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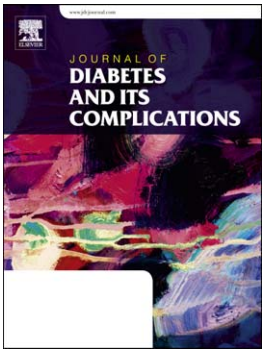

Diabetes mellitus and mortality from all-causes, cancer, cardiovascular and respiratory disease: evidence from the Health Survey for England and Scottish Health Survey cohorts

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Diabetes mellitus and mortality from all-causes, cancer, cardiovascular and respiratory disease: evidence from the Health Survey for England and Scottish Health Survey cohorts

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Abstract

Background: Diabetes mellitus is associated with differing rates of all-cause and cause-specific mortality compared with the general population; although the strength of these associations requires further investigation. The effects of confounding factors, such as overweight and obesity and the presence of co-morbid cardiovascular disease (CVD), upon such associations also remain unclear. There is thus a need for studies which utilise data from nationally-representative samples to explore these associations further.

Methods: A cohort study of 204,533 participants aged 16+ years (7,199 with diabetes) from the Health Survey for England (HSE) (1994-2008) and Scottish Health Survey (SHeS) (1995, 1998 and 2003) linked with UK mortality records. Odds ratios (ORs) of all-cause and cause-specific mortality and 95% confidence intervals were estimated using logistic and multinomial logistic regression.

Results: There were 20,051 deaths (1,814 among those with diabetes). Adjusted (age, sex, and smoking status) ORs for all-cause mortality among those with diabetes was 1.68 (95%CI 1.57-1.79). Cause-specific mortality ORs were: cancer 1.26 (1.13-1.42), respiratory diseases 1.25 (1.08-1.46), CVD 1.96 (1.80-2.14) and 'other' causes 2.06 (1.84-2.30). These were not attenuated significantly after adjustment for generalised and/or central adiposity and other confounding factors. The odds of mortality differed between those with and without comorbid CVD at baseline; the ORs for the latter group were substantially increased..

Conclusions: In addition to the excess in CVD and all-cause mortality among those with diabetes, there is also increased mortality from cancer, respiratory diseases, and 'other' causes. This increase in mortality is independent of obesity and a range of other

confounding factors. With falling CVD incidence and mortality, the raised risks of respiratory and cancer deaths in people with diabetes will become more important and require increased health care provision.

Key words

Diabetes, all-cause, cardiovascular disease, cancer, respiratory disease.

1. Introduction

Globally, more than 366 million individuals currently live with diabetes mellitus, with this figure expected to rise to 552 million by 2030.(1) The World Health Organization estimates that around 1.1 million deaths occur per year as a result of the disease.(2) Around 2.9 million individuals in England currently have diagnosed diabetes, a prevalence of 4.5%.(3) Projections for England estimate that by 2030 over 4.5 million people will be living with diabetes.(4) The number of individuals living with diabetes means that if there were found to be an excess in mortality caused by the disease, this could result in a large number of premature deaths.

The association between diabetes and increased all-cause mortality, particularly from cardiovascular disease (CVD) and renal disease, is well recognised. However, there is heterogeneity between studies for some specific causes of death, particularly in relation to cancer.(5) Some studies have found cancer mortality rates similar to those within the general population,(6,7) while others show an increase(8–10) or decrease(11,12) among people with diabetes; most recent studies have found an increase, including those from Europe and the United States. 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).(13) Investigations of site-specific cancers also demonstrate differences in mortality risk among those with diabetes.(8,14,15) Studies consistently find increased pancreatic cancer mortality among those with diabetes but whether this is due only to reverse causality is still uncertain.(16) Evidence also demonstrates increased risks for bladder, liver and breast cancer mortality.(17) Analysis of Whitehall I data found no significant association between diabetes and colorectal cancer.(18) Chia et al. further found

that women with diabetes subsequently diagnosed with endometrial cancer experienced a 70% increase in all-cause mortality but not mortality from endometrial cancer.(19) There are also mixed findings related to cancer incidence (all-cause and site-specific).(20,21)

