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Ethnicity and prognosis following a cardiovascular event in people with and without type 2 diabetes: Observational analysis in over 5 million subjects in England☆

Sandra C. Remsing [a,1], Sophia C. Abner [b,1], Katharine Reeves [a], Briana Coles [b,c], Claire Lawson [b], Clare Gillies [b,d], Cameron Razieh [b,e], Tom Yates [d,f], Melanie J. Davies [d,f], Richard Lilford [g], Kamlesh Khunti [b,d,h,2], Francesco Zaccardi [b,d,h,2,*]

[a] Department of Research Development and Innovation, University Hospitals Birmingham NHS Foundation Trust, Institute for Translational Medicine, Birmingham, UK
[b] Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK
[c] Biostatistics Research Group, Department of Health Sciences, University of Leicester, Leicester, UK
[d] Diabetes Research Centre, University of Leicester, Leicester, UK
[e] Office for National Statistics, Newport, UK
[f] National Institute for Health Research, Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Leicester, UK
[g] Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, UK
[h] National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care-East Midlands, University of Leicester, Leicester, UK

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ABSTRACT

Aims: To quantify ethnic differences in the risk of all–cause mortality and cardiovascular disease (CVD) events following a first CVD event in people with and without type 2 diabetes.
Methods: We identified 5,349,271 subjects with a first CVD between 1 January 2002 and 31 May 2020 in England; CVD included aortic aneurism, cerebrovascular accident, heart failure, myocardial infarction, peripheral vascular disease, and other cardiovascular diseases. We estimated adjusted hazard ratios (HRs) for type 2 diabetes and ethnicity of three outcomes: fatal and nonfatal second CVD event (different phenotype compared to the first) and all–cause mortality.
Results: Relative to White, HRs indicated lower rates in all ethnicities and for all outcomes in both men (from 0.64 to 0.79 for all–cause death; 0.78–0.79 for CVD–related death; and 0.85–0.98 for a second CVD event) and women (0.69–0.77; 0.77–0.83; 0.83–0.95, respectively). Irrespective of ethnicity and sex, type 2 diabetes increased rates of all outcomes by around a third.
Conclusions: Prognosis following a CVD event was consistently worse in subjects with type 2 diabetes while varied across ethnicities, suggesting the implementation of different strategies for the secondary prevention of CVD in different ethnic groups.

1. Introduction

According to the last United Kingdom (UK) Census, of the 56.1 million people who lived in England and Wales in 2011, around 86.0% were White, followed by Asian (7.5%), Black (3.3%), Mixed (2.2%), and Other (1.0%) ethnic groups; the largest ethnic minority group included people of South Asian origin (from countries of the Indian subcontinent: India, Pakistan, Sri Lanka, Bangladesh, and Nepal), comprising between 5% and 6% of the total population [1].

Epidemiological studies have shown that South Asian people, compared to other ethnic groups, have a higher risk of cardiovascular disease (CVD) [2,3]. Previous investigations have also found that South Asians who migrated to the UK have a worse cardiometabolic risk factors profile compared to family members remaining in their native

☆ Tweet: Diabetes and ethnicity associated with mortality following cardiovascular disease episode.

* Corresponding author at: Leicester Real World Evidence Unit, Diabetes Research Centre, Leicester General Hospital, Gwendolen Rd, Leicester LE5 4PW, UK.
E-mail address: frazac@fastwebnet.it (F. Zaccardi).

[1] Joint first authors.
[2] Joint last authors.

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country [4]. Furthermore, CVD events – such as heart failure and myocardial infarction – tend to occur earlier in South Asians compared to other ethnicities [5–9]. More limited and contrasting is the evidence about the prognosis following a CVD event: initial, very small studies in the UK have suggested higher mortality rates in South Asians compared to White Europeans following a myocardial infarction [10], while more recent observations, based on much larger samples, have reported a similar [7,9,11] or lower [12] risk. Detailed UK data on the risk of a first CVD event and the prognosis following the event are more limited for other ethnic groups [8,13–15].

Although a complex interplay among sociodemographic and biological factors contribute to the heterogeneous risk of CVD across ethnic groups, the different prevalence of cardiometabolic risk factors plays a relevant role [16–18]. Several investigations in the last two decades in the UK have primarily focused on the risk of type 2 diabetes in South Asian subjects, generating robust evidence showing a greater risk in this ethnic group [19–21]. South Asians develop type 2 diabetes earlier, and at a lower body mass index, than White Europeans [20,22,23]; yet, the life expectancy may be up to one year longer than their counterparts without type 2 diabetes, possibly due to an earlier screening and treatment of risk factors in subjects with type 2 diabetes [24]. Evidence on variations in the risk of type 2 diabetes in other UK minority ethnic communities is sparser, albeit suggesting a higher risk in Black ethnic groups [25].

Most of the available studies exploring ethnic differences have therefore sought primarily to describe the epidemiology of CVD in terms of a single, commonly first, coronary heart disease event or CVD mortality in subjects of South Asian ethnicity. As there is more limited contemporary information for other ethnicities and CVD phenotypes, as well as on the prognosis following a first CVD event, investigating and quantifying the risk of recurrent CVD events is important given the better survival following a CVD episode [26], the longer life expectancy compared to the previous decades [27], and the sociodemographic changes which occurred in UK during the last decades [28]; such evidence would also help shape primary and secondary prevention strategies. In this study, we examined the role type 2 diabetes and ethnicity on the risk of a second CVD event, CVD–related mortality, and all–cause mortality in patients hospitalised in England for a CVD event during the last two decades.

2. Materials and methods

This observational study, registered at the local Clinical Audit Department (number 14671), used routine electronic health record data in line with the data sharing agreement with NHS Digital. We followed the REporting of studies Conducted using Observational Routinely–collected health Data (RECORD) guidelines in conducting and reporting this study (checklist in the Supplementary Material) [29].

