Diabetes Ther
https://doi.org/10.1007/s13300-024-01681-9

ORIGINAL RESEARCH

Association of Polypharmacy and Burden of Comorbidities on COVID-19 Adverse Outcomes in People with Type 1 or Type 2 Diabetes

Juhi K. Gupta · Rathi Ravindrarajah · George Tilston · William Ollier · Darren M. Ashcroft · Adrian H. Heald

Received: August 18, 2024 / Accepted: December 2, 2024

ABSTRACT

***Introduction*:** It is widely accepted that the higher the number of medications prescribed and taken by an individual, the higher the risk of poor health outcomes. We have investigated whether polypharmacy and comorbidities conveyed more risk of adverse health outcomes following COVID-19 infection (as a paradigm of serious viral infections in general) in people with type 1 diabetes (T1DM) or type 2 diabetes (T2DM).

***Methods*:** The Greater Manchester Care Record (GMCR) is an integrated database of electronic health records containing data collected from 433 general practices in Greater Manchester. Baseline demographic information (age, body mass index [BMI], gender, ethnicity, smoking status, deprivation index), hospital admission or death within 28 days of infection were extracted for adults (18+) diagnosed with either T1DM or T2DM.

***Results*:** The study cohort included individuals diagnosed as T1DM and T2DM separately. Across the Greater Manchester Region, a total of 145,907 individuals were diagnosed with T2DM and 9705 were diagnosed with T1DM. For the T2DM individuals, 45.2% were women and for the T1DM individuals, 42.7% were women. For T2DM, 16–20 medications ($p=0.005$; odds ratio [OR] [95% confidence interval (CI) 2.375 [1.306–4.319]) and >20 medications ($p<0.001$; OR [95% CI] 3.141 [1.755–5.621]) were associated with increased risk of death following COVID-19 infection. Increased risk of hospital admissions in T2DM individuals was associated with 11 to

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-024-01681-9.

J. K. Gupta · R. Ravindrarajah · G. Tilston
Division of Informatics, Imaging and Data Science, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

W. Ollier
Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK

D. M. Ashcroft
Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

D. M. Ashcroft
NIHR Greater Manchester Patient Safety Research Collaboration (PSRC), University of Manchester, Manchester, UK

A. H. Heald
Department of Diabetes and Endocrinology, Salford Royal NHS Foundation Trust, Salford, UK

A. H. Heald (✉)
Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
e-mail: adrian.heald@nca.nhs.uk

Published online: 20 December 2024

15 medications ($p = 0.013$; OR = 1.341 (95% CI) [1.063–1.692]). This was independent of comorbidities, metabolic and demographic factors. For T1DM, there was no association of polypharmacy with hospital admission. Additionally, respiratory, cardiovascular/cerebrovascular and gastrointestinal conditions were associated with increased risk of hospital admissions and deaths in T2DM ($p < 0.001$). Many comorbidities were common across both T1DM and T2DM.

Conclusions: We have shown in T2DM an independent association of multiple medications taken from 11 upwards with adverse health consequences following COVID-19 infection. We also found that individuals with diabetes develop comorbidities that were common across both T1DM and T2DM. This study has laid the foundation for future investigations into the way that complex pharmacological interactions may influence clinical outcomes in people with T2DM.

Keywords: Polypharmacy; Comorbidity; Electronic health records; COVID-19; Virus

Key Summary Points

Why carry out this study?
It is widely accepted that the higher the number of medications prescribed and taken by an individual, the higher the risk of poor health outcomes. Recent reviews have reported a high prevalence of polypharmacy in older people diagnosed with diabetes and an association with several health-related outcomes.
To date, few studies have looked at the associations between polypharmacy and adverse health outcomes in terms of hospital admission or death. We here investigated this, specifically focussing on the sequelae of COVID-19 infection in people with a diagnosis of diabetes, in relation to polypharmacy.
What was learned from the study?
We identified that multiple medications were prescribed to many people living with diabetes and that this was associated with a higher risk of adverse health outcomes following COVID-19 infection.
This can be seen as informing our understanding of the risks of becoming seriously unwell following other viral infections.
We also found that individuals with diabetes developed comorbidities that were common across both type 1 and 2 diabetes.

INTRODUCTION

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 is the pathogenic coronavirus that led to the 2020 pandemic. COVID-19 infections can lead to adverse outcomes, such as hospital admission or death, the risk of which is increased further for individuals diagnosed with either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) [1, 2]. Increased risk of adverse health outcomes following COVID-19 infection have also been linked to other underlying medical conditions, which has raised concerns for chronic disease care [3–7]. It has been shown that socially marginalised and psychiatrically vulnerable individuals are at higher risk of severe health outcomes following COVID-19 infection [8]. McQueenie et al. investigated the UK Biobank data to determine the association between multimorbidity (including polypharmacy as a proxy) and COVID-19 infection risk [9] and reported that individuals diagnosed with ≥ 2 cardiometabolic conditions and increasing polypharmacy were associated with increased the risk of COVID-19 infection [9].

Previous studies of COVID-19 in individuals with T1DM and T2DM (in the Greater Manchester (GM) area) have shown that the prescribing of certain medications influenced the likelihood

of hospitalisation or death following COVID-19 infection [10, 11]. Many individuals in this population are often prescribed (and are taking) multiple medications as they live with other long-term conditions.

