)	1.76 (1.28-2.42)	2.02 (1.50-2.73)	1.46 (1.12-1.91)	1.97 (1.42-2.75)
+ DM[c]	1.12 (0.87-1.45)	1.11 (0.80-1.55)	1.08 (0.73-1.62)	1.35 (0.92-2.00)	0.97 (0.69-1.38)	1.58 (1.02-2.44)

a CVD was removed from the models when the analyses were stratified by CVD.
b Sex was removed from the models when the analyses were stratified by sex.
[c] DM: Diagnosed diabetes.

The use of models which included different measurements of overweight and obesity (waist-to-hip ratio (WHR) and waist circumference (WC)) had little impact upon the increased risk of all-cause mortality among those with an $HbA1_c$ measurement ≥6.5% compared with those with a measurement below this threshold. The results of these analyses can be found in Table 10-8.

Table 10-8: Mortality ORs (adjusting for measures of overweight and obesity)

Progressive adjustment	**WHOLE SAMPLE**	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		NO	**YES**	**WOMEN**	**MEN**	
Basic & BMI	1.66 (1.36-2.02)	1.61 (1.24-2.09)	1.45 (1.07-1.97)	2.08 (1.54-2.81)	1.42 (1.09-1.84)	2.00 (1.44-2.79)
Basic & WHR[a]	1.63 (1.35-1.98)	1.64 (1.28-2.10)	1.40 (1.04-1.89)	2.05 (1.54-2.73)	1.38 (1.06-1.79)	1.96 (1.42-2.69)
Basic & WC[b]	1.68 (1.39-2.03)	1.69 (1.32-2.16)	1.45 (1.07-1.96)	2.09 (1.57-2.78)	1.42 (1.10-1.84)	1.95 (1.42-2.68)
Additional adjustment for baseline CVD status						
Basic & WHR &CVD	1.54 (1.27-1.87)	N/A	N/A	1.95 (1.46-2.60)	1.30 (1.00-1.68)	1.88 (1.36-2.59)
Basic & WC & CVD	1.58 (1.31-1.92)	N/A	N/A	1.99 (1.49-2.66)	1.33 (1.03-1.72)	1.86 (1.35-2.57)

[a] WHR: Waist-to-hip ratio
[b] WC: Waist circumference

In order to assess the impact that the inclusion of a variable related to overweight and obesity had upon the association between glycated haemoglobin and all-cause mortality, analyses were then performed with these variables removed. As can be seen from Table 10-9, the inclusion of these variables had very little impact upon the increased risk of all-cause mortality among this group when compared with the basic model. The results contained in Table 10-10 and Table 10-11 demonstrate

that only when adjustment included diabetes was the association between an $HbA1_C$ ≥6.5% and all-cause mortality significantly attenuated.

Table 10-9: All-cause mortality ORs among those with raised $HbA1_C$ (without adjustment for overweight and obesity)

Further adjustment	WHOLE SAMPLE	STRATIFIED BY CVD		STRATIFIED BY GENDER		NEVER SMOKERS ONLY
		NO	YES	WOMEN	MEN	
Basic & Education	1.54 (1.28-1.85)	1.58 (1.25-2.00)	1.28 (0.96-1.71)	1.89 (1.44-2.49)	1.32 (1.03-1.69)	1.81 (1.33-2.47)
Basic & Social Class	1.61 (1.34-1.94)	1.61 (1.27-2.05)	1.34 (1.00-1.79)	1.95 (1.48-2.58)	1.39 (1.09-1.78)	1.88 (1.38-2.56)
Basic & Region	1.71 (1.42-2.05)	1.66 (1.31-2.10)	1.61 (1.20-2.17)	2.05 (1.56-2.69)	1.49 (1.16-1.91)	1.90 (1.39-2.58)
Basic & Diabetes	1.11 (0.87-1.41)	1.15 (0.85-1.56)	1.00 (0.68-1.46)	1.36 (0.96-1.94)	0.95 (0.68-1.32)	1.39 (0.92-2.10)

Table 10-10: All-cause mortality ORs among those with raised $HbA1_C$ (further adjustment)

Additional adjustment	WHOLE SAMPLE	STRATIFIED BY GENDER		NEVER SMOKERS ONLY
		WOMEN	MEN	
Advanced model	1.66 (1.36-2.02)	1.61 (1.24-2.09)	1.45 (1.07-1.97)	2.08 (1.54-2.81)
Advanced + Sclass[a], Region & CVD	1.55 (1.26-1.89)	1.84 (1.35-2.49)	1.37 (1.05-1.78)	1.89 (1.35-2.63
Advanced + Education, Region & CVD	1.50 (1.23-1.84)	1.80 (1.33-2.43)	1.32 (1.01-1.72)	1.83 (1.31-2.55)
Advanced & WHR[c], Sclass, Region & CVD	1.56 (1.28-1.89)	1.85 (1.39-2.48)	1.36 (1.05-1.77)	1.86 (1.35-2.56)
Basic + WHR, Education, Region & CVD	1.53 (1.26-1.86)	1.84 (1.38-2.45)	1.32 (1.01-1.72)	1.82 (1.32-2.50)
Basic + WC[d], Sclass, Region & CVD	1.58 (1.30-1.92)	1.89 (1.41-2.53)	1.38 (1.06-1.79)	1.83 (1.33-2.53)
Basic + WC, Education, Region & CVD	1.55 (1.27-1.88)	1.87 (1.40-2.50)	1.33 (1.03-1.73)	1.79 (1.29-2.46)
Additional analyses with DM included				
Advanced + Sclass, Region, CVD & DM	1.14 (0.89-1.46)	1.25 (0.86-1.82)	1.06 (0.77-1.48)	1.54 (1.01-2.34)
Advanced + Education, Region, CVD & DM[b]	1.13 (0.88-1.44)	1.25 (0.86-1.81)	1.04 (0.75-1.45)	1.50 (0.99-2.29)
Basic + WHR, Sclass, Region, CVD & DM	1.20 (0.94-1.52)	1.38 (0.97-1.96)	1.07 (0.77-1.48)	1.48 (0.98-2.23)

Basic + WHR, Education, Region, CVD & DM	1.19 (0.94-1.51)	1.38 (0.97-1.96)	1.05 (0.76-1.45)	1.45 (0.96-2.18)
Basic + WC, Sclass, Region, CVD & DM	1.22 (0.96-1.55)	1.40 (0.99-1.99)	1.09 (0.79-1.51)	1.47 (0.98-2.22)
Basic + WC, Education, Region, CVD & DM	1.21 (0.95-1.53)	1.41 (0.99-1.99)	1.07 (0.77-1.48)	1.44 (0.96-2.16)

[a] Sclass – Social Class
[b] DM – Diabetes
[c] WHR – Waist-to-hip ratio
[d] WC – Waist circumference

Table 10-11: Raised $HbA1_c$ and all-cause mortality (no adjustment for CVD at baseline)

Further adjustment	WHOLE SAMPLE	STRATIFIED BY CVD		STRATIFIED BY GENDER		NEVER SMOKERS ONLY
		NO	YES	WOMEN	MEN	
Advanced + Sclass & Region	1.65 (1.35-2.01)	1.52 (1.17-1.97)	1.76 (1.28-2.42)	1.52 (1.17-1.97)	1.76 (1.28-2.42)	1.98 (1.42-2.76)
Advanced + Sclass, Region & DM	1.16 (0.91-1.49)	1.09 (0.80-1.50)	1.41 (0.94-2.10)	1.09 (0.80-1.50)	1.41 (0.94-2.10)	1.56 (1.02-2.37)
Advanced + Education, Region	1.60 (1.31-1.96)	1.52 (1.17-1.97)	1.69 (1.22-2.33)	1.91 (1.42-2.58)	1.41 (1.08-1.84)	1.93 (1.39-2.69)
Advanced + Education, Region & DM	1.15 (0.90-1.47)	1.11 (0.81-1.52)	1.37 (0.92-2.04)	1.29 (0.89-1.87)	1.04 (0.75-1.45)	1.53 (1.01-2.33)
Advanced + WHR, Sclass & Region	1.64 (1.35-1.98)	1.57 (1.23-2.02)	1.62 (1.18-2.20)	1.93 (1.44-2.57)	1.44 (1.11-1.86)	1.93 (1.40-2.66)
Basic + WHR, Sclass, Region & DM	1.20 (0.95-1.53)	1.18 (0.87-1.60)	1.32 (0.89-1.95)	1.40 (0.98-1.99)	1.06 (0.77-1.48)	1.49 (0.99-2.25)
Basic + WHR, Education & Region	1.61 (1.32-1.95)	1.58 (1.23-2.03)	1.57 (1.15-2.15)	1.92 (1.44-2.55)	1.39 (1.07-1.81)	1.90 (1.38-2.61)
Basic + WHR, Education, Region & DM	1.20 (0.94-1.52)	1.19 (0.88-1.61)	1.30 (0.88-1.92)	1.41 (0.99-1.99)	1.05 (0.76-1.45)	1.47 (0.98-2.20)
Age, Sex, Smoking, WC, Sclass, Region	1.67 (1.37-2.02)	1.61 (1.25-2.06)	1.65 (1.21-2.26)	1.96 (1.47-2.62)	1.47 (1.13-1.90)	1.91 (1.39-2.63)
Basic, WC, Sclass, Region & DM	1.23 (0.97-1.56)	1.21 (0.89-1.64)	1.35 (0.91-2.00)	1.42 (1.00-2.02)	1.09 (0.79-1.51)	1.49 (0.99-2.24)
Basic + WC, Education & Region	1.63 (1.34-1.97)	1.60 (1.25-2.05)	1.61 (1.18-2.20)	1.95 (1.46-2.60)	1.41 (1.09-1.83)	1.87 (1.35-2.57)
Basic + WC, Education, Region & DM	1.22 (0.96-1.55)	1.22 (0.90-1.64)	1.34 (0.90-1.98)	1.43 (1.01-2.03)	1.07 (0.77-1.48)	1.46 (0.97-2.19)

10.3 $HbA1_C$ (continuous and tertiles) and all-cause mortality

Using data from all participants with a valid $HbA1_C$ measurement, an assessment of the association between $HbA1_C$ and all-cause mortality was also undertaken using a continuous variable and then using tertiles of $HbA1_C$. The analyses which included the continuous variable demonstrated that there was a small increase in risk of all-cause mortality with each unit increase in $HbA1_C$. This increase remained statistically significant in both the basic and advanced models, but not when CVD, education or diabetes were included in the model (Table 10-12). When alternative measurements of overweight and obesity were included, the increase remained statistically significant, although the increase remained only at the point estimate when CVD was added to the model. Further analyses included a range of these covariates, but did not significantly alter the results shown below.

Table 10-12: All-cause mortality ORs (and 95% CI) and $HbA1_C$ (continuous variable)

Progressive adjustment	**All-cause mortality**
Age, sex	1.10 (1.03-1.17)
& Smoking	1.08 (1.01-1.16)
& BMI	1.09 (1.01-1.17)
Basic & CVD Status	1.05 (0.98-1.13)
Additional adjustment (advanced + the following variables)	
+ CVD	1.06 (0.98-1.14)
+ Education	1.05 (0.97-1.13)
+ Social Class	1.07 (1.00-1.16)
+ Region	1.13 (1.06-1.22)
+ Diabetes	0.93 (0.85-1.02)

Table 10-13: All-cause mortality ORs (adjusting for alternative measures of overweight and obesity) and $HbA1_C$ (continuous variable)

Further adjustment	All-cause mortality
Basic + BMI	1.09 (1.01-1.17)
Basic & WHR	1.08 (1.01-1.16)
Basic & WC	1.09 (1.02-1.18)
Basic + WHR & CVD	1.06 (0.88-1.14)
Basic + WC & CVD	1.07 (0.99-1.15)

A variable was then derived to categorise $HbA1_C$ into tertiles; within the analyses the lowest tertile was used as the reference category. As can be seen in Table 10-14, those with an $HbA1_C$ measurement in the middle tertile had a substantial and statistically significant increase in odds of all-cause mortality (basic model: 1.38, CI 1.19-1.61, advanced: 1.36, 1.15-1.59). However, those in the top tertile had only a small increase at the point estimate (basic: 1.05, 0.91-1.21, advanced: 1.04, 0.90-1.21). Both of these increases remained unchanged after adjustment for a range of covariates, when different measurements of overweight and obesity were included in the model, and when a combination of variables were also included (data not shown).

Table 10-14: All-cause mortality odds ratios ($HbA1_C$ tertiles)

Progressive adjustment	All-cause mortality	
	Tertile 2	Tertile 3
Age & sex	1.32 (1.13-1.54)	1.02 (0.89-1.18)
& Smoking	1.38 (1.19-1.61)	1.05 (0.91-1.21)
& BMI	1.36 (1.15-1.59)	1.04 (0.90-1.21)
Additional adjustment (Advanced + the following variables)		
+ CVD	1.42 (1.21-1.66)	1.08 (0.92-1.26)
+ Education	1.44 (1.22-1.69)	1.09 (0.94-1.27)
+ Social class	1.38 (1.17-1.62)	1.04 (0.90-1.22)

+ Region	1.09 (0.93-1.29)	0.98 (0.84-1.14)
+ DM	1.51 (1.28-1.78)	1.17 (1.00-1.37)

Table 10-15: All-cause mortality ORs ($HbA1_C$ tertiles) including measurements of overweight/obesity

Alternative measurements of overweight and obesity	**All-cause mortality**	
	Tertile 2	**Tertile 3**
WC	1.37 (1.16-1.60)	1.01 (0.87-1.17)
WHR	1.39 (1.19-1.63)	1.03 (0.88-1.19)
Additional adjustment for baseline CVD status		
WC & CVD	1.42 (1.21-1.67)	1.04 (0.90-1.22)
WHR & CVD	1.45 (1.23-1.70)	1.06 (0.91-1.23)

The analyses above demonstrate an association between raised $HbA1_C$ and all-cause mortality. Of particular note is the result that those in the middle tertile appear to have substantially and statistically significant increased odds of all-cause mortality compared with those with a lower measurement, while those in the top tertile have a small increase at the point estimate only.

In order to further test the hypotheses of the current study, and examine how the associations between diabetes and mortality from cancer and other causes may have changed over time, analyses were also performed using data from Whitehall I linked to mortality data. The following chapter details these results.

11. Chapter 11: Results: Whitehall I

11.1 Whitehall I: Further analyses of the associations between diabetes and mortality

11.1.1 Whitehall I: descriptive statistics

As detailed previously, health-related information was collected from 19,019 men working within the Civil Service for the Whitehall I study. Within the dataset there were 237 men who indicated doctor-diagnosed diabetes at baseline (>1% of the total study population). At baseline, the majority of participants were between the ages 46 and 64 years (78%). 15,214 died during the follow-up period (81%), 4,076 from cancer (27%). Table 11-1 gives further information about the study cohort.

Table 11-1: Whitehall I descriptive statistics

Variable	No. (%)	Variable	No. (%)
Age		Social class	
Age-grouped		Administrative	967 (5)
16-64	18,404 (97)	Professional/Exec	12,350 (65)
65-74	615 (3)	Clerical	3,007 (16)
Diabetes		Other	1,809 (10)
Yes	237 (>1)	BCDS	886 (5)
No	18,648 (>98)	Blood glucose	
Overweight/obesity		Normal glucose	17,574 (94)
BMI		Impaired glucose tolerance	1,074 (6)
<20kg/m^2	950 (5)		
20-24.99kg/m^2	9,490 (50)	New diabetes	56 (<1)
25-29.99kg/m^2	7,764 (41)	Insulin dependent DM	48 (<1)
≥30kg/m^2	812 (4)	Non-insulin dependent diabetes	132 (<1)
Smoking status			
Never smoker	3,502 (18)	Unknown IDD/NIDDM	1 (<1)
Ex-smoker	6,934 (36)		
Pipe/cigar smoker	657 (3)	Cause-specific mortality	
Current smoker	7,921 (42)	Cancer	4,076 (27)
Mortality status		CVD	7,105 (47)
Alive	3,664 (19)	Within CVD: CHD	4,346 (29)
Dead	15,214 (81)	Within CVD: Stroke	1,415 (9)

11.1.2 All-cause and cause-specific mortality

Within the Whitehall I dataset, binary variables had already been created for mortality from all causes, cancer, CVD, coronary heart disease (CHD) and stroke. Within this section of the analyses, logistic regression models were developed to explore the association between diabetes and mortality from these causes. The table below indicates the number of deaths from these causes by

diabetes status. In total 219 of the 237 (92%) cases with diabetes at baseline had died within the study follow-up period. This compared with 14,887 of the 18,646 (80%) who did not answer the diabetes-specific question positively. For cancer only 12% of those with diabetes had died from this cause, compared with 22% of those without diabetes. For both CVD and coronary heart disease (CHD), a higher percentage of those with diabetes were recorded as having died from these causes, while 7% of each group had died from stroke.

Table 11-2: Deaths within Whitehall I by diabetes status

Cause of death	Diabetes at baseline	Did not indicate diabetes	TOTAL
All-cause	219 (92)	14,887 (80)	15,106 (79)
Cancer	29 (12)	4,018 (22)	4,047 (27)
CVD	120 (51)	6,935 (37)	7,055 (47)
CHD	87 (37)	4,240 (23)	4,327 (29)
Stroke	16 (7)	1,381 (7)	1,397 (9)

As can be seen from Table 11-3, those who indicated diabetes at baseline had an increased risk of all-cause mortality; the greatest excess was found within the 'basic' model (age and smoking) which gave an OR of 3.39, CI 2.03-5.66. Within all of the models, those with diabetes experienced at least a doubling in odds for all-cause mortality. Unlike the results found within the analyses of Health Survey for England and Scottish Health Survey data, those with diabetes within Whitehall I were found to have a lower risk of dying from cancer compared with those who did not indicate the presence of diabetes. This result remained unchanged within all the models developed ('basic' model: 0.51, CI 0.35-0.75 and 'advanced': 0.51, 0.35-0.76). When the variable related to blood glucose group was added to the model, collinearity was achieved and diabetes was removed by Stata from the model. Therefore this model was dropped from the analyses undertaken for this section of the thesis.

For CVD and CHD increased odds ratios were found for those with diabetes within each of the models. For CVD the ORs ranged from 1.47 (CI 1.13-1.91) within the analysis which only adjusted for age (continuous) to 1.72 (1.33-2.23) for the 'basic' model. Within the analyses focused upon CHD the model which included social class gave an OR of 1.90 (1.45-2.49), while the basic model gave a substantially increased OR of 2.70 (2.18-3.34). Those with diabetes appeared to not have an increased risk of mortality from stroke, within all of the logistic regression models, compared with those without diabetes.

Table 11-3: All-cause and cause-specific mortality among the diabetic cohort within Whitehall I

PROGRESSIVE ADJUSTMENT	All-cause	Cancer	CVD	CHD	Stroke
Age (continuous)	2.22 (1.29-3.80)	0.47 (0.32-0.69)	1.47 (1.13-1.91)	2.28 (1.84-2.82)	0.79 (0.54-1.49)
Age (grouped)	3.27 (1.96-5.44)	0.51 (0.34-0.75)	1.72 (1.33-2.22)	2.69 (2.18-3.34)	0.89 (0.54-1.49)
Age (grouped) & Smoking	3.39 (2.03-5.66)	0.51 (0.35-0.75)	1.72 (1.33-2.23)	2.70 (2.18-3.34)	0.89 (0.53-1.48)
Age (grouped) + Smoking & BMI (grouped)	3.32 (1.99-5.54)	0.51 (0.35-0.76)	1.69 (1.31-2.20)	2.67 (2.16-3.31)	0.89 (0.53-1.48)
Age (grouped) + Smoking & BMI (continuous)	3.34 (1.99-5.58)	0.50 (0.34-0.74)	1.67 (1.29-2.17)	2.63 (2.12-3.25)	0.89 (0.53-1.47)
Additional adjustment (Basic model + the following variables)					
+ Social class	2.99 (1.79-5.00)	0.50 (0.34-0.74)	1.68 (1.30-2.17)	1.90 (1.45-2.49)	0.89 (0.54-1.50)
+ Blood glucose	N/A	N/A	N/A	N/A	N/A
Further adjustment (Advanced model + the following variables)					
+ Social class	2.99 (1.77-4.96)	0.50 (0.34-0.75)	1.66 (1.28-2.15)	1.88 (1.43-2.46)	0.90 (0.54-1.50)
+ Blood glucose	N/A	N/A	N/A	N/A	N/A

11.2 Whitehall I resurvey: all-cause and cause-specific mortality

11.2.1 Whitehall I resurvey: descriptive statistics

In 1997 a second survey utilising a sub-set of participants from Whitehall I occurred (n=7,035). Within this survey, similar health-related questions were asked, as well as lifestyle questions related to behaviours such as smoking and alcohol consumption and socio-economic/demographic factors. Within the resurvey dataset there was information pertaining to the presence of CVD-related comorbidities; this enabled models to be developed, for the purposes of this research, within this section of the analyses which were not possible with the baseline Whitehall I data.

