



Mortality in People with Type 2 Diabetes Following SARS-CoV-2 Infection: A Population Level Analysis of Potential Risk Factors

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Received: March 6, 2022 / Accepted: March 21, 2022 / Published online: April 13, 2022
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ABSTRACT

Introduction: Research is ongoing to increase our understanding of how much a previous diagnosis of type 2 diabetes mellitus (T2DM) affects someone's risk of becoming seriously unwell following a COVID-19 infection. In this study we set out to determine the relative

likelihood of death following COVID-19 infection in people with T2DM when compared to those without T2DM. This was conducted as an urban population study and based in the UK.

Methods: Analysis of electronic health record data was performed relating to people living in the Greater Manchester conurbation (population 2.82 million) who had a recorded diagnosis

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of T2DM and subsequent COVID-19 confirmed infection. Each individual with T2DM ($n = 13,807$) was matched with three COVID-19-infected non-diabetes controls ($n = 39,583$). Data were extracted from the Greater Manchester Care Record (GMCR) database for the period 1 January 2020 to 30 June 2021. Social disadvantage was assessed through Townsend scores. Death rates were compared in people with T2DM to their respective non-diabetes controls; potential predictive factors influencing the relative likelihood of admission were ascertained using univariable and multivariable logistic regression.

Results: For individuals with T2DM, their mortality rate after a COVID-19 positive test was 7.7% vs 6.0% in matched controls; the relative risk (RR) of death was 1.28. From univariate analysis performed within the group of individuals with T2DM, the likelihood of death following a COVID-19 recorded infection was lower in people taking metformin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glucagon-like peptide 1 (GLP-1) agonist. Estimated glomerular filtration rate (eGFR) and hypertension were associated with increased mortality and had odds ratios of 0.96 (95% confidence interval 0.96–0.97) and 1.92 (95% confidence interval 1.68–2.20), respectively. Likelihood of death following a COVID-19 infection was also higher in those people with a diagnosis of chronic obstructive pulmonary disease (COPD) or severe enduring mental illness but not with asthma, and in people taking aspirin/clopidogrel/insulin. Smoking in people with T2DM significantly increased mortality rate (odds ratio of 1.46; 95% confidence interval 1.29–1.65). In a combined analysis of patients with T2DM and controls, multiple regression modelling indicated that the factors independently relating to a higher likelihood of death (accounting for 26% of variance) were T2DM, age, male gender and social deprivation (higher Townsend score).

Conclusion: Following confirmed infection with COVID-19 a number of factors are associated with mortality in individuals with T2DM. Prescription of metformin, SGLT2is or GLP-1 agonists and non-smoking status appeared to be associated with a reduced the risk of death for

people with T2DM. Age, male sex and social disadvantage are associated with an increased risk of death.

Keywords: SARS-CoV-2; Covid-19; Type 2 diabetes; Mortality

Key Summary Points

In this study we set out to determine the relative likelihood of death following COVID-19 infection in people with type 2 diabetes mellitus (T2DM) when compared to those without T2DM.

A number of factors are linked to subsequent mortality rate in individuals with T2DM following a confirmed COVID-19 infection including specific pharmacological treatments and intrinsic risk factors.

Use of metformin, sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 (GLP-1) agonists and non-smoking status appear to be associated with a reduced the risk of death for people with T2DM. Age, male sex and social disadvantage are associated with an increased risk of death.

We believe that the findings have enabled a greater understanding of the factors that put individuals with T2DM at greater risk of becoming seriously unwell and dying following a COVID-19 infection.

INTRODUCTION

Throughout 2020 and 2021 the SARS-CoV-2 (COVID-19) pandemic seriously challenged and significantly changed global healthcare systems [1]. People already living with diabetes are now known to be at a higher risk of becoming seriously unwell following COVID-19 infection and in some cases dying, when compared to people without diabetes [2–4]. A statistically significant

elevated COVID-19-related mortality rate among people with type 2 diabetes mellitus (T2DM) has been reported [4] and a body of work is now emerging, identifying the reasons why this is the case.

An increased rate of hospital admissions among patients with T2DM and a high body mass index (BMI) leading to death or assisted mechanical ventilation has been reported [5]. However, there is limited evidence to indicate whether longer-term blood glucose control (as assessed by HbA1c measurement) is associated with a more adverse outcome following COVID-19 infection. Increasing age and microvascular and macrovascular complications have been independently associated with death in patients with T2DM following hospital admission [5].

