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ORIGINAL ARTICLE

Ethnicity-specific association of BMI levels at diagnosis of type 2 diabetes with cardiovascular disease and all-cause mortality risk

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Abstract

Aim To evaluate the risk of CVD and all-cause mortality at different BMI levels in conjunction with weight change prior to diagnosis of T2DM in a multi-ethnic population.

Methods Longitudinal study of 51,455 patients with T2DM and without a history of comorbid diseases at diagnosis. Weight changes prior to diagnosis of T2DM were evaluated, and the risk of CVD and all-cause mortality at different BMI levels among three ethnic groups estimated using treatment effects model.

Results White Europeans (WE), African-Caribbeans (AC), and South Asians (SA) were mean 52, 49, and 47 years with a mean BMI of 33.0, 32.0, and 30.0 kg/m^2 at diagnosis, respectively. Among WE, normal weight patients developed CVD significantly earlier by 0.5 years (95% CI 0.1, 0.9 years; $p=0.018$) compared to obese patients. Furthermore, those with normal body weight at diagnosis were significantly more likely to die earlier by 0.6 years (95% CI 0.03, 1.2 years; $p=0.037$) among WE and by 2.5 years (95% CI 0.3, 4.6 years; $p=0.023$) among SA compared to their respective obese patients. However, BMI at diagnosis was not associated with increased risk of CVD and death among AC.

Conclusions This study suggests a paradoxical association of BMI with cardiovascular and mortality risks in different ethnic groups, which may partially be driven by different cardiovascular and glycaemic risk profiles at diagnosis.

Keywords Body mass index · Type 2 diabetes · Mortality · Ethnicity · Weight change pattern

Introduction

Recent studies have reported an inverse association of body mass index (BMI) with mortality risk among adults with type 2 diabetes mellitus (T2DM), where patients who were normal weight (BMI 18.5–24.9 kg/m^2) at diagnosis had significantly elevated mortality risk compared to their obese counterparts (BMI ≥ 30 kg/m^2) [1–5]. While the explanation for this phenomenon, referred to as the obesity paradox in T2DM, remains unclear, weight loss before the diagnosis of T2DM as a result of underlying/undiagnosed medical condition was postulated as one of the possible reasons [6–8]. However, an analysis of body weight changes over 3 years before diagnosis in patients with T2DM under different BMI categories has shown otherwise [9]. It is possible that ethnicity might play an essential role in understanding the underlying mechanism, as the distribution of adiposity levels in relation with cardiovascular disease (CVD) and mortality risk has been shown to be different for different ethnic groups [10–13].

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Previous studies have evaluated the incidence of CVDs either in different ethnic groups [14–19] or in relation with BMI [20, 21]. However, these studies did not evaluate the possible difference in the BMI-related risk paradigm in different ethnic groups. To the best of our knowledge, only one study has examined the modifiable association of ethnicity on the observed phenomenon of the obesity paradox in T2DM. Kokkinos and colleagues [22] used data from two Veteran Affairs Medical Centres in the US to assess the association between BMI, fitness, and mortality in African-Americans and Caucasians. However, this study was based on only male patients, and the BMI measures were not evaluated at the time of diagnosis of diabetes.

A better understanding of the potential role of ethnicity in the obesity paradox in both male and female patients with T2DM is important as this would enable clinicians to better manage diabetes amongst patients of different ethnicities and adiposities. Therefore, to address these knowledge gaps, the aim of this study was to use a cohort of incident T2DM patients from United Kingdom primary care database, to evaluate for each ethnic group, (1) the CVD and mortality rate in each BMI category, by weight change pattern before diagnosis and (2) the association of BMI categories at diagnosis with CVD and mortality risk, controlling for weight change pattern before diagnosis and other risk factors.

Materials and methods

Data source and identification of T2DM cohort

The data for this study were obtained from The Health Improvement Network (THIN) database. The detailed description of this database has been previously presented [23]. Patients diagnosed with T2DM between January 1990 and September 2014 ($n = 406{,}098$) were identified using a robust machine learning algorithm, which uses a combination of Read codes [24], anti-diabetes drugs (ADD), and lifestyle modification interventions [25]. Those included in this study satisfied the following criteria: (1) age (18–70 years), sex, BMI (≥ 18.5 kg/m^2), and date of diagnosis of T2DM from January 2000 with a minimum 1 year of follow-up; (2) ethnicity identified as White European (WE), African-Caribbean (AC), or South Asian (SA); and (3) no history of CVD, renal diseases, cancer, retinopathy, neuropathy, or bariatric surgery at diagnosis. SAs were defined as patients with Indian, Pakistani, Sinhalese, and Bangladeshi origin, while ACs were defined as patients with Black-African and Caribbean origin. Patients with White, European, Caucasian, and New Zealand European origins were defined as WEs. Those with Read codes for type 1 diabetes mellitus (T1DM) or gestational diabetes, and those who received insulin as the first antidiabetic drug (highly likely to be patients with T1DM) were excluded. A final cohort of 51,455 patients with T2DM was used for this study. Given the fact that only a proportion of the patients in the THIN database have ethnicity record, and to explore the potential selection bias in this study, we have provided a flowchart and table of basic statistics for patients from the database under the inclusion–exclusion criteria for this study (Fig. 1 and Online Resource 1). The study protocol was approved by the Independent Scientific Review Committee for the THIN database (Protocol Number: 15THIN030) and the Institutional Review Board of QIMR Berghofer Medical Research Institute.