2.1. Population

We used the Hospital Episode Statistics (HES) database linked to Office for National Statistics (ONS) death data and Index of Multiple Deprivation (IMD) socioeconomic data. HES contains details on all emergency and elective patient admissions, outpatient appointments, and emergency department attendances at all public hospitals in England. Data include patient sociodemographic information, such as age, sex and ethnicity, and administrative information; all diagnoses are coded using the International Classification of Diseases version 10 (ICD–10).

In patients aged $\geq$ 18 years, we identified the first (index) CVD event across all admissions to the hospital during the study period 1 January 2002 to 31 May 2020 with a primary diagnosis code of one of the following CVD phenotypes: aortic aneurism (AA), cerebrovascular accident (CVA), heart failure (HF), myocardial infarction (MI), peripheral vascular disease (PVD), and other CVD–related conditions (Other); the ICD–10 codes for each phenotype are reported in the Supplementary Material. We excluded patients with a missing death date in ONS; a CVD event after death; or with an unknown sex or ethnicity (Supplementary Material Fig. S1).

2.2. Exposure

Two main exposures were considered: type 2 diabetes, identified with ICD–10 code E11 in any position at the first CVD admission or any previous hospital admission; and ethnicity, categorised into four distinct groups to reflect the most prevalent ethnic groups in the 2011 Census in England and Wales: White, South Asian, Black and Mixed/Other [30]. White included British, Irish, any other White; South Asian included Pakistani, Indian, Bangladeshi, other Asian ethnic groups, White and Asian; Black included African, Caribbean, any other Black ethnic group, White and Black Caribbean, White and Black African; Mixed/Other included Chinese, any other ethnic group, any other mixed background. While in the 2011 Census White and Asian, White and Black Caribbean, and White and Black African were all considered as Mixed ethnic group, we considered White and Asian as Asian, and White and Black Caribbean/African as Black, to reflect differences in several outcomes and mortality between Black and Asian subjects [31].

2.3. Outcome

Following the first recorded CVD event, we collected information on three outcomes: all–cause mortality; CVD–related mortality (mortality with any CVD event as the underlying cause); and a second fatal or non–fatal CVD event. ONS death data were used to determine all–cause and CVD–related mortality. The second CVD event was defined as a fatal or non–fatal CVD event following the first CVD event and reporting a primary diagnosis code of a different phenotype compared to that of the first CVD event (i.e., cerebrovascular accident as first event followed by a fatal or non–fatal myocardial infarction as second event), in order to exclude codes that had been repeated due to re-recording of previous diagnoses. Patients were followed from the first recorded CVD event to the outcome occurrence or end of the study period, whichever occurred earlier.

2.4. Statistical analysis

We reported the median and interquartile range (IQR) of age at first CVD event by ethnicity and type 2 diabetes. The number of each outcome was calculated overall and stratified by ethnicity and type 2 diabetes: to estimate the person–years of observation, subjects were followed up from the first CVD event to the occurrence of the outcome or end of the study period: for each outcome, overall and stratified rates were calculated as number of outcome events per 1,000 person–years (PYs). We estimated the survival probability using the Kaplan–Meier method. Cumulative incidences, accounting for the competing risk of deaths for other causes, were estimated to obtain the probability of a second CVD event over time, by ethnicity and type 2 diabetes. Separate Cox proportional hazard models for each outcome were used to quantify the hazard ratio (HR) of ethnicity (reference: White) and type 2 diabetes (reference: no type 2 diabetes), adjusted for age at first CVD event and deprivation. All analyses were stratified by sex and performed in Stata/SE version 15.1; the *stcompet* command was used to estimate the cumulative incidences.

3. Results

3.1. Study cohort

A total of 5,349,271 patients (men: 2,982,509; 55.8%) met the inclusion criteria (Fig. S1). Among them, 885,281 (16.5%) had type 2 diabetes: 85.1% were of White, 9.4% South Asian, 3.2% Black, and 2.3%

Table 1
Number of and median age at first (index) cardiovascular event by type 2 diabetes and ethnicity.

	White (85.1%)			South Asian (9.4%)			Black (3.2%)			Mixed/Other (2.3%)			All subjects (100%)		
Type 2 diabetes	*n*	*Median age*	*IQR*	*n*	*Median age*	*IQR*	*n*	*Median age*	*IQR*	*n*	*Median age*	*IQR*	*n*	*Median age*	*IQR*
AA	8,566	75	70–80	117	71	64–77	102	75	68–79	99	74	67.5–79	8,884	75	70–80
CVA	127,945	77	69–84	10,394	69	60–77	5,889	73	62–79	3,588	71	61–79	147,816	76	67–83
HF	92,788	78	71–85	8,046	72	64–80	3,975	74	65–81	1,979	74	65–81	106,788	78	70–84
MI	114,551	73	63–81	16,690	64	55–74	2,872	69	58–77	3,130	65	55–74	137,243	72	61–81
Other	380,325	71	63–79	47,718	63	55–72	14,372	68	58–76	10,833	65	56–74	453,248	70	61–78
PVD	29,213	72	64–79	886	66	58–74	814	73	64–79	389	69	60–79	31,302	72	64–79
Total	**753,388**	**73**	**65–81**	**83,851**	**65**	**56–74**	**28,024**	**70**	**59–78**	**20,018**	**67**	**57–76**	**885,281**	**72**	**63–80**
No type 2 diabetes															
AA	75,460	75	69–81	448	70	54–77	519	71	59–77	868	73	64–80	77,295	75	69–81
CVA	719,902	77	65–84	17,349	66	51–77	13,507	61	48–75	13,765	66	52–79	764,523	76	64–84
HF	291,380	82	74–88	7,321	74	63–82	5,408	69	53–79	3,746	76	63–85	307,855	82	73–88
MI	600,642	69	58–80	26,304	58	48–70	5,883	58	49–71	10,148	59	49–71	642,977	68	57–79
Other	2,385,318	68	57–77	87,615	57	46–68	46,950	53	42–67	43,604	57	45–70	2,563,487	67	56–77
PVD	104,901	71	61–79	988	63	51–73	1,079	68	54–76	885	66	55–78	107,853	71	61–79
Total	**4,177,603**	**71**	**59–81**	**140,025**	**59**	**47–71**	**73,346**	**56**	**44–71**	**73,016**	**60**	**48–73**	**4,463,990**	**70**	**58–80**