Two recent UK studies of COVID-19 vaccinated and non-vaccinated individuals have highlighted factors that mediate an increased risk of serious consequences of a COVID-19 infection in relation to hospital admission and mortality [6, 7]. In the post-vaccination study, a risk algorithm explained 74.1% of the variation in time to COVID-19-related death [7]. In light of this observation a more focussed examination of outcomes in T2DM is merited.

It was previously shown in a study in Salford, UK that the month by month mortality rate for people with T2DM was up to 2.2 times higher than in the same month averaged over the previous 5 years in the early stages of the COVID-19 pandemic; age was the strongest independent predictor of death [8].

Given the current clinical landscape in regard to the continuing high number of COVID-19 cases in the UK and elsewhere, we have examined the relative likelihood of death in people with T2DM compared with people who do not have T2DM following a confirmed COVID-19 infection. We conducted a population-based study in a UK large urban conurbation using electronic health records to gain understanding of diabetes-specific risk factors for mortality following COVID-19 infection.

METHODS

This matched case–control study project was approved and overseen by Health Innovation Manchester [9] whose Governance Board [10] also granted ethical approval for the study.

Study Design and Participants

A retrospective case-controlled study was conducted on people with a confirmed diagnosis of T2DM as recorded and coded in the general practice record. We accessed SNOMED Clinical Terms and codes for this [11].

All participants included had a positive COVID-19 diagnosis based on their electronic patient records from 1 January 2020 to 30 June 2021. Patients eligible for the study had matched controls selected on a 3:1 ratio to those with a T2DM diagnosis; controls were selected on the basis of no T2DM diagnosis, a positive COVID-19 record and matching to a case for biological gender and age (age within 3–5 years).

Variables

Data were put through a rigorous checking and cleaning process where all values were ‘sense checked’ for credible physiological ranges and internal clinical and demographic logic (e.g. dates of birth, height, weight, BMI, biomarker ranges). BMI was included only if recorded within 6 months of the positive COVID-19 test. Deaths were ascertained from general practice records.

Data Sources/Measurement

Data were de-identified at source and were extracted from the Greater Manchester Care Record (GMCR) database [9]. This database pools information from all general practices across the Greater Manchester conurbation (total population 2.85 million). Following cleaning, the data extracted were split into two comparable groups i.e. those with T2DM and their controls (1:3 matching).

Statistical analyses were performed on the final data set to investigate the potential risk factors contributing to increased likelihood for hospital admission in diabetes following infection with COVID-19. Social disadvantage was assessed by Townsend score [12]. The Townsend score is based on UK postcode and can be calculated using a combination of four census variables for any geographical area (provided census data is available for that area). The measure has been widely used in research for health, education and crime to establish whether relationships exist with deprivation. A higher Townsend score equates to greater social disadvantage. Ethnicity was included as a potential factor associated with the risk of serious consequences following COVID-19 infection.

The 2001 census and NHS 5 groups [13] were used to define ethnicity.

Ethics

This project was approved and overseen by Health Innovation Manchester [9] whose Governance Board [10] also granted ethical approval for the study.

The study was also reviewed and approved by the Greater Manchester Care Record (GMCR) Expert Research Group (ERG) reference number R 2020 020. All data used in the analysis was fully anonymised. The data used in the analyses presented was obtained with the permission of the Greater Manchester Care Record Board.

Statistical Methods

Where data for medication or past medical history were missing, it was assumed that individuals were either not on the medication or did not have a specific diagnosis. Imputation in relation to the comparison between individuals with and without diabetes was not possible because of the degree of difference in availability of anthropometric and metabolic variables between the two groups. Therefore, a complete case analysis was conducted. Comparison between continuous variables was completed by analysis of variance (ANOVA).

Following this we used logistic regression, with death up to 30 June 2021 as the binary outcome variable and diabetes status as the main exposure variable of interest. Individuals were coded as having the outcome if they died within 28 days of COVID-19 diagnosis. Other variables were adjusted for in specific models as detailed below. Townsend score comparisons were relative to a Townsend score of 1.

Where there was more than one COVID-19 positive test result, the most recent test was used. In order to take account of COVID-19 positive status being confirmed after death, we included all individuals with a COVID-19 virus positive test within 48 h of death in our analysis.

In order to investigate potential factors associated with admission in patients with diabetes, we analysed separately the individuals with T2DM without the matched individuals. Univariate logistic regression was then applied for the two groups separately, considering each possible factor in turn.

We then studied whether the difference in risk between patients with T2DM and people without diabetes was explained by other measured factors. In order to do so we examined the T2DM group with their matched cohort and compared the odds ratios (OR) of T2DM in a model including only age, sex and diabetes with the OR for T2DM; this was adjusted for each additional factor in turn.