Demographic and longitudinal measurements

Data on deprivation score (based on residential address) were extracted where available, and the smoking status for individuals was classified as current, ex, or never smokers. Longitudinal measurements including BMI, body weight, glycated haemoglobin (HbA_{1c}), blood pressure, and lipids were extracted for all patients. All available measures at or within 3 months before diagnosis of T2DM were considered as the baseline measures. If more than one measurement existed within this interval, the closest to the T2DM diagnosis date was taken. Longitudinal measures before and after the T2DM diagnosis were arranged in 6-monthly windows. BMI categories for WEs and ACs were defined as normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2). For SAs, BMI in the ranges 18.5–22.9, 23–27.4, and ≥ 27.5 kg/m^2 were used to define normal weight, overweight, and obese patients, respectively [26].

As weight loss before clinical diagnosis of T2DM is a common clinical manifestation, it was hypothesized that a weight loss of at least 2 kg before diagnosis of diabetes was clinically significant [27]. Therefore, using 6 possible longitudinal body weight measures over 36 months before diagnosis, we classified patients who lost body weight (LBW) by at least 2 kg before diagnosis (if average of 5 prior measurements minus the body weight measure in the 6 months prior to diabetes diagnosis was ≥ 2 kg) and those who did not lose body weight (NWL)—i.e., they remained on the same level or increased body. Complete records on the prescriptions for different classes of ADDs, antihypertensive drugs, weight lowering drugs, anti-depressant drugs, and lipid-modifying drugs were extracted along with the dates of prescriptions.

Mortality and comorbidity data

Records of CVDs, renal diseases [including chronic kidney disease (CKD)], and cancer with dates of diagnoses before and after T2DM diagnosis date were obtained. Information on deaths with dates and possible reasons were extracted. A composite variable for CVD (any CVD) was defined as the occurrence of angina, myocardial infarction, coronary

