# Risk factors for COVID-19 related mortality in people with Type 1 and Type 2 diabetes in England: a population cohort study

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**Abstract**

Background

Diabetes has been associated with higher COVID-19 related mortality, but the relationship between modifiable risk factors, including hyperglycaemia and obesity, with COVID-19 related mortality among people with diabetes is unclear.

Methods

National population data on people with Type 1 and Type 2 diabetes in England were linked to mortality records from 2nd January 2017 to 11th May 2020. The associations between risk factors and COVID-19 related mortality were investigated by Cox proportional hazards models.

Findings

Between 16th February and 11th May 2020, weekly death registrations in people with Type 1 and Type 2 diabetes exceeded the corresponding 2017-19 three-year weekly averages by 50·9% and 64·3% respectively. Among 264,390 people with Type 1 and 2,874,020 people with Type 2 diabetes, there were 464 and 10,525 COVID-19 related deaths respectively, of which 62·3% and 55·4% occurred in people with prior cardiovascular or renal disease. Older age, renal impairment, non-white ethnicity and previous stroke and heart failure were associated with higher COVID-19 related mortality. The hazard ratio (HR) for people with an HbA1c ≥86mmol/mol compared to 49-53mmol/mol was 2·23 (95% CI 1·50-3·30) in Type 1 diabetes and 1·61 (1·47-1·77) in Type 2 diabetes. The relationship between body mass index (BMI) and COVID-19 related mortality was U-shaped. Compared to a BMI of 25-29·9kg/$m^2$, the HRs for a BMI <20kg/$m^2$ and BMI ≥ 40 kg/$m^2$ were 2·45 (1·60 – 3·75) and 2·33 (1·53-3·56) respectively for Type 1 and 2·33 (2·11-2·56) and 1·60 (1·47-1·75) respectively for Type 2 diabetes.

Interpretation

Deaths in people with Type 1 and Type 2 diabetes rose sharply during the initial COVID-19 pandemic in England. Higher COVID-19 related mortality was associated not only with cardio-renal complications of diabetes but, independently, with glycaemic control.

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**Research in context**

**Evidence before this study**

From March 2020, we performed weekly searches of PubMed and MedRxiv using the terms COVID-19, SARS-CoV-2, coronavirus, SARS virus and diabetes. Although previous studies have identified diabetes as a risk factor for mortality with COVID-19 in selected populations, it is unclear whether that increased risk is found in all types of diabetes and whether the association with diabetes is confounded by other known risk factors such as age, male sex, social deprivation, black, Asian and minority ethnic (BAME) ethnicity, obesity, renal disease, hypertension and cardiovascular disease. The detailed relationship between the level of prior glycaemic control and COVID-19 related mortality in people with diabetes in a population-based study, stratified by the two main types of diabetes with comprehensive inclusion of potential confounders, has not previously been investigated systematically.

**Added value of this study**

This population cohort study of people with diagnosed diabetes in England demonstrated that the COVID-19 pandemic was associated with a sharp rise in mortality in people with both Type 1 and Type 2 diabetes compared to the same time of year in the previous three years. Many, but not all, additional deaths had COVID-19 recorded on the death certificate. The study further demonstrated that COVID-19 related mortality in people with both Type 1 and Type 2 diabetes was associated not only with the risk factors found in all people i.e. age, male sex, social deprivation, non-white ethnicity, established cardiovascular disease and impaired renal function, but also with the level of preceding hyperglycaemia (HbA1c) and with both obesity and underweight. Raised preceding blood pressure was associated with lower COVID-19 related mortality but in people with Type 2 diabetes treatment for hypertension was associated with very slightly higher risk while statin therapy was associated with a lower risk. By using a contemporary comparison of mortality and risk factors in people with diabetes who did and who did not have recognised COVID-19 related death, similarities and differences in associations with risk factors were observed.

**Implications of all the available evidence**

Improved achievement of standard diabetes care recommendations that target prevention of cardio-renal, lower limb and ocular complications may also serve to modify some of the risk factors that we have found to be associated with COVID-19 mortality. It would seem important therefore to further strengthen clinical services

that support people with diabetes in achieving and sustaining effective self-management.

## Introduction

By 11th May 2020, 4,252,290 people worldwide, from 213 countries and territories, were known to have had Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 infection, and 287,131 had died.[1] One third of COVID-19 deaths in hospital have been in people with diabetes.[2] This excess burden in people with diabetes is similar to previous coronavirus epidemics; the prevalence of diabetes was approximately 50% in Middle East respiratory syndrome (MERS), and in severe acute respiratory syndrome (SARS), diabetes was an independent predictor of mortality and morbidity.[3-6]

Diabetes, cardiovascular disease and hypertension are the most common chronic co-morbidities in people with severe COVID-19.[7-16] We present two papers as linked publications. In the other paper, we demonstrate that the odds of dying in hospital with COVID-19 were 3·51 (95% CI 3·16-3·90) for Type 1 diabetes and 2·03 (1·97-2·09) for Type 2 diabetes compared to those without diagnosed diabetes.[2] An association between in-hospital hyperglycaemia and poorer outcomes with COVID-19 has been suggested, [12, 13] and hyperglycaemia is associated with increased severity of other infections.[18, 19] Although one study found preceding glucose control to be a risk factor,[20] others did not.[15, 17] It is possible that hyperglycaemia may modulate the hyperimmune response found in life-threatening COVID-19.[21]

For this paper, we analysed COVID-19 related mortality by diabetes type from a cohort consisting of 98% of all people with diagnosed diabetes in England using a national dataset linked to national civil death registrations (hospital and community). We report weekly mortality before and during the pandemic and investigate the associations between risk factors and COVID-19 related mortality.

## Methods

### Data sources

The National Diabetes Audit (NDA) has collated data on people with diagnosed diabetes registered with a healthcare provider in England since 2003 (see Supplementary information for full details). [22] These data were linked using unique NHS number to Hospital Episode Statistics (HES), a record of all hospital admissions in England, and to civil death registrations collated by the Office for National Statistics (ONS).

The legal basis for the NDA data collection and linkage is a Direction from NHS England to NHS Digital according to section 254 of the Health and Social Care Act (HSCA) for England 2012.[23] Data are not extracted if the person has registered their dissent from permission to use their record for secondary analysis which is

estimated to apply to less than 1% of records.[24] NHS England and NHS Digital are the joint data controllers. Data linkage and analysis are undertaken within NHS Digital. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure.

Study population, observation period and outcomes

Individuals included in any NDA data collection were used to quantify the number of deaths from all causes in all settings, registered each week during the first 19 weeks of 2017, 2018, 2019 and 2020.

The study population comprised individuals with Type 1 or Type 2 diabetes from the latest full extract of the NDA, covering the period 1st January 2018 to 31st March 2019, whose most recent General Practice was in England and who were alive on 16th February 2020. People with a recorded date of birth giving an age of 110 or greater were excluded from the analysis. Individuals were linked to HES (data available from 1st April 2017 to 31st December 2019) and to ONS recorded deaths between 16th February and 11th May 2020. COVID-19 related death was defined as a death where an International Classification of Diseases (ICD) version 10 code U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified) was recorded as either a primary underlying or secondary cause of death.

