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

Naomi Holman, Peter Knighton, Partha Kar, Jackie O'Keefe, Matt Curley, Andy Weaver, Emma Barron, Chirag Bakhai, Kamlesh Khunti, Nicholas J Wareham, Naveed Sattar, Bob Young, Jonathan Valabhji

Summary

Background Diabetes has been associated with increased COVID-19-related mortality, but the association between modifiable risk factors, including hyperglycaemia and obesity, and COVID-19-related mortality among people with diabetes is unclear. We assessed associations between risk factors and COVID-19-related mortality in people with type 1 and type 2 diabetes.

Methods We did a population-based cohort study of people with diagnosed diabetes who were registered with a general practice in England. National population data on people with type 1 and type 2 diabetes collated by the National Diabetes Audit were linked to mortality records collated by the Office for National Statistics from Jan 2, 2017, to May 11, 2020. We identified the weekly number of deaths in people with type 1 and type 2 diabetes during the first 19 weeks of 2020 and calculated the percentage change from the mean number of deaths for the corresponding weeks in 2017, 2018, and 2019. The associations between risk factors (including sex, age, ethnicity, socioeconomic deprivation, HbA_{1c}, renal impairment [from estimated glomerular filtration rate (eGFR)], BMI, tobacco smoking status, and cardiovascular comorbidities) and COVID-19-related mortality (defined as International Classification of Diseases, version 10, code U07.1 or U07.2 as a primary or secondary cause of death) between Feb 16 and May 11, 2020, were investigated by use of Cox proportional hazards models.

Findings Weekly death registrations in the first 19 weeks of 2020 exceeded the corresponding 3-year weekly averages for 2017–19 by 672 (50·9%) in people with type 1 diabetes and 16 071 (64·3%) in people with type 2 diabetes. Between Feb 16 and May 11, 2020, among 264 390 people with type 1 diabetes and 2 874 020 people with type 2 diabetes, 1604 people with type 1 diabetes and 36 291 people with type 2 diabetes died from all causes. Of these total deaths, 464 in people with type 1 diabetes and 10 525 in people with type 2 diabetes were defined as COVID-19 related, of which 289 (62·3%) and 5833 (55·4%), respectively, occurred in people with a history of cardiovascular disease or with renal impairment (eGFR <60 mL/min per 1·73 m²). Male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes. Compared with people with an HbA_{1c} of 48–53 mmol/mol (6·5–7·0%), people with an HbA_{1c} of 86 mmol/mol (10·0%) or higher had increased COVID-19-related mortality (hazard ratio [HR] 2·23 [95% CI 1·50–3·30, p<0·0001] in type 1 diabetes and 1·61 [1·47–1·77, p<0·0001] in type 2 diabetes). In addition, in people with type 2 diabetes, COVID-19-related mortality was significantly higher in those with an HbA_{1c} of 59 mmol/mol (7·6%) or higher than in those with an HbA_{1c} of 48–53 mmol/mol (HR 1·22 [95% CI 1·15–1·30, p<0·0001] for 59–74 mmol/mol [7·6–8·9%] and 1·36 [1·24–1·50, p<0·0001] for 75–85 mmol/mol [9·0–9·9%]). The association between BMI and COVID-19-related mortality was U-shaped: in type 1 diabetes, compared with a BMI of 25·0–29·9 kg/m², a BMI of less than 20·0 kg/m² had an HR of 2·45 (95% CI 1·60–3·75, p<0·0001) and a BMI of 40·0 kg/m² or higher had an HR of 2·33 (1·53–3·56, p<0·0001); the corresponding HRs for type 2 diabetes were 2·33 (2·11–2·56, p<0·0001) and 1·60 (1·47–1·75, p<0·0001).

Interpretation Deaths in people with type 1 and type 2 diabetes rose sharply during the initial COVID-19 pandemic in England. Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycaemic control and BMI.

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Correspondence to: Prof Jonathan Valabhji, NHS England and NHS Improvement, London SE1 6LH, UK **jonathan.valabhji@nhs.net**

For the **COVID-19 dashboard** see https://coronavirus.jhu.edu/map.html

Introduction

By May 11, 2020, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had affected 4 181 009 people worldwide, contributing to 287 624 deaths. In a companion paper,[1] we have shown that a third of COVID-19-related deaths in hospital in England between March 1 and May 11, 2020, were in people with diabetes. This excess burden in people with diabetes is

Research in context

Evidence before this study

From March 1 to June 14, 2020, we did weekly searches of PubMed and *medRxiv* using the search terms "COVID-19", "SARS-CoV-2", "coronavirus", "SARS virus", and "diabetes" for English-language publications. Although previous studies have identified diabetes as a risk factor for mortality with COVID-19 in selected populations, it was unclear whether that increased risk is found across different types of diabetes and whether the association with diabetes is confounded by other known risk factors such as age; male sex; socioeconomic deprivation; black, Asian, and minority ethnicity; obesity; renal disease; hypertension; and cardiovascular disease. Additionally, the detailed relationship between the level of previous glycaemic control and COVID-19-related mortality in people with diabetes, stratified by the two main types of diabetes with comprehensive inclusion of potential confounders, had not previously been investigated systematically in a population-based study.

Added value of this study

In this population-based cohort study of people with diagnosed diabetes in England, our data show that the COVID-19 pandemic was associated with a sharp rise in mortality in people with both type 1 and type 2 diabetes compared with the same period in the previous 3 years. Many, but not all, additional deaths (10 989 [65·6%] of 16 743) had COVID-19 recorded on the death certificate. COVID-19-related mortality in people with both type 1 and type 2 diabetes was associated not only with the risk factors identified in the general population (ie, older age, male sex, socioeconomic deprivation, non-white ethnicity, established cardiovascular disease, and impaired renal function), but also with the level of preceding hyperglycaemia (HbA_{1c}) and with both obesity and underweight. Preceding raised systolic blood pressure was associated with reduced COVID-19-related mortality in people with type 2 diabetes, but in people with type 2 diabetes use of antihypertensive drugs was associated with very slightly higher risk, whereas statin therapy was associated with a reduced risk. By using a contemporary comparison of mortality and risk factors in people with diabetes who died with COVID-19 and those who died without a diagnosis of COVID-19 in the same period, we were able to identify similarities and differences in associations with various risk factors. Similar associations were seen for age, HbA_{1c}, and cardiovascular comorbidities, and similar associations, but with greater impact with respect to COVID-19 deaths, were also seen for sex, socioeconomic deprivation, estimated glomerular filtration rate, and BMI. There were significant differences in associations between COVID-19-related and non-COVID-19-related deaths for ethnicity and tobacco smoking.

