Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes: A Population-Based Cohort Study Quantifying Relationships in Ethnic Sub-Groups

Short running title: Cause-specific Mortality in Type 2 Diabetes

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Abstract

Objectives:a)To investigate life expectancy and cause-specific mortality rates associated with type 2 diabetes, and b) to quantify these relationships in ethnic subgroups.

Research Design and Methods:Cohort study using Clinical Practice Research Datalink data from 383 general practices in England with linked hospitalization and mortality records. 187,968 incident type 2 diabetes patients from 1998-2015 were matched to 908,016 controls.Abridged life tables estimated years of life lost and a competing risk survival model quantified cause-specific hazard ratios (HR).

Results: 40,286 deaths were observed in type 2 patients. At age 40, White men with diabetes lost 5 years of life and White women lost 6 years compared to those without diabetes. A loss of between 1-2 years was observed for South Asian and Blacks with diabetes. Above 65 years, South Asians with diabetes had up to 1.1 years longer life-expectancy compared to South Asians without diabetes. When compared to Whites with diabetes, South Asians with diabetes had lower adjusted risks for mortality from cardiovascular (HR 0.82 [95% CI 0.75-0.89]), cancer (HR 0.43 [95% CI 0.36-0.51]), and respiratory diseases (HR 0.60 [95% CI 0.48-0.76]). A similar pattern was observed in Blacks with diabetes compared to Whites with diabetes.

Conclusions: Type 2 diabetes was associated with more years of life lost among Whites than South Asians or Blacks, with older South Asians experiencing longer life-expectancy compared to South Asians without diabetes. The findings support optimized CVD risk factor management, especially in Whites with type 2 diabetes.

The worldwide prevalence of type 2 diabetes is increasing rapidly.(1) A large body of evidence shows that type 2 diabetes is associated with a 1.3-2.0 times higher risk of death, mostly due to cardiovascular disease.(2–4) However, contemporary data on cause-specific mortality and life expectancy in type 2 diabetes are limited.

It is widely acknowledged that ethnicity influences the presentation of diabetes, the development of complications and all-cause mortality.(5) However, no study has reported the influence of ethnicity on life expectancy or cause-specific mortality in type 2 diabetes, since the majority of studies have focused on all-cause or simply cardiovascular mortality.(6–8) Cause-specific mortality data could provide mechanistic insights into any observed ethnic disparities in all-cause mortality and thereby guide future research and public health strategies in type 2 diabetes.

The aims of this research were: a) to compare years of life lost and cause-specific mortality associated with type 2 diabetes; and b) to quantify these relationships in White, Black and South Asian populations.

RESEARCH DESIGN AND METHODS

Data Sources

The Clinical Practice Research Datalink (CPRD) provides anonymised, longitudinal primary care medical records from participating UK general practices.(9) Linkage with Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) mortality data is also available for English practices where they agree to record-linkage. We included 383 eligible general practices. The study was approved by the Independent Scientific Advisory Committee (ISAC) for CPRD research (ref. 15\_123Mn).

Study Population

We identified an incident cohort of patients with diabetes (type 1 and type 2), who had their first diagnostic code for diabetes in the study period 1 January 1998 to 31 March 2015. The study period corresponds to the time window for which all patient-level datasets (CPRD, HES, ONS) were eligible for linkage and had data coverage. An algorithm established by De Lusignan et al.,(10) was implemented to classify patients with type 2 diabetes (Supplemental Figure S1). This validated algorithm has been used in a number of studies using Electronic Health Records (EHRs) data.(11–13) Incident type 2 diabetes cases were matched with up to five controls on year of birth (± 2 years), gender, general practice and index date of diabetes diagnosis (details of control selection are shown in Supplemental Figure S2). Controls were defined as patients without diabetes.

Type 2 diabetes cases and controls were followed-up from the index date until the study end date (31 March 2015), the practice’s last data collection date, death, or transfer out of practice.

Study Variables

Cause of death was based on International Classification of Diseases (ICD)-10 chapters or relevant sub-chapters from the linked national mortality records. Chapter headings were subsequently grouped into ten mutually exclusive categories (see Supplemental Methods).

