Post-COVID syndrome in individuals hospitalised with COVID-19: a retrospective cohort study

Journal:	*BMJ*
Manuscript ID	BMJ-2021-064273.R2
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	10-Feb-2021
Complete List of Authors:	Ayoubkhani, Daniel; Office for National Statistics Khunti, Kamlesh; University of Leicester, Primary Care Diabetes and Vascular Medicine Nafilyan, Vahe; Office for National Statistics, Maddox, Thomas; Office for National Statistics Humberstone, Ben; Office for National Statistics Diamond, Ian; Office for National Statistics Banerjee, Amitava; University College London, Farr Institute of Health Informatics Research
Keywords:	COVID-19, Respiratory disease, Cardiovascular disease, Diabetes, Renal failure, Liver disease, Long COVID, Post-COVID syndrome

Post-COVID syndrome in individuals hospitalised with COVID-19: a retrospective cohort study

Daniel Ayoubkhani[1] (ORCID: 0000-0001-6352-0394), *Principal Statistician, daniel.ayoubkhani@ons.gov.uk*
Kamlesh Khunti[2], *Professor of Primary Care Diabetes and Vascular Medicine and Co-Director of the Leicester Diabetes Centre, kk22@leicester.ac.uk*
Vahé Nafilyan[1], *Principal Statistician, vahe.nafilyan@ons.gov.uk*
Thomas Maddox[1], *Statistician, thomas.maddox@ons.gov.uk*
Ben Humberstone[1], *Deputy Director of Health Analysis and Life Events Division, ben.humberstone@ons.gov.uk*
Sir Ian Diamond[1], *UK National Statistician, ian.diamond@statistics.gov.uk*
Amitava Banerjee[3,4,5] (ORCID: 0000-0001-8741-3411), *Associate Professor of Clinical Data Science and Honorary Consultant Cardiologist, ami.banerjee@ucl.ac.uk*

[1] *Office for National Statistics, Newport, UK*
[2] *Diabetes Research Centre, University of Leicester, Leicester, UK*
[3] *Institute of Health Informatics, University College London, London, UK*
[4] *University College London Hospitals NHS Trust, London, UK*
[5] *Barts Health NHS Trust, The Royal London Hospital, London, UK*

Corresponding author 1: Daniel Ayoubkhani
Address: Office for National Statistics, Government Buildings, Cardiff Road, Newport, UK, NP10 8XG
Email: daniel.ayoubkhani@ons.gov.uk

Corresponding author 2: Amitava Banerjee
Address: Institute of Health Informatics, 222 Euston Road, University College London, UK, NW1 2DA
Email: ami.banerjee@ucl.ac.uk

Word count: 3,664
Abstract word count: 321

Abstract

Objectives: The epidemiology of post-COVID syndrome is currently undefined. We quantified rates of organ-specific impairment following discharge from COVID-19 hospitalisation compared with those in a matched control group from the general population, and determined how the rate ratio (RR) varies by age, sex, and ethnicity.

Design: Observational, retrospective, matched cohort study.

Setting: NHS hospitals in England.

Participants: 47,780 individuals (mean age 65 years, 55% male) in hospital with COVID-19 and discharged alive by 31 August 2020, exactly matched to controls from a pool of approximately 50 million people in England on demographic and clinical characteristics using 10 years of electronic health records.

Outcome measures: Rates of hospital readmission, all-cause mortality, and diagnoses of respiratory, cardiovascular, metabolic, kidney and liver diseases until 30 September 2020.

Results: Over a mean follow-up time of 140 days, nearly a third of individuals were re-admitted to hospital and more than 1 in 10 died following COVID-19 discharge, with these events occurring at rates 4 and 8 times greater, respectively, than in the matched control group. Rates of respiratory, diabetes and cardiovascular events were also significantly elevated in COVID-19 cases, at 770 (95% confidence interval: 758 to 783), 127 (122 to 132) and 126 (121 to 131) events per 1,000 person-years, respectively. RRs were greater for individuals aged <70 than ≥70 years, and in ethnic minority groups than the White population, with the biggest differences observed for respiratory disease: 10.5 [9.7 to 11.4] for <70 years versus 4.6 [4.3 to 4.8] for ≥70 years, and 11.4 (9.8 to 13.3) for Non-White versus 5.2 (5.0 to 5.5) for White.

