Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland

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Summary

Background We aimed to ascertain the cumulative risk of fatal or critical care unit-treated COVID-19 in people with diabetes and compare it with that of people without diabetes, and to investigate risk factors for and build a cross-validated predictive model of fatal or critical care unit-treated COVID-19 among people with diabetes.

Methods In this cohort study, we captured the data encompassing the first wave of the pandemic in Scotland, from March 1, 2020, when the first case was identified, to July 31, 2020, when infection rates had dropped sufficiently that shielding measures were officially terminated. The participants were the total population of Scotland, including all people with diabetes who were alive 3 weeks before the start of the pandemic in Scotland (estimated Feb 7, 2020). We ascertained how many people developed fatal or critical care unit-treated COVID-19 in this period from the Electronic Communication of Surveillance in Scotland database (on virology), the RAPID database of daily hospitalisations, the Scottish Morbidity Records-01 of hospital discharges, the National Records of Scotland death registrations data, and the Scottish Intensive Care Society and Audit Group database (on critical care). Among people with fatal or critical care unit-treated COVID-19, diabetes status was ascertained by linkage to the national diabetes register, Scottish Care Information Diabetes. We compared the cumulative incidence of fatal or critical care unit-treated COVID-19 in people with and without diabetes using logistic regression. For people with diabetes, we obtained data on potential risk factors for fatal or critical care unit-treated COVID-19 from the national diabetes register and other linked health administrative databases. We tested the association of these factors with fatal or critical care unit-treated COVID-19 in people with diabetes, and constructed a prediction model using stepwise regression and 20-fold cross-validation.

Findings Of the total Scottish population on March 1, 2020 (n=5 463 300), the population with diabetes was 319 349 (5·8%), 1082 (0·3%) of whom developed fatal or critical care unit-treated COVID-19 by July 31, 2020, of whom 972 (89·8%) were aged 60 years or older. In the population without diabetes, 4081 (0·1%) of 5 143 951 people developed fatal or critical care unit-treated COVID-19. As of July 31, the overall odds ratio (OR) for diabetes, adjusted for age and sex, was 1·395 (95% CI 1·304–1·494; p<0·0001, compared with the risk in those without diabetes. The OR was 2·396 (1·815–3·163; p<0·0001) in type 1 diabetes and 1·369 (1·276–1·468; p<0·0001) in type 2 diabetes. Among people with diabetes, adjusted for age, sex, and diabetes duration and type, those who developed fatal or critical care unit-treated COVID-19 were more likely to be male, live in residential care or a more deprived area, have a COVID-19 risk condition, retinopathy, reduced renal function, or worse glycaemic control, have had a diabetic ketoacidosis or hypoglycaemia hospitalisation in the past 5 years, be on more anti-diabetic and other medication (all p<0·0001), and have been a smoker (p=0·0011). The cross-validated predictive model of fatal or critical care unit-treated COVID-19 in people with diabetes had a C-statistic of 0·85 (0·83–0·86).

Interpretation Overall risks of fatal or critical care unit-treated COVID-19 were substantially elevated in those with type 1 and type 2 diabetes compared with the background population. The risk of fatal or critical care unit-treated COVID-19, and therefore the need for special protective measures, varies widely among those with diabetes but can be predicted reasonably well using previous clinical history.

Funding None.

Introduction

Initial case series of people hospitalised with COVID-19 in several countries found over-representation of people with diabetes.[1–8] More than a quarter of those admitted for COVID-19 in the UK had diabetes.[9] Just four studies, three from the UK, have compared risks in defined populations with and without diabetes, all of which found increased risks in those with diabetes for

Research in context

Evidence before this study

We searched PubMed and the META database for studies examining risks of COVID-19 associated with diabetes that had appropriate comparator populations, and for studies among those with diabetes exploring what risk factors predict COVID-19, using the terms ("COVID-19" OR "novel coronavirus" OR "SARS-CoV-2") AND "diabetes", until Oct 5, 2020, restricted to English language. Case-series have reported a high prevalence of diabetes among those hospitalised and a high test-positivity rate for diabetes among those tested. However, diabetes is a common condition, so to quantify the risk ratios for COVID-19, comparison with the background population is needed. Only four such studies were found; these reported relative risks of 2·04 for type 2 diabetes and 3·5 for type 1 diabetes for COVID-19 hospitalised death, and 1·9 for COVID-19 hospitalisation and 2·4 for COVID-19 hospitalised death respectively for all diabetes. The range of potential determinants explored in these studies has been low.

Added value of this study

In this cohort study, we captured the data encompassing the first wave of the pandemic in Scotland, ie, from March 1, 2020, when the first case was identified, to July 31, 2020, when infection rates had dropped sufficiently that shielding measures were officially terminated. Including critical care-treated and out-of-hospital deaths from COVID-19 for the first time, as well as hospitalised deaths, we showed that the risk of fatal or critical care unit-treated COVID-19 is increased by 2·4 times in type 1 diabetes and 1·4 times in type 2 diabetes. For the first time, to our knowledge, we have shown that people with recent admissions history for hypoglycaemia and diabetic ketoacidosis have an increased risk of severe or fatal disease. People with a history of smoking had increased risks. Prior specific comorbidities, including heart disease, liver disease, and chronic lower respiratory disease, also increased risk. We showed for the first time, to our knowledge, that being exposed to more drug classes and having more previous hospital admissions are markers of risk. A risk prediction model achieved a C-statistic of 0·85. We provided a Shiny app to give the reader a sense of how individual risk factor profiles in people with diabetes translate into elevated risks compared with those without diabetes.

Implications of all the available evidence

During phases of the COVID-19 pandemic, when the effective reproduction number is high, those people with diabetes who are most at risk might warrant special protection measures. A risk prediction score based on medical history can usefully identify those with diabetes who are most at risk, and we provide an example of such a score.

in-hospital and total deaths.[10–14] Guidelines accordingly describe all individuals with diabetes as being at elevated risk,[8,15] but it is probable that among those with diabetes some are at very high risk, warranting special protection measures, whereas others are not at much more risk than the general population. As we continue through the second wave of the pandemic, greater understanding of variation in COVID-19 risk in people with diabetes is needed to tailor protection measures and inform vaccine strategies.

Only one study[13] has explored determinants of COVID-19 risk among people with diabetes to any extent, and Black and south Asian ethnicity, lower socioeconomic status, poorer glycaemic control, and previous cardiovascular disease are reported to increase risks.[13,14] Beyond age, sex, and diabetes duration, BMI was the only other predictor for being hospitalised with COVID-19 in a large French case series.[16]

In this study, for the total population of Scotland, we aimed to compare the cumulative risk of fatal or critical care unit-treated COVID-19 in all people with and without diabetes, to ascertain which factors were associated with fatal or critical care unit-treated COVID-19 among people with diabetes, and to build a cross-validated risk prediction model. Our focus was on fatal or critical care unit-treated COVID-19 because rates of testing positive or being hospitalised with COVID-19 are biased due to selective testing and hospitalisation policies.