Definitions of exposures

Age was grouped as <40 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years and ≥80 years. Social deprivation was defined by the Indices of Multiple Deprivation 2019 based on individual home postcode.[26] Ethnicity was classified as Asian, black, mixed, white, other ethnic groups, or missing. Individuals were allocated to one of seven regions based on their home postcode to adjust for the geographical variation in SARS-CoV-2 exposure in England.

We included data on the latest HbA1c, systolic blood pressure, total serum cholesterol and estimated glomerular filtration rate (eGFR) recorded between 1st January 2019 and 31st December 2019. HbA1c data was categorised as <48 mmol/mol, 48-53 mmol/mol, 54-58 mmol/mol, 59-74 mmol/mol, 75-85 mmol/mol, and ≥86 mmol/mol or missing. Systolic blood pressure was categorised as ≤ 140mmHg, >140mmHg or missing and serum total cholesterol as <5mmol/l, ≥5mmol/l or missing. People who had received one or more prescriptions for anti-

hypertensive drugs or statins between 1st January and 31st December 2019 were identified from General Practice prescribing records. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate eGFR and results were grouped as <15ml/min/1.73m$^2$, 15-29ml/min/1.73m$^2$, 30-44ml/min/1.73m$^2$, 45-59 ml/min/1.73m$^2$, 60-89ml/min/1.73m$^2$ and ≥90ml/min/1.73m$^2$ or missing. Body mass index (BMI) and smoking status were identified using the latest recorded measurement between 1st January 2017 and 31st December 2019. BMI was grouped as <20 kg/m$^2$, 20-24·9 kg/m$^2$, 25-29·9 kg/m$^2$, 30-34·9 kg/m$^2$, 35-39·9 kg/m$^2$, ≥40 kg/m$^2$ or missing. Smoking status was identified as current smoker, ex-smoker, non-smoker (not a current smoker but not known if they previously smoked), never smoker or missing.

A history of myocardial infarction (ICD-10 codes I21-22), stroke (ICD-10 codes I61, I63-64 and I67.9) and heart failure (ICD-10 code I50) were identified from HES between 1st April 2017 and 31st December 2019 as either the primary or one of up to 14 secondary diagnoses.

Statistical analysis

The weekly number of deaths in people with Type 1 and Type 2 diabetes during the first 19 weeks of 2020 were identified. The percentage change from the mean number of deaths for the corresponding weeks in 2017, 2018 and 2019 was calculated.

We created Cox proportional hazards survival analysis models with COVID-19 related death as the outcome for Type 1 and Type 2 diabetes respectively. Deaths without COVID-19 recorded on the death certificate were treated as a censoring event. A corresponding model was created with death without COVID-19 recorded as the outcome and deaths from COVID-19 treated as a censoring event. Hazard ratios (HRs) associated with demographic characteristics (age, sex, social deprivation, ethnicity, region of residence), clinical characteristics (HbA1c, duration of diagnosed diabetes, BMI, systolic blood pressure, prescription for anti-hypertensive drugs, total serum cholesterol, prescription for statins, smoking status), and co-morbidities (history of myocardial infarction, stroke, heart failure and eGFR) were identified for people with Type 1 and Type 2 diabetes. Kaplan-Meier curves and plots of Schoenfeld residuals were created to assess the proportionality of hazard over time for each variable included in the models. The large cohort size meant that plots were restricted to random samples of 10,000. Separate models were run for males, females, those aged less than 70 years and those aged 70 and older. Given the greater numbers of people with Type 2 diabetes compared to Type 1 diabetes, individual models were run for each ethnicity, social deprivation quintile and BMI category in those with Type 2 diabetes.

Sensitivity analyses were undertaken restricting the definition of COVID-19 related death to those where it was identified only as the primary cause of death, and separately to deaths where only the code U07.1 was used.

Statistical significance was defined as p-value <0.05 and confidence intervals (CI) were set at 95%. Statistical calculations were undertaken in SAS Enterprise Guide 7.1 (https://support.sas.com/en/software/enterprise-guide-support.html). All numbers taken directly from the National Diabetes Audit are rounded to the nearest five persons to protect confidentiality.

**Results**

Between 16th February 2020 and 11th May 2020 there were 1604 and 36,291 deaths from all causes in people with Type 1 and Type 2 diabetes respectively. A total of 10,989 deaths (464 Type 1 and 10,525 Type 2 diabetes) had COVID-19 included on the death certificate of which 10,417 (94·7%) had COVID-19 as the underlying cause of death. Comparison of the weekly number of deaths registered in people with Type 1 and Type 2 diabetes in 2020 with the previous three years showed an increase in mortality from mid-March 2020 (Figure 1). In this same period, the number of death registrations exceeded the mean number of deaths for the corresponding weeks in 2017, 2018 and 2019 by 672 (50·9%) and 16,071 (64·3%) in people with Type 1 and Type 2 diabetes respectively. Of the additional deaths, 70·0% and 68·3% had COVID-19 recorded on the death certificate.

There were 264,390 people with Type 1 diabetes and 2,874,020 people with Type 2 diabetes included in the NDA and alive on the 16th February 2020, and therefore included in the survival analysis. The characteristics of these people are provided in Table 1; the mean ages were 46·6 years (standard deviation 19.6) for Type 1 and 67·5 years (standard deviation 13.4) for Type 2 diabetes. Of the people with Type 1 diabetes 5·6% were of Asian ethnicity and 3·5% of black ethnicity. For Type 2 diabetes, the corresponding figures were 14·0% and 4·8% respectively. Among people with Type 1 diabetes, 11·4% had a last reported HbA1c of 75-85 mmol/mol and 11·8% ≥86 mmol/mol. A quarter (25·1%) of people with Type 2 diabetes had a last reported HbA1c of <48mmol/mol and 6·1% ≥86 mmol/mol. A history of cardiovascular or renal disease (defined as myocardial infarction, stroke, heart failure or eGFR < 60 ml/min/1.73m$^2$) was found in 12·0% of those with Type 1 diabetes and 21·7% of people with Type 2 diabetes (Table 1).

Results from the survival analysis showed that older age and male sex were associated with higher COVID-19 related mortality for both Type 1 and Type 2 diabetes (Figure 2). In Type 1 diabetes, COVID-19 related mortality was higher in black and Asian ethnicities compared to those of white ethnicity, with HRs of 1·77 (95%

CI 1·25-2·49) and 1·57 (1·16-2·12) respectively. There was no significant difference for those of mixed ethnicity. In Type 2 diabetes, risks were higher in people of black, Asian and mixed ethnicities with HRs of 1·63 (1·51-1·77), 1·08 (1·01-1·15) and 1·30 (1·10-1·55) respectively (Figure 2). The higher HRs for COVID-19 related mortality in people from all non-white ethnicities (apart from mixed ethnicity in Type 1 diabetes) contrasts with lower HRs for non-COVID-19 related mortality during the same period (see Supplementary information, Table S2). All non-white ethnicity HRs for COVID-19 related death were higher in people aged <70 years (Supplementary information, Table S5).

