Received: 4 July 2021 | Revised: 14 November 2021 | Accepted: 1 December 2021

DOI: 10.1111/dom.14614

ORIGINAL ARTICLE

WILEY

# Body mass index and cancer mortality in patients with incident type 2 diabetes: A population-based study of adults in England

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**Funding information**
Cancer Research UK Manchester Centre, Grant/Award Numbers: C147/A18083, C147/A25254; Manchester NIHR Biomedical Research Centre, Grant/Award Number: IS-BRC-1215-20007

## Abstract

**Aims:** We evaluated the relationship between body mass index (BMI) and cancer mortality in incident type 2 diabetes.

**Methods:** We used the Clinical Practice Research Datalink GOLD (1998-2015), linked with the Office of National Statistics mortalities, and derived an incident type 2 diabetes cohort (N = 176 886; aged 30-85 years). We determined BMI ±12 months diabetes diagnosis. The primary outcome was cancer mortality, categorized into deaths from obesity-related cancers (ORCs) and non-ORCs. Secondary outcomes were site-specific cancer mortality and main causes of deaths [cancer, cardiovascular disease (CVD), non-cancer non-CVD]. We developed gender-specific Cox models and expressed risk as hazard ratios and 95% confidence intervals, stratified by smoking status.

**Results:** With 886 850 person-years follow-up, 7593 cancer deaths occurred. Among women who never smoked, there were positive associations between BMI and deaths from endometrial (hazard ratios per 5 kg/m$^2$: 1.43; 95% confidence interval 1.26-1.61). Among men, associations between BMI and ORC mortality were inverse but attenuated towards null among never smokers and excluding deaths in the first 2 years. In men, the proportion of CVD deaths increased from 36.8% in BMI category 22.5 to 24.9 kg/m$^2$ to 43.6% in BMI category ≥40 kg/m$^2$ ($p$ < .001).

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**Conclusions:** We found some relationships between BMI and cancer mortality in patients with type 2 diabetes, but interpretations need to account for smoking status, reverse causality and deaths from CVD.

**KEYWORDS**
BMI, cancer, mortality, obesity, type 2 diabetes

## 1 | INTRODUCTION

Individuals with type 2 diabetes have two to four times higher risk of premature mortality than those without type 2 diabetes.[1-3] Until recently, many studies reported that cancer is the second commonest cause of death in type 2 diabetes,[4-6] with cardiovascular disease (CVD) as the most common cause.[4,7] A recent study,[8] using the UK Clinical Practice Research Datalink (CPRD), linked with the Office of National Statistics (ONS) mortality data, indicates that cancer may be emerging as the leading cause of death in type 2 diabetes. In addition, from a systematic review,[9] we know that the relative risks from cancer death in individuals with type 2 diabetes compared with non-diabetes populations may be greater among women than men.

Understanding the underlying mechanisms associated with the higher risk for cancer mortality seen among individuals with type 2 diabetes is important. These mechanisms are likely to be multifactorial, including a role for excess adiposity. The latter, commonly approximated by body mass index (BMI), is a modifiable risk factor for up to 13 different cancer types,[10,11] referred to as obesity-related cancers (ORCs). However, the role of BMI in cancer mortality among type 2 diabetes populations is understudied and inconsistent. Four studies evaluated these associations, respectively, from Japan (N = 3851; 421 cancer deaths),[12] the Netherlands (N = 1353; 122 cancer deaths),[13] Taiwan (N = 89 056; 4786 cancer deaths)[14] and Sweden (N = 26 953; 2848 cancer deaths).[15] The first three studies broadly showed null[12,13] or inverse[14] associations between baseline BMI and cancer mortality risk; while the Swedish study[15] reported a positive association between BMI and cancer mortality. There are several factors that might explain these inconsistent findings, including small event numbers, heterogeneity of participants including patients with prevalent and incident diabetes, effect modification from smoking, reverse causation and competing risk from other causes of death, such as CVD. Thus, a study[16] combining data from the Nurses' Health Study and Health Professionals Follow-up Study, evaluating the relationship between BMI and all-cause mortality among incident type 2 diabetes, reported a non-linear relationship for all participants but a linear relationship in analyses limited to never smokers and excluding deaths from the first 4 years after type 2 diabetes diagnosis. They argued the following 'Smoking is a concern in analyses of body weight and mortality because it is associated with decreased body weight but an increased risk of death. Statistical adjustment for smoking status (e.g., ever smoked vs. never smoked) is often insufficient to control for varying degrees of smoking duration and intensity. Thus, stratification according to smoking status can be an important way to examine the association between body weight and the risk of death; in addition, the subgroup analysis among persons who have never smoked can reduce residual bias related to smoking'.[16]

In this study, we evaluated gender-specific associations between peri-diagnosis BMI and cancer mortality among incident type 2 diabetes accounting for effect modification of smoking and reverse causation. to understand better the mechanisms and in common with Drake et al.,[15] we categorized cancer deaths as ORC and non-ORC mortality.

## 2 | METHODS

### 2.1 | Population

We performed a population-based cohort study using the CPRD GOLD in England with data from 383 primary care practices (57% of all CPRD) that were linked to other national datasets to obtain cause of death (ONS) and ethnicity data (Hospital Episode Statistics, HES). The study was approved by the Independent Scientific Advisory Committee for CPRD research (Ref: 17_137R).

To address our hypothesis, we derived an incident cohort of patients with type 2 diabetes, described in detail elsewhere,[4] whose first diagnostic code for diabetes was from 1 January 1998 to 31 March 2015 (index date), using the de Lusignan algorithm.[17] The algorithm uses clinical Read codes to identify individuals with diabetes and using additional information such as age, BMI and ethnicity-specific BMI cut-offs. Individuals with type 1 diabetes were excluded. The cohort with type 2 diabetes was observed from the index date until the study end date (31 March 2015), the practices' last data collection date, death or transfer out of practice, whichever occurred earliest. We restricted our cohort to those aged between 30 and 85 years at diagnosis.