Implications of all the available evidence

Improved achievement of standard diabetes care recommendations that target prevention of cardiovascular and microvascular complications might also serve to beneficially modify some of the risk factors that we have shown to be associated with COVID-19-related mortality. Clinical services that support people with diabetes in achieving and sustaining effective self-management should be strengthened.

similar to previous coronavirus epidemics: the prevalence of diabetes was about 50% among people with Middle East respiratory syndrome, and diabetes was an independent predictor of mortality and morbidity in severe acute respiratory syndrome.[2–5]

Diabetes, cardiovascular disease, and hypertension are the most common chronic comorbidities in people with severe COVID-19.[6–15] In a companion study,[1] we showed that, compared with individuals without diagnosed diabetes, the odds ratios for dying in hospital with COVID-19 were 3·51 (95% CI 3·16–3·90) in people with type 1 diabetes and 2·03 (1·97–2·09) in people with type 2 diabetes. However, in this companion study, it was not possible to adjust for hypertension, chronic kidney disease, BMI, and tobacco smoking status, due to limitations in the datasets used for the whole population. An association between in-hospital hyperglycaemia and poorer outcomes with COVID-19 has been suggested,[11,12] and hyperglycaemia has also been associated with increased severity of other infections.[16,17] Although findings from one study showed preceding suboptimal glucose control to be a risk factor for COVID-19-related mortality,[18] findings from others did not.[14,19] It is possible that hyperglycaemia might modulate the hyperimmune response seen in people with life-threatening COVID-19.[20]

In this study, we investigated the associations between various risk factors and COVID-19-related mortality in people with type 1 and type 2 diabetes.

Methods

Study design and data sources

We did a population-based cohort study of people with diagnosed diabetes in England using a national dataset linked to national civil death registrations (hospital and community) to assess risk factors associated with COVID-19-related mortality. This dataset included 6774 (98%) of 6920 general practices in England.[21]

The National Diabetes Audit (NDA) has collated data on people with diagnosed diabetes who are registered with a general practice in England since 2003 (appendix p 1).[21] These data were linked by use of unique UK National Health Service (NHS) numbers 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

See Online for appendix

according to section 254 of the Health and Social Care Act for England 2012.[22] Data are not extracted if the person has withdrawn their permission to use their record for secondary analyses, which is estimated to apply to 2·6% of records.[23] NHS England and NHS Digital are the joint data controllers. Data linkage and analysis are done by 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 health-care services to the public, and monitoring and managing the COVID-19 outbreak and incidents of exposure.

NDA data were used to quantify the numbers 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 for the suvival analysis consisted of individuals with type 1 or type 2 diabetes from the latest full extract of the NDA, covering the period from Jan 1, 2018, to March, 31 2019, whose most recent general practice registration was in England and who were alive on Feb 16, 2020. People with a recorded date of birth giving an age of 110 years or older were excluded from the analysis as they were assumed to have an incorrect date of birth recorded. Data for individuals in the NDA dataset were linked to HES records (data available from April 1, 2017, to Dec 31, 2019) and to ONS-recorded deaths between Feb 16 and May 11, 2020.

Outcome and exposures

The outcome used in the survival analysis was COVID-19-related death, defined on the basis of International Classification of Diseases (version 10; ICD-10) code U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified), recorded as either a primary underlying or secondary cause of death.

With respect to potential risk factors assessed as exposures, we obtained data for age, socioeconomic deprivation, ethnicity, duration of diagnosed diabetes, and region from the NDA. Age was grouped as younger than 40 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older. Socioeconomic deprivation was defined by the English indices of deprivation 2019 on the basis of individual home postcode and grouped into quintiles.[24] Ethnicity was classified as Asian, black, mixed, white, other ethnic groups, or missing data. Duration of diagnosed diabetes on Feb 16, 2020, was calculated using the date of diagnosis recorded in the NDA and grouped into less than 1 year, 1–2 years, 3–4 years, 5–9 years, 10–14 years, 15–19 years, and 20 years or longer. Individuals were allocated to one of seven regions used for health-care administration purposes on the basis of their home postcode to adjust for the geographical variation in SARS-CoV-2 exposure in England.

We used data from the NDA for the latest measurements of HbA_{1c}, systolic blood pressure, serum total cholesterol, and estimated glomerular filtration rate (eGFR) recorded between Jan 1, 2019, and Dec 31, 2019. HbA_{1c} data were categorised as less than 48 mmol/mol (6·5%), 48–53 mmol/mol (6·5–7·0%), 54–58 mmol/mol (7·1–7·5%), 59–74 mmol/mol (7·6–8·9%), 75–85 mmol/mol (9·0–9·9%), and 86 mmol/mol (10·0%) or higher, or missing data. Systolic blood pressure was categorised as 140 mm Hg or less, greater than 140 mm Hg, or missing data. Serum total cholesterol was categorised as less than 5 mmol/L, 5 mmol/L or higher, or missing data. People who had received one or more prescriptions for antihypertensive drugs or statins between Jan 1 and Dec 31, 2019, were identified from general practice prescribing records. The Modification of Diet in Renal Disease formula was used to calculate eGFR and results were grouped as less than 15, 15–29, 30–44, 45–59, 60–89, and 90 mL/min per 1·73 m² or higher, or missing data. BMI and tobacco smoking status were identified from the latest recorded status in the NDA between Jan 1, 2017, and Dec 31, 2019. BMI was grouped as less than 20·0, 20·0–24·9, 25·0–29·9, 30·0–34·9, 35·0–39·9, and 40·0 kg/m² or higher, or missing data. Tobacco 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 data.

