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Life expectancy following a cardiovascular event in individuals with and without type 2 diabetes: A UK multi-ethnic population-based observational study

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KEYWORDS
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Abstract *Background and aims:* We aimed to evaluate the life expectancy following the first cardiovascular disease (CVD) event by type 2 diabetes (T2D) status and ethnicity.
Methods and results: We used the Clinical Practice Research Datalink database in England (UK), linked to the Hospital Episode Statistics information, to identify individuals with and without T2D who survived a first CVD event between 1st Jan 2007 and 31st Dec 2017; subsequent death events were extracted from the Office for National Statistics database. Ethnicity was categorised as White, South Asian (SA), Black, or other. Flexible parametric survival models were used to estimate survival and predict life expectancy. 59,939 individuals with first CVD event were included: 7596 (12.7%) with T2D (60.9% men; mean age at event: 69.7 years [63.2 years in SA, 65.9 in Black, 70.2 in White]) and 52,343 without T2D (56.7% men; 65.9 years [54.7 in Black, 58.2 in SA, 66.3 in White]). Accounting for potential confounders (sex, deprivation, lipid-lowering medication, current smoking, and pre-existing hypertension), comparing individuals with vs without T2D the mortality rate was 53% higher in White (hazard ratio [HR]: 1.53 [95% CI: 1.44, 1.62]), corresponding to a potential loss of 3.87 (3.30, 4.44) life years at the age of 50 years in individuals with T2D. No evidence of a difference in life expectancy was observed in individuals of SA (HR: 0.82 [0.52, 1.29]; −1.36 [-4.58, 1.86] life years), Black (HR: 1.26 [0.59, 2.70]; 1.21 [-2.99, 5.41] life years); and other (HR: 1.64 [0.80, 3.39]; 3.89 [-2.28, 9.99] life years) ethnic group.

Abbreviations: CI, Confidence interval; CPRD, Clinical Practice Research Datalink; CVD, Cardiovascular disease; GP, General Practice; HES, Hospital Episode Statistics; HR, Hazard ratio; IMD, Index of Multiple Deprivation; ONS, Office for National Statistics; RECORD, Reporting of studies conducted using observational routinely-collected data; SA, South Asian; SD, Standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; T2D, Type 2 diabetes; UK, United Kingdom; YLL, Years of life lost.

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Conclusion: Following a CVD event, T2D is associated with a different prognosis and life years lost among ethnic groups.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality across the globe [1]. However, with recent improvements in the diagnosis and treatment of CVDs, there has been a decline in mortality, with more individuals surviving a CVD event [2]. A study reporting trends for acute myocardial infarction from 2002 to 2010 in England has shown a reduction in mortality rates by 50% in men and 53% in women [3]. Similarly, another study showed a decrease in stroke mortality rates by 55% between 2001 and 2010 [4], although rates were found to be especially higher in the younger population aged under 55 years, possibly in relation to the increasing prevalence of obesity and type 2 diabetes (T2D) in younger people [3–5]. Epidemiological studies have robustly shown that diabetes is a major independent risk factor for CVDs [6–8], where chronic hyperglycaemia, as well as insulin resistance, high blood pressure, and high cholesterol – commonly clustering in individuals with T2D – contribute to the development of CVD and to mortality rates which are around two times higher in adults with diabetes than in those without [7,8]. However, less established is the impact of diabetes on the risk of subsequent death in individuals who have experienced a CVD event, and whether this differs across ethnic groups.

Ethnicity plays a major role in the development and prognosis of CVD. People with ethnic backgrounds from South Asian (SA) countries are known to have a higher prevalence of T2D – which is diagnosed at a much younger age than their White European counterparts, a higher prevalence of CVD, and an increased risk of premature mortality [9–13]. Individuals of African or Caribbean heritage have a higher risk of certain CVD events, such as stroke, compared to White ethnicity [9], and an increased mortality risk after acute myocardial infarction [14]. Despite the number of studies evaluating ethnic disparities in CVD outcomes, there is still limited evidence of the survival after the prognosis of CVD among different ethnic groups.