Importantly in this univariate analysis, any change of the diabetes OR in this comparison was interpreted as the additional factor explaining part of the association between diabetes and hospitalisation (e.g. through confounding or mediation).

This was followed up with a fully adjusted multivariable model for each matched cohort, to measure the extent of attenuation of the T2DM OR when all additional factors were considered. We picked the significant variables and excluded metformin plus any variable with significant missingness. This component of the analyses was conducted using R (version 3.6.2).

Patient and Public Involvement

The GMCR patient group were actively involved in all aspects of the study at all stages including review of this article.

RESULTS

The sample size of the study comprised 13,807 people with T2DM, all of whom were alive on 1 January 2020 and over the follow-up period to 30 June 2021 had at least once COVID-19 positive test. The control (non-diabetes) sample size was 39,583 people.

As seen in Table 1, the mortality rate in individuals with T2DM after a general practice recorded COVID-19 positive test was 7.7% vs 6.0% in matched controls; this gave a relative risk (RR) for death of 1.28. A significant difference in Townsend score (1.8 ± 3.7 for T2DM vs 0.4 ± 3.6 for matched controls) was observed with a higher proportion of people with T2DM in the top two quintiles of social disadvantage. BMI was significantly higher in individuals with T2DM than in matched controls (31.8 ± 6.9 vs 28.6 ± 6.1 kg/m²).

The mean disease duration of T2DM was calculated as being 7.4 years. The mean HbA1c level for individuals with T2DM was significantly higher in cases than in matched controls (56.6 mmol/mol (7.3%) \pm 21.0 mmol/mol (1.9%) vs 36.2 mmol/mol (5.5%) \pm 8.9 mmol/mol (0.9%). Mean vitamin D level was lower in individuals with T2DM than in controls. There was a higher proportion of people with asthma or chronic obstructive pulmonary disease (COPD) in individuals with T2DM compared with controls. A significantly higher proportion of those with T2DM were taking aspirin, clopidogrel, an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) compared with matched controls.

Breakdown by ethnic group is reported in Table 1; 24.4% of the individuals with T2DM were of South Asian origin compared with 7.9% of the non-T2DM control group.

Individuals of South Asian origin with T2DM were marginally younger than their

counterparts from other ethnic groups at 56 years compared with 57 years for individuals with T2DM of African origin and 64 years for individuals with T2DM of Caucasian origin. Age of death as recorded was 73 years for patients with T2DM of South Asian origin compared with 77 years for patients of African origin and 81 years for Caucasian origin patients.

There were insufficient numbers of men with a recent measure of serum testosterone (250 men with T2DM and 400 men without diabetes) to conduct any meaningful analysis on the relation between androgen status and mortality rate.

Univariate Analysis

Univariate analysis within individuals with T2DM shows that the likelihood of death following a COVID-19 infection was lower in people taking metformin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or glucagon-like peptide 1 (GLP-1) agonist (Table 2). We did not find any association between dipeptidyl peptidase 4 (DPP4) inhibitor use and change in mortality rate.

Lower eGFR level was associated with a higher mortality rate as was a history of hypertension. Likelihood of death following a confirmed COVID-19 infection was also higher in those patients with T2DM with a comorbidity of COPD or severe enduring mental illness (SMI) but not with asthma, people taking aspirin or clopidogrel and in those treated with insulin. Smoking in the context of T2DM was associated with significantly increased mortality rate. Lower levels of HbA1c, BMI, LDL-cholesterol and cholesterol were all associated with a higher mortality rate in T2DM cases. Patients with T2DM of South Asian origin had a lower mortality rate vs other ethnic groups and were also younger as a group.

Analyses of Combined Individuals with T2DM and Controls

In Fig. 1 and Table 3 the change in OR compared to the base model indicates how much each factor changes the baseline odds ratio for

Table 1 Baseline data for individuals with type 2 diabetes (T2DM) and the matched cohort

