ORIGINAL ARTICLE

Cardiovascular events and mortality in people with and without type 2 diabetes: An observational study in a contemporary multi-ethnic population

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ABSTRACT

Aims/Introduction: The aim of this study was to examine ethnicity-specific associations between type 2 diabetes mellitus and the risk of a cardiovascular disease (CVD) event as well as risk of specific CVD phenotypes in England.

Methods: We obtained data from the Clinical Practice Research Datalink for adults with and without type 2 diabetes mellitus diagnosed 2000–2006. The outcome was the first CVD event during 2007–2017 and the following components: aortic aneurysm, cerebrovascular accidents, heart failure, myocardial infarction, peripheral vascular disease and other CVD-related conditions. Flexible parametric survival models were used to estimate ethnicity-specific adjusted hazard ratios.

Results: A total of 734,543 people with and without type 2 diabetes mellitus (29,847; 4.1%) were included; most were of white ethnicity (93.0% with and 92.3% without type 2 diabetes mellitus) followed by South Asian (3.2 and 4.6%). During a median follow-up period of 11.0 years, 67,218 events occurred (6,156 in individuals with type 2 diabetes mellitus). Type 2 diabetes mellitus was associated with a small increase in CVD events (adjusted hazard ratio 1.06, 95% confidence interval 1.02–1.09) in individuals of white ethnicity; whereas the adjusted hazard ratios were considerably higher in individuals of South Asian ethnicity (1.28, 95% confidence interval 1.09–1.51), primarily due to an increased risk of myocardial infarction (1.53, 95% confidence interval 1.08–2.18).

Conclusions: Despite universal access to healthcare, there are large disparities in CVD outcomes in people with and without type 2 diabetes mellitus. Other non-traditional risk factors might play a role in the higher CVD risk associated with type 2 diabetes mellitus in individuals of South Asian ethnicity.

INTRODUCTION

Within England and Wales, people identifying as South Asian (originating from countries of the Indian subcontinent: India, Pakistan, Sri Lanka, Bangladesh, Nepal, etc.) constitute 5.9% of the population, black individuals (from African or Caribbean backgrounds) account for 4.5%, and individuals of other ethnicities account for 3.7%[1]. Over the years, epidemiological studies from several countries including Canada[2–4], South Africa[5] and the UK[6–8] have shown that individuals of South Asian ethnicity are at higher risk for coronary heart disease and mortality compared with other ethnicities. Coronary heart disease develops at a younger age in migrant South Asian populations compared with indigenous populations: compared with white Europeans, South Asians admitted with a myocardial infarction were younger by approximately 5 years and had a higher prevalence of cardiovascular risk factors, including diabetes[9].

Studies have also consistently shown an increased risk of type 2 diabetes mellitus in people of South Asian and African

Caribbean ethnic backgrounds compared with white Europeans[10]. In individuals of South Asian ethnicity, type 2 diabetes mellitus develops 10–12 years earlier than in white Europeans and at a lower body mass index (BMI)[11]. Although type 2 diabetes mellitus is a recognized risk factor for cardiovascular disease (CVD), whether the excess risk of CVD associated with type 2 diabetes mellitus is different across ethnicities is not known[12]. Furthermore, most current global studies in different ethnic groups have sought primarily to describe the epidemiology of coronary heart disease and mortality, while there is very little information on other cardiovascular outcomes. The availability of medications that have substantially reduced the risk of acute atherothrombotic events might have resulted in a phenotypical change in the manifestation of CVD in people with and without type 2 diabetes mellitus.

In the present study, we address these gaps in research by examining contemporary ethnicity-specific associations between type 2 diabetes mellitus and the risk of a composite CVD event, as well as the risk of specific CVD phenotypes, including aortic aneurysm, cerebrovascular accidents, heart failure, myocardial infarction, peripheral vascular disease and other CVD-related conditions.