There is a limited amount of evidence relating to diabetes and respiratory disease mortality.(7,8,22) Current evidence suggests a biological link between inflammation, reduced levels of adiponectin within the body and the development of diabetes and respiratory disease.(23) A correlation has also been found between measurements of abdominal obesity and respiratory conditions.(24)

The need for national studies exploring the association between diabetes and cause-specific mortality is highlighted by differences in the strength of the associations between countries.(25) De Marco et al. concluded that these may be caused by differences in the severity of diabetes or differing national treatment cultures.(7) Therefore, research is required that further explores the association between diabetes and mortality from cancer and respiratory disease. Current research indicates that, for mortality from a number of causes, it may be diabetes-related comorbidities that increase an individual's risk of death rather than diabetes itself.(26) This paper examines associations between diabetes and a range of causes of mortality but also assesses the contribution to the associations of overweight/obesity, social class and region, and the presence of comorbidities.

2. Materials and methods

2.1 Participants and data

Study participants were adults within the Health Survey for England (HSE) or Scottish Health Survey (SHeS) who gave permission for their data to be flagged with national mortality data. Detailed descriptions of the HSE and SHeS have been reported elsewhere.(27,28) The

surveys select a random, nationally representative, general population sample (with a different sample selected each year). All participants were visited by an interviewer, who asks questions related to health and lifestyle behaviour, requests consent for data linkage to administrative datasets, and measures weight and height. If the participant agreed, a nurse visited to collect further physical measurements (including waist and hip circumference), biological samples and information about prescribed medications.

Within the HSE and SHeS, participants with diabetes were identified via at least one of three variables: the participant volunteered diabetes as a longstanding illness, or a positive response to a diabetes-specific question (only available in some years) or a diabetes-related prescribed medication was recorded by the nurse. Individuals with CVD were identified after volunteering a positive response to the longstanding illness question (as with diabetes).

Data from HSE years 1994-2008 and SHES years 1995, 1998 and 2003 linked to UK mortality data up to March 2011 were analysed. Participants were asked to consent to survey data linkage, with consent rates ranging from 80% to 95%. Mortality records were available only for deaths that occurred within the UK. Variables were created for cancer (C00-C97), respiratory diseases (J00-J99) and CVD (ICD10 codes I00-I99); 'other' causes included all remaining deaths.

A raised waist circumference was defined as >102cm for men and >88cm for women.(29) As there is no consensus for thresholds for a raised waist-to-hip ratio,(30) those used within the HSE since 1997 were selected: >0.949 for men and >0.849 for women. Raised glycated haemoglobin (HbA_{1C}) was considered to be >6.49mmol/mol. In total 28,754 individuals within the study had a measurement for glycated haemoglobin. Although this biomarker was adjusted for within the regression models, because the focus of the study was an

exploration of the potential excess mortality among those with doctor diagnosed diabetes compared with the general population, it was not used to identify those with undiagnosed diabetes. Region was divided into four areas (South, Midlands, North, and Scotland) and education into three groups (Degree or equivalent level, Other, No qualifications). Social class was separated into seven groups based upon the Registrar-General's Social Class based on Occupation bandings (I: Professional occupations, II: Managerial and technical, IIINM: Skilled non-manual, IIIM: Skilled manual, IV: Partly-skilled, V: Unskilled and other).

147 cases were excluded from the analyses due to missing data for age or gender; survey participants reporting cancer at baseline were also excluded (n=3,656), leaving 204,533 participants (7,199 with diabetes) in the sample.

2.2 **Statistical analysis**

The primary outcome measures were all-cause and cause-specific mortality (CVD, cancer, respiratory and 'other' causes). Odds Ratios (ORs) and 95% Confidence Intervals (CI) were calculated using logistic regression to explore the associations between diabetes and all-cause mortality; multinomial regression was utilised for the cause-specific mortality analyses. Unless otherwise indicated, all ORs are adjusted for age (grouped: 16-64, 65-74, 75+), sex, and smoking status (current smoker, ex-regular smoker, never smoked). BMI (grouped: <20kg/m^2, 20-24.9kg/m^2, 25-29.9kg/m^2, ≥30kg/m^2), CVD at baseline, demographic/socio-economic factors, and glycated haemoglobin were added to the model where indicated. Analyses were repeated first stratified by gender and secondly stratified by diagnosed CVD at baseline. Within all analyses the basic model refers to adjustment for age, sex and smoking, while the advanced model also includes BMI. The reference group for each

analysis was those without diagnosed diabetes. All analyses were undertaken using SPSS V. 17 (SPSS Inc).