Table 11-4: Whitehall I resurvey descriptive statistics

Variable	No. (%)	Variable	No. (%)
Age		Smoking status	
Age-grouped		Current smoker	803 (12)
65-74	2,532 (36)	Ex-smoker	3,731 (57)
75+	4,503 (64)	Never smoker	2,011 (31)
Diabetes		Mortality status	
Yes	446 (6)	Alive	2,695 (38)
No	6,566 (94)	Dead	4,333 (62)
Overweight/obesity		Cause-specific	
BMI		Cancer	1,038 (15)
<20	258 (4)	CVD	1,816 (26)
20-24.99	2,860 (47)	Within CVD: CHD	889 (13)
25-29.99	2,525 (42)	Within CVD: Stroke	504 (7)
≥30	441 (4)		
CVD at baseline			
Heart attack	825 (11)		
Stroke	579 (8)		
Angina	1,019 (14)		

Table 11-5: Deaths within Whitehall I resurvey by diabetes status

Cause of death	Diabetes at baseline	Did not indicate diabetes
All-cause	337 (76)	3,996 (61)
Cancer	60 (14)	978 (15)
CVD	140 (32)	1,676 (25)
CHD	72 (16)	817 (12)
Stroke	43 (10)	461 (7)

Table 11-6: All-cause and cause-specific mortality among the diabetic cohort within Whitehall I

PROGRESSIVE ADJUSTMENT	All-cause	Cancer	CVD	CHD	Stroke
DM	2.06 (1.65-2.58)	0.90 (0.68-1.19)	1.35 (1.10-1.66)	1.37 (1.05-1.78)	1.43 (1.03-1.98)
Age (continuous)	2.37 (1.86-3.02)	0.90 (0.68-1.19)	1.36 (1.10-1.69)	1.37 (1.05-1.78)	1.42 (1.02-1.98)
Age (grouped)	2.26 (1.79-2.86)	0.90 (0.68-1.19)	1.37 (1.11-1.70)	1.38 (1.06-1.80)	1.44 (1.04-2.00)
Age (grouped) & Smoking	2.19 (1.71-2.79)	0.81 (0.59-1.10)	1.37 (1.11-1.73)	1.37 (1.04-1.81)	1.50 (1.06-2.11)
Basic + Smoking & BMI (grouped)	2.10 (1.61-2.74)	0.80 (0.57-1.12)	1.36 (1.06-1.74)	1.44 (1.07-1.95)	1.44 (0.98-2.12)
Basic & BMI (continuous)	2.14 (1.64-2.78)	0.79 (0.57-1.11)	1.36 (1.06-1.74)	1.43 (1.06-1.94)	1.45 (0.98-2.14)
Basic + CVD	1.93 (1.51-2.48)	0.82 (0.60-1.12)	1.19 (0.94-1.49)	1.08 (0.81-1.44)	1.45 (1.02-2.06)
Advanced + CVD	1.84 (1.40-2.40)	0.81 (0.58-1.14)	1.16 (0.89-1.49)	1.13 (0.83-1.55)	1.38 (0.93-2.04)

Within this logistic regression analysis of data from Whitehall I it appears that those with diabetes are at a decreased risk of mortality from cancer and have similar risks of dying of stroke as those without diabetes. For the former, this result contradicts that found within the analyses which utilised data from the Health Survey for England and Scottish Health Survey. At the same time this analyses confirms the substantially increased odds of mortality from CVD found amongst those with diabetes within the earlier analyses. The following section details the results related to the associations between diabetes and all-cause and cancer mortality assessed using Cox regression/survival analysis and Whitehall I data.

11.3 Whitehall I: All-cause and cancer specific mortality (Cox regression)

Cox regression models were developed which analysed the association between diabetes and all-cause and cancer-specific mortality. For all-cause mortality, the HRs were significantly raised within each stage of the analyses, and remained statistically unchanged throughout the analyses. The HRs were 1.88 (CI 1.88-2.45) and 2.15 (1.88-2.45) for the 'basic' and 'advanced' models, respectively. Those with diabetes were found to have no increased risk of cancer mortality. The 'basic' model produced an HR of 1.01 (CI 0.70-1.46), while the HR for the 'advanced' model was 1.01 (CI 0.70-1.46). When analyses were run that adjusted for blood glucose level, Stata automatically removed

diabetes from the model because collinearity had been achieved. Table 11-7 details the HRs produced within the Cox regression related to the associations between all-cause and cancer-specific mortality found among those with diabetes compared with those who did not indicate the disease at baseline.

Table 11-7: All-cause and cancer-specific mortality HRs among those with diabetes

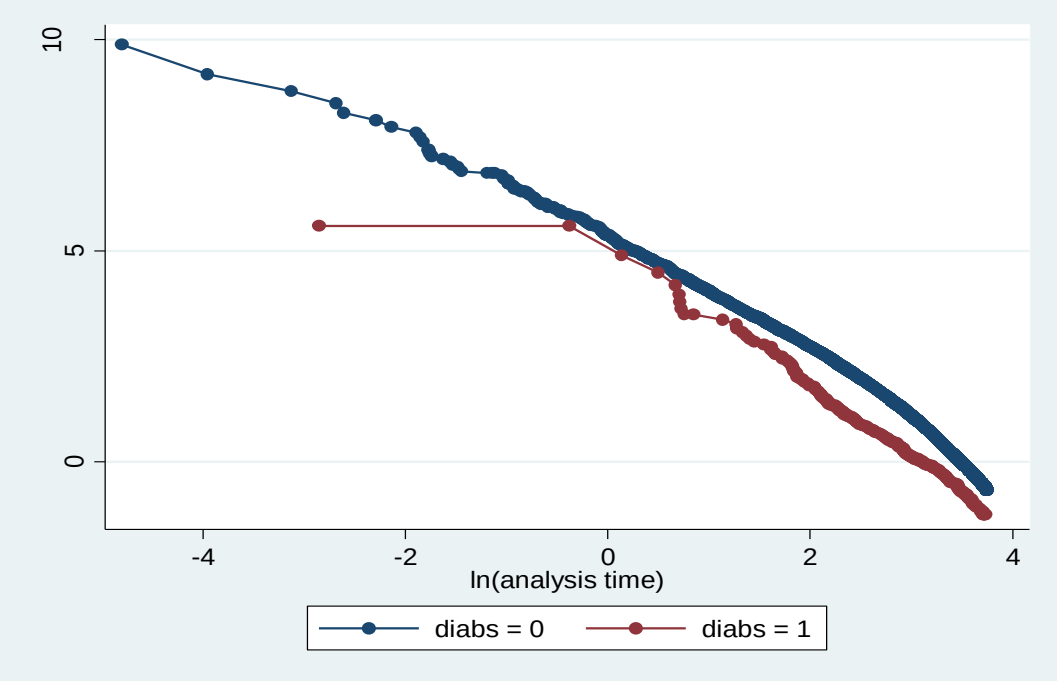
PROGRESSIVE ADJUSTMENT	**All cause**	**Cancer**
DM	2.20 (1.93-2.52)	1.03 (0.72-1.49)
+ age (continuous)	1.82 (1.59-2.08)	0.88 (0.61-1.26)
DM + age (grouped)	2.14 (1.88-2.45)	1.01 (0.70-1.45)
DM + age (grouped) & smoking[a]	2.14 (1.88-2.45)	1.01 (0.70-1.46)
DM + age (grouped) + smoking & BMI (grouped)[b]	2.15 (1.88-2.45)	1.01 (0.70-1.46)
DM + age (grouped) + smoking & BMI (continous)	2.12 (1.86-2.42)	1.01 0.70-1.46)
Further adjustment		
Basic & social class	2.05 (1.79-2.34)	0.97 0.68-1.41
Basic & Blood glucose	N/A	N/A
Advanced & social class	2.05 (1.79-2.34)	0.98 (0.68-1.41)
Advanced & Blood glucose	N/A	N/A

a Within this analyses adjustment for age and smoking is referred to as the 'basic' model.
b Within this analyses adjustment for age, smoking and BMI (grouped) is referred to as the 'advanced' model.

The following survival curves were produced for the models above for all-cause and cancer-specific mortality. The inclusion of a range of covariates did little to alter the results and thus only the survival curve which adjusted for age is shown below.

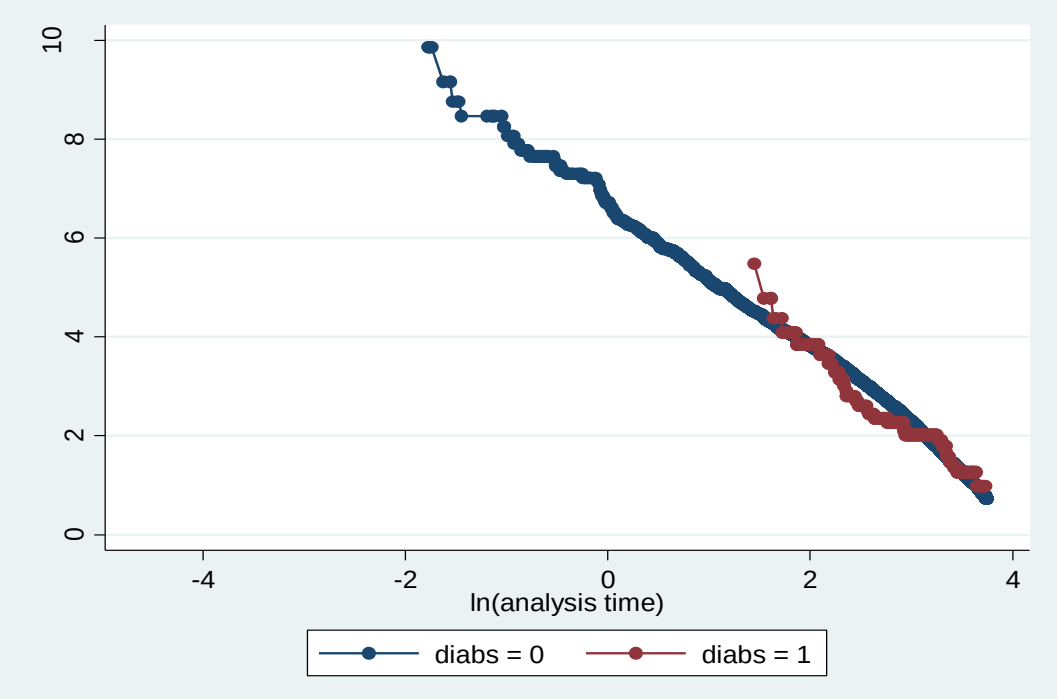
11.3.1 All-cause mortality survival curves

Figure 11-1: All-cause mortality: Whitehall I (age)



11.3.2 Cancer-specific survival curves

Figure 11-2: Cancer mortality: Whitehall I (age)



11.4 All-cause and cancer-specific mortality: Whitehall I resurvey

Within the Whitehall I resurvey data there were binary mortality variables related to all causes and cancer. Using these variables Cox regression analyses were performed which explored the associations between diabetes and mortality from these causes. Among those with diabetes there was found to be an excess in all-cause mortality which remained statistically significant at each stage of the regression modelling. However, there was no association with cancer within any models.

Table 11-8: All-cause and cancer mortality HRs among those with diabetes (Whitehall I resurvey)

PROGRESSIVE ADJUSTMENT	**All-cause**	**Cancer**
DM	1.55 (1.39-1.74)	1.12 (0.86-1.46)
+ age (continuous)	1.58 (1.42-1.77)	1.13 (0.87-1.47)
DM + age (grouped)	1.57 (1.40-1.75)	1.13 (0.87-1.46)
DM + age (grouped) & smoking[a]	1.53 (1.36-1.72)	1.01 (0.76-1.34)
DM + age (grouped) + smoking & BMI (grouped)[b]	1.51 (1.32-1.72)	0.98 (0.72-1.34)
DM + age (grouped) + smoking & BMI (continuous)	1.51 (1.33-1.72)	0.98 (0.72-1.34)
Further adjustment		
Basic & CVD	1.36 (1.21-1.53)	1.02 (0.76-1.32)
Advanced & CVD	1.30 (1.14-1.49)	0.97 (0.71-1.33)

11.5 Diabetes and site-specific cancer mortality: Whitehall I

To further explore the association between diabetes and site-specific cancers, analyses of the Whitehall I data were undertaken using Cox regression. Table 11-9 details the number of cancers within the dataset for which there was available information related to diabetes status (in descending order by number of deaths). For the site-specific cancers, only a small number of cases with diabetes died of each cause; for cancers of the kidney, lymphoid leukaemia, lymphoma and rectum/sigmoid junction/anus no one who had indicated diabetes at baseline had died from these causes by the end of the follow-up period.

Despite the small number of cases among those with diabetes, the association between diabetes and site-specific cancer mortality was assessed using models within Cox regression. Similarly to the results found within the analysis of HSE and SHeS data, the results indicate that the only cancer with a consistent association with diabetes was pancreatic cancer. Contradicting the earlier results, this analysis undertaken using data from Whitehall I suggests that those with diabetes also had a consistently increased risk of mortality from cancer of the liver. This increase also remained throughout the basic, advanced models and further adjustment. Within the Whitehall I data there were binary variables associated with a number of site-specific cancers not available within the HSE and SHeS dataset. For mortality from melanoma and skin cancer, those with diabetes appeared to have a substantial increase in risk, although caution should be taken when exploring these results as only two cases with diabetes died of these causes. The diabetic cohort participants also appeared to have a non-significant increase in mortality from brain tumours compared with those without diabetes. For myeloid leukaemia and cancers of the oesophagus and stomach there were non-significant increases in the HRs. The results for cancers of the colon, prostate, lung and bladder were suggestive of a possible protective effect of diabetes upon site-specific cancer mortality. A power calculation undertaken using the total number of cases with diabetes, within the Whitehall I dataset, and the small number of deaths from some of the site-specific cancers suggested that the analyses were under-powered.

Table 11-9: Site-specific cancer mortality by diabetes status (Whitehall I)

Site-specific cancer	Diabetes	No Diabetes	Total
Lung	<5	975	979
Prostate	<5	631	632
Colon	<5	350	351
Stomach	<5	230	234
Lymphoma	0	215	215
Pancreas	6	198	204
Bladder	<5	193	194
Oesophagus	<5	163	166
Leukaemia	<5	145	146
Rectum, sigmoid junction & anus	0	136	136
Kidney	0	88	88
Myeloid leukaemia	<5	81	82
Skin	<5	65	67
Brain	<5	64	65
Liver	<5	61	64
Melanoma	<5	46	48

Lymphoid leukaemia	0	53	53
TOTAL	30	3,694	3,724

Table 11-10: Site-specific cancer mortality HRs among those with diabetes (Whitehall I)

Progressive adjustment	**Pancreas**	**Liver**	**Colon**	**Lung**	**Melanoma**	**Skin**	**Oesophagus**
DM	4.50 (1.99-10.16)	7.10 (2.22-22.72)	0.40 (0.06-2.87)	0.51 (0.19-1.37)	7.26 (1.75-30.08)	5.13 (1.25-21.02)	2.95 (0.94-9.24)
+Age (cont)	3.94 (1.74-8.91)	6.81 (2.12-21.87)	0.35 (0.05-2.49)	0.41 (0.15-1.09)	7.07 (1.70-29.34)	4.69 (1.14-19.26)	2.64 (0.84-8.30)
+ Age (grouped)	4.48 (1.99-10.13	7.18 (2.24-22.99)	0.40 (0.06-2.83)	0.50 (0.19-1.34)	7.30 (1.76-30.24)	5.03 (1.23-20.65)	2.91 (0.93-9.12)
+Smoking	4.45 (1.97-10.05)	0.40 (0.06-2.83)	0.40 (0.06-2.83)	0.52 (0.19-1.39)	7.30 1.76-30.24)	5.02 (1.22-20.61)	2.82 (0.90-8.84)
+ BMI (grouped)	4.48 (1.98-10.12)	7.35 (2.29-23.58)	0.40 (0.06-2.83)	0.53 (0.20-1.42)	7.38 (1.78-30.54)	5.04 (1.23-20.67)	2.82 (0.90-8.86)
+BMI (cont)	4.43 (1.96-10.01)	7.31 (2.28-23.42)	0.39 (0.06-2.81)	0.53 (0.20-1.41)	7.30 (1.76-30.26)	5.03 (1.23-20.62)	2.79 (0.89-8.76)
Basic + Social class	4.29 (1.90-9.70)	7.21 (2.24-23.14	0.39 (0.05-2.78)	0.48 (0.18-1.29)	7.41 (1.79-30.80)	5.11 (1.24-21.02)	2.82 (0.90-8.86)
Advanced + Social class	4.32 (1.91-9.77)	7.19 (2.23-23.16)	0.39 (0.05-2.77)	0.49 (0.19-1.32)	7.36 (1.77-30.55)	5.10 (1.24-20.97)	2.83 (0.90-8.90)

Table 11-11: **Site-specific cancer mortality HRs among those with diabetes (Whitehall I)(continued)**

	Bladder	Brain	Leukaemia	Myeloid Leukaemia	Prostate	Stomach
DM	0.77 (0.11-5.53)	1.73 (0.24-12.46)	1.03 (0.14-7.35)	1.93 (0.27-13.90)	0.27 (0.04-1.91)	2.22 (0.82-5.97)
+Age (cont)	0.64 (0.09-4.56)	1.62 (0.22-11.72)	0.91 (0.13-6.52)	1.77 (0.25-12.79)	0.23 (0.03-1.63)	1.85 (0.69-4.98)
+ Age (grouped)	0.74 (0.10-5.31)	1.68 (0.23-12.16)	1.02 (0.14-7.32)	1.90 (0.26-13.72)	0.26 (0.37-1.86)	2.18 (0.81-5.87)
+Smoking	0.74 (0.10-5.29)	1.69 (0.23-12.24)	1.00 (0.14-7.14)	1.84 (0.26-13.26)	0.26 (0.04-1.85)	2.23 (0.83-6.01)
+ BMI (grouped)	0.75 (0.11-5.38)	1.70 (0.23-12.27)	0.99 (0.14-7.10)	1.82 (0.25-13.11)	0.26 (0.04-1.85)	2.24 (0.83-6.02)
+BMI (cont)	0.74 (0.10-5.25)	1.69 (0.23-12.19)	1.00 (0.14-7.12)	1.84 (0.26-13.28)	0.26 (0.04-1.85)	2.23 (0.83-5.99)
Basic + Social class	0.73 (0.10-5.19)	1.73 (0.24-12.54)	1.01 (0.14-7.21)	1.92 (0.27-13.84)	0.26 (0.05-1.84)	2.10 (0.79-5.65)
Advanced + Social class	0.74 (0.10-5.32)	1.73 (0.24-12.54)	1.00 (0.14-7.18)	1.90 (0.26-13.66)	0.26 (0.04-1.84)	2.09 (0.78-5.64)

11.6 Site-specific cancer mortality (Whitehall I resurvey)

Within the Whitehall I resurvey dataset, there was a limited amount of information related to site-specific cancers. Table 11-12 details the cancers for which there was available information; only three of the cancers had caused deaths among the diabetic cohort, therefore regression models were developed only for these sites.

Table 11-12: Number of site-specific cancers (Whitehall I resurvey)

Site-specific cancer	Diabetes	Did not indicate Diabetes	Total
Lung	8	146	154
Oesophagus	0	57	57
Pancreas	7	49	56
Rectum etc	<5	33	37
Stomach	0	36	36
TOTAL	19	321	340

Those with diabetes were found to have an excess risk of mortality from pancreatic cancer which was significant within the basic (2.39, CI 1.02-5.61) but not advanced (2.43, 0.96-6.17) models (at

each step of the analyses the point estimate was raised for those with diabetes compared with those without the disease). The HRs were also increased for mortality from cancers of the rectum (and surrounding sites), but the increase was non-significant. For lung cancer those with diabetes appeared to have no excess in mortality risk compared with those without diabetes.

Table 11-13: HRs for those with diabetes (Whitehall I resurvey)

Progressive adjustment	Pancreas	Lung	Rectum
DM	2.61 (1.18-5.68)	0.97 (0.48-1.98)	2.17 (0.77-6.14)
+Age (cont)	2.62 (1.18-5.79)	0.98 (0.48-2.00)	2.20 (0.78-6.22)
+ Age (grouped)	2.62 (1.18-5.79)	0.97 (0.48-1.99)	2.18 (0.77-6.16)
+Smoking	2.39 (1.02-5.61)	0.88 (0.41-1.89)	1.75 (0.53-5.75)
+ BMI (grouped)	2.43 (0.96-6.17)	0.93 (0.41-2.12)	1.42 (0.34-6.02)
+BMI (cont)	2.39 (0.94-6.06)	0.94 (0.41-2.13)	1.38 (0.32-5.86)
Basic + CVD	2.45 (1.04-5.79)	0.92 (0.43-1.96)	1.67 (0.50-5.55)
Advanced + CVD	2.33 (0.91-6.00)	0.97 (0.42-2.12)	1.30 (0.30-5.59)

The results presented in this section suggest that those with diabetes have an increased risk of mortality from a number of the site-specific cancers under investigation. Within both the analyses of the HSE and SHeS (combined) and Whitehall I datasets, it appears that the strongest association is between diabetes and cancer of the pancreas. This association was present within both the multinomial logistic regression and Cox regression and remained after adjustment for a range of covariates. The point estimate increases for a number of the site-specific cancers suggests that there may be an association between diabetes and these cancers that requires further analysis with datasets with sufficient numbers and the power to fully assess the association between the two diseases.

The chapters above detailed the associations between diabetes, $HbA1_C$ and incidence of and mortality from cancer (both all-cause and site-specific) as well as all-cause and cause-specific mortality. The results suggest that there are differences in the excess mortality experienced by those with diabetes dependent upon the group being investigated (in terms of the study cohort, sex, whether or not comorbid CVD is present and whether the participants were smokers). Within the Health Survey for England and Scottish Health Survey dataset, which includes >204,000 participants aged 16 and over, followed from 1994-2008 to 2011 (England) or from 1995-2003 to 2008 (Scotland), it appears that those with diabetes have an excess of cancer mortality (compared with the general public) which is little attenuated by the inclusion of potential confounding factors within the regression models. The results from analysing Whitehall I participants, at baseline and resurvey, contradict this result and find that those with diabetes have similar cancer mortality risk when compared with those without diabetes. The reasons for these differences in results are explored in the discussion chapter below.

12. Chapter 12: Discussion

12.1 Key findings of the current study

What is already known

- Diabetes is associated with an excess in mortality from all-causes and CVD.
- The biological cause of this excess is thought to relate primarily to the biological impact that hyperglycaemia has upon the body.
- There is heterogeneity within study results related to the associations between diabetes and cancer incidence and mortality.
- Hyperinsulinaemia and hyperglycaemia are thought to increase the risk of cancer among those with diabetes, although related factors (such as overweight and obesity) may also play a role.
- The most consistent evidence of an association relates to cancers of the liver, pancreas and endometrium, as well as less consistent results relating to those of the colorectum, breast and bladder. There also appears to be some evidence that those with diabetes have a reduced risk of mortality from cancers of the lung and prostate.

What this study adds:

- Evidence of associations between diabetes and incidence of and mortality from cancer, within a recent, nationally representative general population sample, that remains after adjustment for a range of confounding factors. Of particular interest is the persistence of the association after inclusion of different measures of overweight and obesity and the presence of comorbid CVD within the regression models.
- Support for there being an association between raised $HbA1_C$ and cancer incidence and mortality, and mortality from other causes.
- Evidence of diabetes and $HbA1_C$ being associated with increased site-specific cancer incidence and mortality.
- Results suggestive of differences in cancer risk dependent upon sex and comorbid CVD status.
- Evidence of increased risk of developing and dying from a range of cancers,
- Support for diabetes, rather than related factors such as overweight and obesity, being associated with cancer incidence and mortality and mortality from other causes.

