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Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study

Emma Barron, Chirag Bakhai, Partha Kar, Andy Weaver, Dominique Bradley, Hassan Ismail, Peter Knighton, Naomi Holman, Kamlesh Khunti, Naveed Sattar, Nicholas J Wareham, Bob Young, Jonathan Valabhji

Summary

Background Although diabetes has been associated with COVID-19-related mortality, the absolute and relative risks for type 1 and type 2 diabetes are unknown. We assessed the independent effects of diabetes status, by type, on in-hospital death in England in patients with COVID-19 during the period from March 1 to May 11, 2020.

Methods We did a whole-population study assessing risks of in-hospital death with COVID-19 between March 1 and May 11, 2020. We included all individuals registered with a general practice in England who were alive on Feb 16, 2020. We used multivariable logistic regression to examine the effect of diabetes status, by type, on in-hospital death with COVID-19, adjusting for demographic factors and cardiovascular comorbidities. Because of the absence of data on total numbers of people infected with COVID-19 during the observation period, we calculated mortality rates for the population as a whole, rather than the population who were infected.

Findings Of the 61414470 individuals who were alive and registered with a general practice on Feb 16, 2020, 263 830 (0.4%) had a recorded diagnosis of type 1 diabetes, 2 864 670 (4.7%) had a diagnosis of type 2 diabetes, 41 750 (0.1%) had other types of diabetes, and 58 244 220 (94.8%) had no diabetes. 23 698 in-hospital COVID-19-related deaths occurred during the study period. A third occurred in people with diabetes: 7434 (31.4%) in people with type 2 diabetes, 364 (1.5%) in those with type 1 diabetes, and 69 (0.3%) in people with other types of diabetes. Unadjusted mortality rates per 100 000 people over the 72-day period were 27 (95% CI 27–28) for those without diabetes, 138 (124–153) for those with type 1 diabetes, and 260 (254–265) for those with type 2 diabetes. Adjusted for age, sex, deprivation, ethnicity, and geographical region, compared with people without diabetes, the odds ratios (ORs) for in-hospital COVID-19-related death 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. These effects were attenuated to ORs of 2.86 (2.58–3.18) for type 1 diabetes and 1.80 (1.75–1.86) for type 2 diabetes when also adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure.

Interpretation The results of this nationwide analysis in England show that type 1 and type 2 diabetes were both independently associated with a significant increased odds of in-hospital death with COVID-19.

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Introduction

By May 11, 2020, 4 181 009 people were known to have had COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and 287 624 had died. Findings from a systematic review and from studies that used univariate analyses from China,^{1,2} Italy,³ and the USA⁴ and studies that used multivariable analyses from China,^{5,6} the USA,⁷ and England⁸ have all suggested that people with diabetes have increased risks of more severe outcomes with COVID-19, including death. The English study⁸ used data from general practices in England covering about 40% of the English population, and included adjustments for age, ethnicity, and socioeconomic deprivation. However, none of these studies differentiated between type 1 diabetes and type 2 diabetes, a distinction that is important in both understanding the pathophysiological mechanisms underlying the increased risk of COVID-19 in people with diabetes and

in informing potential clinical and public health responses to that risk.

Data, including for type of diabetes, are routinely collected for people diagnosed with diabetes through the National Diabetes Audit (NDA) and, in 2018–19, 6774 (98%) of 6920 general practices in England participated in the NDA.⁹ In this study, we assessed the independent effects of diabetes status, by type, on in-hospital death in England with COVID-19 during the period from March 1 to May 11, 2020. This investigation required a whole-population approach, and only parameters recorded reliably for the whole population, including age, sex, ethnicity, socioeconomic deprivation, diabetes status, and previous hospital admissions with some cardiovascular comorbidities, were assessed.

Additionally, in a companion study reported separately,¹⁰ we assessed total numbers of deaths, in both hospital and community settings, and risk factors associated with

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Public Health England, York, UK (E Barron MSc); NHS England and NHS Improvement, London, UK (C Bakhai MBA, Prof P Kar MD, A Weaver MSc, D Bradley PhD, H Ismail BSc, N Holman PhD, Prof J Valabhji MD); Portsmouth Hospitals NHS Trust, Portsmouth, UK (Prof P Kar); NHS Digital, Leeds, UK (P Knighton MPhys, N Holman); Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK (N Holman, Prof N Sattar FMedSci); Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK (Prof K Khunti MD); MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK (Prof N J Wareham PhD); Diabetes UK, London, UK (B Young MD); Department of Diabetes and Endocrinology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK (Prof J Valabhji); and Division of Diabetes, Endocrinology and Metabolism, Imperial College London, London, UK (Prof J Valabhji)

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>

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", restricted to English language publications. Findings from studies from China, Italy, the USA, and England have suggested that people with diabetes have an increased risk of more severe outcomes with COVID-19, including death. In one population-based study done in England, an increased risk of COVID-19-related death was reported in people with diabetes after adjustment for demographic factors and comorbidities. However, none of these studies have reported differences in risk by type of diabetes, which is important in view of the need for specific advice for people with different types of diabetes and their families.

Added value of this study

To our knowledge, this is the largest COVID-19-related population study, covering almost the entire population of England, and is the first study to investigate the relative and absolute risks of death in hospital with COVID-19 by type of diabetes, adjusting for key confounders. Our results show that a third of all in-hospital deaths with COVID-19 in England between March 1 and May 11, 2020 occurred in people with diabetes. Unadjusted mortality rates over the 72-day

observation period were significantly higher for people with type 2 diabetes than for people with type 1 diabetes, with both being significantly higher than for people without diabetes. Mortality rates were calculated for the population as a whole, rather than the population who were infected because of the absence of data on the total numbers of people infected with COVID-19 during the observation period. After adjustment for age, sex, deprivation, ethnicity, and geographical region, people with type 1 diabetes had 3.5 times the odds of in-hospital death with COVID-19 and people with type 2 diabetes had twice the odds, relative to people without diabetes. Further adjustment for cardiovascular comorbidities slightly attenuated the odds for people with type 1 and type 2 diabetes, but these remained significantly greater than for people without diabetes.