METHODS

Study design and data source

We carried out the present study following the RECORD guidelines (checklist reported in the Appendix S2). This observational retrospective cohort included a sample of primary care patients in England who were registered with practices contributing to the Clinical Practice Research Datalink (CPRD). The CPRD includes anonymized primary care electronic health records for >11.3 million patients from 674 UK practices with data on approximately 6.9% of the UK population[13]. Patients are broadly representative of the UK general population in terms of age, sex and ethnicity[13]. This study was approved by the Independent Scientific Advisory Committee of CPRD, protocol number 18_202.

Exposure

The exposed group comprised all individuals registered in the CPRD with at least one diagnosis code for type 2 diabetes mellitus from 1 January 2000 to 31 December 2006, and who were over the age of 18 years on the index date 1 January 2007 ($n = 100,126$; Table S1; Figure S1). An additional 1,000,000 individuals registered in the CPRD without a diagnosis code for type 2 diabetes mellitus before the index date and who were aged >18 years on the index date were randomly selected as the unexposed group. Individuals were excluded if linkage to Hospital Episode Statistics (HES) and Office of National Statistics Death Registration was not available ($n = 39,421$), if the date of death was before the index date ($n = 5,363$; details reported in Figure S1), if the individual had a diagnosis code for CVD in either HES (any position) or CPRD any time before the index date ($n = 118,764$, Table S2), or if the

individual was missing data on sex, deprivation or ethnicity (missing in both HES and CPRD; $n = 202,035$; Figure S1). At the index date, all individuals in the cohort belonged to an 'up to standard' practice, had at least 12 months' registration in the practice and were certified by CPRD as of acceptable research standards.

Outcomes

The outcome was the first diagnosis code for a CVD condition in either CPRD or HES (first diagnosis position) or a CVD-related underlying cause of death in the Office of National Statistics Death Registration. Fatal and non-fatal CVD events were treated as a composite primary end-point as well as stratified into the following CVD phenotypes: aortic aneurysm, cerebrovascular accidents, heart failure, myocardial infarction, peripheral vascular disease and all other CVD-related conditions (Table S2). All individuals were followed up from the index date until the first CVD event or censoring (non-CVD-related death or end of study on 31 December 2017, whichever came first). Subsequent events were ignored.

Ethnicity and other covariates

Demographic information, clinical diagnoses, drug therapy and lifestyle factors were obtained from CPRD. Ethnicity was obtained from HES and CPRD (when unavailable in HES), and categorized as white, South Asian, black or other. Pre-existing hypertension was defined as any diagnosis code in CPRD or HES before the index date (Table S3). Current smoking was defined as one or more CPRD records indicating current smoking within 6 months before or after the index date; all other patients were considered non-current smokers. Lipid-lowering medication was determined from prescriptions recorded in CPRD within 6 months before or after the index date (Table S4). Deprivation was measured by the 2007 Index of Multiple Deprivation quintiles (1, least deprived; 5, most deprived).

Statistical analysis

Characteristics of individuals were summarized as the mean and standard deviation for continuous variables, and the number and percentage for categorical variables. Crude and adjusted (age, sex, deprivation, lipid-lowering medication, current smoking, pre-existing hypertension) hazard ratios (HR and adjusted HR [aHR]) for the primary end-point were estimated using flexible parametric survival modeling[14]. The main goal of the present study was to investigate the association rather than predict probabilities of events. Therefore, cause-specific HRs for the different CVD phenotypes were estimated using flexible parametric survival modeling, as this approach remains valid in the context of competing events, and the resulting HRs provide etiologically interpretable estimates[15]. Covariate adjustment was used as an alternative to matching to obtain statistically reliable aHRs[16]. All analyses were carried out in Stata/IC 15.1 (StataCorp, College Station, TX, USA) and SAS v9.4 (SAS Institute,

Cary, NC, USA); results are reported with 95% confidence interval (CI), and nominal statistical significance was defined at $P < 0.05$.