Ethnicity was identified from CPRD and through linkage with HES (details in Supplemental Figure S3). All ethnicity codes were collapsed into five headings, developed by the Office for National Statistics;(14) White, South Asian (a sub-classification of Asian/British Asian), Black/Black British, Other and Unknown. The overarching Asian/British Asian heading includes Indian, Pakistani, Bangladeshi, Chinese and Other Asian. For South Asian classification, patients defined as Chinese were excluded and re-classified as “Other” (which includes East/Southeast Asian ethnicities; for example, Korean, Japanese, Vietnamese etc.). Deprivation was quantified with the Index of Multiple Deprivation (IMD) 2010, a national scheme based on seven deprivation domains and available at small-area level to link with the address of the patient, categorized into five quintiles: IMD 1 (least deprived) up to IMD 5 (most deprived).(15) Further details on IMD are provided in Supplemental Methods.

Drug prescriptions at baseline were defined as a prescription within 90 days before or after the index date. Poly regimens in antidiabetic medications occurred if there were multiple different class of drug prescribed within the same month. Biological measures at baseline (BMI, HbA1c, total cholesterol, blood pressure) were defined as the closest measure up to 6 months before and 3 months after the index date. Smoking status (categorized into three classes; current, ex, never) was defined according to the closest smoking recording prior to the index date. Cardiovascular disease and renal disease (defined as CKD stage 4 and above) were defined by Read code, up to the index date.

All code lists used are available for download from [www.clinicalcodes.org](http://www.clinicalcodes.org).(16)

Statistical Methods

Abridged period life tables, based on the Chiang II method,(17) were used to estimate life expectancy among patients with type 2 diabetes and controls without diabetes. The life tables were constructed from 1998 to 2015, aggregating death and population data into 5-year age intervals up to 80 years (as outlined in Supplemental Methods). The difference in life expectancy was calculated as the estimated life expectancy in patients without diabetes minus the estimated life expectancy in people with type 2 diabetes.

Causes of death, categorized into ten headings, were identified in men and women. In the primary analysis, unadjusted proportions of deaths in these categories were compared for type 2 diabetes versus control patients. Under a competing-risks framework, and using a flexible parametric survival model, hazards ratios for all-cause and cause-specific morality associated with the presence of type 2 diabetes were calculated after adjusting for age, gender, ethnicity, deprivation and calendar year.

Secondary analyses were performed to observe ethnic differences in life expectancy and mortality. Life expectancy estimates were calculated within ethnic-age-gender strata for White, South Asian and Black diabetes and control patients. Stratification was applied in generating estimates of life expectancy as we were unable to match people with type 2 diabetes with control patients on the basis of ethnic group (further details in Supplemental Methods). Plots of the differences in life expectancy by ethnic group and gender were constructed over age groups. All-cause and cause-specific mortality rates, stratified by diabetes (likelihood ratio test Supplemental Figure S4), were calculated for South Asian and Black people in comparison to Whites.

All analyses were computed using Stata version 14.1 (StataCorp LP).

RESULTS

There were 187,968 patients with incident type 2 diabetes (mean (SD) age: 61.8 ± 14 years; 55% males; 942,412 years of follow-up) and 908,016 controls without diabetes (9,287,474 years of follow-up) matched for age, gender, practice and index date in the study (Table 1). At baseline, those with type 2 diabetes had higher BMI, blood glucose and blood pressure levels, more likely to be receiving antihypertensives, antiplatelets and lipid agents, and were more likely to have cardiovascular disease and renal disease than those without diabetes. In both groups, the majority of patients were White (77% of type 2 diabetes patients; 72% of controls). Baseline characteristics in White, South Asian and Black ethnic groups are shown in Supplemental Table S1. In the group with type 2 diabetes, 143,724 were White (mean (SD) age: 63±14 years), 9,523 were South Asian (age: 53±14 years) and 4,461 were Black (age: 54±14 years). At baseline, South Asians (8.2±2.0%; 66±22mmol/mol) and Blacks (8.5±2.5%; 69±27mmol/mol) had higher HbA1c values than Whites (7.9±2.0%; 63±22mmol/mol), and received more antidiabetic medications, including more poly-regimens. BMI and blood pressure levels were lower in South Asians compared with Whites. Smoking (current and ex), cardiovascular disease and renal disease were more prevalent in Whites than other ethnic groups.

Differences in life expectancy in age-gender strata were compared for those with type 2 diabetes and the controls without diabetes (Supplemental Table S2). At the age of 40 years, men and women with type 2 diabetes experienced loss of several years of life when compared to people without diabetes (men: 5.4 years; women 6.3 years). The difference in life expectancy between those with type 2 diabetes and without diabetes was greater for women than men at all ages and declined by age attained.