Implications of all the available evidence

People with diabetes are at higher risk of COVID-19-related mortality than people without diabetes. However, mortality risk was very low for people younger than 40 years with either type 1 or type 2 diabetes. Future studies should establish the key pathophysiological mechanisms underlying the determinants of more severe outcomes of COVID-19 and inform potential clinical and public health responses to the pandemic.

COVID-19-related deaths, in people with type 1 diabetes and people with type 2 diabetes. Data for demographic and clinical characteristics, and for some microvascular and cardiovascular complications, were recorded reliably in the datasets used for the analysis in the companion study,¹⁰ allowing assessment of the independent effects of each factor in each cohort on COVID-19-related mortality, including the role of previous glycaemic control and associations with BMI.

See Online for appendix 1

Methods**Study design and data sources**

We did a whole-population study assessing the risk of in-hospital death relating to COVID-19, covering all individuals registered with a general practice in England and alive on Feb 16, 2020, assessing risk in people with type 1 diabetes and people with type 2 diabetes.

In response to the increasing demand for analysis relating to the COVID-19 outbreak, NHS England and NHS Improvement created a bespoke hub of relevant datasets in the National Commissioning Data Repository.

To fulfil its statutory duties, NHS England and NHS Improvement require access to and linkage of various national pseudonymised datasets, in line with the requirements of the General Data Protection Regulation. Furthermore, 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. The following datasets were included in the Commissioning Data Repository and used in this study: Master Patient Index, NDA, Bridges to Health national population segmentation, and COVID patient notification system (appendix 1 pp 1–3).

This study used deidentified data from the February, 2020, Master Patient Index, a reference dataset of every individual registered with a general practice in England. Patient demographics, birth month and year, sex, and local geographical location (lower layer super output area, based on postcode of residence) are included in the dataset.

The latest full extract of the NDA, covering the period Jan 1, 2018, to March 31, 2019, was used to identify individuals with diagnosed diabetes.⁹ Individuals were identified for inclusion in the NDA if they had a valid Systematized Nomenclature of Medicine (SNOMED) code for diabetes (excluding gestational diabetes) in their electronic health record. Type of diabetes was based on the codes recorded in clinical records: type 1 diabetes, type 2 diabetes, or other diabetes (such as maturity-onset diabetes of the young; appendix 2).

The Bridges to Health national population segmentation dataset was used to identify individuals' long-term

For more information on NHS COVID-19 data see <https://www.england.nhs.uk/ourwork/tsd/data-info/>

See Online for appendix 2

conditions and ethnicity.¹¹ The dataset incorporates more than 10 years of data from the Secondary Uses Service, a collection of data from all hospitals in England, including admitted patient care data, outpatient data, and emergency care data. The segmentation dataset includes comorbidity and ethnicity data for individuals, derived from activity occurring up to March 31, 2019, for comorbidity and Feb 28, 2020, for ethnicity.

Deaths in hospital with COVID-19 were taken from the COVID patient notification system, a bespoke daily data collection set up on March 1, 2020, as part of England's response to COVID-19. Inclusion in this dataset initially required a positive test for SARS-CoV-2 infection. However, on April 28, 2020, inclusion was extended to also encompass patients without a positive test but with COVID-19 registered as a cause of death on the basis of clinical judgement. This study used data reported and occurring up to May 11, 2020.

Antigen testing for COVID-19 during the observation period was mostly done on patients in hospital and it was not possible to establish the true number of people in the total population who were infected. Therefore, we calculated mortality rates for the population as a whole, rather than for the population who were infected.

Outcome

The outcome assessed was death in hospital with COVID-19 between March 1 and May 11, 2020, ascertained through the COVID patient notification system. COVID-19-related in-hospital death was used rather than total deaths with COVID-19 because of limitations in available data linkages; unlike COVID patient notification system data, data from the Office for National Statistics regarding total deaths could not be linked to the Master Patient Index dataset.

Covariates

In addition to diabetes status, age, sex, ethnicity, and deprivation were identified as potential confounding factors. Diabetes status was categorised as type 1, type 2, other diabetes, or no diabetes recorded. Age was calculated as of Feb 1, 2020, from birth month and year and grouped into 10-year age bands. Sex was recorded as male, female, or missing data. Ethnicity was classified as white, Asian, black, mixed, other, or unknown. Socioeconomic deprivation was defined by the English indices of deprivation 2019 associated with the lower layer super output area derived from the individual's home postcode and grouped into quintiles.¹² In view of the geographical variation in population exposure to SARS-CoV-2 across England, region was also identified as a potential outcome moderator. Individuals were allocated to one of the seven regions in England used for health-care administration purposes according to their home postcode.

We included data on admissions with a record of significant cardiovascular comorbidities (coronary heart disease, cerebrovascular disease, and heart failure)

ascertained through coding in the Bridges to Health segmentation dataset.¹¹ Cardiovascular comorbidities were identified by searching through hospital records for coronary heart disease, cerebrovascular disease, and heart failure International Classification of Diseases version 10 and SNOMED codes. Full details of the criteria used are in appendix 1 (pp 2–3).

Other factors of interest, including BMI, chronic kidney disease, hypertension, and tobacco smoking status were either not recorded reliably or not recorded at all at population level in the hospital-derived datasets available, so could not be included; these factors were examined in detail in our companion study investigating risk factors for COVID-19-related mortality in people with diabetes.¹⁰

Statistical analysis

The associations between diabetes status, sex, age group, ethnicity, deprivation, region, and comorbidities and in-hospital death with COVID-19 were analysed. Unadjusted mortality rates over the 72-day observation period per 100 000 people were calculated, with the Master Patient Index population used as the denominator. Mortality rates for a given subgroup were calculated with respect to the Master Patient Index population for that subgroup.