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

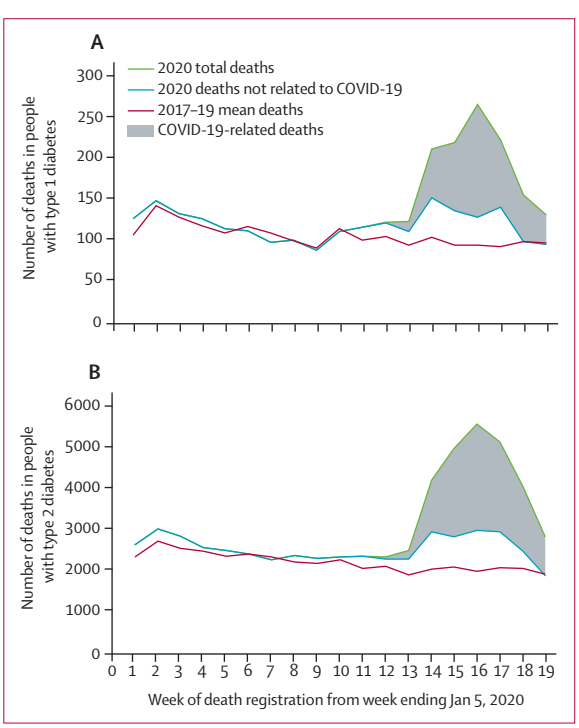


Figure 1: **Weekly numbers of deaths registered from week 1 to week 19 in people with type 1 (A) and type 2 (B) diabetes in England, 2017–19 and 2020**

Deaths in 2020 are stratified into COVID-19-related deaths and deaths not related to COVID-19.

between April 1, 2017, and Dec 31, 2019, as either the primary or one of up to 20 secondary diagnoses.

Statistical analysis

We identified the weekly number of deaths in people with type 1 and type 2 diabetes who had been included in one or more NDA data collections for the first 19 weeks of 2017, 2018, 2019, and 2020. We calculated the percentage change in 2020 from the mean number of deaths in the corresponding weeks in the preceding 3 years.

We created Cox proportional hazards survival analysis models with COVID-19-related death as the outcome for type 1 and type 2 diabetes. 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 with COVID-19 treated as a censoring event. Hazard ratios (HRs) associated with demographic characteristics (age, sex, socioeconomic deprivation, ethnicity, and region of residence), clinical characteristics (HbA_{1c}, duration of diagnosed diabetes, BMI, systolic blood pressure, prescription for antihypertensive drugs, serum total cholesterol, prescription for statins, and smoking status), and history of cardiovascular or renal comorbidities (history of myocardial infarction, stroke, heart failure, and eGFR) were calculated separately 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 male sex, female sex, individuals younger than 70 years, and those aged 70 years and older. Individual models were run for each ethnicity, socioeconomic deprivation quintile, and BMI category in people with type 2 diabetes; the same approach could not be used for type 1 diabetes because numbers were too low.

Sensitivity analyses were done in which the definition of COVID-19-related death was restricted to deaths for which COVID-19 was identified as the primary cause of death, and in which the definition was restricted to deaths classified with the U07.1 (virus identified) code.

Statistical significance was defined as a p value of less than 0·05 and CIs were set at 95%. Statistical analyses were done in SAS Enterprise Guide (version 7.1). All numbers of people taken directly from the NDA were rounded to the nearest five people to protect confidentiality of individuals.

	Type 1 diabetes		Type 2 diabetes	
	Population (n=264 390)	Deaths (n=464)	Population (n=2 874 020)	Deaths (n=10 525)
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, years				
<40	100 860 (38·1%)	6 (1·3%)	67 845 (2·4%)	24 (0·2%)
40–49	41 745 (15·8%)	17 (3·7%)	213 180 (7·4%)	98 (0·9%)
50–59	49 220 (18·6%)	56 (12·1%)	520 480 (18·1%)	485 (4·6%)
60–69	36 230 (13·7%)	84 (18·1%)	724 990 (25·2%)	1274 (12·1%)
70–79	24 290 (9·2%)	115 (24·8%)	769 175 (26·8%)	2694 (25·6%)
≥80	12 045 (4·6%)	186 (40·1%)	578 345 (20·1%)	5950 (56·5%)
Index of multiple deprivation quintile				
1 (most deprived)	56 280 (21·3%)	133 (28·7%)	700 915 (24·4%)	2817 (26·8%)
2	54 260 (20·5%)	106 (22·8%)	641 610 (22·3%)	2558 (24·3%)
3	53 345 (20·2%)	109 (23·5%)	575 030 (20·0%)	1983 (18·8%)
4	51 360 (19·4%)	67 (14·4%)	513 925 (17·9%)	1692 (16·1%)
5 (least deprived)	48 975 (18·5%)	49 (10·6%)	440 990 (15·3%)	1468 (13·9%)
Missing data	175 (0·1%)	0	1555 (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 and Yorkshire	43 850 (16·6%)	55 (11·9%)	462 480 (16·1%)	1506 (14·3%)
Missing data	175 (0·1%)	0	1555 (0·1%)	7 (0·1%)
Ethnicity				
Asian	14 725 (5·6%)	60 (12·9%)	403 355 (14·0%)	1313 (12·5%)
Black	9310 (3·5%)	47 (10·1%)	137 695 (4·8%)	884 (8·4%)
Mixed	3230 (1·2%)	NA	30 885 (1·1%)	133 (1·3%)
Other*	4035 (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 data	22 675 (8·6%)	28 (6·0%)	356 945 (12·4%)	926 (8·8%)
HbA_{1c}, mmol/mol (%)				
<48 (<6·5%)	17 950 (6·8%)	50 (10·8%)	721 950 (25·1%)	2789 (26·5%)
48–53 (6·5–7·0%)	21 550 (8·2%)	38 (8·2%)	591 815 (20·6%)	1811 (17·2%)
54–58 (7·1–7·5%)	25 200 (9·5%)	31 (6·7%)	365 955 (12·7%)	1151 (10·9%)
59–74 (7·6–8·9%)	77 380 (29·3%)	133 (28·7%)	551 530 (19·2%)	1988 (18·9%)
75–85 (9·0–9·9%)	30 150 (11·4%)	55 (11·9%)	157 030 (5·5%)	588 (5·6%)
≥86 (≥10·0%)	31 280 (11·8%)	76 (16·4%)	174 835 (6·1%)	674 (6·4%)
Missing data	60 885 (23·0%)	81 (17·5%)	310 905 (10·8%)	1524 (14·5%)