3. Results

3.1 Descriptive results

7,199 participants had diabetes (3.5%); 21,892 (10.7%) had CVD at baseline. Participants' mean age was 47y (SD± 19.2). Those with diabetes were considerably older (mean age 63y (SD 15.1) than those without the disease (mean 47y (SD 19.1)). The former also had a higher BMI (Table 1). 55% of participants were female (48% among those with diabetes, 56% among those without). There were 20,051 deaths recorded, including 1,814 in those with doctor-diagnosed diabetes (25% of those with diabetes) and 18,237 among those without diabetes (9% of the non-diabetic sample). In terms of cause of death, 7,489 participants died of CVD; 5571 from cancer; 2,828 from respiratory disease; and 4,153 from other causes.

Table 1: Baseline Data Used in Analyses of Diabetes and All-Cause and Cause-Specific Mortality by Participant Diabetes Status

<Table 1 here>

3.2 All-cause mortality

After adjustment for sex, age and smoking status, the OR for all-cause mortality for those with diabetes was 1.68 (95% CI 1.57-1.79) compared with those without the disease (Table 2). Further adjustment for BMI (1.69, 1.57-1.82) did not affect the results, while adjustment for CVD at baseline attenuated the results minimally (1.56, 1.45-1.68). The increased OR among those with diabetes was maintained when analysis adjusted for waist-to-hip ratio (1.56, 1.43-1.70) or waist circumference (1.59, CI 1.46-1.73) rather than BMI; baseline CVD

again attenuated these a little (1.45, CI 1.33-1.58 and 1.48, CI 1.36-1.61, respectively). Adding education, socioeconomic class or region had no significant impact upon the increased odds of all-cause mortality among those with diabetes. Adjusting for raised glycated haemoglobin increased the point estimate ,of the odds of death but not significantly so (1.93, 1.49-2.49).

Table 2: Odds Ratios for all-cause mortality among participants with diabetes compared with those without diabetes

<Table 2 here>

For most analyses, the OR for all-cause mortality were similar for men and women (Table 2). When analysis was stratified by baseline CVD status, diabetes conferred a higher odds of all-cause mortality among those without CVD (1.66, 1.52-1.81) compared with those with CVD (1.33, 1.20-1.46) in the basic model. This increase remained when adjustment included other confounding factors (Table 2). Because of residual confounding caused by smoking, sensitivity analysis was undertaken among those who indicated that they never smoked regularly. The ORs for all-cause mortality among those with diabetes within this group were increased within both the basic and advanced models.

3.3 **Cause-specific mortality**

After adjustment for age, sex and smoking, those with diabetes had increased ORs for CVD (1.96, 1.80-2.14), respiratory (1.25, 1.08-1.46), cancer (1.26, 1.13-1.42), and 'other' causes of death (2.06, 1.84-2.30). When adjustment included a range of confounding factors, these

increased odds among those with diabetes remained statistically significant (Table 3). Adjusting for glycated haemoglobin (HbA_{1c}) produced an increase in the OR point estimates for mortality for cancer and respiratory disease that were not statistically significant.

Table 3: Odds Ratios for cause-specific mortality among participants with diabetes as compared with those without diabetes

<Table 3>

Women had an increased odds of mortality from each cause considered: CVD (1.92, 1.69-2.18), respiratory (1.38, 1.12-1.71), cancer (1.33, 1.12-1.59), and 'other' (1.80, 1.54-2.11). For men, similar increases were found for CVD (1.99, 1.78-2.24), cancer (1.21, 1.03-1.40) and 'other' causes (2.36, 2.03-2.75). There were also increased odds of mortality from respiratory disease when adjusted for multiple confounding factors (Table 4). This increase remained, for both genders, after adjustment for the full range of confounders.