A multivariable logistic regression analysis was used to examine whether diabetes status was associated with in-hospital death in England with COVID-19, with adjustment for age, sex, ethnicity, deprivation quintile, and region. A further logistic regression model included coronary heart disease, cerebrovascular disease, and heart failure to assess the effect of these comorbidities on the association between diabetes and in-hospital death with COVID-19. Separate models were run by sex, age group (<70 years and ≥70 years), ethnicity, and deprivation quintile. The C statistic was calculated to assess model fit. A sensitivity analysis was done excluding people of unknown ethnicity. The proportions of different ethnicities in the population with known ethnicity were compared with the 2011 census and the characteristics of people with unknown ethnicity were investigated.¹³

Statistical significance was defined as $p < 0.05$ and CIs were set at 95%. All data were analysed with Stata (version 16). All numbers taken directly from the NDA were rounded to the nearest five people to protect confidentiality of individuals. Data cells with between one and four counts in the COVID patient notification system were suppressed because of data protection regulations.

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

61414470 individuals were registered with a general practice in England and were alive on Feb 16, 2020. Of

those, 263 830 (0·4%) had a recorded diagnosis of type 1 diabetes, 2 864 670 (4·7%) had a recorded diagnosis of type 2 diabetes, 41 750 (0·1%) had other types of diabetes, and 58 244 220 (94·8%) had no diagnosis of diabetes (table 1). In the baseline population, 30 635 515 (49·9%) were men and 30 778 160 (50·1%) were women; the mean

age was 40·9 years (SD 23·2). 8 245 740 (13·4%) were black, Asian, or minority ethnic (BAME): Asian (3 769 395 [6·1%]), black (1 867 605 [3·0%]), mixed (937 125 [1·5%]), or other (1 671 615 [2·7%]). Previous coronary heart disease was recorded in 2 154 900 (3·5%) people, cerebrovascular disease in 915 555 (1·5%), and

	Overall population (n=61 414 470)	Type 1 diabetes (n=263 830)	Type 2 diabetes (n=2 864 670)	Other diabetes (n=41 750)	No diabetes (n=58 244 220)
Age, years					
0–39	30 506 055 (49·7%)	100 760 (38·2%)	67 735 (2·4%)	6 815 (16·3%)	30 330 745 (52·1%)
40–49	8 073 780 (13·1%)	41 680 (15·8%)	212 945 (7·4%)	5 630 (13·5%)	7 813 525 (13·4%)
50–59	8 266 300 (13·5%)	49 160 (18·6%)	519 825 (18·1%)	8 520 (20·4%)	7 688 795 (13·2%)
60–69	6 359 460 (10·4%)	36 125 (13·7%)	723 790 (25·3%)	8 510 (20·4%)	5 591 035 (9·6%)
70–79	5 057 230 (8·2%)	24 180 (9·2%)	766 815 (26·8%)	7 215 (17·3%)	4 259 020 (7·3%)
≥80	3 151 645 (5·1%)	11 925 (4·5%)	573 560 (20·0%)	5 060 (12·1%)	2 561 095 (4·4%)
Sex					
Female	30 778 160 (50·1%)	114 495 (43·4%)	1 263 615 (44·1%)	19 140 (45·8%)	29 380 910 (50·4%)
Male	30 635 515 (49·9%)	149 330 (56·6%)	1 601 045 (55·9%)	22 610 (54·2%)	28 862 530 (49·6%)
Unknown	790 (<0·1%)	5 (<0·1%)	10 (<0·1%)	0	775 (<0·1%)
Ethnicity					
Asian	3 769 395 (6·1%)	14 030 (5·3%)	344 780 (12·0%)	4 355 (10·4%)	3 406 230 (5·8%)
Black	1 867 605 (3·0%)	8 570 (3·2%)	122 985 (4·3%)	2 095 (5·0%)	1 733 955 (3·0%)
Mixed	937 125 (1·5%)	3 025 (1·1%)	22 265 (0·8%)	465 (1·1%)	911 365 (1·6%)
Other*	1 671 615 (2·7%)	4 880 (1·8%)	74 385 (2·6%)	1 265 (3·0%)	1 591 085 (2·7%)
White	40 132 970 (65·3%)	222 795 (84·4%)	2 042 950 (71·3%)	28 370 (68·0%)	37 838 855 (65·0%)
Unknown	13 035 760 (21·2%)	10 530 (4·0%)	257 300 (9·0%)	5 200 (12·5%)	12 762 725 (21·9%)
Index of multiple deprivation quintile					
1 (most deprived)	12 757 060 (20·8%)	55 930 (21·2%)	696 675 (24·3%)	10 360 (24·8%)	11 994 095 (20·6%)
2	12 817 805 (20·9%)	53 965 (20·5%)	638 920 (22·3%)	9 430 (22·6%)	12 115 490 (20·8%)
3	12 306 130 (20·0%)	53 325 (20·2%)	573 660 (20·0%)	8 430 (20·2%)	11 670 715 (20·0%)
4	11 876 020 (19·3%)	51 425 (19·5%)	513 315 (17·9%)	7 245 (17·4%)	11 304 040 (19·4%)
5 (least deprived)	11 606 690 (18·9%)	48 985 (18·6%)	440 200 (15·4%)	6 250 (15·0%)	11 111 255 (19·1%)
Unknown	50 765 (0·1%)	200 (0·1%)	1 905 (0·1%)	30 (0·1%)	48 625 (0·1%)
Region					
East of England	7 071 470 (11·5%)	32 500 (12·3%)	311 680 (10·9%)	5 275 (12·6%)	6 722 010 (11·5%)
London	10 499 665 (17·1%)	33 080 (12·5%)	461 510 (16·1%)	7 130 (17·1%)	9 997 945 (17·2%)
Midlands	11 396 320 (18·6%)	53 135 (20·1%)	583 655 (20·4%)	8 495 (20·3%)	10 751 035 (18·5%)
North East and Yorkshire	9 164 525 (14·9%)	43 765 (16·6%)	461 285 (16·1%)	6 160 (14·8%)	8 653 315 (14·9%)
North West	7 670 550 (12·5%)	32 100 (12·2%)	371 930 (13·0%)	4 335 (10·4%)	7 262 185 (12·5%)
South East	9 591 390 (15·6%)	41 500 (15·7%)	401 230 (14·0%)	5 600 (13·4%)	9 143 060 (15·7%)
South West	5 969 785 (9·7%)	27 550 (10·4%)	271 470 (9·5%)	4 725 (11·3%)	5 666 040 (9·7%)
Unknown	50 765 (0·1%)	200 (0·1%)	1 905 (0·1%)	30 (0·1%)	48 625 (0·1%)
Coronary heart disease					
No	59 259 570 (96·5%)	238 460 (90·4%)	2 314 195 (80·8%)	36 680 (87·9%)	56 670 235 (97·3%)
Yes	2 154 900 (3·5%)	25 375 (9·6%)	550 475 (19·2%)	5 065 (12·1%)	1 573 985 (2·7%)
Cerebrovascular disease					
No	60 498 915 (98·5%)	254 155 (96·3%)	2 674 260 (93·4%)	39 735 (95·2%)	57 530 765 (98·8%)
Yes	915 555 (1·5%)	9 680 (3·7%)	190 410 (6·6%)	2 010 (4·8%)	713 455 (1·2%)
Heart failure					
No	60 783 235 (99·0%)	255 350 (96·8%)	2 686 460 (93·8%)	39 880 (95·5%)	57 801 545 (99·2%)
Yes	631 235 (1·0%)	8 485 (3·2%)	178 210 (6·2%)	1 865 (4·5%)	442 675 (0·8%)