Conclusions: Individuals discharged from hospital following COVID-19 face elevated rates of multi-organ dysfunction compared with background levels, and the increase in risk is neither confined to the elderly nor uniform across ethnicities. The diagnosis, treatment and prevention of post-COVID syndrome will require integrated rather than organ- or disease-specific approaches, and urgent research is required to establish its risk factors.

Summary box

What is already known on this topic

- COVID-19 may result in extrapulmonary dysfunction, affecting the cardiovascular, metabolic, renal, and hepatic systems
- Recent evidence has demonstrated that post-discharge mortality and readmission are common among individuals in hospital with COVID-19, but the long-term epidemiology of multi-organ morbidity has not been quantified

What this study adds

- Individuals discharged from hospital following acute COVID-19 had elevated rates of multi-organ (and particularly respiratory and cardio-metabolic) impairment compared to those in a control group from the general population with similar demographic and clinical profiles
- The rate ratio of post-discharge adverse events (contrasting individuals with COVID-19 and matched controls) was greater in those aged <70 years than ≥70 years, and in ethnic minority groups than in the White population
- Our findings suggest that the diagnosis, treatment and prevention of post-COVID syndrome require integrated rather than organ- or disease-specific approaches

Introduction

In the early coronavirus disease (COVID-19) pandemic, the estimated severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection rate in the UK was 6% (13% in London).[1] Research, health services and the media have mostly focused on direct (through infection) and indirect (through changes in individual behaviours and health systems) effects of COVID-19 on mortality,[2] particularly in the short-term.[3,4] Studies of longer-term effects on morbidity are needed to effectively plan healthcare delivery and capacity.

Since SARS-CoV2 infection was recognised in late 2019, academic and clinical emphasis has been on respiratory manifestations.[5] However, there is increasing evidence for direct multi-organ effects,[6-10] as well as indirect effects on other organ systems and disease processes, such as cardiovascular diseases and cancers, through changes in healthcare delivery and patient behaviours.[11-13] Although the long-term impact of COVID-19 on individuals and health systems is becoming clear, there is an urgent need for investigation across organ systems.

Long COVID, or post-COVID syndrome, is not a single condition and defined by the National Institute for Health and Care Excellence (NICE) as “signs and symptoms that develop during or following an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis.”[14] NICE guidelines recommend referral to post-COVID syndrome assessment clinics if post-COVID symptoms persist for 6-12 weeks.[14] Pre-existing conditions and risk factors are predictors of acute COVID-19 outcomes (such as intensive care admissions and mortality[2]), but the epidemiology of post-COVID syndrome has been less well defined[15,16] due to unclear medium- and long-term pathophysiology across organ systems. As post-COVID syndrome clinics are implemented, characterisation of disease epidemiology will aid appropriate diagnosis, care, public health interventions and policy, and resource planning.

The existing evidence suggest large variations in estimates of post-COVID syndrome prevalence and incidence due to differences in study populations, recruitment methods, follow-up periods, and sample sizes. Most studies to-date have concentrated on symptoms associated with post-COVID syndrome rather than organ impairment, and few have made use of a control group permitting the inference of counterfactual outcomes.

We aimed to estimate the excess morbidity following severe COVID-19, reflecting an urgent need for such evidence by policymakers. Using national electronic health records and death registrations for individuals in England, we quantified the incidence of mortality, health service utilisation, and organ-specific impairment following discharge from hospital with COVID-19. We estimated rate ratios of post-discharge adverse events compared with those in a matched general population control group, and heterogeneity in this rate ratio (comparing adverse events following COVID-19 hospitalisation with background levels) across demographic groups.