From ethnic-stratified life expectancy estimates, the effect of diabetes in White men and women was greater than in South Asian and Black individuals (Figure 1 and Supplemental Table S3). For example, in White men aged 40 years, the estimated years of life expectancy loss associated with type 2 diabetes was 5.5 years (95% CI 5.3-5.7), and in White women, 6.7 years (95 % CI 6.4-6.9). By comparison, in South Asian men aged 40 years, 1.0 year (95% CI 0.6-1.3) was lost to type 2 diabetes and in South Asian women, 0.5 years (95% CI 0.1-0.9) were lost. Correspondingly, for Black men, 2.4 years (95% CI 1.7-3.2) were lost, and among Black women 1.7 years (95% CI 1.0-2.3) were lost. In Whites aged >65 years, the presence of type 2 diabetes was associated with 3-4 years shorter life expectancy. In contrast, in South Asian men and women aged >65 years, the presence of type 2 diabetes was associated with up to 1.1 years longer life expectancy compared to South Asians without diabetes.

There were 40,286 deaths among patients with type 2 diabetes (crude mortality: 42.7/1,000 person-year) and 181,338 deaths in those without diabetes (crude mortality: 19.5/1,000 person-years), Table 2. In comparison to those without diabetes, type 2 diabetes was associated with a 2-fold higher all-cause mortality; HR 2.19 (95% CI 2.16-2.21). The most common causes of death were similar across both populations (cardiovascular disease, malignancy and respiratory disease). After taking into account the competing risks of different causes of death, type 2 diabetes was associated with significantly higher risks of death from every cause except suicide (Table 2 & Supplemental Table S4).

Crude mortality rates in Whites, South Asians and Blacks are shown in Supplemental Table S5. In the adjusted analysis (Table 3), compared to Whites with type 2 diabetes, South Asian and Black patients with type 2 diabetes had lower all-cause mortality; HR 0.70 (95% CI 0.65-0.76) and HR 0.82 (95% CI 0.74-0.91), respectively. Compared to Whites with type 2 diabetes, South Asians with type 2 diabetes had significantly lower adjusted risks for mortality from cardiovascular disease (HR 0.82; 95% CI 0.75-0.89), cancer (HR 0.43; 95% CI 0.36-0.51) and respiratory diseases (HR 0.60; 95% CI 0.48-0.76), and higher mortality (but not significantly) from renal disease (HR 1.50; 95% CI 0.93-2.46). A similar pattern was observed in Black patients compared to White patients with type 2 diabetes, with a lower risk of death from cardiovascular disease (HR 0.83; 95% CI 0.75-0.93), cancer (HR 0.84; 95% CI 0.70-0.99), and respiratory disease (HR 0.62; 95% CI 0.46-0.84).

CONLCUSION

Main findings

This large population-based retrospective cohort study provides several novel insights: a) when compared to South Asians and Blacks, Whites (especially women) experienced more years of life lost associated with the presence of type 2 diabetes; b) older South Asian men and women with type 2 diabetes had longer life expectancy compared to South Asians without diabetes; c) compared to Whites with type 2 diabetes, South Asians and Blacks with type 2 diabetes had lower risks of all-cause mortality, and lower mortality from cardiovascular, respiratory and cancer specified causes. Further research into the mechanisms underlying these findings might provide useful insights into these ethnic disparities in type 2 diabetes outcomes, which may in turn guide public health strategies.

Impact of diabetes on life expectancy by gender and ethnicity

*Gender*: In our cohort, the presence of type 2 diabetes was associated with a potential loss of life of 5 years in men and 6 years in women, at an attained age of 40 years. Using data from prospective population-based studies involving participants recruited from 1960 to 2007, the Emerging Risk Factors Collaboration reported that at the age of 40, the presence of diabetes was associated with a loss of life of around 7.9 years in men and 8.2 years in women.(18) We showed a lower number of life years lost associated with incident diabetes in a more contemporary cohort identified from 1998 to 2015. Mortality trends from years 2000-2011 in type 2 diabetes patients from Australia also indicate significant decreases in all-cause, cardiovascular and diabetes mortality across all age-groups from 40 years.(19) We extend these important pieces of work using linked primary care, hospitalization and national mortality electronic health record data to show that this loss of life is driven largely by diabetes-associated mortality in White women and men. The greater impact of developing diabetes among women (compared to men) on all-cause mortality and coronary events has been reported previously - and we now extend these observations to include cause-specific mortality and life expectancy.(20–22) The explanation for these observations is unclear, but could relate to: a) women gaining more weight than men prior to developing diabetes and thereby undergoing larger obesity-related CVD risk factor changes; or b) to sex disparities in risk factor management.(23,24)