The literature review undertaken as part of this thesis suggested that there were still a number of unanswered questions in relation to the associations between diabetes and cancer. One of these questions related to whether it was the presence of diabetes (via hyperglycaemia and/or hyperinsulinaemia and the other consequences of the condition) or underlying factors present at a

high rate among people with diabetes (for example overweight and obesity) that increased an individual's risk of developing or dying from cancer. The results of the current study suggest that the presence of overweight and obesity has little impact upon the excess mortality and incidence of cancer among those with diabetes compared with the general population. This finding lends support to diabetes, in and of itself, being the cause of the excess in cancer among those with diabetes. The key hypotheses at the heart of this study, that '*the specifics of having diabetes directly increase the risk of an individual developing cancer. This increase in cancer incidence is above that caused by related factors such as adiposity.*' and '*individuals with diabetes are more likely to die of cancer than individuals who do not have diabetes*', are supported by the following results:

- Diabetes was associated with an increased risk of cancer incidence and mortality, which remained after adjustment for a range of confounding factors including overweight and obesity and socioeconomic and demographic status.
- Adjusting for BMI, waist-to-hip ratio or waist circumference had little impact upon the associations between diabetes and cancer incidence and mortality.

The literature review also demonstrated a lack of evidence related to the associations between $HbA1_C$ and cancer incidence and mortality, as well as mortality from other causes. In this regard the study produced a number of novel findings, including evidence of:

- $HbA1_C$ being associated with an excess in cancer mortality and incidence within a nationally representative UK sample linked to up-to-date mortality and Cancer Registry data.
- $HbA1_C$ being associated with an increased risk of dying from all-causes and causes other than cancer.
- Differences in cancer incidence and mortality between those with diabetes but with or without comorbid CVD.
- Comorbid CVD altering the all-cause and cause-specific mortality risk among those with diabetes.

There was also a limited amount of evidence related to the impact comorbid CVD might have upon the associations between diabetes, $HbA1_C$ and cancer incidence and mortality. A further hypothesis, developed in light of the results of the literature review, that 'comorbid CVD alters the strength of the association between diabetes and incidence of and mortality from cancer' was also supported by the results of this research.

- Those with diabetes and comorbid CVD had differences in their cancer mortality risk compared with those with diabetes but without CVD.
- Only those with diabetes but without comorbid CVD at baseline had an increased risk of cancer incidence.
- There were differences in the risk of all-cause and cause-specific mortality between those with diabetes and comorbid CVD and those with only diabetes.

One of the key weaknesses of previous studies, which sought to explore the associations between diabetes, $HbA1_C$ and site-specific cancer incidence and mortality, was the small number of site-specific cancer events within study follow-up periods. This issue was also relevant to the current study, but the consistency within results – in finding point estimate increases in site-specific cancer risk among those with diabetes when compared with the general population – are indicative of an association and add further evidence to the results of earlier studies. The strength of the results related to $HbA1_C$ are hindered by a lack of power, but again, many of them suggest an association between raised $HbA1_C$ and incidence and mortality from a number of site-specific cancers.

12.2 Diabetes and cancer mortality

Two hypotheses were explored within the literature review carried out for this study, which seek to explain the current evidence related to the biological plausibility of a causal relationship between diabetes and cancer (Section 2.6). The first of these suggests that the proliferative (encourages cell growth and multiplication), mitogenic (triggers mitosis) and anti-apoptotic (reduces cell suicide) effects of hyperinsulinaemia (increased insulin in the blood often in response to reduced insulin sensitivity within the body) and increased levels of Insulin-like Growth Factor-1 (IGF-1) are the main cause of the relationship.(207–209) There is also a limited amount of evidence that some cancer cells produce, and may even over-produce, receptors for IGF-1 and insulin.(214) Hypothesis two takes into account a more diverse range of factors, related to diabetes itself as well as confounding factors such as obesity, which may explain the association between diabetes and cancer. The earliest finding in this area was made by Warburg, who found that cancer cells utilised insulin at higher rates than normal cells and could survive without oxygen if they were in a glucose-containing serum.(99) Following this finding it has been postulated that inducing hypoglycaemia could cause cancer remission, although because cancer cells utilise glucose at near full-capacity regardless of environment, this has been disputed and the evidence is limited.(215)

An element of the second hypothesis also relates to the increased risk of cancer incidence and mortality among those who are overweight/obese. (216,217) Overweight and obesity are associated with increased levels of adipose tissue which are, in turn, associated with altering the levels of cytokines such as Inter-leukin-6 and leptin (which may reduce cell apoptosis and encourage insulin sensitivity and cell metastases) and adiponectin (an insulin sensitiser) within the body.(216,220,221) In short, the second hypothesis supports the view that the increase in cancer mortality found among those with diabetes is due to factors related to diabetes, as well as factors related to the body being in a state of overweight/obesity.

The detailed literature review presented in chapter 2 outlines the history of studies investigating suggested associations between diabetes and cancer. During the 1980s studies began to be undertaken which overcame some of the weaknesses of earlier studies, although there was still heterogeneity within study results and a number of studies still had small numbers of concurrent diabetes and cancer or failed to adjust for confounding factors.(75,302) Perhaps as a consequence of this, a number of studies found lower cancer mortality among those with diabetes,(109) some found rates similar to the general population,(75) while others found increased risk.(84)

Within the HSE and SHeS combined dataset, a total of 5,571 cases died of cancer during the follow-up period, including 355 who had indicated diabetes at baseline. The results of the analyses of the HSE and SHeS combined dataset are in agreement with the Emerging Risk Factors Collaboration (ERFC) study which utilised pooled data from 97 prospective studies and a recent meta-analysis which included 12 studies.(84,110) The adjusted (age, sex, smoking and BMI) all-cause cancer mortality HR found within the ERFC study was 1.27, 95%CI 1.20-1.34, while the RR within the meta-analysis was 1.16, 1.03-1.30. Within this HSE/SHeS study the adjusted (age, sex, smoking and BMI) OR for those with diabetes was 1.27, 1.12-1.43. Across the various HSE/SHeS models, the increased odds of dying of cancer among those with diabetes compared with the general population changed little and were indicative of around a 20% increased odds of dying of cancer among those with diabetes. Of particular note is the finding that, whether a measurement of overweight and obesity was adjusted for or not, and whichever anthropometric measurement was included within the regression model, the increase in odds of dying of cancer was unchanged and remained statistically significant among those with diabetes. This suggests that the association between diabetes and cancer mortality may relate to the specifics of having diabetes, and goes some way to refuting the conclusions of earlier commentators that the association was caused by the confounding factors which accompany diabetes, particularly obesity.(303) The result also differs from those found for the association between diabetes and mortality from respiratory disease among men, which was

indicative of overweight/obesity being the underlying mechanism. The only covariate which reduced the statistical significance of the association between diabetes and mortality from cancer was $HbA1_C$; as with the results related to respiratory disease, this may relate to the small number of deaths from this cause among the substantially smaller number of participants with both diabetes and a valid $HbA1_C$ measurement.

Within the Whitehall I dataset there were 4,047 deaths from cancer, including 29 among those who indicated diabetes at baseline. When the binary cancer death variable (death from cancer vs. alive or other cause of death) was used within logistic regression models, those with diabetes were found to have a lower risk of dying of cancer compared with those without diabetes (OR adjusted for age, smoking status and BMI at baseline 0.51, 0.35-0.76 and at resurvey 0.80, 0.57-1.12). However, when Cox regression models were developed, those with diabetes, within the advanced model, were found to have the same cancer mortality as those without diabetes (baseline 1.01, 0.70-1.46; resurvey 0.98, 0.72-1.34). The differences in these results are probably caused by the inclusion of time to event within the Cox regression models. An earlier study, that utilised the same Whitehall I data with a follow-up period of 25 years rather than the 40 years available for this study, found that those with Non-Insulin Dependent Diabetes (NIDDM) had an HR of 0.73 (0.44-1.19) compared with those without diabetes.(89)

The Whitehall results appear to contradict the findings of the analyses of the HSE and SHeS data. This discrepancy is likely to be a result of the provision of a binary variable which categorises cases into either 1) those who are still alive or have died of any cause other than cancer (including CVD which those with diabetes were found to have a substantially increased risk of dying from within the analyses of both Whitehall I and HSE/SHeS datasets) or 2) those who have died of cancer, rather than having a variable which allows for competing causes of death to be considered. Because of this, the multinomial logistic regression used with the HSE and SHeS combined dataset, which does utilise the competing cause of death technique, was considered to be more accurately representative of the risk of dying of cancer among those with diabetes compared with those without diabetes. Another explanation, the issue of possible changes in cancer mortality risk over time among people with diabetes, is discussed in more detail below.

Two recent studies explored the associations between diabetes and cancer mortality among men and women. The first used data from the Cancer Prevention Study-II (CPS-II) in America, mentioned previously, and found an increased relative risk of mortality from cancer among those with diabetes (men 1.07, 1.04-1.11 and women 1.11, 1.06-1.15).(110) The second used data from 17 population-

based or occupational cohorts from Europe and found HRs of 1.71, 1.35-2.17 among men with known diabetes and 1.27, 1.02-1.57 for men with undiagnosed diabetes; the corresponding HRs for women were 1.43, 1.01-2.02 and 1.31, 1.00-1.70, respectively.(80) The use of occupational cohorts may be different to those from the general population due to the 'healthy worker effect' wherein those in work are found to have lower overall mortality compared with the general population because those who are too ill to work are not included within the cohort.(304) Despite this, both of these results are in agreement with the results of this current HSE/SHeS study, which found adjusted ORs of 1.27, 1.05-1.54 and 1.25, 1.10-1.47 among men and women, respectively. The results of these three studies demonstrate that there may be country differences in the magnitude of the effect that diabetes has upon cancer mortality, although the differences may be a chance finding and the confidence intervals indicate that there may not be a difference. Although future studies could explore whether or not there are differences in diabetes treatment regimens administered and the severity of diabetes within countries, further research might also wish to consider whether or not those with diabetes are offered different cancer-related treatments once they are diagnosed with the disease (affecting mortality but not incidence).(276,305)

An intriguing finding of the stratified analyses was that when $HbA1_C$ was included within the HSE/SHeS model, the OR for women increased substantially (2.45, 1.24-4.86) while for men the same analyses produced a non-significant reduction in risk of mortality from cancer among those with diabetes (0.73, 0.39-1.35). This result will be further explored within the discussion related to $HbA1_C$ and cancer mortality (below), but it appears that further studies could be undertaken which clarify this potential difference in risk between the sexes and establish whether this was a chance or substantive finding. Further to this, although adjusting for BMI did not significantly alter the increased odds of dying from cancer among those with diabetes compared with the general population, when the abdominal obesity measurements (waist-to-hip ratio and waist circumference) were included, the association among both men and women became non-significant but remained raised at the point estimate. This lack of significance may relate to the number of participants who had valid measurement for these variables: within the whole sample 89% had a measurement related to BMI compared with 56% for waist-to-hip ratio and waist circumference.

Those who had diabetes but did not indicate CVD at baseline were found to have statistically significant increased odds of mortality from cancer, while those with diabetes and comorbid CVD had an increase at the point estimate, but the result was not significant. It may be that those with diabetes and comorbid CVD are diagnosed with cancer earlier than those with only diabetes because the former make more visits to their healthcare providers. Those with diabetes and CVD may also

have their insulin and glycaemic levels under tighter control compared with those with only diabetes, which may increase cancer cell apoptosis, while reducing the ability of a developing cancer to proliferate. Those with diabetes and CVD may also be taking CVD-related medications which alter their cancer risk – although whether there is a biological plausible relationship between these medications and increased cancer risk has yet to be confirmed or refuted. Finally, cases are at risk of experiencing morbidity from a number of different causes simultaneously, but can only experience death from one. Those with diabetes and comorbid CVD were found to have age-standardised mortality that was above those with only diabetes. Among women 12% of those with diabetes had died, compared with 16% of those with diabetes and comorbid CVD. The corresponding figures were 14% and 17% among men, respectively. Among women and men who had neither diabetes nor CVD the figure was 9% and for only CVD 11% and 13%, respectively. It could therefore be postulated that those with diabetes, but not comorbid CVD, are living longer and therefore have the opportunity to live to an age within which the risk of developing and dying from cancer are raised.

Because those with diabetes have lower smoking rates, and when they do smoke are more likely to attempt to quit,(306) it would be expected that those without diabetes would have higher mortality than those with diabetes from cancer if it were caused by residual confounding from smoking. In analysis restricted to those who indicated that they had never been a regular smoker, the results within the basic (age and sex) and advanced (basic + BMI) models demonstrated an increase in risk of dying of cancer; this persisted but the confidence intervals were indicative of a non-significant association when alternative measures of overweight and obesity were included. Similarly to the results for CVD, those for cancer mortality suggest that the increase in cancer mortality may be due to the presence of diabetes itself and not confounding from related factors. However, the small number of those within the non-smoking group who indicated having diabetes means that caution should be taken when drawing conclusions from these results.

One explanation for the increased risk of mortality from cancer among HSE and SHeS participants with diabetes may relate to those with diabetes being diagnosed with cancer at a later stage of the disease. Within a recent study focussed upon women over the age of 66, those with diabetes had a 19% increased odds of being diagnosed with late-stage breast cancer compared with those without a comorbidity.(307) In contrast some earlier research, particularly the work of Berkson, suggests that those with diabetes may be more likely to be diagnosed with other diseases because they come into regular contact with healthcare services.(103) Other reasons for such an increase in cancer mortality may be the biological impact that hyperinsulinaemia and hyperglycaemia have upon the whether or not cancers proliferate and metastasize within the body,(308) the differences in the cancer

treatments offered to those with and without diabetes,(305) and the reduction in the effectiveness of chemotherapy upon cancer within the body of someone with diabetes.(309) There is also some evidence that treatments for cancer have higher rates of toxicity in people with diabetes and may increase the risk of mortality from other causes, and that this group may be more likely to be unsuitable for cancer-related surgery.(310) A study by Renehan et al. concluded that diabetes increases mortality from cancer because of delays in cancer diagnosis, differences in cancer treatment, and differences in outcomes related to specific cancer types between those with and without diabetes.(311) Finally, if those with diabetes have increased cancer incidence compared with the population without diabetes (discussed in the next section), then the increased mortality from cancer may have more to do with factors which produce this increased incidence rather than those which occur post-diagnosis.

Within the Whitehall I baseline and resurvey data analyses it appeared that those with diabetes had a similar risk of cancer mortality compared with people without diabetes, or even a substantially reduced risk using the baseline data. This result may be a statistical artefact related to the use of a binary variable within the analyses or the impact of the 'healthy worker effect' mentioned above. Those with diabetes in Whitehall I had a substantially increased risk of mortality from CVD. Therefore if the risk of cancer mortality is analysed in comparison with those with diabetes who had died of CVD, then it is likely that the outcome will be an apparent reduced risk of cancer mortality. Binary logistic regression was also used in a number of the earlier studies focused upon diabetes and cancer and may explain why they also found a reduced cancer risk among those with diabetes.

The next section considers the results for diabetes and cancer incidence, in the context of these findings on cancer mortality.

12.3 Diabetes and cancer incidence

While mortality from a particular cause is a combined measure of the development of disease and deaths from it, incidence enables a more detailed explanation of the former. Understanding whether those with diabetes develop cancer at an increased rate compared with the general population can inform our knowledge related to the underlying causes of the associations between the two diseases and enable the development of measures and treatments to reduce the excess. If an association were to be found, programmes which sought to address the increasing prevalence of diabetes could also be considered in the context of cancer prevention. Within the literature review it was observed that the majority of studies were focussed upon mortality from cancer. The cause of this may be the

availability of mortality data compared with that for cancer incidence: within this current study, mortality data were more easily accessible than that for the Cancer Registry.

Among studies which were focussed upon the associations between diabetes and cancer incidence, the results were heterogeneous. A 1997 study found a marginally increased incidence of cancer among those with diabetes compared with the general population, although their use of data from patients who had been hospitalised makes the extrapolation of their results to the general population problematic.(172) Zendehdel found that those with type-1 diabetes also had an increased risk of developing cancer (standardized incidence ratio: 1.2, CI 1.0 to 1.3).(173) A number found similar incidence among those with diabetes compared with the general population.(168) Gu et al. found similar cancer incidence among those with type-2 diabetes whether or not they were being treated with insulin.(312) A number of studies focussed upon site-specific cancer incidence and these results will be discussed in the appropriate sections below.

Within the current study those with diabetes were found to have an increased odds of developing cancer compared with the general population of over 10%; this increase remained within the basic (adjusted for age, sex and smoking status), the advanced model (basic + BMI) and when alternative measurements of overweight and obesity were included within the model. The biological plausibility of such an association was discussed extensively within the literature review above, related to cancer mortality. Specifically to cancer incidence, it appears that the state of hyperinsulinaemia, which occurs in the initial stages of diabetes (and may start during the pre-diabetes state), IGF-1 and hyperglycaemia facilitate the proliferation of cancer cells and reduce the occurrence of cell apoptosis. It therefore appears that those with diabetes are more likely to develop cancer and are consequently more likely to die of the disease compared with the general population. As mentioned previously, those with diabetes may come into contact with health care services more regularly than those without diabetes, so may be more likely to be diagnosed with other conditions, including cancer. At the same there is some evidence that women with diabetes are less likely to take up cancer screening for breast and cervical cancer; the reasons for this are complex and may relate to the complex healthcare needs of those with diabetes leaving less time for services related to disease prevention, the age of those with diabetes compared with the general population and the perception of reduced survival among those with diabetes among their healthcare providers.(313)

One issue that was not addressed within this current study was the influence that diabetes medications have upon an individual's risk of developing and dying from cancer. There is a growing body of evidence suggesting that metformin reduces cancer risk (in terms of incidence and

mortality) compared with other diabetes medications.(314,315) This reduced risk appears to relate to the pro-apoptotic and anti-mitogenic nature of metformin; rosiglitazone, another drug used to treat diabetes, was also found to have the same properties.(316) If the alterations in insulin levels which define diabetes are a causal factor within the increase in cancer incidence among those with diabetes, then the use of exogeneous insulin could also be altering cancer risk. Insulin has been found to encourage cell proliferation and chemoresistance; the latter may contribute to the excess in cancer mortality found among those with diabetes.(316) Additionally, as the disease progresses individuals with type-2 diabetes may be prescribed a plethora of different oral medications as well as exogeneous insulin. The changing drug regimens administered to those with diabetes means that unravelling the impact of one medication (over the confounding caused by the other medications that an individual may be taking) upon cancer risk is beyond the scope of a study of this nature. Future randomised controlled trials could be undertaken which would enable an effective exploration of the impact of individual diabetes treatments upon the association between diabetes and cancer.

An American study used data from the National Institutes of Health - American Association of Retired Persons Diet and Health Study and found that cancer incidence among women with diabetes was raised (HR 1.07, CI 1.02-1.12) but that among men, the inverse was true (HR 0.96, 0.93-0.98).(317) A 2006 study from Japan contradicts this result, and found that men with diabetes had an increased risk in relation to cancer incidence while women did not.(318) A contributing factor to this may be the differing CHD risk among these populations – the mortality rate for CHD in Japan is the lowest in the developing world and has been estimated to be between one-third to one-fifth that of America.(319) For a middle-aged Japanese man, the incidence rate for CHD was found to be ≤2 per 1000 compared with 5 to 6 per 1000 for an American man, while for women the equivalent figures were ≤1 and 2 to 3 per 1000, respectively. Adding further inconsistency to the results of previous studies, a Korean study found that both men (HR 1.24, 1.20-1.8) and women (1.33, 1.25-1.41) with diabetes had increased risk of cancer incidence.(320) The result of this current study support those of the first study: women had a statistically significant increased odds of developing cancer (after adjusting for age, sex, smoking and BMI the OR was 1.16, 1.02-1.33) while for men the OR was indicative of similar risk to those found among the general population (1.03, 0.91-1.17). The reason for these similarities, and differences, in results may be the make-up of the study samples. The cohort from the US and current study were made up of samples taken from the diverse populations of these countries, while the populations of Japan and Korea are relatively homogeneous, genetically. There are also differences in the baseline CHD risk (including when CHD develops and sex differences in risk) between the countries within the studies.

The results of analyses related to diabetes and cancer incidence which utilise a grouped variable (all site-specific cancers) are likely to be altered by the site-specific cancers which make up the variable. If, within a study cohort, there are more cases of a cancer for which those with diabetes have a reduced incidence, compared with the general population, then analyses are likely to produce results which show a decrease or no increase in incidence. Correspondingly, if the variable includes a large number of cases of cancers for which those with diabetes have an increased incidence, then the result is likely to be contradictory. Within the current study, a large number of deaths were from lung cancer, and as shown below, those with diabetes were found to have an increased incidence of this cancer. The American study, mentioned above, suggested that the reduced risk of cancer incidence among men may be driven by the reduced risk of prostate cancer incidence found among men with diabetes; once they excluded this cancer site from their analyses men with diabetes were also found to have an increased risk of cancer incidence.(317) The key difference between that study and the current one is that 43% of incident cancers were from prostate cancer in the former, while in this study it only accounted for 13%. Further to this, as can be seen from the results given in the section related to prostate cancer within the current study (Section 12.4), men with diabetes were found to have similar cancer incidence to the general population for a number of site-specific cancers. Future studies should be aware of the rates of each site-specific cancer making up the overall cancer incidence variable and may conclude that analyses of such a variable is not advisable.

When the analyses were stratified by CVD status, those with diabetes but without comorbid CVD were found to have a statistically significant increased incidence of cancer, while those with diabetes and CVD had a non-significant reduced odds. As with cancer mortality, the reasons for this are unclear but could be a result of the increased mortality from other causes among those with diabetes and CVD. In essence, that those with both diabetes and CVD die of another cause before reaching an age where cancer incidence is more likely. The sensitivity analysis, performed using data only from those who indicated that they had never been a regular smoker, indicates that those with diabetes do not have an increased incidence of cancer compared with the general population. If this result is not a chance finding, in collaboration with those for cancer mortality, it indicates that those with diabetes do not have an increased incidence of cancer but are more likely to die of the disease than their non-diabetic counterparts. The reasons for this increased mortality are discussed in the previous section.

Because of the differing aetiologies and incidence of site-specific cancers a number of commentators suggest analysing the associations between individual cancers rather than cancer overall.(303,321) In order to assess the associations between diabetes and site-specific cancer incidence and

mortality, analyses were then performed for a number of specific cancers. The next section details these results within the context of earlier studies and explores the biological reasons why these associations may exist.

12.4 Site-specific cancer incidence and mortality

Lung cancer

Lung cancer causes the greatest number of site-specific cancer deaths within the UK (around one in five cancers among men and women combined).(111) None of the studies which explored the association between diabetes and cancer commented upon the specific biological mechanism that may underpin an association between the two conditions.