Methods

Study design and data sources

This was an observational, retrospective, matched cohort study of hospitalised individuals with COVID-19 using Hospital Episode Statistics Admitted Patient Care (HES APC)[17] records for England until 31 August 2020, and General Practice Extraction Service (GPES) Data for Pandemic Planning and Research (GDPPR)[18] until 30 September 2020. GDPPR is an extract of primary care records collected from surgeries by NHS Digital for pandemic research and analysis (supported by the British Medical Association and Royal College of General Practitioners), including over 56 million individuals registered at NHS surgeries in England and updated fortnightly. The extract includes a subset of approximately 35,000 clinical codes, selected for potential utility in pandemic-related analysis. Office for National Statistics (ONS) death registrations were linked for deaths until 30 September 2020 and registered by 7 October 2020.

Study population

Individuals were included if they had a hospital episode from 1 January to 31 August 2020 with a primary diagnosis of COVID-19, identified using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes U07.1 (virus identified) and U07.2 (virus not identified); that is, by a positive laboratory test or clinical diagnosis. We included cases coded as U07.2 to recognise that not all COVID-19 patients received a test during their hospital episode, particularly during the early weeks of the pandemic, recognising the role of clinical judgement. In sensitivity analysis, we restricted the case definition to diagnoses coded to U07.1 only. Individuals with COVID-19 were excluded if they were not discharged alive by 31 August 2020 or had an unknown date of birth and/or sex. Index date was set to date of discharge following the first hospital episode with COVID-19 as the primary diagnosis.

Candidate controls were individuals in the general population who: (i) did not meet the above COVID-19 inclusion criteria; (ii) had not died before 1 January 2020; and (iii) had at least one GDPPR record between 1 January 2019 (one year before the start of the follow-up period) and 30 September 2020 (end-of-study). We applied criterion (iii) to ensure controls were currently active NHS patients (for example, they had not emigrated without deregistering from their general practice). Each control had the same index date as their matched case. We selected controls from the general population rather than matching to non-COVID hospital admissions to determine the increased risk following COVID-19 hospitalisation versus no COVID-19 hospitalisation; that is, compared with the background risk for people of similar demographic and clinical characteristics.

Outcome variables

Individuals were followed-up from index date to 30 September 2020 or date of death (whichever was earlier) for all-cause mortality, all-cause hospital readmission (cases: post-discharge; controls: any post-index admission), respiratory disease, major adverse cardiovascular event (MACE: a composite

of heart failure [HF], myocardial infarction [MI], stroke, arrhythmia), diabetes (type 1 or 2), chronic kidney disease (CKD) stages 3-5 (including dialysis and kidney transplant), and chronic liver disease (CLD).

Respiratory, MACE, diabetes, CKD and CLD events were identified from diagnoses made in primary care and hospital, except for the arrhythmia component of MACE for which primary care data were not available (though we were able to capture diagnoses made in hospitals). Full code lists are provided in the supplementary material.

Matching variables

We matched cases to controls on potential confounders of the relationship between COVID-19 hospitalisation and outcomes (Supplementary Table 1), established from electronic health records over the 10-year look-back period 1 January 2010 to 31 December 2019. Demographic factors comprised age, sex, ethnicity, region, and deprivation. Comorbidities included conditions listed above plus hypertension and cancer, identified from diagnoses made in primary care and in hospital (using primary and secondary ICD-10 codes for the latter). We also included smoking status and BMI in the matching set as risk factors.

Statistical techniques

Distributions of baseline characteristics were compared between individuals with COVID-19 and a random 0.5% sample of the general population using Chi squared tests and standardised differences in proportions, where a standardised difference >10% indicated large imbalance between groups.[19] Cases were 1:1 matched to controls using coarsened exact matching (CEM),[20] resulting in perfect balance of joint distributions across the full range of (coarsened) variables included in the matching set, derived from 10 years of records. Matched pairs were discarded if the control died before the corresponding case's index date. All covariates were discretised prior to matching, including an 'Unknown' category comprising individuals with missing values. The size of the pool of candidate controls (approximately 50 million individuals) precluded use of multiple imputation.