Table 4: Odds Ratios for cause-specific mortality among participants with diabetes compared with those without diabetes (analyses stratified by gender)

<Table 4>

Among those with CVD at baseline, diabetes was significantly associated with deaths from CVD (1.40, 1.24-1.59) and 'other' causes (1.67, 1.39-2.00) but not from cancer or respiratory disease. For those without CVD at baseline, diabetes was associated with CVD (1.90, 1.69-2.14), respiratory disease (1.26, 1.04-1.52), cancer (1.26, 1.09-1.46), and 'other' causes (2.13, 1.86-2.45). Similarly to analyses stratified by gender, additional adjustment did not significantly affect the excess mortality experienced by those with diabetes. Among never smokers, diabetes was associated with increased adjusted ORs for mortality from each of the causes analysed.

Table 5: Odds Ratios for cause-specific mortality among participants with diabetes compared with those without diabetes (analyses stratified by CVD at baseline status)

<Table 5>

4. Discussion

This longitudinal study is one of the largest to be undertaken using nationally representative data linked to current mortality records and demonstrates a substantial increase among those with diabetes, compared with the general population, in the risk of mortality from all-cause and cause-specific mortality not only from CVD but also from cancer and respiratory disease. These associations remained unchanged when adjusted for different measures of adiposity, suggesting that overweight/obesity does not mediate the association between diabetes and mortality. Although there is a wealth of evidence demonstrating the association between diabetes and CVD mortality, there is less of a consensus concerning the

extent to which diabetes impacts upon causes of death traditionally thought to be unrelated to the disease itself, such as cancer and respiratory disease. There is biological plausibility between diabetes and cancer; recent research suggests that the association may be related to hyperglycaemia, hyperinsulinaemia, the use of diabetes related drugs and/or exogenous insulin.(31–34) Within this study, adjusting for raised glycated haemoglobin had little impact upon the association between diabetes and cancer mortality but this may relate to the small number of deaths from these causes among those who had a recorded measurement for this factor. As the focus of this study was doctor diagnosed diabetes, glycated haemoglobin was not used to identify those with undiagnosed diabetes. Whether those with undiagnosed diabetes have differing mortality rates to those living with the disease diagnosed could be an area for future research.

The results of our study are compatible with those from recent, large-scale international studies in finding substantially increased risk or odds of dying from cancer amongst those with diabetes after adjustment for age, sex, smoking status and BMI. 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.(35) A large study undertaken by The Emerging Risk Factors Collaboration (ERFC) found a hazard ratio (HR) of 1.80 (95% CI 1.70-1.90)(13), while a US study found a relative risk (RR) for all-cause mortality of 1.90 (CI 1.87-1.93 for women and 1.73 (1.70-1.75) for men.(36) Koskinen found a substantial increase in mortality among diabetic women (SMR 3.39, CI 3.30-3.49) and men (SMR 2.41, CI 2.41-2.48)(37), although most studies have found smaller increases.(9,38,39)

Prior to our study, evidence suggested the biological plausibility of a relationship between diabetes and respiratory disease.(22–24) We found minimal changes in the excess mortality

from respiratory disease experienced by those with diabetes after adjustment for adiposity. We also found no increase in mortality from respiratory disease among those with CVD at baseline.

Research demonstrating the relationship between diabetes and CVD has a long history.(40) The biological plausibility of a relationship between diabetes and CVD is focussed upon the vascular complications of the former.(37,41–43) The results of this current study support the increase in CVD-related mortality among those with diabetes. The reduction in the magnitude of the association between diabetes and CVD mortality among those with baseline CVD, compared with those without, is probably related to the substantially increased case-fatality rate among people with diabetes. This probably also explains the lack of increased ORs in relation to mortality from of respiratory disease among diabetics with diagnosed CVD at baseline.