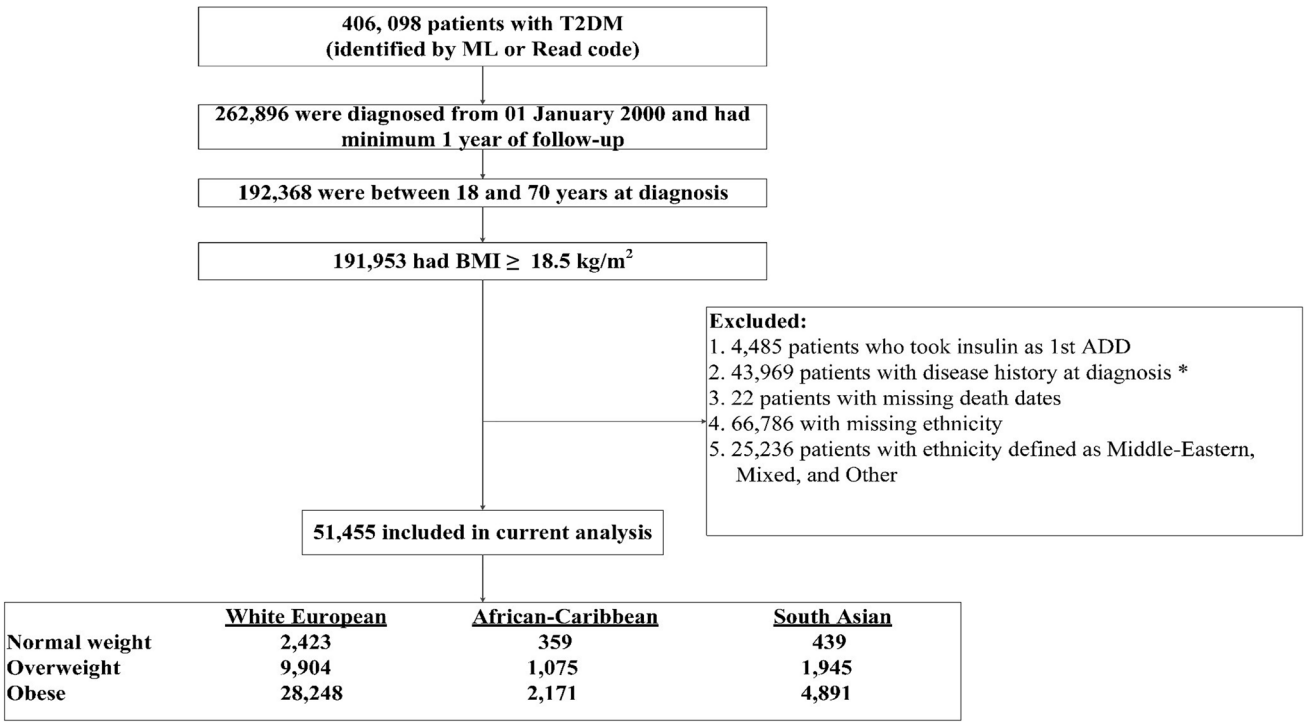

Fig. 1 Cohort selection flowchart. *history of disease defined as clinical diagnosis of CVD or renal diseases or cancer at diagnosis or retinopathy or neuropathy or bariatric surgery before diagnosis of T2DM; *ML* machine learning, *ADD* anti-diabetes drug

artery disease (including bypass surgery and angioplasty), heart failure, or stroke. Patients with a recorded diagnosis of cancer, any CVD, retinopathy, neuropathy, or renal diseases before the T2DM diagnosis date were considered to have a relevant disease history. Time to a specific disease event and time to death were calculated as the time from T2DM diagnosis date to the first occurrence of the disease event and date of death, respectively. Patients who were still alive at the end of the study data collection (September 2014) or dropped out were censored on the respective end date or drop out date.

Statistical analysis

The basic summary statistics were presented by number (%), mean (SD), or median (Q1, Q3), by ethnicity as appropriate. Among patients who were identified to have lost body weight (LBW) or not (NWL), age-weighted CVD and all-cause mortality (ACM) rates (per 1000 person-years) were estimated by BMI categories for each ethnic group. Cox proportional hazard regression is a widely used approach to analyse survival time data because of its flexible semi-parametric property. However, the key assumption of the proportional hazards regression model is unlikely to be true for patients with incident T2DM under different adiposity levels. To account for the inherent differences in risk factors between the defined BMI categories and the fact that risk may not be proportional, treatments effects modelling approach was used to provide robust inferences on the time to cardiovascular events or ACM. This modelling approach uses the potential outcomes framework to allow comparison of survival time for CVD and ACM for patients with different BMI categories, separately for each ethnic group [28–31]. A survival model with an inverse-probability weight estimator was used to estimate average time to events for each BMI category. Variables that were conditioned on include sex, weight change pattern before diagnosis, age at diagnosis, smoking status, the incidence of cancer and renal diseases post-diagnosis, and receipt of lifestyle advice before and after diagnosis. Statistical analyses were performed using STATA version 15 MP, at a two-tailed α level of 0.05.

Data availability

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

Basic demographic and clinical characteristics

In this study of 40,575 WEs, 3605 ACs, and 7275 SAs adults with T2DM, the median follow-up time was 7 years

for all three ethnic groups. The demographic and clinical profiles of these patients at diagnosis of T2DM in the three ethnic groups are presented in Table 1. SAs had the clinical diagnosis of T2DM at a younger age (47 years) and at lower BMI (30.0 kg/m^2) compared to WEs (age: 52 years, BMI: 33 kg/m^2) and ACs (age: 49 years, BMI: 32.0 kg/m^2). WEs had the highest proportion (58%) of ever-smokers (defined as current or ex-smokers) and a higher proportion of patients with systolic blood pressure above 140 mmHg (Table 1). ACs had higher proportions of patients in the normal weight (10%) and overweight (30%) groups, as well as the highest LDL-cholesterol levels (129 mg/dl) at diagnosis compared to WE and SA patients (Table 1).

The distribution of clinical characteristics separately for each ethnic group within the three defined BMI categories is presented in Table 2. ACs had similar levels of ever-smokers across BMI categories, while SAs who were normal weight at diagnosis had significantly higher proportion of ever-smokers (35%) compared to their counterparts who were overweight (26%) and obese (25%) at diagnosis. Furthermore, the proportion of ever-smokers among WEs who were normal weight at diagnosis (60%) was significantly higher compared to their WEs' obese counterparts (57%). While

Table 1 Basic clinical and demographic characteristics of patients with T2DM by ethnicity