There was a clear relationship between COVID-19 related death and social deprivation among people with diabetes of either type. The HR for COVID-19 related mortality for people with Type 1 diabetes in the most deprived quintile was 1·93 (1·36–2·72) compared to people living in the least deprived quintile. For Type 2 diabetes, the HR was 1·46 (1·37-1·56), significantly higher than observed for non-COVID-19 related mortality (1·26, 1·21-1·32). The HR gradient between social deprivation and COVID-19 related mortality was steeper in those of Asian ethnicity (Supplementary information, Table S6) with a HR of 2·17 (1·68-2·81) for the most deprived quintile compared to the least deprived.

Preceding hyperglycaemia was strongly associated with COVID-19 related death after adjusting for other risk factors. Compared to those whose latest HbA1c was 49-53mmol/mol, HRs were 1·22 (1·15–1·30) and 1·61 (1·47-1·77) for those with Type 2 diabetes whose most recent HbA1c was 59-74 mmol/mol and ≥86mmol/mol respectively. Though a similar pattern was seen in people with Type 1 diabetes, statistical significance was only achieved in those whose most recent HbA1c ≥ 86 mmol/mol (2·23 (1·50-3·30)). The HR for low HbA1c (<48mmol/mol) was 1·11 (1·05–1·18) in people with Type 2 diabetes and was similar, but not significant, in people with Type 1 diabetes (1·37 (0·89–2·09)). For those with Type 2 diabetes, the gradient of the HRs between HbA1c level and COVID-19 related mortality was steeper in those aged < 70 years (see Supplementary information, Table S5).

There was a U-shaped relationship between COVID-19 related mortality and BMI. For those with Type 1 diabetes compared to a BMI 25-29.9 kg/m$^2$, the HRs for BMIs <20 kg/m$^2$, 35-39·9kg/m$^2$ and ≥40 kg/m$^2$were 2·45 (1·6 –3·75), 1·72 (1·21-2·46) and 2·33 (1·53-3·56) respectively. For Type 2 diabetes, the corresponding HRs were 2·33 (2·11-2·56), 1·17 (1·08-1·26) and 1·60 (1·47-1·75) respectively. This pattern of risk differed from that observed for non-COVID-19 related deaths during the same period, where a BMI 35-39·9 kg/m$^2$ was not associated with higher mortality (see Supplementary information, Table S2). The HRs associated with

obesity were significantly greater in people aged < 70 compared to those ≥ 70 years (see Supplementary information, Table S5).

Impaired renal function was associated with higher HRs for COVID-19 related death. Individuals with Type 1 diabetes and impaired renal function (eGFR of 30-44 mL/min/1.73m$^2$) had a HR of 2·46 (1·72-3·52) compared to those with eGFR ≥90 mL/min/1.73m$^2$, while the HR for an eGFR of less than 15 mL/min/1.73m$^2$ was 8·35 (5·50–12·7). The corresponding HRs for people with Type 2 diabetes were 1·76 (1·63-1·89) and 4·91 (4·34-5·56) respectively. Impaired renal function was associated with even greater hazard ratios in younger people (aged < 70 years) and those of Asian ethnicity (see Supplementary information, Tables S5, S6).

Previous hospital stays for stroke or heart failure were associated with increased COVID-19 related mortality in both Type 1 and Type 2 diabetes, and for myocardial infarction in Type 2 diabetes (see Figure 2). In people with Type 2 diabetes a history of one or more prescriptions for anti-hypertensive drugs was associated with higher COVID-19 related mortality whilst a prescription for statins was associated with lower mortality. A history of cardiovascular or renal disease was present in 62·3% and 55·4% of COVID-19 related deaths in Type 1 and Type 2 diabetes respectively.

After adjustment for other risk factors, being a current smoker with Type 2 diabetes was associated with lower COVID-19 related mortality (0·67, 0·62–0·74). This finding was consistent across all ethnicities, social deprivation, and BMI categories and more marked in those aged < 70 (See Supplementary information, Table S5, S6, S7 and S8). This contrasted with the HR for current smokers of 1·40 (1·34-1·47) for non-COVID-19 related deaths in the same time period (Supplementary information, Table S2).

In a sensitivity analysis, if deaths were limited to only those with COVID-19 recorded as a primary cause or to only those using the ICD-10 code U07.1 (indicating a positive test for the SARS-CoV-2 virus) the results of the survival models were not materially different (Supplementary information, Table S3).

**Discussion**

We have demonstrated in an analysis of more than 98% of people with diagnosed Type 1 and Type 2 diabetes in England, that there was a rapid and sizeable increase in deaths from all causes in people with Type 1 and Type 2 diabetes after the emergence of COVID-19. The data suggest that, at the peak, approximately 3,500 additional deaths per week occurred in people with diabetes, the majority of which had COVID-19 recorded on the death certificate.

There was an independent association between HbA1c and COVID-19 related mortality in both types of diabetes. In people with Type 2 diabetes, risk was significantly higher in those with an HbA1c ≥58mmol/mol than in those with an HbA1c 49-53 mmol/mol and increased with higher HbA1c levels. In one study of an undifferentiated population of people with diabetes,[20] deaths from COVID-19 were higher if preceding HbA1c was ≥58mmol/mol but no relationship was found in three other studies, possibly due to small sample sizes.[13, 15, 17] Our observations show that the risk of COVID-19 related mortality is significantly and independently related to the preceding level of hyperglycaemia in people with Type 1 and Type 2 diabetes and in Type 2 diabetes this risk relationship is steeper in those aged < 70 years. Hyperglycaemia is known to impair host defences including granulocyte and macrophage function. People with diabetes are at increased risk of many serious infections.[18] Poor glycaemic control has been associated with serious infections and hospitalisation[19] and is hypothesised to amplify the hyperimmune response associated with severe COVID-19.[21]

With respect to the other cardiometabolic targets of routine diabetes care, higher systolic blood pressure was weakly associated with lower COVID-19 related death, whereas treatment of hypertension was associated with higher mortality and prescription of statins with lower mortality. Whilst these data are of interest, it is impossible to draw conclusions about the potential direct impacts of anti-hypertensive drugs or statins on COVID-19 related mortality. However, as these medications prevent cardiovascular and renal disease, their continued use will help lessen not only non-COVID-19 related mortality but may contribute to reducing future COVID-19 related mortality.