Variable	Controls <i>n</i> = 39,583	T2D <i>n</i> = 13,807	<i>p</i> value
Age	62.0 (14.4)	62.9 (14.4)	< 0.001
Sex			< 0.001
Female	18,054 (45.6%)	6058 (43.9%)	
Male	21,529 (54.4%)	7749 (56.1%)	
Townsend score (higher is more deprived)	0.4 (3.6)	1.8 (3.7)	< 0.001
Townsend quintile as factor (higher quintile is more deprived)			< 0.001
1	7911 (20%)	1634 (11.8%)	
2	6415 (16.2%)	1563 (11.3%)	
3	7279 (18.4%)	2180 (15.8%)	
4	8327 (21%)	3108 (22.5%)	
5	9651 (24.4%)	5322 (38.5%)	
Latest BMI	28.6 (6.2)	31.8 (6.9)	< 0.001
Latest LDL	2.8 (1.0)	2.2 (1.0)	< 0.001
Latest HDL	1.4 (0.4)	1.2 (0.3)	< 0.001
Latest eGFR	76.0 (15.6)	75.4 (18.7)	0.001
Latest SHBG	57.3 (38.2)	30.7 (26.2)	< 0.001
Latest HbA1c	36.2 (8.9)	56.6 (21.0)	< 0.001
Latest vitamin D	54.2 (28.5)	48.4 (28.0)	< 0.001
Latest cholesterol	4.9 (1.1)	4.3 (1.2)	< 0.001
Latest testosterone	11.5 (8.7)	9.7 (6.9)	0.004
Current smoking status			0.08
Non-smoker	23,432 (59.2%)	8055 (58.3%)	
Trivial-smoker	16,151 (40.8%)	5752 (41.7%)	
Patient has asthma			< 0.001
Yes	6157 (15.6%)	2507 (18.2%)	
Patient has COPD			0.001
No	36,925 (93.3%)	12,766 (92.5%)	
Yes	2658 (6.7%)	1041 (7.5%)	
Patient has SMI			< 0.001
No	38,243 (96.6%)	13,179 (95.5%)	
Yes	1340 (3.4%)	628 (4.5%)	
Patient has hypertension			< 0.001

Table 1 continued

Variable	Controls <i>n</i> = 39,583	T2D <i>n</i> = 13,807	<i>p</i> value
No	27,837 (70.3%)	6121 (44.3%)	
Yes	11,746 (29.7%)	7686 (55.7%)	
Is on ACE-I or ARB	7949 (20.1%)	6810 (49.3%)	< 0.001
Is on aspirin	3198 (8.1%)	2655 (19.2%)	< 0.001
Is on clopidogrel	1650 (4.2%)	1076 (7.8%)	< 0.001
Is on metformin	238 (0.6%)	8438 (61.1%)	< 0.001
Is on Insulin	0%	1714 (12.4%)	< 0.001
Is on SGLT1 inhibitor	0%	2121 (15.4%)	< 0.001
Is on GLP-1 agonist	0%	589 (4.3%)	< 0.001
Is on sulfonylurea	0%	2429 (17.6%)	< 0.001
As factor (ethnicity)			< 0.001
White	30,723 (77.6%)	8406 (60.9%)	
African	848 (2.1%)	526 (3.8%)	
Asian	3133 (7.9%)	3374 (24.4%)	
Mixed	285 (0.7%)	147 (1.1%)	
Other	1170 (3%)	533 (3.9%)	
Not available	3424 (8.7%)	821 (5.9%)	
Died	2378 (6.0%)	1062 (7.7%)	< 0.001
Diabetes duration (years) median and IQR	NA	7.4 (2.9–13.3)	

death in T2DM cases vs individuals without T2DM in the months after a confirmed COVID-19 infection (up to 30 June 2021), thus indicating whether each factor may be related to more serious consequences of COVID-19 virus infection in people with diabetes. Thus we report change of the diabetes OR as the additional factor explaining part of the association between diabetes and hospitalisation (e.g. through confounding or mediation).

In COVID-19-infected individuals with T2DM, factors related to difference in mortality rate vs age and gender-matched controls were Townsend score, ethnicity, smoking status,

BMI, HbA1c, diagnosis of hypertension, total cholesterol, LDL-cholesterol, and eGFR. Our analysis showed a change in mortality rate with vitamin D level and prior diagnosis of COPD, asthma or SMI and ethnicity. Being on a range of medications (ACE-inhibitor/ARB, aspirin/clopidogrel, metformin, insulin, and SGLT2i, GLP-1 agonist or insulin) was also associated with an altered risk of death as was taking a sulfonylurea (SU). There was no difference in HbA1c between people on and off metformin treatment.