Data are n (%). *Including Chinese, Vietnamese, Japanese, Filipino, Malaysian, and any other ethnicity.

Table 1: Individuals registered with a general practice in England and alive on Feb 16, 2020, by diabetes status

heart failure in 631235 (1.0%). Data were missing for sex (790 [$<0.1\%$]), ethnicity (13035760 [21.2%]), deprivation quintile (50765 [0.1%]), and region (50765 [0.1%]); there were no missing data for age.

Compared with people without diabetes, individuals with type 1 diabetes and type 2 diabetes were older (mean age 46.6 years [SD 19.5] for those with type 1 diabetes, 67.4 years [13.4] for those with type 2 diabetes, and 39.5 years [22.8] for those with no diabetes) and had higher proportions of men, and higher proportions of people with previous coronary heart disease, cerebrovascular disease, and heart failure (table 1). Higher proportions of individuals with type 2 diabetes than those with type 1 or no diabetes were of BAME ethnicities and from the most deprived quintile. The proportion of missing ethnicity data was lower for people with type 1 diabetes (10530 [4.0%]) and type 2 diabetes (257300 [9.0%]) than for those without diabetes (12762725 [21.9%]; table 1).

23698 people with COVID-19 died in hospital in England up to May 11, 2020. A third of these deaths occurred in people with diabetes: 7434 (31.4%) deaths in people with type 2 diabetes, 364 (1.5%) in people with type 1 diabetes, and 69 (0.3%) in people with other types of diabetes (table 2). Of the 23698 people who died, 14579 (61.5%) were men; the mean age was 78.6 years (SD 12.1); and 16.0% were from BAME ethnicities (1769 [7.5%] Asian, 1354 [5.7%] black, 171 [0.7%] mixed, and 509 [2.1%] other). The highest proportion of deaths across deprivation quintiles was in people from the most deprived quintile of the population (5632 [23.8%, compared with 3762 [15.9%] in the least deprived quintile). Previous coronary heart disease was recorded in 7323 (30.9%) people who died, cerebrovascular disease in 4703 (19.8%), and heart failure in 4214 (17.8%; table 2).

Compared with those without diabetes who died, individuals with type 1 diabetes and type 2 diabetes who died were younger (mean age 72.2 years [SD 13.0] in those with type 1 diabetes, 77.9 years [11.0] in those with type 2 diabetes, and 79.2 years [12.5] in those with no diabetes), a higher proportion were from BAME ethnicities, and a higher proportion had a history of coronary heart disease, cerebrovascular disease, or heart failure. There was an inverse association between COVID-19-related death and deprivation, with substantially more deaths in the most deprived quintile than in the least deprived quintile, particularly for individuals with type 1 diabetes and type 2 diabetes, and to a lesser extent for those without diabetes (table 2).

The unadjusted rate of in-hospital mortality with COVID-19 from March 1 to May 11, 2020, was 39 deaths (95% CI 38–39) per 100000 people for the general population (figure 1; table 2). The rate per 100000 people in this period was 138 (124–153) for the population with type 1 diabetes, 260 (254–265) for those with type 2 diabetes, 165 (129–209) for people with other types of

diabetes, and 27 (27–28) for those without diabetes (table 2). Mortality rates increased substantially by age group (figure 1). Within each age group, rates were significantly higher for people with type 1 and type 2 diabetes than for those without diabetes (table 2).

Regression analysis showed that there was a strong association between death in hospital with COVID-19 and age. Compared with the 60–69 years reference age group, the odds ratio (OR) was 0.012 (95% CI 0.010–0.014) for individuals younger than 40 years and 9.20 (8.83–9.58) for individuals aged 80 years or older (figure 2). Odds for COVID-19-related death were higher for men (OR 1.94 [1.89–1.99]) versus women and for those in the most deprived quintile (1.88 [1.80–1.96]) versus those in the least deprived quintile. People of BAME ethnicities had higher odds for COVID-19-related death than white people (1.35 [1.28–1.42] for Asian people; 1.71 [1.61–1.82] for black people; 1.43 [1.23–1.67] for mixed; and 1.10 [1.01–1.20] for other). There were significant differences in ORs for COVID-19-related death by region (appendix 1 p 4).