Methods

Study design and participants

In this cohort study, we used data from the first wave of the pandemic in Scotland, from March 1, 2020, when the first case was identified, to July 31, 2020, when infection rates had dropped sufficiently that shielding measures were officially terminated. The participants were the total population of Scotland (n=5 463 300), including all those with diabetes nationwide (n=319 349), who were alive 3 weeks before the start of the pandemic in Scotland (estimated as Feb 7, 2020).

This research was conducted with approval from the Public Benefit Privacy Protection Panel (1617-0147), with approval from the Scotland A Research Ethics Committee (11/AL/0225).

Procedures

For the total population of Scotland, evidence of any detected COVID-19 was defined as having had a positive RT-PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a hospital discharge code for COVID-19, or a COVID-19 code (U071 or U072) anywhere on the death certificate. The databases used were the Electronic Communication of Surveillance in Scotland database, which captures all National Health Service (NHS) virology testing, the RAPID database of daily hospitalisations, the Scottish Morbidity Records-01 of hospital discharges, and the National Records of

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Scotland death registrations data. These health-related databases in Scotland are linkable because they all use the Community Health Index unique identifier. The Community Health Index database also yielded data on age, sex, residential postcode, and residential care home status. For all cases, whether critical care had been provided was obtained by linkage to the Scottish Intensive Care Society and Audit Group (SICSAG) database. Critical care included all admissions to an intensive care unit, high dependency unit, or combined intensive care and high dependency unit. Fatal COVID-19 was defined on the basis of a U071 or U072 code anywhere on the death certificate or any death within 28 days of testing positive for COVID-19. These are the official death definitions used by National Register of Scotland and Public Health Scotland.

To identify diabetes status among all people with COVID-19, we linked COVID-19 data to the national diabetes register (Scottish Care Information (SCI)-Diabetes) and its associated research platform. As described elsewhere,[17,18] the diabetes research database has more than 99% coverage of all people with a diabetes diagnosis in Scotland. Inception into SCI-Diabetes occurs when a diagnostic code for diabetes is assigned in primary or secondary care across Scotland, followed by nightly uploads of key data items from primary, secondary, and community clinical care into a federated NHS database. These data include diabetes type and clinical measurements, such as BMI, blood pressure, laboratory results, smoking history, and annual screening retinopathy grade, which we have used in our analysis. Regular extracts from this database are linked to other datasets, including hospitalisations (Scottish Morbidity Records-01), dispensed prescriptions (Prescribing Information System), renal registry, deaths, and other routine datasets, using the Community Health Index number, and they are then anonymised and imported into the research platform. Records for all people who were alive in the register at the start of the epidemic were used in this analysis (n=319 349). A detailed description of key variables from the database that were used in the analysis is in the appendix (p 2).

See Online for appendix

All people with diabetes were assigned to their relevant quintile of the residential postcode-based indicator, the Scottish Index of Multiple Deprivation.[19] Self-assigned ethnic group was obtained from SCI-Diabetes and residential care home status was captured from the Community Health Index database.

From the diabetes research platform, all hospital discharge codes from Scottish Morbidity Records-01 during the past 5 years, as well as Anatomical Therapeutic Chemical codes from Prescribing Information System data for the past 3 years were extracted and used to define comorbid conditions and previous drug exposure. We derived the history of a specific list of conditions and drug classes that have been included as risk conditions for COVID-19 by public health agencies, hereafter termed listed conditions[15] (codes are in the appendix pp 3–8).

For the **WHO anatomical therapeutic chemical classification** see https://www.whocc.no/atc_ddd_index/

Outcomes

We assessed the cumulative incidence of fatal or critical care unit-treated COVID-19 in people with and without diabetes between March 1, 2020, and July 31, 2020. We calculated excess deaths as the difference between the weekly death counts in 2020 and the average weekly deaths for the same week during 2015–19. The excess death for any given period is the sum of the weekly excess death in that period. We also calculated the association of risk factors for fatal or critical care unit-treated COVID-19 among people with diabetes, which we used to construct a risk prediction model for fatal or critical care unit-treated COVID-19 among those with diabetes.

Statistical analysis

For calculating cumulative incidence (risk), we used the age-specific and sex-specific counts of people with fatal or critical care unit-treated COVID-19 in those with and without diabetes across the study period. The age and sex distribution of people with diabetes as of 3 weeks before the first observed positive test nationally was available from SCI-Diabetes. To obtain the at-risk population for those without diabetes, we used the most recent publicly available 1-year age and sex band counts of the total Scottish population available from National Records of Scotland, from mid-2019.[20] We assumed these counts pertained at the start of the pandemic. From this number, we subtracted the number of people who were alive in the diabetes register in each sex-specific age band, to give the population without diabetes. We summarised the relative difference in cumulative incidence of fatal or critical care unit-treated COVID-19 up to July 31, 2020, in people with and without diabetes by sex as the odds ratio from a logistic regression model using 1-year age band and sex-specific counts of cases and denominators.

For the population with diabetes, the weekly counts of total deaths for the at-risk population in each of the past 5 years was available from the SCI-Diabetes research. We plotted the total number of deaths per week in 2020 in people with diabetes, along with the weekly average for the same week for 2015–19, with the difference representing excess deaths.

Using the SCI-Diabetes research platform, we described sociodemographic variables, the listed conditions,[15] and potential vascular and diabetes-specific risk factors in individuals with diabetes who did and did not develop fatal or critical care unit-treated COVID-19. The association of each risk factor with fatal or critical care unit-treated COVID-19 was then reported using logistic regression, adjusting for age, sex, diabetes duration, and type of diabetes. In total, the associations of 35 variables were tested. We report p values unadjusted for multiplicity. Global p values were calculated using a likelihood ratio test, comparing models with and without the variable using the R stats[21] drop1 function (R version 3.6.0). For regression, missing variables were imputed using