*Ethnicity*: Here, we report for the first time that, in older South Asians, the presence of diabetes is associated with modest protection from all-cause mortality. Although ‘protection’ from death has been described in elderly type 2 diabetes patients,(2) our data in South Asians are somewhat surprising. However, several factors could help to explain our findings: 1) South Asian patients with type 2 diabetes were diagnosed younger (by 10 years) and at lower BMI levels than Whites (mean 28.8 kg/m2 compared to 31.6 kg/m2). Treating South Asian and Black patients with lifestyle intervention and medication at a young age, often prior to the development of macrovascular disease may have preferentially slowed the progression of atherosclerosis and lowered the risk of cardiovascular death compared to those without diabetes; 2) In our study the prevalence of undiagnosed diabetes (~5%) among South Asians is likely to have been around twice as high as in Whites.(25) Therefore, undiagnosed (and untreated) individuals with diabetes in the community may have made a modest contribution to the higher mortality in the group of South Asians without known diabetes.

Impact of ethnicity on mortality in people with type 2 diabetes

*Prior studies*: We observed that, when compared to Whites with type 2 diabetes, South Asians and Blacks with type 2 diabetes had lower risks of all-cause mortality, and lower cardiovascular, respiratory, and cancer disease mortality. A small number of studies in type 2 diabetes have compared total mortality in different ethnic groups but none have provided cause-specific mortality data. For example, in research trial participants, the United Kingdom Prospective Diabetes Study (UKPDS) investigators reported that Afro-Caribbean (n=312) and South Asian (n=418) patients with type 2 diabetes experienced an 11-16% lower all-cause mortality compared to Whites with type 2 diabetes.(26) Further studies from the UK and Canada reported ~40% lower total mortality risk in South Asian patients with diabetes compared to Whites with diabetes.(5,27)

*Interpretation*: Our findings suggest that in people with type 2 diabetes, the lower mortality risks in South Asians compared to Whites may be partly explained by the lower prevalence of smoking, hypertension, obesity and cardiovascular disease and greater exposure to antidiabetic medications except sulfonylureas (linked to higher mortality). Mortality rates may also have been affected by the ethnic mix within our South Asian group: 52% were Indian; 23% were Pakistani and 6.5% were Bangladeshi. Individuals of Indian origin have lower rates of chronic conditions and cardiovascular mortality than those of Bangladeshi and Pakistani origin.(28,29) Similarly, smoking tends to be low in Indians,(30) which would influence cancer, respiratory and cardiovascular deaths.(3,4,31) There may be further genetic, biological or lifestyle factors which play a role in lower mortality observed in the South Asians compared to Whites such as enhanced cholesterol lowering with statins compared to Whites(32) and perhaps a weaker relationship between body mass index and cardiovascular mortality.(33,34)

Clinical and research implications

We have highlighted health disparities between ethnic groups that have important research and public health implications. Further research is required to determine the reasons for the marked ethnic differences in the years of life lost associated with type 2 diabetes. The results of these research efforts will inform the design of appropriate clinical interventions. From a clinical perspective, the potential years of life years lost to type 2 diabetes is improving but is still higher than ideal, particularly in Whites. Since we have shown that cardiovascular mortality remains the leading cause of death in patients with type 2 diabetes, there is a need to intensify efforts to optimize cardiovascular risk factor management knowing that this can halve the risk of death in type 2 diabetes.(35,36)

Strengths and Limitations

The study has several strengths. First, we used a large population-based cohort of patients with type 2 diabetes identified in primary care and linked with national hospital and mortality records which offers advantages over research generated from hospital records-based databases only (e.g. US insurance claims databases). This is because patients diagnosed with diabetes in hospital settings tend to have more advanced disease and are sicker with a higher mortality compared to those seen in primary care;(37) and people using insurance-based healthcare systems may be unrepresentative of the general population. Second, we used a sophisticated algorithm to identify individuals with type 2 diabetes based on several consistent clinical codes, age, prescriptions, BMI, and ethnicity. Third, we used an inception cohort thereby reducing the important risks of survivor-bias and healthy-subject-bias observed in prevalent cohorts.(38–40) Fourth, we used linked health records to gain greater completeness of ethnicity data and to obtain a more reliable classification. Finally, we had adequate follow-up to assess mortality.