The definition of 'polypharmacy' has been shown to widely vary in the published literature [12]. In addition to this term, Masnoon et al. summarised that the terms minor, moderate and major polypharmacy were used in literature to describe when between 2 and 11 or more medications are consumed. The most commonly reported number of medications across these 'polypharmacy' terms was greater than or equal to 5, as identified in the review [12].

Recent reviews have reported a high prevalence of polypharmacy in older people diagnosed with diabetes and an association with several health-related outcomes, including falls, syncope, hospitalization, and death, as well as highlighting the need to reduce inappropriate prescribing [13–15]. Several studies have also investigated the relationship between polypharmacy and severe COVID-19 health outcomes [16, 17]. However, there is little understanding of how polypharmacy in people with diabetes might affect their risk of severe health outcomes post-COVID-19 infection, other than the public health burden and impact of adverse drug–drug interactions in individuals [18].

Electronic health records (EHR) emerged as a useful tool for public health and COVID-19 research, as described by Madhavan et al. and Casey et al. [19, 20]. It is also useful for improving health service for example by identifying and understanding health inequalities [21, 22].

To date, few studies have examined the associations between polypharmacy and comorbidity with adverse health outcomes, such as hospital admission or death, following a first COVID-19 infection, specifically in individuals with diabetes. This retrospective cohort study aimed to investigate whether polypharmacy independent of comorbidity conveys greater risk of adverse outcomes in people with diabetes when testing positive for COVID-19 infection (as a paradigm for other serious viral infections) in UK using EHR data.

METHODS

Cohort Data Source

The Greater Manchester Care Record (GMCR) is an integrated database of primary care, secondary care and mental health trusts from across GM (https://gmwearebettertogether.com/research-and-planning/) for analyses covering a population of approximately 3 million people. Health and care data were collected from 433 of 435 (99.5%) general practices in GM. Data were de-identified at the source and were extracted from the GMCR database. This was a retrospective cohort study with the period of follow-up 2020–2022 in relation to the main impact period of the COVID-19 pandemic. The inclusion criteria for this study were defined, as individuals that are registered with a GM GP practice and with a diagnosis of T1DM or T2DM and age 18 or above. Patients with monogenic diabetes were not included. Individuals with a positive test for COVID-19 were included in this study. The study included all people diagnosed with diabetes and with data available in the GMCR in January 2020. No power calculation was performed, as we included all people with that diagnosis.

Variables and Data Cleaning

Baseline demographic information (age, body mass index [BMI], gender, ethnicity, smoking status, deprivation index), hospital admission or death within 28 days of infection were extracted for adults (18+) diagnosed with either T1DM or T2DM (the codes applied are summarised in Appendix 1). Other rare forms of diabetes were not included.

Hospital admissions were recorded within 4 weeks after, or 2 weeks before, a positive COVID-19 test (between January 2020 and May 2022). The exposure was defined as prescribed medications (we used numbers of types of medication), which were recorded in the EHRs and mapped to the corresponding BNF (British National Formulary) chapters. For this study, medications were considered at a single point in time, the month closest to first COVID-19 infection date

(January 2020 onwards). The BNF groups were not mutually exclusive; therefore medications that are grouped under more than one chapter were counted. History of comorbidity was collected before March 2020.

Individuals who were not assigned a gender were excluded. A total of 410 individuals having a code for both T1DM and T2DM were excluded. T1DM and T2DM were diagnosed (according to the primary care record) by 1 January 2020, in other words, prior to any diagnosis of COVID-19.

Gender was as coded in the general practice record as were ethnicity and smoking status. Index of multiple deprivation was derived from United Kingdom postcode as now stated in the text. The outcome was hospitalisation or death.

The study confounders were determined by a literature review. In studies using real-world data analysis, a number of factors were not covered in the coded data such as household makeup and employment. Links to the codes used for diabetes can be found in the supplementary information. Data were checked for extreme outliers or inconsistent values and removed as appropriate.

Ethics

This project was reviewed, and ethical approval for COVID-19 research was overseen by Health Innovation Manchester and granted by the Greater Manchester Care Record (GMCR) review board (ref: IDCR-RQ-046). This research was performed with anonymised data, in line with the Health Research Authority's Governance arrangements for research ethics committees.

Statistical Methods

Multivariable logistic regression analyses using a forward stepwise approach were performed on the T1DM and T2DM individuals, measuring exposure to the number of medications and comorbidities, with either hospital admission or death after COVID-19 infection (within 28 days of COVID-19 diagnosis) as the outcome. The models were adjusted for age, BMI, ethnicity, smoking status, index of multiple deprivation (IMD), estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, cholesterol, glycated haemoglobin (HBA1C) and blood pressure. Analyses were performed in STATA v17. This manuscript follows the reporting recommendation of RECORD-PE [23]. A p value of <0.05 was taken as statistically significant. The outcome was hospitalisation or death. Potential modifiers included age, sex, BMI, index of multiple deprivation (IMD), ethnicity, smoking status and comorbidity.

RESULTS

The study cohort included patients diagnosed as T1DM and T2DM separately. Across the Greater Manchester Region, a total of 145,907 individuals were diagnosed with T2DM and 9705 were diagnosed with T1DM (Tables 1, 2); 30.8% of people with T1DM had a positive COVID-19 diagnosis and 20.4% of people with T2DM as now stated.

The number of deaths in T1DM was too low ($n=30$) for further statistical analyses to explore the association with mortality. Only the first COVID-19 test was recorded.