We computed adverse event rates per 1,000 person-years in cases and controls, deriving rate ratios from these rates. 95% confidence intervals (CIs) were estimated using the Poisson distribution. We estimated event rates using all adverse events (new-onset cases and exacerbation of pre-existing conditions), and only new-onset cases (that is, no previous diagnosis for the condition over the 10-year look-back period). All event rates were stratified by sex, age group (<70 years, ≥70 years), and ethnic group (White, Non-White). Cases were further stratified based on whether they were admitted to an intensive care unit (ICU) during their hospital admission. Sensitivity analysis investigated possible residual confounding by age, smoking status, and BMI after matching, since we had to use coarse versions of the variables to ensure a sufficient match rate. We assessed the robustness of our main results by adjusting for a second-order polynomial of age and non-coarsened versions of smoking status and BMI in a Poisson regression of outcome counts, including the natural logarithm of person-years as an offset term. All statistical analyses were conducted using R version 4.0.2.

Patient and public involvement

Although we did not directly involve patients and the public due to the COVID-19 pandemic,, views expressed by patient groups in meetings attended by DA, VN, and BH (for example, NHS England's long COVID taskforce, Department of Health and Social Care's long COVID round-table) informed the study objectives and design.

Results

Study participants

Of 86,955 individuals in hospital with COVID-19 during the study period, 53,795 (61.9%) had been discharged alive by end-of-study (Figure 1). After excluding individuals with unknown age or sex and those who could not be matched to a control, 47,780 COVID-19 cases (4,745 ICU and 43,035 non-ICU) were included in the analysis, representing 90.8% of those discharged alive with known age and sex. Mean follow-up times were 140 days (standard deviation [SD] 50 days, maximum 253 days) for COVID-19 cases and 153 days (SD 33 days, maximum 253 days) for controls.

At baseline, individuals with COVID-19 had a mean age of 64.5 years (SD 19.2 years) and 54.9% were male. Compared with the general population, individuals in hospital with COVID-19 were more likely to be aged ≥50 years, male, living in a deprived area, a former smoker, and overweight or obese (Table 1). Individuals with COVID-19 were also more likely to be comorbid than the general population, with a higher prevalence of prior hospitalisation and all measured pre-existing conditions (most notably hypertension, MACE, respiratory disease, and diabetes).

Standardised differences in baseline characteristics between cases and controls were generally below 10%, and most were exactly zero due to the use of exact matching. Individuals aged <30 years and those with unknown smoking status and/or BMI were more common among cases than in the control group (as we matched on coarsened versions of these variables). Sensitivity analysis investigating the impact of adjusting for these variables revealed minimal change in estimated rate ratios of adverse events between cases and controls, even when stratified by demographic characteristics, indicating the absence of residual confounding after matching (see the Supplementary Appendix).

Rates of adverse events in individuals with COVID-19 following discharge

Of 47,780 individuals in hospital with COVID-19 over the study period, 29.4% were re-admitted and 12.3% died following discharge (Table 2). These events occurred at rates of 766 (CI: 753 to 779) readmissions and 320 (312 to 328) deaths per 1,000 person-years, which were 3.5 (3.4 to 3.6) and 7.7 (7.2 to 8.3) times greater, respectively, than those in matched controls. Respiratory disease was diagnosed in 14,140 individuals (29.6%) following discharge, with 6,085 of these being new-onset cases; the resulting event rates of 770 (758 to 783) and 539 (525 to 553) per 1,000 person-years, respectively, were 6.0 (5.7 to 6.2) and 27.3 (24.0 to 31.2) times greater than those in controls.