Number of subjects with an index cardiovascular event and age at event occurrence.
AA: Aortic aneurism; **CVA:** cerebrovascular accident; **HF:** Heart Failure; **MI:** Myocardial infarction; **Other:** other cardiovascular disease conditions; **PVD:** Peripheral vascular disease.
IQR: Interquartile range.

Mixed/Other ethnic background; corresponding figures in subjects without type 2 diabetes were 93.6%, 3.1%, 1.7%, and 1.6%, respectively (Supplementary Material Table S1).

Overall, the median age at first CVD event was 72 (IQR, 63–80) years in subjects with type 2 diabetes and 70 (58–80) in those without (Table 1). The median age, however, varied by ethnicity: in subjects with type 2 diabetes, it was 73 (65–81) years in White, 65 (56–74) in South Asian, 70 (59–78) in Black, and 67 (57–76) in Mixed/Other ethnicity. In patients without type 2 diabetes, corresponding values were 71 (59–81), 59 (47–71), 56 (44–71), and 60 (48–73) years, respectively (Table 1). Regardless of ethnicity and type 2 diabetes, the median age at first CVD event was higher in women than in men (Table S2).

3.2. *All–cause mortality*

During the follow–up (maximum, 18.4 years), 2,346,957 deaths were recorded (1,210,266 in men; 51.7%), of which 455,355 occurred in subjects with type 2 diabetes (51.4% of all subjects with type 2 diabetes with a first CVD event) and 1,891,602 in those without (42.4% of all subjects without type 2 diabetes with a first CVD event; Table S3).

Crude incidence proportions of death varied across ethnicity, ranging from a minimum of 32.5% in South Asian to a maximum of 54.4% in White for subjects with type 2 diabetes and from 22.3% to 43.7% in the same ethnic groups in those without type 2 diabetes; proportions were higher in women than in men, except in the Black ethnicity group (Table S3). Similarly, crude mortality rates differed substantially across ethnicity and type 2 diabetes status: in subjects of White ethnicity, rates were 116.1 (95% CI: 115.7–116.4) and 71.2 (71.1–71.3) per 1,000 PYs in those with and without type 2 diabetes, respectively; corresponding estimates in other ethnic groups were 52.2 (51.6–52.8) and 29.6 (29.2–29.9) in South Asian, 76.8 (75.4–78.2) and 35.0 (34.5–35.5) in Black, and 58.6 (57.2–60.1) and 36.6 (36.1–37.5) in Mixed/Other ethnicity (Table 2). Regardless of type 2 diabetes, crude rates were higher in women than in men of all ethnicities, except in the Black ethnicity group (Table 2). Differences in mortality rates were also observed by deprivation: 69.5 and 75.9 deaths per 1,000 PYs in the most and least affluent group, respectively (Table S4).

The unadjusted risk of death during the follow–up was persistently higher amongst individuals with type 2 diabetes: in men, survival probabilities were 61.0% at 5 years, 42.2% at 10 years, and 28.4% at 15 years; corresponding estimates in subjects without type 2 diabetes were 72.1%, 58.2%, and 45.7% (Fig. S2). In women, survival probabilities were 53.8% at 5 years, 35.2% at 10 years, and 23.2% at 15 years in subjects with type 2 diabetes and 63.3%, 48.6%, and 37.4%, respectively, in those without (Fig. S2). Survival probabilities also varied by ethnicity: in men with type 2 diabetes, at 10 years survival was 39.1% in White, 48.2% in Black, 62.1% in Mixed/Other, and 63.1% in South Asian ethnicity (Fig. 1); corresponding estimates in those without type 2 diabetes were 56.9%, 71.2%, 75.2%, and 78.0%. In women with type 2 diabetes, at 10 years survival was 31.7% in White, 50.8% in Black, 54.6% in Mixed/Other, and 59.4% in South Asian ethnicity and 47.2%, 74.2%, 67.6%, and 73.2%, respectively, in those without.

After accounting for age at first CVD event, deprivation, and type 2 diabetes, compared to White ethnicity the mortality rates were lower in all minority ethnic groups, with HRs of 0.64 (95% CI: 0.63–0.65), 0.79 (0.78–0.80), and 0.74 (0.73–0.75) in men of South Asian, Black, and Mixed/Other ethnicity, respectively; corresponding estimates in women were 0.69 (0.68–0.70), 0.74 (0.72–0.75), and 0.77 (0.75–0.78) (Table 3). The adjusted HR for type 2 diabetes was 1.34 (1.34–1.35) in both men and women.

3.3. *Cardiovascular disease mortality*

During the study period, 814,157 CVD–related deaths (434,994 in men; 53.4%) occurred: 162,892 in subjects with type 2 diabetes (18.4%

Table 2
Rate of events following the first (index) cardiovascular event by type 2 diabetes, ethnicity and sex.