	0–39 years	40–49 years	50–59 years	60–69 years	70–79 years	≥80 years	Total
All	22 264	24 863	58 438	81 606	80 909	51 269	319 349
Patients with fatal or critical care unit-treated COVID-19	5 (<0·05%)	25 (0·1%)	80 (0·1%)	134 (0·2%)	306 (0·4%)	532 (1·0%)	1082 (0·3%)
Sex							
Male	11 821	14 402	34 968	49 001	46 201	24 093	180 486
With fatal or critical care unit-treated COVID-19	2 (<0·05%)	15 (0·1%)	54 (0·2%)	99 (0·2%)	206 (0·4%)	281 (1·2%)	657 (0·4%)
Female	10 443	10 461	23 470	32 605	34 708	27 176	138 863
With fatal or critical care unit-treated COVID-19	3 (<0·05%)	10 (0·1%)	26 (0·1%)	35 (0·1%)	100 (0·3%)	251 (0·9%)	425 (0·3%)
Diabetes type							
Type 1	14 732	5747	6333	4486	2227	858	34 383
With fatal or critical care unit-treated COVID-19	2 (<0·05%)	5 (0·1%)	10 (0·2%)	7 (0·2%)	14 (0·6%)	13 (1·5%)	51 (0·1%)
Type 2	6507	18 072	50 273	75 031	76 792	49 285	275 960
With fatal or critical care unit-treated COVID-19	2 (<0·05%)	17 (0·1%)	68 (0·1%)	125 (0·2%)	285 (0·4%)	511 (1·0%)	1008 (0·4%)
Other types	1025	1044	1832	2089	1890	1126	9006
With fatal or critical care unit-treated COVID-19	1 (0·1%)	3 (0·3%)	2 (0·1%)	2 (0·1%)	7 (0·4%)	8 (0·7%)	23 (0·3%)

Data are n or n (%).

Table 1: **Cumulative incidence of fatal or critical care unit-treated COVID-19 in people with diabetes in Scotland, by age, sex, and diabetes type by July 31, 2020**

chained equations assuming data were missing at random using the Amelia[22] package (appendix p 9).

Using the same data on 35 covariates, we constructed a multivariable risk prediction model of fatal or critical care unit-treated COVID-19 among individuals with diabetes. Age, sex, diabetes type, diabetes duration were fitted simultaneously as the baseline model. The 35 covariates and interaction terms for age–sex, age–diabetes type, sex–diabetes type were made available for selection into the final model. We used the *mfp* package in R[23,24] to first ascertain whether any of the continuous variables should be fitted with any additional polynomial terms because of departure from linearity (appendix p 9). We then used stepwise regression, alternating between forward and backward steps, implemented in the R function stats::step, to maximise the Akaike Information Criterion, selecting any additional potential factors as being predictive of fatal or critical care unit-treated COVID-19. The predictive performance of the base model and final model were evaluated by 20-fold cross validation with performance, calculated across all test folds as the C-statistic, and also as the expected information for discrimination using the *wevid* package (appendix p 9).[25]

The COVID-19-age for an individual with diabetes can be defined as the age at which the risk of COVID-19 in an individual of the same sex without diabetes equates to the risk in the individual with diabetes under study. This age can be derived from the final risk model in those with diabetes and the modelled risks in those without diabetes (appendix p 9). To enable a user to calculate the COVID-19-age for an individual with diabetes and a given set of characteristics, we generated a Shiny application. The purpose of the Shiny app is to give the reader a sense of how individual risk factor profiles in people with diabetes translate into elevated risks compared with people without diabetes. This modelling study is registered as an International Standard Randomised Controlled Trial, ISCRTN45562523.

For the **Shiny application** see https://diabepi.shinyapps.io/covidrisk/

Role of the funding source

There was no funding source for this study. The corresponding author (HMC) and SJM had full access to the data, and the corresponding author had the final decision to submit for publication.

Results

Of the total Scottish population at the start of the pandemic on March 1, 2020 (n=5 463 300), the population without diabetes was 5 143 951 (94·2%). Among the remaining 319 349 people with diabetes, by July 31, 2020, 2724 (0·9%) had any evidence of COVID-19, including 1082 (0·3%) who had developed fatal or critical care unit-treated COVID-19, of whom 963 (0·3%) died. More details of case and severity ascertainment are in the appendix (appendix pp 10, 12).

Among people with diabetes in Scotland, the risk of fatal or critical care unit-treated COVID-19 increased with age (table 1). Just 30 (2·8%) of 1082 people with fatal or critical care unit-treated COVID-19 were younger than 50 years (all aged >20 years) and 972 (89·9%) were aged 60 years or more. The overall risk was 0·4% in males and 0·3% in females. Overall, 51 (0·1%) of 34 383 people with type 1

diabetes and 1008 (0·4%) of 275 960 with type 2 diabetes developed fatal or critical care unit-treated COVID-19 (table 1).

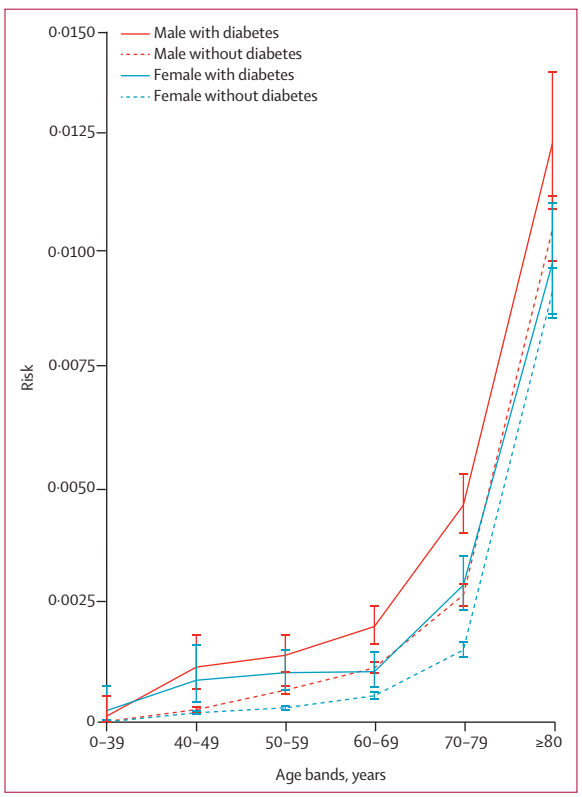

Figure 1: **Risk of fatal or critical care unit-treated COVID-19 in the national population of Scotland with and without diabetes by age band and sex by July 31, 2020**
Solid lines represent people with diabetes and dashed lines represent people without diabetes. Error bars indicate 95% CIs.