RESULTS

Cohort characteristics

The cohort comprised 704,696 individuals without type 2 diabetes mellitus: 655,088 white (93.0%); 15,627 black (2.2%); 22,473 South Asian (3.2%); and 11,508 other ethnicities (1.6%, Table 1). A total of 29,847 individuals had a diagnosis of type 2 diabetes mellitus (4.1% of the cohort): 27,552 white (92.3%); 555 black (1.9%); 1,378 South Asian (4.6%); and 362 other ethnicities (1.2%). The median age at type 2 diabetes mellitus diagnosis was 61.0 years (interquartile range [IQR] 51.0–70.0 years): 61.0 years (IQR 52.0–70.0 years) for white people; 56.0 years (IQR 45.0–66.0 years) for black people; 51.0 years (IQR 44.0–60.0 years) for South Asian people; and 56.0 years (IQR 47.0–65.0 years) for other ethnicities. Overall, the prevalence of current smoking was similar in individuals with and without type 2 diabetes mellitus, whereas hypertension and prescription of lipid-lowering medication were more frequent in individuals with diabetes. Regardless of type 2 diabetes mellitus, all traditional risk factors were more frequent in white individuals (Table 1).

Primary outcome: Fatal and non-fatal cardiovascular outcomes

During 7,435,165 person-years of follow up (median follow up: 11.0 years [IQR 11.0–11.0 years]), 67,218 CVD events occurred, corresponding to a rate of 9.0 per 1,000 person-years (95% CI 9.0–9.1; Table 2); the median time to a CVD event was 5.8 years (IQR 3.0–8.4 years). Of these events, 61,062 (90.8%) occurred in individuals without type 2 diabetes mellitus during 7,168,484 years of follow up (median follow up 11.0 years [IQR 11.0–11.0 years]), corresponding to a rate of 8.5 per 1,000 person-years (95% CI 8.5–8.6); the median time to a CVD event was 5.8 years (IQR 3.1–8.4). In individuals with type 2 diabetes mellitus, 6,156 (9.2%) events occurred during 266,681 person-years of follow up (median follow up 11.0 years [IQR 7.3–11.0 years]), corresponding to a rate of 23.1 per 1,000 person-years (95% CI 22.5–23.7; Table 2); the median time to a CVD event was 5.6 years (IQR 2.9–8.3 years). The crude rate ratio of a CVD event for individuals with and without type 2 diabetes mellitus was 2.71 (95% CI 2.64–2.78). The median age at a CVD event was 68.3 years (IQR 57.4–79.2 years) for individuals without type 2 diabetes mellitus: 68.8 years (IQR 57.9–79.5 years) for white people; 54.2 years (IQR 46.8–66.2 years) for black people; 58.8 years (IQR 48.2–69.9 years) for South Asian people; and 61.8 years (IQR 49.9–72.4 years) for other ethnicities (Table S5). Corresponding figures for individuals with type 2 diabetes mellitus were: 73.1 years (IQR 64.0–80.9 years): 73.4 years (IQR 64.5–81.2 years) for whites people; 68.6 years (IQR 57.7–79.3 years) for blacks people; 66.9 years (IQR 56.6–74.4 years) for South Asian people; and 68.0 years (IQR 57.0–79.3 years) for individuals of other ethnicities.

Among individuals without type 2 diabetes mellitus, CVD events occurred more frequently in white individuals (8.9% of white individuals), followed by South Asian individuals (5.8%), black individuals (4.1%) and other ethnicities (4.9%; Table 2). Corresponding estimates in individuals with type 2 diabetes mellitus were as follows: 20.8, 20.2, 14.4 and 17.4%.

The unadjusted Kaplan–Meier curves showed a higher risk of CVD events in individuals with type 2 diabetes mellitus compared with individuals without type 2 diabetes mellitus overall (HR 2.74, 95% CI 2.67–2.81) and within each ethnic group, with HRs ranging from 2.69 (95% CI 2.62–2.76) in white individuals to 3.96 (95% CI 3.05, 5.14) in South Asian individuals. Adjusting for age, sex, index of multiple deprivation, lipid-lowering medication, smoking and pre-existing hypertension, type 2 diabetes mellitus was associated with a modestly increased risk of a CVD event compared with non-diabetes (aHR 1.06, 95% CI 1.02–1.09; Table 3). The hazard of CVD events was progressively higher in the more deprived groups, with an aHR per each quintile increase of deprivation of 1.06 (95% CI 1.05–1.06).