A multivariable risk model for combined patients with T2DM and controls (Table 4) was

Table 2 Factors associated with 28-day mortality in individuals with T2DM

Variable	OR (95% CI)
Age	1.098 (1.092–1.105)
Sex	1.012 (0.893–1.149)
Townsend score	0.987 (0.971–1.004)
Latest BMI	0.94 (0.929–0.951)
Latest HbA1c	0.983 (0.979–0.986)
Latest cholesterol	0.75 (0.704–0.799)
Latest LDL	0.732 (0.675–0.793)
Latest HDL	1.065 (0.877–1.286)
Latest vitamin D	1.003 (0.997–1.009)
Latest eGFR	0.963 (0.961–0.966)
Comorbidities	
COPD	2.999 (2.519–3.555)
Asthma	1.001 (0.849–1.175)
SMI	1.898 (1.484–2.399)
Medication	
ACE-I or ARB	0.965 (0.851–1.093)
Aspirin	1.913 (1.664–2.196)
Clopidogrel	2.081 (1.723–2.498)
Metformin	0.494 (0.435–0.56)
Hypertension	1.919 (1.677–2.199)
Insulin	1.968 (1.677–2.3)
SGLT1 inhibitor	0.299 (0.226–0.388)
GLP-1 agonist	0.68 (0.464–0.96)
Sulfonylurea	1.015 (0.86–1.193)
Townsend quantile	
Townsend quantile 2	1.227 (0.94–1.603)
Townsend quantile 3	1.267 (0.992–1.625)
Townsend quantile 4	1.412 (1.127–1.783)
Townsend quantile 5	1.018 (0.819–1.276)
Trivial-smoker	1.459 (1.287–1.654)
Ethnicity	
African	1.026 (0.744–1.382)

Table 2 continued

Variable	OR (95% CI)
Asian	0.514 (0.429–0.611)
Mixed	0.763 (0.374–1.382)
Other	0.78 (0.545–1.083)

Odds ratios and 95% confidence intervals from logistic regression models for 28-day mortality following COVID-19 diagnosis in individuals, including each variable in a univariable analysis

applied to determine the factors independently and significantly associated with a higher likelihood of death. Variables showing the most significant difference in univariate analysis between individuals with T2DM and non-T2DM controls in mortality risk were selected for the multivariate analysis. Following confirmed COVID-19 infection for combined individuals with T2DM and controls (Table 4), factors independently relating to a higher likelihood of death in model that also included BMI, ethnicity, medication, smoking status, COPD, SMI and hypertension were having T2DM, age, male gender and Townsend score, together with a lower LDL-cholesterol level. The model accounted for 24% of the difference between individuals with T2DM and individuals without T2DM in relation to mortality.

DISCUSSION

The analysis that was conducted over a 16-month period has indicated that many factors already known to influence the likelihood of serious consequences of a COVID-19 also influenced mortality rate in the 16-month follow-up period of our study. However when all factors were considered together, only age, male sex and social disadvantage were associated with an increased risk of death, as was a lower LDL-cholesterol level, likely as marker of use of high dose statin treatment in people with a history of cardiovascular disease. This suggests