We acknowledge some limitations. First, although we studied large numbers of South Asian (n=9,994) and Black patients (n=4,798) with type 2 diabetes, these were made up of smaller sub-groups which were too small to analyze separately. Second, agreement in ethnicity recording in CPRD and HES data is high for those coded as “White” but may be less reliable for other ethnic groups (41,42) – in cases of discrepant ethnicity recordings, we defined ethnicity as ‘unknown’. Third, ethnicity data may have been more likely to be missing if a patient died early rather than later during follow-up due to a greater likelihood of having a hospital episode. However, in our study, only 18.5% of those patients who died had an unknown ethnicity status. Fourth, we were unable to match on ethnicity which may have influenced the risk estimates from our life expectancy and mortality analyses. Matching on CPRD ethnicity, prior to linkage to HES where a large proportion of ethnicity data was obtained, would have resulted in a substantially reduced cohort of cases and controls as 59.5% of patients did not have an ethnicity recorded in CPRD or had multiple discrepant ethnicities recorded. Therefore matching using CPRD data only would have led to a loss of statistical power and precision in risk estimates relating to the minority ethnic groups. Matching for ethnicity after HES/ONS data linkage would have led to a 68-78% reduction in the sample size of Black and South Asian groups and therefore this was not undertaken. The distribution of the matching variables in those with and without diabetes within each ethnic group was comparable and therefore the impact of not matching for ethnicity is likely to be small. Finally, there is a need to confirm our findings in other populations outside England.

Summary

From this large primary care-based cohort, we have shown that White women and men experienced the greatest loss of life expectancy associated with type 2 diabetes compared with other ethnic groups, whilst older South Asian patients with type 2 diabetes had longer life expectancy than South Asians without diabetes. Compared to Whites with type 2 diabetes, South Asian and Black patients with type 2 diabetes had lower all-cause mortality and lower mortality due to cardiovascular, respiratory, and cancer diseases. These data call for replication studies and further research into the reasons for these marked ethnic differences. The findings support efforts to optimize CVD risk factor management, especially in Whites with type 2 diabetes, and to optimize type 2 diabetes screening among South Asians and Blacks.

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Table 1: Baseline characteristics for those with type 2 diabetes and without diabetes (any type)