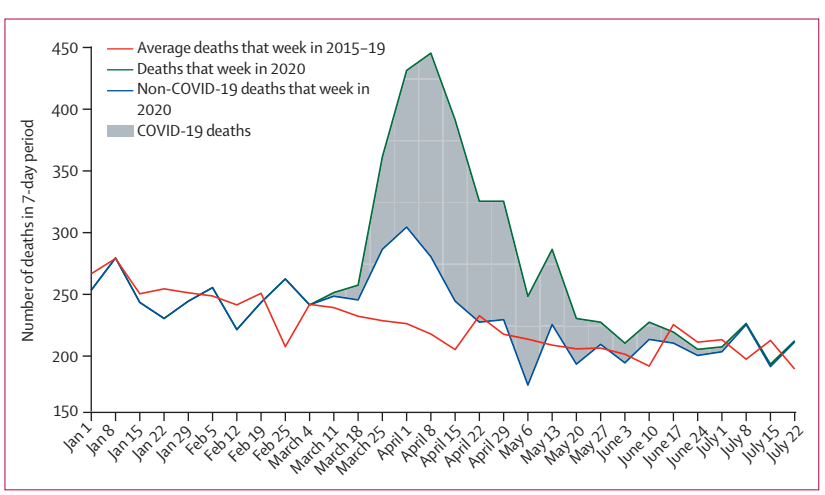

Figure 2: **Weekly deaths from all causes and causes other than COVID-19 in people with diabetes in Scotland during 2020 compared with average deaths in that week from 2015–19**
Dates denote the start of each 7-day interval. The difference between the deaths in 2020 and average deaths in 2015–19 is excess deaths during that period. The grey zone depicts how many deaths were attributable to COVID-19.

In the total population of Scotland without diabetes, 4081 (0·1%) of 5 143 951 people developed fatal or critical care unit-treated COVID-19 (appendix p 16). The increase in risk of fatal or critical care unit-treated COVID-19 that was associated with diabetes was apparent in both sexes and at all age bands (figure 1).

We plotted the total deaths among people with diabetes for every 7-day period since Jan 1, 2020, against the average number of deaths in that same period in 2015–19, the difference between which represents excess deaths (figure 2). Total deaths exceeded the weekly average from 2015–19 from early March and returned to the average by early June. Altogether, in the first wave of the pandemic between March 1 and July 31, 2020, there were 1228 excess deaths in comparison to the average for this period in 2015–19, and 963 (78·4%) of these were due to COVID-19.

Adjusted for age and sex in a logistic regression, as of July 31, 2020, diabetes was associated with an odds ratio (OR) of 1·395 (95% CI 1·304–1·494; p<0·0001) for fatal or critical care unit-treated COVID-19, with similar ORs for males and females (appendix p 17). For type 1 diabetes, the OR was 2·396 (1·815–3·163; p<0·0001), and for type 2 diabetes the OR was 1·369 (1·276–1·468; p<0·0001). There was a statistically significant interaction between diabetes and age on the risk of fatal or critical care unit-treated COVID-19 (p<0·0001), with an OR of 2·494 (2·032–3·061) for those aged 0–59 years, an OR of 1·764 (1·457–2·136) for those aged 60–69 years, and an OR of 1·327 (1·227–1·434) for those aged 70 years or more (appendix p 17). When the analysis was limited to various timepoints after the start of the pandemic, the OR associated with diabetes was highest at the end of March at 1·770 (1·566–2·002) and fell to 1·446 (1·343–1·557) by the end of April.

We assessed the associations of risk factors with fatal or critical care unit-treated COVID-19 among people with diabetes; unadjusted characteristics are in table 2. These data are shown by type of diabetes in the appendix (pp 16–19). The ORs for fatal or critical care unit-treated COVID-19 for age, sex, diabetes type, diabetes duration, and other risk factors (separately adjusted for age, sex, and diabetes type and duration) are shown in table 3. Our analysis is based on these adjusted data. Data for continuous variables divided into categories, including missingness, are in the appendix (pp 20–21).

As shown in table 3, older age, male sex, and longer diabetes duration were all associated with significant increased risk of fatal or critical care unit-treated COVID-19. Adjusted for these factors, the type of diabetes was not associated with any significant difference in risk. Living in a residential care home was associated with a large, significant increased risk of fatal or critical care unit-treated COVID-19 (OR 16·570, 95% CI 14·326–19·165; p<0·0001). The sociodemographic quintile showed a significant gradient in risk falling from the most to least deprived quintile. There was no significant variation in risk by ethnic group. It should be noted, however, that the

prevalence of non-White ethnicities in this diabetes population (table 2) is too low, commensurate with the background general population of Scotland, to have any power to detect ethnic variation in COVID-19 risk among people with diabetes.

In terms of comorbidities and clinical factors, the number of previous hospitalisations for hypoglycaemia, diabetic ketoacidosis, and other reasons in the past 5 years was strongly associated with fatal or critical care unit-treated COVID-19 (table 3). Each of the co-morbid conditions listed as risk conditions for COVID-19 showed strong, significant associations with fatal or critical care unit-treated COVID. Risk increased with increasing HbA_{1c}. There was no significant linear relationship between BMI and disease (OR 1·002, 95% CI 0·991–1·013; p=0·71; table 3). However, the multivariable fractional polynomials analysis revealed evidence for a statistically significant, non-linear, J-shaped relationship with BMI (appendix p 13 shows the relationship from the *mfp* analysis). People who developed fatal or critical care unit-treated COVID-19 had significantly lower systolic blood pressure than those who did not. Being on any antihypertensive was associated with a significantly lower risk of fatal or critical care unit-treated COVID-19 (OR 0·801, 0·705–0·909; p=0·0006). More detailed exploration of type of antihypertensives showed that the point estimate for the OR for each antihypertensive subclass was below 1, except for the rarely used centrally-acting class (appendix pp 20–21). In people who developed fatal or critical care unit-treated COVID, the estimated glomerular filtration rate was significantly lower and the prevalence of albuminuria was higher than in those who did not. Having retinopathy was significantly associated with developing fatal or critical care unit-treated COVID-19, as was having a history of smoking, although the risk was not significantly higher in current versus never smokers.

Significant increased risks were found in recipients versus non-recipients of several drug classes, including non-steroidal anti-inflammatory drugs, proton-pump inhibitors and anti-coagulants (table 3). The more diabetes drug subclasses used in the past three years, the greater the risk of fatal or critical care unit-treated COVID-19 disease. Having been on insulin or sulphonylureas was associated with the highest risks (appendix p 21). The number of different types of drugs other than those used for diabetes that a person had been exposed to in the past 3 years was strongly associated with fatal or critical care unit-treated COVID (table 3).