(Table continues on next page)

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 16 and May 11, 2020, 1604 people with type 1 diabetes and 36 291 people with type 2 diabetes died from all causes. 10 989 deaths (464 in type 1 and 10 525 in type 2 diabetes) had COVID-19 included on the death certificate, of which 10 417 (94·7%; 432 [93·1%] with type 1 diabetes and 9991 [94·9%] with type 2 diabetes) had COVID-19

recorded as the underlying cause of death. Comparison of the weekly number of deaths registered in people with type 1 and type 2 diabetes in the first 19 weeks of 2020 with the mean numbers of deaths in the same period over the previous 3 years showed an increase in mortality from mid-March (week 13), 2020 (figure 1). In this same period, the number of death registrations exceeded the mean number of deaths for the corresponding weeks in the proceeding 3 years by 672 (50·9%) in people with type 1 diabetes and 16 071 (64·3%) in people with type 2 diabetes. Of the additional deaths in people who had been included in the 2018–19 NDA data collection, 464 (69·0%) people with type 1 diabetes and 10 525 (65·5%) people with type 2 diabetes had COVID-19 recorded on their death certificates (table).

264 390 people with type 1 diabetes and 2 874 020 people with type 2 diabetes were included in the 2018–19 NDA data collection and were alive on Feb 16, 2020, and therefore included in the survival analysis (table). The mean ages were 46·6 years (SD 19·6) for people with type 1 diabetes and 67·5 years (13·4) for those with type 2 diabetes.

Results from the fully adjusted survival models showed that older age and male sex (*vs* female sex) were associated with increased COVID-19-related mortality for both people with type 1 and people with type 2 diabetes (figure 2). In type 1 diabetes, COVID-19-related mortality was significantly higher in people of black and Asian ethnicities than in those of white ethnicity; there was no significant difference for people of mixed ethnicity compared with those of white ethnicity. In type 2 diabetes, COVID-19-related mortality was significantly higher in people of black, Asian, and mixed ethnicities than in those of white ethnicity (figure 2). The association between black ethnicity and higher COVID-19-related mortality compared with white ethnicity in type 2 diabetes was more pronounced in males than females (appendix p 9). The increased risk for COVID-19-related mortality in people from all non-white ethnicities apart from mixed ethnicity in type 1 diabetes contrasts with a reduced risk for non-COVID-19-related mortality during the same period (appendix p 4). Among people with type 1 and type 2 diabetes, the HRs for non-white ethnicities compared with white ethnicities were higher for people aged younger than 70 (than those aged 70 years and older; appendix p 11).

A clear association was identified between COVID-19-related death and socioeconomic deprivation among people with diabetes of either type. COVID-19-related mortality was significantly higher among people in the most deprived quintile than in those in the least deprived quintile for both type 1 (HR 1·93 [95% CI 1·36–2·72], p=0·0002) and type 2 diabetes (1·46 [1·37–1·56], p<0·0001; figure 2); the equivalent HRs for non-COVID-19-related deaths were 1·35 (1·12–1·64) for type 1 and 1·26 (1·21–1·32) for type 2 diabetes (appendix p 4). The HR gradient between socioeconomic deprivation and COVID-19-related

	Type 1 diabetes		Type 2 diabetes	
	Population (n=264 390)	Deaths (n=464)	Population (n=2 874 020)	Deaths (n=10 525)
(Continued from previous page)				
Duration of diagnosed diabetes, years				
<1	840 (0·3%)	NA	25 940 (0·9%)	53 (0·5%)
2–3	14 690 (5·6%)	6 (1·3%)	378 905 (13·2%)	728 (6·9%)
4–5	16 335 (6·2%)	NA	374 960 (13·0%)	877 (8·3%)
5–9	37 465 (14·2%)	18 (3·9%)	792 110 (27·6%)	2158 (20·5%)
10–14	39 940 (15·1%)	45 (9·7%)	628 730 (21·9%)	2315 (22·0%)
15–20	42 820 (16·2%)	108 (23·3%)	426 890 (14·9%)	2378 (22·6%)
≥20	112 305 (42·5%)	282 (60·8%)	246 475 (8·6%)	2016 (19·2%)
BMI, kg/m²				
<20·0	19 990 (7·6%)	28 (6·0%)	42 160 (1·5%)	488 (4·6%)
20·0–24·9	73 950 (28·0%)	109 (23·5%)	398 390 (13·9%)	2143 (20·4%)
25·0–29·9	82 005 (31·0%)	107 (23·1%)	905 290 (31·5%)	2962 (28·1%)
30·0–34·9	42 095 (15·9%)	98 (21·1%)	743 100 (25·9%)	2097 (19·9%)
35·0–39·9	15 455 (5·8%)	44 (9·5%)	367 230 (12·8%)	975 (9·3%)
≥40·0	8160 (3·1%)	29 (6·3%)	241 570 (8·4%)	676 (6·4%)
Missing data	22 740 (8·6%)	49 (10·6%)	176 280 (6·1%)	1184 (11·2%)
Systolic blood pressure, mm Hg				
≤140	173 870 (65·8%)	301 (64·9%)	1 922 985 (66·9%)	7141 (67·8%)
>140	44 750 (16·9%)	124 (26·7%)	690 215 (24·0%)	2602 (24·7%)
Missing data	45 775 (17·3%)	39 (8·4%)	260 825 (9·1%)	782 (7·4%)
On antihypertensive 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 data	2685 (1·0%)	6 (1·3%)	22 215 (0·8%)	84 (0·8%)
Total cholesterol, mmol/L				
≤5	133 765 (50·6%)	282 (60·8%)	1 935 740 (67·4%)	6694 (63·6%)
>5	46 635 (17·6%)	65 (14·0%)	508 185 (17·7%)	1416 (13·5%)
Missing data	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 data	2685 (1·0%)	6 (1·3%)	22 215 (0·8%)	84 (0·8%)
Tobacco 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	6245 (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 data	13 645 (5·2%)	0	2460 (0·1%)	18 (0·2%)
eGFR, mL/min per 1·73 m²				
≥90	125 475 (47·5%)	76 (16·4%)	1 072 390 (37·3%)	1989 (18·9%)
60–89	72 940 (27·6%)	127 (27·4%)	1 225 575 (42·6%)	3721 (35·4%)
45–59	13 445 (5·1%)	89 (19·2%)	307 705 (10·7%)	2060 (19·6%)
30–44	7475 (2·8%)	72 (15·5%)	145 560 (5·1%)	1577 (15·0%)
15–29	3280 (1·2%)	42 (9·1%)	40 195 (1·4%)	644 (6·1%)
<15	1845 (0·7%)	38 (8·2%)	10 560 (0·4%)	315 (3·0%)
Missing data	39 925 (15·1%)	20 (4·3%)	72 040 (2·5%)	219 (2·1%)

