Type 2 diabetes and COVID-19 related mortality in the critical care setting: A national cohort study in England, March-July 2020

John M. Dennis (PhD)[1], Bilal A Mateen (MBBS)[2,3]*, Raphael Sonabend (BSc)[4], Nicholas J Thomas (MRCP)[1,5], Kashyap A Patel (PhD)[1,5], Andrew T Hattersley (FRS, DM)[1,5], Spiros Denaxas (PhD)[2,6,7], Andrew P McGovern (MD Res)[1,5], Sebastian J Vollmer (PhD)[2,8]

1 University of Exeter Medical School. Address: Institute of Biomedical & Clinical Science, RILD Building, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK
2 The Alan Turing Institute. Address: British Library, 96 Euston Road, London, NW1 2DB, UK
3 University of Warwick Medical School. Address: Social Science and Systems in Health Unit, Medical School Building, University of Warwick, Coventry, CV4 7AL, UK
4 University College London, Department of Statistical Science. Address: University College London, Gower Street, London, WC1E 6BT, UK
5 Royal Devon and Exeter NHS Foundation Trust, Diabetes and Endocrinology, Exeter, Barrack Road, EX2 5DW
6 University College London, Institute of Health Informatics. Address: University College London, 222 Euston Rd, London NW1 2DA, London, UK
7 Health Data Research UK. Address: Gibbs Building, 215 Euston Road, London, NW1 2BE, UK
8 University of Warwick, Department of Statistics. Address: Department of Statistics, University of Warwick, Coventry, CV4 7AL, UK

Author for Correspondence (*)
Dr. Bilal A. Mateen
Social Science and Systems in Health Unit
Warwick Medical School, University of Warwick
Coventry, CV4 7AL, UK
Email: b.mateen@warwick.ac.uk
Tel: +44 (0)24 7657 4880

Short Running Title: Diabetes and COVID-19 in Critical Care

Word Count: 3,501

Number of figures and tables: 2 tables, 2 figures

Abstract

Objective: To describe the relationship between type 2 diabetes and all-cause mortality amongst adults with COVID-19 in the critical care setting.

Research Design and Methods: Nationwide retrospective cohort study in people admitted to hospital in England with COVID-19 requiring admission to a high dependency unit (HDU) or intensive care unit (ICU) between March 1, 2020 and July 27, 2020. Cox proportional hazards models were used to estimate 30 day in-hospital all-cause mortality associated with type 2 diabetes, adjusted for age, sex, ethnicity, obesity, and other major comorbidities (chronic respiratory disease, asthma, chronic heart disease, hypertension, immunosuppression, chronic neurological disease, chronic renal disease, and chronic liver disease).

Results: 19,256 COVID-19 related HDU and ICU admissions were included in the primary analysis, including 13,809 HDU (mean age 70), and 5,447 ICU admissions (mean age 58). 3,524 (18.3%) had type 2 diabetes. 5,077 people (26.4%) died during the study period. People with type 2 diabetes were at increased risk of death (adjusted hazard ratio (aHR) 1.23 [95%CI 1.14;1.32]), results were consistent in HDU and ICU subsets. The relative mortality risk associated with type 2 diabetes decreased with increasing age (age 18-49 aHR 1.50 [95%CI 1.05;2.15]; age 50-64 1.29 [1.10;1.51]; age 65 or greater 1.18 [1.09;1.29], p-value for age:type 2 diabetes interaction 0.002).

Conclusions: Type 2 diabetes may be an independent prognostic factor for survival in people with severe COVID-19 requiring critical care treatment, and in this setting the risk increase associated with type 2 diabetes is greatest in younger people.

Introduction

In early 2020, coronavirus disease 2019 (COVID-19), caused by the new highly-infectious organism now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2), was formally declared a pandemic by the World Health Organisation.(1) With a global prevalence of 9.3%,(2) it is unsurprising that diabetes is one of the most common comorbidities seen in people with COVID-19, second only to hypertension.(3) People with type 2 diabetes are known to be not only more susceptible to infections in general,(4) but also require hospitalization more often,(5) resulting in an overall worse prognosis.(6) As the COVID-19 pandemic has progressed, a similar pattern of a worse prognosis for people with diabetes who contract COVID-19 has been reported in population-based studies,(7, 8) with an increased risk of intensive care admission,(9-11) and worse mortality outcome in some but not all hospital cohorts.(12-14)

For people admitted to intensive care, studies published early in the course of the global pandemic suggested diabetes is an important prognostic factor even in severe COVID-19 (New York n=373, 40.2% with diabetes; unadjusted odds ratio (OR) for mortality in those with diabetes 2.31 [95%CI 1.34, 4.00]; Wuhan, China, n= 193, 24.9% with diabetes; adjusted hazard ratio 1.53 [95%CI 1.02, 2.30]).(11, 15) Two larger, more recent critical care studies have reported smaller effect sizes (Italy, n=3988, 12.9% with diabetes; adjusted OR 1.18 [95%CI 1.01, 1.39]; USA, n=2,215, 38.9% with diabetes; adjusted OR 1.14 [95%CI 0.91, 1.43]).(16, 17) Heterogeneity across these studies likely reflects a combination of local variation in prevalence of diabetes, variation in the characteristics of people with diabetes, and the limited geo-temporal snapshots each study represents. Data on the additional mortality associated with diabetes in critical care across the entire first wave

of COVID-19 are lacking in these studies, and potential heterogeneity in the risk associated with diabetes by age and other clinical features has yet to be fully explored.

We aimed to establish the clinical utility of type 2 diabetes as a prognostic factor for survival in people admitted to critical care with COVID-19, using national data over the course of the entire first wave of COVID-19 from hospitals in England.

Methods

Data Source

Data were accessed from the COVID-19 Hospitalisation in England Surveillance System (CHESS), established by Public Health England.(18) Reporting to CHESS is daily via web tool and is mandatory for hospitals in England. The data specification comprises epidemiological information for people with proven or a high likelihood of COVID-19 requiring hospitalisation and high dependency unit (HDU) or intensive care unit (ICU) management, including demographics, comorbidities including diabetes and obesity, and outcome. Confirmation of infection was by reverse transcriptase polymerase chain reaction (PCR) of nasopharyngeal and/or oropharyngeal swabs as it was the only available method during the study period. National testing policy changed throughout the study period, however, all people with a suspicion of COVID-19 and who were admitted to hospital were tested,(19) and people were potentially re-tested multiple times if the initial results were negative but clinical suspicion remained high. At the time of data extraction (27th July, 2020), data on 23,935 cases across 108 hospitals had been submitted to CHESS.

Study population

Inclusion and Exclusion Criteria

The study population comprised people in CHESS aged 18-99 inclusive who required HDU or ICU admission with confirmed or clinically diagnosed COVID-19 (91.4% were PCR swab positive result at some point in their admission) from 1st March 2020 to 27th July 2020 inclusive, and were not pregnant (n=22,082). Pregnancy is associated with altered metabolic physiology; due to the limited information about this group, an a priori decision was made to exclude them from the analysis.

Cohorts

The primary cohort for analysis was all patients admitted to either HDU or ICU at any point during the study period (HDU/ICU cohort*)*. We separately examined the subsets of all patients admitted to HDU but not ICU during the study period (HDU cohort), and all patients admitted to ICU during the study period (ICU cohort). People with type 1 diabetes were excluded from these primary cohorts and are analysed separately.

Recorded clinical features

Available clinical features comprised demographic characteristics (age, sex, ethnicity), obesity status, and comorbidities, as defined in the CHESS data specification,(18) recorded during critical care admission. We grouped ethnicity into major UK ethnic census groups: white, black, Asian, mixed, other, or not recorded. We defined obesity as non-obese (BMI<30), obese (BMI≥30), or not recorded, as derived from recorded BMI category (coded in CHESS as <18.5, 18.5-24.9, 25-29.9, 30-39.9, >39.9, No, Missing or Unknown) where available or recorded clinical obesity (coded as No, Borderline, Yes, Missing or Unknown) if BMI was not available. Coded comorbidities were diabetes (separated by type 1 and 2), chronic respiratory disease; asthma requiring medication; chronic/congenital heart disease; hypertension; immunosuppression (due to disease or treatment); chronic neurological disease; chronic renal disease; and chronic liver disease, all coded as No, Yes, Missing or Unknown.