The distribution of characteristics in people with and without fatal or critical care unit-treated COVID-19 by type of diabetes is in the appendix (pp 18–19). Broadly the same pattern of associations was found for type 1 and type 2 diabetes. The main differences were that diabetic ketoacidosis and hypoglycaemia admission rates, and the differences between people with and without fatal or critical care unit-treated COVID-19 were greater for type 1 than type 2 diabetes. A sensitivity analysis restricted to the fatal cases showed the same pattern of associations as was found for fatal or critical care unit-treated COVID-19.

For the risk prediction model for fatal or critical care unit-treated COVID-19 among those with diabetes,

	Without fatal or critical care unit-treated COVID-19 (n=318 267)	Fatal or critical care unit-treated COVID-19 (n=1082)	Total diabetes population (n=319 349)
Sociodemographic characteristics			
Age, years	66·7 (56·3–75·8)	79·9 (71·4–85·7)	66·7 (56·3–75·8)
Diabetes duration, years	10·5 (5·7–16·6)	13·5 (8·0–19·2)	10·5 (5·7–16·6)
Care home resident	5897 (1·9%)	397 (36·7%)	6294 (2·0%)
Deprivation index			
Quintile 1 (most deprived)	73 188 (23·0%)	322 (29·8%)	73 510 (23·0%)
Quintile 2	71 102 (22·3%)	264 (24·4%)	71 366 (22·3%)
Quintile 3	63 401 (19·9%)	188 (17·4%)	63 589 (19·9%)
Quintile 4	56 203 (17·7%)	173 (16·0%)	56 376 (17·7%)
Quintile 5 (least deprived)	46 251 (14·5%)	102 (9·4%)	46 353 (14·5%)
Unknown	8122 (2·6%)	33 (3·0%)	8155 (2·6%)
Ethnicity			
White	237 205 (74·5%)	870 (80·4%)	238 075 (74·6%)
South Asian	9218 (2·9%)	16 (1·5%)	9234 (2·9%)
Black	1589 (0·5%)	5 (0·5%)	1594 (0·5%)
Chinese	1205 (0·4%)	4 (0·4%)	1209 (0·4%)
Other	12 103 (3·8%)	30 (2·8%)	12 133 (3·8%)
Unknown	56 947 (17·9%)	157 (14·5%)	57 104 (17·9%)
Comorbidities			
Any diabetic ketoacidosis admission in past 5 years	6623 (2·1%)	23 (2·1%)	6646 (2·1%)
Any hypoglycaemia admission in past 5 years	5769 (1·8%)	73 (6·7%)	5842 (1·8%)
Number of other hospital admissions in past 5 years	1·0 (0·0–3·0)	5·0 (2·0–11·0)	1·0 (0·0–3·0)
Any heart disease	100 482 (31·6%)	696 (64·3%)	101 178 (31·7%)
Asthma or chronic lower airway disease	105 066 (33·0%)	504 (46·6%)	105 570 (33·1%)
Neurological and dementia (excluding epilepsy)	15 076 (4·7%)	232 (21·4%)	15 308 (4·8%)
Liver disease	3075 (1·0%)	29 (2·7%)	3104 (1·0%)
Immune disease or on immunosuppressants	4078 (1·3%)	24 (2·2%)	4102 (1·3%)
Any listed condition	165 813 (52·1%)	896 (82·8%)	166 709 (52·2%)
Other clinical measures			
Insulin pump use	4811 (1·5%)	1 (0·1%)	4812 (1·5%)
Flash glucose monitor use	11 711 (3·7%)	6 (0·6%)	11 717 (3·7%)
HbA_{1c}, mmol/mol	57 (49–70)	58 (47–71)	57 (49–70)
HbA_{1c}, %	7·37 (6·63–8·55)	7·46 (6·45–8·65)	7·37 (6·63–8·55)
BMI, kg/m²	30 (27–35)	29 (25–33)	30 (27–35)
Systolic blood pressure, mm Hg	134 (124–142)	132 (122–142)	134 (124–142)
Diastolic blood pressure, mm Hg	77 (70–82)	74 (67–80)	77 (70–82)
Total cholesterol, mmol/L	4 (4–5)	4 (3–5)	4 (4–5)
Estimated glomerular filtration rate, mL/min/1·73m²	83 (65–97)	64 (44–82)	83 (65–97)

(Table 2 continues on next page)

	Without fatal or critical care unit-treated COVID-19 (n=318 267)	Fatal or critical care unit-treated COVID-19 (n=1082)	Total diabetes population (n=319 349)
(Continued from previous page)			
Albuminuric status			
Normal	131 192 (41·2%)	300 (27·7%)	131 492 (41·2%)
Micro	55 417 (17·4%)	235 (21·7%)	55 652 (17·4%)
Macro	11 353 (3·6%)	77 (7·1%)	11 430 (3·6%)
Unknown	120 305 (37·8%)	470 (43·4%)	120 775 (37·8%)
Retinopathy			
None	200 428 (63·0%)	618 (57·1%)	201 046 (63·0%)
Non referable	48 624 (15·3%)	160 (14·8%)	48 784 (15·3%)
Referable or eye clinic	28 170 (8·9%)	134 (12·4%)	28 304 (8·9%)
Unknown	41 045 (12·9%)	170 (15·7%)	41 215 (12·9%)
Tobacco smoking status			
Current smoker	50 734 (15·9%)	111 (10·3%)	50 845 (15·9%)
Ex-smoker	153 181 (48·1%)	679 (62·8%)	153 860 (48·2%)
Never smoked	111 292 (35·0%)	287 (26·5%)	111 579 (34·9%)
Unknown	3060 (1·0%)	5 (0·5%)	3065 (1·0%)
Drug exposures			
Lipid lowering	210 701 (66·2%)	806 (74·5%)	211 507 (66·2%)
Proton pump inhibitors	132 581 (41·7%)	582 (53·8%)	133 163 (41·7%)
Non-steroidal anti-inflammatory drugs	143 947 (45·2%)	698 (64·5%)	144 645 (45·3%)
Anti-coagulants and anti-platelets	112 983 (35·5%)	667 (61·6%)	113 650 (35·6%)
Antihypertensives (any)	198 117 (62·2%)	713 (65·9%)	198 830 (62·3%)
Number of ATC level 3 drug classes (excluding for diabetes)	8·0 (4·0–12·0)	11·0 (8·0–15·0)	8·0 (4·0–12·0)
Number of diabetes drug classes prescribed	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)

Data are n (%) or median (IQR). Comorbid conditions and drug exposures are for the past 3 years. ATC=anatomical therapeutic classification.