Ethnicity	Rate per 1,000 person-years (95% confidence interval)					
	All-cause mortality		Cardiovascular disease mortality		Different second cardiovascular event	
	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes
Men	95.6 (95.2–95.9)	59.0 (58.9–59.1)	35.8 (35.5–36.0)	21.0 (20.9–21.1)	37.9 (37.7–38.1)	24.5 (24.4–24.6)
White	104.5 (104.1–105.0)	61.4 (61.3–61.5)	38.8 (38.5–39.0)	21.7 (21.6–21.8)	39.3 (39.1–39.6)	24.9 (24.8–25.0)
South Asian	49.1 (48.3–49.9)	27.1 (26.7–27.5)	21.3 (20.8–21.8)	11.4 (11.1–11.6)	31.0 (30.4–31.6)	20.7 (20.4–21.1)
Black	78.4 (76.4–80.4)	37.1 (36.4–37.8)	25.5 (24.4–26.7)	13.6 (13.2–14.1)	33.9 (32.7–35.3)	18.8 (18.3–19.3)
Mixed/Other	52.5 (50.9–54.3)	31.7 (31.1–32.4)	21.1 (20.0–22.2)	11.9 (11.5–12.3)	28.9 (27.6–30.2)	18.2 (17.7–18.7)
Women	120.8 (120.3–121.3)	81.7 (81.5–81.8)	40.8 (40.5–41.1)	27.2 (27.1–27.3)	37.9 (37.6–38.2)	23.0 (22.9–23.1)
White	134.2 (133.5–134.8)	85.1 (85.0–85.3)	44.9 (44.5–45.2)	28.3 (28.2–28.4)	39.7 (39.4–40.1)	23.6 (23.5–23.7)
South Asian	57.1 (56.3–58.1)	34.0 (33.4–34.6)	22.3 (21.7–23.0)	12.3 (11.9–12.7)	29.7 (28.9–30.4)	16.2 (15.8–16.6)
Black	75.2 (73.3–77.2)	32.5 (31.8–33.2)	24.1 (23.0–25.2)	11.1 (10.7–11.5)	30.7 (29.5–32.0)	14.4 (13.9–14.9)
Mixed/Other	69.0 (66.4–71.5)	44.5 (43.5–45.5)	23.6 (22.1–25.1)	15.3 (14.8–15.9)	28.0 (26.4–29.6)	15.6 (15.0–16.1)
All subjects	105.5 (105.2–105.8)	68.4 (68.3–68.5)	37.7 (37.5–37.9)	23.5 (23.4–23.6)	37.9 (37.7–38.1)	23.9 (23.8–24.0)
White	116.1 (115.7–116.4)	71.2 (71.1–71.3)	41.2 (41.0–41.4)	24.4 (24.4–24.5)	39.5 (39.3–39.7)	24.4 (24.3–24.4)
South Asian	52.2 (51.6–52.8)	29.6 (29.2–29.9)	21.7 (21.3–22.1)	11.7 (11.5–11.9)	30.5 (30.0–31.0)	19.1 (18.8–19.4)
Black	76.8 (75.4–78.2)	35.0 (34.5–35.5)	24.8 (24.0–25.6)	12.5 (12.1–12.8)	32.4 (31.5–33.3)	16.8 (16.4–17.1)
Mixed/Other	58.6 (57.2–60.1)	36.6 (36.1–37.5)	22.0 (21.2–22.9)	13.2 (12.9–13.6)	28.5 (27.6–29.6)	17.2 (16.8–17.6)