Missing Data

We found variation in reporting of information on comorbidity at hospital level, with a limited number of hospitals reporting very little information on comorbidity. For our primary analysis we

excluded all patients from 15 hospitals where comorbidity recording was missing for over 50% of people (n=2,151; sFlowchart 1). After filtering the CHESS cohort by missingness, we defined binary variables for each comorbidity (Yes versus No/Missing/Unknown), assuming that, in this mostly complete subset, missing or unknown coded data represented the absence of that condition. We tested the validity of this assumption in the sensitivity analysis described later.

Outcome

The outcome was in-hospital all-cause mortality. People were followed up from admission to hospital until the earliest of: death, hospital transfer, date of last follow-up in CHESS, or a length of stay of 30 days. To account for discharge from hospital as a competing risk, people who were discharged were assumed no longer at risk of death and so were not censored at the day of discharge and instead had their follow-up time set to 30 days.(12)

Statistical Analysis

Primary analysis

Recorded clinical features were described, overall and by recorded type 2 diabetes status. We estimated the risk of 30-day mortality for each cohort by type 2 diabetes status using survival analysis with days at risk as the timescale. 30-day mortality covered 98% of the deaths observed over the maximum cohort follow-up. Kaplan-Meier survival functions and Cox proportional hazards models were used to evaluate the association between type 2 diabetes and mortality, with proportional hazards assumptions tested through examination of the schoenfeld residuals. All models included type 2 diabetes status, and were sequentially increased in complexity with adjustment firstly for age (with exploration of age as linear, category, and as a 3-knot non-linear restricted cubic spline), before

adding sex, ethnicity, obesity, and comorbidities. The primary, fully adjusted, model comprised all these features. For the ICU cohort, we started follow up on the date of ICU admission, and adjusted for days from hospitalisation to ICU admission.

Subgroup analysis

Analysis of the primary outcome for the HDU/ICU cohort was repeated in subgroups defined by major clinical characteristics; age (18-49, 50-64, 65+), sex, ethnicity, by the presence or absence of obesity, and by the presence or absence of at least one other comorbidity. To explore temporal trends, subgroups were defined by calendar month of hospital admission (March, April, May-July, 2020).

Sensitivity analysis

To explore the sensitivity to the decision to filter patients by degree of missing comorbidity data at hospital level, we described recorded characteristics of patients in included and excluded hospitals, and assessed whether the mortality associated with type 2 diabetes differed in included and excluded hospitals. To explore sensitivity of our findings to potential temporal changes in mortality over the study period, calendar week of hospital admission was included as an additional linear continuous covariate in multivariable analysis.

We conducted a propensity score matched analysis to evaluate whether the presence of type 2 diabetes increased the risk of death compared with people with the same clinical characteristics but without type 2 diabetes. The full set of recorded clinical features previously described were considered potential confounders and used for matching. Missing information for ethnicity and

obesity were coded as missing categories, providing a full patient set.(20) Pairs were matched without replacement on the logit of the propensity score, and a caliper size of 0.05 was applied for all matched pairs. Separate propensity-score models were fitted for each cohort. Cox proportional models were stratified by matched set to account for the matched nature of the propensity score defined cohorts.

We repeated the primary analysis with the following changes to formally assess the impact of the assumptions made: 1) excluding transferred patients and patients who remained in hospital; 2) including only patients with PCR swab positive results during admission; 3) including only hospitals with at least 75% complete comorbidity data; 4) including all patients in all hospitals and assuming Missing/Unknown represented the absence of a comorbidity; 5) extending the Cox proportional hazards model to incorporate hospital level random effects to account for within-hospital homogeneity in outcomes (frailty model with a random effect per hospital trust);(21) 6) to check the validity of our approach by accounting for discharge as a competing risk we used a Fine & Gray model.

Evaluation of missing data

To evaluate the appropriateness of equating diabetes status coded as missing in CHESS to the absence of diabetes, we used multiple imputation by chain equations (5 imputations) to fill missing values for diabetes status and all other missing values for ethnicity, obesity, and other comorbidities. This approach assumes missing values are missing at random.(22) We then repeated the full multivariable analysis for each cohort using the imputation model, to determine whether this model gave different results to our primary analysis.

COVID-19 mortality risk in people with Type 1 diabetes

Mortality in people with recorded type 1 diabetes was compared to people with type 2 diabetes using adjusted Cox regression, as described above. A propensity matched analysis was also utilised, as previously described, to compare the mortality risk for people with type 1 diabetes to similar patients without type 1 diabetes. Analyses was limited to the combined HDU/ICU cohort due to sample size.

Computational Resources

Analyses were conducted with R (version 3.6.2),(25) including use of the packages survival, rms, coxme, paf, mlr3, mlr3tuning, mlr3proba, xgboost, and mice.

Results

Clinical characteristics

19,256 patients were included in the primary cohort admitted to HDU (n=13,809) or ICU (n=5,447) [sFlowchart 1 and sTable 1]. Mean age was 67, 60.1% of patients were male, 27.0% of patients were of non-white ethnicity, and 18.3% had type 2 diabetes. sTable 1 shows the overall characteristics of patients in the separate HDU and ICU cohorts. ICU patients were younger, and more commonly male and of non-white ethnicity (mean age 58, 70.6% male, 37.1% non-white) than HDU only admitted patients (mean age 70, 55.9% male, 23.1% non-white).

In the primary HDU/ICU cohort, people with type 2 diabetes (n=3,524, 18.3%) were of similar age to those without type 2 diabetes (mean 67 verses 66), and were more commonly recorded as being of non-white ethnicity (41.5% versus 23.5%) and obese (45.1% versus 31.4%) (Table 1). All comorbidities were more common in people with type 2 diabetes.

Type 2 diabetes is an independent prognostic factor for mortality in severe COVID-19

5,077 (26.4%) patients in the primary HDU/ICU cohort died within the 30-day study period. Mean follow-up was 21.2 (SD 10.9) days in people with type 2 diabetes and 21.2 (SD 19.4) days in those without.

Risk of mortality was consistently higher in people with type 2 diabetes in all analyses performed. The overall unadjusted cumulative incidence of 30-day mortality was higher in people with diabetes (34.7% [95%CI 33.1, 36.3]) than without diabetes (25.5% [95%CI 24.8, 26.2]) (Figure

1). Mortality did not differ between people with diabetes recorded as missing/unknown diabetes status and those recorded as no diabetes (sFigure 1), supporting the assumption that missing coding represents the absence of diabetes. Unadjusted and adjusted hazard ratios showed higher mortality risk in people with diabetes, with a 23% increase in mortality risk observed in the fully adjusted model (Table 2). Full multivariable model outputs are provided in sTable 2. A 23% increase in mortality risk for diabetes was also observed in the propensity score matched analysis (Table 2).

The mortality increase in people with type 2 diabetes was consistent in HDU cohort (type 2 diabetes 30-day mortality 29.2% [95%CI 27.2, 31.1] versus 22.4% [95%CI 21.6, 23.2] without) and ICU cohort (30-day mortality 45.2% [42.4, 47.9] versus 36.3% [34.7, 37.8]) (sFigure 2, Table 2).

The mortality risk for type 1 diabetes (n=203) was similar to that observed for type 2 diabetes (adjusted hazard ratio (aHR) 0.98 [95%CI 0.75, 1.28], p=0.89), and in propensity score matched analysis the hazard ratio for type 1 diabetes was similar to that observed for matched controls without diabetes (aHR 1.25 [95%CI 0.86, 1.84], p=0.25) (sTable 3).

Subgroup analysis suggests lower excess mortality risk associated with type 2 diabetes at older ages and in males compared to females

Results of subgroup analyses for the primary outcome are shown in Figure 2. The association between type 2 diabetes and mortality was attenuated by age at hospital admission (age 18-49 aHR 1.50 [95%CI 1.05;2.15]); age 50-64 aHR 1.29 [95%CI 1.10;1.51]; age 65 or greater aHR 1.18 [95%CI 1.09;1.29], *p*=0.002 for age category:type 2 diabetes interaction), and there was a numerically lower excess mortality risk in males (aHR 1.15 [95%CI 1.05, 1.26]) than females (aHR 1.36 [95%CI 1.20,

1.54], p=0.06 for sex:diabetes interaction). There was no evidence of a difference in the mortality associated with type 2 diabetes in subgroups defined by ethnicity (p=0.08), obesity (p=0.28), or by the presence or absence of other recorded comorbidity (p=0.41). There was no evidence of a temporal trend in the mortality associated with type 2 diabetes by calendar month (HR range 1.13-1.34 over March-July, sTable 3), or with adjustment for calendar week of hospital admission as an additional covariate (aHR for diabetes in the primary HDU/ICU cohort 1.21 [95%CI 1.13, 1.31], sTable 3).