The aim of this study was therefore to estimate the relative and absolute risk of death after the first CVD event according to T2D status in individuals of different ethnic groups living in England (UK). This knowledge can help tailor public health strategies to reduce the risk of death and improve the secondary prevention of CVDs [15].

2. Methods

The Clinical Practice Research Datalink (CPRD) is a large database containing anonymised data of primary care patients in the UK, which is representative of the general UK population in terms of age, sex and ethnicity [16,17]. This study followed a pre-specified protocol approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 18_202), and is reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and the REporting of studies Conducted using Observational Routinely-Collected Data (RECORD) guidelines (Supplementary Checklist S1).

2.1. Study population

This retrospective cohort study included a sample of primary care patients in England who were registered with practices contributing to the CPRD. We identified all individuals with at least one diagnosis for T2D using CPRD medical codes between Jan 1, 2000 and Dec 31, 2006 who were aged 18 and over on Jan 1, 2007 as the exposed group (n = 100,126 individuals with T2D; Supplementary Fig. S1) [12]. An additional 1,000,000 individuals registered in the CPRD without a diagnosis code for T2D between Jan 1, 2000 and Dec 31, 2006 who were aged 18 and over on Jan 1, 2007 were randomly selected as the unexposed group (individuals without T2D). We progressively excluded individuals with no linkage to the Hospital Episode Statistics (HES), which was required to access patient's ethnicity and history of CVD; or with no linkage to the Office for National Statistics (ONS) Death Registration data, required to extract information on the date of death (n = 39,421); who died before Jan 1, 2007 (n = 5363); had a diagnosis code of CVD in either HES (any position) or CPRD any time before Jan 1, 2007 (n = 118,764); or with missing data on sex, index of multiple deprivation, or ethnicity (in both HES and CPRD, n = 202,035). Of the remaining 734,543 individuals, 667,325 were excluded as no CVD events were recorded during the follow-up between Jan 1, 2007 and Dec 31, 2017, and 7278 because the date of death was the same as the first CVD event (i.e., with fatal first CVD events; Fig. S1), leaving 59,939 individuals with a first CVD event of the following phenotype [12,15]: aortic aneurysm, cerebrovascular accidents, heart failure, myocardial infarction, peripheral vascular disease, and other CVD-related conditions. All individuals belonged to an "up to standard" practice, had at least 12 months registration in the practice, and were certified by CPRD as acceptable research standards.

2.2. Ethnicity and confounders

Ethnicity was self-reported, obtained from HES and CPRD (when unavailable in HES), and categorised as: White, SA, Black, or other. Pre-existing hypertension was defined as

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Table 1 Characteristics of individuals at the first cardiovascular event by type 2 diabetes and ethnicity.