A varying number of multiple medications were prescribed to individuals with T1DM or T2DM (Table 1). A large proportion of individuals were prescribed between 1 and 5 medications; the distribution of number of medications prescribed and BNF chapters can be seen in Figure S1 and Figure S2. In T2DM, after endocrine and cardiovascular medications, the largest number of multiple prescriptions were from the gastrointestinal (GI) BNF chapter.

Common comorbidities were grouped into broader categories (see Supplementary Information Table S1) and counts were collated for T1DM and T2DM. The top six modal comorbidity groups identified in T2DM were mental health conditions, hypertension, gastrointestinal or liver disease, pain, respiratory conditions (or sinus-related) and cardiovascular/cerebrovascular conditions (Table 2). Of the individuals diagnosed with T2DM, 69.9% were diagnosed with hypertension and 44.9% with mental health conditions (Table 2). The same six comorbidity groups were also identified in the individuals with T1DM (Table S2).

Table 1 Baseline demographics of individuals diagnosed with type 1 diabetes (T1DM) or type 2 diabetes (T2DM)

	Type 1 diabetes *N* = **9705**	**Type 2 diabetes** *N* = **145,907**
Age (years)	47.3 ± 16.8	65.8 ± 13.8
BMI (kg/m^2)	27.7 ± 7.0	31.0 ± 7.7
Sex		
Female	4143 (42.7)	65,922 (45.2)
Male	5562 (57.3)	79,985 (54.8)
Smoking status		
Non-smoker	3967 (40.9)	51,823 (35.5)
Current smoker	1804 (18.6)	20,906 (14.3)
Ex-smoker	3765 (38.8)	71,519 (49.0)
Unknown/missing	169 (1.7)	1659 (1.1)
Ethnicity		
White	8020 (82.6)	102,051 (69.9)
Asian	565 (5.8)	25,359 (17.4)
Black	221 (2.3)	5176 (3.6)
Mixed	107 (1.1)	1528 (1.1)
Other	379 (3.9)	6184 (4.2)
Missing/refused	413 (4.3)	5609 (3.8)
Deprivation index/Townsend quintile (IMD)		
1 (least deprived)	1182 (12.2)	13,471 (9.2)
2	1451 (15.0)	19,080 (13.1)
3	1395 (14.4)	18,017 (12.4)
4	1984 (20.4)	28,863 (19.8)
5 (most deprived)	3680 (37.9)	66,426 (45.5)
Missing	13 (0.1)	50 (0.03)
Total number of medications prescribed[a]		
0	543 (5.60)	13,359 (9.16)
1–5	5822 (59.99)	51,999 (35.64)
6–10	1879 (19.36)	38,533 (26.41)

Table 1 continued

	Type 1 diabetes *N* = 9705	Type 2 diabetes *N* = 145,907
11–15	744 (7.67)	21,433 (14.69)
16–20	348 (3.59)	9880 (6.77)
> 20	369 (3.80)	10,703 (7.34)
Systolic blood pressure (mmHg)[b]	127.1 ± 15.2	131.1 ± 14.5
Diastolic blood pressure (mmHg)[b]	74.8 ± 9.8	75.9 ± 9.6
HBA1C (mmol/mol)[b]	69.3 ± 20.3	56.8 ± 17.0
eGFR (ml/min/1.73 m^2) < 60[c]	907 (9.4)	25,851 (17.7)
eGFR (ml/min/1.73 m^2)[b]	81.0 ± 15.5	75.4 ± 17.2
Cholesterol (mmol/mol)[b]	4.5 ± 1.1	4.3 ± 1.1
LDL (mmol/l)[b]	2.4 ± 0.9	2.2 ± 0.9
HDL (mmol/l)[b]	1.5 ± 0.5	1.2 ± 0.4
Diabetes duration (years)	20.6 ± 14.3	10.4 ± 7.45
Vaccination status: (defined prior to/around the time of first infection)		
Yes	8816 (90.8)	135,141 (92.6)
No	889 (9.2)	10,766 (7.4)
Prescribed medications[a]		
Metformin	1015 (10.5)	72,084 (49.4)
SGLT2[d]	163 (1.7)	16,134 (11.1)
Insulin	6854 (70.6)	12,149 (8.3)
Arb/ACE inhibitors	1759 (18.1)	44,127 (30.2)
Antiplatelet (clopidogrel/aspirin)	1177 (12.1)	31,403 (21.5)
Angiotensin receptor blockers	710 (7.3)	20,168 (13.8)
Sulphonylureas	98 (1.0)	22,011 (15.1)
GLP1 receptor agonists	79 (0.8)	4475 (3.1)
Alogliptin	36 (0.4)	10,196 (7.0)
Linagliptin	37 (0.4)	5388 (3.7)
Saxagliptin	< 10 (0)	944 (0.7)
Sitagliptin	29 (0.3)	6570 (4.5)
Vildagliptin	< 10 (0)	396 (0.27)

Table 1 continued

	Type 1 diabetes *N* = 9705	Type 2 diabetes *N* = 145,907
Admission to hospital (within 28 days of infection)	146(1.5)	2107 (1.4)
Length of stay in hospital (days)	4.5 ± 8.3	7.1 ± 11.9
Deaths (within 28 days of confirmed infection)	30 (0.3)	885 (0.6)

Categorical variables presented as *N* (%) and continuous variables as mean (± SD)

Arb angiotensin II receptor blocker, *ACE* angiotensin-converting enzyme inhibitor, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HBA1C* glycated haemoglobin