Sensitivity and multiple imputation analysis were consistent with the primary analysis

Results were consistent in all sensitivity analysis (sTable 3), including inclusion of only patients with a positive PCR swab result during admission, repeating the primary analysis with hospital added as a random effect, in the multiple imputation model, and, despite differences in clinical characteristics (sTable 4), including patients from all hospitals currently reporting to CHESS irrespective of completeness of comorbidity coding.

Discussion

Our analysis of over 19,000 patients admitted to critical care over the entire first wave of COVID-19 in England demonstrates that type 2 diabetes is associated with around a 20% increase in mortality risk in people with severe COVID-19, independent of age, sex, ethnicity, obesity, and other major comorbidity. Risk is similar in both the HDU and ICU cohorts, despite the fact that in England these groups differed markedly with those admitted to ICU being younger, more commonly male, and more commonly of non-white ethnicity. Additional mortality risk appears similar in type 1 diabetes compared to type 2 diabetes in this setting.

Our national-level study provides evidence for a relatively small, but significant effect of diabetes on mortality risk in one of the largest samples of COVID-19 associated critical care admissions to date. The association between diabetes and COVID-19 mortality we observed is substantially smaller than those reported in studies conducted early in the pandemic.(11, 15) Notably, we extend previous contributions by evaluating both HDU and ICU admissions, which we demonstrate to be very different populations in terms of clinical characteristics. In England these differences between HDU and ICU populations likely result from individualised care strategies based on the patient's best interests (which one UK-based centre implemented for 61% of 429 consecutive admissions),(26) rather than sustained saturation of intensive care units for which there was limited evidence.(27)

Given the large sample available, we were able to evaluate heterogeneity in mortality risk across subgroups defined by clinical features, and demonstrate that, in relative terms, the additional mortality risk associated with type 2 diabetes attenuates markedly in older people. In contrast to age,

we found no evidence of heterogeneity in the mortality risk associated with diabetes in subgroups defined by the presence or absence of obesity, comorbidity, and ethnicity. There was weak evidence of heterogeneity by sex, with a numerically higher excess risk associated with diabetes in females than males (p=0.06), which may warrant future investigation. Importantly, we demonstrate a consistent strength of association between type 2 diabetes and mortality accounting for time trends in in-hospital mortality, and accounting for geographical clustering of hospitals, which is notable as recent studies have demonstrated substantial variation in COVID-19 specific critical care outcomes between institutions,(28) as well as a marked reduction in critical care mortality over the course of the pandemic.(29)

Although direct evaluation of patient characteristics other than diabetes was not the focus of this study, the validity of our results is bolstered by demographic congruence with COVID-19 data from the UK's Intensive Care National Audit and Research Centre (ICNARC),(30) where diabetes status is not available. Notably, both studies found similar effects for males (i.e. no difference), and people of Asian ethnicity (i.e. increased risk) in critical care settings (sTable 2). The exception is that we did not find an association between obesity and mortality, in contrast to ICNARC which reported an association of small magnitude for BMI, but without adjustment for diabetes or hyperglycaemia.

Previous studies of other viral respiratory infections suggest findings of population-level studies should be extrapolated to the critical care setting with caution. For influenza, national surveys suggested increased influenza-specific mortality in people with diabetes,(31) however, large multi-state European studies of ICU admissions for influenza showed no difference in mortality by diabetes status.(32) Our results, contrasted with the numerically much greater associations for diabetes

reported in UK population based studies of COVID-19 mortality mirror this pattern of substantially reduced effect size.(7, 8) Such setting-specific differences likely reflect different frames of reference, wherein each study is capturing a different portion of a complicated pathway including the risk of being infected, then accessing services, subsequently being admitted, hospital treatments, and finally, dying in hospital.

To our knowledge, CHESS is currently the largest critical care database of people with COVID-19 and coded diabetes status, providing near complete capture of severe COVID-19 cases across England during the first wave of the pandemic.(18) Our use of a methodologically robust modelling framework, with adjustment for potential confounders and multiple sensitivity analyses to evaluate the potential influence of missing data, lends additional credibility to our mortality estimates. Despite this, we cannot rule out unmeasured confounding as an explanation of our findings. Any interpretation of our results should be bounded by the knowledge that in the primary analysis we adjusted for variables along the causal pathway (e.g. cardiovascular comorbidities), which precludes any claim that associations relate to the causal role of type 2 diabetes in COVID-19 mortality.(33) However, the consistent size of association for type 2 diabetes observed across models with sequential adjustment of clinical features supports the interpretation that type 2 diabetes is an important prognostic factor for critical care patients.

A limitation of the CHESS critical care dataset is the lack of validated case definitions for recorded comorbidities, and it is possible misclassification of diabetes status may have attenuated the mortality risk estimates observed in this study. A further important limitation is that the lack of standardised measurement of height and weight meant we had to adjust risk models for obesity status

(BMI categorised </>30 kg/m^2), rather than with more granular categorisation of BMI. A recent study of 6916 US patients diagnosed with COVID-19 suggest an independent J-shaped association between BMI category and mortality, with patients of BMI <18.5 kg/m^2 and ≥40 kg/m^2 at higher risk of mortality compared with those of normal BMI (18.5-24 kg/m^2),(34) and an analysis of 1687 hospitalised adults in New York observed a similar J-shaped pattern between BMI and mortality, although with overweight patients at lowest risk.(35) These analyses raise the possibility of residual confounding, due to the limited recording of BMI in CHESS, being a potential explanation of our findings. We lacked data to assess the impact of potentially modifiable diabetes specific risk factors in particular hyperglycaemia prior to, at, or during, hospital admission,(7, 14, 36-39) as well as possible modulatory effects of specific anti-hyperglycaemic medications.,(40-42) Clinical information on duration of diabetes and the presence of diabetes complications were similarly not available. Robustly evaluating the added value of such potential diabetes-specific prognostic factors is an important area for ongoing,(37, 39) and future, research to inform understanding of the mechanisms by which diabetes modifies outcome in severe COVID-19,(43) to establish which risk factors are most useful to identify which people with diabetes are most vulnerable to COVID-19,(44) and to inform individualised care strategies.(40)

Conclusion

Type 2 diabetes may be an independent prognostic factor for in-hospital survival in people with severe COVID-19 admitted to a critical care setting. The additional mortality risk associated with type 2 diabetes is attenuated by age. These results can help inform in-hospital decision-making on appropriate care escalation and treatment provision for people with type 2 diabetes and severe COVID-19.

Funding: This study was supported by Diabetes UK.

Role of the funding source: The funder had no role in the analysis, or reporting of results.

Acknowledgements: JMD is supported by an Independent Fellowship funded by Research England's Expanding Excellence in England (E3) fund. SJV, SD, and BAM are supported by The Alan Turing Institute (EPSRC grant EP/N510129/). RS receives a PhD stipend from EPRSC (EP/R513143/1). SJV is supported by the University of Warwick IAA funding. ATH is a NIHR Senior Investigator and a Wellcome Trust Senior Investigator (098395/Z/12/Z). JMD, NJT, KAP, ATH, and APM are supported by the NIHR Exeter Clinical Research Facility. We thank Public Health England for providing access to CHESS data to the Warwick Research Group and Matt Keeling for his support and establishing data access.

Contributors: JMD, BAM, NJT, APM, and SV designed the study. JMD and RS drafted code on dummy data. SJV adapted and extended the code and executed on CHESS. JMD, BAM, APM, and SJV drafted the article. All authors provided support for the analysis and interpretation of results, critically revised the article, and approved the final article. JMD, BAM and SJV take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interest: APM declares previous research funding from Eli Lilly and Company, Pfizer, and AstraZeneca. SJV declares funding from IQVIA. All other authors declare no competing interests.