Adjusted for age, sex, index of multiple deprivation, ethnicity, and region, the odds for death in people with type 1 diabetes was 3.51 (95% CI 3.16–3.90) and for people with type 2 diabetes it was 2.03 (1.97–2.09) compared with the population without known diabetes (figure 2). The *C* statistic was 0.934 (95% CI 0.933–0.935).

In the model that included history of comorbidities, coronary heart disease (OR 1.32 [95% CI 1.28–1.36]), cerebrovascular disease (2.23 [2.16–2.31]), and heart failure (2.23 [2.15–2.31]) were each significantly associated with in-hospital death with COVID-19 (appendix 1 p 5). Adjustment for these comorbidities slightly attenuated the association with age identified in the model without comorbidity data (appendix 1 p 5). A modest attenuation was also seen between the associations of COVID-19-related mortality with type of diabetes (appendix 1 p 5). Adjusted for age, sex, index of multiple deprivation, ethnicity, region, and cardiovascular comorbidities, the ORs for in-hospital mortality with COVID-19 were 2.86 (2.58–3.18) for people with type 1 diabetes and 1.80 (1.75–1.86) for people with type 2 diabetes compared with people without known diabetes (appendix 1 p 5).

Separate modelling showed that the relative effect of having diabetes was greater in younger people, women, and those of black ethnicity (appendix 1 pp 6–17). In a model restricted to people younger than 70 years, compared with people with no diabetes, ORs were 6.39 (95% CI 5.40–7.56) for people with type 1 diabetes and 3.74 (3.50–3.99) for those with type 2 diabetes; in a model restricted to people older than 70 years, ORs were 2.81 (2.46–3.22) for people with type 1 diabetes and 1.79 (1.74–1.85) for people with type 2 diabetes (appendix 1 p 6). Compared with people without known diabetes, the ORs for type 2 diabetes were

COVID-19-related deaths										COVID-19-related deaths per 100 000 people over 72 days (95% CI)									
	Overall population	Type 1 diabetes	Type 2 diabetes	Other diabetes	No diabetes	Overall population	Type 1 diabetes	Type 2 diabetes	Other diabetes	No diabetes	Overall population	Type 1 diabetes	Type 2 diabetes	Other diabetes	No diabetes				
Total	23 698	364	7434	69	15 831	39 (38-39)	138 (124-153)	260 (254-265)	165 (129-209)	27 (27-28)									
Age, years																			
0-39	160 (0.7%)	..	18 (0.2%)	1 (0-1)	..	27 (16-42)									
40-49	384 (1.6%)	..	89 (1.2%)	..	275 (1.7%)	5 (4-5)	..	42 (34-51)	..	4 (3-4)									
50-59	1313 (5.5%)	49 (13.5%)	399 (5.4%)	16 (15-17)	100 (74-132)	77 (69-85)									
60-69	2865 (12.1%)	73 (20.1%)	1042 (14.0%)	7 (10.1%)	1743 (11.0%)	45 (43-47)	202 (158-254)	144 (135-153)	82 (33-170)	31 (30-33)									
70-79	5904 (24.9%)	97 (26.6%)	2096 (28.2%)	22 (31.9%)	3689 (23.3%)	117 (114-120)	401 (325-489)	273 (262-285)	305 (191-462)	87 (84-89)									
≥80	13 072 (55.2%)	125 (34.3%)	3790 (51.0%)	32 (46.4%)	9125 (57.6%)	415 (408-422)	1048 (872-1249)	661 (640-682)	632 (432-892)	356 (349-364)									
Sex																			
Male	14 579 (61.5%)	232 (63.7%)	4801 (64.6%)	46 (66.7%)	9500 (60.0%)	48 (47-48)	155 (136-177)	300 (291-308)	203 (149-271)	33 (32-34)									
Female	9119 (38.5%)	132 (36.3%)	2633 (35.4%)	23 (33.3%)	6331 (40.0%)	30 (29-30)	115 (96-137)	208 (200-216)	120 (76-180)	22 (21-22)									
Unknown	0	0	0	0	0	0 (0-466)	0 (0-61481)	0 (0-46111)	0	0 (0-475)									
Ethnicity																			
Asian	1769 (7.5%)	44 (12.1%)	955 (12.8%)	47 (45-49)	314 (228-421)	277 (260-295)									
Black	1354 (5.7%)	37 (10.2%)	695 (9.3%)	5 (7.2%)	617 (3.9%)	72 (69-76)	432 (304-595)	565 (524-609)	239 (77-557)	36 (33-39)									
Mixed	171 (0.7%)	..	75 (1.0%)	..	91 (0.6%)	18 (16-21)	..	337 (265-422)	..	10 (8-12)									
Other*	509 (2.1%)	11 (3.0%)	202 (2.7%)	0	296 (1.9%)	30 (28-33)	225 (113-403)	272 (235-312)	0 (0-292)	19 (17-21)									
White	18 968 (80.0%)	266 (73.1%)	5328 (71.7%)	53 (76.8%)	13 321 (84.1%)	47 (47-48)	119 (105-135)	261 (254-268)	187 (140-244)	35 (35-36)									
Unknown	927 (3.9%)	..	179 (2.4%)	7 (7-8)	..	70 (60-81)									
Index of multiple deprivation quintile																			
1 (most deprived)	5632 (23.8%)	107 (29.4%)	2065 (27.8%)	14 (20.3%)	3446 (21.8%)	44 (43-45)	191 (157-231)	296 (284-309)	135 (74-227)	29 (28-30)									
2	5342 (22.5%)	80 (22.0%)	1854 (24.9%)	17 (24.6%)	3391 (21.4%)	42 (41-43)	148 (118-185)	290 (277-304)	180 (105-289)	28 (27-29)									
3	4624 (19.5%)	88 (24.2%)	1404 (18.9%)	12 (17.4%)	3120 (19.7%)	38 (36-39)	165 (132-203)	245 (232-258)	142 (74-249)	27 (26-28)									
4	4308 (18.2%)	51 (14.0%)	1153 (15.5%)	12 (17.4%)	3092 (19.5%)	36 (35-37)	99 (74-130)	225 (212-238)	166 (86-289)	27 (26-28)									
5 (least deprived)	3762 (15.9%)	38 (10.4%)	948 (12.8%)	14 (20.3%)	2762 (17.4%)	32 (31-33)	78 (55-106)	215 (202-230)	224 (122-376)	25 (24-26)									
Unknown	30 (0.1%)	0	10 (0.1%)	0	20 (0.1%)	59 (40-84)	0 (0-1826)	525 (252-965)	0 (0-11528)	41 (25-64)									
Region																			
East of England	2777 (11.7%)	50 (13.7%)	750 (10.1%)	16 (23.2%)	1961 (12.4%)	39 (38-41)	154 (114-203)	241 (224-258)	303 (173-493)	29 (28-30)									
London	5336 (22.5%)	81 (22.3%)	1920 (25.8%)	14 (20.3%)	3321 (21.0%)	51 (49-52)	245 (194-304)	416 (398-435)	196 (107-329)	33 (32-34)									
Midlands	4671 (19.7%)	96 (26.4%)	1500 (20.2%)	9 (13.0%)	3066 (19.4%)	41 (40-42)	181 (146-221)	257 (244-270)	106 (48-201)	29 (28-30)									
North East and Yorkshire	3319 (14.0%)	41 (11.3%)	990 (13.3%)	10 (14.5%)	2278 (14.4%)	36 (35-37)	94 (67-127)	215 (201-228)	162 (78-299)	26 (25-27)									
North West	3586 (15.1%)	43 (11.8%)	1058 (14.2%)	6 (8.7%)	2479 (15.7%)	47 (45-48)	134 (97-180)	284 (268-302)	138 (51-301)	34 (33-36)									
South East	2903 (12.2%)	33 (9.1%)	874 (11.8%)	8 (11.6%)	1988 (12.6%)	30 (29-31)	80 (55-112)	218 (204-233)	143 (62-282)	22 (21-23)									
South West	1076 (4.5%)	20 (5.5%)	332 (4.5%)	6 (8.7%)	718 (4.5%)	18 (17-19)	73 (44-112)	122 (109-136)	127 (47-276)	13 (12-14)									
Unknown	30 (0.1%)	0	10 (0.1%)	0	20 (0.1%)	59 (40-84)	0 (0-1826)	525 (252-965)	0 (0-11528)	41 (25-64)									