With type 2 diabetes	Overall population	Ethnicity			
		White	South Asian	Black	Other
N (%)	7596	7021 (92.4)	373 (4.9)	118 (1.6)	84 (1.1)
Age, y, mean [SD]	69.7 [12.0]	70.2 [11.8]	63.2 [12.6]	65.9 [13.1]	67.5 [12.7]
Sex					
Men	4624 (60.9)	4275 (60.9)	239 (64.1)	60 (50.9)	50 (59.5)
Women	2972 (39.1)	2746 (39.1)	134 (35.9)	58 (49.2)	34 (40.5)
IMD quintile					
1 (least deprived)	1457 (19.2)	1380 (19.7)	59 (15.8)	3 (2.5)	15 (17.9)
2	1676 (22.1)	1591 (22.7)	60 (16.1)	14 (11.9)	11 (13.1)
3	1568 (20.6)	1464 (20.9)	67 (18.0)	14 (11.9)	23 (27.4)
4	1611 (21.2)	1455 (20.7)	96 (25.7)	42 (35.6)	18 (21.4)
5 (most deprived)	1284 (16.9)	1131 (16.1)	91 (24.4)	45 (38.1)	17 (20.2)
Current smoker	695 (9.2)	659 (9.4)	18 (4.8)	9 (7.6)	9 (10.7)
Pre-existing hypertension	5959 (78.5)	5495 (78.3)	296 (79.4)	106 (89.8)	62 (73.8)
Lipid lowering medication	4011 (52.8)	3707 (52.8)	206 (55.2)	53 (44.9)	45 (53.6)
Without type 2 diabetes					
	Overall population	Ethnicity			
		White	South Asian	Black	Other
N (%)	52,343	50,166 (95.8)	1136 (2.2)	553 (1.1)	488 (0.9)
Age, y, mean [SD]	65.9 [14.6]	66.3 [14.5]	58.2 [14.5]	54.7 [14.0]	59.0 [14.9]
Sex					
Men	29,673 (56.7)	28,381 (56.6)	705 (62.1)	295 (53.4)	292 (59.8)
Women	22,670 (43.3)	21,785 (43.4)	431 (37.9)	258 (46.6)	196 (40.2)
IMD quintile					
1 (least deprived)	11,868 (22.7)	11,561 (23.1)	172 (15.1)	41 (7.4)	94 (19.3)
2	12,739 (24.3)	12,383 (24.7)	199 (17.5)	54 (9.8)	103 (21.1)
3	10,880 (20.8)	10,483 (20.9)	231 (20.3)	72 (13.0)	94 (19.3)
4	10,021 (19.1)	9404 (18.8)	334 (29.4)	171 (30.9)	112 (23.0)
5 (most deprived)	6835 (13.1)	6335 (12.6)	200 (17.6)	215 (38.9)	85 (17.4)
Current smoker	5395 (10.3)	5225 (10.4)	75 (6.6)	45 (8.1)	50 (10.3)
Pre-existing hypertension	25,570 (48.9)	24,464 (48.8)	566 (49.8)	323 (58.4)	217 (44.5)
Lipid lowering medication	13,459 (25.7)	12,957 (25.8)	300 (26.4)	94 (17.0)	108 (22.1)

Shown are numbers of subjects (%) unless stated otherwise.
Age is at the first CVD occurrence.
Y = years; SD = standard deviation; IMD = Index of multiple deprivation.

any diagnosis code in CPRD or HES before the first CVD event. Current smoking was defined as one or more CPRD records indicating current smoking within six months before or after the first CVD event; all other individuals were considered non-current smokers. Similarly, lipid-lowering medication was determined from prescriptions recorded in CPRD within six months before or after the first CVD event. Deprivation was measured by the 2007 Index of Multiple Deprivation (IMD) quintiles (1, least deprived; 5, most deprived).

2.3. Outcome

The outcome was all-cause mortality: all individuals were followed-up from the first CVD event date (first non-fatal CVD event from January 1, 2007) until the date of death or the end of the study (Feb 13, 2018).

2.4. Statistical analysis

The characteristics of the individuals were presented as number (%) or mean [standard deviation (SD)] by T2D status and ethnicity. Individuals were followed up from the first CVD event until death or the end of the study. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of all-cause mortality were calculated in complete-case analysis using flexible parametric Royston-Parmar survival models with age as time scale [18]. As this model fits a restricted cubic spline to the baseline log cumulative hazard, it provides greater flexibility to accurately capture the observed data and extrapolate for future predictions, which is relevant when estimating the (adjusted) remaining life expectancy and years of life lost (YLL, i.e. the difference in average life expectancy) [19]. The calculation of YLL involved a two-step process [19]. First, the remaining life expectancy was estimated as the area under the survival curve up to 100 years old, conditional on surviving at ages 50–100 years old (1-year age intervals); survival curves were predicted for each individual and averaged over individuals. Second, YLL and 95% CI were calculated as the difference between the areas under two survival curves (with and without T2D), stratified across each ethnicity group. No power calculation was conducted for these analyses [20], which were adjusted for

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the confounders sex, IMD, lipid lowering medication, current smoking, and pre-existing hypertension. Statistical analyses were performed in Stata/IC v17.0 and SAS v9.4; results were reported with 95% CI and statistical significance was defined at $p < 0.05$. The statistical code is available at GitHub *yc244*.