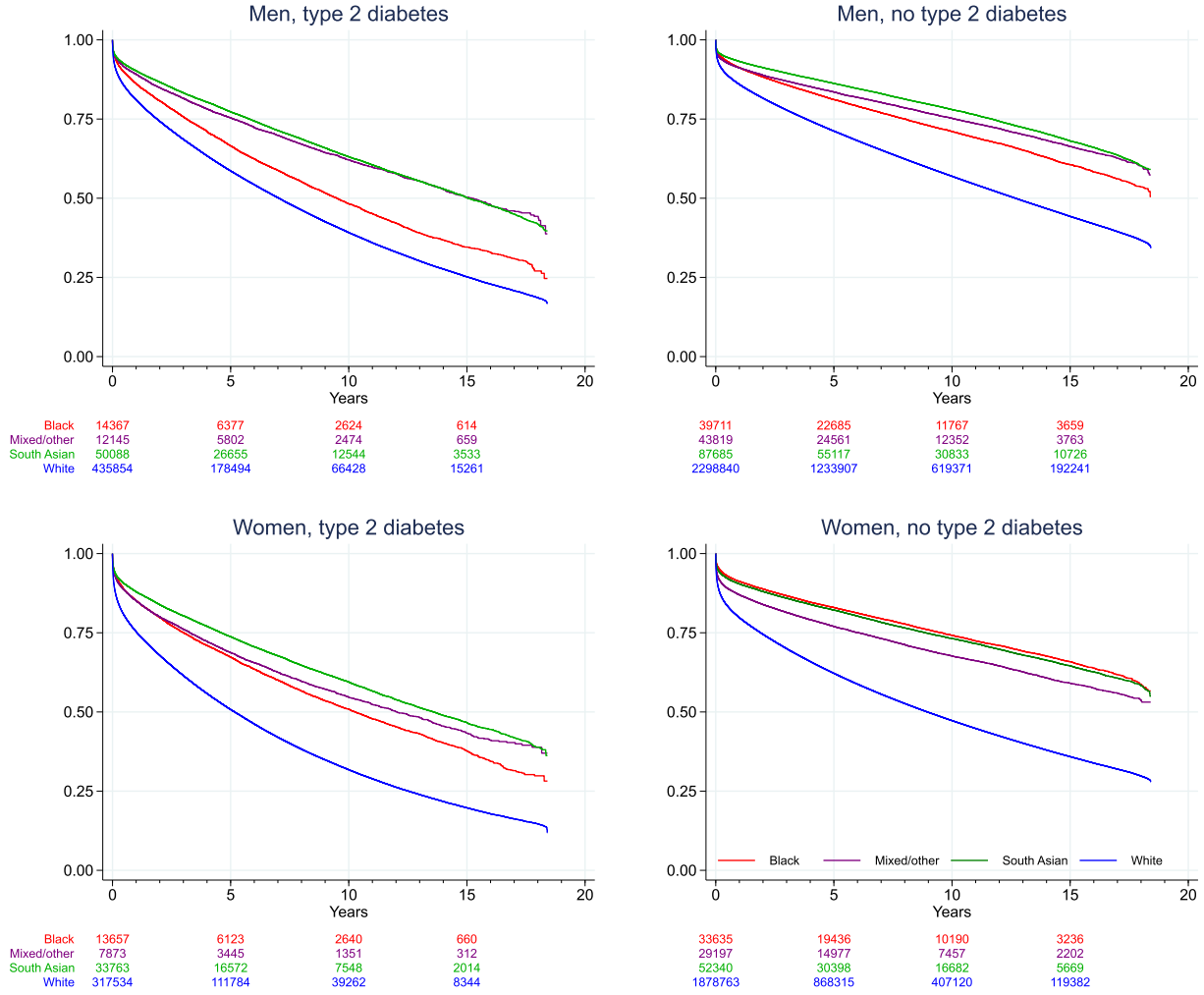

Fig. 1. Kaplan Meier survival by ethnicity and sex, in people with and without type 2 diabetes, Shown are the Kaplan-Meier survival probabilities following the first (index) cardiovascular event and the number of subjects at risk.

Table 3
Hazard ratios of events following the first (index) cardiovascular event.

	Men			Women		
	All-cause mortality	Cardiovascular disease mortality	Different second cardiovascular event	All-cause mortality	Cardiovascular disease mortality	Different second cardiovascular event
Ethnicity						
White	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
South Asian	0.64 (0.63–0.65)	0.78 (0.77–0.79)	0.98 (0.97–1.00)	0.69 (0.68–0.70)	0.83 (0.81–0.85)	0.95 (0.94–0.97)
Black	0.79 (0.78–0.80)	0.79 (0.77–0.81)	0.84 (0.82–0.86)	0.74 (0.72–0.75)	0.77 (0.75–0.79)	0.86 (0.84–0.88)
Mixed/Other	0.74 (0.73–0.75)	0.79 (0.77–0.81)	0.85 (0.83–0.87)	0.77 (0.75–0.78)	0.81 (0.78–0.83)	0.83 (0.81–0.86)
Type 2 diabetes						
No	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Yes	1.34 (1.34–1.35)	1.37 (1.36–1.38)	1.27 (1.26–1.28)	1.34 (1.34–1.35)	1.31 (1.30–1.33)	1.42 (1.41–1.43)
Deprivation quintiles						
5 (most affluent)	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
4	1.08 (1.07–1.09)	1.10 (1.09–1.10)	1.06 (1.05–1.07)	1.07 (1.06–1.08)	1.08 (1.07–1.09)	1.06 (1.04–1.07)
3	1.16 (1.15–1.17)	1.18 (1.16–1.19)	1.10 (1.09–1.11)	1.13 (1.12–1.14)	1.15 (1.14–1.16)	1.11 (1.10–1.12)
2	1.30 (1.29–1.31)	1.29 (1.28–1.30)	1.16 (1.15–1.17)	1.22 (1.21–1.23)	1.22 (1.21–1.23)	1.18 (1.16–1.19)
1 (most deprived)	1.51 (1.50–1.52)	1.48 (1.47–1.49)	1.26 (1.24–1.27)	1.35 (1.34–1.36)	1.33 (1.32–1.35(	1.29 (1.28–1.31)
Unknown	0.50 (0.49–0.51)	0.56 (0.55–0.58)	0.44 (0.43–0.46)	0.55 (0.55–0.57)	0.63 (0.61–0.65)	0.48 (0.46–0.50)
Age (per 5-year increase)						
	1.47 (1.46–1.47)	1.43 (1.42–1.43)	1.10 (1.10–1.11)	1.42 (1.42–1.43)	1.42 (1.41–1.42)	1.15 (1.14–1.15)

Hazard ratios (95% confidence interval) adjusted for all variables shown in the table.

of all subjects with type 2 diabetes) and 651,265 (14.6%) in those without (Table S3).

Crude incidence proportions of CVD–related death were very similar among South Asian, Black, and Mixed/Other ethnic groups, in both subjects with (range, 12.2%–13.5%) and without (8.7%–8.8%) type 2 diabetes; conversely, proportions were higher in White (19.3% and 15.0%, respectively); this pattern was observed in both men and women (Table S3). These estimates mirrored similar findings for rates, which were very similar in South Asian, Black, and Mixed/Other ethnic groups (range, 21.7–24.8 CVD–related deaths per 1,000 PYs in subjects with type 2 diabetes; 11.7–13.2 in those without) but higher in White (41.2 and 24.4, respectively; Table 2). Moderate differences in rates were observed by deprivation: 23.9 and 26.1 CVD–related deaths per 1,000 PYs in the most and least affluent group, respectively (Table S4).

The risk of CVD–related mortality was lower in all minority ethnic groups compared to White ethnicity: adjusted HRs were 0.78 (95% CI: 0.77–0.79), 0.79 (0.77–0.81), and 0.79 (0.77–0.81) in men of South Asian, Black, and Mixed/Other ethnicity, respectively; corresponding estimates in women were 0.83 (0.81–0.85), 0.77 (0.75–0.79), and 0.81 (0.78–0.83) (Table 3). The adjusted HR for type 2 diabetes was 1.37 (1.36–1.38) in men and 1.31 (1.30–1.33) in women.