(Table continues on next page)

	Type 1 diabetes		Type 2 diabetes	
	Population (n=264 390)	Deaths (n=464)	Population (n=2 874 020)	Deaths (n=10 525)
(Continued from previous page)				
Comorbidities				
Previous myocardial infarction	3095 (1·2%)	31 (6·7%)	48 340 (1·7%)	425 (4·0%)
Previous stroke	3160 (1·2%)	51 (11·0%)	57 095 (2·0%)	813 (7·7%)
Previous heart failure	6825 (2·6%)	111 (23·9%)	138 045 (4·8%)	2148 (20·4%)
Any cardiovascular or renal morbidity†	31 790 (12·0%)	289 (62·3%)	624 995 (21·7%)	5833 (55·4%)

Data are n (%). Percentages might not sum to 100% because of rounding. The numbers of people in each category have been rounded to the nearest five people to comply with information governance rules. Cells marked NA (not available) indicate that data for a small number of people (one to four) are not shown to comply with information governance rules. eGFR=estimated glomerular filtration rate. *Including Vietnamese, Japanese, Filipino, Malaysian, and any other ethnicity. †Defined as a previous myocardial infarction, stroke, hospital admission for heart failure, or eGFR less than 60 mL/min per 1·73 m².

Table: **Baseline characteristics and subsequent COVID-19-related deaths in people with type 1 and type 2 diabetes in England up to May 11, 2020**

mortality was steepest in people of Asian ethnicity, with an HR of 2·17 (95% CI 1·68–2·81) for the most deprived versus the least deprived quintile (appendix p 13).

Preceding hyperglycaemia was strongly associated with COVID-19-related death after adjustment for other risk factors (figure 2). In people with type 2 diabetes, COVID-19-related mortality was significantly higher in those with an HbA_{1c} of 59 mmol/mol (7·6%) or higher than in those with an HbA_{1c} of 48–53 mmol/mol (6·5–7·0%), and the risk increased with increasing HbA_{1c} levels (HR 1·22 [95% CI 1·15–1·30, p<0·0001] for 59–74 mmol/mol [7·6–8·9%] and 1·36 [1·24–1·50, p<0·0001] for 75–85 mmol/mol [9·0–9·9%]; figure 2). Although a similar pattern was seen in people with type 1 diabetes, significance was only apparent in people whose latest HbA_{1c} measurement was 86 mmol/mol or higher (HR 2·23 [95% CI 1·50–3·30, p<0·0001] in type 1 diabetes and 1·61 [1·47–1·77, p<0·0001] in type 2 diabetes; figure 2). In type 2 diabetes, low HbA_{1c} (<48 mmol/mol) was also associated with significantly increased COVID-19-related mortality; for type 1 diabetes, the direction of the association for low HbA_{1c} was the same, although the difference was not significant. For people with type 2 diabetes, the gradient of the HRs between HbA_{1c} and COVID-19-related mortality was steeper in those younger than 70 years than in those aged 70 years or older (appendix p 11).

There was a U-shaped relation between COVID-19-related mortality and BMI. For people with type 1 diabetes and people with type 2 diabetes, compared with a BMI of 25·0–29·9 kg/m², BMIs of less than 20·0 kg/m² (HR 2·45 [95% CI 1·60–3·75, p<0·0001] for type 1 diabetes and 2·33 [2·11–2·56, p<0·0001] for type 2 diabetes), 35·0–39·9 kg/m² (1·72 [1·21–2·46, p=0·0028] for type 1 diabetes and 1·17 [1·08–1·26, p<0·0001] for type 2 diabetes), and 40·0 kg/m² or higher (2·33 [1·53–3·56, p<0·0001] for type 1 diabetes and 1·60 [1·47–1·75, p<0·0001] for type 2 diabetes) were associated with significantly increased COVID-19-related mortality (figure 2). This pattern of risk related to BMI category differed from that seen for non-COVID-19-related deaths during the same period, for which a BMI of 35·0–39·9 kg/m² was not associated with increased mortality (appendix p 4). The HRs associated with obesity were significantly greater in people younger than 70 years than in those aged 70 years or older (appendix pp 11–12). The association between obesity and COVID-19-related mortality was steeper in people of Asian and black ethnicities than in those of white ethnicity (appendix pp 13–14).

Impaired renal function was associated with increased COVID-19-related mortality in people with type 1 diabetes and those with type 2 diabetes (figure 2). HRs for impaired renal function were greater for people younger than 70 years than for those aged 70 years or older (appendix pp 11–12) and different by ethnicity (appendix pp 13–15).