The increased risk of CVD events differed by ethnicity. In black individuals, type 2 diabetes mellitus corresponded to a 7% increased risk of a CVD event (aHR 1.07, 95% CI 0.80–1.43). In white individuals, type 2 diabetes mellitus corresponded to a 5% increased risk of a CVD event (aHR 1.05, 95% CI 1.01–1.08), whereas in South Asian individuals, the risk increased 28% (aHR 1.28, 95% CI 1.09–1.51). The difference translated into a 22% excess risk associated with type 2 diabetes mellitus in South Asian compared with white individuals, mainly driven by a higher risk of myocardial infarction (aHR 1.53, 95% CI 1.08–2.18) in South Asian individuals (Table 3).

Cardiovascular disease phenotypes

In both individuals with and without type 2 diabetes mellitus, the most frequent CVD outcome was 'other CVD-related condition', regardless of the ethnicity: the most frequent 'other CVD-related condition' event presentation was 'atherosclerotic heart disease' ($n = 8,888$; 25.9% of other CVD-related conditions), followed by 'atrial fibrillation and flutter' ($n = 5,467$; 15.9%) and 'pulmonary embolism without mention of acute cor pulmonale' ($n = 3,184$; 9.3%; Table S6). Of individuals with type 2 diabetes mellitus who developed CVD, 'other CVD-related condition' was the first presentation in 3,095 (50.3% of all CVD events); cerebrovascular accident in 1,317 (21.4%); and myocardial infarction in 953 (15.5%). Corresponding estimates in individuals without type 2 diabetes mellitus were as follows: 31,260 (51.2%); 13,934 (22.8%); and 10,264 (16.8%).

Within the cohort, compared with individuals without type 2 diabetes mellitus, individuals with type 2 diabetes mellitus had an elevated risk of heart failure (aHR 1.59, 95% CI 1.41, 1.79); other CVD-related conditions (1.32, 95% CI 1.14, 1.54); myocardial infarction (1.08, 95% CI 1.00, 1.17); and peripheral vascular disease (1.05, 95% CI 1.00–1.09; Table 3). In contrast, compared with individuals without type 2 diabetes mellitus, individuals with type 2 diabetes mellitus had a significantly

Table 1 | Cohort characteristics at baseline by diabetes status and ethnicity

Individuals without type 2 diabetes

Variable	Ethnicity				
	White n = 655,088 (93.0%)	Black n = 15,627 (2.2%)	South Asian n = 22,473 (3.2%)	Other n = 11,508 (1.6%)	Overall population n = 704,696 (100%)
Age (years)[†]	48.3 (17.2)	39.7 (12.8)	39.9 (13.7)	40.6 (14.4)	47.7 (17.1)
Sex					
Male	293,411 (44.8%)	6,813 (43.6%)	10,074 (44.8%)	5,076 (44.1%)	315,374 (44.8%)
Female	361,677 (55.2%)	8,814 (56.4%)	12,399 (55.2%)	6,432 (55.9%)	389,322 (55.2%)
IMD quintile					
1	151,668 (23.2%)	851 (5.4%)	3,176 (14.1%)	2,171 (18.9%)	157,866 (22.4%)
2	158,984 (24.3%)	1,318 (8.4%)	3,750 (16.7%)	1,940 (16.9%)	165,992 (23.6%)
3	135,326 (20.7%)	2,170 (13.9%)	4,657 (20.7%)	2,245 (19.5%)	144,398 (20.5%)
4	125,189 (19.1%)	4,941 (31.6%)	6,142 (27.3%)	2,793 (24.3%)	139,065 (19.7%)
5	83,921 (12.8%)	6,347 (40.6%)	4,748 (21.1%)	2,359 (20.5%)	97,375 (13.8%)
Current smoker	76,731 (11.7%)	1,176 (7.5%)	1,260 (5.6%)	946 (8.2%)	80,113 (11.4%)
Pre-existing hypertension	78,436 (12.0%)	1,615 (10.3%)	1,489 (6.6%)	739 (6.4%)	82,279 (11.7%)
Lipid-lowering medication	27,120 (4.1%)	235 (1.5%)	676 (3.0%)	304 (2.6%)	28,335 (4.0%)