There is also a growing body of evidence demonstrating the associations between adiposity and increased cancer mortality.(32) Adjusting for measurements of adiposity, baseline CVD, demographic/socio-economic factors and glycated haemoglobin had only a marginal impact upon the association between diabetes and all-cause and cause-specific mortality. This suggests that factors related to diabetes influence the excess cancer deaths independently, rather than via mediating factors, a theory previously suggested in relation to a number of factors in a consensus report by the American Diabetes Association and the American Cancer Society. (21)

In terms of the broad 'other' category, data specifying more detailed cause of death were not released to us for data protection reasons; it is likely that the increase in mortality among those with diabetes is due to primarily to renal disease.(44) Diabetic nephropathy is

the leading cause of chronic renal disease within Europe and other regions internationally, but chronic kidney disease is relatively rare among those without diabetes.(45) Orchard et al. found that individuals with type-1 diabetes who did not have renal disease had no substantial increase in mortality risk compared with the general population.(46)

A limitation of this study was the inability to differentiate between those with type-1 and type-2 diabetes. Earlier research suggests that these groups may have differing excess all-cause and cause-specific mortality.(47,48) Further work is needed to clarify the excess mortality experienced by those with type-1 diabetes, although the small number with this form of the disease (between 5-10% of all those with diabetes) makes detailed analysis difficult.(49) Further limitations related to diabetes status were that information related to diabetes was available only at baseline. This would tend to underestimate the effect of diabetes on mortality and cause-specific mortality, as those with undiagnosed diabetes or who developed diabetes later were included in the non-diabetic group. Additionally, although information related to the use of diabetes medications was available at baseline for some of the participants, and was used to identify the diabetic cohort, detailed information was not available in relation to changes in diabetes-medication and duration of diabetes.. In terms of the former, the dynamic and often changing drug regimens makes this study inappropriate for analysing the impact different treatments have upon mortality risk.

The study identified those with diagnosed diabetes by a combination of self-report and nurse identification of the use of prescribed medication for diabetes. Some studies have found the former to be accurate enough for use within epidemiological studies,(50) although this is contested due to the prevalence of undiagnosed disease and inaccuracy within self-reporting.(51,52) Because of undiagnosed disease, studies that do not measure

fasting glucose or glycated haemoglobin in all participants are likely to underestimate the true prevalence of diabetes, resulting in individuals with undiagnosed diabetes within the comparison group, leading to underestimation of the excess mortality experienced by those with diabetes.

The cause of death categories used within the analyses were relatively broad, which did not allow for a detailed exploration of cause-specific mortality. Within the HSE and SHeS data, some more detailed cause-specific mortality information was available, but the small numbers within the diabetic sub-group prevented adjusted analysis of this data.

The study population was representative of the general, free-living population in England. The majority of the study population self identified as ethnically white (~85%), similar to that found within the general population of England.(55) Although an early analyses suggested that ethnicity did not substantially alter the ORs, the small number of deaths among those from Black and Minority Ethnic populations made the results of analyses which included this variable difficult to interpret due to a lack of power. further research could explore the impact of ethnicity further.

A key strength of this study was that it utilised a large, nationally-representative, general population sample of over 200,000 individuals, including more than 7,000 with diabetes. Through the use of 15 years of Health Survey for England and three years of Scottish Health Survey data linked to mortality records, the study was able to analyse the associations between diabetes and mortality. It was also able to assess the extent to which the association was mediated via factors such as the presence of adiposity; the use of a variety of measurements in this regard further meant that the effects of both generalised and

central adiposity were considered. Finally, the use of multinomial logistic regression within the analyses allowed for competing causes of death to be considered.

5. Conclusion

This current study contributes to our knowledge of the causes of the excess in mortality experienced by those with diabetes. Within a nationally representative sample, those with diabetes were found to have increased odds of mortality from cancer and respiratory disease; the association between diabetes and all-cause and CVD-related mortality were further confirmed. With the falling CVD incidence and mortality rates in many countries,(53) including among people with diabetes,(54) and rising diabetes prevalence, the increased mortality from cancer and respiratory disease in those without baseline CVD becomes increasingly important for people with diabetes. Our results support the development of programmes seeking to reduce mortality from a wider range of causes within this group.

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Jennifer Mindell and Nicola Shelton had the original idea; Vanessa Gordon-Dseagu prepared the dataset, syntax and conducted the analyses; all authors prepared the analysis plan, interpreted the data, drafted the manuscript, and approved the final version. The authors wish to thank Professor Michael Marmot, Professor Daniel Hochhauser and Jenny Head for their support of this research.