Table 2: **Characteristics of all people with diabetes in Scotland who did and did not develop fatal or critical care unit-treated COVID-19 by July 31, 2020**

For more on **excess mortality during the COVID-19 pandemic** see https://ourworldindata.org/excess-mortality-covid

table 4 shows the final set of covariates retained in the stepwise selection model (in addition to age, sex, and diabetes type and duration) that were entered as fixed covariates. The multivariable fractional polynomials analysis indicated that the association with the number of hospital admission was best entered into the model as log(admissions + 1) and that terms for both BMI and log(BMI) should be included. It should be noted that the selection was based on the Akaike information criterion and not p values. Terms for interactions between age and type of diabetes, sex and type, and age by sex were not selected. The C-statistic for the baseline model (containing only age, sex, and diabetes type and duration) was 0·76 (95% CI 0·75–0·77), whereas the cross-validated, stepwise model retained a further 11 factors and had a C-statistic of 0·85 (0·83–0·86; appendix p 14). The cross-validated model was well calibrated (appendix p 15) and the Hosmer Lemeshow test was not statistically significant at p=0·38.

Discussion

This report highlights the elevation with diabetes in risk of fatal or critical care unit-treated COVID-19. The elevation in risk relative to the population without diabetes adjusted for age and sex was higher for type 1 diabetes (2·4 times) than for type 2 (1·4 times). This greater elevation in type 1 diabetes is probably accounted for by longer duration of diabetes because in the older age bands, cumulative incidence was higher in type 1 than type 2 diabetes and because, among people with diabetes, no significant difference in risk by type was found once age, sex, and diabetes duration were adjusted for. However, the lower overall age distribution in type 1 than type 2 diabetes, and the strong association of older age with risk, meant that overall a lower proportion of people with type 1 than type 2 diabetes developed fatal or critical care unit-treated COVID-19. Although there were no cases of fatal or critical care unit-treated COVID-19 in people with diabetes younger than 20 years, above this age an elevation in the risk associated with diabetes was apparent.

In terms of absolute risk, three people with diabetes in every 1000 developed fatal or critical care unit-treated COVID-19 up to July 31, 2020. The effect on weekly deaths was clearly discernable and peaked in early April. Of note, the excess in deaths was not all explained by COVID-19 designated deaths; this could represent under-ascertainment of COVID-19 deaths but could also reflect the knock-on effect on health services of the pandemic.

We focused on fatal or critical care unit-treated COVID-19 because the probability of being tested or hospitalised for any given level of symptoms could easily vary by diabetes status, leading to observation bias. Another important potential bias might be termed at-risk bias. Diabetes was named early in the pandemic as a moderate risk condition. Therefore, people with diabetes might have adopted social distancing measures more stringently than those without diabetes, which could bias the OR downwards. Indeed, consistent with this factor, when the analysis was limited to various timepoints since the start of the pandemic, the OR associated with diabetes was highest at the end of March, at 1·770, (95% CI 1·566–2·002), falling to 1·395 (1·304–1·494) by the end of July. Depletion of those most susceptible to severe infection early in the pandemic could also have caused the OR to fall over time because susceptibility is higher in people with diabetes. However, we have no direct data to prove these potential explanations.

There are few other studies with general population denominators allowing the relative risk of COVID-19 in those with diabetes relative to the background population to be estimated. In the OpenSAFELY study,[11] primary care records in England were linked to death certification records. The OR adjusted for age and sex for COVID-death associated with diabetes was 1·6 for people with an HbA_{1c} of less than 58 mmol/mol and was 2·6 for people with HbA_{1c} greater than this level, although type of diabetes was not differentiated.[11] In an analysis of the UK

	Odds ratio (95% CI)	p value
Sociodemographic		
Age	1·076 (1·071–1·082)	<0·0001
Sex	..	(global) <0·0001
Male	1 (ref)	..
Female	0·705 (0·623–0·798)	<0·0001
Diabetes type	..	(global) 0·69
Type 2	1 (ref)	..
Type 1	1·087 (0·789–1·498)	0·61
Other types	0·869 (0·574–1·317)	0·51
Diabetes duration	1·016 (1·009–1·022)	<0·0001
Care home resident	16·570 (14·326–19·165)	<0·0001
Any hypoglycaemia admission in past 5 years	3·178 (2·480–4·072)	<0·0001
Deprivation index	..	(global) <0·0001
Quintile 1 (most deprived)	1 (ref)	..
Quintile 2	0·732 (0·622–0·862)	0·0002
Quintile 3	0·545 (0·455–0·653)	<0·0001
Quintile 4	0·556 (0·462–0·669)	<0·0001
Quintile 5 (least deprived)	0·379 (0·303–0·473)	<0·0001
Ethnicity	..	(global) 0·086
White	1 (ref)	..
South Asian	0·616 (0·368–1·033)	0·066
Black	1·770 (0·727–4·311)	0·21
Chinese	0·784 (0·267–2·295)	0·66
Other	0·740 (0·513–1·066)	0·11
Comorbidities		
Any diabetic ketoacidosis admission in past 5 years	2·869 (1·846–4·460)	<0·0001
Any hypoglycaemia admission in past 5 years	3·178 (2·480–4·072)	<0·0001
Ever admitted to hospital in past 5 years	3·307 (2·789–3·922)	<0·0001
Any heart disease	2·425 (2·135–2·754)	<0·0001
Asthma or chronic lower airway disease	1·691 (1·500–1·907)	<0·0001
Neurological and dementia (excluding epilepsy)	3·810 (3·284–4·421)	<0·0001
Liver disease	3·021 (2·082–4·384)	<0·0001
Immune disease or on immunosuppressants	2·334 (1·552–3·510)	<0·0001
Any listed condition	3·167 (2·701–3·713)	<0·0001
(Table 3 continues in next column)		
(Continued from previous column)		
Other clinical measures		
Insulin pump use	0·330 (0·046–2·372)	0·27
Flash glucose monitor use	0·414 (0·176–0·973)	0·043
HbA_{1c}	1·010 (1·006–1·014)	<0·0001
BMI	1·002 (0·991–1·013)	0·71
Systolic blood pressure	0·986 (0·982–0·990)	<0·0001
Diastolic blood pressure	0·994 (0·987–1·001)	0·074
Total cholesterol	1·035 (0·974–1·100)	0·27
Estimated glomerular filtration rate	0·992 (0·988–0·995)	<0·0001
Albuminuric grade	..	(global) <0·0001
Normal	1 (ref)	..
Micro	1·352 (1·155–1·583)	0·0002
Macro	1·922 (1·519–2·430)	<0·0001
Retinopathy grading	..	(global) <0·0001
None	1 (ref)	..
Non referable	1·161 (0·975–1·382)	0·094
Referable or eye clinic	1·672 (1·377–2·032)	<0·0001
Tobacco smoking	..	(global) 0·0011
Never smoked	1 (ref)	..
Ex-smoker	1·296 (1·126–1·491)	0·0003
Current smoker	1·133 (0·907–1·416)	0·27
Drug exposures		
Any lipid lowering	1·126 (0·981–1·293)	0·091
Any proton pump inhibitor	1·412 (1·252–1·593)	<0·0001
Any non-steroidal anti-inflammatory drugs	1·848 (1·630–2·097)	<0·0001
Any anticoagulants	1·663 (1·466–1·887)	<0·0001
Any antihypertensive	0·801 (0·705–0·909)	0·0006
Number of ATC level 3 drug classes (excluding for diabetes)	1·079 (1·068–1·091)	<0·0001
Number of diabetes drug classes prescribed	1·139 (1·083–1·199)	<0·0001