(Table 2 continues on next page)

		COVID-19-related deaths per 100 000 people over 72 days (95% CI)					
		Overall population	Type 1 diabetes	Type 2 diabetes	Other diabetes	No diabetes	No diabetes
(Continued from previous page)							
Coronary heart disease							
No admission	16 375 (69.1%)	190 (52.2%)	80 (69.92)	196 (191-202)	125 (92-167)	20 (20-21)	20 (20-21)
Admission	7323 (30.9%)	174 (47.8%)	686 (588-796)	525 (506-544)	454 (288-681)	269 (261-277)	269 (261-277)
Cerebrovascular disease							
No admission	18 995 (80.2%)	256 (70.3%)	101 (89-114)	217 (211-222)	133 (100-174)	22 (22-23)	22 (22-23)
Admission	4703 (19.8%)	108 (29.7%)	1116 (915-1347)	859 (818-902)	796 (455-1292)	413 (398-428)	413 (398-428)
Heart failure							
No admission	19 484 (82.2%)	257 (70.6%)	101 (89-114)	213 (208-219)	138 (104-180)	23 (23-24)	23 (23-24)
Admission	4214 (17.8%)	107 (29.4%)	1261 (1034-1524)	954 (909-1000)	750 (410-1259)	541 (519-563)	541 (519-563)

Data are n or n (%), unless otherwise indicated. For categories with small numbers (one to four), data were not included to comply with data protection regulations, indicated by .. *Including Chinese, Vietnamese, Japanese, Filipino, Malaysian, and any other ethnicity.

Table 2: In-hospital deaths of people with COVID-19 in England between March 1 and May 11, 2020, by diabetes status

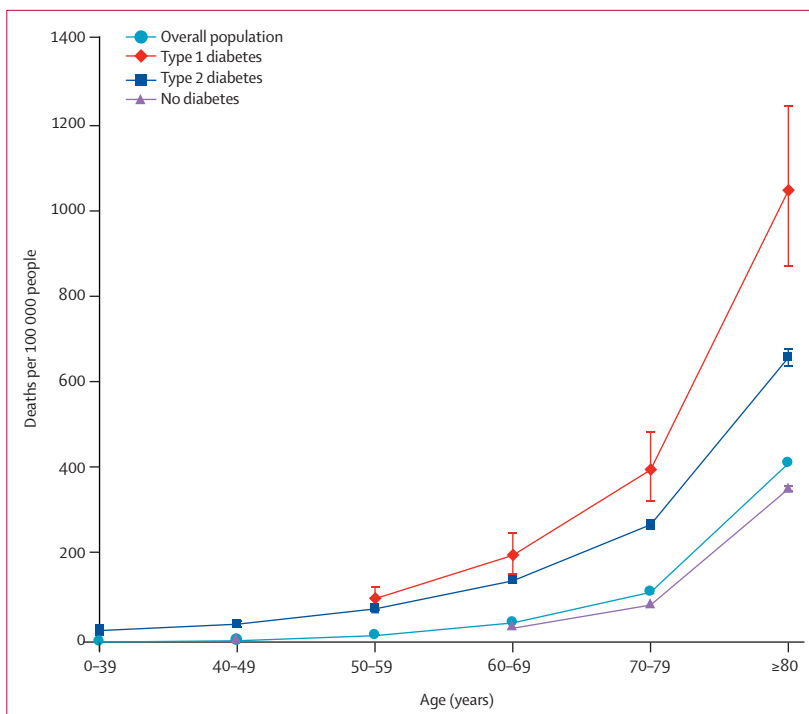


Figure 1: Unadjusted in-hospital COVID-19 mortality rates, March 1 to May 11, 2020, by diabetes status. Error bars show 95% CIs. Data for age groups 0–39 years and 40–49 years for type 1 diabetes and 0–39 years and 50–59 years for no diabetes have been excluded because of small numbers of events (one to four), to comply with data protection regulations.