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Table 1: Baseline Data Used in Analyses of Diabetes and All-cause and Cause-specific Mortality by Participant Diabetes Status[a]		
Characteristics	**Diabetes**	**No diabetes**
Demographic factors		
Total sample (%)	7,199 (3.5)	197,334 (96.5)
Age-groups no. (%)		
16-64	3,448 (48)	156,816 (80)
65-74	2,127 (30)	22,376 (11)
75+	1,624 (23)	18,142 (9)
Sex - no. (%)		
Male	3,762 (52)	87,648 (45)
Female	3,437 (48)	109,511 (55)
Lifestyle factors		
Smoking status-no. (%)		
Never	3,023 (43)	95,084 (48)
Ex-regular smoker	2,828 (39)	47,515 (24)
Current smoker	1,226 (17)	52,719 (27)
Missing	122 (2)	2016 (1)
Anthropometric measures		
BMI		
No. with data (%)	5,986 (84)	176,670 (90)
Mean – kg/m^2 (SD)	29±5.5	26±4.8
BMI: <20	83 (1)	9,836 (6)
BMI: 20-<25	1,019 (17)	64,310 (36)
BMI: 20-<30	2,287 (38)	66,888 (38)
BMI: =>30	2,597 (43)	35,607 (20)
BMI: Missing	1,213 (16)	20,693 (11)
Waist circumference		
No. With data (%)	4,302 (59)	111,935 (57)
Above threshold (Men: 102cm, Women: 88cm)	2,877 (67)	42,716 (38)
Mean-cm (SD)	101 (14)	89 (14)
Waist-to-hip ratio		
No. with data (%)	4,291 (59)	111,785 (57)
Above threshold (Men: 0.949, Women: 0.849) (%)	2,804 (39)	31,503 (28)
Mean (SD)	0.93 (0.09)	0.86 (0.09)
Glycated haemoglobin[b] **(%)**		
<6.5%	415 (33)	26,880 (98)
>=6.5%	827 (67)	632 (2)
Missing	5,957 (83)	
Socio-demographic		

[a] Percentages may not sum to 100 due to rounding.

[b] Percentage given relates to only those with a valid glycated haemoglobin measurement.

Region (%)		
South	3,067 (43)	86,611 (44)
Midlands	1,341 (19)	35,389 (18)
North	1,889 (26)	50,910(26)
Scotland	683 (10)	22,133 (11)
Education (%)		
Degree	595 (8)	28,361 (14)
Other	2,886 (40)	111,443 (57)
No qualifications	3,587 (50)	55,829 (28)
Missing	131 (2)	1,701 (1)
Socio-economic class (%)		
I: Professional	222 (3)	8,591 (4)
II: Managerial	1,614 (22)	50,767 (26)
III: Skilled Non-manual	1,319 (18)	45,614 (23)
III: Skilled Manual	1,667 (23)	35,150 (18)
IV: Semi-skilled Manual	1,363 (19)	32,779 (17)
V: Unskilled manual	553 (8)	11,491 (6)
Other	313 (4)	10,054 (5)
Missing	148 (2)	2,888 (2)
Comorbidity		
CVD at baseline (%)	2,722 (38)	19,170 (10)
Mortality		
Died (%)	1,814 (25)	18,237 (9)
Cause of death-no. (% of all deaths)		
CVD	819 (45)	6,670 (37)
Cancer	355 (20)	5,216 (29)
Respiratory	212 (12)	2,626 (14)
Other	428 (24)	3,725 (20)