Diabetes duration was adjusted for age. Sex and diabetes type were adjusted for age and diabetes duration. All other associations were adjusted for age, sex, diabetes duration, and diabetes type. Comorbid conditions and drug exposures are for the past 3 years. Ref=reference. ATC=anatomical therapeutic classification.

Table 3: **Logistic regression of the association of characteristics with having fatal or critical care unit-treated COVID-19 in people with diabetes**

Biobank study, diabetes was associated with a relative risk of 1·91 for COVID-19 hospitalisation.[26] In the English National Audit cohort,[13,14] the risk ratio of COVID-19 death for type 1 diabetes was 3·51 and for type 2 it was 2·03; these were attenuated in White people (3·06 for type 1 and 1·91 for type 2). In a matched case control study[27] of the total population of Scotland from earlier in the pandemic and not including cases derived solely from hospital admissions (which were not yet available), we reported slightly higher conditional ORs of 2·75 (95% CI 1·96–3·88) for type 1 diabetes and 1·60 (1·48–1·74) for type 2 diabetes. All these studies are therefore consistent in finding elevations in risk for type 1 and type 2 diabetes in the same range. However, the OR for diabetes will vary somewhat depending on the stage of the pandemic and with ethnicity distribution, as well as whether out-of-hospital deaths are captured. Studies that do not capture out-of-hospital deaths might preferentially omit older cases and will report a higher summary OR because the OR varies with age.

We found that risk of fatal or critical care unit-treated COVID-19 in diabetes rose steeply with age and was

	Odds ratio (95% CI)	p value
Sociodemographic		
Age	1·044 (1·036–1·051)	<0·0001
Sex	..	(global) <0·0001
Male	1 (ref)	..
Female	0·535 (0·470–0·608)	<0·0001
Diabetes type	..	(global) 0·62
Type 2	1 (ref)	..
Type 1	1·119 (0·806–1·553)	0·50
Other types	0·866 (0·567–1·321)	0·50
Diabetes duration	0·998 (0·990–1·006)	0·59
Care home resident	10·828 (9·251–12·675)	<0·0001
Deprivation index	..	(global) <0·0001
Quintile 1 (most deprived)	1 (ref)	..
Quintile 2	0·848 (0·718–1·002)	0·052
Quintile 3	0·619 (0·514–0·744)	<0·0001
Quintile 4	0·656 (0·542–0·793)	<0·0001
Quintile 5 (least deprived)	0·484 (0·385–0·607)	<0·0001
Comorbidities		
log(number of other hospital admissions in past 5 years + 1)	1·595 (1·481–1·717)	<0·0001
Neurological and dementia (excluding epilepsy)	1·273 (1·081–1·499)	0·0038
Other clinical measures		
HbA_{1c}	1·005 (1·001–1·009)	0·0084
BMI	1·091 (1·047–1·136)	<0·0001
log(BMI)	0·080 (0·022–0·291)	0·0001
Estimated glomerular filtration rate	0·992 (0·989–0·995)	<0·0001
Systolic blood pressure	0·994 (0·990–0·998)	0·0043
Drug exposures		
Any antihypertensive	0·792 (0·687–0·913)	0·0013
Number of diabetes drug classes prescribed	1·065 (1·004–1·129)	0·036
Number of ATC level 3 drug classes (excluding for diabetes)	1·027 (1·013–1·041)	0·0002

Age, sex, diabetes duration, and type of diabetes were entered as the baseline model. The remaining variables were retained by the stepwise procedure using the Akaike information criterion. The C-statistic for the baseline model was 0·76 (95% CI 0·75–0·77) and for the full model was 0·85 (0·83–0·86). The expected information for discrimination was 0·75 bits for the base model and 1·54 for the full model. Model coefficients are in the appendix (p 22). Comorbid conditions and drug exposures are for the past 3 years. Ref=reference. ATC=anatomical therapeutic classification.

Table 4: **Stepwise logistic regression of association of characteristics with fatal or critical care unit-treated COVID-19 in people with diabetes**

higher in males, as has been reported in many other populations.[28] More than a third of people with diabetes who developed fatal or critical care unit-treated COVID-19 lived in residential care homes, emphasising the crucial importance of protecting such vulnerable individuals during the remainder of this pandemic. There was a strong socioeconomic gradient.

We showed that, when adjusted for age, sex, and diabetes duration, people who developed fatal or critical care unit-treated COVID-19 on average had worse profiles for almost every clinical measure we examined; they were more likely to have other comorbidities and evidence of diabetic microvascular disease (with more impaired renal function and retinopathy). On average, they had worse glycaemic control and were more likely to have had a previous diabetic ketoacidosis or hypoglycaemia hospitalisation and other hospitalisations in the past 5 years. They were on more diabetes and non-diabetes medications. We also found strong associations with non-steroidal anti-inflammatory drugs and proton pump inhibitors, which are among the most commonly prescribed drugs and are often markers of polypharmacy. They were more likely to have smoked. We found a J shaped relationship with BMI. Surprisingly, although strong associations of hypertension with COVID-19 have been reported elsewhere,[5–7] we found that people who developed fatal or critical care unit-treated COVID-19 had slightly lower blood pressures than those who did not, and that being on antihypertensives was associated with a lower risk than not being on any. Among the specific antihypertensive drug classes, thiazides and angiotensin 2 receptor antagonists or blockers had the lowest ORs.