Incidence

Within the HSE and SHeS dataset there were 1,373 incident cases of lung cancer, including 96 among those with diabetes. Within the basic model (adjusted for age, sex and smoking status) there was a statistically significant increased OR, which became marginally non-significant when BMI was added to the model. This result is supported by earlier research by Steenland et al.(322) and a second study found an adjusted HR of 1.05, 0.96-1.26.(113) Contradicting this, Hall et al. used data from the UK's General Practice Research Database (their sample included over 66,000 individuals with diabetes as well as age, sex and GP practice matched controls) and found a decrease in HR for incidence of lung cancer among those with diabetes of 0.88, 0.79-0.97,(112) Some studies did not adjust for smoking and considering the impact that this factor has upon lung cancer incidence the relevance of their results are difficult to assess.(172) Two recent meta-analyses also demonstrated conflicting results. The first demonstrated lower incidence of lung cancer, concluding that the disease may be protective against lung cancer.(323) The second found that women with diabetes had a statistically significant increased risk, while men did not.(116) The results of the analyses when split by sex were raised at the point estimate within each of the models for both men and women; but statistical significance was not maintained across all of the models. For example for men the association only became statistically significant within the advanced model (age, sex, smoking status and BMI), while for women the association became non-significant when this covariate was included.

The small number of studies investigating the associations between diabetes and incident lung cancer and the mixed results found within this, and previous studies, suggests the need for further research in this regard. It is also worth noting that survival for lung cancer is consistently low and those with diabetes, once diagnosed with lung cancer, appear to have shorter survival times than the general population.(324)

Mortality

Within the current study 1,297 participants died of the disease (including 88 who indicated diabetes at baseline). Within the literature review only a small number of studies were found which had explored the potential association between diabetes and mortality from lung cancer and their results had been inconsistent. A study of lung cancer mortality risk among post-menopausal women with and without diabetes found that the former had an increased HR of 1.27, 1.02-1.59(114); the ERFC study found an HR of 1.27, 1.13-1.43 among those with diabetes (86); and a meta-analysis found a RR of 1.11, CI 1.02-1.20 among those with diabetes.(116) The results of the multinomial logistic regression undertaken within the current study support the result of these studies. Within the basic and advanced models those with diabetes had substantially increased odds of dying of lung cancer at the point estimate, but the association was marginally non-significant. Within the Cox regression the increase at the point estimate was increased even further within the basic model (HR: 1.31, 1.05-1.64) but became non-significant when BMI was added to the model (1.22, 0.96-1.56). This lack of association supports the results of an earlier study undertaken among a Hong Kong cohort (≥65 years of age) which found that obesity was associated with reduced mortality from lung cancer; the researchers also suggested that genes which predispose individuals to being overweight/obese may be protective against lung cancer.(325) A meta-analysis also found that overweight/obesity was associated with a reduced risk of developing lung cancer, given the short life-expectancy for those diagnosed with the disease it is likely that any reduction in risk of developing lung cancer would also impact upon mortality risk.(323)

The results of the analyses of the Whitehall I data are in agreement with an earlier study which utilised the same data but had a shorter follow-up period: both were indicative of those with diabetes having a reduced risk of mortality from lung cancer.(89) As with the results related to overall cancer and respiratory disease mortality, it is likely that the differing smoking rates found among those with diabetes compared with the general public mean that the former would have a lower risk of developing, and therefore dying, of lung cancer. Within the current study a categorical variable related to smoking was used within the analyses; this variable categorised cases into three groups (current smokers; ex-regular smokers and never-regular smokers). Although a similar variable is used within the majority of recent studies that explore the associations between diabetes and cancer, further analyses could be undertaken that uses more detailed smoking related information, which would allow for an assessment of whether or not cigarette consumption differs between those with and without diabetes, and the impact that this residual confounding may have upon differences in cancer mortality.

A 2010 study found that diabetes was not associated with a risk of dying of lung cancer among either men or women with diabetes.(80) The results of this current study are indicative of an association between diabetes and lung cancer mortality; although for neither men nor women were the results statistically significant. The point estimates were raised among those with diabetes and without comorbid CVD and were similar for those with diabetes and comorbid CVD. This result implies that there is no difference in risk between the two groups; while the results of earlier studies suggest that the obesity which often accompanies type-2 diabetes may protect those with the disease against developing and consequently dying of lung cancer.

Colorectal cancer

Colorectal cancer includes those of the colon and rectum and is the second largest site-specific cause of cancer mortality in the UK, killing over 16,000 individuals in 2008.(117) Globally, 1.28 million individuals were diagnosed with the disease in 2008.(118) Although the biological plausibility of a causal relationship between diabetes and colorectal cancer is poorly understood, there is a limited amount of evidence that the increased presence of conditions such as autonomic neuropathy among those with diabetes may slow the movement of faecal matter within the colon and increase the risk of developing colon cancer.(222,326)

Incidence

Within the HSE and SHeS dataset there were 989 cases of colorectal cancer within 68 of these occurring among those with diabetes at baseline. While the results of the current study were inconclusive, although the point estimate was raised the confidence intervals were indicative of a non-significant association, those of earlier studies demonstrated an increased risk of developing colorectal cancer among those with diabetes. A case-control study found that those in the highest quintile in relation to c-peptide, an indicator of the insulin level within the blood, were at an increased risk of developing colorectal cancer.(119) One of the reasons for these differing results may be the study samples: in the earlier study the sample was made up of 14,916 male doctors, while the current study uses a sample made up from the general population.

The results in relation to the associations between diabetes and incident colorectal cancer when the dataset was stratified by CVD appear to indicate no difference in risk among either group. Similarly, for both men and women, although the point estimate was raised the association appeared non-significant. These results could be down to chance and require further analyses using data with a greater number of outcomes of interest.

Mortality

Within the current study there were 552 deaths from cancers of the colorectum, with 34 of these being among those with diabetes. Although consensus has not been reached as to the association between diabetes and mortality from colorectal cancer, the majority of studies found within this study's literature review did support an association – including a meta-analysis which utilised data from over 2.5 million study participants.(86,87,121) Those with diabetes who are then diagnosed with colorectal cancer also have a higher risk of all-cause mortality compared with those without diabetes.(120)

Within the multinomial and Cox regression analyses there was found to be point estimate increases within each of the models. These results are compatible with an earlier study which found non-significant increases for risk of dying from this cause.(80,327) The latter study concluded that, although the result appeared non-significant, there was enough evidence to suggest that there appeared to be an association between diabetes and colorectal cancer mortality. The study then went on to stratify their analyses by sex, and found that the association became statistically significant for men, while among women those with diabetes appeared to have a lower risk than women without diabetes. Within the current study, both men and women with diabetes were found to have a non-significant increase in risk of mortality from colorectal cancer compared with those without diabetes. When stratification occurred based upon CVD status, those with diabetes but without CVD did not appear to have an increased risk of mortality. For those with CVD the point estimate was higher but the association was not significant: for the latter group the OR increased to 1.23, 0.73-2.08 when adjusted for age, sex, smoking status and BMI. If a future study, able to explore the associations between diabetes and mortality from colorectal cancer within a sample that included a larger number of cancer endpoints, were to find that those with diabetes did have around a 20% increased risk of dying from this cause then this could result in a significant excess of mortality among those with diabetes and comorbid CVD. The results of the analyses of the Whitehall I data suggested that those with diabetes were at a reduced risk of mortality from cancer of the colon; this result is consistent with that of the earlier study which utilised the same Whitehall I data.(89) The results of both studies should be treated with caution as only a small number of cancers of the colon were found among those with diabetes.

Pancreatic cancer

Pancreatic cancer causes around 7,000 deaths in the UK per year and the disease has one of the lowest median survival times of any site-specific cancers.(117,328) As early as 1934, studies had begun to note the association between diabetes and cancer and in 1971 Kessler undertook an

extensive literature review of all of the research exploring diabetes and cancer and concluded that only for pancreatic did the evidence consistently demonstrate an association.(72,100) The issue for many commentators has been whether it is the diabetes or cancer that comes first, with some concluding that the development of diabetes among lean individuals between the ages of 45 and 50 should be considered an indicator of the presence of pancreatic cancer.(123,124) This finding is supported by an increased incidence of the cancer among those who have had diabetes for the shortest amount of time. For example within the meta-analysis by Huxley et al., those who had had diabetes for less than 4 years were twice as likely to get pancreatic cancer, while those who had the disease for longer had an excess risk of 50% compared with those without diabetes.

Incidence

Two meta-analyses, focussed upon diabetes and the risk of developing pancreatic cancer, were found within the literature review and both of these supported an association between the two diseases. The first, by Huxley mentioned above, included 36 cohort and case-control studies and found an odds ratio of 1.8 (CI 1.7-1.9) among those with diabetes compared with the general population.(122,329) Within the current study, those with diabetes had a substantially increased risk of developing pancreatic cancer which remained unaltered following adjustment for BMI (basic model: 1.58, 1.04-2.40; advanced model: 1.60, 1.02-2.50). When the data were stratified by either sex or CVD status, only men were found to have statistically significant increased odds of developing pancreatic cancer; although for women, and those with and without comorbid CVD, there were increases at the point estimate. The issue of reverse causality between diabetes and pancreatic is addressed within the section related to mortality (below).

Mortality

Within the Cox regression analyses of the HSE and SHeS dataset those with diabetes were found to be at a substantially increased risk of dying of pancreatic cancer compared with the general population. When adjusted for age, sex, smoking and BMI they were found to have odds that were increased by nearly 70%. Within all of the analyses undertaken to assess the association between diabetes and pancreatic mortality the inclusion of a range of covariates had little impact upon the excess found among those with the former. This result is similar to those of previous research, for example an earlier study from the UK found a rate ratio among those with diabetes of 2.2, 1.8-2.7.(330) The increase within the results related to Whitehall I were even more substantial: among those with diabetes, the HR within the advanced model showed a substantially increased risk of pancreatic cancer mortality for this group compared with those without diabetes (around 4.5).

The sex-stratified analyses indicated that men and women with diabetes have similar odds of pancreatic cancer mortality, increased at the point estimate. When the analyses were stratified by CVD status, those with diabetes and comorbid CVD had an excess risk of nearly 90% compared with the general population, while those without comorbid CVD had only non-significant increases within each model. The small number of deaths among those with concurrent diabetes and CVD suggests that future studies should be undertaken which analyse data with a greater number of cases with both conditions. In vivo and In vitro studies could explore whether or not there is a multiplicative association between diabetes and cardiovascular disease and mortality from pancreatic cancer. Future epidemiological studies might also explore the factors which reduce the risk of pancreatic cancer among those with diabetes. The consistency of the excess in pancreatic cancer mortality among those with diabetes suggests that health education programmes, for those with diabetes and their healthcare providers, should be developed which enable both groups to have a better understanding of the associations between the two diseases.

The issue of reverse causality has been addressed within studies by excluding deaths which occurred within a certain number of years (either after diabetes diagnosis or within the follow-up period); an earlier study using Whitehall I data found that the exclusion of deaths within the first ten years of follow-up had little impact upon the excess in death from this cause among those with diabetes.(89) Within the Cox regression, further analyses were undertaken which excluded deaths within the first year. Given the short survival time amongst those with pancreatic cancer it was felt that a year would be enough to address the issue, while maintaining an adequate number of deaths from this cause among those with diabetes. The result supports those of earlier studies in finding that excluding such deaths had little impact upon the excess mortality experienced by those with diabetes.

Oesophageal cancer

Oesophageal cancer causes around 5,000 cancer deaths each year within the UK. The biological plausibility of an association is as yet unconfirmed; one contributing factor may relate to the impact that overweight and obesity have upon an individual's risk of developing diabetes and oesophageal cancer.(331) Another may be the increased risk of Barrett's oesophagus - a condition which causes abnormal cells within the oesophagus and increases the risk of oesophageal cancer - among those with diabetes.(332)

Incidence

A 2012 meta-analysis included 17 studies which sought to assess the associations between diabetes and oesophageal cancer incidence and found a statistically significant summary relative risks for men of 1.28 (1.10-1.49), while for women the corresponding rate was non-significant (1.07, 0.71-1.62).(333) Within the HSE and SHeS dataset there were 262 cases of oesophageal cancer including 16 among those with diabetes and although the point estimates were increased within each model, the association was non-significant within each of the regression models or when the analyses were stratified by sex or baseline CVD status. The small number of cases among those with diabetes indicates that further studies are needed which are able to utilise datasets with a larger number of incident cases of oesophageal cancer.

Mortality

The results of earlier studies are mixed in relation to the association between diabetes and mortality from oesophageal cancer with some finding no association,(131) while others found substantially increased odds.(130) Within the HSE and SHeS dataset there were 261 deaths from this cause, including 15 among those with diabetes. The corresponding figures within the Whitehall I data were 166 and 3, respectively. Within the analyses of the HSE and SHeS dataset, the adjusted ORs for risk of oesophageal cancer mortality among those with diabetes were raised at the point estimate by around 10%. This increase remained after adjustment for a range of covariates. The Cox regression also found similar point estimate results accompanied by confidence intervals suggestive of a non-significant association. Further to this, the results of the Cox regression undertaken using data from Whitehall I found a non-significant nearly 3-fold increase in risk of mortality from oesophageal cancer among those with diabetes, a resulted supported by the earlier Whitehall I study mentioned previously.(89) However, the small number of cases among those with diabetes (n=3) indicates that the study was under-powered. Because of the small number, the results of the stratified analyses will not be discussed.

Stomach cancer

There is a growing body of evidence suggestive of a dose-response effect in relation to increasing adiposity and the risk of developing stomach cancer.(334) The cancer causes around 5,000 deaths in England and Wales each year.(335) Although substantive evidence related to the biological mechanisms behind an association between diabetes and stomach cancer has yet to be compiled, one contributing factor may be the increased stomach cancer risk posed by helicobacter pylori – a bacteria which causes stomach ulcers and evidence suggests is associated with hyperglycaemia.(336)

Incidence

A meta-analyses published in 2013 found that those with diabetes were at an increased risk of developing stomach cancer compared with the general population, with the excess being around 40%.(247) A cohort study from Taiwan found that the risk of developing stomach cancer was lower among those who had had diabetes for a short time compared with the general population, but then increased with the duration of diabetes. After living with diabetes for over for years the HR was 1.76, (1.06-2.91), before this time those with diabetes were at a reduced risk of developing stomach cancer.(129) It is unclear why this might be the case, but a potential contributing factor may be the latency period between infection with helicobacter pylori and its impact upon cancer development. The impact that obesity has upon cancer development is also likely to increase with the number of years that an individual is obese. Interestingly within the current study, those with diabetes were found to have a reduced, although non-significant, risk of developing stomach cancer. This is unlikely to relate to the length of time that participants were in the study as 75% of the sample had been followed for at least four years, the cut-off point mentioned in the earlier study. The location of the study sample may also contribute to these differences in results, the earlier studies were undertaken within Asian populations, a high risk area in relation to stomach cancer incidence and mortality, while the current study was undertaken within a population with relatively low risk.(337,338) The results of the stratified analyses differ in relation to CVD status, those with comorbid CVD had a non-significant reduced risk, while those without comorbid CVD had a non-significant increased risk. The results of the sex-stratified analyses were also ORs that were raised at the point estimate only. These results should be treated with caution and both the underlying biological mechanism and the potential associations between diabetes and incident stomach cancer require further investigation.

Mortality

In total there were 262 deaths from this cause in the HSE and SHeS dataset including 15 among those with diabetes at baseline. Within the Whitehall I sample there were 234 deaths from stomach cancer, of which four were among those with diabetes. A 2012 meta-analysis included 25 studies and found that those with diabetes had nearly a 30% increased risk of mortality from stomach cancer compared with those without the disease and a large cohort study supported this result,(128) although some other studies have indicate no increased risk among those with diabetes.(125) Two large, recent studies both found non-significant increases in risk of mortality from stomach cancer among those with diabetes, although the latter found men to have a statistically significant increased risk.(80,86)

The results of the Cox regression, multinomial logistic regression and the analyses of the Whitehall I data undertaken within this study support the results of earlier research. Men had a substantially increased risk of mortality from stomach cancer at the point estimate (consistently above 70%) but only within the advanced model was the association statistically significant. Women with diabetes had an increase at the point estimate, but the confidence interval suggested that the association was not statistically significant. None of these results were altered by the inclusion of a variety of covariates within the model. Of particular note is that the increase was not attenuated by the inclusion of the various measurements of overweight and obesity, suggestive of an association between diabetes and stomach cancer, rather than via confounding factors as suggested by some commentators.(303) The ORs for those with diabetes and without comorbid CVD were indicative of a substantial increased odds of dying from stomach cancer among this group compared with the general population, while for those with diabetes and comorbid CVD there appeared to be no association with mortality from stomach cancer. No explanation for these differences in risk were found within the literature review and further studies (both epidemiological and biological in nature) are required to establish whether this result is consistently found and what factors form the foundations of this difference in stomach cancer mortality risk.

Kidney cancer

Around 3,500 deaths are caused by kidney cancer each year in England and Wales. Diabetes is the major factor related to the development of nephropathy and chronic kidney disease.(339) There is also a growing body of evidence suggesting that kidney disease may encourage the development of kidney cancer.(340) Overweight and obesity, found at increased rates among those with diabetes, are also associated with an increased risk of developing kidney cancer.(219)

Incidence

A 2013 meta-analysis found uniformity within 24 studies, all of which found an increased incidence of kidney cancer among those with diabetes compared with the general population. The RR for those with diabetes was 1.40 (CI 1.16-1.69).(136) A Swedish cohort study found a 70% increased risk of renal cell cancer among women with diabetes, for men the corresponding figure was 30%.(132) Within the current study there were 261 incident cases of kidney cancer among the HSE/SHeS cohort, including 22 among those with diabetes and those with diabetes were found to have a significantly increased odds of developing kidney cancer. The excess remained within the basic model, but became marginally non-significant when BMI was added to the model. Although the stratified analyses gave increased point estimates within each of the regression models, it was only for men that the association approached statistical significance. As with other cancer sites future

studies could be undertaken which allow a greater exploration of the associations between diabetes and incident kidney cancer; particularly when these results are considered in unison with those related to the risk of kidney cancer mortality among those with diabetes.

Mortality

Despite the relatively strong evidence related to a biologically plausible association between diabetes and kidney cancer, there are mixed results in relation to mortality from the latter. A 2013 meta-analysis found an increased (although marginally non-significant) risk ratio among those with diabetes compared with the general population (1.12, 0.99-1.20).(136) One of the key issues, even among more recent studies investigating the associations between diabetes and kidney cancer mortality, is that they have lacked a large enough number of deaths among those with diabetes. For example a 2007 study found only eight deaths from this cause among their diabetic participants within a total sample of over 100,000.(135) Perhaps because of this a joint consensus report by the American Diabetes Association and the American Cancer Society concluded that there was insufficient evidence to draw any robust conclusions related to whether or not there was an association between diabetes and kidney cancer.(303)

Within the HSE and SHeS dataset there were 140 deaths from kidney cancer, including 11 within the diabetic group. The odds ratios were indicative of a non-significant excess in mortality from kidney cancer. The same result was found within the Cox regression, although the point estimate was substantially raised. This finding mirrors that of an earlier study.(80) An issue of particular note is the attenuation of risk among those with diabetes and comorbid CVD; the reasons for this reduced risk are unclear and not addressed within currently published in vivo and in vitro studies – possible causes could relate to the differing treatment regimens offered to individuals with diabetes and those with diabetes as well as CVD and the increased mortality from other causes among the latter group.(341) This result is particularly surprising considering the inter-related nature of the associations between diabetes and renal disease and diabetes and CVD. Future studies could explore this finding further. There were no cases of kidney cancer among the diabetic cohort within the Whitehall I data so analyses were not performed.

Liver cancer

Globally, around 9% of all cancer deaths are from liver cancer, equating to over 650,000 deaths each year.(342) The biological plausibility of an association between the two diseases related to the carcinogenic properties of cirrhosis of the liver and non-alcoholic fatty liver disease – both of which

are found at increased rates among those with diabetes.(343) 80-90% of primary liver cancers are diagnosed among those with cirrhosis of the liver.(224)

Incidence

A number of systematic reviews were found within the literature that were focussed upon the association between diabetes and incidence of liver cancer and all of them found a substantial increase in the latter amongst those with diabetes.(344–346) A 2013 cohort study using population-based cohorts from China found that those with diabetes had a significant increase in risk in relation to liver cancer incidence (men: HR 1.63, 1.06–2.51, women: 1.64, 1.03–2.61).(138) A case-control study which included 420 patients with liver cancer and 1,104 controls found an increased prevalence diabetes among the cases which gave an OR of 4.2 (CI 3.0-5.9).(137) A second study found that men and women with diabetes were more likely to develop liver cancer than individuals without (men: 1.63, CI 1.06-2.51, women: 1.64, 1.03-2.61). (138) Finally, a study assessing the impact that insulin use had upon the risk of developing liver cancer among those with diabetes found that those with type-2 diabetes who used insulin were more likely to develop the cancer than those who did not.(RR 2.84, 1.12-7.17).(312) The results of the current study are hindered by the small number of incident liver cancers found within the sample; in total there were 81, with four among those with diabetes. Because of this the models produced ORs indicative of a similar cancer risk among those with and without diabetes when the analyses utilised data from the whole sample and inconsistent results within the stratified analyses.

Mortality

The Cancer Prevention Study-II found that both men and women with diabetes had an increased risk of mortality from the liver cancer.(83) This finding was also supported by an earlier study which used data from the Whitehall I cohort,(89) as well as a number of other large recent studies.(80,110,330,347) As with the incidence data related to liver cancer, only a small number of deaths from this cause were found among those with diabetes within the current study, and as such these results should be treated with caution.

The analyses of the HSE and SHeS dataset suggest that those with diabetes are at a reduced risk of mortality from liver cancer, although the association was not significant. The reduction in risk among those with diabetes remained after stratification for sex and for comorbid CVD. None of these results were substantially altered by the inclusion of covariates. Contradicting these findings were those of the analyses of the Whitehall I data; these found that those with diabetes had over a seven-

fold increased risk of mortality from liver cancer. The small number of deaths from this cause within the data was likely to be the explanation for the wide confidence intervals (advanced model HR: 7.35, 2.29-23.58). Given the large number of cancer deaths caused by those of the liver, if an association between the two conditions were to be found it could result in a large number of excess cancer deaths. At the same time, if those with diabetes were found to have a reduced risk of developing liver cancer then knowledge of this attenuated risk may enable a greater understanding of the factors which underpin the development of this specific cancer and concurrently the development of treatments to address it.