Table 2: Odds Ratios for all-cause mortality among participants with diabetes compared with those without diabetes						
Progressive adjustment						
	WHOLE SAMPLE	**STRATIFIED BY CVD**		**STRATIFIED BY GENDER**		**NEVER SMOKERS ONLY**
		NO	**YES**	**WOMEN**	**MEN**	**n=98,107**
Age, sex	1.61	1.58	1.29	1.58	1.64	1.72
	(1.51-1.72)	(1.45-1.72)	(1.18-1.42)	(1.44-1.73)	(1.50-1.79)	(1.55-1.92)
& Smoking[c]	1.68	1.66	1.33	1.67	1.69	N/A
	(1.57-1.79)	(1.52-1.81)	(1.20-1.46)	(1.51-1.83)	(1.54-1.84)	
& BMI[d]	1.69	1.68	1.38	1.63	1.74	1.71
	(1.57-1.82)	(1.53-1.85)	(1.24-1.54)	(1.46-1.81)	(1.58-1.92)	(1.51-1.92)
& CVD	1.56	N/A	N/A	1.52	1.59	1.63
	(1.45-1.68)			(1.37-1.70)	(1.44-1.75)	(1.44-1.83)
Additional Adjustment (Advanced model +)						
Education	1.64	1.64	1.36	1.58	1.69	1.67
	(1.53-1.76)	(1.49-1.80)	(1.22-1.51)	(1.42-1.76)	(1.54-1.86)	(1.48-1.88)
Social Class	1.66	1.65	1.35	1.57	1.73	1.65
	(1.54-1.78)	(1.50-1.82)	(1.22-1.51)	(1.41-1.75)	(1.57-1.90)	(1.47-1.86)
Region	1.69	1.68	1.37	1.62	1.74	1.70
	(1.57-1.81)	(1.53-1.85)	(1.23-1.52)	(1.45-1.80)	(1.58-1.91)	(1.51-1.92)
HbA1c[e]	1.93	1.95	1.57	2.12	1.84	1.49
	(1.49-2.49)	(1.39-2.74)	(1.06-2.31)	(1.43-3.14)	(1.31-2.58)	(0.95-2.35)

[c] Basic Model
[d] Advanced Model
[e] Glycated Haemoglobin

Table 3: Odds Ratios for Cause-Specific Mortality Among those with Diabetes Compared With Those Without Diabetes (Whole Sample)				
Progressive Adjustment				
	CVD	**Respiratory**	**Cancer**	**Other**
Age, sex	1.89	1.18	1.23	1.97
	(1.73-2.05)	(1.02-1.37)	(1.09-1.38)	(1.77-2.20)
& Smoking	1.96	1.25	1.26	2.06
	(1.80-2.14)	(1.08-1.46)	(1.13-1.42)	(1.84-2.30)
& BMI	1.94	1.39	1.27	2.09
	(1.76-2.13)	(1.18-1.64)	(1.12-1.43)	(1.85-2.37)
& CVD	1.69	1.34	1.21	2.01
	(1.54-1.86)	(1.13-1.58)	(1.06-1.36)	(1.78-2.28)
Additional Adjustment (Advanced model +)				
Education	1.89	1.34	1.22	2.03
	(1.72-2.08)	(1.14-1.59)	(1.08-1.38)	(1.79-2.30)
Social Class	1.92	1.37	1.26	2.07
	(1.75-2.11)	(1.16-1.62)	(1.11-1.42)	(1.83-2.34)
Region	1.93	1.40	1.26	2.09
	(1.75-2.12)	(1.18-1.66)	(1.11-1.43)	(1.85-2.37)
HbA1c	2.22	1.46	1.19	3.39
	(1.52-3.25)	(0.72-2.95)	(0.74-1.89)	(2.07-5.55)