3. Results

3.1. Characteristics

Of the 59,939 subjects identified in this cohort with a first non-fatal CVD event, 7596 (12.7%) had a previous diagnosis of T2D: of them, 7021 (92.4%) were White, 373 (4.9%) SA, 118 (1.6%) Black, and 84 (1.1%) other ethnicity. Of the overall population with T2D, 60.9% were men; 9.2% current smokers; 78.5% had pre-existing hypertension; and 52.8% were taking lipid-lowering medications (Table 1). The mean [SD] age at the first CVD event in individuals with T2D was 69.7 [12.0] years, with a range from 63.2 [12.6] years in SA, 65.9 [13.1] years in Black, 67.5 [12.7] years in other ethnicity, to 70.2 [11.8] years in the White ethnic group (Table 1, Fig. 1).

Of the 52,343 (87.3%) individuals with a first non-fatal CVD event without T2D, 50,166 (95.8%) were White, 1136 (2.2%) SA, 553 (1.1%) Black, and 488 (0.9%) other ethnicity. 56.7% of the overall population without T2D were men; 10.3% current smokers; 48.9% had hypertension; and 25.7% were taking lipid-lowering medication (Table 1). The mean age at first CVD event in people without T2D was 65.9 [14.6] years, ranging from 54.7 [14.0] years in the Black ethnicity, 58.2 [14.5] years in SA, 59.0 [14.9] years in other ethnicity, to 66.3 [14.5] years in the White ethnic group (Table 1, Fig. 1).

3.2. All-cause mortality

During an average follow-up of 4.76 [SD (3.24); range 0.003 (~1 day) to 11.12] years and 252,577 total person-years, 8737 deaths were recorded: 1394 (16.0%) in subjects with T2D and 7343 (84.0%) in those without. The mortality rate was highest in the White ethnic group with T2D: 4.45 [95% CI: 4.22, 4.70] rate per 100 person-years, compared to other ethnic group (2.63 [1.41, 4.88]), Black (2.10 [1.17, 3.81]), and SA (1.51 [1.03, 2.20]; Table 2). The mortality rate in those without T2D was also highest in the White ethnic group (2.97 [2.90, 3.04] per 100 person-years), followed by other ethnicity (1.68 [1.23, 2.28]), SA (1.47 [1.18, 1.83], and Black ethnic group (1.18 [0.84, 1.65]).

The adjusted HR comparing individuals with vs without T2D was 1.50 (1.41, 1.59) in the whole population; stratified by ethnicity, it was: 1.64 (0.80, 3.39) for other ethnic group, 1.53 (95% CI 1.44, 1.62) for White, 1.26 (0.59, 2.70) for Black, and 0.82 (0.52, 1.29) for SA (Table 2).

3.3. Life expectancy and years of life lost

After adjustment for confounders, at the age of 50 years the life expectancy following the first CVD event was on average 28.60 years in individuals with T2D and 32.28 years in those without, resulting in a difference of 3.68 (95% CI: 3.12, 4.23) YLL. At the age of 60 years, corresponding estimates were 21.05 years, 24.15 years, and 3.10 (2.64, 3.56) (Fig. 2, Table S1, Fig. S2).

When examining the individual ethnic groups, at the age of 50 years the life expectancy following first CVD event in the White ethnic group was 28.34 years in individuals with T2D and 32.21 years in those without, giving a YLL estimate of 3.87 (95% CI: 3.30, 4.44) years. For other ethnicity group, the corresponding estimates were 36.73 years with T2D and 40.62 years without T2D, YLL 3.89 (−2.28, 9.99) years; for Black ethnic group, 35.38 years with T2D and 36.60 years without T2D, YLL 1.21 (−2.99, 5.41) years; and for South Asian, 37.10 years with T2D and 35.74 without T2D, YLL -1.36 (−4.58, 1.86), indicating a non-significant longer life expectancy in subjects with T2D (Figs. 2 and 3; Table S1, Fig. S3).