2.19 (2.09–2.29) in a model restricted to women only and 1.94 (1.87–2.01) in a model restricted to men only (appendix 1 p 8). In a model restricted to people of black ethnicity, the OR was 2.76 (2.46–3.09) in people with type 2 diabetes (vs no diabetes), whereas the OR in the model restricted to people of Asian ethnicity was 1.96 (1.77–2.16), and in the model restricted to people of white ethnicity it was 1.97 (1.91–2.03; appendix 1 pp 10–11).

Overall, the proportions of people of different ethnicities for whom ethnicity information was available were broadly similar to the proportions in the 2011 census (appendix 1 p 18). There was a greater proportion of missing data for ethnicity in younger age groups and in men, but in a sensitivity analysis excluding individuals with missing ethnicity data, the results were unchanged (appendix 1 pp 18–20).

Discussion

To our knowledge, this is the largest COVID-19-related whole-population study, covering almost the entire population of England, and is the first study to investigate the relative and absolute risk of death in hospital with COVID-19 by type of diabetes, adjusting for key confounding factors. Our results show an increased risk in people with diabetes, with a third of all in-hospital deaths with COVID-19 occurring in people with diabetes.

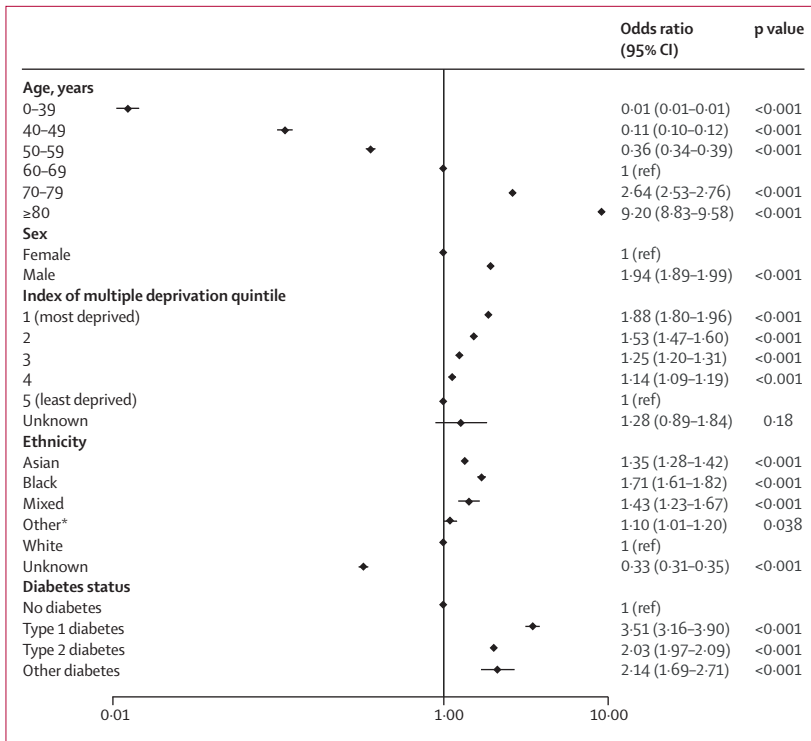


Figure 2: Adjusted odds ratios for in-hospital deaths for people with COVID-19 in England, March 1 to May 11, 2020, by demographic characteristics and diabetes status
 Data are the results of a multivariable logistic regression, which included the explanatory variables shown, plus region, in a population of 61 414 470 people. *Including Chinese, Vietnamese, Japanese, Filipino, Malaysian, and any other ethnicity.

deprivation, and region, individuals with type 1 or type 2 diabetes had greater odds of in-hospital death with COVID-19 than people without a diagnosis of diabetes. Further adjustment for cardiovascular comorbidities attenuated these associations slightly, but the odds of COVID-19-related death remained significantly greater than that in people with no diabetes.

The outcome assessed in this study was death with COVID-19 in hospital settings, so the association of type 2 diabetes with COVID-19-related mortality in general might be underestimated. The prevalence of type 2 diabetes increases with age, and so type 2 diabetes is likely to be overrepresented in people with advanced age, frailty, and multimorbidity, who in turn are likely to be overrepresented in deaths outside of hospital with COVID-19. Data analyses by the Office for National Statistics show that more than 70% of COVID-19-related deaths in people who resided in care homes from March 2 to May 1, 2020, occurred in care-home settings rather than in hospitals and were therefore not included in the datasets analysed in this study.¹⁴

All-cause mortality in people with diabetes is higher than in people without diabetes.¹⁵ In an analysis of deaths during 2017 in people included in the NDA, the age-adjusted and sex-adjusted all-cause mortality rate for people with type 1 diabetes was 148% higher than in the population without diabetes (3170 deaths over

213 400 person-years at risk compared with 1278 deaths expected on the basis of the age and sex profile of the population). The figure for people with type 2 diabetes was 50.2% (89 825 deaths over 2 348 189 person-years at risk compared with 59 795 expected). The ORs we report for COVID-19-related death were 3.51 (95% CI 3.16–3.90) for type 1 diabetes and 2.03 (1.97–2.09) for type 2 diabetes. These findings suggest that for people with type 1 and type 2 diabetes, COVID-19 mortality rates during the pandemic were higher than the usually increased rates for all-cause mortality. People with other diagnoses of diabetes had similar odds to people with type 2 diabetes in both models in our analyses. However, this category of people is small and highly heterogeneous, so further inferences are not possible.

Adjustment for comorbidities allows an interpretation of the independent effect of diabetes on in-hospital death with COVID-19 beyond the well established link between diabetes and cardiovascular comorbidities, which are themselves determinants of COVID-19 mortality risk. We recognise that being unable to adjust for BMI, hypertension, kidney disease, and tobacco smoking, as well as other potential confounders, is likely to have left large residual confounding in the associations described.