The independent association of BMI with risk of COVID-19 related death in these diabetes populations was U-shaped, with a nadir at a BMI 25-29·9 kg/m$^2$. The higher risk seen in people with lower BMI may reflect confounding by factors that are associated with weight loss either not included in our analysis (unmeasured confounding) or for which we have only imperfectly adjusted (residual confounding). The elevated risk of COVID-19 related death in people with diabetes and obesity is significant and differs from that observed in non-COVID-19 related deaths in the same period. The excess risk associated with higher BMI is also more marked in younger people and those of Asian and black ethnicity. This evidence adds to other reports indicating that obesity is an important risk factor for death from COVID-19.[21] However, the association detected between BMI ≥40 kg/m$^2$ and COVID-19 related mortality in people with Type 2 diabetes (HR 1·60 (95% CI 1·47-1·75)) was less than in a study of the general English population (HR 1·92 (95% CI 1·72-2·13)[20] and weaker than we observed in people with Type 1 diabetes (HR 2·33 (95% CI 1·53-3·56)). If the mechanisms behind this association involve, as speculated,[21] metabolic abnormalities linked to excess ectopic fat, the pathway to

developing Type 2 diabetes, then an attenuated association of obesity with mortality risk may be expected in those who already have Type 2 diabetes. Several of the independent associations with COVID-19 related death are risk factors which are not readily clinically modifiable (age, sex, ethnicity and social deprivation) and mirror findings in other recent analyses.[7-12,16-17,20]

Our comparison with deaths in the same period in which COVID-19 was not recorded highlights the importance of these risk factors. While the effect of age is similar, male sex and socio-economic deprivation have a steeper relationship with COVID-19 related mortality than with other causes of mortality. The higher COVID-19 related mortality risk seen in people with diabetes from black or Asian ethnic groups is a reversal of the pattern seen in non-COVID-19 related deaths during the period examined and in observations of mortality pre-pandemic.[27] By contrast the associations of previous myocardial infarction, stroke and heart failure with COVID-19 related mortality were similar to those for other deaths but established renal disease appeared to have stronger association with COVID-19 related mortality.

Current smoking, compared to having never smoked, was associated with a lower risk of COVID-19 related mortality. This is the reverse of what was observed in non-COVID-19 related mortality and has been described elsewhere.[20] It was seen across all BMI categories and all ethnicities. Being an ex-smoker was associated with a higher risk of both COVID-19 related and non-COVID-19 related mortality. This unexpected finding may be the result of confounding by yet unidentified factors or collider bias, and it should not be inferred at this stage that smoking is protective, although another condition characterised by abnormal inflammation, ulcerative colitis, has shown protective effects of smoking.[28] More research is needed into this finding.

Comparison with other studies

One retrospective study from 88 US hospitals of 451 people with COVID-19 and diabetes or hyperglycaemia reported that uncontrolled hyperglycaemia was associated with longer length of stay and higher mortality.[12] However, the definition of diabetes was unclear, and this was contemporary rather than preceding hyperglycaemia. Another retrospective study from China of 952 people with Type 2 diabetes (total cohort 7337) reported that well controlled inpatient blood glucose (glycaemic variability within 3·9 to 10·0 mmol/L) was associated with a lower in-hospital mortality compared to individuals with poorly controlled glycaemia (adjusted HR, 0·14).[13] Recent publications from France[17] and China,[15] of modest non-population-based cohorts of people with Type 2 diabetes did not find any relationship between HbA1c and COVID-19 outcome. The OpenSAFELY Collaborative[20] also took a population approach linking English primary care data from

approximately 17 million individuals to COVID-19 related mortality data. Diabetes (type not specified) was independently associated with a higher risk of death, with an adjusted HR of 1·31 for those with HbA1c <58mmol/mol, and of 1·95 for those with HbA1c ≥58mmol/mol. Our work has established a strong case that the level of preceding hyperglycaemia in people with both Type 1 and Type 2 diabetes is an independent risk factor for whole population COVID-19 related mortality (in the community and in hospital).

Strengths and limitations

A strength of our study is that it includes nearly all people with diagnosed Type 1 and Type 2 diabetes in England and data regarding risk factors from prior to the COVID-19 pandemic. The results are therefore likely to be applicable to other countries with similar populations and healthcare systems. The analysis of mortality among people with diabetes who died without a diagnosis of COVID-19 provides a valuable comparison group. However, potential limitations of comparing deaths with an infectious, mainly pulmonary disease (albeit leading to systemic harm), with deaths predominantly due to cardiovascular disease and cancers, should be acknowledged. It is noted that the number of deaths labelled as non-COVID-19 related (deaths without COVID-19 included on the death certificate) also rose during the study period. The ONS in England considers it likely that many of these additional deaths, highlighted in Figure 1, were due to undiagnosed COVID-19;[29] any under-recognition of COVID-19 related mortality will have attenuated the observed associations provided under-recognition was non-differential.

In our supplementary data, after stratifying the population by age the associations of HbA1c, BMI and renal impairment were somewhat stronger in younger people in whom co-morbidity and frailty are less prevalent. The variables included in this analysis were limited to those collated by the National Diabetes Audit which do not include many non cardiometabolic related comorbidities such as respiratory disease, liver disease, alcohol use or cognitive impairment, potentially leading to confounding due to lack of measurement. Residual confounding may also occur with a single measurement to identify baseline characteristics.

The lack of population level data on tests for COVID-19 means it is not possible to identify whether the associations between risk factors and COVID-19 related mortality are due to increased susceptibility to infection, more severe illness following infection or a combination of both. Our endpoint of all deaths where COVID-19 was identified as a cause of death provides a measure of disease severity independent of clinical decisions, administrative arrangements and resource availability, which are all possible influences on hospital admissions, ICU admissions or exclusively in-hospital deaths.

## Conclusion

While several risk factors identified for COVID-19 related mortality in people with diabetes cannot readily be modified, HbA1c can be influenced by healthcare interventions. Although the association with obesity was more complex, particularly in the Type 2 diabetes population, weight can also be influenced by healthcare interventions and is a goal of routine care. Improved achievement of standard diabetes care recommendations that target prevention of cardio-renal, lower limb and ocular complications would also serve to modify some of the risk factors that we have found to be associated with COVID-19 related mortality. The nature of the COVID-19 pandemic means it would be implausible to seek randomised controlled trial evidence that improving achievement of diabetes care treatment targets would result in better outcomes in people with diabetes. However, there is every reason to advocate continued adherence to guidance. It would seem important to further strengthen clinical services that support people with diabetes in achieving and sustaining effective self-management.

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NHS England & Improvement and NHS Digital provided resources for these analyses.

**Authors contributions**

JV, BY, NS, KK, NH, EB, PK conceived the study. NH, PK, JO, MC, EB, AW managed the data and carried out the statistical analysis. All the authors collaborated in interpretation of the results and drafting of the manuscript.

**Conflicts of Interest**

Jonathan Valabhji is National Clinical Director for Diabetes and Obesity at NHS England & Improvement. Partha Kar is National Specialty Advisor for Diabetes and Obesity at NHS England & Improvement. Bob Young is Clinical Lead for the National Diabetes Audit and a trustee of Diabetes UK. Kamlesh Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. K.K. has also received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Pfizer and Boehringer Ingelheim and has served on advisory boards for Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). NH carries out Diabetes UK funded research. Emma Barron is Head of Health Intelligence (Diabetes), Public Health England. Chirag Bakhai is Primary Care advisor to the NHS Diabetes Programme. NS has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer and Sanofi and received grant support from Boehringer Ingelheim.