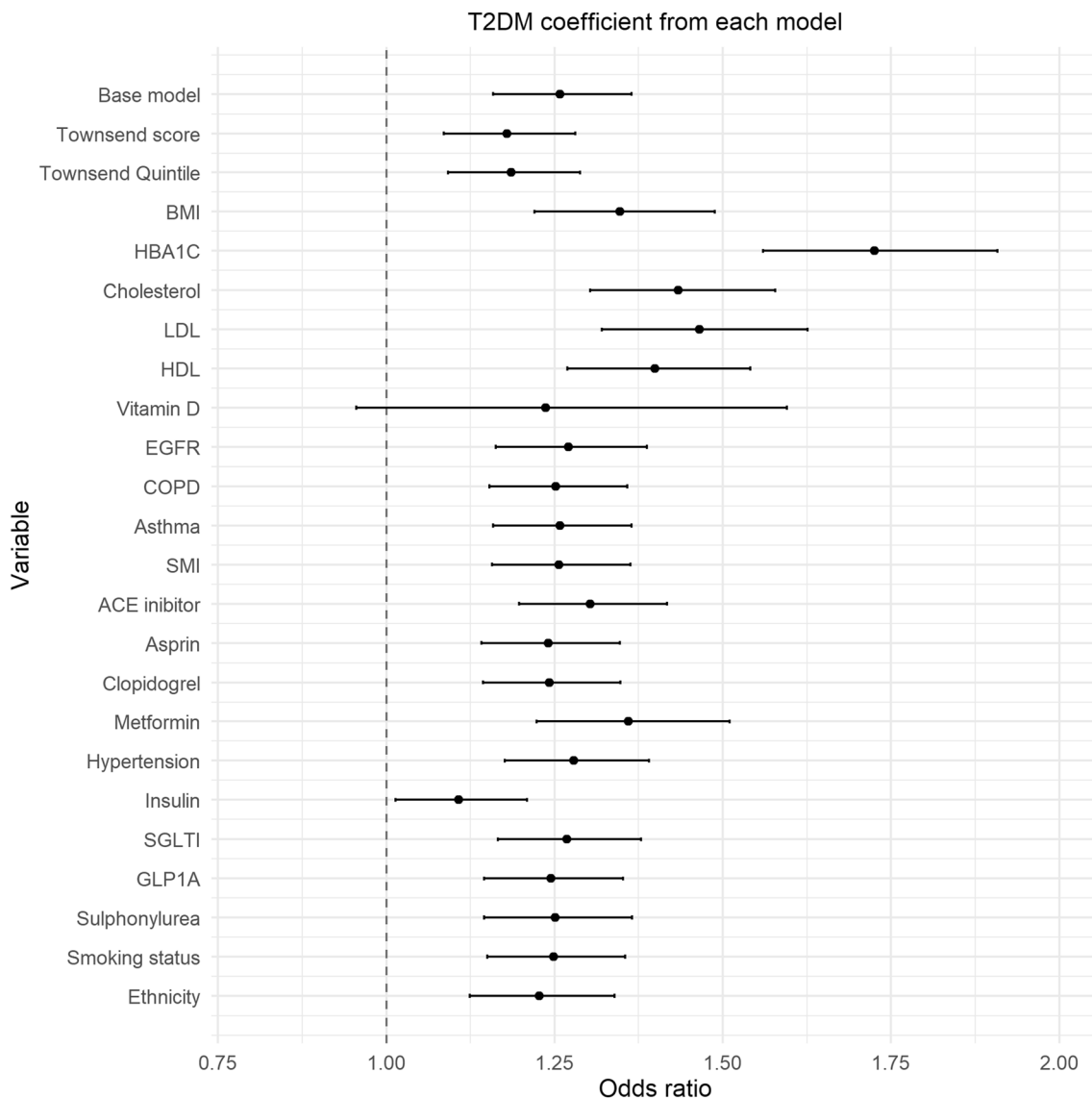


Fig. 1 Factors associated with death following confirmed COVID-19 infection in individuals with diabetes compared to individuals without diabetes

that it is the constitutional characteristics of individuals that are the most important independent determinants of mortality outcome following a COVID-19 infection in individuals with T2DM.

Data obtained over a 16-month period show that 7.7% of people with T2DM who had a GP-confirmed COVID-19 infection died compared to a figure of 6.0% for age and gender-matched individuals without diabetes. Thus, the mortality rate was 1.7% higher in people with T2DM

than in age and sex-matched controls. Although there was a very small difference in mean age between individuals with T2DM and individuals without T2DM, the large sample size means we obtain a significant *p* value. Also, not all individuals had three matches; some only had two and this contributed to a small but statistically significant difference.

We report that for people with T2DM, prescriptions of metformin, an SGLT2i or GLP-1 agonist were each associated with a lower

Table 3 Factors associated with 28-day mortality in diabetes individuals compared to individuals without diabetes

Variable	OR (95% CI)
Base model	1.258 (1.159–1.365)
Townsend score	1.18 (1.086–1.281)
Latest BMI	1.347 (1.22–1.488)
Latest HbA1c	1.725 (1.56–1.908)
Latest cholesterol	1.434 (1.303–1.578)
Latest LDL	1.465 (1.32–1.626)
Latest HDL	1.399 (1.269–1.541)
Latest vitamin D	1.237 (0.956–1.596)
Latest eGFR	1.27 (1.163–1.387)
COPD	1.252 (1.153–1.358)
Asthma	1.258 (1.159–1.365)
SMI	1.256 (1.157–1.363)
ACE-I or ARB	1.303 (1.197–1.417)
Aspirin	1.24 (1.142–1.347)
Clopidogrel	1.242 (1.144–1.348)
Metformin	1.36 (1.224–1.51)
Hypertension	1.279 (1.176–1.39)
Insulin	1.107 (1.013–1.209)
SGLT1 inhibitor	1.268 (1.166–1.379)
GLP-1 agonist	1.244 (1.145–1.351)
Sulfonylurea	1.251 (1.146–1.365)
Townsend quintile	1.186 (1.091–1.288)
Current smoking status	1.249 (1.15–1.355)
Ethnicity	1.227 (1.12–1.339)

Diabetes coefficient and 95% confidence interval from each logistic model

mortality rate for individuals infected with COVID-19. A number of studies have indicated that COVID-19 infection is associated with changes in vascular endothelial function including increased production of pro-inflammatory cytokines and of micro-particles [14]. Metformin, SGLT2is and GLP-1 agonists are all