To understand the role of BMI on cancer mortality in individuals with type 2 diabetes, we calculated peri-diagnosis BMI from height and weight measures within the type 2 diabetes incident cohort, up to 12 months before or after index date. Peri-diagnosis BMI values were missing in a fifth of individuals. Multiple imputation methods have been shown to reduce bias and improve efficiency in variables with a high proportion of missing data.[18] Therefore, we imputed missing data on BMI, and other variables including blood pressure, and cholesterol, using 10 imputed sets (Stata MI command) generated at the index date.

There were 176 886 individuals with incident type 2 diabetes aged 30-85 years (Figure 1). Extreme BMI values (BMI <18.5 kg/m$^2$

and ≥60 kg/m$^2$) were excluded such that the imputed cohort comprised of 175 919 individuals and the complete case cohort comprised of 144 802 individuals.

## 2.2 | Exposure assessment

We modelled peri-diagnosis BMI both as categorical - low-normal weight (18.5-22.4 kg/m$^2$), high-normal weight (22.5-24.9 kg/m$^2$), overweight (25.0-29.9 kg/m$^2$), obese I (30.0-34.9 kg/m$^2$), obese II (35-39.9 kg/m$^2$) and obese III (≥40.0 kg/m$^2$), with high-normal weight as the referent category - and as continuous, expressing risk estimates per 5 kg/m$^2$.[11]

Age was determined at the date of type 2 diabetes diagnosis. We previously showed that ethnicity impacts life expectancy in diabetes[4] and thus ethnicity was identified from HES and CPRD and grouped under five headings: white, black/black British, South Asian, other and unknown (details in supplemental material of Wright et al.[4]). We used the Index of Multiple Deprivation (IMD) 2010 to classify deprivation. IMD is a relative measure of deprivation with ranks based from the least deprived (IMD 1) to the most deprived (IMD 5)[19] (details in supplemental material of Wright et al.[4]).

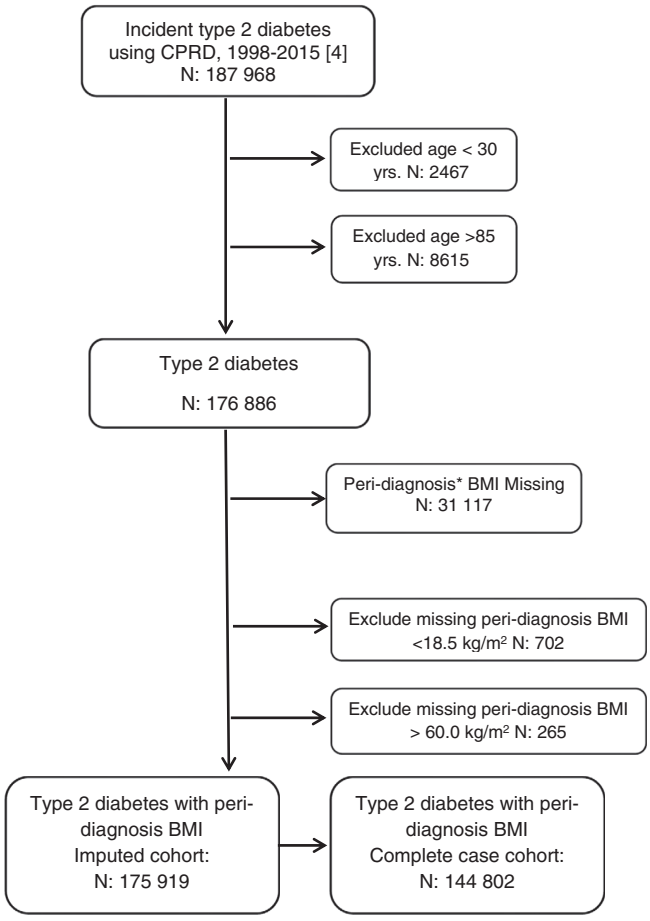


**FIGURE 1** Flow diagram for the imputed and complete case cohorts. BMI, body mass index; CPRD, UK Clinical Practice Research Datalink

Smoking status was categorized as current, former, never or formally coded as unknown using an algorithm as defined by Joseph et al.[20] in 2016 and was determined based on the closest smoking status recording before the index date.

We captured clinical history (e.g. CVD and chronic kidney disease), biochemical measures (e.g. glycated haemoglobin, total cholesterol, other serum lipids), blood pressure and medications (e.g. antidiabetes therapies, aspirin, lipid-lowering agents and antihypertensive agents) at baseline, determined ±12 months type 2 diabetes diagnosis.

## 2.3 | Outcome measures

The primary outcome was risk for cancer mortality (based on underlying cause of death as defined by ONS), categorized into deaths from ORC and non-ORCs. The International Agency for Research on Cancer (IARC) identified 13 ORCs[10] - these are (with ICD-10 codes) as follows: Oesophagus - lower third (C15.5, C15.8); Colorectal (C18.0 -18.9, C19, C20); Liver (C22.0); Gallbladder (C23); Pancreas (C25.0-25.9); Breast (C50.0-50.9); Corpus Uteri/Endometrial (C54.0-54.9, C55); Ovary (C56.0); Kidney (C64); Gastric cardia (C16.0); Malignant meningioma (C70.0, C70.1, C70.9); Thyroid (C73.0); and Multiple myeloma (C90.0). We did not stratify breast cancer by menopausal status. Total cancer mortality was based on ICD-10 codes C00–C97. In our cancer site analyses, reported associations for colorectal, kidney, pancreatic, breast endometrial and ovarian cancers, and combined oesophageal, liver, intra-hepatic ductal, gallbladder, gastric cardia, thyroid cancers, and malignant melanoma and multiple myeloma as 'other obesity-related cancers'. Non-ORCs were classified as all remaining cancer codes not captured under ORCs. Within non-ORC types, we specifically examined associations with Lung (C34.0) and Prostate (C61.0) cancers. Secondary outcomes were site-specific cancer mortality and main causes of deaths - cancer, CVD (ICD-10 codes: I00-I99) and non-cancer non-CVD.