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**Tables and Figures**

Table 1: Baseline characteristics on 16th February 2020 and number (%) of subsequent COVID-19 related deaths in people with Type 1 (n= 264,390) and Type 2 diabetes (n=2,874,020) in England

| | Type 1 diabetes | | | | Type 2 diabetes | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | Deaths | % | n | % | Deaths | % |
| Sex | | | | | | | | |
| Male | 149,680 | 56·6% | 284 | 61·2% | 1,606,430 | 55·9% | 6456 | 61·3% |
| Female | 114,710 | 43·4% | 180 | 38·8% | 1,267,590 | 44·1% | 4069 | 38·7% |
| Age | | | | | | | | |
| <40 years | 100,860 | 38·1% | 6 | 1·3% | 67,845 | 2·4% | 24 | 0·2% |
| 40-49 years | 41,745 | 15·8% | 17 | 3·7% | 213,180 | 7·4% | 98 | 0·9% |
| 50-59 years | 9,220 | 18·6% | 56 | 12·1% | 520,480 | 18·1% | 485 | 4·6% |
| 60-69 years | 36,230 | 13·7% | 84 | 18·1% | 724,990 | 25·2% | 1274 | 12·1% |
| 70-79 years | 24,290 | 9·2% | 115 | 24·8% | 769,175 | 26·8% | 2694 | 25·6% |
| ≥ 80 years | 12,045 | 4·6% | 186 | 40·1% | 578,345 | 20·1% | 5950 | 56·5% |
| Deprivation | | | | | | | | |
| Most deprived | 56,280 | 21·3% | 133 | 28·7% | 700,915 | 24·4% | 2817 | 26·8% |
| 2nd most deprived | 54,260 | 20·5% | 106 | 22·8% | 641,610 | 22·3% | 2558 | 24·3% |
| 3rd least deprived | 53,345 | 20·2% | 109 | 23·5% | 575,030 | 20·0% | 1983 | 18·8% |
| 2nd least deprived | 51,360 | 19·4% | 67 | 14·4% | 513,925 | 17·9% | 1692 | 16·1% |
| Least deprived | 48,975 | 18·5% | 49 | 10·6% | 440,990 | 15·3% | 1468 | 13·9% |
| Missing | 175 | 0·1% | 0 | 0·0% | 1,555 | 0·1% | 7 | 0·1% |
| Region | | | | | | | | |
| London | 33,330 | 12·6% | 106 | 22·8% | 466,165 | 16·2% | 2557 | 24·3% |
| South West | 27,525 | 10·4% | 28 | 6·0% | 271,770 | 9·5% | 590 | 5·6% |
| South East | 41,540 | 15·7% | 42 | 9·1% | 401,810 | 14·0% | 1331 | 12·6% |
| Midlands | 53,210 | 20·1% | 120 | 25·9% | 584,905 | 20·4% | 2061 | 19·6% |
| East of England | 32,590 | 12·3% | 61 | 13·1% | 312,035 | 10·9% | 980 | 9·3% |
| North West | 32,170 | 12·2% | 52 | 11·2% | 373,310 | 13·0% | 1493 | 14·2% |
| North East | 43,850 | 16·6% | 55 | 11·9% | 462,480 | 16·1% | 1506 | 14·3% |
| Missing | 175 | 0·1% | 0 | 0·0% | 1,555 | 0·1% | 7 | 0·1% |
| Ethnicity | | | | | | | | |
| Asian | 14,725 | 5·6% | 60 | 12·9% | 403,355 | 14·0% | 1313 | 12·5% |
| Black | 9,310 | 3·5% | 47 | 10·1% | 137,695 | 4·8% | 884 | 8·4% |
| Mixed | 3,230 | 1·2% | * | - | 30,885 | 1·1% | 133 | 1·3% |
| Other | 4,035 | 1·5% | 11 | 2·4% | 47,570 | 1·7% | 164 | 1·6% |
| White | 210,415 | 79·6% | 314 | 67·7% | 1,897,575 | 66·0% | 7105 | 67·5% |
| Missing | 22,675 | 8·6% | 28 | 6·0% | 356,945 | 12·4% | 926 | 8·8% |
| HbA1c | | | | | | | | |
| <48 mmol/mol | 17,950 | 6·8% | 50 | 10·8% | 721,950 | 25·1% | 2789 | 26·5% |
| 49-53 mmol/mol | 21,550 | 8·2% | 38 | 8·2% | 591,815 | 20·6% | 1811 | 17·2% |
| 54-58 mmol/mol | 25,200 | 9·5% | 31 | 6·7% | 365,955 | 12·7% | 1151 | 10·9% |
| 59-74 mmol/mol | 77,380 | 29·3% | 133 | 28·7% | 551,530 | 19·2% | 1988 | 18·9% |
| 75-85 mmol/mol | 30,150 | 11·4% | 55 | 11·9% | 157,030 | 5·5% | 588 | 5·6% |
| ≥86 mmol/mol | 31,280 | 11·8% | 76 | 16·4% | 174,835 | 6·1% | 674 | 6·4% |
| Missing HbA1c | 60,885 | 23·0% | 81 | 17·5% | 310,905 | 10·8% | 1524 | 14·5% |
| Duration | | | | | | | | |
| < 1 year | 840 | 0·3% | * | - | 25,940 | 0·9% | 53 | 0·5% |
| 2-3 years | 14,690 | 5·6% | 6 | 1·3% | 378,905 | 13·2% | 728 | 6·9% |
| 4-5 years | 16,335 | 6·2% | * | - | 374,960 | 13·0% | 877 | 8·3% |
| 5-9 years | 37,465 | 14·2% | 18 | 3·9% | 792,110 | 27·6% | 2158 | 20·5% |
| 10-14 years | 39,940 | 15·1% | 45 | 9·7% | 628,730 | 21·9% | 2315 | 22·0% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15-20 years | 42,820 | 16·2% | 108 | 23·3% | 426,890 | 14·9% | 2378 | 22·6% |
| ≥20 years | 112,305 | 42·5% | 282 | 60·8% | 246,475 | 8·6% | 2016 | 19·2% |
| Body mass index | | | | | | | | |
| <20 kg/m$^2$ | 19,990 | 7·6% | 28 | 6·0% | 42,160 | 1·5% | 488 | 4·6% |
| 20-24·9 kg/m$^2$ | 73,950 | 28·0% | 109 | 23·5% | 398,390 | 13·9% | 2143 | 20·4% |
| 25-29·9 kg/m$^2$ | 82,005 | 31·0% | 107 | 23·1% | 905,290 | 31·5% | 2962 | 28·1% |
| 30-34·9 kg/m$^2$ | 42,095 | 15·9% | 98 | 21·1% | 743,100 | 25·9% | 2097 | 19·9% |
| 35-39·9 kg/m$^2$ | 15,455 | 5·8% | 44 | 9·5% | 367,230 | 12·8% | 975 | 9·3% |
| ≥40 kg/m$^2$ | 8,160 | 3·1% | 29 | 6·3% | 241,570 | 8·4% | 676 | 6·4% |
| Missing | 22,740 | 8·6% | 49 | 10·6% | 176,280 | 6·1% | 1184 | 11·2% |
| Systolic blood pressure (mmHg) | | | | | | | | |
| ≤ 140 mmHg | 173,870 | 65·8% | 301 | 64·9% | 1,922,985 | 66·9% | 7141 | 67·8% |
| >140 mmHg | 44,750 | 16·9% | 124 | 26·7% | 690,215 | 24·0% | 2602 | 24·7% |
| Missing | 45,775 | 17·3% | 39 | 8·4% | 260,825 | 9·1% | 782 | 7·4% |
| On anti-hypertensive drugs | | | | | | | | |
| Yes | 115,660 | 43·7% | 393 | 84·7% | 2,185,920 | 76·1% | 9241 | 87·8% |
| No | 146,040 | 55·2% | 65 | 14·0% | 665,825 | 23·2% | 1200 | 11·4% |
| Missing | 2,685 | 1·0% | 6 | 1·3% | 22,215 | 0·8% | 84 | 0·8% |
| Total cholesterol | | | | | | | | |
| ≤5mmol/l | 133,765 | 50·6% | 282 | 60·8% | 1,935,740 | 67·4% | 6694 | 63·6% |
| >5mmol/l | 46,635 | 17·6% | 65 | 14·0% | 508,185 | 17·7% | 1416 | 13·5% |
| Missing | 83,990 | 31·8% | 117 | 25·2% | 430,100 | 15·0% | 2415 | 22·9% |
| On statins | | | | | | | | |
| Yes | 118,995 | 45·0% | 338 | 72·8% | 2,099,505 | 73·1% | 7355 | 69·9% |
| No | 142,710 | 54·0% | 120 | 25·9% | 752,245 | 26·2% | 3086 | 29·3% |
| Missing | 2,685 | 1·0% | 6 | 1·3% | 22,215 | 0·8% | 84 | 0·8% |
| Smoking status | | | | | | | | |
| Current smoker | 43,365 | 16·4% | 41 | 8·8% | 368,515 | 12·8% | 568 | 5·4% |
| Ex-smoker | 61,605 | 23·3% | 175 | 37·7% | 1,006,465 | 35·0% | 4509 | 42·8% |
| Non-smoker | 6,245 | 2·4% | 12 | 2·6% | 50,480 | 1·8% | 280 | 2·7% |
| Never smoked | 139,525 | 52·8% | 236 | 50·9% | 1,446,110 | 50·3% | 5150 | 48·9% |
| Missing smoking status | 13,645 | 5·2% | 0 | 0·0% | 2,460 | 0·1% | 18 | 0·2% |
| eGFR | | | | | | | | |
| ≥90 ml/min/1.73m$^{22}$ | 125,475 | 47·5% | 76 | 16·4% | 1,072,390 | 37·3% | 1989 | 18·9% |
| 60-89 ml/min/1.73m$^2$ | 72,940 | 27·6% | 127 | 27·4% | 1,225,575 | 42·6% | 3721 | 35·4% |
| 45-59 ml/min/1.73m$^2$ | 13,445 | 5·1% | 89 | 19·2% | 307,705 | 10·7% | 2060 | 19·6% |
| 30-44 ml/min/1.73m$^2$ | 7,475 | 2·8% | 72 | 15·5% | 145,560 | 5·1% | 1577 | 15·0% |
| 15-29 ml/min/1.73m$^2$ | 3,280 | 1·2% | 42 | 9·1% | 40,195 | 1·4% | 644 | 6·1% |
| <15 ml/min/1.73m$^2$ | 1,845 | 0·7% | 38 | 8·2% | 10,560 | 0·4% | 315 | 3·0% |
| Missing | 39,925 | 15·1% | 20 | 4·3% | 72,040 | 2·5% | 219 | 2·1% |
| Co-morbidities | | | | | | | | |
| Previous MI | 3,095 | 1·2% | 31 | 6·7% | 48,340 | 1·7% | 425 | 4·0% |
| Previous stroke | 3,160 | 1·2% | 51 | 11·0% | 57,095 | 2·0% | 813 | 7·7% |
| Previous heart failure | 6,825 | 2·6% | 111 | 23·9% | 138,045 | 4·8% | 2148 | 20·4% |
| Any cardio-renal morbidity | 31,790 | 12·0% | 289 | 62·3% | 624,995 | 21·7% | 5833 | 55·4% |