Townsend index: 1 denotes the least deprived and 5 the most deprived

[a]Medications prescribed close to January 2020

[b]Closest point before first COVID-19-positive test

[c]Estimated glomerular filtration rate

[d]Sodium glucose co-transporter 2 inhibitor (SGLT2i) or a glucagon-like peptide 1 (GLP-1) agonist

Table 2 Prevalence of comorbidity groups in individuals diagnosed with T2DM

Morbidity group	*N*	%
Hypertension	101,995	69.9
GI/liver disease	82,193	56.3
Mental health disorder	65,487	44.9
Pain	60,237	41.3
Cardiovascular/cerebrovascular	48,213	33.0
Respiratory/sinus	41,653	28.6
Sensory	34,541	23.7
Skin/connective tissue disorder	28,459	19.5
Chronic kidney disease	27,931	19.1
Neurological disorders	22,795	15.6
Thyroid disorders	14,476	9.9
Prostate diseases	9276	6.4
Alcohol substance abuse	9108	6.2
Cancer	7892	5.4
Dementia	6498	4.5
Glaucoma	6262	4.3
Learning disability	1016	0.7

The top six groups are shown in italics

Logistic Regression Analysis

Odds ratios (95% confidence intervals) of the multivariate regression are reported in the individuals with T1DM and T2DM respectively.

T1DM

An increased risk of adverse outcomes post-infection was observed for individuals with T1DM and GI/liver disorders ($p < 0.001$; odds ratio [OR] [95% confidence interval (CI)] 3.452 [2.118–5.625]) and pain-associated conditions ($p = 0.04$; OR [95% CI] 1.556 [1.021–2.372]) (Table 3). Age was determined as slightly protective of hospital admission following COVID-19 diagnosis ($p < 0.001$; OR [95% CI] 0.964 [0.949–0.980]). Other significant variables included eGFR < 60 ($p < 0.001$; OR [95% CI] 2.794 [1.746–4.47]). There was no association with polypharmacy.

T2DM

In individuals with T2DM, an increased number of medications, from 11 upwards was associated with an increased risk of hospital admission following COVID-19 infection (Table 4). Individuals diagnosed with co-morbidities in the following morbidity groups had an increased likelihood of hospital admission: mental health disorders

Table 3 Multivariate logistic regression analyses of hospital admission following COVID-19 diagnosis in individuals with T1DM

Variable	OR (95% CI)	*p* value
Age	0.964 (0.949–0.980)	< 0.001
Sex	0.792 (0.537–1.167)	0.239
BMI	0.989 (0.960–1.02)	0.485
Ethnicity		
Asian	0.919 (0.431–1.956)	0.826
Black	0.388 (0.052–2.882)	0.355
Mixed	1.889 (0.444–8.04)	0.390
Other	0.447 (0.108–1.852)	0.267
Unknown	0.250 (0.035–1.809)	0.170
Smoking status		
Current smoker	0.856 (0.487–1.507)	0.590
Ex-smoker	1.022 (0.665–1.571)	0.921
Unknown/missing	1.237 (0.285–5.359)	0.777
IMD		
2	0.865 (0.404–1.851)	0.708
3	0.650 (0.291–1.452)	0.294
4	0.999 (0.501–1.992)	0.998
5 (most deprived)	0.843 (0.441–1.61)	0.604
eGFR < 60	2.794 (1.746–4.47)	< 0.001
Cholesterol	0.925 (0.780–1.097)	0.369
HBA1C	1.002 (0.993–1.011)	0.681
Systolic BP	0.998 (0.984–1.012)	0.788
Diastolic BP	1.018 (0.996–1.041)	0.105
Comorbidity groups		
Mental health disorder	0.690 (0.463–1.028)	0.068
Hypertension	1.179 (0.746–1.865)	0.480
GI/liver disorder	3.452 (2.118–5.625)	< 0.001
Pain	1.556 (1.021–2.372)	0.040
Respiratory/sinus conditions	0.986 (0.650–1.496)	0.948
Cardiovascular/cerebrovascular	1.327 (0.814–2.162)	0.257

Table 3 continued

Variable	OR (95% CI)	*p* value
Total number of medications		
1–5	1.001 (0.235–4.271)	0.999
6–10	2.139 (0.488–9.381)	0.313
11–15	2.496 (0.539–11.554)	0.242
16–20	3.577 (0.738–17.329)	0.113
> 20	2.158 (0.424–10.989)	0.355

Odds ratios and 95% confidence intervals from the logistic regression model of hospital admission post-COVID-19 diagnosis

($p = 0.003$; OR [95% CI] 1.167 [1.054–1.292]); gastrointestinal/liver disorders ($p < 0.001$; OR [95% CI] 1.977 [1.741–2.245]); pain ($p < 0.001$; OR [95% CI] 1.407 [1.265–1.564]); respiratory/sinus conditions ($p < 0.001$; OR [95% CI] 1.235 [1.115–1.369]) and cardiovascular/cerebrovascular conditions ($p < 0.001$; OR [95% CI] 1.443 [1.292–1.612]). People with T2DM and eGFR level < 60 ($p < 0.001$; OR [95% CI] 1.431 [1.268–1.614]) also had an increased risk of hospital admission, similarly those with HBA1C levels ($p = 0.009$; OR [95% CI] 1.004 [1.001–1.006]) were also at increased risk (Table 4).