Haematopoietic cancers

This group of cancers consists of non-Hodgkins lymphoma (NHL), leukaemia and multiple myeloma and are cancers of the blood. To data only a few studies have investigated whether diabetes is associated with any of these cancers and even less is known about the biological cause of any potential associations. A number of studies have demonstrated that BMI is associated with an increased risk of developing and/ or dying of leukaemia, non-Hodgkins lymphoma or Hodgkins lymphoma,(348) with one demonstrating that diabetes was not associated with leukaemia.(349)

Incidence

The 2012 meta-analysis investigated the association between type-2 diabetes and non-Hodgkins lymphoma, leukaemia and myeloma and found 26 studies in total.(143) The majority of the studies which met the inclusion criteria supported an association between diabetes and cancers of this type. The ORs given were 1.22 (1.07-1.39) for non-Hodgkins lymphoma; 1.22 (1.03-1.44) for leukaemia; and 1.22 (0.98-1.53) for myeloma. A note of caution is needed in relation to the results of this meta-analysis as only 50% of the studies included adjusted or matched for age and only 15% adjusted for BMI. The authors themselves noted that future studies should consider the impact of these confounders upon the associations between diabetes and incidence of haematopoietic cancers. A second meta-analysis focussed upon the risk of non-Hodgkins lymphoma among those with diabetes found an increased risk ratio of 1.19 (1.04-1.35).(142) Within the HSE and SHeS cohort there were 875 cases of haematopoietic cancer, of which 39 were among those with diabetes. All of the analyses resulted in non-significant reduced odds among those with diabetes in relation to incident cancers of this type; the small number of cases lends the result to being one of chance. There were also no cases among diabetic men, which prevented the undertaking of this analysis.

Mortality

The results of an earlier study indicated that men with diabetes had nearly a three-fold increased hazard ratio related to mortality from non-Hodgkins lymphoma, while women with diabetes were found not to have an increased risk of mortality from this cause.(141) Tseng found that those with diabetes were at an increased risk of mortality from non-Hodgkins lymphoma, but also concluded that more studies were required which included greater numbers of concurrent diabetes and deaths from NHL.(151) Within the HSE and SHeS data there were a total of 373 deaths from haematopoietic cancers, including 19 among those with diabetes. The results of the analyses of Whitehall I data should be treated with caution as there were only a small number of deaths from this cause among those with diabetes.

The results of the Cox regression and multinomial logistic regression indicate that different groups have different risks in relation to mortality from haematopoietic cancers; although, similarly with incidence of this specific cancer, the small number of cases makes it likely that these results are a chance finding. The result with which we can be most confident is that which is based upon data from the whole sample, within these analyses there appeared to be no association between diabetes and mortality from haematopoietic cancers. The paucity of evidence related to haematopoietic cancers and their association with diabetes calls for further research to be undertaken that is both biological and epidemiological in nature.

Bladder Cancer

Mortality from bladder cancer is the eighth leading cause of cancer death within the UK, equating to around 8,000 deaths in England and Wales in 2012.(335) The biological plausibility of an association between diabetes and cancer appears to be supported by the increased incidence of urinary and bladder infections among those with diabetes – both of which are associated with an increased risk of bladder cancer.(147)

Incidence

A 2013 meta-analysis found consistency within the results of 23 studies investigating the associations between diabetes and the risk of developing bladder cancer, overall the OR was 1.68 (1.32-2.13).(350) The study also investigated regional and sex differences and found that the increase was only present within the diabetic populations of America and Asia, not Europe, and that there were no differences in risk between the sexes. A second meta-analysis (which included only cohort studies) published in 2013 found an increase in bladder cancer risk among those with diabetes, but when the analyses were stratified by sex the increase only remained among men.(351) A cohort study found that those with diabetes had around a 25% increased risk of developing

cancers of the urothelial, the majority being cancers of the bladder – the study adjusted for confounders, such as obesity, and concluded that these did not explain the association between diabetes and bladder cancer.(148)

Within the current study 516 participants within the HSE/SHeS sample were registered as having bladder cancer, with 46 of those also having indicated the presence of diabetes at baseline. Within each of the multinomial logistic regression models there were point estimate increases, that were marginally non-significant, for those with diabetes compared with the general population. Those with diabetes but without comorbid CVD were found to have a statistically significant increased risk of bladder cancer, while those with comorbid CVD appeared to have a non-significant reduced risk. Again the latter result may relate to the increased mortality, within this group, from other causes. As with the results of a previous study, when the analyses were stratified by sex, only men with diabetes were found to have an increased risk in relation to bladder cancer. The reasons for this are unclear within the current literature, but may relate to the impact that testosterone and other sex-hormones have upon the development of cancer. An in vivo study found that androgens – compounds related to male characteristic – and their receptors were associated with the development of bladder cancer and were found at higher rates among wild type male mice compared with wild-type female mice.(352)

Mortality

Earlier studies suggest that those with diabetes have over double the increased risk of mortality from bladder cancer compared with the general population.(145,146) The results of the analyses of the HSE and SHeS dataset were that those with diabetes had an increased risk at the point estimate, but the association was not found to be statistically significant. Among men with diabetes there was a substantially raised point estimate (>60%) but this was not statistically significant; no women with diabetes died of bladder cancer so this analysis was not performed. Those with diabetes and comorbid CVD had a non-significant lowered risk of mortality from bladder cancer, while those with diabetes but without CVD had a non-significant increased risk. As with haematopoietic cancer mortality, the reasons for this are yet to be clarified and require further investigation. The results for Whitehall I were also contradictory, in finding that those with diabetes were at a lower risk of mortality from bladder cancer compared with their non-diabetic counterparts. However, the small number of deaths from this cause among those with diabetes means that the results of this analyses should be treated with caution.

Breast cancer

Over 10,000 women in England and Wales died of breast cancer in 2012, with the disease being rare among men.(335) Postmenopausal breast cancer is associated with overweight and obesity and women diagnosed with breast cancer who are overweight or obese have poorer prognosis than those who are of normal weight.(353)

Incidence

A meta-analysis found 20 studies which explored whether or not those with diabetes had an increased risk of developing breast cancer; within the meta-analysis the relative risk was found to be 1.20 (1.12-1.28).(153) The meta-analysis found no difference between the results of cohort and case-control studies. A cohort study using data from 1,248 Asian-American women indicated that diabetes was associated with an adjusted increased risk of developing breast cancer of nearly 70%.(151) The study also found that the association was strongest among women who were lean, compared to those with a BMI above 22.7. The ORs for the two groups were 3.50 (1.32-9.24) and 1.39 (0.81-2.36), respectively.(152) Within the current study women with diabetes were found to have an increased risk of incident breast cancer compared with their non-diabetic counterparts, this increase became marginally non-significant when BMI was added to the model. The reason for this may relate to the positive association between increasing BMI and risk of breast cancer found among some groups of women.(354) Whether or not the result related to adjusting for CVD, as well as age, smoking and BMI, was by chance is unclear and requires further exploration.

Mortality

A meta-analysis which explored the association between diabetes and cancer incidence and mortality found five studies focussed upon breast cancer mortality.(149) Within the meta-analysis women with diabetes had over a 20% increased risk of mortality from breast cancer, although the lower confidence interval fell just below one. Within the current study, women with diabetes were found to have a substantially increased risk of mortality from breast cancer. Two results are particularly comment worthy. First, that adjusting for glycated haemoglobin increased the point estimate for mortality for breast cancer among those with diabetes to nearly a three-fold increase. A note of caution: the small number of deaths from this cause among those with a measure for glycated haemoglobin and who indicated that they had diabetes at baseline produced a wide confidence interval – so could still be a chance finding. Secondly, within the Cox regression the increase odds remained after adjustment for BMI, but not for the other measurements of overweight and obesity. The reasons for this are unclear but may relate to the different types of adiposity that BMI, waist circumference (WC) and waist-to-hip ratio (WHR) are measuring. BMI uses

height and weight to give an indicator of whether or not a person is a healthy weight for their height, while WC and WHR are indicators of central adiposity. There is some evidence that the latter are better predictors of risk of overweight and obesity related conditions such as diabetes and CVD.(355,356) It may be the case that the increased risk of breast cancer among women with diabetes is a spurious association, the actual cause of which is centralised adiposity. The Whitehall I sample included only men and there were no cases of breast cancer within the sample.

Cervical, endometrial and ovarian cancer

Over 1,900 women each year die of cervical and endometrial cancer in the UK, with similar numbers newly diagnosed.(154) This current study grouped cancers of the cervix, uterus/endometrium into a single category. The reason for this was to ensure that the dataset was not disclosive in nature.

Ovarian cancer has a high case-fatality rate, with the majority of diagnoses occurring at a later stage of the disease.(357) Whether or not diabetes is associated with an increased incidence of ovarian cancer, and the biological mechanisms that might underpin such an association, are yet to be established.

Incidence

As with breast cancer, women with diabetes were found to have an increased risk of developing cervical/endometrial cancer with the association becoming non-significant when BMI was added to the regression model. The small number of cases among those with diabetes (n=38) demonstrates the need for further research which can utilise data with a larger number of cancer cases.

In terms of the associations between diabetes and incident ovarian cancer, a 2013 meta-analysis found an increased RR of 1.55 (1.11-2.19) among those with diabetes compared with the general population.(250) This increase was found after adjusting for a range of confounding factors including BMI. The small number of incident ovarian cancers among those with diabetes, meant that this group was added to the 'other cancers' category and the analyses related to diabetes and incident ovarian cancer was not performed.

Mortality

Previous studies suggest that women with diabetes are at an increased risk of mortality from these cancers and that, once diagnosed with cervical cancer, they are more likely to die compared with those without diabetes.(358) The ORs and HRs within the multinomial and Cox regression analyses, respectively were indicative of similar risks among those with and without diabetes but the small

number of deaths from these cancers, among those with diabetes, within this study makes the drawing of firm conclusions difficult.

A small number of studies were found within the literature review which focussed upon the associations between diabetes and mortality from ovarian cancer. One study found that women with ovarian cancer who also had diabetes had higher mortality than women with ovarian cancer alone.(161) As with cervical/endometrial cancer, the small number of cases of mortality from ovarian cancer with diabetes meant that the analyses within the current study was likely under-powered. When adjustment included a measurement of overweight and obesity the risk of mortality from this cause was reduced, at the point estimate, among women with diabetes compared with women without diabetes. Further analyses could be undertaken, utilising datasets with larger numbers of deaths from this cause.

Lip, oral cavity and pharynx cancer

There was found to be a lack of research related to the associations between diabetes and mortality from oral cancer. One study did not find an association between diabetes and oral cancer, instead calling for more research to be undertaken to determine whether there is an association between diabetes and site-specific cancers of this nature.(160)

Incidence

There were only six cases of cancers of the lip, oral cavity and pharynx among those with diabetes; within the whole sample there were 225 cases. The results of the multinomial logistic regression were that those with diabetes had a non-significant reduced risk of developing cancers within this category; although the small number of incident cancer among those with diabetes means that the analyses were likely under-powered and should be treated with caution.

Mortality

Only three cases of lip, oral and cavity cancer were found among those with diabetes within the HSE and SHeS dataset, and the ORs and HRs were indicative of no increased risk among those with diabetes compared with the general population.

Prostate cancer

Around 10,000 men die of prostate cancer each year in England and Wales.(335) Although there is a limited amount of evidence of a biologically plausible causal association between diabetes and

prostate cancer, current research suggests that it is related to differing levels of testosterone and circulating sex hormone.(359)

Incidence

Prostate cancer is the only cancer for which the results of previous studies are indicative of a reduced risk of developing the disease among those with diabetes compared with the general population. The results of two meta-analyses demonstrated a negative association; the first found an RR of 0.91 (0.86-0.96) and the second an RR of 0.84, 0.76-0.93.(157,158) The reduced risk was consistent across the results of both cohort and case control studies. Within the data of the current study there were 1,362 incident cases of prostate cancer among men, with 75 among those with diabetes at baseline. The ORs were indicative of a reduced risk, although the confidence intervals were marginally non-significant within a number of the regression models.

Mortality

A meta-analysis involving 11 studies focussing specifically upon prostate cancer mortality found a substantial increase in prostate cancer mortality among those with diabetes; compared with those without diabetes, the pooled hazard ratio was 1.57 (CI 1.12-2.20).(159) Within the HSE and SHeS dataset 347 men died of prostate cancer, including 20 deaths among men who had indicated diabetes at baseline. Other studies have found a reduced risk of prostate cancer among those with diabetes.(110,330) At the same time, other studies have found non-significant increased point estimate for prostate cancer mortality among those with diabetes compared with those without the disease.(80,347) The results of the current study are consistent in finding reduced point estimates that are non-significant; this result was found within the analyses of both the HSE and SHeS and Whitehall I datasets. Understanding whether or not there is a reduced risk of mortality from prostate cancer among those with diabetes and the underlying biology of the reduction - for example, the link between testosterone and the development of prostate cancer is an area that requires further research(360) – is an area that requires further exploration, the results of which may reveal novel ways of preventing and treating the disease.

The above sections demonstrate differences in the associations between diabetes and site-specific cancer incidence and mortality. For cancer incidence the most consistent increased risk among those with diabetes, compared with the general population, was found for cancers of the pancreas; while there were some differences in risk between the sexes and when analyses were stratified by baseline CVD. In terms of mortality, the most consistent associations were found for cancers of the

pancreas and for breast cancer among women. These results suggest that these differing rates of excess mortality for site-specific cancer may, in part explain the differences in international study results focused upon total cancer mortality. If there are differences in the mix and frequency of the different cancers within the study population examined, this will impact upon whether or not the study finds differences in overall cancer mortality risk between those with and without diabetes.

It appears that, because adjusting for overweight and obesity had little impact upon the OR and HRs found within this study, diabetes does have an impact upon cancer mortality that is separate from and additional to the presence of adiposity. At the same time, for some site-specific cancers the inclusion of measures of overweight and obesity did impact upon the risk of mortality among those with diabetes. Further research is needed to fully understand the impact that diabetes has upon site-specific cancer incidence and mortality among those with and without diabetes.

The results of this study suggest that there are still many questions left unanswered in terms of the associations between diabetes and site-specific cancer mortality. The small number of incident cancers and deaths from some of the site-specific cancers is a consequence of the study's use of general population data. This issue will need to be addressed through the undertaking of further analyses which are able to utilise datasets which contain a greater number of cases who had diabetes and either developed or died of site-specific cancers. The following section discusses the potential associations between glycated haemoglobin and all-cause and cause-specific mortality.

12.5 Glycated haemoglobin and cancer mortality and incidence

Cancer mortality

Glycated haemoglobin ($HbA1_C$) is caused by the chemical reaction of glucose meeting haemoglobin in the blood and its measurement offers an accurate assessment of uncontrolled or undiagnosed diabetes within the previous three months.(361) Within the literature review only a small number of papers were found that specifically reported upon the associations between $HbA1_C$ and cancer incidence and mortality; this may be due to a publication bias in favour of studies which show positive associations or because this area of research is relatively new. The World Health Organisation only supported the use of $HbA1_C$ as a diagnosis tool for diabetes in 2011.(11) Perhaps because of this, and the small sample sizes of some of the studies, the results were mixed. Silbernagel et al. found a J-shaped association between $HbA1_C$ and cancer mortality, although the association was not statistically significant in the majority of the regression models used within the study and the sample included only those without diabetes who were undergoing coronary

angiography.(362) A 2012 study counted a measurement ≥ 5.7% as being indicative of raised $HbA1_C$, the results of the study suggested that women in this group were at an increased risk of mortality from cancer (HR 1.58, 1.23,2.05), while men were not.(363) This result again suggests that the impact of $HbA1_C$ begins within the normoglycaemic range and continues as duration of exposure to increase blood glucose and the $HbA1_C$ level increases. A third study found a non-significant association between a 1% increase in $HbA1_C$ and cancer mortality was found among 4,345 participants with diabetes within the European Prospective Investigation of Cancer and Nutrition.(364)

Within the current study 449 participants with a valid measurement for $HbA1_C$ had died of cancer, including 47 with a raised measurement. There was a statistically significant increased risk of cancer mortality among those with a measurement of $HbA1_C$ ≥6.5% within the basic model (OR 1.44, 1.05-1.97) which became marginally non-significant when BMI was added to the model (1.38, 0.98-1.95). Because of the inter-play between overweight and obesity and blood glucose it may be the case that the association between the latter and cancer mortality is not significant when the former is adjusted for. Alternatively the lack of significance may have been caused by the small number of cases within the $HbA1_C$ sample who died of cancer.

The stratified analyses produced mixed results. When stratified by CVD status neither group with raised $HbA1_C$ had a statistically significant increased risk of cancer mortality; although perhaps the product of chance the results for those with raised $HbA1_C$ but no CVD did almost reach significance within the basic model. For women within raised $HbA1_C$ there appeared to be no difference in cancer mortality risk compared with those with a lower measurement, while for men in this group there was a statistically significant increased odds. The reasons for this are unclear, but may relate to the site-specific cancers that are making up the overall cancer mortality variable. This issue will be addressed in more detail within the section related to the associations between $HbA1_C$ and mortality from site-specific cancers. The small number of cases who indicated that they had never been a regular smoker within the group with a valid $HbA1_c$ measurement means that the results of this analysis should be treated with caution; other than to say that there was a point estimate increase which could be further explored in future studies.

Incidence

Jonasson et al. used data from over more than 25,000 Swedish residents with diabetes and found that $HbA1_c$ was not associated with either overall cancer incidence or incidence of any of the site-

specific cancers under investigation.(192) The study also used quartiles to assess the associations between $HbA1_c$ and cancer incidence and found no association; the HR was also not significantly raised when a continuous $HbA1_c$ variable was used within the regression models (1.01, 0.98-1.04). The $HbA1_C$ sample within the HSE and SHeS dataset included 1,137 registered cases of cancer, within this 103 were among those with $HbA1_C \geq 6.5\%$. Within each regression model there was a point estimate increased risk of incident cancer among those with raised $HbA1_C$ compared with those in the normoglycaemic category; although the association was only statistically significant within the basic (age, sex and smoking) model. The point estimate also remained raised when the analyses were stratified by CVD status and sex, and when sensitivity analysis was carried out using data from those who indicated that they had never been a regular smoker. The reason for this increase, from the biological perspective, is likely to be rooted in the mitogenic and proliferative properties of hyperglycaemia. Another factor may also be the hyperinsulinaemia that those with pre-diabetes or the metabolic syndrome may experience before they encounter hyperglycaemia. At the very early stages of diabetes insulin resistance occurs within the insulin sensitive tissue of the body, in order to combat this resistance the body releases ever increasing amounts of insulin which results in hyperinsulinaemia. This continues until insulin secretion becomes restricted and hyperglycaemia occurs. It is possible that this earlier hyperinsulinaemia is the actual cause of the increased risk of cancer incidence among those with hyperglycaemia, and that the latter is just a marker of the occurrence of the former within the body. At present whether or not it is hyperglycaemia or hyperinsulinaemia, or a combination of the two, which is altering the risk of cancer incidence among those with raised $HbA1_C$ has yet to be established. Further in vivo and in vitro studies could begin to unravel this issue. Epidemiological research is also required to elucidate the magnitude of the effect that each factor has upon cancer incidence and mortality.

12.6 Glycated haemoglobin and site-specific cancer incidence and mortality

There was found to be a dearth of prior evidence related to the associations between $HbA1_C$ and site-specific cancer incidence and mortality. Within the studies that were found within the literature review, the cancers for which there was any epidemiological evidence of an association included colorectal,(365) respiratory and endometrial (evidence for both cancers comes from one study),(366) and pancreatic.(367) Concurrently, other studies have found no increased risk of developing site-specific cancers among those with raised blood glucose.(192) The biological plausibility of an association between hyperglycaemia and cancer incidence has been discussed in detail in earlier sections of this thesis.

Mortality

As with diabetes, there was a substantial excess in mortality from pancreatic cancer among those with raised $HbA1_C$, although unlike the results for diabetes the confidence intervals were suggestive of a non-significant association. Despite this, the consistency of this finding, within both the current study and the results of earlier investigations, indicates that those with either uncontrolled or undiagnosed diabetes are at an increased risk of dying from pancreatic cancer compared with the general population. The issue of reverse causality has also been addressed within the current study and the results indicate that diabetes is the antecedent followed by pancreatic cancer. Considering the short life expectancy once pancreatic cancer has been diagnosed, if mortality is to be reduced then interventions must be focussed upon preventing the disease occurring. For a number of the other site-specific cancers there were consistently, and substantially, raised point estimates redolent of excess mortality among those with hyperglycaemia. If these results were to be confirmed within larger population-based studies they could signify a substantial number of excess deaths among those with diabetes/raised glycated haemoglobin.

Incidence

Within the current study a small number of site-specific incident cancers were found among those with a raised measurement related to $HbA1_C$ and this significantly hindered the undertaking of extensive analyses in this area of the study. Within the basic and advanced models there were raised ORs, at the point estimate for cancers of the lip, stomach, colon, liver, pancreas, lung, kidney, 'other' cancers. There were also non-significant increased ORs for cancers of the prostate among men and cervix/endometrium among women. Only for cancers of the stomach and lung were the associations statistically significant; although the consistency of the results, for each site-specific cancer, suggests that, if data were to become available with an appropriate number of cancer end-points, other associations might also be found to be statistically significant.

To conclude this section, although the current study lacked the power required to effectively assess the potential excess in site-specific cancer incidence and mortality among those with hyperglycaemia, the consistency in results within the analyses of $HbA1_c$ and diabetes for a number of the site-specific cancers investigated alludes to an association that requires further investigation.