## 2.4 | Statistical methods

All analyses were computed using Stata version 15 (StataCorp LP, College Station, TX, USA). Differences in baseline characteristics across the BMI categories were explored using Cuzick's non-parametric test and the Cochran-Armitage test for trends (2 × n tables) as appropriate.

For the time-to-event analyses, we estimated gender-specific hazard ratios (HR) and 95% confidence intervals (CIs) using Cox Proportional Hazards models, with time zero (index date) as the date of diabetes diagnosis. In all settings, we tested for the assumptions of proportionality using Schoenfeld's test and visualization of the Kaplan-Meier curves.

We explored several multivariable models. Model A adjusted for the following covariates: age, ethnicity, deprivation and calendar year, which are important confounders. Model B adjusted for model A covariates plus adjusted baseline smoking status. Model C added to models A and B adjusting for CVD, chronic kidney disease, cholesterol, blood pressure, diabetes therapies, aspirin use, clopidogrel use,

**TABLE 1** Baseline characteristics across BMI categories in men and women aged 30-85 years with incident type 2 diabetes

| | BMI, kg/m$^2$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | **18.5-22.4** | **22.5-24.9** | **25.0-29.9** | **30.0-34.9** | **35.0-39.9** | **40.0-59.9** | ***p* value** |
| Women (N = 62 508) | 2948 (4.7) | 5213 (8.3) | 17 447 (27.9) | 17 509 (28.0) | 10 657 (17.1) | 8734 (14.0) | |
| Age, years; mean ± SD | 68.3 ± 12.5 | 67.0 ± 12.3 | 65.4 ± 11.9 | 62.6 ± 12.1 | 59.2 ± 12.2 | 54. ± 11.7 | <.001 |
| Deprivation quintile | | | | | | | <.001 |
| 1 (least deprived) | 606 (20.6) | 1066 (20.5) | 3350 (19.2) | 2957 (16.9) | 1639 (15.4) | 1103 (12.6) | |
| 2 | 669 (22.7) | 1201 (23.0) | 3874 (22.2) | 3751 (21.4) | 2125 (19.9) | 1607 (18.4) | |
| 3 | 587 (19.9) | 1065 (20.4) | 3436 (19.7) | 3576 (20.4) | 2105 (19.8) | 1774 (20.3) | |
| 4 | 583 (19.8) | 987 (18.9) | 3635 (20.8) | 3868 (22.1) | 2425 (22.8) | 2064 (23.6) | |
| 5 (most deprived) | 500 (17.0) | 887 (17.0) | 3115 (17.9) | 3331 (19.0) | 2346 (22.0) | 2165 (24.8) | |
| Unknown | 3 (0.1) | 7 (0.1) | 37 (0.2) | 26 (0.2) | 17 (0.2) | 21 (0.2) | |
| BMI, kg/m$^2$; mean ± SD | 20.9 ± 1.1 | 23.8 ± 0.7 | 27.6 ± 1.4 | 32.3 ± 1.4 | 37.2 ± 1.4 | 44.9 ± 4.3 | Not applicable |
| Smoking status | | | | | | | <.001[a] |
| Current smoker | 886 (30.1) | 1325 (25.4) | 4255 (24.4) | 4164 (23.8) | 2595 (24.4) | 2158 (24.7) | |
| Ex-smoker | 823 (27.9) | 1632 (31.3) | 5965 (34.2) | 6526 (37.3) | 4051 (38.0) | 3378 (38.7) | |
| Never smoked | 1230 (41.7) | 2239 (43.0) | 7199 (41.3) | 6796 (38.8) | 3998 (37.5) | 3187 (36.5) | |
| Unknown | 9 (0.3) | 17 (0.3) | 28 (0.2) | 23 (0.1) | 13 (0.1) | 11 (0.1) | |
| Diabetes therapy | | | | | | | <.001[b] |
| No drugs | 1467 (49.8) | 2581 (49.5) | 9257 (53.1) | 9248 (52.8) | 5482 (51.3) | 4125 (47.2) | |
| Monotherapy | 1238 (42.0) | 2210 (42.4) | 6987 (40.1) | 7093 (40.5) | 4496 (42.2) | 4074 (46.7) | |
| Metformin | 591 (20.1) | 1323 (25.4) | 5223 (29.9) | 6009 (34.3) | 3981 (37.4) | 3777 (43.2) | |
| Sulphonylurea | 468 (15.9) | 664 (12.7) | 1289 (7.4) | 680 (3.9) | 311 (2.9) | 153 (1.7) | |
| Other monotherapy | 196 (6.5) | 239 (4.5) | 505 (2.9) | 434 (2.5) | 212 (2.0) | 151 (1.7) | |
| Dual therapy | 229 (7.8) | 388 (7.4) | 1121 (6.4) | 1050 (6.0) | 610 (5.7) | 466 (5.3) | |
| Triple therapy | 14 (0.5) | 34 (0.7) | 82 (0.5) | 118 (0.7) | 69 (0.7) | 69 (0.8) | |
| Duration of follow-up, years; mean ± SD | 5.3 ± 3.9 | 5.6 ± 3.9 | 5.7 ± 3.9 | 5.5 ± 3.8 | 5.4 ± 3.8 | 5.2 ± 3.7 | |
| Men (N = 82 294) | 2991 (3.6) | 7443 (9.0) | 30 303 (36.8) | 25 216 (30.6) | 10 779 (13.1) | 5562 (6.8) | |
| Age, years; mean ± SD | 63.5 ± 13.8 | 63.7 ± 12.8 | 62.3 ± 11.8 | 59.7 ± 11.5 | 56.6 ± 11.3 | 53.1 ± 10.9 | <.001 |
| Deprivation quintile | | | | | | | <.001 |
| 1 (least deprived) | 607 (20.3) | 1527 (20.5) | 6430 (21.2) | 4750 (18.8) | 1824(16.9) | 801 (14.4) | |
| 2 | 634 (21.2) | 1789 (24.0) | 7125 (23.5) | 5710 (22.6) | 2242 (20.8) | 1075 (19.3) | |
| 3 | 630 (21.1) | 1558 (20.9) | 6086 (20.1) | 5272 (20.9) | 2176 (20.2) | 1123 (20.2) | |
| 4 | 584 (19.5) | 1424 (19.1) | 5918 (19.5) | 5092 (20.2) | 2357 (21.9) | 1329 (23.9) | |