Males were more likely to be admitted to the hospital after infection with COVID-19 ($p < 0.001$; OR [95% CI] 1.312 [1.181–1.457]). High BMI was associated with a higher likelihood of adverse outcomes (hospitalisation and mortality) from COVID-19 ($p = 0.002$; OR [95% CI] 1.011 [1.004–1.018]). Age was protective of hospital admission; however, the odds ratio was only slightly less than 1 ($p = 0.009$; OR [95% CI] 0.993 [0.988–0.998]). Individuals of Asian ($p = 0.006$; OR [95% CI] 1.213 [1.058–1.39]) or Black ($p = 0.003$; OR [95% CI] 1.441 [1.129–1.838]) ethnicities were also more likely to be admitted to the hospital following infection (Table 4).

Individuals who identified as 'current smokers' were not identified as being at increased risk ($p < 0.001$; OR [95% CI] 0.507 [0.419–0.614]). However, individuals who lived in areas with higher social disadvantage were more likely to be admitted to hospital—IMD quintiles 4 and 5 ($p = 0.02$; OR [95% CI] 1.278 [1.039–1.572]; $p = 0.033$; OR [95% CI] 1.236 [1.017–1.503]) (Table 4).

In individuals with T2DM, the number of deaths was 885 (0.6% of the total number of individuals diagnosed with T2DM) (Table 1). An increased number of medications, from 16 to 20 to > 20 was associated with an increased risk of death following COVID-19 infection ($p = 0.005$; OR [95% CI] 2.375 [1.306–4.319] and $p < 0.001$; OR [95% CI] 3.141 [1.755–5.621] respectively) (Table 5).

People diagnosed with the following long-term conditions were at higher risk of death post-infection: mental health disorders ($p < 0.001$; OR [95% CI] 1.544 [1.219–1.954]); respiratory/sinus conditions ($p < 0.001$; OR [95% CI] 1.573 [1.245–1.988]) or cardiovascular/cerebrovascular conditions ($p < 0.001$; OR [95% CI] 1.691 [1.297–2.203]). A protective effect was observed for individuals living with GI/liver disorder ($p < 0.001$; OR [95% CI] 0.519 [0.404–0.666]) or pain ($p < 0.001$; OR [95% CI] 0.513 [0.4–0.657]) (Table 5).

As with hospital admission, the risk of death increased in males and with high BMI ($p = 0.017$; OR [95% CI] 1.35 [1.054–1.728] and $p = 0.004$; OR [95% CI] 1.021 [1.007–1.036] respectively). Age was associated with an increased risk of mortality post-COVID-19 infection ($p < 0.001$; OR [95% CI] 1.092 [1.078–1.107]) (Table 5).

Individuals with T2DM and living in the most deprived regions (IMD 5) were at higher risk of death following COVID-19 infection ($p = 0.021$; OR [95% CI] 1.684 [1.081–2.623]) or if their

Table 4 Multivariate logistic regression analyses of hospital admission within 28 days of COVID-19 diagnosis in individuals with T2DM

Variable	OR (95% CI)	*p* value
Age	0.993 (0.988–0.998)	0.009
Sex	1.312 (1.181–1.457)	< 0.001
BMI	1.011 (1.004–1.018)	0.002
Ethnicity		
Asian	1.213 (1.058–1.39)	0.006
Black	1.441 (1.129–1.838)	0.003
Mixed	1.059 (0.632–1.774)	0.827
Other	0.960 (0.744–1.239)	0.754
Unknown	0.947 (0.701–1.28)	0.725
Smoking status		
Current smoker	0.507 (0.419–0.614)	< 0.001
Ex-smoker	0.998 (0.894–1.115)	0.977
Unknown/missing	0.856 (0.525–1.396)	0.533
IMD		
2	1.070 (0.851–1.345)	0.562
3	1.091 (0.868–1.373)	0.454
4	1.278 (1.039–1.572)	0.020
5 (most deprived)	1.236 (1.017–1.503)	0.033
eGFR < 60	1.431 (1.268–1.614)	< 0.001
Cholesterol	1.021 (0.976–1.068)	0.369
HBA1C	1.004 (1.001–1.006)	0.009
Systolic BP	1.001 (0.997–1.005)	0.709
Diastolic BP	1.002 (0.996–1.008)	0.470
Comorbidity groups		
Mental health disorder	1.167 (1.054–1.292)	0.003
Hypertension	1.074 (0.946–1.219)	0.272
GI/liver disorder	1.977 (1.741–2.245)	< 0.001
Pain	1.407 (1.265–1.564)	< 0.001
Respiratory/sinus conditions	1.235 (1.115–1.369)	< 0.001
Cardiovascular/cerebrovascular	1.443 (1.292–1.612)	< 0.001

Table 4 continued

Variable	OR (95% CI)	*p* value
Total number of medications		
1–5	1.123 (0.901–1.401)	0.302
6–10	1.108 (0.886–1.387)	0.370
11–15	1.341 (1.063–1.692)	0.013
16–20	1.450 (1.124–1.87)	0.004
> 20	1.530 (1.191–1.966)	0.001

Odds ratios and 95% confidence intervals from the logistic regression model of hospital admission post-COVID-19 diagnosis

eGFR level measure was < 60 ($p = 0.011$; OR [95% CI] 1.382 [1.078–1.771]) (Table 5).

DISCUSSION

We have shown in T2DM, an independent association of multiple medications from 11 upwards (in number) with adverse health consequences following COVID-19 infection, independent of the presence of comorbidities. We also found that individuals with diabetes develop comorbidities that were common across both T1DM and T2DM. This study has laid the foundation for future investigations into the way that complex pharmacological interactions may influence clinical outcomes in people with T2DM.