12.7 Diabetes and all-cause and CVD-related mortality

Studies which sought to assess the associations between diabetes and all-cause and CVD-related mortality have a long history; for the latter cause of death, one of the earliest studies from the 1960s

observed that the increased life expectancy experienced by those with diabetes, due to improvements in treatments, corresponded with an increase in mortality from CVD.(270) All the studies found within the literature review undertaken as part of this thesis, found an increase in all-cause mortality among those with diabetes, and the majority concluded that this was being driven by increases in mortality from CVD among those with diabetes compared with the general population.(273,277)

Within the HSE and SHeS combined dataset of 204,533 participants, a total of 20,051 had died and of these 1,814 were among participants who had indicated the presence of doctor-diagnosed diabetes. The results of this analyses support those of earlier studies in finding a substantial increase in the risk of all-cause mortality among those with diabetes compared with the general population. Previous studies found between a 50% and 150% increased risk of all-cause mortality among those with diabetes,(159,238,269) while the logistic regression (detailed in section 0) which utilised data from the whole HSE and SHeS dataset and adjusted for age, sex and smoking status found a 68% increase (CI 57%-79%) among those with diabetes. When the same model was used within Cox regression, to enable a consideration of the participants' time within the study, the Hazard Ratio (HR) was 1.74, 1.66-1.83. The findings of earlier research, that adjusting for overweight and obesity did not significantly attenuate the association between diabetes and all-cause mortality,(272) was also supported by the logistic and Cox regression analyses undertaken within this current study which adjusted for one of three measurements of overweight and obesity (BMI, waist-to-hip ratio or waist circumference) undertaken within this study.

Although previous studies have adjusted for CVD within their analyses, and others have sought to understand the impact of cancer treatments upon the risk of diabetes and CVD(368) only a few found within the literature stratified the sample by CVD status at baseline; one undertook sensitivity analyses among those with CVD at baseline and found an HR of 1.65, 1.56-1.75.(86) Within the analyses of the HSE/SHeS dataset, those with diabetes but without comorbid CVD had a higher point estimate increase in all-cause mortality risk compared with the risk for those with CVD, but this was statistically significant only within the model which adjusted for age, sex and smoking (ORs 1.66, 1.52-1.81 vs. 1.33, 1.20-1.46) not when more advanced models were used which included measurements of overweight/obesity, socio-economic/demographic covariates or raised glycated haemoglobin.

The results of earlier studies related to the associations between diabetes and all-cause mortality have been suggestive of differences in the excess among men and women. A large study using data

from 97 prospective studies undertaken as part of the Emerging Risk Factors Collaboration found that women with diabetes had increased mortality compared with their male counterparts,(86) although the results of other studies have been inconsistent and contradictory in relation to the direction of the difference.(185,277) An important issue for earlier studies has been that stratifying analyses by sex had reduced the power of the study making the results uncertain.(269) The size of the HSE and SHeS sample allowed for stratification by sex and the results indicated that the excess in mortality experienced by people with diabetes when compared with those in the general population was found for both men and women. For example the ORs within the advanced model (age, sex, smoking status and BMI) were 1.74, 1.58-1.92 for men and 1.63, 1.46-1.81 for women. This lack of difference remained when a variety of covariates were included in the models, both consecutively and concurrently.

The number of never regular-smokers within the HSE/SHeS dataset enabled the undertaking of sensitivity analysis using data from only these cases. The results of these analyses were still indicative of a substantial excess in all-cause mortality among those with diabetes, which was not due to residual confounding caused by the consumption of tobacco.

Within the Whitehall I sample there were 19,019 male civil servants, including 237 who indicated diabetes at baseline. The long follow-up period (40 years) gave near complete mortality data; in total 15,214, including 219 deaths among the diabetic cohort (81% of the total sample and 92% of those with diabetes). Similarly to the logistic regression models used within the analyses of the HSE and SHeS data the basic model used with the Whitehall I data adjusted for age and smoking (sex was not required as all the cases were male): for all-cause mortality those with diabetes had over a tripling in the odds compared with those without diabetes. Supporting the results of this and earlier studies, the excess in all-cause mortality among those with diabetes remained after adjustment for BMI, social class and blood glucose. A substantial, but smaller, excess was also found when analyses utilised data from a sub-set of the Whitehall I sample who had participated in a re-survey (basic: 2.19, 1.71-2.79; advanced: 2.10, 1.61-2.74).

The results from analyses of the HSE and SHeS dataset, in relation to diabetes and all-cause mortality, are lower than those from Whitehall I. Factors which may explain this are related to the date at which the baseline data were collected, the consequent longer follow-up period available for the latter and the nature of the samples. In recent years there has been a reduction in the excess in mortality among those with diabetes compared with the general population; analyses undertaken as part of the Framingham Heart Study found that excess mortality had reduced from 2.44 in the years

1950-75 to 1.91 in the years 1976-2001 ($p<0.01$).(281) One of the reasons for this reduction may be the increasing availability and use of preventative medications related to cardiovascular disease and hypertension, such as statins, which have had a clinically important impact upon mortality among those with and without diabetes.(369,370) There is also evidence that the use of lipid lowering treatments, and subsequent improvements in cholesterol levels, have increased more among those with diabetes than the general population.(371) The contrasting results from the two datasets analysed within this study may be indicative of this recent reduction in excess. Further to this, mortality from CVD has fallen within the general population and there is some evidence that the excess all-cause and CVD mortality among those with diabetes compared with the general population has also fallen.(372–375) This, when combined with the increasing absolute risk, but falling relative risk associated with most risk factors may explain the differences between the results from the two different Whitehall I datasets.

The HSE and SHeS dataset represents a nationally representative sample, while the Whitehall I sample is taken only from civil servants working in offices in London. Therefore caution should be taken when extrapolating the results from the latter to the wider, diverse population of the UK.

The associations between diabetes and mortality from CVD are well established although, similarly to the reductions in all-cause mortality experienced by those with and without diabetes, there has been a reduction in the excess over time.(281,376,377) Previous studies have found that the risk of mortality from CVD among those with diabetes ranged from double to over a four-fold increase; with the excess in CVD mortality decreasing among more recent studies. Within the current analyses there was a total of 7,489 deaths from CVD, including 819 among those with diabetes. The results of the analyses of the HSE and SHeS indicate a substantial excess in the odds of dying of CVD among those with diabetes compared with the general population (after adjustment for a range of covariates), are in keeping with those of more recent studies. Those for CHD within Whitehall I indicate a similar excess to studies undertaken which used data from the same time period. As with the results related to all-cause mortality, the association between diabetes and CVD mortality was little altered after adjustment for a range of confounding factors.

The results of the analyses of the baseline Whitehall I data also found a substantial increase in mortality from CVD among those with diabetes, although this increase was found for all-CVD deaths and coronary heart disease (CHD) but not stroke. The known biological mechanisms which underpin the associations between diabetes and stroke make it unlikely that those with diabetes are at a

reduced risk of mortality from this cause. More likely, because the relative death rate for CHD declines with age, while for stroke it increases, this result is more likely the due to the age of the study sample at baseline and then resurvey. This also explains why, within the resurvey data those with diabetes were at an increased risk of stroke and CHD, but their risk of the latter was lower than it was within analyses of the baseline data. In other words, because the excess death rate from CHD and renal and other complications of diabetes was so high at the time of the baseline survey, fewer individuals with diabetes were surviving to an age where they were at substantial risk of developing a stroke. The results from analyses of Whitehall I data (baseline and resurvey) suggests that the excess in CVD mortality among those with diabetes may be substantially driven by CHD.

Earlier studies have suggested that the risk of cardiovascular events among men and women with diabetes differs, with women experiencing increased excess mortality compared with men.(378) The risk differs dependent upon whether or not CVD as a comorbidity is present at baseline.(379) The results of this study contradict this: when analyses were stratified by sex, men and women with diabetes were found to have similar (increased) odds of dying of CVD compared with their counterparts who did not have diabetes. Adjusting for CVD at baseline reduced the excess at the point estimate, but this reduction was not statistically significant. The inclusion of other confounding factors also had little impact upon the excess in CVD-related mortality experienced by men and women with diabetes.

When analyses were stratified by CVD at baseline status, those with diabetes but without CVD had around an 80% increased odds of dying of CVD compared with those with neither disease at baseline. Among those with diabetes and comorbid CVD there was an excess in CVD mortality, but it was less than that found among those with diabetes but no baseline CVD. Earlier studies show that those with diabetes who have experienced a CVD event are the group most likely to die of CVD.(278) The analyses undertaken within this current study demonstrate that, although that is probably true in terms of absolute death rates, the relative excess among those with diabetes is greater among those without baseline CVD. The reasons for the results of this study are unclear but may relate to those with CVD having more regular contact with health professionals and taking medications that prevent CVD-related events; as mentioned previously those with diabetes are taking medications for CVD at increased rates compared with the general public. It may also be the case that those who survive the first event have other traits which reduce their risk of dying of CVD, although an assessment of this was not taken as part of this study. The age of those with diabetes, and with and without comorbid CVD, may also impact upon mortality from CVD: 53% of those without CVD,

compared with 39% with CVD were in the age group 16-64. Age was adjusted for within all of the models with a categorical (16-64, 65-74 and 75+) variable; a continuous variable (which was unavailable within this study due to issues of disclosivity) may have revealed more about this association. There is some evidence that the excess risk of mortality among those with diabetes compared with the general population is at its greatest amongst those newly diagnosed with diabetes and is inversely correlated with age.(274,275,380) At the same time those with diabetes but without having experienced a CVD event are at similar risk of experiencing one as those without diabetes who have.(279) Future research could explore in greater detail the impact that diabetes and comorbid CVD has upon an individual's risk of dying of CVD, and whether those with diabetes who survive their first incidence of CVD are different, in terms of biology and other confounding factors, to those who do not.

A key consequence of diabetes, and one specifically related to hyperglycaemia, is the increased risk of atherosclerosis- a well-established cause of CVD. The results of this study, and those of earlier research, demonstrate a substantial increase in all-cause mortality which is driven primarily by the substantial increase in CVD-related mortality among those with diabetes compared with the general population. The results of the analyses of data from HSE and SHeS, compared with Whitehall I and earlier studies, suggests that this increase has continued to decline in recent years; within the English and Scottish population the odds of dying of CVD are currently around 70% higher among those with diabetes. There did not appear to be any sex differences in risk of all-cause or CVD-related mortality, but the issue of whether or not comorbid CVD alters an individual's risk of dying from this cause requires further exploration.

CVD mortality among those with diabetes is the key cause of the excess in mortality found among this group compared with those without diabetes. The results of the analyses of the HSE/SHeS and Whitehall I data is that the excess mortality from CVD among those with diabetes is reducing; a result which is supported by earlier studies. In order to reduce their risk of all-cause and CVD-related mortality, those with diabetes are often encouraged to make changes in modifiable risk factors related to mortality – for example through weight loss and smoking cessation programmes. Understanding the influence that these factors have upon the excess all-cause and CVD-related mortality experienced by those with diabetes compared with the general population enables the provision of appropriate health care services for those with diabetes. The results of this study suggest that currently those with diabetes have a substantial excess in all-cause and CVD-related mortality which are unrelated to confounding factors and, although the results of the Whitehall I

analyses and previous studies suggests is in decline, require the implementation of further health interventions to reduce it.

12.8 Diabetes and mortality from respiratory disease

Only a small number of studies have focussed upon the impact that diabetes, and its accompanying factors, have upon mortality from respiratory disease.(78,86,110,381) In terms of in vivo and in vitro studies the current hypothesis which explains a potential causal association between the two diseases relates to the impact that overweight and obesity have upon inflammation within the body and conditions (such as Chronic Obstructive Pulmonary Disease and asthma) which contribute to an individual's risk of dying of a respiratory-related disease.(282) Similarly to CVD, cytokines related to adiposity may also increase the risk of respiratory disease, although the biological mechanism is yet to be established.(382) Studies also suggest that weight loss is an effective tool in improving the severity of pre-existing respiratory conditions and reducing an individual's risk of developing respiratory disease.(383) It is also noteworthy that men with diabetes and good or moderate cardio-respiratory fitness were found to have reduced risks of dying of respiratory disease when compared with those with diabetes but poor cardio-respiratory fitness; suggesting a cumulative effect of both diabetes and respiratory disease upon cancer mortality.(384)

Within the HSE and SHeS sample there were a total of 2,828 deaths from respiratory disease, 212 of which were among those who indicated diabetes at baseline (this amounted to 24% of all deaths among those with diabetes and 20% among those who did not have diabetes). The results of this study support those of the small number of earlier studies which investigated the associations between diabetes and mortality from respiratory disease, in finding that those with diabetes were at an increased risk of mortality from this disease. A prospective study utilising data from >1million American adults within the Cancer Prevention Study-II found an increased relative risk (RR) for mortality from respiratory disease of 1.27 (CI 1.19-1.36) among women and 1.13 (CI 1.06-1.19) among men with diabetes after adjustment for a range of confounding factors.(110) These results are comparable with those of the current study, which found increased ORs of 1.34 (1.13-1.58) among those with diabetes compared with the general population. This increase remained statistically significant after adjustment for a range of confounders related to overweight and obesity and socio-economic and demographic factors, although the increase became statistically non-significant when glycated haemoglobin ($HbA1_C$) was added to the model and the analysis was restricted to those with a valid $HbA1_C$ measurement. That result may be due to the small number of those within the overall sample with a valid measurement for $HbA1_C$ (28,754) than with the

association between diabetes and mortality from respiratory disease; the OR remained increased, but was not statistically significant (1.46, 0.72-2.95). It may also be due to the characteristics of those who gave a blood sample being different to those who did not; although there weren't found to be differences in age, sex, BMI, region, educational level or socio-economic status ($p<0.05$).

When the current analyses were stratified by sex, men with diabetes were found to have increased odds of dying of respiratory disease compared with their non-diabetic counterparts. A similar excess was found for women with diabetes when they were compared with women without diabetes. For example, when the analyses adjusted for age, smoking status and BMI women had an OR of 1.41 (1.09-1.82) while for men the corresponding figures were 1.25 (1.10-1.47), a similar difference by sex to that found in the Cancer Prevention Study-II.(110) Dawson et al. explored the association of diabetes with mortality from respiratory disease among those with insulin-treated diabetes. Their sample included 966 participants who had diabetes and were found to have an increased SMRs for respiratory disease (women: SMR 3.31, CI 1.98-4.63; men: 2.32, CI 1.41-3.23).(78) The diabetic group within the current study were made up of those with both type-1 and type-2 diabetes; as with many studies of this type it was not possible to differentiate between the diabetes types, although it is likely that around 90-95% of this group will be type-2 based on figures from the general population.(16) Because of this it is likely that these results will most closely match the increased risk of mortality from respiratory disease among those with type-2 diabetes, rather than those with type-1.

It is noteworthy that when alternative measurements of overweight and obesity were included (waist-to-hip ratio and waist circumference), the increased risk remained significant for women but not for men. This may be due to the biological processes underlying the association between centralised adiposity, found more frequently among men compared with women (women tending to develop peripheral adiposity more than men), and respiratory disease.(282) A number of earlier studies also suggested that most of the apparent association between conditions related to metabolism, such as diabetes, and respiratory disease may be caused by centralised adiposity.(385,386) If the excess in mortality were entirely down to the impact that centralised adiposity had upon respiratory disease risk, then adjusting for it should have also impacted upon the odds found among women with diabetes. It may be the case that the way in which diabetes and adiposity interact to increase an individual's risk of mortality from respiratory disease differs between the sexes. Future epidemiological and biological studies could explore this in more detail.

In order to understand the impact that comorbid CVD had upon the association between diabetes and mortality from respiratory disease, the analyses were then stratified by CVD. The result indicated that those with diabetes but without comorbid CVD had a significantly increased risk of mortality from respiratory disease, which remained unchanged after adjusting for many covariates. Among those with diabetes and CVD there was a consistent, non-significant point estimate increase in odds within each of the models utilised. The only exception was when $HbA1_C$ was added to the model, this group had reduced odds of dying of respiratory disease, although this could be a chance finding due to the small number of cases within this group. Within the sensitivity analyses, using data from those participants who identified themselves as having never been a regular smoker, the increased odds of dying of respiratory disease was still found among those with diabetes compared with the general population. As with the results discussed above, it was only the inclusion of $HbA1_C$ which significantly altered this result.

The results presented above indicate that those with diabetes have an increased risk of mortality from respiratory disease compared with people without diabetes. This study supports the assertion that this increase is related at least in part to the presence of diabetes, although the reduction in excess risk among men, when centralised adiposity was adjusted for, suggests that it may be the accompanying adiposity that is the principal cause of the excess. The sensitivity analysis, among never-regular smokers, supports the hypothesis that there is an increased risk of mortality from respiratory disease among those with diabetes that is not caused by residual confounding of cigarette use. The small number of cases with both diabetes and a measurement related to glycated haemoglobin, and who died of respiratory disease, makes the results of the analyses uncertain in relation to assessing the impact that $HbA1_C$ had upon mortality from respiratory disease among those with diabetes. Future studies which are able to utilise datasets with a large number of cases with valid $HbA1_C$ measurements should further explore this issue. In vivo and in vitro studies could also explore whether or not there are key differences between the sexes in relation to how diabetes, adiposity and other confound factors interact to alter the risk of dying of respiratory disease.

12.9 $HbA1_C$ and all-cause and cardiovascular disease

The majority of studies aiming to explore the associations between $HbA1_C$ and all-cause mortality have found $HbA1_c$ to be positively associated with mortality. A 2001 study found that a 1% increase in $HbA1_C$ was associated with a 28% increase in all-cause mortality risk(387), while a more recent study found an HR of 1.11 (CI 1.06, 1.17) for each 1% increase in $HbA1_c$, perhaps indicative of a reduction in excess all-cause mortality among those with a raised $HbA1_C$ measurement compared with the general population in more recent years.(388) Contradicting these findings, a J-shaped association between $HbA1_C$ and all-cause mortality has also been found among a white German cohort,(362) and no association was found among an older non-diabetic population.(389) One key issue is that a number of the previous studies have used relatively small samples or used data from a defined group, limiting their power and making the extrapolation of their results to the general population difficult.(200,362,364,387,390)

As with the biological plausibility of the associations between diabetes and all-cause and cause-specific mortality, the majority of the excess in mortality among those with raised glycated haemoglobin appears to be related to the consequences of hyperglycaemia and its impact upon CVD occurrence and mortality. For example, raised $HbA1_C$ has been found to be strongly associated with carotid intima-media thickness, a marker of atherosclerosis.(136,391) The use of medications which reduce blood glucose, either within the general population or the early stages along the diabetic pathway, has also been suggested as an effective way of reducing the cardiovascular consequences of raised $HbA1_C$.(392)

Within the current study sample, 28,754 participants had a valid sample related to $HbA1_C$. Among those with a raised measurement the mean value was 7.81 (SD ±1.46), the corresponding figure for those in the normoglycaemic group was 5.37 (0.40). 1,459 participants had a measurement of ≥6.5%. In terms of age, more of those in the raised $HbA1_C$ group were found in the oldest age group (≥75) compared with those in the normoglycaemic group (20% vs. 9%). Unlike among those with diabetes, a similar percentage of those with raised $HbA1_C$ were current smokers when compared with those in the normoglycaemic group (19% vs. 23%). For all three measurements related to adiposity (BMI, waist circumference and waist-to-hip ratio) more of those with an $HbA1_C$ ≥6.5% had measurements that were in the overweight and obese category. There were no differences in the regions that the two groups resided in, but those with raised blood glucose were more likely to indicate that they had no qualifications compared with those in the normoglycaemic group (49% vs. 28%) – although this did not appear to impact upon socio-economic status, with similar percentages

indicating being in either a professional or managerial occupation within each group. 12% of those with a raised $HbA1_C$ measurement had died compared with 4% of those in the normoglycaemic group. In relation to cause of death among those with and without raised glycated haemoglobin 28% vs. 34% had died of cancer; 11% vs. 13% from respiratory disease; 43% vs. 33% of CVD and 17% vs. 20% of other causes, respectively.

Those with raised $HbA1_C$ had an increased risk of all-cause mortality of around 60% in both the basic (age, sex and smoking) and advanced (basic + BMI) models. This increase was little altered by the inclusion of other covariates related to socio-economic/demographic factors or those related to alternative measurements of overweight and obesity. The only models within which the association became non-significant were those which adjusted for diabetes. When a continuous variable was used within the analyses, a 10% increase in all-cause mortality risk was found with each step increase in $HbA1_C$, although the increase did not remain statistically significant when the model included comorbid CVD. This suggests that comorbid CVD may, in part, explain the increased all-cause mortality among those with raised glycated haemoglobin. This result is unsurprising if we consider the inter-related nature of the associations between increased blood glucose and mortality from CVD – and the associated complications such as atherosclerosis.

The analyses then utilised tertiles and compared the odds of all-cause mortality among those in the second and third (highest) tertiles with that of those in the lowest tertile. The results indicated that those in the middle tertile had a statistically significant increased risk of mortality from all causes compared with those in the lowest tertile, while those in the top tertile appeared to have similar risks to those in the bottom tertile. This result suggests a tipping point above which $HbA1_C$ is not associated with mortality. The reasons for this are unclear, but could relate to the aetiologies of the diseases which are causing the mortality. This issue will be discussed in further detail within the section related to $HbA1_C$ and mortality from CVD (below). Evidence also suggests that the impact of raised blood glucose upon health outcomes (particularly those related to CVD) begins at a level within a normoglycaemic range.(393) This points to the need for health interventions which aim to reduce glycated haemoglobin with the entire population and not just those already diagnosed with diabetes; programmes could include reducing calorie intake and increasing regular exercise, both of which have been found to reduce $HbA1_C$, adiposity and the amount of exogenous insulin required by those with diabetes.(394,395)

The two groups made up of those with diabetes and without comorbid and those with diabetes and CVD both had increased ORs in relation to all-cause mortality. Within the former the increase was 67% in the basic and 61% in the advanced models, while the corresponding figures for the latter were 35% and 45%, respectively. These results support those found for increased mortality among those with diabetes (and with and without CVD) and similarly suggests that the presence of CVD is altering the impact of $HbA1_C$ upon mortality.

Research by Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) was ended early because the diabetic group who were tasked with achieving tight glycaemic control (below 6.0%) were found to have an increased HR of 1.22 (CI 1.01-1.46) for all-cause mortality compared with those who were aiming for a higher $HbA1_C$ measurement (7.0-7.9%).(396) It was felt unethical to ask those with diabetes to maintain strict control of their blood glucose, when doing so could increase their risk of mortality. Analyses of data from the United Kingdom Prospective Diabetes Study found that tight glycaemic control (through the use of medications) reduced relative all-cause mortality among those with diabetes by 13% compared with those who only received dietary advice.(397) One of the key differences in the samples of these two studies was that the latter only included those who did not have comorbid CVD, while the former included both those with and without CVD. A 2012 study utilised data from over 100,000 participants from the UK General Practice Research Database with newly diagnosed diabetes and stratified their analyses by CVD status.(398) They found that for those with diabetes, but not comorbid CVD, an $HbA1_C$ of around 6.5-6.99% was associated with increased all-cause mortality, while for those with diabetes and CVD only above 8% was there a statistically significant association. A 2013 study also concluded that glycaemic targets should be set on an individual basis and should take into account factors such as age and the presence of comorbidities.(205) All of these results suggest that tight glycaemic control may be beneficial to those with diabetes, but without CVD, but the same would not be the case for those with diabetes and CVD. The reason for this may be the impact that the latter disease has upon mortality compared with that from raised $HbA1_C$.