Individuals with type 2 diabetes

Variable	Ethnicity				
	White n = 27,552 (92.3%)	Black n = 555 (1.9%)	South Asian n = 1,378 (4.6%)	Other n = 362 (1.2%)	Overall population n = 29,847 (100%)
Age (years)[†]	63.9 (12.9)	58.4 (12.9)	55.2 (12.1)	59.3 (12.8)	63.4 (13.0)
Sex					
Male	14,732 (53.5%)	264 (47.6%)	724 (52.5%)	193 (53.3%)	15,913 (53.3%)
Female	12,820 (46.5%)	291 (52.4%)	654 (47.5%)	169 (46.7%)	13,934 (46.7%)
IMD quintile					
1	5,526 (20.1%)	32 (5.8%)	199 (14.4%)	66 (18.2%)	5,823 (19.5%)
2	6,460 (23.4%)	61 (11.0%)	224 (16.3%)	65 (18.0%)	6,810 (22.8%)
3	5,756 (20.9%)	73 (13.2%)	305 (22.1%)	90 (24.9%)	6,224 (20.9%)
4	5,680 (20.6%)	189 (34.1%)	337 (24.5%)	89 (24.6%)	6,295 (21.1%)
5	4,130 (15.0%)	200 (36.0%)	313 (22.7%)	52 (14.4%)	4,695 (15.7%)
Current smoker	3,736 (13.6%)	55 (9.9%)	106 (7.7%)	35 (9.7%)	3,932 (13.2%)
Pre-existing hypertension	14,827 (53.8%)	278 (50.1%)	528 (38.3%)	162 (44.8%)	15,795 (52.9%)
Lipid-lowering medication	19,593 (71.1%)	304 (54.8%)	877 (63.6%)	233 (64.4%)	21,007 (70.4%)

[†]Age as of the index date, 1 January 2007, is shown as the mean (standard deviation). IMD, Index of multiple deprivation.

decreased risk of aortic aneurism (aHR 0.48, 95% CI 0.37–0.61). There was no clear evidence of an association between type 2 diabetes mellitus and cerebrovascular accident (0.98, 95% CI 0.92–1.05). The aHRs per each quintile increase of deprivation ranged from 1.03 (95% CI 1.02–1.04) for 'other CVD-related condition' to 1.17 (95% CI 1.13–1.21) for peripheral vascular disease.

Comparison among all ethnic groups was possible for cerebrovascular accident, heart failure and peripheral vascular disease. Consistently across ethnicity, there was no evidence of an association between type 2 diabetes mellitus and cerebrovascular accident. The association of type 2 diabetes mellitus with increased risk of heart failure was evident only in white individuals (aHR 1.59, 95% CI 1.09–1.51).

DISCUSSION

In the present study, we investigated the incidence of several CVD phenotypes in individuals with and without type 2 diabetes mellitus of different ethnicities. We observed a small increase of 6% in the risk of fatal and non-fatal CVD events associated with type 2 diabetes mellitus overall. This excess risk, however, was heterogeneous across ethnic groups, ranging from a 5% higher risk in white individuals to 28% in South Asian individuals. Furthermore, among people with type 2 diabetes mellitus, South Asian individuals experienced an event at a younger median age compared with all other ethnic groups.