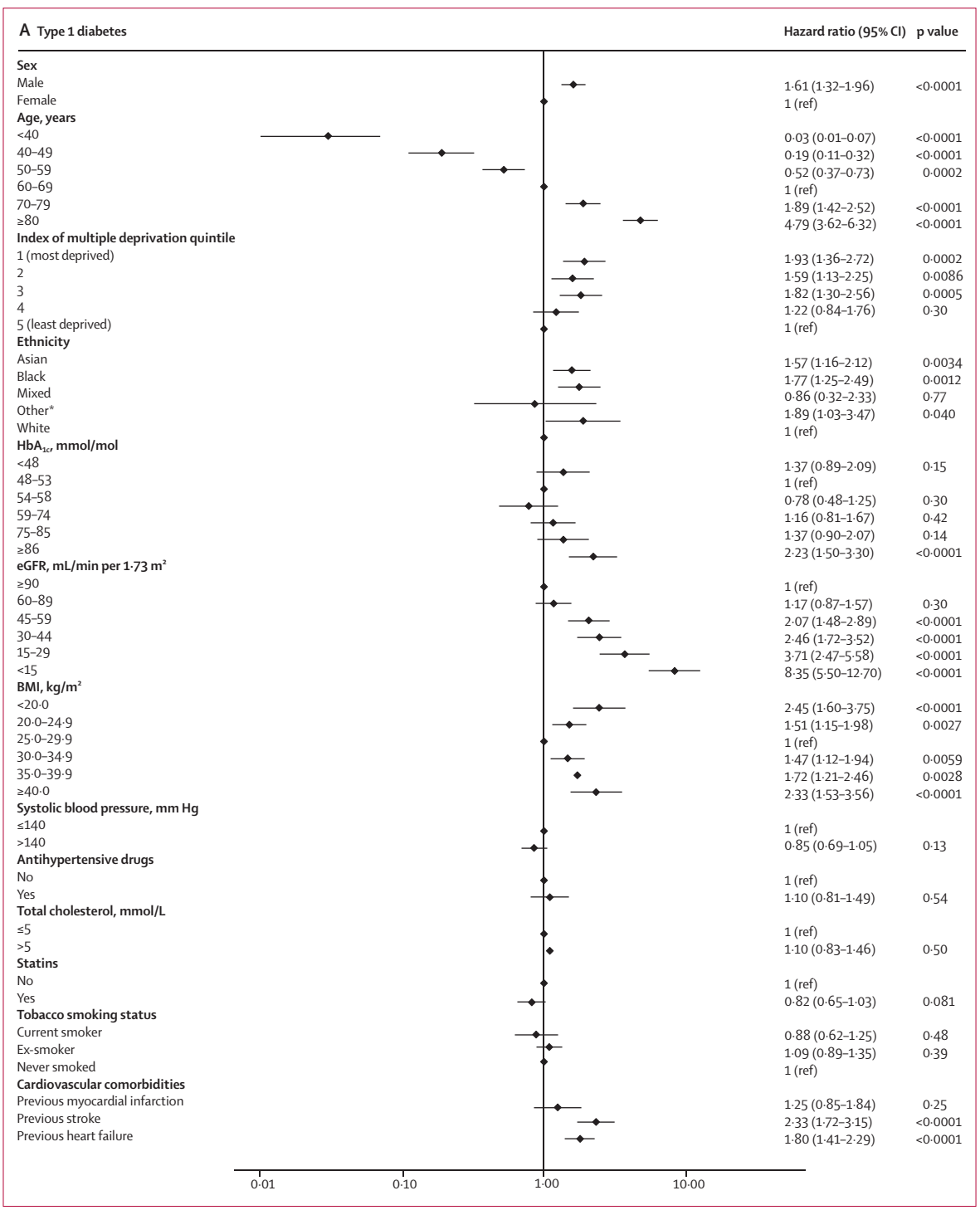
Having a systolic blood pressure of 140 mm Hg or greater was associated with lower COVID-19-related mortality in people with type 2 diabetes but not in those with type 1 diabetes. There was no significant association between total cholesterol and COVID-19-related mortality in people with type 1 or type 2 diabetes (figure 2).

Previous hospital admissions with stroke or heart failure were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes, and previous admission with myocardial infarction was also associated with increased COVID-19-related mortality in type 2 diabetes (figure 2). In people with type 2 diabetes, a recent history of one or more prescriptions for antihypertensive drugs was associated with increased COVID-19-related mortality, whereas a prescription for statins was associated with reduced mortality (figure 2). Similar associations were found in people with type 1 diabetes, but the HRs were not significant. 289 (62·3%) of 464 people with type 1 diabetes and 5833 (55·4%) of 10 525 people with type 2 diabetes whose deaths were related to COVID-19 had a history of cardiovascular or renal disease (table).

After adjustment for the demographic and clinical characteristics included in the survival models, compared with never smokers, being a current smoker with type 2 diabetes was associated with decreased COVID-19-related mortality (HR 0·67 [95% CI 0·62–0·74, p<0·0001]; figure 2). By contrast, the association in type 1 diabetes was not significant (HR 0·88 [95% CI 0·62–1·25, p=0·48]). This finding was consistent across all ethnicities, socioeconomic deprivation quintiles, and BMI categories, and more apparent in people younger than 70 years than in those aged 70 years or older (appendix pp 11–21). By contrast, current smokers had an increased risk of non-COVID-19-related mortality compared with never

smokers (HR 1·40 [95% CI 1·34–1·47]) over the same time period (appendix pp 4–5). Compared with never having smoked, being an ex-smoker with type 2 diabetes was associated with higher COVID-19-related mortality (figure 2), and in type 1 and type 2 diabetes being an ex-smoker was associated with higher non-COVID-19-related mortality (appendix p 5).

In sensitivity analyses, in which the outcome was limited to only those deaths with COVID-19 recorded as a primary cause or to only those deaths registered with



(Figure 2 continues on next page)