3.4. Different second cardiovascular disease event

Of the 824,439 different second CVD events recorded during the follow–up (497,651 in men; 60.4%), 163,501 occurred in subjects with type 2 diabetes (18.5% of all subjects with type 2 diabetes) and 660,938 (14.8%) in those without (Table S3).

Crude incidence proportions of second events varied slightly across ethnicity: in subjects with type 2 diabetes, 15.9% in Mixed/Other, 17.6% in Black, 18.5% in White, and 19.0% in South Asian; corresponding figures in subjects without type 2 diabetes were 11.3%, 11.7%, 14.9%, and 14.4%; differences were small also when considered separately in men and women (Table S3). Crude rates of a second CVD event were also very similar among South Asian (30.5 and 19.1 events per 1,000 PYs in subjects with and without type 2 diabetes, respectively), Black (32.4 and 16.8), and Mixed/Other (28.5 and 17.2) ethnic groups, while they were higher in White (39.5 and 24.4); this pattern was observed in both men and women (Table 2). Modest differences in rates were observed by deprivation: 24.3 and 27.5 events per 1,000 PYs in the most and least affluent group, respectively (Table S4).

In men with type 2 diabetes, the unadjusted cumulative incidence of a different second CVD event 10 years after the first CVD event was 21.8% in White, 21.1% in Black, 19.2% in Mixed/Other, and 22.2% in South Asian; corresponding figures in subjects without type 2 diabetes were 17.5%, 14.6%, 13.8%, and 17.3% (Fig. 2). In women with type 2 diabetes, the estimate was 19.5% in White, 19.4% in Black, 17.3% in Mixed/Other, and 20.4% in South Asian; corresponding figures in those without type 2 diabetes were 14.6%, 11.5%, 11.4%, and 12.9%. When the incidence was evaluated by first CVD event phenotype, there were large differences in the incidence of a different second CVD event: in subjects with or without type 2 diabetes, the incidence was, on average, progressively greater for the first CVD event of the following phenotype: Other; CVA; HF; PVD; MI; and AA (Fig. S3). The incidence of second events was lower in subjects without type 2 diabetes, with the largest differences observed in subjects who experienced a first CVD event of the phenotype CVA or Other. Ethnic differences were mainly observed following a first AA, CVA, HF, or PVD in subjects with type 2 diabetes and following a first HF or PVD in those without (Fig. S3).

Compared to White ethnicity, the adjusted HR for a second CVD event was 0.98 (95% CI: 0.97–1.00), 0.84 (0.82–0.86), and 0.85 (0.83–0.87) in men of South Asian, Black, and Mixed/Other ethnicity,