The numbers of people in each category has been rounded to the nearest five to meet information governance rules.

* - indicates a small number suppressed to meet information governance rules

+ - Defined as a previous myocardial infarction, stroke, hospital admission for heart failure or eGFR less than 60

Figure 1a: Weekly number of deaths registered from January to May in people with Type 1 diabetes in England, 2017-2020

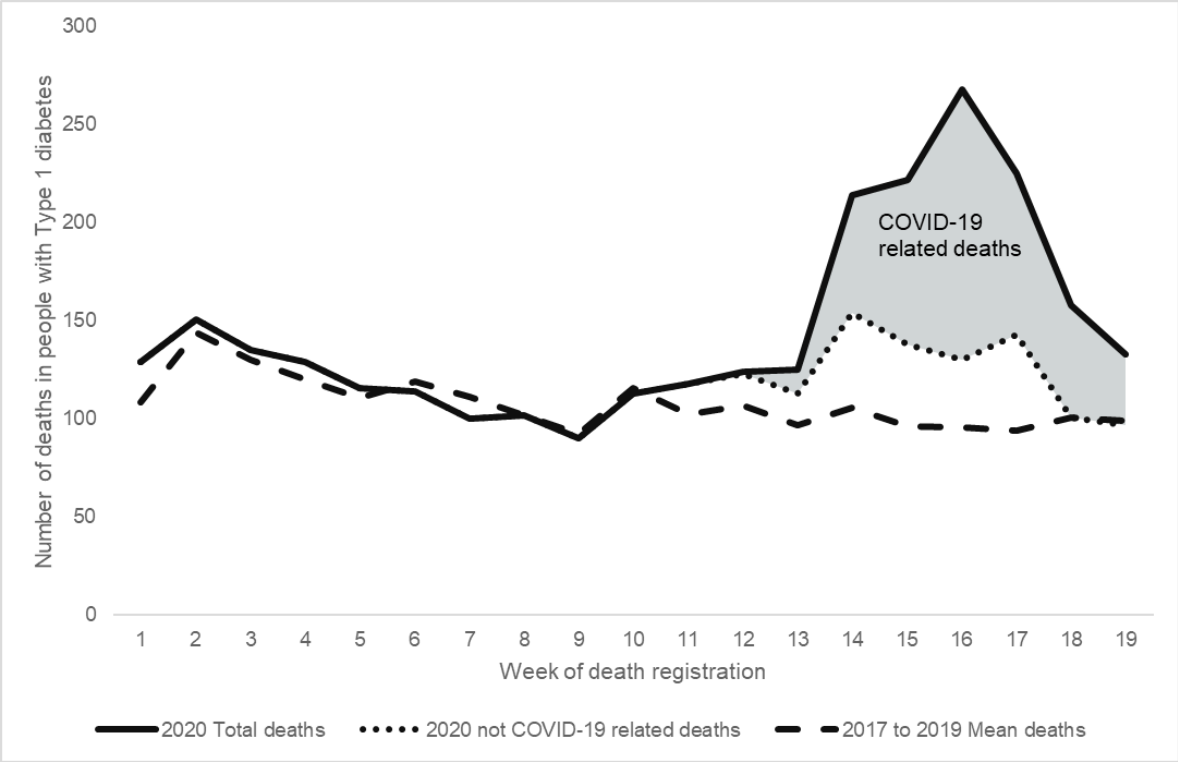



Figure 1b: Weekly number of deaths registered from January to May in people with Type 2 diabetes in England, 2017-2020