(Continues)

**TABLE 1** (Continued)

| | BMI, kg/m$^2$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | **18.5-22.4** | **22.5-24.9** | **25.0-29.9** | **30.0-34.9** | **35.0-39.9** | **40.0-59.9** | ***p* value** |
| 5 (most deprived) | 529 (17.7) | 1142 (15.3) | 4703 (15.5) | 4359 (17.3) | 2168 (20.1) | 1228 (22.1) | |
| Unknown | 7 (0.2) | 3 (0.0) | 41 (0.1) | 33 (0.1) | 12 (0.1) | 6 (0.1) | |
| BMI, kg/m$^2$; mean ± SD | 21.1 ± 1.0 | 23.9 ± 0.7 | 27.6 ± 1.4 | 32.2 ± 1.4 | 37.0 ± 1.4 | 44.2 ± 3.9 | Not applicable |
| Smoking status | | | | | | | <.001[a] |
| Current Smoker | 1109 (37.1) | 2193 (29.5) | 7895 (26.1) | 6207 (24.7) | 2707 (25.1) | 1403 (25.2) | |
| Ex-smoker | 1031 (34.5) | 3043 (40.9) | 14 352 (47.4) | 12 561 (50.0) | 5300 (49.2) | 2522 (45.3) | |
| Never smoked | 837 (28.0) | 2180 (29.3) | 7997 (26.4) | 6315 (25.1) | 2752 (25.5) | 1632 (29.3) | |
| Unknown | 14 (0.5) | 27 (0.4) | 59 (0.2) | 46 (0.2) | 20 (0.2) | 5 (0.1) | |
| Diabetes therapy | | | | | | | <.001[b] |
| No drugs | 1208 (40.4) | 3470 (46.6) | 15 598 (51.5) | 13 118 (52.0) | 5312 (49.3) | 2477 (44.2) | |
| Monotherapy | 1473 (49.3) | 3387 (45.2) | 12 549 (41.4) | 10 407 (41.3) | 4726 (43.8) | 2698 (48.5) | |
| Metformin | 669 (22.4) | 1900 (25.5) | 9385 (31.0) | 8954 (35.5) | 4260 (39.5) | 2521 (45.3) | |
| Sulphonylurea | 597 (20.0) | 1106 (14.9) | 2264 (7.5) | 945 (3.8) | 265 (2.5) | 96 (1.7) | |
| Other monotherapy | 207 (6.9) | 353 (4.7) | 900 (3.0) | 508 (2.0) | 201 (1.9) | 81 (1.5) | |
| Dual therapy | 293 (9.8) | 562 (7.6) | 1966 (6.5) | 1525 (6.1) | 656 (6.1) | 349 (6.3) | |
| Triple therapy | 17 (0.6) | 52 (0.7) | 190 (0.6) | 166 (0.7) | 85 (0.8) | 38 (0.7) | |
| Duration of follow-up, years; mean ± SD | 5.0 ± 3.9 | 5.4 ± 3.9 | 5.5 ± 3.9 | 5.3 ± 3.7 | 5.1 ± 3.7 | 4.9 ± 3.6 | |

*Note*: Values are n (%), unless otherwise stated.

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]n × 2 Cochran-Armitage test for trends - never smokers versus all other categories.

[b]n × 2 Cochran-Armitage test for trends - any antidiabetes therapy versus no antidiabetes therapy.

statin use, other lipid-lowering agents and antihypertensive agents determined at baseline. The risk estimates from these models were essentially the same as those for model B; thus, we reported this as our main model.

We noted differences in mean ages across BMI categories and explored models adjusting for age, age$^2$ and age as the time scale (left truncated at date of diabetes diagnosis). Smoking is a potential confounder but may also be an effect modifier[16] - thus, we stratified a priori by smoking status (ever/never).

We examined for potential effects of reverse causation (prevalent cancer leading to changes in BMI) by excluding individuals with less than 2 years follow-up and deaths within the first 2 years.

Finally, we assessed for potential competing risks and described the relationships between peri-diagnosis BMI and relative proportions of deaths attributed to CVD, and non-cancer non-CVD deaths, by gender. Competing risks were explored using a Fine and Gray regression model, which links the effects of risk factors directly to the cause-specific cumulative incidences of death and allows different causes of death to be visualized using cumulative incidence functions (CIFs) ('stacked plots') as described by Hinchliffe and Lambert.[21]

Because of the problem of multiple testing, we used $p < .005$ to indicate statistical significance. In sensitivity analyses, we assessed for differences between risk estimates from multiple imputed models versus complete case analysis.

## 3 | RESULTS

### 3.1 | Baseline characteristics across body mass index categories

The gender-specific baseline characteristics in 144 802 individuals (aged 30-85 years) with incident type 2 diabetes and peri-diagnosis BMI measurements are shown in Table 1. There were stepwise differences in mean ages across the BMI range - with individuals in the high-normal BMI category (BMI 22.5-24.9 kg/m$^2$) being older than those in the younger obese III category (BMI 40.0-59.9 kg/m$^2$) in both women (mean age ± SD: 67.0 ± 12.3 vs. 54.8 ± 11.7 years, $p < .001$ and men: 63.7 ± 13.8 vs. 53.1 ± 10.9 years, $p < .001$). Elevated BMI was associated with higher deprivation ($p < .001$ both genders), greater use of diabetes therapies, ($p < .001$ both genders) and lower prevalence of never smoking ($p < .001$ both genders).