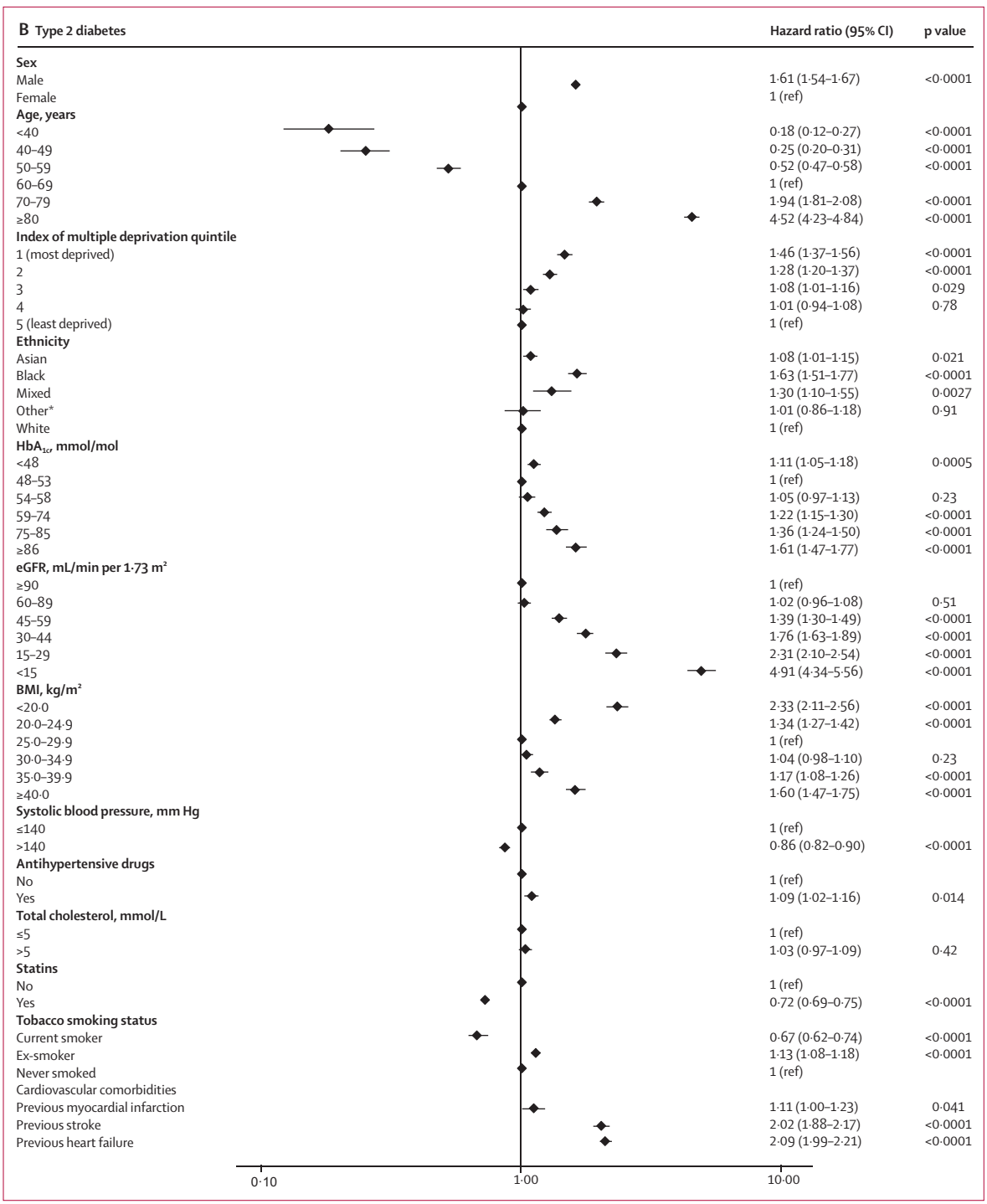


Figure 2: **Forest plots showing adjusted hazard ratios for COVID-19-related death in people with type 1 (n=264 390) and type 2 diabetes (n=2 874 020) in England up to May 11, 2020**

(A) COVID-19-related deaths in people with type 1 diabetes. (B) COVID-19-related deaths in people with type 2 diabetes. eGFR=estimated glomerular filtration rate. *Including Vietnamese, Japanese, Filipino, Malaysian, and any other ethnicity.

the ICD-10 code U07.1 (indicating a positive test for SARS-CoV-2), the results of the survival models were not materially different (appendix pp 6–8).

Discussion

In this analysis of data covering 98% of general practices in England for people with type 1 and type 2 diabetes,[21]

we have shown a rapid and sizeable increase in deaths from all causes in people with both types of diabetes with the emergence of COVID-19. The data suggest that, at the peak of the English outbreak in April, 2020, about 3500 additional deaths per week occurred in people with diabetes, the majority of which had COVID-19 recorded on the death certificate.

We identified an independent association between HbA_{1c} and COVID-19-related mortality in people with both types of diabetes. In people with type 2 diabetes, risk was significantly higher in those with an HbA_{1c} of 59 mmol/mol (7·6%) or higher than in those with an HbA_{1c} of 48–53 mmol/mol (6·5–7·0%), and the risk increased with increasing HbA_{1c} levels. In one previous study of an undifferentiated population of people with diabetes,[18] COVID-19-related mortality was higher among those in whom the preceding HbA_{1c} measurement was 58 mmol/mol or higher, but no such association was identified in three other studies, possibly because of small sample sizes.[12,14,19] Our results 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 the gradient of this risk association is steeper in people younger than 70 years than in those aged 70 years or older. Hyperglycaemia is known to impair host defences, including granulocyte and macrophage function. People with diabetes are at increased risk of many serious infections.[16] Poor glycaemic control has been associated with serious infections and hospital admission[17] and has been hypothesised to amplify the hyperimmune response associated with severe COVID-19.[20]

With respect to the other cardiometabolic targets of routine diabetes care, higher systolic blood pressure was weakly associated with lower COVID-19-related mortality in people with type 2 diabetes, whereas use of antihypertensive drugs was associated with increased mortality and prescription of statins with lower mortality in type 2 diabetes, but associations in type 1 diabetes were not significant. Although these data are of interest, it is impossible to draw conclusions about the potential direct effects of antihypertensive drugs or statins on COVID-19-related mortality due to potential confounding by indication. However, as these medications prevent cardiovascular and renal disease, their continued use will help to lessen not only non-COVID-19-related mortality but might also contribute to reducing future COVID-19-related mortality, since our results also showed that a history of cardiovascular disease and impaired renal function were associated with 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 of 25·0–29·9 kg/m². The higher risk seen in people with lower BMI might 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 increased risk of COVID-19-related death in people with diabetes and obesity is significant and differs from that seen in non-COVID-19-related deaths in the same period. The excess risk associated with higher BMI was also more apparent in people younger than 70 years than in those aged 70 years or older and was most apparent in those of Asian and black ethnicity. This evidence adds to that from other reports suggesting that obesity is an important risk factor for death from COVID-19.[20] However, the association detected between a BMI of 40·0 kg/m² or higher and COVID-19-related mortality in people with type 2 diabetes in our study (HR 1·60 [95% CI 1·47–1·75]) was less than in a study of the general English population (1·92 [1·72–2·13])[18] and weaker than the association we identified in people with type 1 diabetes (2·33 ([1·53–3·56]). If the mechanisms behind this association involve, as speculated,[20] metabolic abnormalities linked to excess ectopic fat, which is also involved in the aetiological pathway for type 2 diabetes, then an attenuated association of obesity with mortality risk might be expected in people who already have type 2 diabetes.