Similar associations of age, sex, diabetes duration, socioeconomic status, prior cardiovascular disease, renal status, blood pressure, and glycaemic control with death from COVID-19 were found in the English National Audit study.[13,14] In that study, non-White ethnicity was found to be associated with COVID-19 death, whereas in Scotland the prevalence of non-White ethnic groups is too low to allow detection of any ethnicity-related differences in COVID-19; only 2·9% of those with diabetes are known to be of south Asian origin and 0·5% of Black origin. We found that being on antihypertensive drugs was associated with a lower risk, but the English National Audit study found an increased risk.[13,14] However, that higher risk was driven by a large effect in south Asian and mixed ethnicity groups and was not seen in White people or other ethnic groups. The U-shaped association with BMI in the English National Audit study was stronger than the J-shaped relationship that we found. This difference is probably also driven by the different ethnic mix in the studies, because the relationship of higher BMI to higher risk was most apparent in those of non-White ethnicity in the English National Audit study. The increased risk at lower BMI, including underweight, in both studies probably reflects comorbid effects related to fatal or critical care unit-treated COVID-19 that are associated with weight loss. Given the elevation in BMI among people with type 2 diabetes, it would not be surprising to see such comorbid effects resulting in the nadir of the curve being around the average BMI of 30 kg/m², as was found here. In the English National Audit study, as in ours, ex-smokers were at increased risk, but that study reported that current smokers were at

reduced risk, which we did not find. This difference might reflect that in that study, smoking effects were reported adjusted for all other variables, including possible mediators such as cardiovascular disease. The extensive data on other factors that we examined were not evaluated in the English National Audit study. The extensive factors include previous admissions for diabetic ketoacidosis, hypoglycaemia, and other reasons, and comorbidities and drug exposures.

Such minimally adjusted associations that we have reported are useful as a prelude to building the predictive model of fatal or critical care unit-treated COVID-19 discussed further in what follows. They are also useful for suggesting possible causal mechanisms. Thus, the Scottish Index of Multiple Deprivation differential might be partly mediated through higher levels of smoking, and worse glycaemic control and onward effects on cardiovascular disease and other comorbidities, but might also relate to other unmeasured factors determining infection, such as overcrowding or occupation. However much more extensive modelling methods[29] are needed to infer causality for each of the associated factors and is out of scope here. Such methods are especially needed to understand drug associations, which are hugely susceptible to confounding by indication. Meanwhile, it is worth considering which of the associations we report, if causal, would be modifiable. Improved protection in residential care homes, smoking cessation, improved glucose control, reduction of BMI, optimised management of comorbidities, and medication reviews of polypharmacy are all possible interventions to reduce risk suggested by this analysis, but they require formal analysis. Additionally, the data suggest a protective effect of antihypertensives, but this also requires more detailed causal analyses.

We obtained a reasonable predictive accuracy in our multivariable model with a C-statistic of 0·85; therefore, faced with a case and non-case pair, the model would correctly assign the case as being at higher risk 85% of the time. This level of predictive accuracy disproves the notion that all people with diabetes have similar risk. The variables retained in the model are those that are the most predictive and not necessarily causal; some of the most valuable predictors include the number of hospital admissions in the past 5 years and number of diabetes and non-diabetes drugs, which were not evaluated in other diabetes COVID-19 studies.

The absolute risk of fatal or critical care unit-treated COVID-19 will mostly reflect the stage of the pandemic and the current effective reproduction number (R) in the population.[30] Accordingly, we produced the Shiny app to convert the absolute risk score produced by the prediction model to the COVID-age, ie, the age at which the same absolute risk was observed in a person of the same sex in the population without diabetes at the same stage of the pandemic. This concept of COVID-age is becoming increasingly used in occupational health and is more interpretable than scores that produce absolute risks, such as the QCOVID score.[31] COVID-age should be less susceptible to the prevailing R than absolute risk, but we will monitor the need to recalibrate the underlying models as the pandemic unfolds.

Some key strengths of our study are the total population coverage, the inclusion of out-of-hospital deaths and people who might have died without critical care, the much more extensive exploration of potential prior risk factors than previously studied, and the development of the Shiny app for COVID-age. Limitations of our study are the potential biases noted earlier and that we, as others, do not have quality control data on the assignment of COVID-19 deaths. Furthermore, we do not have the detailed clinical data needed to define severe cases according to WHO criteria[32] or to capture all possible comorbidities. Another limitation is that we had to make an assumption that age and sex band population numbers will not have changed much between mid-2019 and the start of the pandemic in February–March 2020. This is, however, a very reasonable assumption; between 2018 and 2019, the overall change in the Scottish population size was just 0·5%, with no change in those aged 75 years or older.[20] An important limitation is that we have not been able access any other datasets in which to externally validate the risk prediction model. Therefore, its presentation here is primarily to facilitate an understanding of the magnitude of increase in risk that occurs with different risk factor combinations, which is not easily intuited from looking at a table of ORs associated with specific risk factors or markers. We also hope that the model serves as an illustration to those in other countries of an approach they might usefully adopt, which could help people with diabetes and their clinicians to make shielding decisions during the rest of the pandemic. It is likely that our data are relevant to many high-income settings but that in low-income and middle-income countries, the background mixture of other infectious and non-infectious diseases among people with diabetes might vary considerably. Additionally, for many countries, the low prevalence of non-White people in our population means that potentially important ethnicity effects that might pertain are not represented in our model.

Both type 1 and type 2 diabetes are associated with substantial increases in the risk of COVID-19 disease compared with the risks in people of the same age in the background population. However, it is important to consider the absolute number of people with diabetes in our population that have developed severe or fatal disease; three in 1000 people have had fatal or critical care-treated disease. We have shown that, among those with diabetes, the risk of severe disease varies widely and is predictable. This insight should inform shielding policies and vaccine prioritisation strategies. The Shiny app has been provided for illustrative purposes only, to allow a greater understanding of how a prediction model broadly translates into COVID-age in individuals with

For the **COVID-age online toolkit by the Society of Occupational Medicine** see https://www.som.org.uk/covid-age-online-toolkit

diabetes. External validation, regulatory approval, and appropriate licensing would be required before this app could be used in clinical practice.

Contributors

SJM, PMM, and HMC created the concept and design of the manuscript. SJM, AW, PMM, and HMC, developed the first draft of the paper. TMC and EB did the literature review. JB, SK, LAKB, DM, SHa, SHW, CR, NL, EB, JMu, JP, BK, RM, RL, EP, NS, JMcK, SP, AC, JMcM, AS-P, and DG contributed to the data acquisition. SJM, AW, TMC, JMe, AJ, JEO'R, SHa, AH, MC, PMM, and HMC did the data analysis. All co-authors contributed to critically revising the manuscript for important intellectual content and all co-authors approved the final manuscript.

Declaration of interests

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Data sharing

NHS data governance rules do not permit us to secondarily share the data directly. However, researchers can apply to the Scottish Public Benefits and Privacy Protection Committee for access to these data.

To apply to the **Scottish Public Benefits and Privacy Protection Committee** see https://www.informationgovernance.scot.nhs.uk/pbpphsc/

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