### 3.2 | Cancer mortalities across body mass index categories

With 886 850 person years follow-up, 7593 cancer deaths occurred (3023 in women; 4570 in men). Among all women with type 2 diabetes, there were mainly inverse associations between BMI and risk of

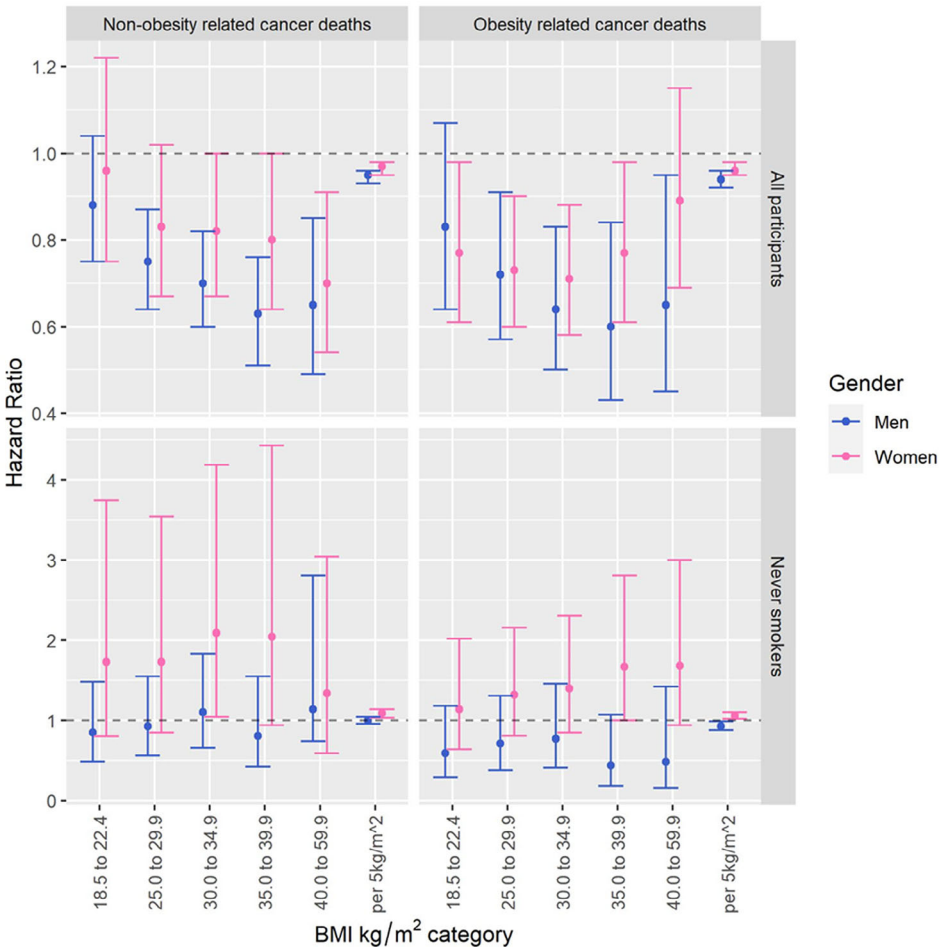


**FIGURE 2** Gender-stratified hazard ratios (95% CI) for obesity-related and non-obesity-related cancer mortality associated with type 2 diabetes across body mass index (BMI) categories as all participants and never smokers in individuals aged 30-85 years