Post-discharge diagnoses of diabetes, MACE, CKD, and CLD were made for 4.9%, 4.8%, 1.5%, and 0.3% of individuals with COVID-19, respectively, occurring at rates of 127 (122 to 132) diabetes, 126 (121 to 131) MACE, 39 (36 to 42) CKD, and 7 (6 to 9) CLD events per 1,000 person-years (Figure 2). A similar pattern was observed when only new-onset cases were considered, but at lower rates of 29 (26 to 32) diabetes, 66 (62 to 70) MACE, 15 (13 to 17) CKD and 4 (3 to 5) CLD events per 1,000 person-years. Those with COVID-19 received post-discharge diagnoses of MACE, CLD, CKD, and diabetes 3.0 (2.7 to 3.2), 2.8 (2.0 to 4.0), 1.9 (1.7 to 2.1), and 1.5 (1.4 to 1.6) times more frequently, respectively, than in the matched control group (detailed results in Supplementary Table 2).

Rates of post-discharge adverse events remained significantly elevated among individuals with COVID-19 compared with matched controls after stratifying by ICU versus non-ICU admission (Supplementary Table 3). Individuals requiring ICU admission had higher rates of post-discharge respiratory disease and diabetes, but lower rates of death, readmission, and MACE, than those not in ICU.

In sensitivity analysis, comparisons between adverse event rates for cases and controls were robust to restricting the former to laboratory-confirmed diagnoses, representing 80.2% of all COVID-19 cases in the study. We also explored the robustness of our findings to the exclusion from our main analysis of the 4,865 COVID-19 cases (9.2%) that remained unmatched, finding that adverse event rates in the matched population may slightly underestimate the rates in the full population of discharged COVID-19 cases. The estimates presented in our main results may therefore be conservative (detailed results in the Supplementary Appendix).

Rate ratios of adverse events across demographic characteristics

Rates of all post-discharge adverse events were greater in individuals with COVID-19 aged ≥70 years than <70 years, while rates of all events other than diabetes were greater in the White ethnic group than the Non-White group (Supplementary Table 4). However, the rate ratio of adverse events (contrasting COVID-19 cases and matched controls) was greater in individuals aged <70 years than ≥70 years for all event types (Figure 3). The largest differences in rate ratios were for death (14.1 [11.0 to 18.3] for <70 years versus 7.7 [7.1 to 8.3] for ≥70 years) and respiratory disease (10.5 [9.7 to 11.4] for <70 years versus 4.6 [4.3 to 4.8] for ≥70 years). Ethnic differences in rate ratios were greatest for respiratory disease, at 11.4 (9.8 to 13.3) for individuals in the Non-White group compared with 5.2 (5.0 to 5.5) in the White group. Differences in rate ratios of adverse events between males and females were generally small (detailed results in Supplementary Table 4).

Discussion

Principal findings

In the largest study to-date to examine post-COVID syndrome in individuals hospitalised with COVID-19 in England, comprising 47,780 COVID-19 cases with matched controls, we describe three major findings. First, COVID-19 hospitalisation was associated with increased risk of readmission and death

following discharge compared with individuals of similar demographic and clinical profiles in the general population over the same period. Following COVID-19 hospitalisation, 29% were re-admitted and 12% died within a mean follow-up of 140 days. Second, rates of post-discharge multi-organ dysfunction were elevated in individuals with COVID-19 compared with those in the matched control group, suggesting extrapulmonary pathophysiology. Diabetes and MACE were particularly common, whether incident or prevalent disease. Third, the absolute risk of post-discharge adverse events was greater for individuals aged ≥70 years than <70 years, and for individuals of White ethnic background than in the Non-White group. However, when compared with background rates of adverse events that might be expected to occur in these groups in the general population, younger and ethnic minority individuals faced greater relative risks than those aged ≥70 years and those in the White group, respectively.