Table 4: Odds Ratios for cause-specific mortality among participants with diabetes compared with those without diabetes (analyses stratified by gender)								
Progressive Adjustment								
	WOMEN				**MEN**			
	CVD	**Respiratory**	**Cancer**	**Other**	**CVD**	**Respiratory**	**Cancer**	**Other**
Age	1.83	1.29	1.27	1.71	1.94	1.09	1.19	2.30
	(1.61-2.07)	(1.05-1.60)	(1.07-1.51)	(1.46-2.00)	(1.73-2.17)	(0.89-1.34)	(1.02-1.38)	(1.98-2.68)
& Smoking (Basic Model)	1.92	1.38	1.33	1.80	1.99	1.14	1.21	2.36
	(1.69-2.18)	(1.12-1.71)	(1.12-1.59)	(1.54-2.11)	(1.78-2.24)	(0.93-1.41)	(1.03-1.40)	(2.03-2.75)
& BMI (Advanced Model)	1.92	1.41	1.27	1.72	1.95	1.37	1.25	2.51
	(1.67-2.22)	(1.09-1.82)	(1.05-1.54)	(1.43-2.08)	(1.72-2.22)	(1.10-1.71)	(1.10-1.47)	(2.13-2.96)
& CVD	1.72	1.36	1.22	1.68	1.67	1.31	1.18	2.39
	(1.49-1.99)	(1.05-1.76)	(1.00-1.48)	(1.39-2.03)	(1.47-1.90)	(1.05-1.64)	(1.01-1.39)	(2.02-2.82)
Additional Adjustment (Advanced model +)								
Education	1.88	1.37	1.22	1.68	1.91	1.32	1.21	2.43
	(1.63-2.16)	(1.06-1.77)	(1.00-1.48)	(1.39-2.02)	(1.68-2.16)	(1.06-1.65)	(1.03-1.43)	(2.05-2.86)
Social Class	1.88	1.37	1.26	1.69	1.94	1.37	1.25	2.49
	(1.63-2.18)	(1.06-1.77)	(1.04-1.52)	(1.40-2.04)	(1.71-2.20)	(1.09-1.70)	(1.06-1.47)	(2.11-2.94)
Region	1.91	1.41	1.25	1.74	1.95	1.39	1.25	2.49
	(1.65-2.21)	(1.09-1.83)	(1.03-1.52)	(1.44-2.11)	(1.72-2.21)	(1.11-1.73)	(1.06-1.47)	(2.11-2.95)
HbA1c	1.94	1.58	2.45	2.56	2.55	1.44	0.73	4.07
	(1.08-3.50)	(0.59-4.22)	(1.24-4.86)	(1.13-5.80)	(1.56-4.17)	(0.53-3.94)	(0.39-1.35)	(2.20-7.52)

Table 5: Odds Ratios for cause-specific mortality among participants with diabetes compared with those without diabetes (analyses stratified by CVD at baseline status)								
	NO				YES			
Progressive Model	**CVD**	**Respiratory**	**Cancer**	**Other**	**CVD**	**Respiratory**	**Cancer**	**Other**
Age, sex	1.81	1.18	1.22	2.04	1.37	1.05	1.03	1.63
	(1.61-2.03)	(0.97-1.42)	(1.05-1.41)	(1.77-2.34)	(1.22-1.55)	(0.83-1.33)	(0.86-1.24)	(1.36-1.96)
& Smoking	1.90	1.26	1.26	2.13	1.40	1.09	1.06	1.67
	(1.69-2.14)	(1.04-1.52)	(1.09-1.46)	(1.86-2.45)	(1.24-1.59)	(0.86-1.38)	(0.88-1.27)	(1.39-2.00)
& BMI	1.91	1.40	1.27	2.18	1.45	1.23	1.11	1.71
	(1.67-2.17)	(1.13-1.73)	(1.08-1.48)	(1.86-2.55)	(1.26-1.66)	(0.95-1.61)	(0.91-1.35)	(1.40-2.10)
& CVD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Additional Adjustment (Advanced model +)								
Education	1.86	1.36	1.22	2.12	1.43	1.20	1.09	1.67
	(1.63-2.12)	(1.10-1.69)	(1.04-1.44)	(1.81-2.49)	(1.25-1.64)	(0.92-1.57)	(0.89-1.33)	(1.37-2.05)
Social Class	1.89	1.37	1.26	2.16	1.44	1.22	1.10	1.70
	(1.66-2.15)	(1.11-1.71)	(1.07-1.48)	(1.84-2.52)	(1.26-1.65)	(0.94-1.60)	(0.90-1.34)	(1.39-2.08)
Region	1.92	1.42	1.25	2.18	1.42	1.23	1.11	1.70
	(1.68-2.19)	(1.15-1.77)	(1.07-1.47)	(1.86-2.56)	(1.24-1.63)	(0.94-1.61)	(0.91-1.35)	1.39-2.09)
HbA1c	2.70	2.09	1.02	2.75	1.42	0.74	1.33	3.51
	(1.62-4.5)	(0.86-5.07)	(0.55-1.90)	(1.39-5.42)	(0.81-2.47)	(0.24-2.27)	(0.64-2.76)	(1.71-7.2)