	White European (WE)	African-Caribbean (AC)	South Asian (SA)
Patients†	40,575	3605	7275
Age at diagnosis (years)‡	52 (12)	49 (11)	47 (12)
Age group†			
≤40	6936 (17)	923 (26)	2228 (31)
41–50	9515 (24)	1129 (31)	2073 (29)
51–60	12,971 (32)	902 (25)	1848 (25)
61–70	11,153 (28)	651 (18)	1126 (16)
Male†	22,534 (56)	1851 (51)	3911 (54)
Smoking status†			
Never smoker	17,132 (42)	2496 (69)	5371 (74)
Current smoker	9718 (24)	461 (13)	952 (13)
Ex-smoker	13,649 (34)	640 (18)	917 (13)
Weight (kg)‡	95 (19)	89 (16)	82 (15)
BMI (kg/m^2)‡	33 (6)	32 (5)	30 (5)
BMI categories†			
Normal weight	2423 (6)	359 (10)	439 (6)
Overweight	9904 (24)	1075 (30)	1945 (27)
Obese	28,248 (70)	2171 (60)	4891 (67)
SBP (mmHg)‡	139 (16)	137 (16)	134 (16)
SBP ≥ 140 mmHg†	19,578 (48)	1516 (42)	2442 (34)
HBA_{1c} (%)(DCCT)‡	9 (2)	9 (2)	9 (2)
HBA_{1c} (mmol/mol)‡	75 (21.9)	75 (21.9)	75 (21.9)
HBA_{1c} ≥ 7.5% or 58 mmol/mol	28,510 (70)	2651 (74)	5262 (72)
LDL (mg/dl)‡	125 (29)	129 (29)	125 (29)
HDL (mg/dl)‡	45 (11)	47 (11)	44 (10)
Triglycerides (mg/dl)§	170 (136–212)	127 (97–159)	160 (126–201)
LBW prior to diagnosis†	7595 (18)	662 (18)	1225 (18)
Lifestyle advice†			
Before diagnosis	12,861 (32)	909 (25)	1983 (27)
After diagnosis	27,855 (69)	2130 (59)	4352 (60)
Follow-up (years)§	7 (4–11)	7 (4–10)	7 (4–10)

BMI body mass index, *SPB* systolic blood pressure, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *LBW* lost at least 2 kg body weight before diagnosis, *Any CVD* cardiovascular disease defined as the occurrence angina, myocardial infarction, coronary heart disease (including bypass surgery and angioplasty), heart failure, and stroke on or before diagnosis of T2DM

†*n* (%)

‡Mean (SD)

§Median (Q1, Q3)

Table 2 Distribution of clinical characteristics among patients with T2DM by ethnicity in each BMI category

	Normal weight ($n=3221$)			Overweight ($n=12,924$)			Obese ($n=35,310$)		
	WE ($n=2423$)	AC ($n=359$)	SA ($n=439$)	WE ($n=9904$)	AC ($n=1075$)	SA ($n=1,945$)	WE ($n=28,248$)	AC ($n=2171$)	SA ($n=4891$)
Age (years)[a‡]	55 (12)	49 (11)	49 (13)	55 (10)	50 (11)	49 (11)	51 (12)	48 (11)	47 (12)
Male[†]	1371 (57)	259 (72)	281 (64)	6529 (66)	686 (64)	1227 (63)	14,634 (52)	906 (42)	2403 (49)
Smoking status[a†]									
Never smokers	982 (41)	236 (66)	285 (65)	3978 (40)	722 (67)	1427 (73)	12,172 (43)	1538 (71)	3659 (75)
Current smokers	794 (33)	66 (18)	90 (21)	2411 (24)	137 (13)	278 (14)	6513 (23)	258 (12)	584 (12)
Ex-smokers	645 (27)	57 (16)	62 (14)	3498 (35)	212 (20)	240 (12)	9506 (34)	371 (17)	615 (13)
HbA_{1c} (%) (DCCT)[a‡]	9 (2)	10 (3)	9 (2)	9 (2)	9 (2)	9 (2)	9 (1)	9 (2)	9 (1)
HBA_{1c} (mmol/mol)[a‡]	75 (21.9)	86 (32.8)	75 (21.9)	75 (21.9)	75 (21.9)	75 (21.9)	75 (10.9)	75 (21.9)	75 (10.9)
SBP[a‡]	136 (19)	134(20)	129(18)	139 (17)	137 (17)	132 (17)	140 (16)	138 (16)	135 (15)
Cardiovascular diseases during follow-up[†]									
Hypertension	822 (34)	125 (35)	109 (25)	4091 (41)	452 (42)	610 (31)	11,813 (42)	867 (40)	1593 (33)
Angina	51 (2)	2 (0.6)	7 (2)	284 (3)	10 (0.9)	49 (3)	714 (3)	17 (0.8)	92 (2)
MI	60 (3)	3 (0.8)	14 (3)	267 (3)	6 (0.6)	44 (2)	536 (2)	17 (0.8)	94 (2)
CHD	111 (5)	6 (2)	25 (6)	563 (6)	18 (2)	118 (6)	1264 (5)	33 (2)	201 (4)
HF	36 (2)	1 (0.3)	1 (0.2)	153 (2)	11 (1)	14 (0.7)	464 (2)	22 (1)	39 (0.8)
Stroke	83 (3)	10 (3)	10 (2)	393 (4)	21 (2)	43 (2)	877 (3)	46 (2)	96 (2)
Any CVD	331 (14)	22 (6)	48 (11)	1416 (14)	62 (6)	183 (9)	3183 (11)	107 (5)	395 (8)
Lifestyle advice[†]	1676 (69)	226 (63)	258 (59)	6906 (20)	640 (60)	1237 (64)	19,273 (68)	1264 (58)	2857 (58)
LBW[†]	699 (29)	105 (29)	125 (29)	2098 (21)	214 (20)	459 (24)	4798 (17)	343 (16)	641 (13)
Antidiabetic drugs[†]									
OAD	2033 (84)	325 (91)	402 (92)	8055 (81)	956 (89)	1722 (89)	23,306 (83)	1808 (83)	4031 (82)
Metformin	1867 (77)	295 (82)	370 (84)	7751 (78)	908 (85)	1658 (85)	22,750 (81)	1758 (81)	3897 (80)
Sulphonylureas	1246 (51)	213 (59)	268 (61)	4217 (43)	531 (49)	896 (46)	10,357 (37)	855 (39)	1888 (39)
TZD	310 (13)	41 (11)	71 (16)	1416 (14)	112 (10)	261 (13)	3965 (14)	230 (11)	584 (12)
DPP4-i	292 (12)	48 (13)	51 (12)	1347 (14)	123 (11)	245 (13)	4228 (15)	260 (12)	645 (13)
GLP1-RA	9 (0.4)	1 (0.3)	1 (0.2)	179 (2)	12 (1)	11 (0.6)	2007 (7)	71 (3)	130 (3)
SGLT2-i	11 (0.5)	1 (0.3)	0 (0)	55 (0.6)	5 (0.5)	13 (0.7)	352 (1)	10 (0.5)	46 (0.9)
Alpha-glucosidase	11 (0.5)	3 (0.8)	3 (0.7)	46 (0.5)	6 (0.6)	10 (0.5)	125 (0.4)	8 (0.4)	19 (0.4)
Meglitinide	29 (1)	5 (1)	5 (1)	66 (0.7)	7 (0.7)	14 (0.7)	190 (0.7)	20 (0.9)	40 (0.8)
Insulin	433 (18)	48 (13)	44 (10)	1120 (11)	115 (11)	162 (8)	3693 (13)	253 (12)	464 (10)
Other medications[†]									
CPM	1967 (81)	281 (78)	333 (76)	8609 (87)	852 (79)	1601 (82)	23,669 (84)	1631 (75)	3629 (74)
Diuretics	579 (24)	64 (18)	55 (13)	2901 (29)	273 (25)	317 (16)	9419 (33)	582 (27)	965 (20)
Beta-blockers	482 (20)	46 (13)	55 (13)	2373 (24)	164 (15)	326 (17)	6759 (24)	332 (15)	839 (17)
Calcium blockers	592 (24)	111 (31)	92 (21)	3197 (32)	412 (38)	497 (26)	8883 (31)	912 (42)	1272 (26)