In this study and in previous analyses, heart failure and cerebrovascular disease have been shown to be associated with serious outcomes related to COVID-19.^{7,8} We show an association between previous coronary heart disease and in-hospital mortality with COVID-19, an association seen in some, but not all, previous studies.^{7,8} Although we adjusted for these factors in our second model, this might represent an overadjustment, because diabetes itself predisposes to the development of cardiovascular disease.

As in a previous multivariable analysis of data from England,⁸ our analyses showed increased odds of in-hospital death with COVID-19 for older people; men; people of black, Asian, or mixed ethnicities; and those who live in areas of high socioeconomic deprivation. Although some studies have reported an association between diabetes and severe outcomes of COVID-19,¹⁻⁸ the findings here are novel in suggesting that the effect of diabetes on risk of death with COVID-19 is independent of age, ethnicity, deprivation, and cardiovascular comorbidities, and is in people with all types of diabetes.

There were differences in the ORs for in-hospital mortality with COVID-19 for type 1 diabetes and type 2 diabetes by age, sex, and ethnicity, with increased odds for type 2 diabetes for women, for both type 1 and type 2 diabetes for younger age groups, and for type 2 diabetes for black ethnicity. For younger age groups, although the relative risk of in-hospital death for type 1 diabetes and type 2 diabetes was significantly higher than in older age groups, the absolute risk in the lower age groups was small. This finding might be at least partly because of the outcome used in this study of in-hospital death with COVID-19, with older age groups with frailty and

multimorbidity potentially disproportionately represented in deaths with COVID-19 outside of the hospital setting.

Although all diabetes types were associated with an increased odds of in-hospital COVID-19-related deaths, our findings showed a greater increased odds in people with type 1 diabetes than in people with type 2 diabetes. Many possible reasons could account for this finding. The difference between type 1 and type 2 diabetes with respect to COVID-19-related mortality could relate to the different causes and pathophysiologies of the types of diabetes; varying patterns of diabetes complications or iatrogenic harms (such as hypoglycaemia); differing patterns, treatments, intensity, and duration of glycaemia; or the effects of comorbidities that were either not adjusted for in these analyses or that were adjusted for imperfectly.

An excess risk of other infectious disease morbidity and mortality has previously been reported in patients with type 1 diabetes compared with those with type 2 diabetes. The risk of developing pneumonia was reported to be 2.98 times higher for patients with type 1 diabetes and 1.58 times greater for those with type 2 diabetes compared with the general population.¹⁶ Because we could not express mortality risk as a proportion of deaths among those who were truly infected (since this was unknown), it is possible that increased susceptibility to infection with SARS-CoV-2 could explain some of the excess mortality risk associated with diabetes that was identified in this study.

On a relative scale, our findings show that type 1 and type 2 diabetes were both associated with increased odds of in-hospital death with COVID-19 (OR 3.51 for type 1 diabetes and 2.03 for type 2 diabetes, compared with people without known diabetes). Importantly, however, on an absolute scale, the unadjusted rates of in-hospital death with COVID-19 over the same 72-day period for type 1 diabetes (138 per 100 000 people) were about half that for type 2 diabetes (260 per 100 000 people), largely reflecting the different age structure of the two populations. Even with the additional risk conferred by diabetes, people younger than 40 years with either type of diabetes were at very low absolute risk of in-hospital death with COVID-19 during the observation period of this study in England.

A strength of our study is its size, covering almost the whole population of England and nearly all people with diagnosed type 1 and type 2 diabetes. However, there were several limitations. Only three cardiovascular comorbidities (coronary heart disease, cerebrovascular disease, and heart failure) were included in analyses; we did not adjust for other comorbidities because of limitations in the datasets used and available. Notably, hypertension and chronic kidney disease were not included because of incomplete recording in the hospital-derived segmentation dataset. Findings from a previous systematic review suggested an association between poor COVID-19-related

outcomes and hypertension,¹⁷ although this association has not been detected in some multivariable analyses, which did show significant associations with chronic kidney disease.^{7,8} Similarly, BMI and tobacco smoking status could not be reliably ascertained at the population level from the datasets used in our study. These risk factors (hypertension, chronic kidney disease, BMI, and tobacco smoking status), as well as the role of previous glycaemic control, are assessed in detail in our companion paper.¹⁰

Only data regarding diabetes status and comorbidities up to the end of March, 2019, were used. Therefore, a small proportion of the population for whom diabetes or cardiovascular comorbidities were first recorded after April, 2019, will have been misclassified. Finally, since we were unable to include data for out-of-hospital deaths with COVID-19, which might have occurred disproportionately in older people, our results might have underestimated the risk associated with type 2 diabetes in particular.

The findings of the study have important implications for people with diabetes, health-care professionals, and policy makers. We encourage the use of these findings, along with those from other studies investigating risk factors for COVID-19-related outcomes, to provide reassurance for young people who are at low absolute risk, despite having diabetes. For older people who are at higher absolute risk, the results can inform public guidance, including recommendations for shielding.

Further elucidation of the modifiable risk factors for poorer COVID-19 outcomes in people with diabetes will be crucial in guiding management and providing targeted support.

Contributors

JV, EB, CB, PKa, AW, NH, KK, NS, NJW, and BY conceived the study. EB, DB, HI, NH, and PKn managed the data and did the statistical analysis. All authors collaborated in interpretation of the results and drafting and revision of the report.

Declaration of interests

JV is the national clinical director for diabetes and obesity at NHS England and NHS Improvement. PKa is a national specialty adviser for diabetes and obesity at NHS England and NHS Improvement. CB is an adviser to the NHS Diabetes Programme. BY is clinical lead for the National Diabetes Audit and a trustee of Diabetes UK. NH is funded by Diabetes UK. 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 trials 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. All other authors declare no competing interests.

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