Several large epidemiological studies have shown that type 2 diabetes mellitus is associated with a higher risk of CVD events,

Table 2 | Number of fatal and non-fatal cardiovascular disease events by diabetes status and ethnicity

Individuals without type 2 diabetes

CVD phenotype	Ethnicity				
	White $n = 655,088$	Black $n = 15,627$	South Asian $n = 22,473$	Other $n = 11,508$	Overall population $n = 704,696$
Aortic aneurism	1,064 (0.2%)	5 (0.0%)	†	8 (0.1%)	1,081 (0.2%)
Cerebrovascular accident	13,462 (2.1%)	146 (0.9%)	207 (0.9%)	119 (1.0%)	13,934 (2.0%)
Heart failure	2,547 (0.4%)	30 (0.2%)	38 (0.2%)	20 (0.2%)	2,635 (0.4%)
Myocardial infarction	9,793 (1.5%)	69 (0.4%)	303 (1.4%)	99 (0.9%)	10,264 (1.5%)
Peripheral vascular disease	1,857 (0.3%)	9 (0.1%)	15 (0.1%)	7 (0.1%)	1,888 (0.3%)
Other CVD-related condition	29,834 (4.6%)	376 (2.4%)	735 (3.3%)	315 (2.7%)	31,260 (4.4%)
All CVD	58,557 (8.9%)	635 (4.1%)	1,302 (5.8%)	568 (4.9%)	61,062 (8.7%)

Individuals with type 2 diabetes

CVD phenotype	Ethnicity				
	White $n = 27,552$	Black $n = 555$	South Asian $n = 1,378$	Other $n = 362$	Overall population $n = 29,847$
Aortic aneurism	73 (0.3%)	†	†	†	77 (0.3%)
Cerebrovascular accident	1,236 (4.5%)	19 (3.4%)	46 (3.3%)	16 (4.4%)	1,317 (4.4%)
Heart failure	410 (1.5%)	11 (2.0%)	12 (0.9%)	†	436 (1.5%)
Myocardial infarction	883 (3.2%)	7 (1.3%)	56 (4.1%)	7 (1.9%)	953 (3.2%)
Peripheral vascular disease	267 (1.0%)	†	7 (0.5%)	†	278 (0.9%)
Other CVD-related condition	2,866 (10.4%)	40 (7.2%)	155 (11.3%)	34 (9.4%)	3,095 (10.4%)
All CVD	5,735 (20.8%)	80 (14.4%)	278 (20.2%)	63 (17.4%)	6,156 (20.6%)

†Less than five. CVD, cardiovascular disease.

Table 3 | Adjusted† hazard ratios for fatal and non-fatal cardiovascular disease events associated with type 2 diabetes by ethnicity

CVD phenotype	Ethnicity				
	White	Black	South Asian	Other	Overall population
Aortic aneurism	0.47 (0.36–0.60)	‡	‡	‡	0.48 (0.37– 0.61)
Cerebrovascular accident	0.97 (0.91–1.04)	1.00 (0.56–1.80)	1.21 (0.82–1.78)	1.62 (0.86–3.05)	0.98 (0.92–1.05)
Heart failure	1.59 (1.40–1.80)	1.83 (0.74–4.52)	1.70 (0.77–3.74)	0.74 (0.19–2.94)	1.59 (1.41–1.79)
Myocardial infarction	1.06 (0.98–1.15)	‡	1.53 (1.08–2.18)	‡	1.08 (1.00–1.17)
Peripheral vascular disease	1.32 (1.13–1.54)	‡	‡	‡	1.32 (1.14–1.54)
Other CVD-related condition	1.04 (0.99–1.09)	1.01 (0.68–1.51)	1.17 (0.94–1.45)	1.15 (0.75–1.77)	1.05 (1.00–1.09)
All CVD	1.05 (1.01–1.08)	1.07 (0.80–1.43)	1.28 (1.09–1.51)	1.13 (0.83–1.54)	1.06 (1.02–1.09)

†Hazard ratios (95% confidence interval) adjusted for sex, age, index of multiple deprivation, lipid-lowering medication, current smoking and pre-existing hypertension. ‡Hazard ratios could not be estimated due to a small number of events. CVD, cardiovascular disease.