|  |  |  |
| --- | --- | --- |
|  | **With Type 2 Diabetes N=187,968** | **Without Diabetes N=908,016** |
| **n (%)** | **n (%)** |
| **Male** | 103,740 (55.2) | 496,443 (54.7) |
| **Age** (years*)* **\*** | 61.8 ± 14.3 | 61.5 ± 14.3 |
| **Ethnicity** |  |  |
| *White* | 143,724 (76.5) | 653,390 (72.0) |
| *South Asian* | 9,523 (5.1) | 13,985 (1.5) |
| *Black* | 4,461 (2.4) | 10,576 (1.2) |
| *Other* | 2,486 (1.3) | 8,313 (0.9) |
| *Unknown* | 27,774 (14.8) | 221,752 (24.4) |
| **Deprivation quintile** |  |  |
| *1 (least deprived)* | 34,341 (18.3) | 197,565 (21.8) |
| *2* | 40,992 (21.8) | 210,770 (23.2) |
| *3* | 38,618 (20.5) | 186,310 (20.5) |
| *4* | 39,220 (20.9) | 173,541 (19.1) |
| *5 (most deprived)* | 34,463 (18.3) | 138,599 (15.3) |
| *Unknown* | 334 (0.2) | 1,231 (0.1) |
| **HbA1c**, % [mmol/mol]\* | 8.0 ± 2.1 [64 ± 22] | 5.8 ± 0.6 [40 ± 7] |
| Missing | 59,843 (31.8) | 890,960 (98.1) |
| **BMI**, kg/m2\* | 31.4 ± 6.4 | 27.3 ± 5.5 |
| Missing | 55,550 (29.6) | 733,067 (80.7) |
| **Cholesterol**, mmol/L\* | 5.2 ± 1.3 | 5.2 ± 1.2 |
| Missing | 51,756 (27.5) | 714,131 (78.6) |
| **Blood pressure**, mmHg\* |  |  |
| *Systolic* | 140 ± 19 | 137 ± 19 |
| *Diastolic* | 81 ± 11 | 79 ± 10 |
| Missing | 34,841 (18.5) | 510,539 (56.2) |
| **Cardiovascular disease** | 37,767 (20.1) | 68,435 (7.5) |
| **Renal disease** (≥Stage 4) | 2,339 (1.2) | 2,381 (0.3) |
| **Smoking status** |  |  |
| *Current Smoker* | 55,902 (29.7) | 279,910 (30.8) |
| *Ex-smoker* | 72,102 (38.4) | 261,700 (28.8) |
| *Never Smoked* | 9,284 (4.9) | 43,627 (4.8) |
| *Unknown* | 50,680 (27.0) | 322,779 (35.6) |
| **Diabetes therapy** |  |  |
| *No drugs* | 105,070 (55.9) | 908,016 (100.0) |
| *Monotherapy* | 70,962 (37.8) |  |
| *Metformin* | 54,097 (28.8) |  |
| *Sulfonylurea* | 11,790 (6.3) |  |
| *Other monotherapy* | 5,075 (2.7) |  |
| *Dual therapy* | 10,882 (5.8) |  |
| *Triple therapy* | 1,054 (0.6) |  |
| **Antihypertensive Agent** |  |  |
| *No drugs* | 84,955 (45.2) | 93,728 (10.3) |
| *Thiazides* | 33,741 (18.0) | 49,836 (5.5) |
| *Loop diuretics* | 19,045 (10.1) | 16,759 (1.9) |
| *Potassium-sparing diuretic* | 6,108 (3.3) | 92,908 (10.2) |
| *Beta-blocker* | 36,323 (19.3) | 20,387 (2.3) |
| *Alpha-blocker* | 8,040 (4.3) | 105,225 (11.6) |
| *ACE inhibitor* | 55,202 (29.4) | 38,531 (4.3) |
| *Angiotensin-II receptor* | 16,333 (8.7) | 96,915 (10.7) |
| *Calcium-channel blocker* | 38,611 (20.5) | 93,728 (10.3) |
| **Antiplatelet agent** |  |  |
| *No drug* | 139,230 (74.1) | 793,048 (87.3) |
| *Aspirin* | 46,172 (24.6) | 107,925 (11.9) |
| *Clopidogrel* | 5,053 (2.7) | 11,855 (1.3) |
| **Lipid agent** |  |  |
| *No drug* | 105,262 (56.0) | 767,752 (84.6) |
| *Statin* | 81,043 (43.1) | 136,191 (15.0) |
| *Fibrate* | 2,076 (1.1) | 2,914 (0.3) |
| *Other* | 2,562 (1.4) | 5,383 (0.6) |
| **Duration of follow-up from index date** (years) **\*** | 5.0 ± 3.8 | 10.2 ± 4.9 |
| **Exit from study** |  |  |
| *Death* | 40,286 (21.4) | 181,338 (20.0) |
| *Transferred out* | 26,004 (13.8) | 202,692 (22.3) |
| *Last Collection of data* | 47,121 (25.1) | 209,753 (23.1) |
| *Study End* | 74,557 (39.7) | 314,233 (34.6) |

\* Data are mean ± SD. Type 2 diabetes patients were matched to up to five patients without diabetes on year of birth (± 2 years), gender, general practice and index date of diabetes diagnosis. Groups were not matched for ethnicity.

Table 2:All-cause and cause-specific mortality rates among patients with Type 2 diabetes compared with matched patients without diabetes, by gender