Data Sharing: Data cannot be shared publicly as it was collected by Public Health England (PHE) as part of their statutory responsibilities, which allows them to process patient confidential data without explicit patient consent. Data utilised in this study were made available through an agreement between the University of Warwick and PHE. Individual requests for access to CHESS data are considered directly by PHE (contact via covid19surv@phe.gov.uk).

Ethics and governance: The study was reviewed and approved by the Warwick BSREC (BSREC 119/19-20) and sponsorship is being provided by University of Warwick (SOC.28/19-20).

Guarantors: The corresponding (BAM) and the senior author (SJV) had full access to all data and had final responsibility for the decision to submit for publication. Both guarantors affirm that manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1. COVID-19 situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed May 20, 2020).
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-62.
4. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018;41(10):2127-35.
5. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003;26(2):510-3.
6. Magliano DJ, Harding JL, Cohen K, Huxley RR, Davis WA, Shaw JE. Excess Risk of Dying From Infectious Causes in Those With Type 1 and Type 2 Diabetes. Diabetes Care. 2015;38(7):1274-80.
7. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
8. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. The Lancet Diabetes & Endocrinology.
9. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical research in cardiology : official journal of the German Cardiac Society. 2020;109(5):531-8.
10. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. Journal of Clinical Virology. 2020;127:104354.
11. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama. 2020;323(20):2052-9.
12. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.
13. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study. Diabetes Care. 2020:dc200598.
14. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metabolism. 2020;31(6):1068-77.e3.
15. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Research & Care. 2020;8(1):e001343.

16. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Internal Medicine. 2020.
17. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. JAMA Internal Medicine. 2020.
18. Public_Health_England. COVID-19 Hospitalisation in England Surveillance System (CHESS) 2020 [Available from: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/phe-letter-to-trusts-re-daily-covid-19-hospital-surveillance-11-march-2020.pdf.
19. Public Health England. COVID-19: investigation and initial clinical management of possible cases. 2020; published online Jan 10. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection (accessed May 26, 2020).
20. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ. 2012;184(11):1265-9.
21. Austin PC. A Tutorial on Multilevel Survival Analysis: Methods, Models and Applications. International Statistical Review. 2017;85(2):185-203.
22. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
23. Lundberg SM, Lee S-I. A Unified Approach to Interpreting Model Predictions. In: Guyon I, Luxburg UV, Bengio S, et al., eds. Advances in Neural Information Processing Systems 30. Curran Associates, Inc., 2017: 4765–74.
24. Spiegelhalter D. How old are you, really? Communicating chronic risk through 'effective age' of your body and organs. BMC Medical Informatics and Decision Making. 2016;16(1):104.
25. Development Core Team RR. R: A language and environment for statistical computing. 2011.
26. Vlachos S, Wong A, Metaxa V, Canestrini S, Lopez Soto C, Periselneris J, et al. Hospital mortality and resource implications of hospitalisation with COVID-19 in London, UK: a prospective cohort study. medRxiv. 2020:2020.07.16.20155069.
27. Mateen BA, Wilde H, Dennis Jm, Duncan A, Thomas NJM, McGovern AP, et al. A geotemporal survey of hospital bed saturation across England during the first wave of the COVID-19 Pandemic. medRxiv. 2020:2020.06.24.20139048.
28. Qian Z, Alaa AM, van der Schaar M, Ercole A. Between-centre differences for COVID-19 ICU mortality from early data in England. Intensive Care Medicine. 2020.
29. Dennis J, McGovern A, Vollmer S, Mateen BA. Improving COVID-19 critical care mortality over time in England: A national cohort study, March to June 2020. medRxiv. 2020:2020.07.30.20165134.
30. Intensive Care National Audit & Research Centre (ICNARC). ICNARC report on COVID-19 in critical care 31 July 2020. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports (accessed Aug 15, 2020).

31. Valdez R, Narayan KM, Geiss LS, Engelgau MM. Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic black and white US adults. American journal of public health. 1999;89(11):1715-21.
32. Adlhoch C, Gomes Dias J, Bonmarin I, Hubert B, Larrauri A, Oliva Domínguez JA, et al. Determinants of Fatal Outcome in Patients Admitted to Intensive Care Units With Influenza, European Union 2009-2017. Open forum infectious diseases. 2019;6(11):ofz462.
33. Huitfeldt A. Is caviar a risk factor for being a millionaire? BMJ. 2016;355:i6536.
34. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. Annals of internal medicine. 2020:M20-3742.
35. Goyal P, Ringel JB, Rajan M, Choi JJ, Pinheiro LC, Li HA, et al. Obesity and COVID-19 in New York City: A Retrospective Cohort Study. Annals of Internal Medicine. 2020.
36. Riddle MC. Diabetes and COVID-19: Moving From News to Knowledge and a Glucose Hypothesis. Diabetes Care. 2020:dci200045.
37. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 2020;63(8):1500-15.
38. Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, et al. Hyperglycemia at Hospital Admission Is Associated With Severity of the Prognosis in Patients Hospitalized for COVID-19: The Pisa COVID-19 Study. Diabetes Care. 2020:dc201380.
39. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. The Lancet Diabetes & Endocrinology.
40. Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports. Diabetes & Metabolism. 2020.
41. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. The Lancet Diabetes & Endocrinology. 2020;8(9):782-92.
42. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. Diabetes Care. 2020:dc200660.
43. Mauvais-Jarvis F. Aging, Male Sex, Obesity, and Metabolic Inflammation Create the Perfect Storm for COVID-19. Diabetes. 2020;69(9):1857-63.
44. Riddle MC, Buse JB, Franks PW, Knowler WC, Ratner RE, Selvin E, et al. COVID-19 in People With Diabetes: Urgently Needed Lessons From Early Reports. Diabetes Care. 2020:dci200024.

Table 1: Recorded characteristics of HDU/ICU cohort, by recorded type 2 diabetes status

		No type 2 diabetes (n=15,732)	Type 2 diabetes (n=3,524)
Age (years)		66 (17.4)	67 (14.1)
Age Group			
	18-24	164 (1.0)	8 (0.2)
	25-34	612 (3.9)	40 (1.1)
	35-44	1,010 (6.4)	142 (4.0)
	45-54	2,039 (13.0)	429 (12.2)
	55-64	2,814 (17.9)	848 (24.1)
	65-74	2,978 (18.9)	872 (24.7)
	75-84	3,334 (21.2)	718 (20.4)
	85+	2,781 (17.7)	467 (13.3)
Sex			
	Female	6,440 (40.9)	1,243 (35.3)
	Male	9,292 (59.1)	2,281 (64.7)
Ethnicity*			
	White	9,624 (76.5)	1,815 (58.5)
	Asian	1,356 (10.8)	680 (21.9)
	Black	737 (5.9)	360 (11.6)
	Mixed	163 (1.3)	48 (1.5)
	Other	694 (5.5)	201 (6.5)
Obesity**			
	Non-obese	6,034 (68.6)	1,509 (54.9)
	Obese	2,764 (31.4)	1,240 (45.1)
Comorbidity			
	Any comorbidity	6228 (39.6)	2945 (83.6)
	Chronic respiratory disease	1,250 (7.9)	423 (12.0)
	Asthma	1,200 (7.6)	428 (12.1)
	Hypertension	3,439 (21.9)	2,218 (62.9)
	Chronic heart disease	1,828 (11.6)	834 (23.7)
	Chronic renal disease	996 (6.3)	831 (23.6)
	Chronic liver disease	252 (1.6)	138 (3.9)
	Chronic neurological disease	1,098 (7.0)	310 (8.8)
	Immunosuppressive disease	374 (2.4)	94 (2.7)

*Ethnicity not recorded for 3,578 patients. **Obesity not recorded for 7,709 patients.

Table 2: Hazard ratios for diabetes for the primary outcome of 30 day in-hospital mortality for people with type 2 diabetes admitted to critical care with COVID-19. Age fitted as a restricted cubic spline with 3 knots in all models.