Table 2 (continued)

	Normal weight ($n=3221$)			Overweight ($n=12,924$)			Obese ($n=35,310$)		
	WE ($n=2423$)	AC ($n=359$)	SA ($n=439$)	WE ($n=9904$)	AC ($n=1075$)	SA ($n=1,945$)	WE ($n=28,248$)	AC ($n=2171$)	SA ($n=4891$)
Renin–angiotensin	1152 (48)	169 (47)	192 (44)	5803 (59)	553 (51)	954 (49)	16,863 (60)	1055 (49)	2364 (48)
Ace inhibitors	286 (12)	56 (16)	67 (15)	1593 (16)	167 (15)	330 (17)	4823 (17)	366 (17)	909 (19)
Statins	1072 (44)	147 (41)	172 (39)	5257 (53)	485 (45)	834 (43)	14,778 (52)	898 (41)	1979 (41)
Lipid modifiers	1796 (74)	226 (63)	312 (71)	7837 (79)	693 (65)	1454 (75)	20,714 (73)	1289 (59)	3129 (64)
Anti-depressants	1807 (75)	227 (63)	313 (71)	7918 (80)	695 (65)	1455 (75)	20,914 (74)	1295 (60)	3154 (65)

Data are presented for patients without history of disease at diagnosis

OAD use of oral antidiabetic drug, *CPM* use of cardio-protective medications, *SPB* systolic blood pressure, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *LBW* lost at least 2 kg body weight before diagnosis, *TZD* thiazolidinedione, *DPP4-i* dipeptidyl peptidase 4 inhibitors, *GLP1-RA* glucagon-like peptide-1 receptor agonists, *SGLT2-i* sodium–glucose transport protein 2 inhibitors, *WE* White European, *AC* African-Caribbean, *SA* South Asian

[†]*n* (%)

[‡]Mean (SD);

[a]Value obtained at diagnosis

the proportion of normal weight patients who lost at least 2 kg weight loss before diagnosis was almost double that of obese patients across BMI categories, similar proportion of patients experienced this weight loss before diagnosis across the three ethnic groups.