The OR for women with diabetes was substantially increased within the basic and advanced models (2.05, 1.56-2.70 and 2.08, 1.54-2.81, respectively) as it was for men (1.41, 1.10-1.80 and 1.42, 1.09-1.84, respectively). This excess remained for both sexes after adjustment for a range of covariates and suggests that there are no sex differences in the impact that $HbA1_C$ has upon all-cause mortality. Among those with diabetes, who indicated that they had never been a regular smoker, there were also increased ORs compared with those without diabetes. As with the results for diabetes, this

suggests that the increase in all-cause mortality is not related to potentially reduced rates of smoking among those with diabetes/residual confounding caused by smoking.

The results of the current study, and those of earlier epidemiological and biological research, suggest that $HbA1_C$ is associated most strongly with incidence and mortality from CVD but that those with raised blood glucose may also be at risk of mortality from cancer. This area of research is relatively new, with a measure of $HbA1_C$ only beginning to be considered a diagnostic tool for diabetes in 2011. This absence of available evidence demonstrates the need for further research which investigates these associations. Should a consistent and clinically important association be found the development of public health programmes and medications may also be required; particularly within those populations within which obesity and an ageing population are increasing the number of individuals living with raised $HbA1_C$. The finding that the impact that raised $HbA1_C$ has upon excess mortality begins at a level within the normoglycaemic range is also suggestive of the need for interventions which reduce its level not only among those with diagnosed diabetes but among the general population.

The biological plausibility of an association between raised $HbA1_C$ and CVD incidence and mortality has been discussed above. The majority of studies that investigated the associations between $HbA1_C$ and incidence of and mortality from disease have been focussed upon cardiovascular disease.(200,392,399) Myint et al. found a threshold above which risk of stroke was increased,(400) suggestive of a tipping point rather than a continuous association. The results of the current study related to $HbA1_C$ and all-cause mortality, which utilised tertiles, is also suggestive of a threshold relationship. The large number of deaths within the all-cause mortality category which were caused by CVD within the current study (35% of total deaths among those with a valid $HbA1_C$ measurement) may explain why the results of the Myint et al. and current study are in agreement. There was a substantially (around 200%) increased odds of dying of CVD among those with $HbA1_C \geq 6.5\%$ compared with those with a measurement below this. It is this increase that is likely to be driving the excess in all-cause mortality. Within the current study, analyses were not performed with a variable which included the sub-categories of mortality from CVD. Using the current HSE and SHeS dataset future research could explore this issue in more detail.

When the analyses were stratified by CVD status, only those with diabetes but without comorbid CVD had a consistently statistically significant increased risk of mortality from CVD, while those with comorbid CVD did not. As with diabetes this is likely to be a consequence of the impact that the

presence of a comorbidity has upon health service usage and the medications and treatments that are used by those with CVD compared with those without the disease. For women with diabetes the OR exceeded 3 within the advanced model (3.02, 1.97-4.62) and did not fall below two even when adjustment included diabetes. For men the association was not as statistically significant, and the point estimate was reduced (although not significantly) when diabetes was included in the model. If this finding were to be extrapolated out to the general population then it indicates that men and women have differing risks related to $HbA1_C$ and mortality from CVD and health care providers and patients should be made aware of this when making decisions about levels of glycaemic control.

12.10 $HbA1_C$ and respiratory disease and other causes of mortality

As with the associations between diabetes and respiratory disease, there was found to be a very limited amount of evidence related to $HbA1_C$ and mortality from respiratory disease. A small study which included 60 diabetic and 60 healthy male participants found that $HbA1_C$ was not associated with poorer respiratory function.(401) As detailed in Section 12.8 the biological plausibility of an association between diabetes and/or raised glycated haemoglobin is yet to be fully understood, but current evidence suggests that localised and systemic inflammation may be a contributory factor.

Only a small number of deaths from respiratory disease occurred among those with raised $HbA1_C$ within the current study (n=19 out of a total of 173 within the $HbA1_C$ sample).When the regression models were used with data from all those with a valid measurement for glycated haemoglobin those with a raised measure had an increase at the point estimate within each of the models; although the association never achieved statistical significance. Within the stratified analyses women with raised $HbA1_c$ were found to have an increased risk of mortality from respiratory disease, while men in this group were found to have a non-significant reduced risk. As mentioned previously, women and men store adipose tissue in different regions of the body and this may alter their risk of respiratory disease.

For 'other' causes of death those with raised $HbA1_C$ had an excess risk compared with those in the normoglycaemic group (basic model: OR 1.57, 1.06-2.34; advanced model: 1.70, 1.11-2.60). This category of mortality is likely to include a diverse range of causes of death such as renal disease, a condition found at low rates among the general population but high rates among those with hyperglycaemia and diabetes,(9,283) as well as accidents and suicide. As such, further analyses are required which can utilise data with more detailed information about cause of death. Analyses could be undertaken using the current HSE and SHeS dataset linked to more recent mortality data, and so

a greater number of deaths from each specific cause, this will in turn address some of the issues related to the disclosive nature of the data.

12.11 Strengths and limitations of the study

The current study utilised three datasets from England and Scotland (the Health Survey for England, Scottish Health Survey and Whitehall I). The HSE and SHeS allowed for an assessment of the excess in incidence of and mortality from cancer among those with diabetes compared with the general population. Therefore, unlike those of some of the previous studies which utilised data from a defined homogeneous cohort, the results of this study are generalisable to the population of the UK. Comparing the results of the analyses of the HSE/SHeS with those found for the diabetic cohort within Whitehall I also enabled a comparison to be made between the excess found among a cohort for whom their baseline data had been collected 40 years ago and the more up-to-date data from the HSE and SHeS. Complementing this, the use of Whitehall I also enabled analyses of a dataset with near complete mortality records and a comparison of previous research which had been undertaken using the same data but with a 27 year follow-up.

The large number of cases who had indicated cardiovascular disease at baseline enabled an exploration of the impact that this comorbidity had upon the associations between diabetes and cancer incidence and mortality. Before the current study only a limited number of studies had explored this issue in detail and their results were often contradictory. The current study, in finding differences in disease incidence and mortality furthers our knowledge in this regard.

The majority of previous research which explored the associations between diabetes and cancer incidence and mortality, as well as published papers detailing the impact that diabetes had upon incidence and mortality from other diseases, used self-report to identify the diabetic cohort. Within the current study, self-reported diabetes was combined with the use of diabetes-related medications (recorded during the nurse visit element of the HSE and SHeS survey process); within Whitehall I self-reported diabetes was also used. In an earlier study, when the specificity (those correctly identified as not having diabetes) and sensitivity (those correctly identified as having diabetes) of this method was compared with those that used Fasting Plasma Glucose levels or medication use it was found to have a specificity ranging from 84% to 97% and a sensitivity ranging from 55% to 80%, over time it was found to be 92% reliable,(402) while Molenaar et al. found specificity of 99.4% and sensitivity of 58.9%.(403) A third study found that 99.9% of those who did not report diagnosed diabetes did not have any medically recorded use of diabetes medications and

concluded that self-reported diabetes was an appropriate method for identifying individuals with diabetes within epidemiological studies.(404) Sensitivity and specificity analyses undertaken within the current study found that the diabetes specific question (which was only asked in some of the years of the HSE but all years of the SHeS) had a sensitivity of 90% across all study years, while the use of the longstanding illness variable and medication variable combined had a sensitivity of 94%. Specificity across survey years was also found to be >99%. This suggests that only a small number of those with diabetes were categorised as not having diabetes and, correspondingly a small number of those without doctor-diagnosed diabetes were identified as having diabetes. The impact of misclassification, based upon the results of the current study and previous research, would be to underestimate the associations between diabetes and incidence of and mortality from cancer and other diseases. Therefore, it is likely that if those with diabetes were to be identified by a more stringent method, for example within a study sample with complete data related to $HbA1_C$, the magnitude of the effect of diabetes would have been even greater.

Although the use of diabetic medications was used to identify a participant as having the disease, no adjustment was made within the analyses to try and ascertain the impact that the use of such drugs might have upon cancer incidence and mortality. The overarching reason for this was the lack of information in relation to the medication that participants were taking; within earlier years of the HSE it was not possible to differentiate between exogenous insulin use and oral medications. Another reason was that those with type-2 diabetes often undergo rapid changes in their drug regimens, as their diabetes progresses, and may require insulin injections to control their insulin levels in the latter part of the disease progression. Individuals with diabetes may also change the oral medications they are on, or take a combination of therapies, in order to control their diabetes; this may explain some of the contradictory results of earlier studies, especially if individuals are taking multiple drugs (some of which increase, while others decrease, their risk of cancer). Finally, within the dataset it was not possible to determine the dose of medication that an individual was taking, this prevented analyses of any potential dose-response effect between diabetes treatments and disease incidence and mortality. These issues meant that it was beyond the scope of this study to attempt analysis of the impact that individual diabetes treatments have upon cancer incidence and mortality. A recommendation of this current study is that future randomized controlled trials are undertaken which have the ability to assign individuals to specific treatments arms and are therefore able to understand the associations between specific diabetes drugs and disease outcomes. A cheaper and quicker option would be to ensure that participants in previous randomized trials are followed up long-term and that cancer incidence and mortality are included in the longer term health outcomes considered.

One potential confounding factor that was not included within the analyses was cholesterol. The reasons for this relate to the lack of information related to HDL, LDL and the use of cholesterol lowering drugs within the HSE. This meant that it would not have been possible to unravel the influence that these different types of cholesterol had upon disease occurrence. Current evidence suggests the need for analyses, when assessing any potential excess in cancer incidence and/or mortality, that is able to differentiate between the two types of cholesterol.(405) Although limited by the short duration of follow-up time within many studies, the current evidence suggests that the use of lipid-lowering drugs does not influence cancer risk.(406,407) Further research could explore this issue in greater detail and in combination with an assessment of the role that diabetes has within cancer incidence and mortality. The study did not explore the impact that other confounders, such as physical activity, diet and the presence of other comorbidities have upon the associations between diabetes, $HbA1_C$ and cancer. Their impact may be significant and further research could explore the impact that these factors have upon such associations.

The majority of previous studies found within the current literature review did not differentiate between type-1 and type-2 diabetes within their analyses. At the same time those which sought to analyse the potential differences in incidence and mortality from specific diseases among those with the different types of diabetes used a range of measures to determine which type was present; these ranged from the use of exogenous insulin to age at onset. One of the issues for the current study is that, within the data from the HSE, SHeS and Whitehall I, it was not possible to develop a clear picture of the types of diabetes treatments that participants were taking or what age they had been diagnosed with diabetes. Because of this, the decision was made to explore the associations between diabetes (as a single group) and the outcomes of interest to the study. Only around 5% of the diabetic population have type-1 diabetes and, within the literature review, inconsistent results were found between this type of diabetes and cancer incidence and mortality. These factors suggest that the impact that type-1 diabetes has upon overall results would be minimal, and depending upon the outcome investigated would either marginally increase or decrease (within the literature review the results of cohort studies investigating the associations between type-1 diabetes and cancer incidence and mortality were inconsistent) any potential excess when compared with the general population.

Due to issues of disclosivity and time constraints, analyses were performed only using deaths and incidence of a select number of site-specific cancers – for each an adequate number were found within the data to guarantee that individual participants could not be identified. Given the lack of

power for some of the analyses within the current study, it is likely that separating out the 'other' category would have further limited power. Another variable that could have elicited more information about the excess in mortality among those with diabetes compared with the general population was that used within the cause-specific (cancer, respiratory and CVD) analyses. If the 'other' category had been separated out, the current study would have been able to explore this issue of diabetes and these other causes of mortality; although this was not the focus of the current study and could be undertaken in future studies able to utilise a dataset with a greater number of mortality end-points.

To avoid the issue of the data being disclosive, information related to BMI, age and date of death were also only available as categorical variables (for date of death, information was not available related to the day of death and the month of death was available only as quarters within the year). Although this may not have had a substantial impact upon the study results, the use of continuous variables may have elicited a greater understanding of the associations under investigation.

Although the study was under powered within the analyses related to $HbA1_C$ and site-specific cancer incidence and mortality, the rest of the study was able to assess the magnitude of the effect that diabetes and $HbA1_C$ had upon cancer incidence, mortality and the other causes of death under investigation. Overwhelmingly the results presented within this thesis, even when non-significant statistically, converge and support the hypotheses at the heart of this study – that diabetes and $HbA1_C$ alter an individual's risk of developing or dying from cancer- and thus enable more soundly based conclusions to be drawn than if the study had been more limited in the scope of its analyses. If this had not been the case, the issue of multiple significance tests, the results being difficult to interpret due to the large number of tests undertaken, may have arisen.

The limited amount of previous research detailing the associations between diabetes and cancer incidence give the results of the current study the potential to further our knowledge in an area of increasing public health importance. The size of the dataset also allowed for an exploration of the role of key confounders within the association between diabetes and/or $HbA1_C$ and cancer incidence and mortality. The use of COX regression and multinomial logistic regression enabled an assessment of the temporality of associations between diabetes and cancer incidence and competing causes of death. The large number of deaths from CVD enabled results which further confirm the associations between diabetes and CVD, but also detail the magnitude of the effect within a sample of the general population of England and Scotland. Finally, the impact that diabetes has upon mortality

from respiratory disease is an under researched area. The results of this study are indicative of an association which requires further research.

Because of the categories used to define those with raised blood glucose within the Whitehall I data, it was not possible to analyse the impact of this variable upon mortality; although this issue was addressed in full using the HSE and SHeS dataset. Given the under- powered nature of the analyses using the latter data, it is likely that analyses of the Whitehall I data which used this variable would have been even further under powered. If the associations between $HbA1_C$ and cancer incidence and mortality are to be successfully explored, future studies will have to have access to datasets with larger number of cases with valid measurements related to glycated haemoglobin.

The use of a cohort study design allowed for an exploration of the temporal sequence between diabetes and cancer incidence and mortality. Within the HSE/SHeS dataset those with cancer at baseline were excluded from the analyses and the exclusion of those who had died of cancer within one year of participating in the survey, within the Cox regression analyses, adds further support to diabetes increasing the risk of cancer – rather than reverse causality. A second advantage of the study design was that, through the use of multinomial logistic regression, multiple outcomes could be assessed at the same time. This was particularly beneficial when the analyses were focussed upon competing causes of death and site-specific cancer outcomes. Thirdly, the use of a cohort study design enabled the calculation of a cancer event occurring and the development of hazard and odds ratios.

As seen within the analyses which sought to assess the impact of $HbA1_C$ upon cancer incidence and mortality, the key disadvantages of the cohort study design are the need for a large sample/size and /or a long follow-up period in order to collect the necessary number of events to achieve power. At the same time, diabetes status was confirmed at baseline only and it was therefore not possible to assess whether or not a participant's disease status had changed during the follow-up period. Among those with type-2 diabetes, this is particularly relevant as it can be possible to reverse some of the aspects of the disease with changes to lifestyle. A participant's $HbA1_C$ measurement may also have changed during follow-up. Future studies could overcome this issue by using longitudinal data within which diabetes and $HbA1_C$ status are regularly collected for each individual. The English Longitudinal Study of Ageing is one such dataset available within the UK, and future studies could use different waves of the study to explore how changes in diabetes and or $HbA1_C$ impact upon cancer risk.

Only those who agreed to have their records flagged within mortality data and the Cancer Registry were included within the analyses of the current study. It was also not possible to gather this information about those who left the UK. This selection bias could have the potential to bias the study results, although most of those involved agreed to their data being flagged.

The analyses of site-specific cancer incidence and mortality demonstrate that diabetes impacts upon the risk of each cancer differently. Although the use of the all-cancers variable enabled the study to have the power required to analyse the associations between diabetes and cancer over all, it is clear that this variable is likely to mask the differences in risk for each site-specific cancer. It may be advisable for future studies to avoid the use of an all-cancers variable, although the number of site-specific cancers will need to be carefully considered before undertaking analyses of this nature.

Within a large portion of this study, mortality from cancer was the focus of the analyses. Throughout the duration of the study a participant could have died of a different cause and this competing cause of mortality would therefore exclude the participant from experiencing mortality from cancer. The Cox regression undertaken within the current study did not take into account such competing risks and this may have produced biased, overestimated, numerical results when compared with those produced by analyses which did take such factors into account, particularly given the strong associations between diabetes and CVD mortality. It is interesting to note that only a few of the earlier studies carried out with the intention of assessing the associations between diabetes and cancer mortality undertook analyses which utilised competing risk analysis methods; it appears that methods which do take into account competing events have not been fully taken advantage of in this field of research. Perhaps as our understanding of the subject evolves, researchers will undertakestudies which utilise such methods.

12.12 Implications for further research

The current study has demonstrated that those with diabetes have an increased risk of cancer incidence and mortality. At the same time the study encountered a number of the weaknesses inherent to the use of cohort study methods such as portions of the analyses being underpowered. Future studies could utilise data from other sources which may be able to overcome this issue. These could include:

- Primary care data – the majority of those diagnosed with diabetes are likely to receive some form of support and/or treatment from their GP.
- Hospital Episode Statistics –covering the whole of England this data includes records from over 125 million patients from A & E, outpatient and those admitted to hospital.

- Longitudinal datasets – the English Longitudinal Study of Ageing and the Health and Retirement Study (USA) give opportunities to not only explore the impact of diabetes upon cancer within a single study with repeat measures but it is also possible to combine and compare results from each dataset.

The current study did not explore the role that diabetes treatments had within the associations between diabetes and cancer; further research could use RCTs to explore this further. However, the requirements of participants to treat their diabetes in the most appropriate way possible will always limit the feasibility of RCTs which seek to compare the impact of single treatments upon cancer risk. The biological plausibility of an association between diabetes, $HbA1_C$ and cancer is yet to be fully understood, studies using both in vivo and in vitro studies could play a key role in this regard. At the same time, as the measurement of biological biomarkers becomes more reliable and common place, this information can also assist in understanding this research area more fully. Finally, the prevalence of type-1 diabetes is increasing by around 3% each year, the cause of this is not clear and needs to be more widely explored.

12.13 Implications for policy and practice

Diabetes mellitus is a disease of increasing public health concern in the UK and internationally. The incidence and prevalence of the disease is increasing substantially, caused by increases in overweight and obesity and the ageing population found within most developed countries. In the UK around 2.9 million individuals are currently living with diabetes and this figure is predicted to increase to five million by 2025. At the same time the incidence and prevalence of cancer is also increasing, with 275,000 new cases in the UK each year. Diabetes and cancer carry a substantial emotional, physical and financial cost to the individual, as well as a high financial cost to societies aiming to prevent and treat both diseases. The high prevalence of diabetes means that if it were to produce even a small excess in cancer incidence and mortality this could equate to a large number of cancer cases and deaths within a population.

Overweight and obesity are inextricably linked with diabetes; preventing both conditions is likely to be more effective and require less resource than treating them. Effective management of diabetes has been shown to increase reduce the number of complications experienced. Policy related to diabetes and adiposity should be developed which aims to reduce the incidence and prevalence of both conditions. This could take the form of policies which seek to decrease calorie consumption while increasing exercise uptake.

The results of this study suggest that raised $HbA1_C$ is associated with an increased risk of mortality from and incidence of cancer. Health care provision should therefore seek to enable those with diabetes to reduce their blood glucose to a level that does not impact upon their risk of mortality from other causes. This requires on-going treatment and an understanding of the particular circumstances of each diabetic individual. Health services should also be encouraged to identify those who are living with pre-diabetes and support them in making the changes in lifestyle required to slow or prevent the occurrence of diabetes. Currently those with diabetes are informed of their increased risk of developing complications related to CVD and renal disease. If the results of the current study are confirmed then information will need to be disseminated about cancer in much the same way that it is about these other conditions. Individuals with diabetes should also be encouraged to utilise cancer screening services where available and those who are diagnosed with both conditions should receive care which addresses the particular circumstance of having both comorbidities.

As described in chapter 1, diabetes and cancer incidence and prevalence are increasing substantially: this has a corresponding impact upon both the health of individuals and communities and the financial costs to health care systems of both diseases. Further to this, the results of the current study – in finding diabetes to be associated with cancer – suggest that the increase in the number of cases of the former will have an impact upon the financial burden of the latter. These associations also suggest that the increasing numbers of diabetes cases would result in a substantial increase in cancer incidence and/or mortality. Although the results of the current study (within its analyses of the HSE and SHeS combined dataset) confirm the associations between diabetes, $HbA1_C$ and cancer incidence and mortality, the results from Whitehall I did not. There is also heterogeneity within the results of previous studies which may relate to differences in study design, the population under investigation, the cancer outcome investigated and the confounding factors adjusted for. If the results of this current study were to be further confirmed this would enable the development of methods to reduce the cancer risk among those with diabetes and evidence-based public health messages for those with diabetes.

12.14 Conclusions

In relation to the associations between diabetes and incidence of and mortality from cancer the results of previous studies have been heterogeneous and often contradictory. Among those which have shown a positive association, the strength of the association appeared to be dependent upon the population being studied and the methods used within the study. The primary aim of this current

study was therefore to explore the associations between diabetes, glycated haemoglobin and cancer (both overall and site-specific incidence and mortality) using data from England and Scotland. Secondary to this, analyses of the same data also sought to assess the impact that diabetes and glycated haemoglobin might have upon mortality from all-causes, cardiovascular and respiratory disease and other causes. Finally, the study sought to understand if any of these associations were mediated through confounding factors related to adiposity and the impact of the presence of CVD as a comorbidity.

Within the current analyses of HSE/SHeS data, those with diabetes were found to have around a 20% increased odds of dying of cancer compared with the general population; the increase remained after adjustment for the various measurements of adiposity. This goes some way to supporting the hypothesis that it is the specifics of having diabetes which increases an individual's cancer mortality risk rather than associated factors. Within the stratified analysis men and women with diabetes had a similar excess in cancer mortality, while there were differences in the odds of dying of cancer between those with diabetes but either with or without comorbid CVD. This latter result is novel and suggests the need for the development of health service practice which takes into account the underlying characteristics of those with diabetes when considering their disease risk. The increased mortality from CVD among those with CVD at baseline may be the underlying cause of this difference in cancer risk: those with diabetes and CVD are likely to be dying before the age when cancer mortality occurs. Further research exploring whether those with diabetes are at an increased risk of developing cancer, are diagnosed with cancer at a later stage of the disease, receive different cancer treatments, or have differing outcomes related to their reactions to chemotherapy and radiotherapy compared with those without diabetes is needed.