Table 4 Coefficient and 95% confidence intervals from the full adjusted multivariate logistic model in individuals with T2DM and the matched cohort

Variable	OR (95% CI)
Intercept	0.000 (0.000–0.001)
Age	1.105 (1.099–1.112)
Sex (male)	1.432 (1.267–1.621)
Diabetes	1.318 (1.159–1.498)
BMI	0.995 (0.985–1.006)
LDL-cholesterol	0.870 (0.812–0.931)
Ethnicity–African	1.321 (0.933–1.837)
Ethnicity–Asian	0.855 (0.699–1.039)
Ethnicity–mixed	1.353 (0.661–2.516)
Ethnicity–other	0.964 (0.692–1.313)
Townsend	1.050 (1.032–1.068)
Hypertension	0.920 (0.810–1.047)

known to reduce cardiovascular event rate in individuals with T2DM [15] and the mechanisms by which they do this may be linked to their potential protective effect in COVID-19-infected individuals with T2DM. Prescription of insulin was associated with a higher mortality rate. A potential explanation is that insulin is usually given to people with T2DM who have had T2DM for longer, have historically poorer blood glucose control and potentially a greater burden of multiple morbidity/diabetes tissue complications.

In the pathogenesis of SARS-CoV-2 (COVID-19) infection, it is important to reflect on the role played by serine protease expression in human cells, a leading cause of the entrance and replication of SARS-CoV-2 and in parallel the different cellular expression of ACE2 in humans [16], as has been described in T2DM and in altered glycemia [17].

It has been suggested that the population at higher risk of worse prognosis are people with hypertension [18], and in people with diabetes [19, 20]. Indeed, these patients are at higher risk for intensive care unit (ICU) admission and

death. It is likely that the risk factors are closely linked.

The analysis described an association of lower BMI and lower HbA1c with a higher mortality rate in T2DM. This has been reported previously [21]. The observation was found to correspond to a U-shaped relation between BMI/HbA1c and mortality. In other words, people with a both a high and very low BMI were found to have a higher mortality rate. This is likely due to confounding factors as previously described [21].

The association seen here between South Asian ethnicity and a lower mortality rate may be related to there being a higher number of younger South Asian people with T2DM vs Caucasians, given the younger age of diagnosis of many South Asians with T2DM. Nevertheless the age of death of South Asian individuals with T2DM was significantly lower than for other ethnic groups. The absence of an ethnicity effect but presence of social disadvantage in the final model, as described in Table 4, may be a consequence of the link between socio-demographic situation and greater likelihood of adverse outcome following a COVID-19 infection, such that this outweighs any specific ethnicity effects, because of the close linkage between socio-economic status and ethnicity.

When the T2DM and matched controls are analysed together, the effects of higher age, prior diagnosis of T2DM, male gender and greater social disadvantage were independent determinants for risk of dying following a confirmed COVID-19 infection. The significant relation between socio-economic disadvantage and higher mortality rate is important even if the underlying factors are not easily modified. The association of lower LDL-cholesterol with a higher mortality rate may be associated with a more aggressive lipid-lowering therapeutic strategy for people with a history of cardiovascular events (themselves being at greater risk of adverse consequences of a COVID-19 infection) [22, 23] resulting in a lower LDL-cholesterol. We would speculate that people who know that they are at greater cardiovascular risk may be more likely to take lipid-lowering medication as prescribed and to be prescribed a more potent statin. Clearly this finding needs to be

examined in other post-COVID-19 infection population cohorts. The absence of any independent effect of prior diagnosis of hypertension and of ethnicity in the final combined analysis suggests that there is no specific effect of these factors in individuals with T2DM, above and beyond that seen in the population as a whole.

These findings can be compared with an early COVID-19 pandemic study from Mexico [24] which concluded that early-onset T2DM conferred an increased risk of hospitalization and obesity conferred an increased risk for ICU admission and intubation. The predictive score for COVID-19-related death included age 65 years or older, diabetes, early-onset diabetes, obesity, age less than 40 years, chronic kidney disease (CKD), and hypertension.

A number of previous studies have described a relation between diagnosis of COPD [23, 25] and SMI [26] with more adverse outcome following a COVID-19 infection. Although the final multiple regression model in our study did not find an independent influence of these factors, they remain important in terms of evaluating risk of any patient becoming seriously unwell following COVID-19 infection.