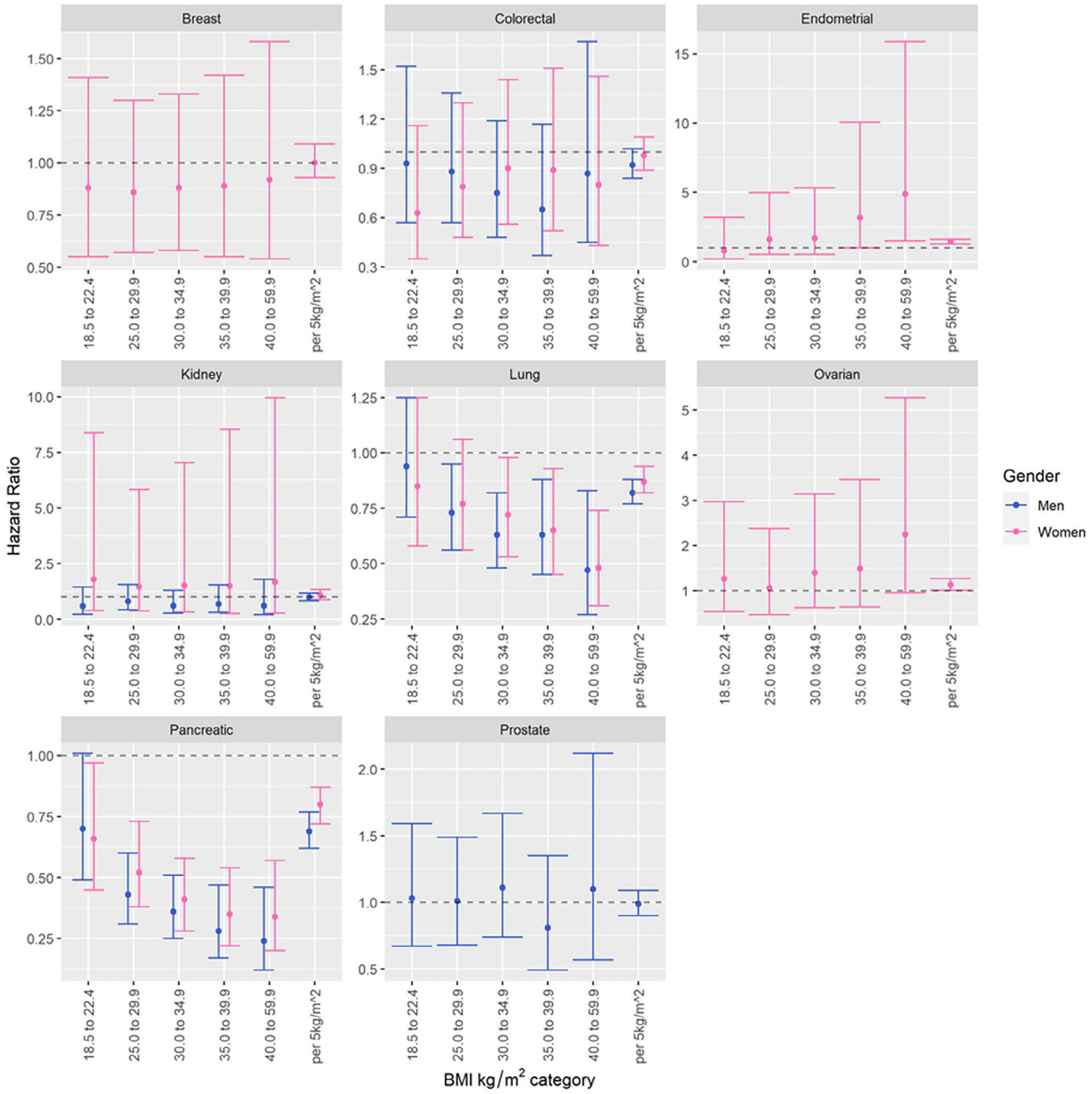


**FIGURE 3** Gender-stratified hazard ratios (95% CI) for site-specific cancer-related mortalities associated with type 2 diabetes across body mass index (BMI) categories in individuals aged 30-85 years

ORC-related or non-ORC-related death (Figure 2, Table S1). However, in analyses limited to never smokers, BMI was positively associated with ORC-related mortality (HR per 5 kg/m$^2$: 1.06; 95% CI 1.02-1.10) and non-ORC-related mortality (HR per 5 kg/m$^2$: 1.096; 95% CI 1.03-1.14).

Among all men with type 2 diabetes, we observed mainly inverse associations between elevated BMI and mortality from ORCs (Figure 2, Table S1). In analyses limited to never smokers, associations remained inverse for ORC deaths but were null for non-ORC deaths.

### 3.3 | Site-specific cancer mortalities across body mass index categories

The associations of BMI and risk of site-specific cancer-related mortalities by gender are shown in Figure 3 (Table S2). Among women, there were positive associations between BMI and deaths from endometrial (HR per 5 kg/m$^2$: 1.43; 95% CI 1.26-1.61) and possibly ovarian (HR per 5 kg/m$^2$: 1.13; 95% CI 1.01-1.27) cancers and inverse associations with deaths from pancreatic (HR per 5 kg/m$^2$: 0.80; 95% CI

**TABLE 2** Numbers and percentages of deaths by main causes across BMI categories in women and men

| | BMI kg/m$^2$ category | | | | | | % change per BMI category (se) | $p_{trend}$[a] |
|---|---|---|---|---|---|---|---|---|
| | 18.5-22.4 | 22.5-24.9 | 25.0-29.9 | 30.0-34.9 | 35.0-39.9 | 40.0-59.9 | | |
| Women, death from: | | | | | | | | |
| All causes | 1040 | 1347 | 3285 | 2675 | 1357 | 929 | | |
| Cancer | 226 (21.7) | 336 (24.9) | 967 (29.4) | 807 (30.6) | 420 (31.3) | 267 (28.7) | 1.6 (0.3) | <.001 |
| Cardiovascular disease | 365 (35.1) | 469 (34.8) | 1143 (34.8) | 916 (34.8) | 470 (35.1) | 334 (36.0) | 0 (0.4) | .907 |
| Non-cancer non-CVD | 449 (43.2) | 542 (40.2) | 1175 (35.8) | 952 (35.6) | 467 (35.6) | 328 (34.4) | −1.6 (0.3) | <.001 |
| Men, death from: | | | | | | | | |
| All causes | 1001 | 1972 | 5756 | 3822 | 1270 | 594 | | |
| Cancer | 278 (27.7) | 599 (30.4) | 1977 (34.4) | 1219 (32.2) | 354 (28.1) | 143 (24.1) | 0.6 (0.3) | .059 |
| Cardiovascular disease | 308 (30.8) | 725 (36.8) | 2117 (36.8) | 1514 (40.0) | 547 (43.3) | 259 (43.6) | 2.4 (0.4) | <.001 |
| Non-cancer non-CVD | 415 (41.5) | 648 (32.9) | 1662 (28.9) | 1089 (28.5) | 369 (29.1) | 192 (32.3) | −1.8 (0.3) | <.001 |

*Note*: Values in parentheses are percentages.
Abbreviations: CVD, cardiovascular disease; SE, standard error.
[a]n x2 Cochran-Armitage test for trends - for example, CVD deaths versus all other deaths.

0.72-0.87) and lung (HR per 5 kg/m$^2$: 0.87; 95% CI 0.82-0.94) cancers.

Among men, there were no associations between BMI and deaths from most site-specific cancers examined but inverse associations with deaths from pancreatic (HR per 5 kg/m$^2$: 0.69; 95% CI 0.62-0.77) and lung (HR per 5 kg/m$^2$: 0.82; 95% CI 0.77-0.88) cancers.

## 3.4 | Testing for reverse causation

We tested for presence of reverse causation by excluding individuals with less than 2 years follow-up or deaths in the first 2 years after the diagnosis of type 2 diabetes (Table S3). Among all women, there was a positive association between peri-diagnosis BMI and risk of ORC deaths (per 5 kg/m$^2$: 1.08; 95% CI 1.03-1.13) but not for risk of non-ORC deaths. In analyses limited to never smokers, similarly there was a positive association between peri-diagnosis BMI and risk ORC deaths (per 5 kg/m$^2$: 1.10; 95% CI 1.01-1.19) but not for risk of non-ORC deaths.

Among all men, there were no associations between peri-diagnosis BMI and risks of ORC and non-ORC deaths. Similarly, in analyses limited to never smokers, there were no associations between peri-diagnosis BMI and risks of ORC and non-ORC deaths.