Adjustment	Cohort 1: All patients (n=19,256)	Cohort 2: HDU only patients (n=13,809)	Cohort 3: ICU patients (n=5,447)
Unadjusted	1.44 (1.35, 1.54), p<0.001	1.38 (1.26, 1.51), p<0.001	1.34 (1.22, 1.48), p<0.001
Age	1.42 (1.33, 1.51), p<0.001	1.31 (1.20, 1.44), p<0.001	1.28 (1.16, 1.41), p<0.001
Age and sex	1.40 (1.31, 1.49), p<0.001	1.30 (1.19, 1.42), p<0.001	1.28 (1.16, 1.41), p<0.001
Age, sex, ethnicity	1.36 (1.27, 1.45), p<0.001	1.29 (1.18, 1.41), p<0.001	1.23 (1.11, 1.36), p<0.001
Age, sex, ethnicity, obesity	1.32 (1.23, 1.41), p<0.001	1.27 (1.16, 1.39), p<0.001	1.29 (1.17, 1.43), p<0.001
Full covariate set adjusted model (Age, sex, ethnicity, obesity, comorbidity*)	**1.23 (1.14, 1.32), p<0.001**	**1.19 (1.08, 1.31), p<0.001**	**1.24 (1.11, 1.38), p<0.001**
Propensity score matched model, adjusted full covariate set	1.25 (1.14, 1.36), p<0.001 [n=3,289 with diabetes matched]	1.17 (1.04, 1.32), p=0.01 [n=2,007 with diabetes matched]	1.19 (1.05, 1.35), p=0.009 [n=1,244 with diabetes matched]
Competing risk model, adjusted full covariate set (Fine-Gray)**	1.27 (1.18, 1.36), p<0.001	1.24 (1.13, 1.36), p<0.001	1.24 (1.12, 1.38),p<0.001

*Chronic respiratory disease, Asthma, Chronic heart disease, Hypertension, Immunosuppression, Chronic neurological disease, Chronic renal disease, Chronic liver disease.

**Fine-Gray model subdistribution hazard ratios taking into account the competing event of being discharged alive.

Figure legends

Figure 1: Kaplan-Meier plots for in-hospital COVID-19 death in 19,256 patients admitted to critical care (HDU or ICU) in CHESS by time since hospital admission. Plot shows the proportion of individuals at risk who were still alive at regular intervals up to 30 days from admission, stratified by the presence of type 2 diabetes. People discharged from hospital prior to 30 days were assumed to survive to 30 days and are included in the number at-risk until 30 days, in keeping with the standard practice for time-to-event modelling in analysis of critical care patients.

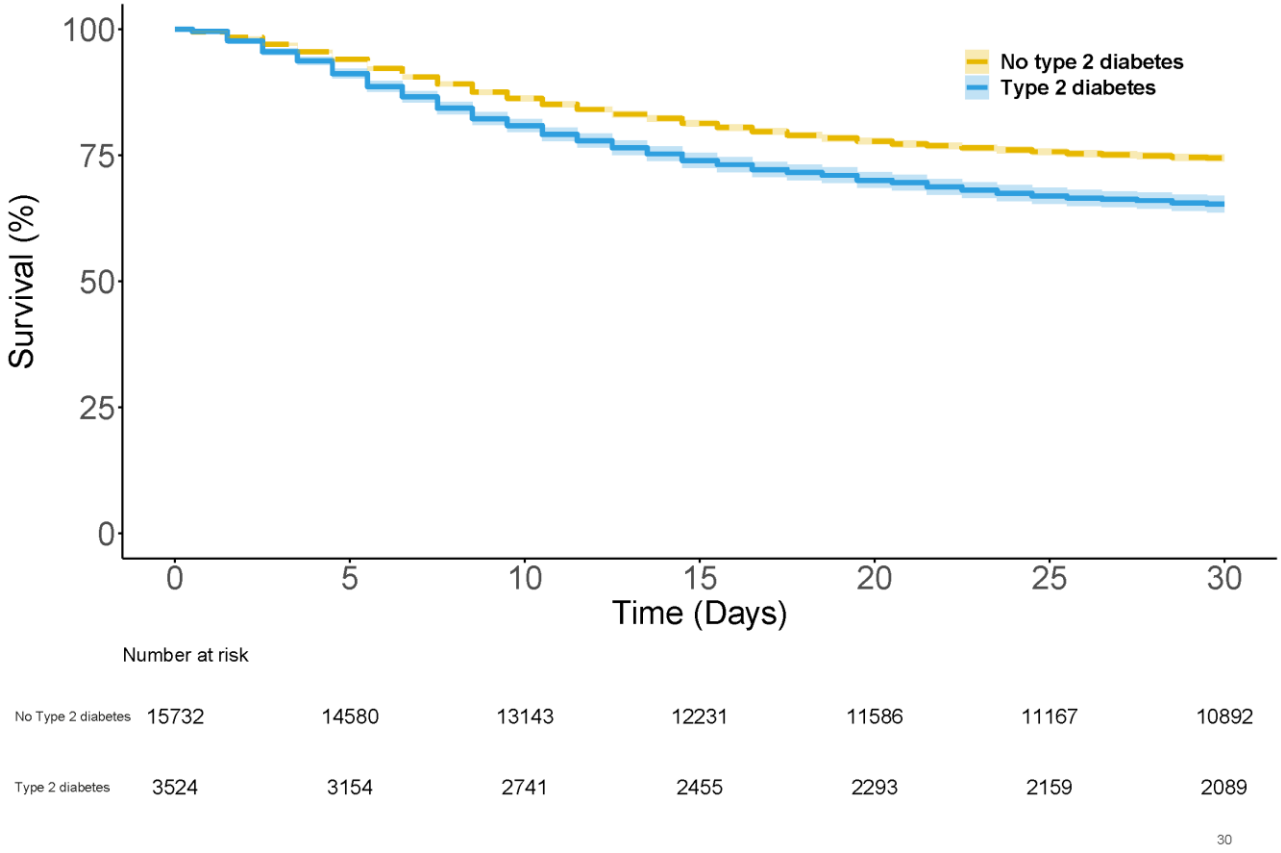
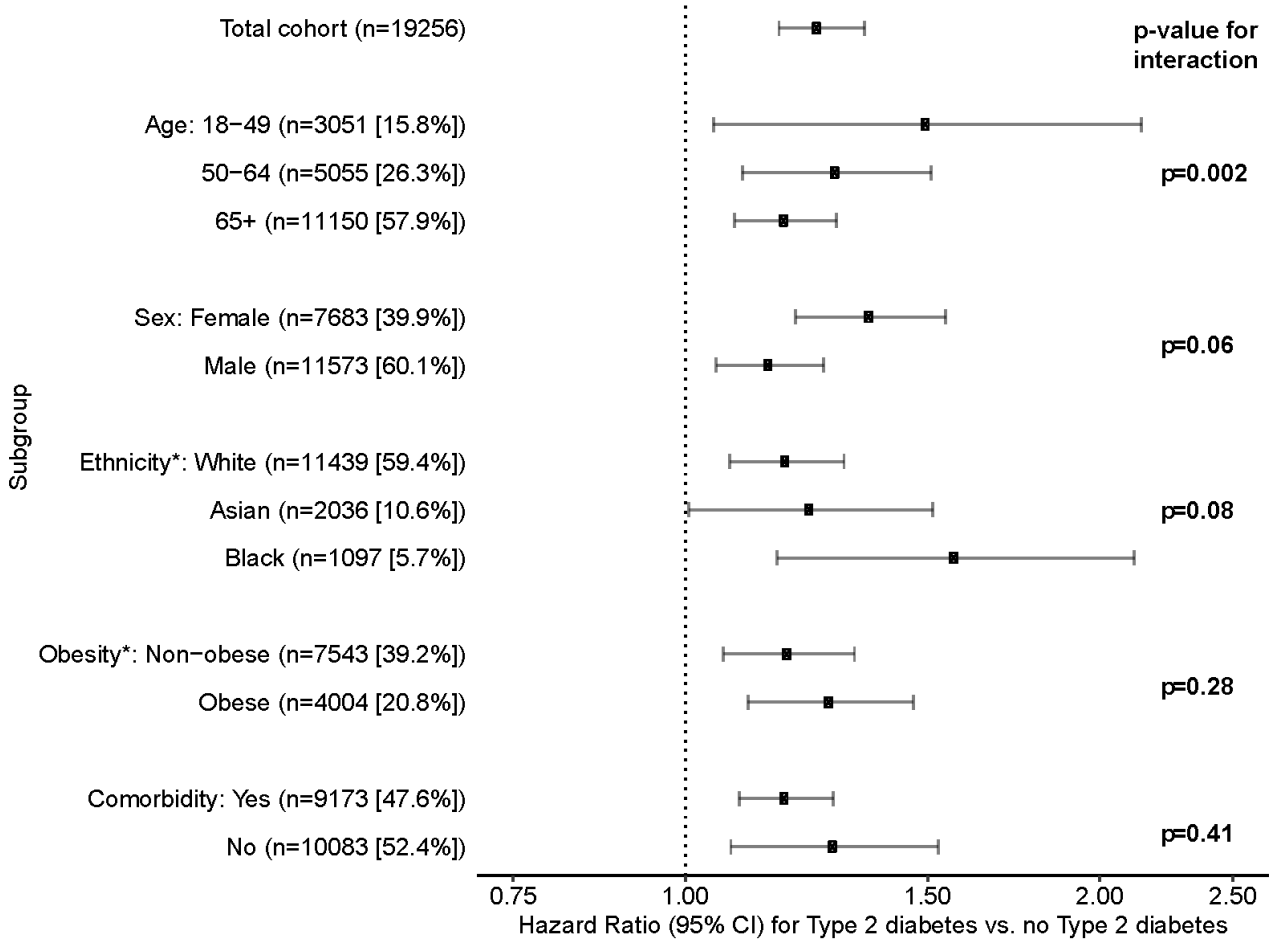