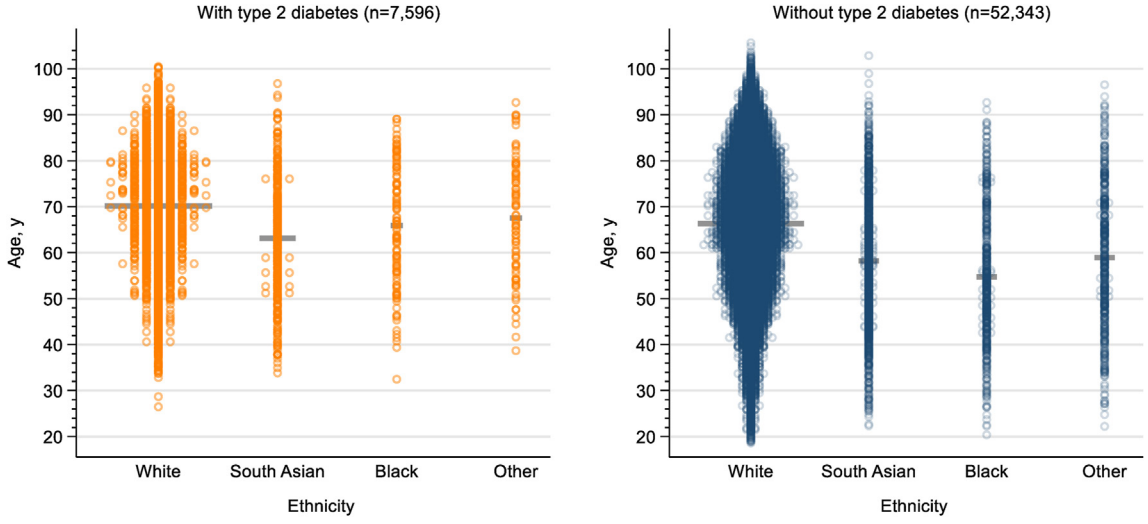

Figure 1 Age at the first cardiovascular event by type 2 diabetes status and ethnicity. Y = years. Reference line represents the average age in the ethnic group.

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Table 2 Survival following the first cardiovascular event by type 2 diabetes and ethnicity.

	Overall population	Ethnicity			
		White	South Asian	Black	Other
With type 2 diabetes					
No. deaths/No. subjects	1394/7596	1346/7021	27/373	11/118	10/84
Total person-years	32,935	30,242	1790	522	381
Mortality rate per 100 p-y	4.23 (4.02, 4.46)	4.45 (4.22, 4.70)	1.51 (1.03, 2.20)	2.10 (1.17, 3.81)	2.63 (1.41, 4.88)
Without type 2 diabetes					
No. deaths/No. subjects	7343/52,343	7187/50,166	82/1136	33/553	41/488
Total person-years	252,577	241,752	5578	2807	2440
Mortality rate per 100 p-y	2.91 (2.84, 2.97)	2.97 (2.90, 3.04)	1.47 (1.18, 1.83)	1.18 (0.84, 1.65)	1.68 (1.23, 2.28)
Mortality HR, with vs without type 2 diabetes					
Unadjusted	1.35 (1.27, 1.43)	1.37 (1.30, 1.46)	0.86 (0.55, 1.33)	0.97 (0.48, 1.96)	1.51 (0.75, 3.06)
Adjusted	1.50 (1.41, 1.59)	1.53 (1.44, 1.62)	0.82 (0.52, 1.29)	1.26 (0.59, 2.70)	1.64 (0.80, 3.39)

P-y = person years; HR = hazard ratio.
Rate and hazard ratio are reported with 95% confidence interval.
Hazard ratios adjusted for sex, index of multiple deprivation, lipid-lowering medication, current smoking, and pre-existing hypertension.

4. Discussion

Our study, investigating the long-term mortality following a first non-fatal CVD event in around 60,000 individuals living in England (UK), showed that in people of White ethnicity, T2D was associated with a 53% higher mortality rate. This translates into around 3.9 years of life lost (28.3 vs 32.2) at the age of 50 years. Conversely, there was no evidence of differences in life expectancy between individuals with and without T2D in other ethnic minority groups. These results suggest a heterogeneous impact of T2D on the mortality risk in individuals experiencing a non-fatal CVD event. Moreover, irrespective of the presence of T2D, following the CVD event, life expectancy was higher in ethnic minority populations (between 85.4-87.1 and 85.7–90.6 years in those with and without T2D, respectively) compared to individuals of White ethnicity (78.3 and 82.2 years, respectively).