CVD and mortality rates

To avoid potential bias resulting from already existing severe disease that may independently induce weight loss in patients, CVD and mortality risk assessments were carried out excluding patients with clinically diagnosed cancer, any CVD, retinopathy, neuropathy, or CKD at diagnosis of T2DM. For each ethnic group, the age-weighted CVD and ACM rates per 1000 person-years (95% CI), by BMI categories and weight change pattern prior to diagnosis, are presented in Figs. 2 and 3. Among WEs, CVD event rates per 1000 person-years were significantly higher in normal weight patients (rate: 23.7; 95% CI 21.3, 26.5) compared to obese patients (rate: 20.3; 95% CI 19.6, 21.0), independent of weight change pattern before diagnosis. In no other ethnic group did CVD event rates vary across different BMI categories and weight change pattern before diagnosis. However, the CVD event rates in WEs with normal weight were significantly higher than the rates in ACs with normal weight (rate: 11.6; 95% CI 7.6, 18.6), and similar to the rates in SAs with normal weight (rate: 21.3; 95% CI 16.1, 28.7) (Fig. 2).

Irrespective of weight change pattern before diagnosis, mortality rates per 1000 person-years were significantly higher among WEs with normal weight (rate: 12.2; 95% CI 10.6, 14.1) compared to obese WEs (rate: 7.6; 95% CI 7.2, 8.0). Furthermore, these mortality rates among WEs with normal weight were about threefold higher compared to ACs (rate: 3.2; 95% CI 1.5, 8.4) and SAs (rate: 4.6; 95% CI 3.1, 7.0) with normal weight (Fig. 3).

Association of BMI categories with survival time for CVD and mortality

The adjusted average time to first CVD event (95% CI) and adjusted average time to ACM (95% CI) in normal weight and overweight patients compared to obese patients with T2DM, within each ethnic group are presented in Table 3. Among WEs, compared to obese patients (mean time to CVD of 4.6 years), normal weight patients developed CVD significantly earlier by 0.5 years (95% CI 0.1, 0.9 years; $p=0.018$). Furthermore, there was no significant difference between overweight WEs and obese WEs with regard to time to first CVD event ($p>0.05$). The risk of developing CVD was not significantly higher in normal weight ACs and SAs, compared to their obese counterpart. However, overweight ACs developed CVDs about 1.2 years (95% CI 0.6, 2.2 years; $p=0.040$) later compared to obese African-Caribbeans.

With a mean time to death of 7.0 and 7.3 years among obese WEs and SAs, respectively, those with normal body weight at diagnosis were significantly more likely to die earlier by 0.6 years (95% CI 0.03, 1.2 years; $p=0.037$)

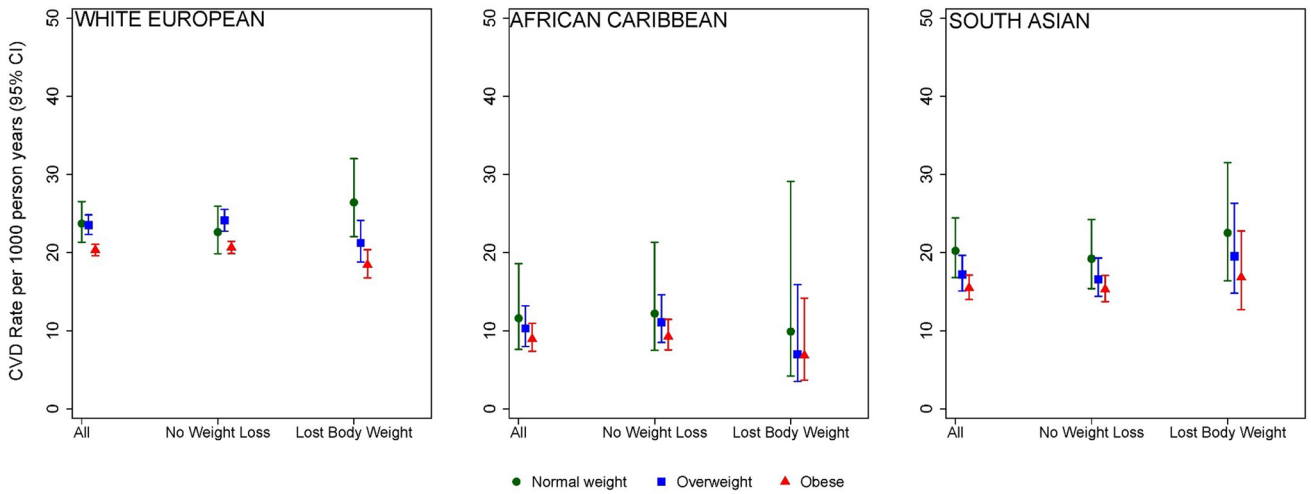

Fig. 2 Age-weighted CVD event rates per 1000 person-years (95% CI) by BMI categories and weight change pattern before diagnosis in patient without disease history at diagnosis separately for three ethnic groups. *CVD* cardiovascular disease defined as the occurrence angina, myocardial infarction, coronary heart disease (including bypass surgery and angioplasty), heart failure, and stroke post-diagnosis of T2DM