Figure 2: Major subgroup analysis of the primary outcome of 30 day in-hospital mortality.

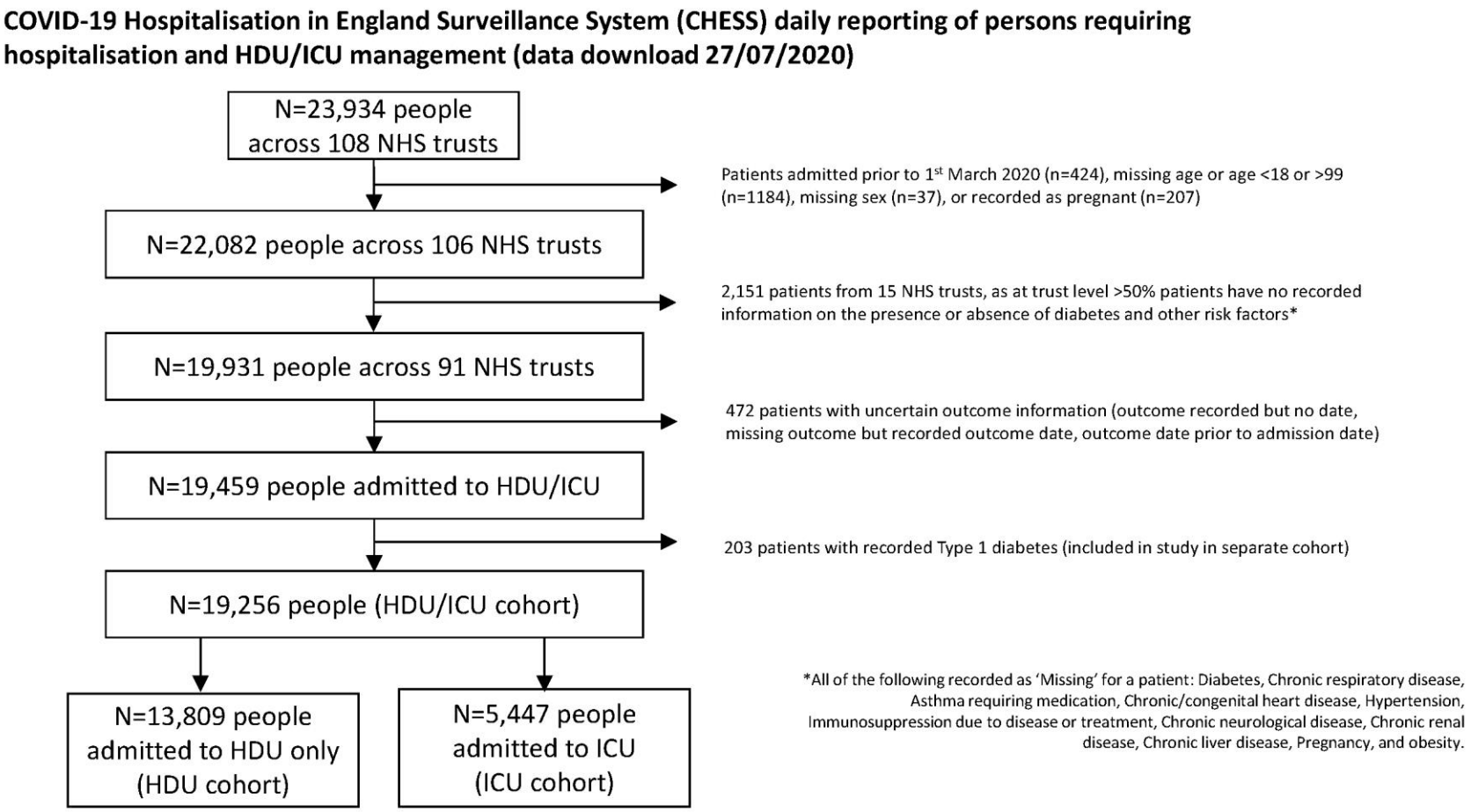


*Legend: Hazard ratios represent the mortality risk associated with the presence of type 2 diabetes in each subgroup. Bars represent 95% confidence intervals. *Hazard ratios (95% CI) for other subgroups: mixed ethnicity 1.91 (1.03, 3.56), other ethnicity 0.96 (0.67, 1.39), missing ethnicity 1.34 (1.11, 1.62), missing obesity 1.28 (1.08, 1.46).*

Supplementary Material for Diabetes and COVID-19 related mortality in the critical care setting: A national cohort study in England, March-July 2020

Authors: John M. Dennis, Bilal A. Mateen, Raphael Sonabend, Nicholas J. Thomas, Kashyap A. Patel, Andrew T Hattersley, Spiros Denaxas, Andrew P. McGovern, Sebastian J. Vollmer

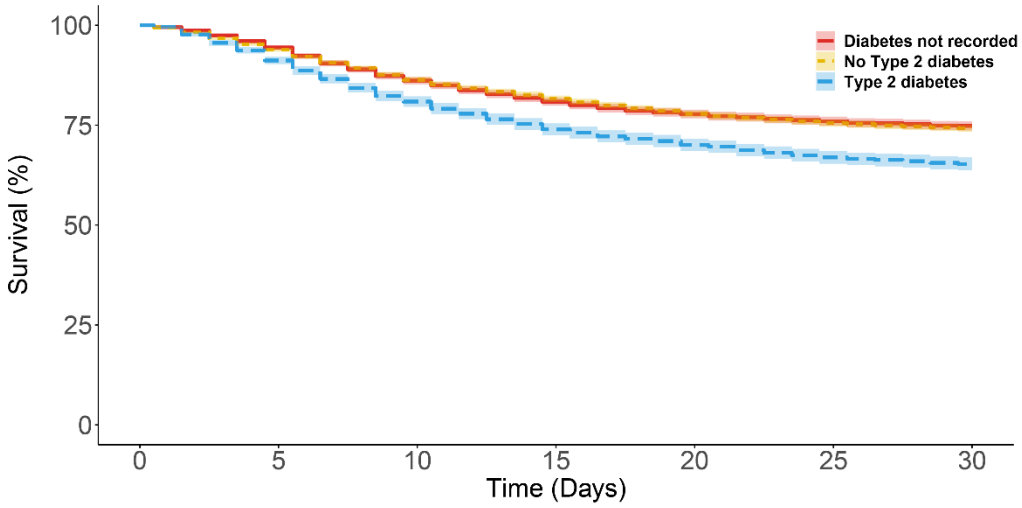
SFlowchart 1: Patient flow diagram



sTable 1: Recorded characteristics of study cohorts.