In addition, we tested for presence of reverse causation at the level of site-specific cancer mortalities. After excluding individuals with less than 2 years follow-up or deaths in the first 2 years after the diagnosis of type 2 diabetes, among women, there were again associations between BMI and deaths from endometrial (HR per 5 kg/m$^2$: 1.43; 95% CI 1.26-1.61) and possibly ovarian (HR per 5 kg/m$^2$: 1.13; 95% CI 1.01-1.27) cancers (Table S4). Previous inverse associations between BMI and pancreatic cancer deaths were now null, and associations with lung cancer deaths attenuated but remained inverse.

Among men, again, there were no associations between BMI and deaths from most site-specific cancers examined (Table S4). Similar to women, previous inverse associations between BMI and pancreatic cancer deaths were now null, and associations with lung cancer deaths attenuated but remained inverse.

## 3.5 | Sensitivity analysis

We repeated the analyses of the relationships between peri-diagnosis BMI and site-specific cancer deaths in women and men as complete case analyses. We found the risk estimates were broadly similar to those estimates for most cancer types in the multiple imputation models (Table S5). However, there were notable new positive associations in women for deaths from kidney (HR per 5 kg/m$^2$: 1.18; 95% CI 1.05-1.33) and breast (HR per 5 kg/m$^2$: 1.06; 95% CI 1.01-1.11) cancers, and in men for deaths from prostate cancer (HR per 5 kg/m$^2$: 1.08; 95% CI 1.02-1.15).

We examined for differences between estimates from models A, B and C, and found broadly similar findings (Table S6).

We adjusted for age as a quadratic function (age$^2$) and conducted analysis with age as the time scale and found similar patterns of associations as in the main models (data not shown).

## 3.6 | All cause and other causes of death

There were 25 048 deaths from any cause (10 633 in women; 14 415 in men). We observed the obesity paradox for the association between peri-diagnosis BMI and all-cause mortality (Table S7). There were 9167 deaths from CVD (3697 in women; 5470 in men). We observed no association between elevated BMI and increased risk of CVD mortality in women (per 5 kg/m$^2$: 1.02; 95% CI 1.00-1.04) but a

positive association between BMI and CVD mortality in men (HR per 5 kg/m$^2$: 1.06; 95% CI 1.04-1.07) (Table S8).

We tabulated the numbers and proportions of deaths attributed to cancer, CVD and non-cancer non-CVD (Table 2). In women, the proportion of deaths from CVD did not increase across BMI categories. However, there was an increasing trend in the proportion of deaths from CVD with increasing BMI in men (30.8% for BMI 18.5-22.4 kg/m$^2$ to 43.6% for BMI 40.0-59.9; $p < .001$).

Death was also modelled as an endpoint to compare the cause-specific HRs calculated as CIFs. Individuals were categorized as normal weight, overweight (BMI 25.0-29.9 kg/m$^2$) or obese (BMI 30.0-59.9 kg/m$^2$). Stacked CIF plots suggested that deaths from CVD, cancer and non-CVD non-cancer were similar across BMI categories in men and women (Figure S1). Absolute and relative CIFs at 17 years demonstrated similar proportions of deaths from CVD, cancer and non-CVD non-cancer causes across BMI categories.

## 4 | DISCUSSION

We examined the relationship between peri-diagnosis BMI and cancer mortality in individuals with incident type 2 diabetes in a large cohort and reported four main findings. First, among women, in never smokers, we found a positive association between peri-diagnosis BMI and ORC mortality. There were positive associations between BMI and type-specific cancer mortality risks for endometrial and ovarian cancers. Second, among men, in never smokers and accounting for reverse causation, we found no associations between peri-diagnosis BMI and risks for ORC mortality. Third, we found no associations between peri-diagnosis BMI and non-ORC mortality in either gender arguing that the associations between BMI and cancer mortality are specific for obesity-related cancers. Fourth, the proportions of deaths attributed to CVD increased with increasing BMI in men but not women. This may be a competing risk for death and may partly explain the lack of association between BMI and cancer mortality in men.

We identified four published studies that evaluated the associations between peri-diagnosis BMI and cancer mortality, respectively, from Japan (N = 3851),[12] the Netherlands (N = 1353),[13] Taiwan (N = 89056)[14] and Sweden (N = 26953).[15] To our knowledge, our study, which included 175 919 individuals, is the largest addressing this question. Previous studies have used prevalent[12-14] or mixed incident-prevalent[15] diabetes cohorts, such that subsequent modelling fails to account for age at diagnosis and diabetes duration.

Our findings that associations between peri-diagnosis BMI and ORC mortality were apparent in women but not men are consistent with the findings from the Ohkuma and colleagues (a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million cancer incident events).[9] They found that cancer incidence risk was greater among women than men. In that analysis, men with type 2 diabetes were at increased risk of cancer compared with men without diabetes. While cancer mortality is conditional on cancer incidence, additional factors such as cancer stage, treatment and competing risks, may ultimately influence mortality risk.

Drake et al.[15] performed a competing risk analysis using cause-specific HRs and sub-distribution HRs to evaluate actual risk of total and ORC incidence and mortality. They considered all non-cancer deaths as competing events for cancer incidence and mortality and concluded that competing risk might lower cancer incidence among patients with type 2 diabetes. They were concerned that if competing events are not accounted for (particularly in individuals with long-term or severe type 2 diabetes), then cancer risk may be overestimated. We have observed this in other settings.[22] However, they did not specifically evaluate CVD mortality. We examined this question and found that the proportion of CVD deaths increased across BMI categories in men, but not in women.

In the link between obesity and cancer, three biological mechanisms are speculated - namely altered sex hormones, hyperinsulinaemia and insulin resistance, and subclinical inflammation.[23] These might equally apply in the links between diabetes and cancer risk. In addition, there are hypothesized diabetes-specific mechanisms such as the recognized reduced mean serum testosterone levels in diabetes and the reduced risk of prostate cancer. Currently, these are hypotheses and not targets for clinical interventions.