Previous studies have shown that the outcomes after a CVD event are significantly worse in individuals with diabetes, with a higher burden of mortality, recurrent events, and hospitalisations compared to those without diabetes [21–30]. Our findings are in agreement with current evidence, as we found that after the first CVD event, individuals with T2D had an increased risk of mortality compared to those without (adjusted HR in the overall population: 1.50). Furthermore, existing literature also highlights ethnic disparities after CVD events [14,31,32]. However, most studies limit the comparisons between SA and White European ethnicities [33–39]. For instance, a cohort of 5789 individuals newly admitted with heart failure found that overall mortality was lower for SA individuals (adjusted HR: 0.82 [0.68 to 0.99]) compared with White [34]. From the perspective of population-level data, our findings match a recent report from the ONS on ethnic health differences in England and Wales between

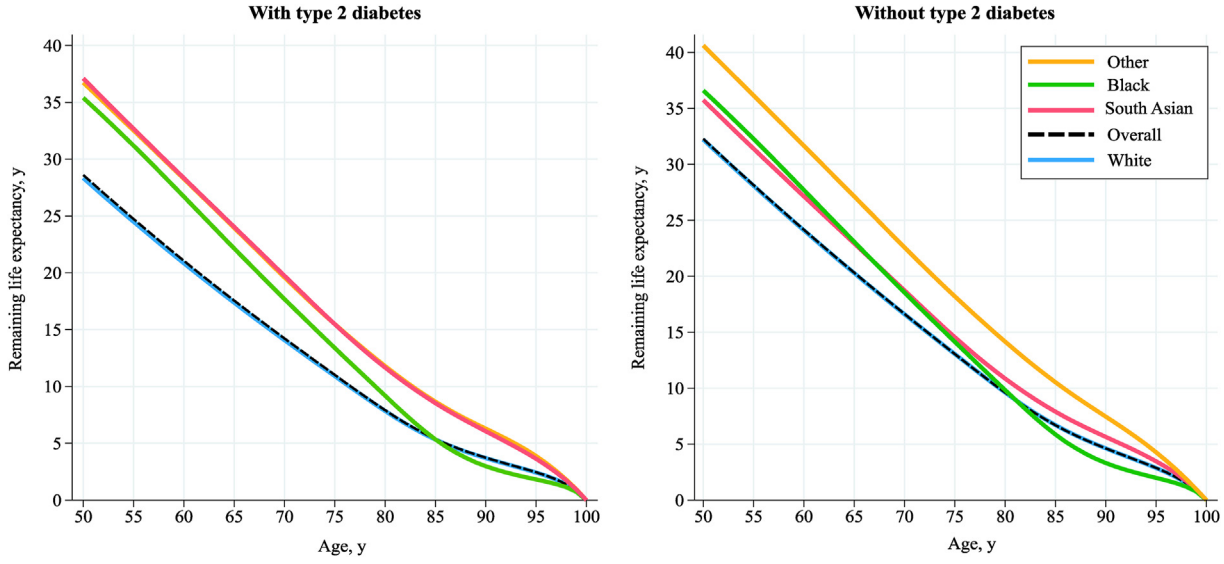

Figure 2 Life expectancy following the first cardiovascular event by type 2 diabetes and ethnicity. Y = years. Models adjusted for sex, index of multiple deprivation, lipid-lowering medication, current smoking, and pre-existing hypertension.