	HDU/ICU cohort (n=19,256)	HDU only cohort (n=13,809)	ICU cohort (n=5,447)
Age in years (Mean [SD])	67 (16.88)	70 (17.21)	58 (12.66)
Age Group			
18-24	172 (0.9)	134 (1.0)	38 (0.7)
25-34	652 (3.4)	446 (3.2)	206 (3.8)
35-44	1,152 (6.0)	695 (5.0)	457 (8.4)
45-54	2,468 (12.8)	1,331 (9.6)	1,137 (20.9)
55-64	3,662 (19.0)	1,900 (13.8)	1,762 (32.3)
65-74	3,850 (20.0)	2,550 (18.5)	1,300 (23.9)
75-84	4,052 (21.0)	3,551 (25.7)	501 (9.2)
85+	3,248 (16.9)	3,202 (23.2)	46 (0.8)
Sex			
Female	7,683 (39.9)	6,084 (44.1)	1,599 (29.4)
Male	11,573 (60.1)	7,725 (55.9)	3,848 (70.6)
Ethnicity			
White	11,439 (73.0)	8,413 (76.9)	3,026 (63.9)
Asian	2,036 (13.0)	1,204 (11.0)	832 (17.6)
Black	1,097 (7.0)	727 (6.6)	370 (7.8)
Mixed	211 (1.3)	72 (0.7)	139 (2.9)
Other	895 (5.7)	523 (4.8)	372 (7.8)
Obesity			
Non-obese	7,543 (65.3)	5,467 (75.8)	2,076 (47.9)
Obese	4,004 (34.7)	1,742 (24.2)	2,262 (52.1)
Comorbidity			
Type 2 diabetes	3,524 (18.3)	2,139 (15.5)	1,385 (25.4)
Chronic respiratory disease	1,673 (8.7)	1,166 (8.4)	507 (9.3)
Asthma	1,628 (8.5)	929 (6.7)	699 (12.8)
Hypertension	5,657 (29.4)	3,602 (26.1)	2,055 (37.7)
Chronic heart disease	2,662 (13.8)	2,034 (14.7)	628 (11.5)
Chronic renal disease	1,827 (9.5)	1,426 (10.3)	401 (7.4)
Chronic liver disease	390 (2.0)	244 (1.8)	146 (2.7)
Chronic neurological disease	1,408 (7.3)	1,174 (8.5)	234 (4.3)
Immunosuppressive disease	468 (2.4)	274 (2.0)	194 (3.6)
Time in hospital			
Days from hospital to ICU admission per day increase (Mean [SD])	NA	NA	2 (5.62)

SFigure 1: Kaplan-Meier plots for in-hospital COVID-19 death in 19,256 patients admitted to critical care (HDU or ICU) in CHESS by time since hospital admission, with type 2 diabetes status coded as Yes, No, and Not recorded. Plots show the proportion of individuals at risk who were still alive at regular intervals up to 30 days from admission. People discharged from hospital prior to 30 days were assumed to survive to 30 days and are included in the number at-risk until 30 days, in keeping with the standard practice for time-to-event modelling in analysis of critical care patients.

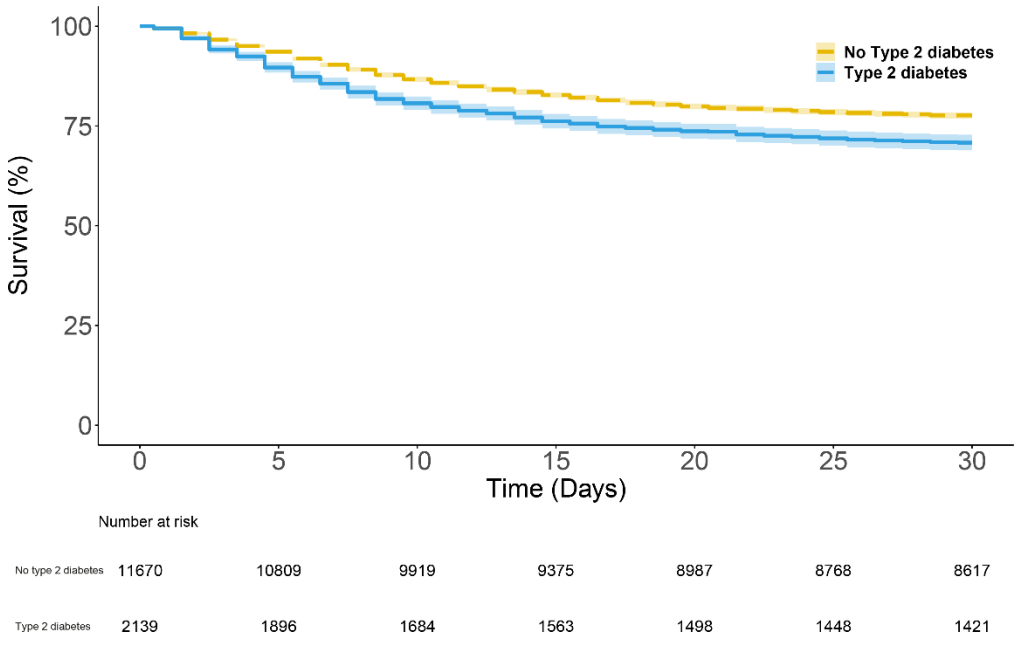


Number at risk

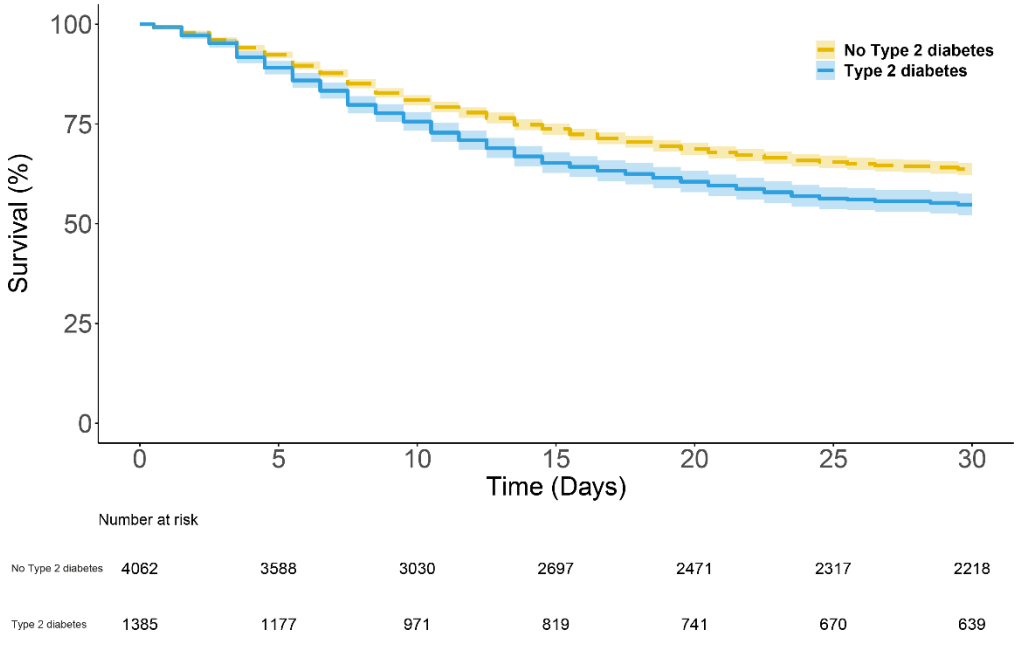
Diabetes not recorded	5723	5340	4817	4474	4257	4122	4025
No type 2 diabetes	10009	9240	8326	7757	7329	7045	6867
Type 2 diabetes	3524	3154	2741	2455	2293	2159	2089

SFigure 2: Kaplan-Meier plots for in-hospital COVID-19 death over time, by diabetes status for:

a) HDU only cohort, n=13,809)



a) ICU cohort, n=5,447)



sTable 2: Hazard ratios for full covariate set in multivariable analysis of the primary outcome of 30 day all-cause in-hospital mortality for each study cohort. Data in brackets are 95% confidence intervals.