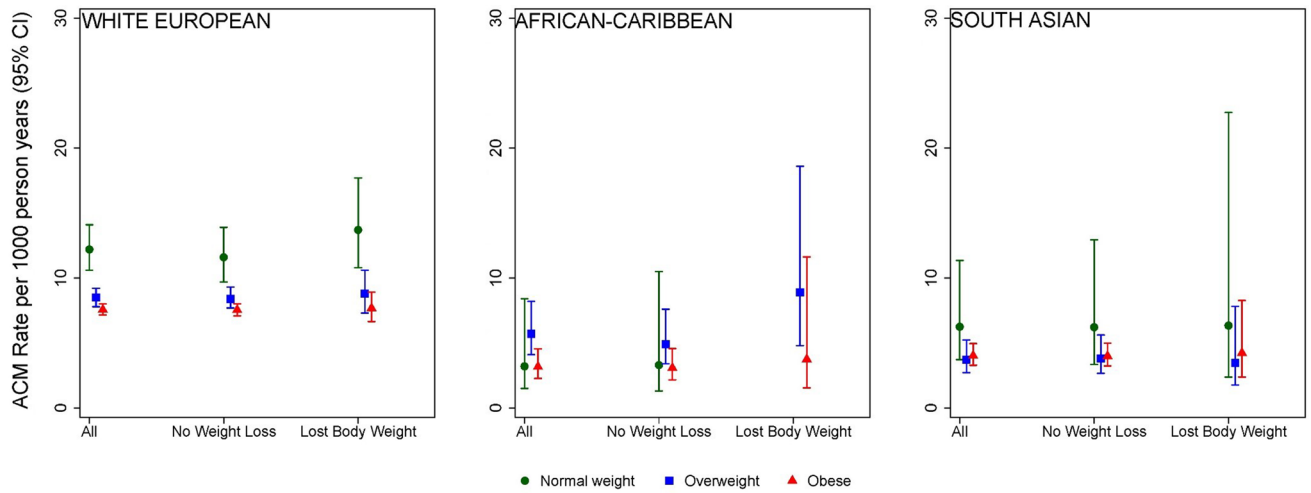

Fig. 3 Age-weighted ACM rates per 1000 person-years (95% CI) by BMI categories and weight change pattern before diagnosis in patient without disease history at diagnosis separately for three ethnic groups. *ACM* all-cause mortality; rates were not calculated for events less than or equal to 5

in the WE group and by 2.5 years (95% CI 0.3, 4.6 years; $p = 0.023$) in the SA group.

Discussion

The novelty of this electronic medical record-based study from a nationally representative primary care database in incident T2DM patients includes assessment of risk profile for different ethnic groups at the time of clinical diagnosis of diabetes by different adiposity levels, extensive exploration of weight change patterns prior to diagnosis of diabetes, a robust evaluation of the rates, and risk of CVD and ACM in different ethnic groups with different adiposity levels. In this longitudinal outcome study based on three well-defined ethnic groups, we found that (1) the paradoxical association of lower BMI with high CVD rate appeared only in WEs, and this was not modified by weight change pattern before diagnosis; (2) normal weight WEs and SAs appear to have significantly higher mortality risk compared to their obese counterparts, independent of weight change patterns prior to diagnosis of T2DM; and (3) the BMI at diagnosis was not associated with increased risk of CVD and death among ACs.

Table 3 Adjusted average time to first CVD event or ACM (95% CI) in obese patients, and the difference in time to such events in patients with normal body weight or overweight compared to obese counterpart

	White European ($n=40,575$)		African-Caribbean ($n=3605$)		South Asian ($n=7275$)	
Any CVD						
Mean time (years)—obese	4.6 (4.5, 4.7)		4.5 (3.9, 5.2)		4.9 (4.6, 5.3)	
Difference (years)		*p* value		*p* value		*p* value
Normal weight vs obese	−0.5 (−0.9, −0.1)	0.018	−1.1 (−2.5, 0.3)	0.117	−0.3 (−1.4, 0.9)	0.659
Overweight vs obese	0.1 (−0.2,0.3)	0.521	1.2 (0.1, 2.2)	0.040	−0.6 (−1.2, 0.0)	0.054
ACM						
Mean time (years)—obese	7.0 (6.8,7.2)		6.6 (5.6, 7.7)		7.3 (6.6, 7.9)	
Difference (years)						
Normal weight vs obese	−0.6 (−1.2, −0.03)	0.037	−1.0 (−2.5, 0.6)	0.207	−2.5 (−4.6, −0.3)	0.023
Overweight vs obese	−0.3 (−0.6, 0.0)	0.048	−0.02 (−1.7, 1.6)	0.978	0.1 (−1.2, 1.3)	0.899

Separate analyses were conducted for males and females within each ethnic group. Patients were without history of disease at diagnosis

Any CVD cardiovascular disease defined as the occurrence angina, myocardial infarction, coronary heart disease (including bypass surgery and angioplasty), heart failure, and stroke post-diagnosis of T2DM