particularly ischemic heart disease and peripheral vascular disease[17]. Additionally, previous studies have suggested that the increased CVD risk is greater in people of South Asian ethnicity[2–8]. However, more recent studies have shown declining trends of CVD events and CVD mortality in individuals with type 2 diabetes mellitus[18]. A Swedish cohort study found the excess cardiovascular risk associated with type 2 diabetes mellitus disappeared when other risk factors (glycated hemoglobin, systolic and diastolic blood pressure, albuminuria, smoking, and low-density lipoprotein cholesterol) were within targets, with the exception of heart failure[19]. These results are largely confirmed in the present study. Accounting for many of the same key risk factors, we observed an attenuation in the unadjusted HR associated with type 2 diabetes mellitus, from 2.74 to 1.06. The magnitude of this reduction indicated that the widely accepted figure of a two- to threefold higher CVD risk associated with type 2 diabetes mellitus is largely an overestimation in contemporary patients with type 2 diabetes mellitus.

It is plausible that most of the reduction in the relative risk observed in the past few years might be attributable to a wider screening and treatment of hyperglycemia and other CVD risk factors. Despite improvements in care, disparities are still present. Furthermore, in line with the Swedish study, we confirmed that heart failure is becoming a predominant CVD phenotype in individuals with type 2 diabetes mellitus.

Understanding the differential impact of type 2 diabetes mellitus on CVD risk by ethnicity has direct clinical relevance. The higher CVD burden in South Asians could either be the result of a higher prevalence of type 2 diabetes mellitus in this ethnic group (two- to fourfold that of white individuals) or the consequence of a combined effect of a higher prevalence and a higher relative risk of CVD in South Asian individuals compared with white individuals[20]. In the latter case, strategies aimed only at preventing type 2 diabetes mellitus in South Asian individuals will not suffice to reduce the CVD burden gap between South Asian and white individuals.

The primary aim of the present study was to compare the risk of different CVD event phenotypes across ethnic groups. The low incidence of CVD events, which occurred at rates lower than those observed in type 2 diabetes mellitus cardiovascular outcome trials and primarily related to the absence of prevalent CVD at baseline[21], hampered the possibility to reliably quantify the excess risk of all CVD phenotypes in each ethnic group including the risk of aortic aneurism, myocardial infarction and other CVD-related conditions.

The present results showed that the type 2 diabetes mellitus-related excess risk for CVD events is higher in South Asian individuals compared with white individuals, mainly driven by an excess in the risk of myocardial infarction; this difference might be related to other risk factors that have not been accounted for in this analysis, and have a differential impact on the risk of CVD in white versus South Asian individuals. Among them, several biological and non-biological factors might play a role.

Differences in BMI could explain the heterogeneous association between type 2 diabetes mellitus and CVD events, as a higher BMI results in a greater risk of CVD events in both ethnic groups[22]. Furthermore, some studies have shown that the same BMI is associated with a higher risk of CVD events in South Asian compared with white individuals[23]; this epidemiological observation tallies with the evidence of a different fat distribution, whereby South Asian individuals have a greater accumulation of abdominal fat compared with white individuals for the same BMI[24]. The accumulation of visceral fat, in turn, has been linked to a high CVD risk independent of BMI[25], and to immune, inflammatory and endothelial dysfunctions[26].

Although in our analyses we accounted for differences in deprivation across ethnicities, a residual impact of socioeconomic factors, including access to and quality of care, working condition, and education, might still be present and contribute to the ethnic differences observed in the present study[27].

To our knowledge, this is the first study designed to investigate the risk of specific fatal and non-fatal CVD phenotypes across ethnic groups and the age at which the events occurred. A previous study showed an increased adjusted risk of several CVD phenotypes, ranging from 1.28 for intracerebral hemorrhage to 2.98 for peripheral vascular disease[28]. That study found a reduced impact of type 2 diabetes mellitus on the risk of CVD over time, with the exception of heart failure[28]. The authors did not explicitly report ethnicity-specific HRs, but reported that they were consistent across ethnic groups for the most frequent CVD phenotypes, whereas they were more uncertain for rarer outcomes[28].