The excess in the risk of cancer incidence was raised among those with diabetes, compared with the general population, by around 10%. Similarly to cancer mortality, this excess remained after adjustment for measurements of overweight and obesity again supporting the impact that the underlying biology of diabetes impacts upon cancer risk. When stratified by sex only women were found to have an increased risk of developing cancer; this may relate to the different rates of CVD mortality among men and women with diabetes and is an issue which requires further exploration. The results of the current study found raised point estimates for a number of site-specific cancers in terms of incidence and mortality; although for the majority the confidence intervals were indicative of a non-significant association. The combination of these results with those of earlier studies suggest that those with diabetes are at an increased risk of developing and/or dying from a number

of site-specific cancers compared with those without diabetes. These associations require further analyses within larger studies which would be able to confirm whether these are chance findings or indicate true associations that were underpowered within the current study. One exception is the finding that diabetes is associated with pancreatic cancer, and that this increase remains after deaths within the first year are excluded, a result which suggests that it is not due to reverse causality . If a true understanding of the associations between diabetes and site-specific cancers is to be developed, future studies would need to use dataset that include a greater number of cancer endpoints.

Prior to this study there was a limited amount of research that had been dedicated to exploring the associations between diabetes and respiratory disease. The results of the current study indicate that those with diabetes are at an increased risk of mortality from respiratory disease; in vivo and in vitro studies have suggested that this is associated with inflammation related to the presence of overweight and obesity among those with diabetes. Although the excess in mortality from respiratory disease remained among women with diabetes when alternative measurements of adiposity were adjusted for, the same was not found for men. Such sex differences call for diabetes-related services which take into account that those with diabetes may have differing mortality risks which are dependent upon their specific circumstances.

Analyses of data from the Health Survey for England, Scottish Health Survey and Whitehall I linked to the Cancer Registry and mortality data within the current study demonstrated an excess in all-cause mortality, which was predominantly caused by an excess in mortality caused by CVD among those with doctor-diagnosed diabetes compared with that found within the general population. Contrary to the results of a number of previous studies, this excess was little altered within either the multinomial or Cox regression analyses when adjustment was made for confounding factors related to adiposity or socio-economic/demographic factors. This result supports the biological relationship between diabetes and CVD – focussed upon the impact that the former has upon atherosclerosis – and those of some earlier epidemiological studies. By comparing the results of the analyses of the HSE and SHeS combined dataset with those of the analyses of Whitehall I it appears that the excess in all-cause and CVD mortality found among those with diabetes compared with the general population is in decline. This demonstrates that such inequalities in disease risk can be successfully addressed if they are fully understood and programmes are developed to combat them.

Although the biological plausibility of a relationship between diabetes and cardiovascular disease is well established, the potential for a relationship with cancer incidence and mortality has yet to be fully established and requires further exploration. This task was beyond the scope of the current study, but its results are indicative of an association between diabetes, raised glycated haemoglobin and cancer incidence and mortality, as well as mortality from a number of other causes. The differences in the excess mortality experienced by those with diabetes who also had comorbid CVD, compared with those who did not have CVD calls for personalised healthcare which takes into account the underlying health of each diabetic patient. Similarly, the differences in excess mortality among men and women with diabetes compared with those without the disease further calls for individualised care which takes into account the many facets of an individual's experience of living with diabetes. Only through the provision of such care and services can those with diabetes be enabled to live their lives as healthily and free from complications as possible.

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Appendix One: Syntax for the creation of the site-specific cancer variables

For example, the syntax below was used to capture all of those cases who died of cancers of the lip, oral cavity and pharynx (it was necessary to write syntax similar to this for each of the grouped cancers).

```
RECODE DRN_or_CS (CONVERT)
( 'C10'=1)( 'C11'=1)( 'C12'=1)( 'C13'=1)( 'C14'=1)
( 'C100'=1)( 'C110'=1)( 'C120'=1)( 'C130'=1)( 'C140'=1)
( 'C101'=1)( 'C111'=1)( 'C121'=1)( 'C131'=1)( 'C141'=1)
( 'C102'=1)( 'C112'=1)( 'C122'=1)( 'C132'=1)( 'C142'=1)
( 'C103'=1)( 'C113'=1)( 'C123'=1)( 'C133'=1)( 'C143'=1)
( 'C104'=1)( 'C114'=1)( 'C124'=1)( 'C134'=1)( 'C144'=1)
( 'C105'=1)( 'C115'=1)( 'C125'=1)( 'C135'=1)( 'C145'=1)
( 'C106'=1)( 'C116'=1)( 'C126'=1)( 'C136'=1)( 'C146'=1)
( 'C107'=1)( 'C117'=1)( 'C127'=1)( 'C137'=1)( 'C147'=1)
( 'C108'=1)( 'C118'=1)( 'C128'=1)( 'C138'=1)( 'C148'=1)
( 'C109'=1)( 'C119'=1)( 'C129'=1)( 'C139'=1)( 'C149'=1)
INTO ICD10Cancervgd.
execute.
```

Appendix Two: Lay description of diabetes and glycated haemoglobin

The term diabetes mellitus is rooted in the ancient Greek words for 'siphon' and 'sugar' which demonstrates the key symptom of the disease, the passing of urine that contains sugar (glucose) caused by too much sugar in the blood. It is called diabetes mellitus ('sugar' diabetes) to distinguish it from the much rarer condition of diabetes insipidus, a totally unrelated condition in which an individual is unable to concentrate the urine and therefore passes copious amounts of dilute urine. Because the former is common and the latter is rare, the term diabetes is frequently used by itself to refer to diabetes mellitus.

The level of sugar within the body is controlled via the production of insulin which occurs within a gland called the pancreas. Within the pancreas there are ducts which contain regions called the Islets of Langerhans: within these are the cells which produce insulin (as well as glucagon). Insulin is a hormone, a chemical that is released into the blood stream from a particular organ in order to tell other areas of the body to react in a particular way. Insulin is secreted directly into the bloodstream and acts to control the levels of sugar within the blood.

There are two main types of diabetes mellitus:

Type-1 diabetes

This form of the disease is caused by the body destroying the cells within the pancreas that produce insulin. In most cases the body is left without any of these cells, resulting in a total deficiency of insulin. In order for individuals with this form of diabetes to maintain a balanced blood sugar level, and good health, it is necessary to replace the insulin via injections. Type-1 diabetes is most commonly diagnosed among the young.

Type-2 diabetes

Type-2 diabetes is defined primarily by insulin resistance (when areas of the body do not react effectively to the release of insulin) which is often followed by a reduction in the production of insulin. This form of the disease accounts for around 90% of all cases of diabetes and is more commonly diagnosed among those in older age groups, although an increasing number of children are being diagnosed. Lifestyle factors related to overweight and obesity and excessive calorie intake

predispose an individual to developing the disease. Diagnosis of diabetes may occur many years after increased levels of sugar have been present in the blood. The progression of the disease can be slowed by changes to diet (reduced calorie intake) and weight loss, while tablets can be taken which control the level of blood glucose. In the later stages of the disease, insulin injections may also be required to prevent high levels of sugar in the blood.

Gestational diabetes

There is a certain level of glucose intolerance during pregnancy which protects the growing foetus. In 2-3% of pregnancies this intolerance is at a level defined as gestational diabetes. The presence of the disease may increase an individual's risk of developing type-2 diabetes in the future; gestational diabetes also increases the risk of complications during pregnancy and poorer health outcomes for the baby once it is born.

Glycated haemoglobin is the amount of haemoglobin circulating in the blood that has glucose attached to it. It is a measurement of blood glucose that gives an indication of the levels of sugar in the blood over the preceding two to three months. The more blood sugar present, the higher the glycated haemoglobin measurement will be.

Within this study, a boundary of 6.5% is considered to be indicative of diabetes. During the period of the study, the International Federation of Clinical Chemistry suggested that glycated haemoglobin measurements should be given in mmol/mol. The corresponding values are given in the table below.

%	Mmol/mol
6.0	42
6.5	48
7.0	53
7.5	58

Appendix Three: Lay description of cancer

Cancer (known medically as malignant neoplasms) is the term used to describe over 200 different diseases defined by the abnormal growth and division of cells within the body, and the ability of these cells to invade (metastasise) other areas of the body. These cells form when the DNA of a normal cell becomes damaged instead of dying the cell may continue to produce new cells which form a tumour. Because there are a large number of types of cancer, there are also a diverse range of causes of the disease; an increasing age is considered one of the key risk factors for all cancers. Other risk factors can relate to lifestyle (smoking, alcohol, diet) and genetic predisposition (for example the BRCA1 & 2 genes which increase the risk of developing breast cancer) and the presence of some viruses, diseases and carcinogens (Human Papilloma Virus (HPV), increases the risk of cervical cancer and may increase the risk of other site-specific cancers).

Cancers are usually named after the organ or cell type in which they originate and can be placed in a number of key categories.

- Carcinoma is a cancer that begins in the lining or covering of organs or the skin.
- Sarcoma begins in tissue related to a number of areas including bone, muscle, fat and connective/supportive tissue.
- Leukaemia begins in tissue within the body that produces blood and results in abnormal blood cells within the body.
- Cancers of the nervous system originate in either the brain or spinal cord.

There is a further category termed ‘benign’ tumours. Although they form a mass, these cells are unable to spread to other areas of the body and can usually be removed via surgery.

Appendix Four: Glossary

Name	Definition
Adiponectin	Adipokine produced by adipose tissue-inversely correlated with body fat, may exert a protective effect on breast epithelial cells through inhibiting proliferation and enhanced apoptosis.
AMPK	Induces glucose uptake by muscles
Apoptosis	Programmed cell death
Cytokine	Regulatory proteins, such as interleukins, TNF α and interferons. They act as intercellular regulators, have a specific effect on communications between cells or on behaviour of cells and trigger such things as inflammation and responses to infection. Bind to a particular receptor.
IGF-1 (Insulin-like growth factor 1)	Endocrine hormone and protein encoded by IGF1 gene and produced primarily by the liver. Similar to insulin molecularly and can bind to the insulin receptor. Potent activator of AKT signalling pathway, stimulator of cell growth and proliferation, and a potent inhibitor of apoptosis. IGF1-1 signalling plays a key role in tumour progression (cancer promoting factor) and glucose homeostatis.
Leptin	Adipocyte derived cytokine-been found to promote breast cancer cell proliferation
LKB1	Tumour suppressor protein
TNFα (Tumour necrosis factor α)	Pro-inflammatory cytokine produced by adipose tissue. Induces development and progression of many tumours by strongly activating nuclear factor-kappa B (NF-kB) which mediates the pro-tumoral effects of TNFα.

Appendix Five: Publications related to thesis

Aresu, M., Gordon-Dseagu, V. and Shelton, N. (2010) 'Diabetes and glycaemia'. Chapter 4 in Craig R, Hirani V (Eds). *Health Survey for England 2009. Volume 1 Health and Lifestyle*. The Health and Social Care Information Centre: Leeds(peer-reviewed report chapter, not included at the end of the thesis). Available from: http://www.hscic.gov.uk/catalogue/PUB00414/heal-surv-heal-life-eng-2009-rep-v2.pdf.

Gordon-Dseagu, V. (2011). Diabetes. In M. Stange, C. Oyster, and J. Sloan (Eds.), *Encyclopedia of women in today's world.* (pp. 386-388). Thousand Oaks, CA: SAGE Publications, Inc. doi: 10.4135/9781412995962.n206.

Gordon, V.L.Z., Mindell, J. and Shelton, N. All-Cause and Cause-Specific Mortality among Individuals with and without Diabetes in England and Scotland (OP57) *J Epidemiol Community Health* 2012; 66: A22 doi:10.1136/jech-2012-201753.057

Gordon-Dseagu, V.L., Shelton, N., Mindell, J.S. Epidemiological evidence of a relationship between type-1 diabetes mellitus and cancer: a review of the existing literature. *Int J Cancer.* 2013 Feb 1; 132(3):501-8. Doi: 10.1002/ijc.27703. (Included in the body of the thesis).

Oyebode, O., Gordon-Dseagu, V., Walker, A. And Mindell, J. Fruit and Vegetable Consumption and Mortality: A Cox Regression Analysis (OP57). *J Epidemiol Community Health.* 2013: 67: A40.

Oyebode, O., Gordon-Dseagu, V., Walker, A. And Mindell, J. Fruit and vegetable consumption and all-cause, cancer and CVD mortalty: analysis of Health Survey for England data. J Epdemiol Community Health. 2014;**68**:856-862 doi:10.1136/jech-2013-203500

Gordon-Dseagu, V.L.Z., Shelton, N. and Mindell, J. Exploring the Associations between Diabetes and Site-Specific cancer Mortality: Evidence from the Health Survey for England and Scottish Health Survey linked to Mortality Data (PP28-Poster presentation). *J Epidemiol Community Health.* 2013: 67: A60.

Copies of the papers are available at the end of the thesis.

Appendix Six: Focus of the Health Survey for England 1991-2010

Year	Specific Issue
2010	Respiratory disease, sexual health, kidney disease, and wellbeing
2009	Kidney disease and diabetes
2008	Physical activity and fitness
2007	Healthy lifestyles and behaviours
2006	Cardiovascular disease and obesity in children
2005	Older People
2004	Black and minority ethnic communities
2003	Cardiovascular disease
2002	Children and young people
2001	Respiratory and other atopic conditions, accidents and disability
2000	Older People
1999	Black and minority ethnic communities
1998	Cardiovascular disease
1997	Children and young people
1996	Respiratory and other atopic conditions, accidents and disability
1995	Respiratory and other atopic conditions, accidents and disability
1994	Cardiovascular disease
1993	Cardiovascular disease
1992	Cardiovascular disease
1991	Cardiovascular disease

Paper abstracts

Gordon, V.L.Z., Mindell, J. and Shelton, N. All-Cause and Cause-Specific Mortality among Individuals with and without Diabetes in England and Scotland (Oral presentation at SSM: OP57) *J Epidemiol Community Health* 2012; 66: A22 doi:10.1136/jech-2012-201753.057

Abstract

Background

Although a growing body of evidence demonstrates an increase in cardiovascular disease (CVD) mortality among those with diabetes mellitus, the results related to other causes of death are less homogenous. The strength of the association between diabetes and mortality appears to differ by geographic location. The role that Body Mass Index (BMI) plays also requires further exploration. In the UK, one in 20 individuals is estimated to have diabetes. Therefore, even a small increase in mortality risk among those with diabetes, could result in a large number of deaths among those with the disease. This large general-population cohort study used data from England and Scotland to explore the associations between diabetes and risk of all-cause and cause-specific mortality, and examine the extent to which any increase was attributable to raised BMI.

Methods

Nationally-representative, cross-sectional data from 15 years of the Health Survey for England (HSE) (1994–2005) and Scottish Health Survey (SHeS) (1995, 1998 and 2003) were linked with mortality records up to the first quarter of 2011. Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age-group and sex (model 1), plus smoking status (model 2) and additionally for BMI category (model 3) were estimated using logistic and multinomial logistic regression. Participants mentioning cancer at baseline were excluded from the study.

Results

Within this sample of 166,600 participants (5,131 with diabetes) there were 19,483 deaths (1,060 among those with diabetes, 18,423 without diabetes). All-cause mortality was greater among those with diabetes when adjusted for age, sex and smoking status (OR 1.52, 95% CI 1.41–1.65), with no reduction when adjusting for BMI category (OR 1.49, 1.37–1.64). Cause-specific mortality among those with diabetes was raised for CVD (model 2 OR 1.73, 1.55–1.93), cancer (1.24, 1.08–1.43) and

'Other' (1.77, 1.54–2.04) with a non-significant increase for respiratory diseases (1.21, CI 0.99–1.47). Additional adjustment for BMI had a minimal impact upon the excess mortality found among those with diabetes: CVD (OR 1.69, 1.49–1.93), cancer (1.24, 1.05–1.45), 'Other' causes (1.75, 1.49–2.07), and respiratory diseases (1.16, 0.92–1.47). Survival was also lower among those with diabetes compared with those without the disease at baseline.

Conclusion

Diabetes is associated with an excess of all-cause and cause-specific mortality from CVD, cancer, and 'Other' causes but probably not respiratory diseases. Increased BMI does not appear to be a mediating factor within the association between diabetes and cause-specific mortality.

Oyebode, O., Gordon-Dseagu, V., Walker, A. And Mindell, J. Fruit and Vegetable Consumption and Mortality: A Cox Regression Analysis (Oral presentation at SSM: OP57*). J Epidemiol Community Health*. 2013: 67: A40.

Abstract

Background

Following World Health Organisation recommendations, the UK government promotes a daily intake of at least five portions of fruit and vegetables.

Methods

We used Cox regression to estimate hazard ratios and 95% confidence intervals for an association between fruit and vegetable consumption and all-cause, cancer and cardiovascular (CVD) mortality, adjusting for age, sex, BMI and social class in data from 85,347 adult participants in the Health Survey for England 2001-2008.

Results

Fruit and vegetable consumption had a substantial protective effect for all-cause mortality (adjusted HR for 6-<7 portions 0·64 (95% CI 0·54–0·76)), stronger when deaths within a year of baseline were excluded (HR 0·57 (0·45–0·72) or when fully-adjusting for physical activity (0·48 (0·36–0·66). Consumption was significantly associated with reduced cancer (HR for 5- < 7 portions 0·78 (0·63–0·96) and CVD mortality, with increasing benefits being seen up to more than seven daily portions of

fruit and vegetables for CVD (0·69 (0·53–0·89)). Consuming up to three to four portions of fruit daily and up to 3 + portions of vegetables a day was associated with decreased mortality. Vegetables had a greater effect than fruit (HR for 2- < 3 portions 0·82 (0·74–0·91) and 0·91 (0·83–0·99) respectively).

Conclusion

There is no threshold for the association between fruit and vegetable consumption and CVD survival up to a total of seven portions daily. Maximal benefit was conferred by six daily portions for all deaths and five portions for cancer. Vegetables have greater benefit than fruit.

Oyebode, O., Gordon-Dseagu, V., Walker, A. And Mindell, J. Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. J Epidemiol Community Health. Doi: 10.1136/jech-2013-203500

Abstract

Background

Governments worldwide recommend daily consumption of fruit and vegetables. We examine whether this benefits health in the general population of England.

Methods

Cox regression was used to estimate HRs and 95% CI for an association between fruit and vegetable consumption and all-cause, cancer and cardiovascular mortality, adjusting for age, sex, social class, education, BMI, alcohol consumption and physical activity, in 65 226 participants aged 35+ years in the 2001–2008 Health Surveys for England, annual surveys of nationally representative random samples of the non-institutionalised population of England linked to mortality data (median follow-up: 7.7 years).

Results

Fruit and vegetable consumption was associated with decreased all-cause mortality (adjusted HR for 7+ portions 0.67 (95% CI 0.58 to 0.78), reference category <1 portion). This association was more pronounced when excluding deaths within a year of baseline (0.58 (0.46 to 0.71)). Fruit and vegetable consumption was associated with reduced cancer (0.75 (0.59–0.96)) and cardiovascular mortality (0.69 (0.53 to 0.88)). Vegetables may have a stronger association with mortality than fruit (HR for 2 to 3 portions 0.81 (0.73 to 0.89) and 0.90 (0.82 to 0.98), respectively). Consumption of vegetables (0.85 (0.81 to 0.89) per portion) or salad (0.87 (0.82 to 0.92) per portion) were most

protective, while frozen/canned fruit consumption was apparently associated with increased mortality (1.17 (1.07 to 1.28) per portion).

Conclusions

A robust inverse association exists between fruit and vegetable consumption and mortality, with benefits seen in up to 7+ portions daily. Further investigations into the effects of different types of fruit and vegetables are warranted.

Gordon-Dseagu, V.L.Z., Shelton, N. and Mindell, J. Exploring the Associations between Diabetes and Site-Specific cancer Mortality: Evidence from the Health Survey for England and Scottish Health Survey linked to Mortality Data (Poster presentation at SSM: PP28). *J Epidemiol Community Health.* 2013: 67: A60.

Abstract

Background

The associations between diabetes and mortality from a number of causes, such as cardiovascular and renal disease, are clearly understood. Concurrently, there is a growing body of evidence demonstrating an increase in cancer mortality among those with diabetes, although there is heterogeneity regarding the strength of the association and uncertainty around confounding by overweight/obesity. Around 2.9 million individuals in the UK are currently living with diabetes; this figure is expected to increase to 5 million by 2025, caused by rising rates of obesity and population ageing. The high prevalence of diabetes means that even a small increased risk of cancer mortality could equate to a large number of deaths among the diabetic population. This large cohort study utilised data from the Health Survey for England and the Scottish Health Survey, linked to mortality data, to explore overall and site-specific cancer mortality.

Methods

Nationally-representative, cross-sectional data from the Health Survey for England (HSE: 1994-2008) and Scottish Health Survey (SHeS: 1995, 1998 and 2003) linked with mortality records up to the first quarter of 2011 and 2008 respectively. Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age-group, sex and smoking status and additionally for BMI category were estimated for all and site-specific cancer mortality using logistic and multinomial logistic regression respectively. To allow for a consideration of the time sequence of any association between the two diseases, individuals with cancer at baseline were excluded from the analyses.

Results

The study sample included 204,537 participants (6,258 with diabetes) and 5,562 cancer deaths. After adjustment for age, sex and smoking status, those with diabetes were at greater risk of dying from cancer compared with those without diabetes (OR 1.16 (1.02, 1.31)). This increase remained after adjustment also included BMI (1.19, 1.04-1.36). For site-specific cancer mortality, there were statistically significant increases for pancreatic (1.77 (1.16, 2.72)), breast (1.62 (1.02, 2.65)) and lung (1.34 (1.05, 1.72)) cancer when adjustment included age, sex, smoking and BMI; as well as point estimate increased risk for cancers of the colorectum, bladder, stomach, lymphoid and haematopoietic, kidney and oesophagus.

Conclusion

The high and rising prevalence of diabetes is of public health concern. Those with diabetes have increased overall cancer mortality and site-specific cancers of the pancreas, breast and lung, unaffected by measurements of overweight/obesity. Although some cases of pancreatic cancer may be reverse causality, health services for people with diabetes need to be aware of the increased cancer mortality found among this cohort.