Polypharmacy, independent of other factors including major multimorbidity, was associated with an increased likelihood of hospital admission in people with T1DM and of hospitalisation and death in T2DM following COVID-19 infection. This has not been specifically reported previously, although it was described in older individuals [18]. One potential reason for this is that with many medications, there may be unexpected and unknown interactions between multiple agents that are not seen with a single medication vs another. This is of relevance to the consequences following any serious viral infection in people with diabetes, while also highlighting the importance of regular medicine reviews in everyone with diabetes, where there may be an opportunity to reduce the prescribed medications [24].

The mean ages of individuals diagnosed with T1DM or T2DM are similar to the mean ages of a Swedish cohort [1]. In our study, we also identified several co-morbidities that increased the risk of adverse health outcomes post-COVID-19 infection. This is relevant because of the way that specific long-term conditions may lead to polypharmacy. Similar co-morbidities were identified for both individuals with T1DM and T2DM. Notably, we also identified that there were a large proportion of diagnoses of mental health conditions in people with T2DM (Table 2), though the highest number of diagnoses was observed in people with T1DM (Table S2). The relationship between physical health conditions and poor mental health is an area that is not fully understood. In addition to this, the impact of polypharmacy is unknown.

The risk of hospital admission in current smokers was less than ex- and non-smokers. The reason for this may be that people with multiple health issues and who are smokers may have stopped smoking in the weeks or months before a COVID-19 infection and therefore not be deemed as a smoker at the time of the COVID-19 infection. Regarding the higher hospitalisation rate and lower mortality in the presence of a GI or liver condition—these are added comorbidities that may increase the likelihood of hospital admission in the context of any intercurrent illness but were not identified in the epidemiological studies as associated with increased mortality after COVID-19 infection.

Table 5 Multivariate logistic regression analyses of deaths within 28 days of COVID-19 diagnosis in individuals with T2DM

Variable	OR (95% CI)	*p* value
Age	1.092 (1.078–1.107)	< 0.001
Sex	1.350(1.054–1.728)	0.017
BMI	1.021 (1.007–1.036)	0.004
Ethnicity		
Asian	0.719 (0.46–1.123)	0.147
Black	0.666 (0.272–1.631)	0.374
Mixed	1.418 (0.447–4.5)	0.553
Other	0.696 (0.357–1.36)	0.289
Smoking status		
Unknown	1.259 (0.717–2.212)	0.423
Current smoker	1.015 (0.665–1.549)	0.945
Ex-smoker	0.945 (0.724–1.234)	0.677
Unknown/missing	Omitted	
IMD		
2	1.444 (0.88–2.37)	0.146
3	1.181 (0.7–1.993)	0.534
4	1.481 (0.921–2.381)	0.105
5 (most deprived)	1.684 (1.081–2.623)	0.021
eGFR < 60	1.382 (1.078–1.771)	0.011
Cholesterol	1.084 (0.973–1.207)	0.145
HBA1C	1 (0.992–1.008)	0.967
Systolic BP	0.993 (0.985–1.002)	0.122
Diastolic BP	1.001 (0.987–1.015)	0.906
Comorbidity groups		
Mental health disorder	1.544 (1.219–1.954)	< 0.001
Hypertension	0.794 (0.574–1.099)	0.164
GI/liver disorder	0.519 (0.404–0.666)	< 0.001
Pain	0.513 (0.4–0.657)	< 0.001
Respiratory/sinus conditions	1.573 (1.245–1.988)	< 0.001
Cardiovascular/cerebrovascular	1.691 (1.297–2.203)	< 0.001

Table 5 continued

Variable	OR (95% CI)	*p* value
Total number of medications		
1–5	0.583 (0.32–1.06)	0.077
6–10	0.945 (0.536–1.665)	0.844
11–15	1.429 (0.802–2.545)	0.226
16–20	2.375 (1.306–4.319)	0.005
> 20	3.141 (1.755–5.621)	< 0.001

Odds ratios and 95% confidence intervals from the logistic regression model of mortality post-COVID-19 diagnosis

BP blood pressure, *eGFR* estimated glomerular filtrate rate, *GI* gastrointestinal, *HBA1C* glycated haemoglobin, *IMD* index of multiple deprivation, *T2DM* type 2 diabetes

Over-prescribing is an issue in the current healthcare system. Medication is routinely recorded; therefore in clinical practice, there is the potential to flag the number of medications prescribed to clinicians to monitor. Thereby the number of prescriptions given to vulnerable individuals could be limited as appropriate and effective for the individual, though this does require both routine monitoring and structured reviews of the medications that people are taking. The UK healthcare system looks to improve the management of prescriptions, and the removal of unnecessary medications is key to reducing the burden of polypharmacy [25, 26].

We accept that a number of potential confounding factors were not covered in the coded data such as household makeup, urban vs suburban vs rural living and employment status. Less than 2% of individuals were prescribed corticosteroids in primary care. We did not have access to inpatient hospital prescriptions of dexamethasone for management of acute COVID-19 infection-related hypoxia.