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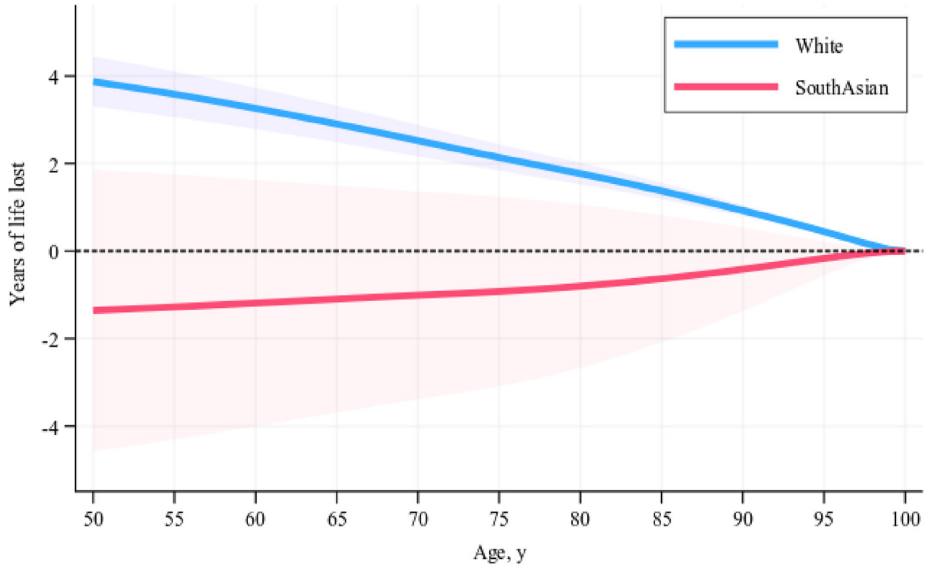

Figure 3 Difference in years of life lost following the first cardiovascular event by type 2 diabetes in White and South Asian ethnicity. Y = years. Years of life lost: remaining life expectancy without type 2 diabetes − remaining life expectancy with type 2 diabetes. Shaded area represents 95% confidence intervals. Models adjusted for sex, index of multiple deprivation, lipid-lowering medication, current smoking, and pre-existing hypertension.

2011 and 2014, whereby those of White ethnicity had a lower life expectancy than all other ethnic groups [40]. Potential reasons explaining a longer life expectancy in ethnic minority groups could be due to the 'healthy immigrant effect' or the 'migrant mortality advantage', whereby migrants are likely to be younger and healthier than the average person in both the home and host countries. They may also benefit from cultural factors such as adherence to a healthy diet (i.e. Mediterranean diet), low smoking and alcohol consumption, or because of poor health and a preference to die in familiar surroundings, they may wish to return to their place of birth, known as the salmon bias effect [41,42]. Other reasons could be the legacy benefits of cardioprotective therapies and risk factor control following an event in ethnic minority groups [43], as we found their first CVD events up to 7 years earlier compared to White ethnicity. Although ethnic minority groups with T2D are living longer, they are living in poor health with multimorbidity, including mental health conditions such as depression [44–46].

To our knowledge, only one study has evaluated the relative risk of death after the first CVD event by T2D in different ethnic groups [13]. In a small cohort study based in London including 801 individuals with a first non-fatal CVD event between 1 Jun 1988 and 1 Jan 2015, they found T2D was associated with an increased risk of death in individuals of SA ethnicity (adjusted HR: 1.64 [1.15 to 2.34]) but not of European (1.01 [0.58–1.78]) or African Caribbean (1.94 [0.86–4.36)] ethnicity [13]. Our study, using a contemporary and significantly larger cohort, found opposite results whereby T2D was significantly associated with an increased risk of mortality in the White ethnic group, while no statistical evidence of a differential risk associated with T2D was observed in ethnic minority groups. To what extent these discrepant findings are related to changing patterns of mortality and quality of life among ethnic groups in the UK or to differences in the study characteristics (i.e., age at diagnosis of T2D and CVD, follow-up time) could be ascertained in further epidemiological studies using prospective data.