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Underlying Cause** | **All Patients (N=221,624)** | | | | | **Men (N=114,526)** | | **Women (N=107,098)** | |
| **With Type 2 Diabetes** | | **Without Diabetes** | |  | **With Type 2 Diabetes** | **Without Diabetes** | **With Type 2 Diabetes** | **Without Diabetes** |
| **n (%)** | **Rate/**  **1,000 py** | **n (%)** | **Rate**  **/1,000 py** | **Adj HR †**  **(95% CI)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **All causes** | **40,286** | **42.7** | **181,338** | **19.5** | **2.19 (2.16,2.21)** | **20,888** | **93,638** | **19,398** | **87,700** |
| Malignant neoplasms | 10,398 (25.8) | 11.0 | 54,028 (29.8) | 5.8 | 1.63 (1.60,1.67) | 6,020 (28.2) | 30,745 (32.8) | 4,378 (22.6) | 23,283 (26.6) |
| Circulatory disease | 14,965 (37.2) | 15.9 | 59,075 (32.6) | 6.4 | 2.11 (2.07,2.15) | 7,950 (38.1) | 30,727 (32.8) | 7,015 (36.2) | 28,348 (32.3) |
| *Ischemic heart disease* | 5,315 (35.5) |  | 19,553 (33.1) |  |  | 3,226 (40.6) | 12,135 (39.5) | 2,089 (29.8) | 7,418 (26.2) |
| *Cerebrovascular disease* | 4,068 (27.2) |  | 17,391 (29.4) |  |  | 1,860 (23.4) | 7,263 (23.6) | 2,208 (31.5) | 10,128 (35.7) |
| *Heart Failure* | 3,510 (23.5) |  | 12,099 (20.5) |  |  | 1,889 (23.8) | 6,366 (20.7) | 1,621 (23.1) | 5,733 (20.2) |
| *Other circulatory* | 2,072 (13.9) |  | 10,032 (17.0) |  |  | 975 (12.3) | 4,963 (16.2) | 1,097 (15.6) | 5,069 (17.9) |
| Diabetes Mellitus (Diabetic Coma/DKA, other complications) | 75 (0.2) | 0.1 | - | - | - | 48 (0.2) | - | 27 (0.1) | - |
| Renal failure | 571 (1.4) | 0.6 | 1,559 (0.9) | 0.2 | 3.33 (3.00,3.69) | 269 (1.3) | 766 (0.8) | 302 (1.6) | 793 (0.9) |
| Infectious/parasitic disease | 1,064 (2.6) | 1.1 | 3,803 (2.1) | 0.4 | 2.51 (2.33,2.69) | 485 (2.3) | 1,659 (1.8) | 579 (3.0) | 2,144 (2.4) |
| Respiratory disease | 6,316 (15.7) | 6.7 | 31,204 (17.2) | 0.3 | 1.84 (1.79,1.89) | 3,060 (14.7) | 15,215 (16.3) | 3,256 (16.8) | 15,989 (18.2) |
| Diseases of digestive system | 2,095 (5.2) | 2.2 | 8,603 (4.7) | 0.9 | 2.16 (2.06,2.27) | 1,028 (4.9) | 4,280 (4.6) | 1,067 (5.5) | 4,323 (4.9) |
| Disease of nervous system | 1,140 (2.8) | 1.2 | 7,569 (4.2) | 0.8 | 1.48 (1.39,1.58) | 559 (2.7) | 3,645 (3.9) | 581 (3.0) | 3,924 (4.5) |
| Suicide | 88 (0.2) | 0.1 | 717 (0.4) | 0.1 | 1.07 (0.85,1.34) | 66 (0.3) | 584 (0.6) | 22 (0.1) | 133 (0.2) |
| Other Causes | 3,574 (8.9) | 3.8 | 14,780 (8.2) | 1.6 | 2.41 (2.31,2.50) | 1,403 (6.7) | 6,017 (6.4) | 2,171 (11.2) | 8,763 (10.0) |

py, person-years. Type 2 diabetes patients were matched to up to five patients without diabetes on year of birth (± 2 years), gender, general practice and index date of diabetes diagnosis. Groups with and without diabetes were not matched for ethnicity.

†Hazard ratios comparing groups with and without diabetes were adjusted for between-group differences in age, gender, ethnicity, deprivation, and calendar year.

Table 3: Adjusted all-cause and cause-specific mortality associated with age, sex and ethnicity (compared to Whites), in people with type 2 diabetes and without diabetes