The study has several strengths. First, the large cohort size ensured that several cancer types had a sufficient sample size for secondary analyses. Second, we used a validated algorithm,[17] which combines diagnostic codes, administrative codes and medications, to classify type 2 diabetes, thus reducing misclassification bias. Third, we use multiple imputation methods not only to improve precision of estimates as the use of complete case analysis in real-world case tends to overestimate risk[24] and the alternative use of missing indicator analysis is associated with unpredictable biases.[25] Fourth, a priori, based on the approach by Tobias et al.,[16] we reported results in never smokers and excluding deaths in the first 2 years (to account for reverse causation). While this approach derives a selective cohort, it also derives a cohort with fewer confounders and effect modifiers. Fifth, we performed several sensitivity analyses, including adjusting for age, age$^2$ and age as the time scale, and found no material difference. Sixth, we linked our data to the national mortality registry to classify cancer deaths and other causes of deaths as potential competing risks. Finally, we ran 'internal checks' on our data; for example, associations between peri-diagnosis BMI and all-cause mortality and with CVD mortality were consistent with much of the literature.

Our study has limitations. First, follow-up was relatively short. The links between BMI and cancer risk in the general population typically manifests after a decade of follow-up.[11] Second, a single measure of peri-diagnosis BMI was used that might be a crude approximation of long-term body fatness. Multiple measurements of BMI and a time-varying model would be appropriate; however, peri-diagnosis BMI has been shown to be a useful predictor for all-cause mortality and CVD mortality in individuals with type 2 diabetes.[26,27] Third, there was multiple statistical testing such that some of our significant findings might have occurred by chance. Fourth, a high proportion of the individuals with type 2 diabetes were diet-controlled (approximately half at onset) such that severe diabetes might have been underrepresented. Future studies will evaluate, for example,

individuals with type 2 diabetes and on antidiabetes therapies and cancer incidence and mortality.

The clinical implications of our study should be viewed in light of the recent work published by Pearson-Stuttard and colleagues,[8] using the UK Clinical Practice Research Datalink (CPRD) (2001-2018), linked with the ONS mortality data, reported that cancer may be emerging as the leading cause of death in type 2 diabetes after CVD, at least in the UK. Specifically, while deaths due to CVD declined over two decades, and the absolute number of deaths due to cancer also reduced, the diabetes associated contribution gap widened for cancer. Pearson-Stuttard et al.[8] argued that the overall declines in deaths are probably due to 'improvements in treatment pathways, risk factor management, and lifestyle behaviours'. However, these clinical interventions may differentially impact upon CVD deaths compared with cancer. Thus, future efforts aimed at preventing deaths in individuals with type 2 diabetes need to be broader and think about cancer prevention strategies. There were also increased proportions of deaths due to dementia and liver disease over time - and these need to be considered in the broader prevention approach.[8]

There are at least two key unanswered questions from this study. First, a once-only determination of BMI at diabetes diagnosis is probably a crude approximation of adiposity exposure. Alternative approaches, such as obese-year metrics[28] might be more informative. Second, there is a need to address whether severity of type 2 diabetes and glycaemic control is relevant to cancer mortality risk as this will better inform how to shape therapeutic approaches to reduce cancer deaths. This question requires more sophisticated statistical models, such as marginal structural models, to account for time-varying drug exposures, covariates such as BMI and glycated haemoglobin, as the latter two may act as both confounders and causal pathway variables.[29]

## 5 | CONCLUSION

Among patients with type 2 diabetes, our findings add information to the rationale for weight control management and serve as a baseline for future research evaluating competing causes for cancer death, particularly as evidence is emerging that cancer may be the leading cause of death ahead of CVD, in some countries.

### ACKNOWLEDGMENTS

We acknowledge the support of statistical and support staff, and other researchers at Vaughan House, Health eResearch Centre, University of Manchester and the Manchester Cancer Research Centre for the constant culture to attain high-quality research. This work was supported by CRUK via the funding to Cancer Research UK Manchester Centre: (C147/A18083 and C147/A25254). AGR is supported by the Manchester NIHR Biomedical Research Centre (IS-BRC-1215-20 007).

### CONFLICT OF INTEREST

AGR has received lecture honoraria from Merck Serona and Janssen-Cilag, and independent research funding and lecture honoraria from Novo Nordisk and Sanofi Pasteur MSD. DMA has received independent research funding from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Novartis, UCB, and the Leo Foundation. Dr. Buchan reports personal fees and other from Microsoft Research, outside the submitted work. MKR reports receiving consultancy and speaker fees from Novo Nordisk and consultancy fees from Roche Diabetes Care, and modest owning of shares in GlaxoSmithKline, all outside the submitted work. All other authors declare that they have no competing interests.

### AUTHOR'S CONTRIBUTIONS

Andrew G. Renehan and Matthew Sperrin conceived the project. Andrew G. Renehan, Matthew Sperrin and Darren M Ashcroft are the joint principal investigators for the study. Nasra N. Alam is the clinical research fellow and is responsible for management of the project. Nasra N. Alam and Alison K Wright conducted the analyses. Andrew G. Renehan, Matthew Sperrin Darren M Ashcroft and Martin K. Rutter provided supervision and had input to all aspects of the project. Nasra N. Alam wrote the first draft of the manuscript. All authors critically revised the manuscript. All authors confirm that they meet ICMJE criteria for authorship.

### PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14614.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ETHICS STATEMENT

This study is based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The study was approved by the independent scientific advisory committee (ISAC) for Clinical Practice Research Datalink research (protocol number: 17_137R). Mortality data from the Office for National Statistics (2018) and inpatient secondary-care Hospital Episode Statistics© (2018) were re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The interpretation and conclusions contained in this study are those of the authors alone.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Alam NN, Wright AK, Rutter MK, et al. Body mass index and cancer mortality in patients with incident type 2 diabetes: A population-based study of adults in England. *Diabetes Obes Metab*. 2022;24(4):620-630. doi:10.1111/dom.14614