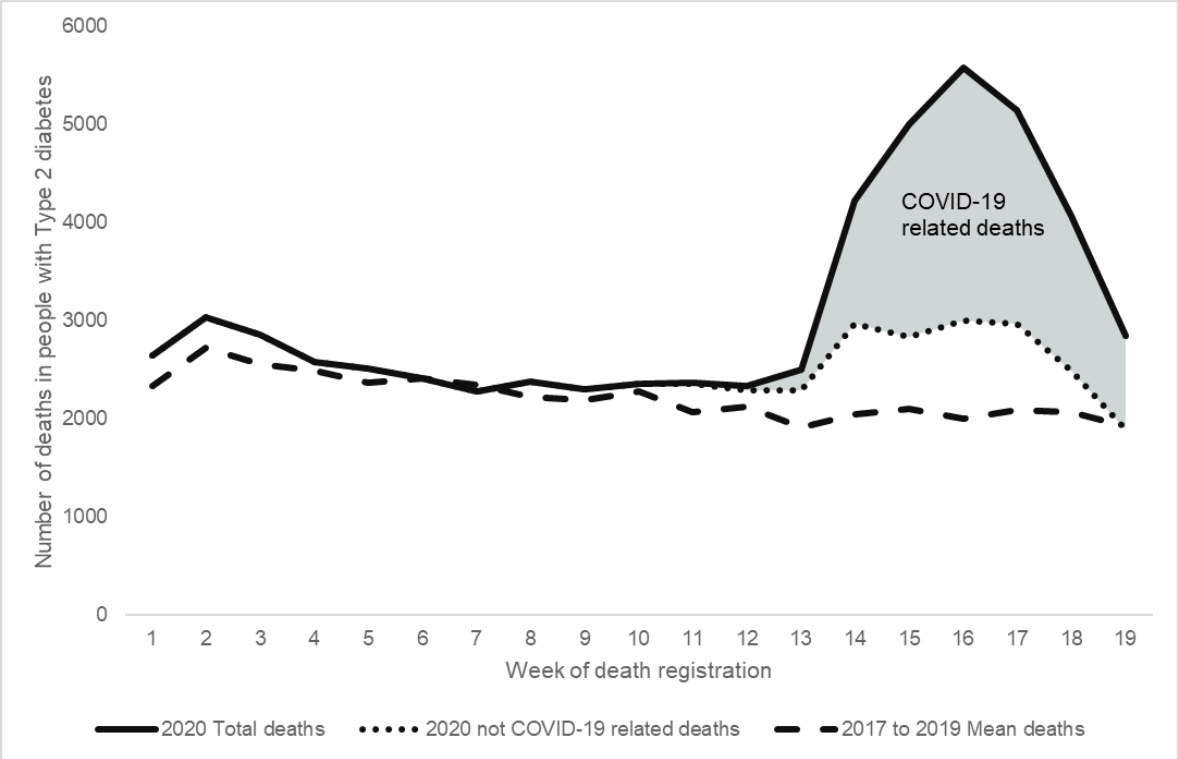
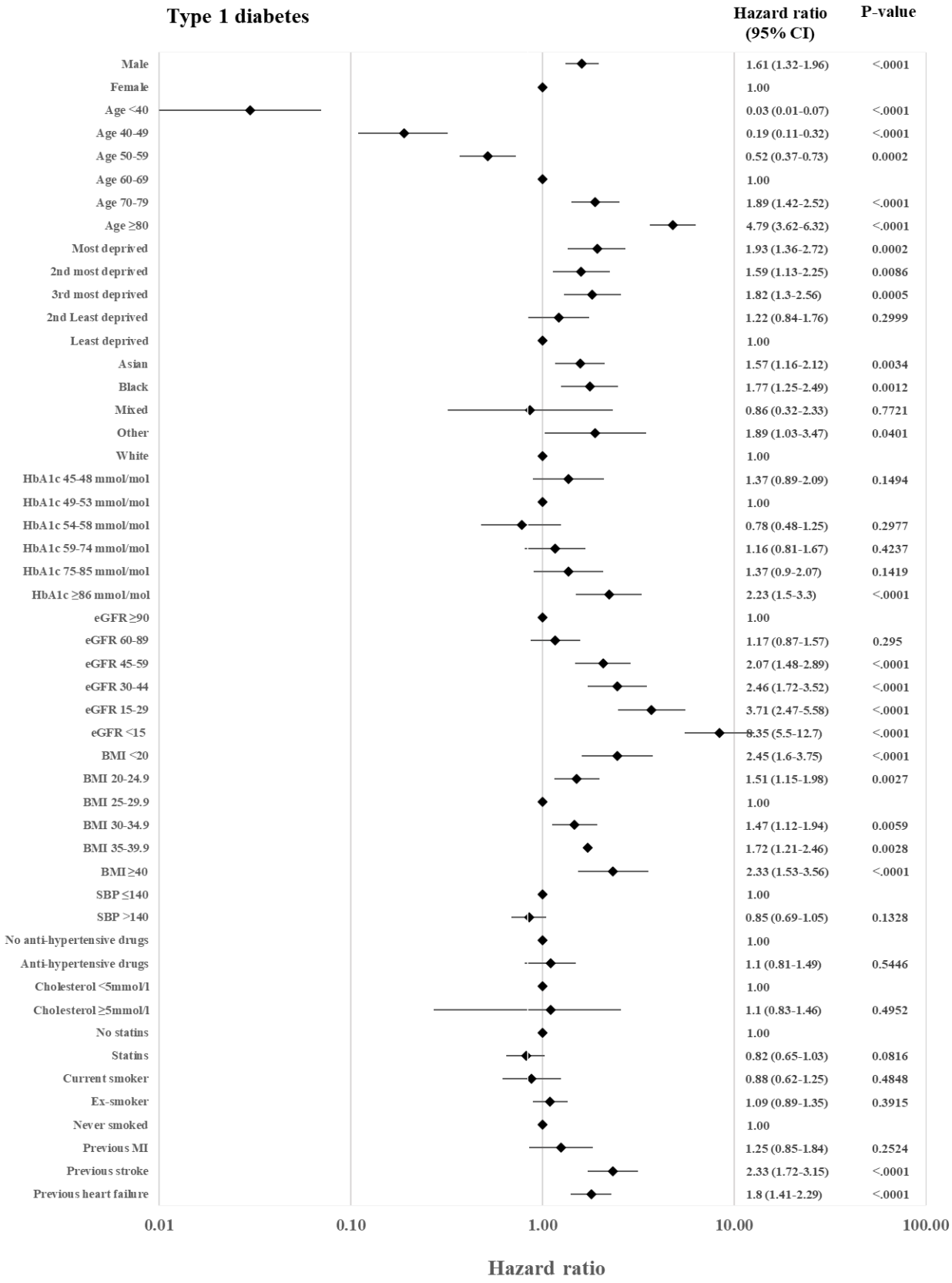
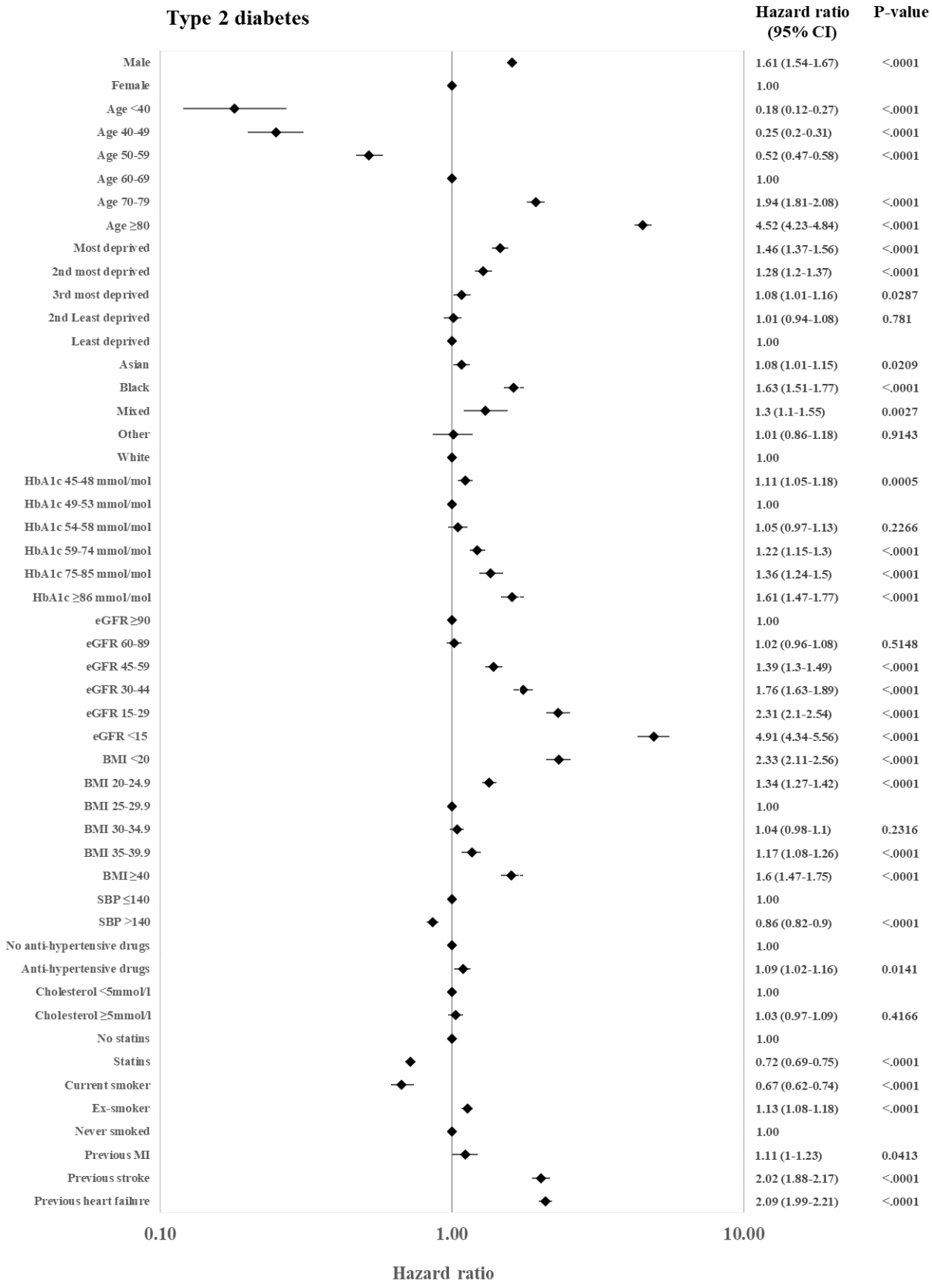