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cause of death; Adjusted Hazard Ratio (95% CI)** *†* | | | | | | | | | |
| **All-Cause** | **Circulatory**  **disease** | **Malignant Neoplasms** | **Renal**  **Failure** | **Infectious**  **Disease** | **Respiratory**  **Disease** | **Diseases of**  **Digestive Sys** | **Diseases of**  **Nervous Sys** | **Suicide** | **Other** |
| **Type 2 Diabetes** |  |  |  |  |  |  |  |  |  |  |
| Male | 1.22 \* | 1.33 \* | 1.41 \* | 1.08 | 0.96 | 1.18 \* | 0.95 | 1.08 | 2.34 \* | 0.80 \* |
|  | (1.19,1.24) | (1.29,1.37) | (1.35,1.47) | (0.91,1.28) | (0.85,1.09) | (1.12,1.24) | (0.87,1.04) | (0.96,1.21) | (1.44,3.81) | (0.75,0.86) |
| Age (years) | 1.09 \* | 1.10 \* | 1.06 \* | 1.11 \* | 1.10 \* | 1.12 \* | 1.06 \* | 1.10 \* | 0.99 | 1.12 \* |
|  | (1.09,1.10) | (1.09,1.10) | (1.06,1.07) | (1.10,1.11) | (1.09,1.10) | (1.12,1.13) | (1.05,1.06) | (1.09,1.10) | (0.97,1.00) | (1.11,1.12) |
| White | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| South Asian | 0.70 \* | 0.82 \* | 0.43 \* | 1.50 | 1.01 | 0.60 \* | 0.48 \* | 0.62 | 0.94 | 1.28 \* |
|  | (0.65,0.76) | (0.75,0.89) | (0.36,0.51) | (0.93,2.46) | (0.67,1.54) | (0.48,0.76) | (0.34,0.69) | (0.37,1.03) | (0.34,2.63) | (1.02,1.61) |
| Black | 0.82 \* | 0.83 \* | 0.84 \* | 1.06 | 0.98 | 0.62 \* | 0.28 \* | 0.81 | . | 1.59 \* |
|  | (0.74,0.91) | (0.75,0.93) | (0.70,0.99) | (0.50,2.24) | (0.55,1.73) | (0.46,0.84) | (0.14,0.53) | (0.43,1.52) | (0,.) | (1.21,2.08) |
| **Without Diabetes** |  |  |  |  |  |  |  |  |  |  |
| Male | 1.39 \* | 1.49 \* | 1.53 \* | 1.49 \* | 1.09 \* | 1.37 \* | 1.18 \* | 1.20 \* | 3.67 \* | 0.97 |
|  | (1.37,1.40) | (1.47,1.52) | (1.51,1.56) | (1.35,1.65) | (1.02,1.16) | (1.34,1.40) | (1.13,1.23) | (1.15,1.26) | (3.04,4.43) | (0.94,1.00) |
| Age (years) | 1.09 \* | 1.11 \* | 1.06 \* | 1.14 \* | 1.11 \* | 1.12 \* | 1.07 \* | 1.09 \* | 0.98 \* | 1.12 \* |
|  | (1.09,1.10) | (1.10,1.11) | (1.05,1.06) | (1.14,1.15) | (1.11,1.12) | (1.11,1.12) | (1.06,1.07) | (1.09,1.10) | (0.98,0.99) | (1.11,1.12) |
| White | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| South Asian | 0.93 \* | 1.05 | 0.67 \* | 1.46 | 1.59 \* | 0.95 | 0.73 \* | 0.67 | 0.77 | 1.79 \* |
|  | (0.87,0.99) | (0.93,1.18) | (0.59,0.76) | (0.78,2.72) | (1.11,2.27) | (0.80,1.11) | (0.53,0.99) | (0.46,0.98) | (0.32,1.87) | (1.48,2.16) |
| Black | 1.07 | 1.19 \* | 1.11 | 1.88 | 1.88 \* | 0.55 \* | 0.59 \* | 1.12 | 0.49 | 1.55 \* |
|  | (0.99,1.15) | (1.03,1.36) | (0.98,1.26) | (0.94,3.78) | (1.25,2.84) | (0.42,0.72) | (0.38,0.90) | (0.77,1.64) | (0.12,1.95) | (1.20,1.99) |

*\* indicates significance; P<0*.*05 † all hazard ratios (HRs) are adjusted for gender, age, ethnicity, deprivation, calendar year (when appropriate)*

Figure 1: Difference in life expectancy between patients with type 2 diabetes and without diabetes at different ages in groups stratified by sex and ethnicity

*Life expectancy (unadjusted) at different ages is compared in people without diabetes and with type 2 diabetes stratified by sex and ethnicity. E.g. the line representing Whites males indicates that at the age of 40 years, White males with type 2 diabetes are predicted to die approximately 6 years earlier than White males without diabetes.*