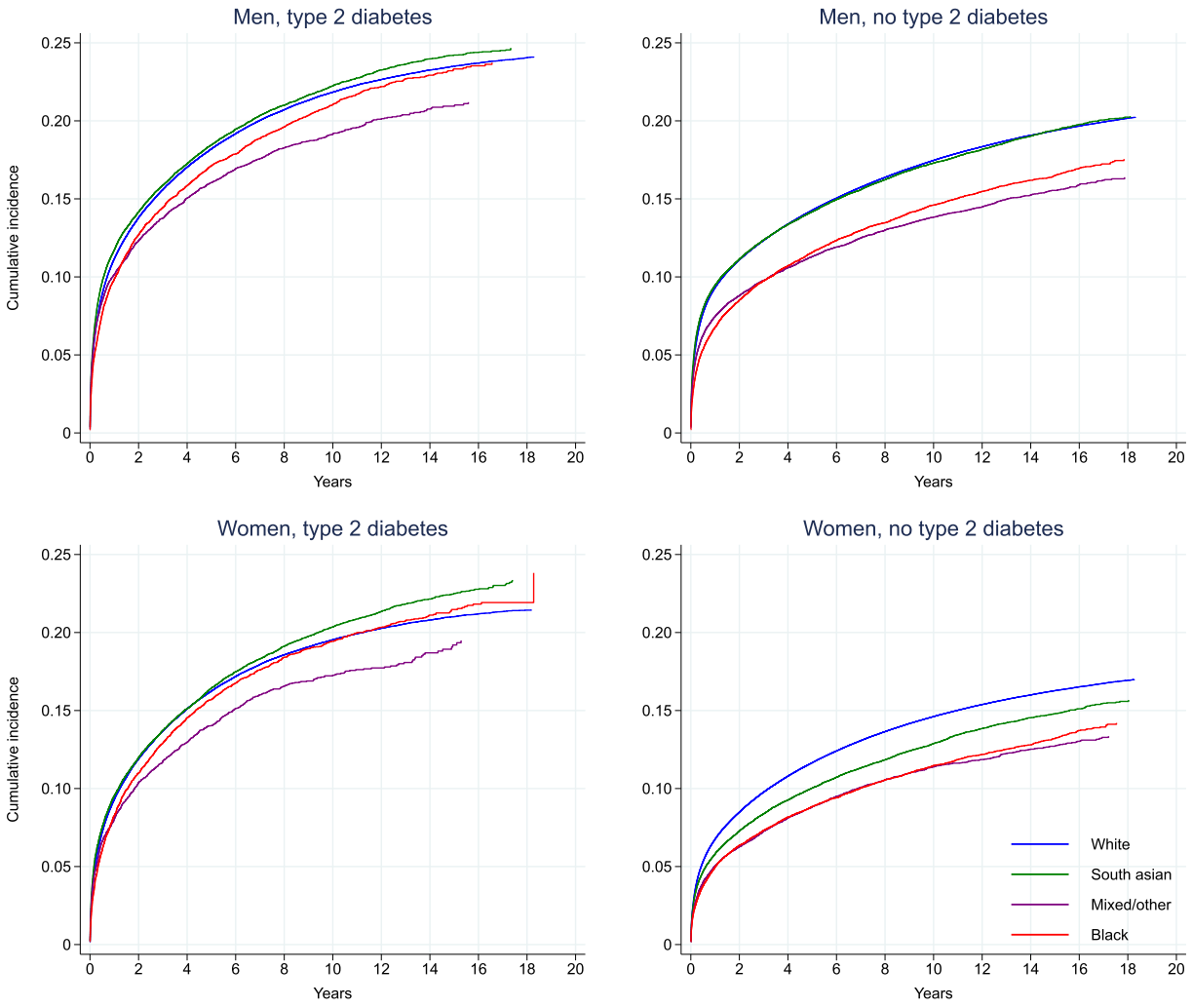

Fig. 2. Cumulative incidence of a different second cardiovascular disease event by ethnicity and sex, in people with and without type 2 diabetes. Cumulative incidence of any second CVD event different from the first (index) cardiovascular event.

respectively; corresponding estimates in women were 0.95 (0.94–0.97), 0.86 (0.84–0.88), and 0.83 (0.81–0.86) (Table 3). The adjusted HR for type 2 diabetes was 1.27 (1.26–1.28) in men and 1.42 (1.41–1.43) in women.

4. Discussion

In this study, we found that subjects of South Asian, Black, and Mixed/Other ethnicity experienced a first CVD event at a younger age compared to White, regardless of the presence of type 2 diabetes. Following the event, the adjusted rates of a second CVD event were 2%–15% lower in men and 5%–17% lower in women of ethnic minority groups compared to subjects of White ethnicity; rates of CVD–related and all–cause mortality were also consistently lower in men of South Asian (22% and 36%, respectively), Black (21% and 21%), and Mixed/Other ethnic groups (21% and 26%) as well as in women (17% and 31%; 23% and 26%; 19% and 23%, respectively). Lastly, the presence of type 2 diabetes increased the adjusted risk of all three outcomes by approximately a third. These findings therefore indicate the presence of a substantial "diabetes gap" in the prognosis of patients with CVD and highlight the importance of considering ethnicity when implementing complementary primary and secondary prevention strategies to reduce the total CVD burden.

An earlier occurrence of first CVD events in subjects of ethnic minority groups has been reported in recent studies including subjects from the UK. Coles et al. reported the age at occurrence of approximately 67,000 first CVD event in around 735,000 UK primary care subjects with and without type 2 diabetes: the median age was 73.1 years (ranging from 66.9 in South Asian to and 73.4 in White) in those with type 2 diabetes and 68.3 years (from 54.2 in Black to 68.8 in White) in those without [8]. These findings are in line with our results, which are based on a considerably larger sample of CVD events, confirming that subjects of White ethnicity – with or without type 2 diabetes – have a first CVD event at an older age compared to other ethnic groups. Two other recent studies have investigated the age at CVD occurrence across ethnic groups, yet with no details in relation to type 2 diabetes: in the first [7], based on a small number of CVD events (537 composite cerebrovascular, coronary, and CVD–related mortality events), Vyas et al. reported a median age of 70, 69, and 66 years in African Caribbeans, Europeans, and South Asians, respectively. In the second study [9], including about 280,000 subjects with non–ST elevation myocardial infarction (NSTEMI), Moledina et al. reported a median age of 73 in White vs 66 years in ethnic minority individuals. From this perspective, our findings – based on the largest UK cohort of patients with a first CVD event and with information on both ethnicity and diabetes status – aligns with previous evidence and compellingly show that the primary prevention strategies implemented in the last two decades in the UK to reduce the risk of CVD have not translated into the same benefit in subjects with and without type 2 diabetes and across ethnic groups [2,3,12].

In contrast with the extensive literature around risk factors for single

(first) CVD events, the evidence on the recurrence of CVD events and the prognosis after a first event is more limited, particularly among ethnic minority groups. While type 2 diabetes has been associated with a worse prognosis (higher mortality) in subjects with a previous MI [32], HF [33], or stroke [34], conflicting data are available on ethnic disparities. Vyas et al. showed differences in the crude rates of fatal and non–fatal recurrent CVD events and all–cause mortality in the UK among South Asian, African Caribbean, and European subjects; however, accounting for demographic, vascular, and lifestyle risk factors, there was no evidence of an excess risk in South Asians and African Caribbeans, compared to White subjects, for both outcomes [7]. In the study of Moledina et al. [9], the authors similarly found no difference between White and minority ethnic group subjects in the prognosis (evaluated in terms of in–hospital events – death or cardiovascular events) following NSTEMI, once differences in cardiometabolic risk factors and treatments were accounted for. These findings were also observed in another UK study by Jones et al. [11], where there was no difference in the short–(in–hospital major fatal and non–fatal CVD events) and medium–term (all–cause death) prognosis comparing South Asians to White patients undergoing percutaneous coronary intervention, once the differences in the risk factors between the two groups were accounted for. Viewed from an aetiological perspective, the results from these three UK studies would suggest that the differential risk in the cardiovascular prognosis and mortality observed across ethnicities could be explained by differences in the prevalence of risk factors among the ethnic groups. In contrast with these and other similar observations [35,36], in subjects with prior angina or myocardial infarction Zaman et al. showed a 22% lower mortality risk in South Asian compared to White ethnicity, regardless of the presence of diabetes [12].