Obesity is a strong risk factor for CVDs in the general population and in some clinical populations. However, increasing evidence is pointing to a paradoxical phenomenon, where overweight or obese patients may have better survival outcomes regarding developing heart failure or coronary heart disease, compared to normal weight patients [21, 32]. Our analysis in patients with T2DM goes further to show that this paradoxical association between lower BMI and higher CVD risk was present only among WEs. In keeping with the previous studies, our data shows higher proportions of current smokers among normal weight WEs [33, 34] and this could contribute to increased CVD risk among this group of patients. We previously reported that contrary to the notion that the observed obesity paradox could be due to weight loss from latent diseases, weight loss before diagnosis of T2DM was not associated with increased mortality in normal weight patients [9]. The current study shows that the significantly higher event rates for CVD and mortality among normal weight patients were independent of weight change pattern before diagnosis of T2DM. This clearly supports the fact that weight change pattern before diagnosis does not impact on the observed obesity paradox in patients with T2DM.

Furthermore, we found that the paradoxical association of lower BMI with higher mortality risk was more prominent in SAs than WEs. Some studies in patients with T2DM have compared ACM in different ethnic groups and different BMI categories, but to the best of our knowledge, none have provided ethnicity-specific mortality risk estimates by BMI categories at diagnosis. While the study by Kokkinos and colleagues [22] reported significantly higher mortality risk among African-Americans and Caucasians with normal weight compared to patients with BMI ≥ 35 kg/m^2 (reference group), the BMI measure used in this study was not obtained at diagnosis of diabetes and only male participants were used. Our risk assessments were based on BMI measured at diagnosis of T2DM and a more pragmatic approach of estimating the time to the events under consideration compared at different adiposity levels with an average 7 years of follow-up time, rather than estimating the hazard ratios which might provide misleading inference under highly heterogeneous characteristics in different ethnic groups. We also ensured the exclusion of patients with already existing diseases at diagnosis that are associated with increased mortality risk.

One of the novel findings of this study was that SAs with normal body weight at diagnosis were significantly more likely to die earlier by about 2.5 years compared to their counterparts who were obese at diagnosis. One may argue that above finding was due to the fact that the proportion of ever-smokers in normal weight SAs (35%) was significantly higher than that in the obese group (25%), while the distribution of ever-smokers was similar between normal weight and obese WEs. However, while we do not know the change in smoking behaviour during the 7 years of median follow-up, our analyses were balanced for such possible baseline differences. Our current observation of lower prevalence of current or ex-smokers among SAs compared to WEs was consistent with our previous study [23] and the study by Wright and colleagues [35]. Nonetheless, our observation agrees in principle with the study by Bellary and colleagues [17] who reported mean age at death for SAs to be significantly lower by 7 years compared to that in WEs. Furthermore, Penno and colleagues [36] showed that CKD is a major risk factor for mortality in patients with T2DM is CKD and given that SAs are at disproportionate risk of CKD [37], it is possible that our finding of excess mortality among SAs with normal BMI

could be due to the several pathophysiological mechanisms linking CKD to CVD and ACM [36]. Notwithstanding, future studies evaluating the interaction of albuminuria levels with glycaemic and cardiovascular risk factors for each BMI category within each ethnic group are needed.

Our findings should be interpreted considering the limitations of this study, which include: (1) availability of ethnicity data on a limited number of patients; (2) non-availability of longitudinal data on smoking cessation; and (3) potential for residual confounding as with all observational studies. Despite the issue of limited ethnicity data on some patients, the previous work with this cohort by our research group showed that the distribution of sex, smoking status and BMI among persons with missing information on ethnicity was similar to the respective distributions among those with available information on ethnicity [23]. Furthermore, we also attempted to minimize bias introduced by confounders using the "treatment effect" modelling approach. With this approach, robust inferences are provided through appropriate adjustments and balancing of a detailed list of confounders. However, patient-level data from electronic health records still present challenges regarding accuracy and completeness.

In conclusion, our study confirms a paradoxical association BMI and mortality among patients with T2DM and provides new insight into the possible role of ethnicity in explaining the obesity paradox both regarding CVD and total mortality.

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Author contributions SKP and ESOA conceived the idea and contributed to the study design. ESOA conducted the data extraction, data manipulation, and statistical analyses and developed the first draft of the manuscript. SKP contributed to the statistical analyses and had full access to all the data in the study and is the guarantor, taking responsibility for the integrity of the data and the accuracy of the data analysis. ESOA, KKR, and SKP were involved in writing the paper and had final approval of the submitted and published versions.

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Compliance with ethical standards

Conflict of interest SKP has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator-initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi Aventis and Pfizer. KKR has acted as a speaker or consultant for Abbvie, Amgen, Pfizer, Astra Zeneca, Sanofi Resverlogix, Regeneron, Esperion, ACKCEA, Medicines Company, BI, Novo Nordisk. ESOA has no conflicts of interest to declare.

Statement of human and animal rights This article does not contain any studies with human or animal subjects performed by the any of the authors.

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