In another more recent study, Wright *et al.*[29] used CPRD to investigate the rates of CVD and non-CVD events comparing individuals with and without type 2 diabetes mellitus, in the overall population and in different ethnic groups. That study included only fatal CVD events and took into account calendar time (aHR 2.11, 95% CI 2.07, 2.15)[29]. Among individuals with type 2 diabetes mellitus, South Asian individuals had a significantly lower risk compared with white individuals (HR 0.82, 95% CI 0.75–0.89), whereas the risk was not significantly different among individuals without type 2 diabetes mellitus (HR 1.05, 95% CI 0.93–1.18)[29]. That study did not examine whether type 2 diabetes mellitus is associated with an excess risk whose magnitude is different between ethnic groups, and in contrast to the present study, the composite outcome included only fatal events[29].

The present study had several strengths. Given the increasing evidence of a calendar time effect on the excess risk of CVD associated with type 2 diabetes mellitus, we defined a large, primary care contemporary cohort of type 2 diabetes mellitus individuals. Data were linked to HES to obtain a more precise self-reported ethnicity and to extract information on non-fatal events. Using a prevalent cohort, the median follow-up period was 11 years, a significantly longer observational time compared with the two previous studies[28,29], which captured the effect of type 2 diabetes mellitus over the course of the disease. We also defined CVD phenotypes using more restricted definitions; for example, we considered 'atherosclerotic heart disease' in the 'other CVD-related conditions', as this phenotype does not indicate an acute myocardial infarction.

There were also some limitations to the present study. We defined type 2 diabetes mellitus exposure using a prevalent design rather than an incident design, which is appropriate when the exact time of the exposure is questionable[30], the exposure–outcome association extends for a long period[31,32], and for complex exposures that are difficult to translate into a framework of a randomized controlled trial[31]. Furthermore, causality cannot be inferred from an observational study. We also focused on key, well-established confounders of the association between ethnicity and CVD events; namely, hypertension, dyslipidemia and deprivation. However, there might be unmeasured or non-traditional confounders that were not adjusted for; namely, data on body fat distribution, physical activity and

dietary factors were not available. The lack of enough events to quantify the HRs for specific CVD phenotypes in each ethnic group might be regarded, at first glance, as a study limitation. However, this further validates the small absolute risk of some CVD phenotypes in individuals of certain ethnicities with and without type 2 diabetes mellitus.

In the present study, we observed a modest increase in the risk of fatal and non-fatal CVD events comparing UK primary care patients with type 2 diabetes mellitus with those without; this finding is in line with large, contemporary epidemiological studies carried out in other countries. However, a gap between South Asian and white individuals still exists, whereby type 2 diabetes mellitus is associated with a larger negative effect in the former compared with the latter ethnic group, specifically in the case of myocardial infarction. As key potential confounders of CVD risk do not fully explain this difference, other risk factors and/or biological differences should be investigated to reduce the excess CVD burden associated in South Asian patients with type 2 diabetes mellitus.

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DISCLOSURE

KK is consultant and speaker for Amgen, AstraZeneca, Bayer, NAPP, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Berlin-Chemie AG/ Menarini Group, Sanof-Aventis, Servier and Boerhringer Inghelheim; and received grants from Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme and Servier.

MJD is 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 a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Janssen. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Cohort flow diagram.
Table S1 | Codes for type 2 diabetes mellitus.
Table S2 | Codes for cardiovascular disease events.
Table S3 | Codes for pre-existing hypertension.
Table S4 | Product codes for lipid-lowering medication.
Table S5 | Median age at cardiovascular disease event by diabetes status and ethnicity.
Table S6 | Number of patients with other cardiovascular disease events.
Appendix S1 | ISAC application form.
Appendix S2 | The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.