It should be pointed out that the advent of treatment of COVID-19 hospitalised patients with dexamethasone has significantly reduced mortality rates across the world. In hospitalised patients, use of dexamethasone resulted in significantly lower 28-day mortality in those who were receiving either invasive mechanical ventilation or oxygen alone at randomization [27]. However, close monitoring of blood glucose is recommended in all patients treated with dexamethasone [28].

Additional agents are also now available for COVID-19-affected patients who become severely unwell [29] including tocilizumab, a recombinant humanised monoclonal antibody that inhibits binding of interleukin-6 (IL-6) to both membrane and soluble IL-6 receptors. These continue to reduce mortality rate in severely unwell patients infected with COVID-19.

Potential pathogenic links between the SARS-CoV-2 virus and diabetes include the influence of glucose homeostasis and

potentially altered immune status on the progression of the viral infection once established [30–32]. COVID-19 infection aggravates inflammation and alters immune system responses, leading to difficulties in blood glucose control. COVID-19 infection also increases the risk of thromboembolism and is more likely to induce cardiopulmonary failure in patients with diabetes than in patients without diabetes [33]. All of these mechanisms are now believed to contribute to the poor prognosis of some patients with pre-existing diabetes and a COVID-19 infection [34].

The reason why studies may show a difference in outcome for statin users vs non statin users may relate to differences in the level of risk in the groups studied. For example, the Coronado study [5] described a higher mortality rate in statin users whereas other studies have described a relative protective effect of statins in COVID-19-affected individuals with T2DM [35]. There is no question that statin use is overall hugely beneficial as reported in a recent very large study on US veterans [36].

During the COVID-19 pandemic, the achievement of tight blood glucose control and targeted management of cardiovascular risk factors are important for patients with diabetes mellitus [37, 38]. Medications used for both T2DM and cardiovascular disease need to be adjusted accordingly for people at high risk of COVID-19 infection in order to optimize their risk profile [39].

Strengths/Limitations

- We recognise that a limitation of our study is that not all COVID-19 tests were fed back to general practice surgeries and coded. Furthermore we used the cut point of death up to 28 days after a COVID-19 positive test as the definition of a COVID-19-related death.
- There is thus an underestimate of the total number of COVID-19 positive test results. However there is no reason to suspect that this would affect individuals with diabetes vs individuals without diabetes differentially.
- The risk of severe outcomes has varied over time as the vaccination programme in the

UK took hold in during December 2020–January 2021, so our findings may not reflect current risks given impact of vaccination, natural immunity and new variants of concern. This is the subject of ongoing work.

- The data only covers the Greater Manchester conurbation and we have relied on general practice record coded diagnoses. Nevertheless the cohort whose outcomes we have analysed covers all general practices in the culturally and ethnically diverse Greater Manchester conurbation and is therefore representative of the 2.82 million people who live there in relation to the consequences of a COVID-19 infection.

CONCLUSION

In this matched case–control study a number of factors are linked to subsequent mortality rate in individuals with T2DM following a confirmed COVID-19 infection including specific pharmacological treatments and intrinsic risk factors. Use of metformin, SGLT2is and GLP-1 agonists and non-smoking status appear to be associated with a reduced the risk of death for people with T2DM. Age, male sex and social disadvantage are associated with an increased risk of death.

We believe that the findings have enabled a greater understanding of the factors that put individuals with T2DM at greater risk of becoming seriously unwell and dying following a COVID-19 infection and that healthcare professionals and patients themselves can have greater awareness or remediable factors that can be modulated to reduce that risk in the future.

ACKNOWLEDGEMENTS

There was involvement from our patient participation group in this study, in relation to its design, implementation and conclusions.

Funding. No external funding was utilised in relation to the work presented here. The

journal's Rapid Service Fee was funded by the authors.

Author Contributions. All authors contributed equally to the preparation of the manuscript.

Disclosures. Adrian H Heald, David A Jenkins, Richard Williams, Matthew Sperrin, Rajshekhar N Mudaliar, Akheel Syed, Asma Naseem, Kelly A Bowden Davies, Yonghong Peng, Niels Peek, William Ollier, Simon G Anderson, Gayathri Delanerolle and J Martin Gibson have no conflicts of interest.

Compliance with Ethics Guidelines. This project was approved and overseen by Health Innovation Manchester whose Governance Board also granted ethical approval for the study. The study was also reviewed and approved by the Greater Manchester Care Record (GMCR) Expert Research Group (ERG) reference number R 2020 020. The data used in the analyses presented was obtained with the permission of the Greater Manchester Care Record Board and was fully anonymised prior to being made available to the investigators.

Data Availability. A derivative data set will be available on application to the corresponding author.

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