Identifying the precise pattern of interrelated causes underpinning our (and previous) findings is difficult, given the complex interplay between numerous biological, environmental, demographic, social, and healthcare related factors which have been suggested to explain ethnic differences in health outcomes [37,38]. However, as our data were obtained from admitted patients, it is worth noting that ethnic inequalities exist in hospital admission in England: investigating around 41 million hospitalisations between 2009 and 2014, Petersen et al. showed large variations among ethnic groups in the age– and deprivation–adjusted overall and cause–specific number of admissions, particularly for CVD–and diabetes–related hospitalisation [39]; therefore, information on CVD and type 2 diabetes from hospital data may reflect inequalities in the access to healthcare services rather than the population burden of these two conditions [40,41]. A further element to consider is the variable proportion of migrants among ethnics group [16]: as there is evidence that people who migrate to UK are generally healthier than UK–born population [42–44], variations in these proportions may contribute to the lower mortality rates in some ethnic groups. Whether differences in hospital treatments or in primary or secondary prevention strategies also contribute to the observed ethnic inequalities is uncertain, as the existing studies investigating these hypotheses are very heterogeneous in their designs and available data [7,9,11,12].

When examining differences in the prognosis in relation to the phenotype of the first CVD event, several patterns emerged. First, the unadjusted absolute risk of a second CVD event was largest following an index AA or MI (between 35% and 60% at 10 years) event, followed by PVD and HF (20%–35%), and CVA and CVD event of other type (7%–18%). Second, the excess risk associated with type 2 diabetes was greater if the index event was a CVA or a CVD event of other type, while it was modest or absent for other index CVD events. Third, the excess risk associated with ethnicity was different across both the index event and type 2 diabetes: for example, in subjects with type 2 diabetes, the risk at 10 years was highest in South Asians if the index event was a CVA, PVD, or HF; conversely, in subjects without type 2 diabetes the risk was highest only for an index PVD event. Although two previous studies, including UK primary care patients, have explored the risk of phenotypically–different first CVD events by ethnicity and type 2 diabetes [8,45], to our knowledge there are no previous investigations aimed at quantifying the risk of recurrent CVD events in relation to the index CVD phenotype and type 2 diabetes among ethnic different groups.

The use of a large cohort of individuals with around a 20–year coverage of the population of England is a major strength of this study, as it allowed us to obtain precise and sex-specific estimate in clinically relevant subgroups defined by type 2 diabetes status, ethnicity, and first CVD event type. Furthermore, we reported both relative (hazard ratio) and absolute (survival and cumulative incidence probabilities) estimates, as these metrics are complementary: however, while relative estimates accounted for differences across ethnic groups in the prognostic factors associated with the outcomes, variations in the probabilities amongst ethnic groups reflected also differences in the these factors, including age at first CVD event; nevertheless, the adjusted estimates were consistent with the unadjusted probabilities. Although diseases in HES are recorded using the ICD–10 codes, facilitating comparisons with similar studies in other countries, variations in how diseases are coded exist among hospitals and financial incentives to improve coding have resulted in an increase in the number of codes [46]. Compared to primary care electronic health records and registries, patient–level information (i.e., cardiometabolic risk factors, medications, type 2 diabetes duration) is less granular in HES, limiting the possibility to explore putative causal factors underpinning differences among ethnic groups, type 2 diabetes status, or index CVD event; however, we were able to adjusted for key factors robustly associated with CVD and mortality (i.e., age and deprivation). Nonetheless, the main goal of our study was to explore whether potentially relevant differences in the prognosis among subjects of different ethnicity and by type 2 diabetes are present in subjects admitted to hospital for a CVD event, rather than investigate and quantify causes [47]. In line with the available information on ethnicity in HES and the most prevalent ethnic groups in the 2011 Census in England and Wales, we defined four ethnic groups; however, there is emerging evidence that there are variations in the risk of health–related outcomes within ethnic groups (i.e., among Pakistani, Indian, and Bangladeshi within South Asians) [31]. Moreover, instead of grouping them together as Mixed ethnicity, we considered White and Asian as Asian and White and Black Caribbean/African as Black as differences in multiple health–related outcomes and mortality between Black and Asian subjects have been shown [31]. While highlighting that discrepancy exists in coding Mixed ethnic group [48], we believe that considering these three groups as Mixed (like in the 2011 Census) would not change our estimates because the proportion of subjects in these three groups, combined, is the 0.22% of all subjects in our study. Although our findings align with the evidence of a greater mortality in White people in UK [10,49], the effect of ethnicity on recurrent CVD events may in part reflect a selection bias (subjects with a first CVD event [50]) and cannot be entirely generalised to countries with different healthcare systems. Lastly, it is possible that some patients had a CVD event before 1st January 2002 (starting date of the study), which was not captured in the population definition: however, data before this date were sparse and therefore not included in the analysis.

Building upon previous evidence – mostly based on classical observational studies exploring differences in the occurrence of a single, first CVD event of interest – in this study we detailed the long–term prognosis in subjects admitted to hospital for a CVD event in relation to type 2 diabetes and ethnicity. We found that the risk of a second CVD event and death was consistently higher in subjects with type 2 diabetes while varied across ethnic groups, suggesting that strategies accounting for ethnic disparities should be implemented in a life course approach to primary and secondary cardiovascular disease prevention.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MJD 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, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grant/research support from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen. KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi–Aventis, Lilly and Merck Sharp & Dohme; has received grants in support of investigator and investigator–initiated trials from Novartis, Novo Nordisk, Sanofi–Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme; and has received funds for research and served on advisory boards for Lilly, Sanofi–Aventis, Merck Sharp & Dohme and Novo Nordisk. FZ has received honoraria for speaking at meetings from NAPP Pharmaceuticals and Boehringer Ingelheim outside the submitted work. All other authors: no conflicts of interest.

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Ethical Approval

This study, registered with the local Clinical Audit Department (Clinical Audit Registration and management System number 14671), did not require ethics approval or patient consent. Data were used in line with the data sharing agreement with NHS Digital.

Availability of data and materials

Linked HES and ONS data may be obtained from NHS Digital via the Data Access Request Service (DARS) and are not publicly available.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109967.

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