One of the limitations of this study is that a measure of 'frailty' was not included [27]. However, a count of comorbidities is included that could possibly be used as a proxy for frailty. As the data from this study originated from electronic health records, it is also subject to the limitations of how information is coded when originally entered into the systems, such as missing data. Only 70.6% of individuals with T1DM were recorded with a prescription of insulin (Table 1). This could be due to lack of recording or unclear diagnosis, which highlights another issue with routinely collected data. Another issue is that medications are recorded in the health care records are not true reflections of medications that are concordant with the choices of the individual [28]. A study in the United States demonstrated that EHR-related medication errors can occur at different stages, including at ordering, preparation, dispensing, administering or monitoring stage, these can ultimately affect the data in EHRs [29]. Inaccuracies of coding are inherent in any project that relies on primary coded data. Nevertheless, the large number of people included in the study means that such inaccuracies are unlikely materially to influence the results. Furthermore, medications can also be counted in more than one BNF chapter, making it difficult to determine unique counts. Strengths of the study are that we were able to include everyone alive and with a diagnosis of T1DM or T2DM living in Greater Manchester on 1 January 2020 and that we had access to the full anonymised data set for diagnoses and prescribed medication. Furthermore, we were able to adjust for major comorbidities in the regression analysis.

As of these data were from one region in the UK, it is difficult to generalise to the rest of the population. Finally in studies using real-world data analysis, there will be a number of factors that are not covered in the coded data such as household makeup and employment.

It should be pointed out that there a number of definitions of polypharmacy, e.g.

polypharmacy (6–10 medications) and excessive polypharmacy (≥ 11 medications) [30]. Polypharmacy has no generally accepted definition, though criteria for major and minor polypharmacy have been suggested in the literature. Polypharmacy has been defined using different approaches, including numerical and descriptive methods [31].

Future work would include investigating the modal medications prescribed in this cohort and explore possible drug–drug interactions between medications that could contribute to increasing the risk of adverse outcomes post-COVID-19 infection. The burden of mental health conditions on people with diabetes and how to effectively manage multiple long-term conditions, could also be explored. The knowledge gained would be helpful in future pandemics and better prepare our healthcare system.

In conclusion, we have identified that multiple medications were prescribed to many people living with diabetes and that this was associated with a higher risk of adverse health outcomes following COVID-19 infection. This can be seen as a paradigm for risks of becoming seriously unwell following other viral infections. We also found that individuals with diabetes developed comorbidities that were common across both type 1 and 2 diabetes. Our analysis confirmed the impact of higher levels of deprivation on increasing a person's risk of adverse outcomes post-COVID-19 infection. This study has laid the foundation for future investigations into the increased and complex treatments that people living with diabetes are offered.

ACKNOWLEDGEMENTS

This work uses data provided by patients and collected by the NHS as part of their care and support.

Author Contributions. Rathi Ravindrarajah performed the data cleaning and data analyses. Juhi Gupta, William Ollier and Adrian Heald conceived the study. Juhi Gupta prepared the figures and the manuscript. George Tilston extracted the original dataset. Darren Ashcroft, William Ollier and Adrian Heald contributed to all sections of the paper and Darren Ashcroft provided expert input from a pharmacological perspective. All authors were involved in designing the study, interpreting results and drafting, reviewing and editing the manuscript.

Funding. This work was supported by the Turing-Manchester Feasibility Project Funding. The authors recognise the Greater Manchester Care Record (a partnership of Greater Manchester Health and Social Care Partnership, Health Innovation Manchester and Graphnet Health, on behalf of Greater Manchester localities) in the provision of data required to undertake this work. GT was funded by the NIHR Manchester Biomedical Research Centre (NIHR203308) for this work. DMA is supported by the NIHR Greater Manchester Patient Safety Research Collaboration (PSRC). The journal's Rapid Service Fee was supported by the authors.

Data Availability. The datasets generated during and analysed during the current study are not publicly available as all data access is subject to review by Health Innovation Manchester.

Declarations

Conflict of Interest. Juhi K Gupta, Rathi Ravindrarajah, George Tilston, William Ollier, Darren M Ashcroft and Adrian H Heald have no conflicts of interest.

Ethical Approval. This project was reviewed, and ethical approval for COVID-19 research was overseen by Health Innovation Manchester and granted by the Greater Manchester Care Record (GMCR) review board (ref: IDCR-RQ-046). This research was performed with anonymised data, in line with the Health Research Authority's Governance arrangements for research ethics committees.

REFERENCES

1. Rawshani A, Kjölhede EA, Rawshani A, et al. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: a nationwide retrospective cohort study. Lancet Region Health Eur. 2021;4: 100105. https://doi.org/10.1016/j.lanepe.2021.100105.

2. Izzi-Engbeaya C, Distaso W, Amin A, et al. Adverse outcomes in COVID-19 and diabetes: a retrospective cohort study from three London teaching hospitals. BMJ Open Diabetes Res Care. 2021;9(1): e001858. https://doi.org/10.1136/bmjdrc-2020-001858.

3. Kone AP, Martin L, Scharf D, et al. The impact of multimorbidity on severe COVID-19 outcomes in community and congregate settings. Dialogues Health. 2023;2: 100128. https://doi.org/10.1016/j.dialog.2023.100128.

4. Li Y, Ashcroft T, Chung A, et al. Risk factors for poor outcomes in hospitalised COVID-19 patients: a systematic review and meta-analysis. J Glob Health. 2021;11:10001. https://doi.org/10.7189/jogh.11.10001.

5. Fekadu G, Bekele F, Tolossa T, et al. Impact of COVID-19 pandemic on chronic diseases care follow-up and current perspectives in low resource settings: a narrative review. Int J Physiol Pathophysiol Pharmacol. 2021;13(3):86–93.

6. Danhieux K, Buffel V, Pairon A, et al. The impact of COVID-19 on chronic care according to providers: a qualitative study among primary care practices in Belgium. BMC Fam Pract. 2020;21(1):255. https://doi.org/10.1186/s12875-020-01326-3.

7. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81(2):e16–25. https://doi.org/10.1016/j.jinf.2020.04.021.

8. Nilsson SF, Laursen TM, Osler M, et al. Adverse SARS-CoV-2-associated outcomes among people experiencing social marginalisation and psychiatric vulnerability: a population-based cohort study among 4,4 million people. Lancet Region Health Eur. 2022;20: 100421. https://doi.org/10.1016/j.lanepe.2022.100421.

9. McQueenie R, Foster HME, Jani BD, et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. PLoS ONE. 2020;15(8): e0238091. https://doi.org/10.1371/journal.pone.0238091.

10. Heald AH, Jenkins DA, Williams R, et al. The risk factors potentially influencing hospital admission in people with diabetes, following SARS-CoV-2 infection: a population-level analysis. Diabetes Ther. 2022;13(5):1007–21. https://doi.org/10.1007/s13300-022-01230-2.

11. Heald AH, Jenkins DA, Williams R, et al. Mortality in people with type 2 diabetes following SARS-CoV-2 infection: a population level analysis of potential risk factors. Diabetes Ther. 2022;13(5):1037–51. https://doi.org/10.1007/s13300-022-01259-3.

12. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230. https://doi.org/10.1186/s12877-017-0621-2.

13. Remelli F, Ceresini MG, Trevisan C, Noale M, Volpato S. Prevalence and impact of polypharmacy in older patients with type 2 diabetes. Aging Clin Exp Res. 2022;34(9):1969–83. https://doi.org/10.1007/s40520-022-02165-1.

14. Rochon PA, Petrovic M, Cherubini A, et al. Polypharmacy, inappropriate prescribing, and deprescribing in older people: through a sex and gender lens. Lancet Healthy Longev. 2021;2(5):e290–300. https://doi.org/10.1016/S2666-7568(21)00054-4.

15. Bhagavathula AS, Vidyasagar K, Chhabra M, et al. Prevalence of polypharmacy, hyperpolypharmacy and potentially inappropriate medication use in older adults in India: a systematic review and meta-analysis. Front Pharmacol. 2021. https://doi.org/10.3389/fphar.2021.685518.

16. McKeigue PM, Kennedy S, Weir A, et al. Relation of severe COVID-19 to polypharmacy and prescribing of psychotropic drugs: the REACT-SCOT case-control study. BMC Med. 2021;19(1):51. https://doi.org/10.1186/s12916-021-01907-8.

17. Iloanusi S, Mgbere O, Essien EJ. Polypharmacy among COVID-19 patients: a systematic review. J Am Pharm Assoc (2003). 2021;61(5):e14–25. https://doi.org/10.1016/j.japh.2021.05.006.

18. Rahman S, Singh K, Dhingra S, et al. The double burden of the COVID-19 pandemic and polypharmacy on geriatric population—public health implications. Ther Clin Risk Manag. 2020;16:1007–22. https://doi.org/10.2147/TCRM.S272908.

19. Madhavan S, Bastarache L, Brown JS, et al. Use of electronic health records to support a public health response to the COVID-19 pandemic in the United States: a perspective from 15 academic medical centers. J Am Med Inform Assoc. 2021;28(2):393–401. https://doi.org/10.1093/jamia/ocaa287.

20. Casey JA, Schwartz BS, Stewart WF, Adler NE. Using electronic health records for population health research: a review of methods and applications. Annu Rev Public Health. 2016;37(1):61–81. https://doi.org/10.1146/annurev-publhealth-032315-021353.

21. Kruse CS, Stein A, Thomas H, Kaur H. The use of electronic health records to support population health: a systematic review of the literature. J Med Syst. 2018;42(11):214. https://doi.org/10.1007/s10916-018-1075-6.

22. Cowie MR, Blomster JI, Curtis LH, et al. Electronic health records to facilitate clinical research. Clin Res Cardiol. 2017;106(1):1–9. https://doi.org/10.1007/s00392-016-1025-6.

23. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ. 2018. https://doi.org/10.1136/bmj.k3532. (**Published online November 14**).

24. Kerr L. Polypharmacy in diabetes and solutions for greater adherence. Pract Diabetes Int. 2009;26(7):289–290i. https://doi.org/10.1002/pdi.1402.

25. The ASHN Network. Polypharmacy. The AHSN network. Published 2022. https://www.ahsnnetwork.com/programmes/medicines/polypharmacy/. Accessed 7 Apr 2023

26. Department of Health and Social Care. National overprescribing review report. GOV.UK. Published 2023. https://www.gov.uk/government/publications/national-overprescribing-review-report. Accessed 7 Apr 2023

27. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018;3(7):e323–32. https://doi.org/10.1016/S2468-2667(18)30091-4.

28. Marzec LN, Maddox TM. Medication adherence in patients with diabetes and dyslipidemia: associated factors and strategies for improvement. Curr Cardiol Rep. 2013;15(11):418. https://doi.org/10.1007/s11886-013-0418-7.

29. Carayon P, Du S, Brown R, Cartmill R, Johnson M, Wetterneck TB. EHR-related medication errors in two ICUs. J Healthc Risk Manag. 2017;36(3):6–15. https://doi.org/10.1002/jhrm.21259.

30. Lu WH, Wen YW, Chen LK, et al. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. CMAJ. 2015;187:E130–7.

31. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. Ther Adv Drug Saf. 2020;12(11):2042098620933741.