Figure 2: Forest plots showing adjusted hazard ratios for COVID-19 related death in people with Type 1 (n=264,390) and Type 2 diabetes (n=2,874,020) in England up until 11th May 2020·




Type 2 diabetes
Hazard ratio (95% CI)
P-value
Male 1.61 (1.54-1.67) <.0001
Female 1.00
Age <40 0.18 (0.12-0.27) <.0001
Age 40-49 0.25 (0.2-0.31) <.0001
Age 50-59 0.52 (0.47-0.58) <.0001
Age 60-69 1.00
Age 70-79 1.94 (1.81-2.08) <.0001
Age ≥80 4.52 (4.23-4.84) <.0001
Most deprived 1.46 (1.37-1.56) <.0001
2nd most deprived 1.28 (1.2-1.37) <.0001
3rd most deprived 1.08 (1.01-1.16) 0.0287
2nd Least deprived 1.01 (0.94-1.08) 0.781
Least deprived 1.00
Asian 1.08 (1.01-1.15) 0.0209
Black 1.63 (1.51-1.77) <.0001
Mixed 1.3 (1.1-1.55) 0.0027
Other 1.01 (0.86-1.18) 0.9143
White 1.00
HbA1c 45-48 mmol/mol 1.11 (1.05-1.18) 0.0005
HbA1c 49-53 mmol/mol 1.00
HbA1c 54-58 mmol/mol 1.05 (0.97-1.13) 0.2266
HbA1c 59-74 mmol/mol 1.22 (1.15-1.3) <.0001
HbA1c 75-85 mmol/mol 1.36 (1.24-1.5) <.0001
HbA1c ≥86 mmol/mol 1.61 (1.47-1.77) <.0001
eGFR ≥90 1.00
eGFR 60-89 1.02 (0.96-1.08) 0.5148
eGFR 45-59 1.39 (1.3-1.49) <.0001
eGFR 30-44 1.76 (1.63-1.89) <.0001
eGFR 15-29 2.31 (2.1-2.54) <.0001
eGFR <15 4.91 (4.34-5.56) <.0001
BMI <20 2.33 (2.11-2.56) <.0001
BMI 20-24.9 1.34 (1.27-1.42) <.0001
BMI 25-29.9 1.00
BMI 30-34.9 1.04 (0.98-1.1) 0.2316
BMI 35-39.9 1.17 (1.08-1.26) <.0001
BMI ≥40 1.6 (1.47-1.75) <.0001
SBP ≤140 1.00
SBP >140 0.86 (0.82-0.9) <.0001
No anti-hypertensive drugs 1.00
Anti-hypertensive drugs 1.09 (1.02-1.16) 0.0141
Cholesterol <5mmol/l 1.00
Cholesterol ≥5mmol/l 1.03 (0.97-1.09) 0.4166
No statins 1.00
Statins 0.72 (0.69-0.75) <.0001
Current smoker 0.67 (0.62-0.74) <.0001
Ex-smoker 1.13 (1.08-1.18) <.0001
Never smoked 1.00
Previous MI 1.11 (1-1.23) 0.0413
Previous stroke 2.02 (1.88-2.17) <.0001
Previous heart failure 2.09 (1.99-2.21) <.0001
0.10
1.00
10.00
Hazard ratio