This study has several limitations. Firstly, as we only used data from England, the results are not fully applicable to other countries, particularly the life expectancy estimates. Second, caution is also required when interpreting ethnic differences in life expectancy [19], since the proportion of those in minority ethnic groups may not be representative of those in the general population. Also, the number of patients with T2D in the non-white groups is small, which may potentially limit the power of the study; further, larger studies (or meta-analysis across similar studies) [20] should be conducted to confirm our results. Third, there may be possible bias in the codes for ethnicity as the ethnic grouping was self-reported [40]; however, ethnicity data − obtained from both CPRD and HES − have shown good validity [47]. Fourth, although we adjusted for key confounders of the association between T2D and mortality available in our data, residual confounding is still possible; furthermore, the selection of individuals with a CVD event could potentially result in the 'index event bias' [48]. While previous evidence aligns with our findings showing a longer life expectancy in subjects of SA ethnicity with T2D compared to those without [49], conditioning on the population with a CVD may result in a biased causal association between T2D and mortality compared to that observed in the general population [50]. Fifth, we were unable to assess associations based on the severity or phenotype of the first CVD event, and for outcomes other than all-cause mortality such as CVD recurrences. Moreover, as individuals may have other long-term conditions causing reductions in the life expectancy which vary across ethnic groups − for instance, the ONS reported that people from White ethnicity with cancer had shorter life

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expectancy than any other ethnicity groups [40], – future studies could account for the competing risk of other specific causes of death. Finally, this was an observational study, which limits our ability to establish causality.

Key strengths of our study included: the length of follow-up time; the identification of ethnicity and CVD from both CPRD and HES to ensure that patients' entire healthcare history was captured whether diagnoses were made in primary or secondary care; and the estimation of both relative and absolute measures of association (i.e. hazard ratios, remaining life expectancy and YLL) to provide clinically meaningful results [19]. Lastly, data were from real-world primary care settings, thus reflecting routine clinical practice in the UK.

As the number of individuals surviving their first CVD events is increasing [51], detailing their prognosis is relevant for risk stratification and tailored screening and interventions. However, while a diagnosis of diabetes was included in the most recent update of the algorithm for the prediction of fatal and non-fatal CVD events in individuals with established CVD (SMART), potential differences in the prognosis across ethnic backgrounds were not accounted for [15]. Our study therefore provides important information for policymakers and healthcare professionals, highlighting the differential impact of both diabetes and ethnicity in the prognosis of individuals with CVD. In individuals who survived a CVD event, the life expectancy and the prognostic impact of T2D varied across ethnic groups. Future prognostic algorithms should account for such differences to enable better, more stratified approaches of disease progression to potentially lower the risk of death. In addition, alongside improving mortality outcomes, it is also important to improve the quality of life – including social and emotional well-being – by reducing the burden of disabilities associated with mental health and multiple chronic cardiometabolic conditions, thus ensuring that all ethnic groups equally benefit from timely pharmacological and non-pharmacological interventions to tackle ethnic inequalities.

In conclusion, using a large primary care cohort, our study demonstrated that the life expectancy after first CVD event differs by T2D and ethnicity. Further research is essential to understand the primary factors contributing to these differences, in order to help tailor public health strategies and improve the treatments in the increasing number of people who survived a CVD.

Ethical approval

This research was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency Database Research (protocol 18_202).

Author contribution

Conceptualization: KK, NJS; Study design: FZ, BC; Data preparation: BC; Data analysis: YC; First draft: YC, FZ, KK; Study critical revision and manuscript draft: All authors. All authors provided final approval of the version to publish. YC had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

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Data access and sharing

Patient-level electronic health records obtained from CPRD cannot be shared. However, the authors will share aggregate statistics if requested. Statistical codes for this study are available at GitHub *yc244*.

Declaration of competing interest

Professor Khunti is the National Lead for multiple long-term conditions for National Institute for Health Research Applied Research Collaboration (NIHR ARC). Professor Khunti has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Abbott, Amgen, Bayer, Novartis, Novo Nordisk, Roche, Servier, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals and Applied Therapeutics.

Dr Zaccardi is a speaker fees from Napp Pharmaceuticals and Boehringer Ingelheim.

Professor Davies has acted as a consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, an advisory board member for Servier and Gilead Sciences Ltd and as a speaker for Napp Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. Professor Davies has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen.

All other authors have no conflict of interest.

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Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.04.003.

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