	HDU/ICU cohort (n=19,256)	HDU only cohort (n=13,809)	ICU cohort (n=5,447)
Type 2 diabetes			
No type 2 diabetes	1.00 (ref)	1.00 (ref)	1.00 (ref)
Type 2 diabetes	1.23 (1.14;1.32), p<0.001	1.19 (1.08;1.31), p<0.001	1.24 (1.11;1.38), p<0.001
Age			
Age spline	1.06 (1.06;1.07), p<0.001	1.10 (1.09;1.11), p<0.001	1.04 (1.03;1.05), p<0.001
Age spline'	0.97 (0.96;0.98), p<0.001	0.96 (0.95;0.97), p<0.001	1.00 (0.99;1.01), p=0.699
Sex			
Female	1·00 (ref)	1·00 (ref)	1·00 (ref)
Male	1.33 (1.25;1.41), p<0.001	1.30 (1.21;1.39), p<0.001	1.08 (0.98;1.20), p=0.121
Ethnicity*			
White	1.00 (ref)	1.00 (ref)	1.00 (ref)
Asian	1.32 (1.20;1.46), p<0.001	1.24 (1.07;1.45), p=0.005	1.27 (1.11;1.44), p<0.001
Black	1.19 (1.04;1.35), p=0.010	1.19 (0.99;1.44), p=0.065	1.33 (1.11;1.59), p=0.002
Mixed	1.74 (1.34;2.25), p=0.000	1.52 (0.90;2.58), p=0.119	1.24 (0.92;1.67), p=0.157
Other	1.00 (0.85;1.17), p=0.964	0.83 (0.63;1.08), p=0.165	0.99 (0.81;1.20), p=0.887
Missing	1.10 (1.01;1.18), p=0.020	1.16 (1.06;1.27), p=0.001	1.03 (0.90;1.19), p=0.645
Obesity**			
Non-obese (BMI<30)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Obese (BMI≥30)	1.06 (0.99;1.15), p=0.113	0.84 (0.74;0.95), p=0.007	0.95 (0.86;1.06), p=0.393
Missing	0.94 (0.88;1.01), p=0.089	0.89 (0.82;0.97), p=0.005	1.51 (1.35;1.70), p<0.001
Comorbidity (versus No/Missing)			
Chronic respiratory disease	1.29 (1.18;1.41), p<0.001	1.35 (1.21;1.51), p<0.001	1.11 (0.96;1.28), p=0.175
Asthma	1.02 (0.92;1.13), p=0.755	0.99 (0.85;1.14), p=0.862	0.92 (0.79;1.06), p=0.253
Hypertension	1.04 (0.97;1.11), p=0.237	0.91 (0.83;0.99), p=0.024	1.01 (0.91;1.12), p=0.846
Chronic heart disease	1.11 (1.03;1.20), p=0.009	1.11 (1.01;1.22), p=0.026	1.10 (0.97;1.26), p=0.146
Chronic renal disease	1.17 (1.07;1.27), p<0.001	1.24 (1.11;1.37), p<0.001	1.29 (1.11;1.50), p=0.001
Chronic liver disease	0.99 (0.81;1.21), p=0.924	1.21 (0.93;1.58), p=0.162	0.91 (0.67;1.23), p=0.540
Chronic neurological disease	1.12 (1.02;1.23), p=0.022	1.20 (1.07;1.33), p=0.001	1.13 (0.91;1.39), p=0.276
Immunosuppressive disease	1.23 (1.05;1.44), p=0.009	1.20 (0.97;1.49), p=0.095	1.01 (0.80;1.27), p=0.938
Time in hospital			
Days from hospital to ICU admission (per day increase)	NA	NA	1.00 (0.99;1.01), p=0.722

*Ethnicity not recorded for HDU/ICU 3,578 patients; HDU 2,870; ICU 708. **Obesity not recorded for HDU/ICU 7,709 patients; HDU 6,600; ICU 1,109.

sTable 3: Hazard ratios for additional subgroup and sensitivity analysis. Data in brackets are 95% confidence intervals.

Subgroup and sensitivity analysis. All adjusted for the full covariate set.	HDU/ICU cohort	HDU only cohort	ICU cohort
Admitted to hospital in March 2020 (All n=5606, HDU n=3,725, ICU n=1881)	1.34 (1.18, 1.51), p<0.001	1.39 (1.18, 1.64), p<0.001	1.30 (1.09, 1.54), p=0·003
Admitted to hospital in April 2020 (All n=9440, HDU n=6,666, ICU n=2774)	1.13 (1.02, 1.26), p=0.02	1.05 (0.92, 1.21), p=0.47	1.19 (1.02, 1.39), p=0.03
Admitted to hospital in May-July 2020 (All n=4210, HDU n=3418, ICU n=792)	1.24 (1.01, 1.52), p=0.04	1.24 (0.96, 1.60), p=0.10	1.19 (0.84, 1.69), p=0.34
Calendar week of hospital admission added as an addition covariate (All n=19,256, HDU n=13,809, ICU n=5,447)	1.21 (1.13, 1.31), p<0.001	1.18 (1.07, 1.30), p<0.001	1.22 (1.10, 1.36), p<0.001
Exclude transferred patients and patient who remain in hospital (All n=17,044, HDU n=13,033, ICU n=4,483)	1.22 (1.14, 1.31), p<0.001	1.17 (1·06, 1·29), p=0·002	1·24 (1.11, 1.38), p<0·001
Include only patients with PCR swab positive result during admission (All n=17,606, HDU n=12,550, ICU n=5056)	1.23 (1.14, 1.32), p<0.001	1.22 (1.11, 1.35), p<0.001	1.18 (1.06, 1.32), p=0.004
NHS Trust as additional random effect (All n=19,256, HDU n=13,809, ICU n=5,447)	1·19 (1·11, 1·29), p<0·001	1.20 (1.09, 1.32), p<0.001	1.18 (1.06, 1.32), p=0·003
Multiple imputation model (All n=19,256, HDU n=13,809, ICU n=5,447)	1.25 (1.15, 1.36), p<0.001	1.16 (1.03, 1.31), p=0.02	1.31 (1.16, 1.49), P<0.001
Include patients from all hospitals, assuming non-coded comorbidity represents the absence of a comorbidity (All n=21452 , HDU n=15,637, ICU n=5,815)	1.26 (1.17, 1.35), p<0·001	1.24 (1.13, 1.36), p<0·001	1.25 (1.12, 1.39), p<0·001
Include patients only from hospitals with <25% missing comorbidity coding (All n=13,995, HDU n=8,8981, ICU n=4,482)	1·25 (1·16, 1·35), p<0·001	1·25 (1·12, 1·39), p<0·001	1·27 (1·13, 1·42), p<0·001

sTable 4: Recorded characteristics of patients in hospitals included and excluded from study cohorts. Data are N (%) unless stated.

	Hospitals excluded (hospital n= 15, patient n=1,993)	Hospitals included (hospital n=91, patient n=19,256)
Age in years (Mean [SD])	70 (16.26)	67 (16.88)
Age Group		
18-24	14 (0.7)	172 (0.9)
25-34	39 (2.0)	652 (3.4)
35-44	91 (4.6)	1,152 (6.0)
45-54	235 (11.8)	2,468 (12.8)
55-64	282 (14.1)	3,662 (19.0)
65-74	398 (20.0)	3,850 (20.0)
75-84	509 (25.5)	4,052 (21.0)
85+	425 (21.3)	3,248 (16.9)
Sex		
Female	827 (41.5)	7,683 (39.9)
Male	1,166 (58.5)	11,573 (60.1)
Ethnicity		
White	735 (36.9)	11,439 (59.4)
Asian	80 (4.0)	2,036 (10.6)
Black	11 (0.6)	1,097 (5.7)
Mixed	7 (0.4)	211 (1.1)
Other	14 (0.7)	895 (4.6)
Not recorded	1,146 (57.5)	3,578 (18.5)
Obesity		
Non-obese	61 (3.1)	7,543 (39.1)
Obese	36 (1.8)	4,004 (20.8)
Not recorded	1,896 (95.1)	7,709 (40.0)
Comorbidity (recorded yes)		
Diabetes	80 (4.0)	3,524 (18.3)
Chronic respiratory disease	66 (3.3)	1,673 (8.7)
Asthma	27 (1.4)	1,628 (8.5)
Hypertension	123 (6.2)	5,657 (29.4)
Chronic heart disease	70 (3.5)	2,662 (13.8)
Chronic renal disease	38 (1.9)	1,827 (9.5)
Chronic liver disease	3 (0.2)	390 (2.0)
Chronic neurological disease	40 (2.0)	1,408 (7.3)
Immunosuppressive disease	15 (0.8)	468 (2.4)
Time in hospital		
Admitted to ICU	294 (14.8)	5,447 (28.2)