Several of the independent associations with COVID-19-related death are risk factors that are not readily clinically modifiable (age, sex, ethnicity, and socioeconomic deprivation) and mirror findings in other recent analyses.[6–11,15,18,19] Our comparison with deaths in the same periods that were not known to be related to COVID-19 emphasises the importance of these risk factors. In type 2 diabetes, the gradient of the association with age in COVID-19-related deaths was similar to that for those not related to COVID-19. However, male sex and socioeconomic deprivation had steeper gradients in COVID-19-related mortality than in mortality for which COVID-19 was not identified as a cause of death. A similar pattern was shown in type 1 diabetes, but significance was not reached. The higher COVID-19-related mortality risk seen in people with diabetes from black or Asian ethnic groups compared with people of white ethnicity is a reversal of the pattern seen in non-COVID-19-related deaths during the period examined and in mortality data from before the pandemic.[25] By contrast, the associations of previous myocardial infarction, stroke, and heart failure with COVID-19-related mortality were similar to the associations with other deaths, but established renal disease seems to have a stronger association with COVID-19-related mortality than with mortality not known to be related to COVID-19.

Current tobacco smoking, compared with having never smoked, was associated with a lower risk of COVID-19-related mortality in people with type 2 diabetes. This finding was seen across all BMI categories and all ethnicities. It is the reverse of what was found in non-COVID-19-related mortality over the same time period. Being an ex-smoker was associated with an increased risk

of both COVID-19-related and non-COVID-19-related mortality. Another English population based study has reported similar associations with tobacco smoking.[18] The unexpected finding with regard to current smoking status should not be taken to imply that tobacco smoking is protective of COVID-19 and might be the result of confounding by as yet unidentified factors or collider bias. Other studies[26,27] have shown that, among people with diagnosed COVID-19, smokers have poorer outcomes. The need for more research into smoking and COVID-19 is indicated. Meanwhile, it should be emphasised that tobacco smoking increases the risk of non-communicable diseases, including cardiovascular and respiratory diseases, which are themselves risk factors for poor COVID-19 outcomes.

In one previous retrospective study from 88 US hospitals of 451 people with COVID-19 and diabetes or hyperglycaemia,[11] uncontrolled hyperglycaemia was associated with increased length of hospital stay and increased mortality. However, the definition of diabetes in this study was unclear, and the uncontrolled hyperglycaemia assessed was contemporary with COVID-19 rather than preceding the infection. In another retrospective study of 952 people with type 2 diabetes (total cohort 7337) in China, inpatients with well controlled blood glucose (glycaemia maintained between 3·9 mmol/L and 10·0 mmol/L) had lower in-hospital mortality than individuals with poorly controlled glycaemia (>10·0 mmol/L; adjusted HR 0·14 [95% CI 0·04–0·60]).[12] Other studies from France[19] and China,[14] of modestly sized, non-population-based cohorts of people with type 2 diabetes, did not identify any association between HbA_{1c} and COVID-19 outcome. The OpenSAFELY Collaborative[18] used a population-based approach similar to that used in the present study, linking English primary care data from roughly 17 million individuals to COVID-19-related mortality data. Diabetes (type not specified) was independently associated with an increased risk of death, with an adjusted HR of 1·31 (95% CI 1·24–1·37) for people with an HbA_{1c} of less than 58 mmol/mol (7·5%), and of 1·95 (1·87–2·07) for those with an HbA_{1c} of 58 mmol/mol or higher. 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 COVID-19-related mortality (in the community and in hospital).

A strength of our study is that it includes nearly all people with diagnosed type 1 and type 2 diabetes in England and data for risk factors from before the COVID-19 pandemic. The results are therefore likely to be applicable to other countries with similar populations and health-care 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. Notably, the number of deaths labelled as non-COVID-19-related (deaths without COVID-19 included on the death certificate) also increased during the study period. The ONS considers it likely that many of such additional deaths, shown in figure 1 for people with diabetes, were due to undiagnosed COVID-19;[28] any under-recognition of COVID-19-related mortality will have attenuated the associations identified in our study, assuming this under-recognition was non-differential.

In our study, after stratifying the population by age, the associations of HbA_{1c}, BMI, and renal impairment with COVID-19-related mortality were somewhat stronger in younger people (those younger than 70 years), in whom comorbidity and frailty are less prevalent, than in older people (those aged 70 years or older). The variables included in this analysis were limited to those collated by the NDA, which do not include many non-cardiometabolic-related comorbidities such as respiratory disease, liver disease, alcohol use, or cognitive impairment, potentially leading to confounding as a result of lack of measurement. Residual confounding might also have resulted from the use of a single measurement to identify baseline characteristics.

Importantly, the absence of population-level data on tests results for COVID-19 for the study period means that 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 outcome of all deaths in which 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, intensive care unit admissions, or exclusively in-hospital deaths.

Although several risk factors identified for COVID-19-related mortality in people with diabetes cannot readily be modified, HbA_{1c} can be improved by health-care interventions. Although the association with obesity was more complex, particularly in the type 2 diabetes population, bodyweight can also be affected by health-care interventions—a goal of routine care. Improved achievement of standard diabetes care recommendations that target prevention of cardiovascular and microvascular complications would also serve to modify some of the risk factors that we have shown to be associated with COVID-19-related mortality. The nature of the COVID-19 pandemic means that 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 and the strengthening of clinical services that support people with diabetes in achieving and sustaining effective self-management.

Contributors

NH, PKn, PKa, EB, KK, NS, BY, and JV conceived the study. NH, PKn, JO'K, MC, AW, and EB managed the data and did the statistical analysis.

All the authors collaborated in interpretation of the results and drafting and revision of the report.

Declaration of interests

NH is funded by Diabetes UK. PKa is national specialty adviser for diabetes and obesity at NHS England and NHS Improvement. CB is an adviser to the NHS Diabetes Programme. KK has been a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme; has received grants in support of investigator-initiated studies from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Pfizer, and Boehringer Ingelheim; has served on advisory boards for Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme; and is supported by the UK National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands and the NIHR Leicester Biomedical Research Centre. NS has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer, and Sanofi; and received grant support from Boehringer Ingelheim. BY is clinical lead for the National Diabetes Audit and a trustee of Diabetes UK. JV is the national clinical director for diabetes and obesity at NHS England and NHS Improvement. All other authors declare no competing interests.

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