In secondary analysis, we found that individuals discharged from ICU following COVID-19 experienced greater rates of death and readmission than those not admitted to ICU, perhaps due to at-risk COVID-19 patients (whether based on age, multimorbidity, or irreversible causes of deterioration) being treated outside of ICU based on local protocols. Moreover, given the greater proportion of non-ICU versus ICU patients discharged alive (63% versus 53%), our results may at least in part reflect a survivorship effect.

Comparison with related studies

Our results are consistent with proposed biological mechanisms associated with respiratory,[21] cardiovascular,[22] metabolic,[23] renal,[10] and hepatic[8] involvement in COVID-19, extending the early evidence base surrounding post-COVID syndrome which has been described as “limited” and low quality.[24]

In a recent study of 1,775 US veterans hospitalised with COVID-19, 20% were readmitted and 9% died within 60 days of discharge.[25] After restricting follow-up time in our study to the same duration, we found similar prevalence rates of 23% and 9%, respectively. The US study did not analyse organ-specific endpoints and was conducted in a specific population. Our study extends the findings to add that COVID-19 is associated with post-discharge manifestations in a range of organs in a broader hospitalised population.

Multi-organ involvement following COVID-19 was detected in 201 low-risk individuals in the UK (18% hospitalised with COVID-19), with impairment of the lungs (33%), heart (32%), kidneys (12%), and liver (10%) found to be common.[26] These prevalence rates are higher than those estimated in our study, though organ impairment was mild and potentially subclinical. Among 213 discharged individuals with COVID-19 in the US, 10% were re-admitted and 2% died over a median follow-up of 80 days,[27] compared with our estimates of 29% and 12%, respectively (but with a longer median follow-up of 160 days). However, the small sample size precludes extrapolation to broader populations.

COVID-19 was associated with increased odds of acute kidney injury, renal replacement therapy, insulin use, pulmonary embolism, stroke, myocarditis, arrythmia, and elevated troponin in US veterans

hospitalised with COVID-19 versus a control of seasonal influenza.[28] The index event was admission rather than discharge, so the results are not strictly comparable with our study, but suggest physiological changes in multiple organs following COVID-19 hospitalisation, supporting our findings.

Pulmonary lesions were found in hospitalised COVID-19 patients in Wuhan, China at a short follow-up duration of three weeks post-discharge.[29] Cardiovascular magnetic resonance imaging revealed myocardial inflammation in German participants who recovered from acute COVID-19,[6] and myocarditis in post-acute US college athletes.[30] These studies suggest pulmonary and myocardial involvement in individuals with COVID-19 and, although small sample sizes and highly specific study populations make it difficult to generalise the results, they shed some light on possible pathophysiological mechanisms underlying our own findings.

Whilst we found readmission following COVID-19 hospitalisation to occur frequently, we did not analyse the most common reasons for readmission. A US study of over 2,000 hospitalisations found COVID-19, sepsis, pneumonia, and HF to be the most common post-COVID-19 readmission diagnoses.[25] However, further research is needed, particularly the extent to which improvements in the management of post-COVID syndrome (such as recent NICE clinical guidelines[14]) may reduce readmission rates.

Implications of findings

With over 3 million people in the UK having tested positive for COVID-19 at the time of writing,[31] and many more who had the disease but never received a test, our findings suggest that the long-term burden of COVID-related morbidity on hospitals and broader healthcare systems may be substantial. Moreover, organ impairment in hospital patients represents only part of the full picture; other symptomatic manifestations of post-COVID syndrome in individuals not requiring hospitalisation have the potential to be debilitating for sufferers, placing significant burden on healthcare resources, particularly in primary care.

Post-COVID syndrome comes on a backdrop of healthcare challenges, particularly sustainable high-quality care for long-term conditions: inequalities in health, access and provision; incomplete pathways across community and hospital care; inadequate research translation to clinical practice; and insufficient resources. Our findings across organ systems suggest that the diagnosis, treatment and prevention of post-COVID syndrome will require integrated rather than organ- or disease-specific approaches. Integrated care pathways,[32] effective in other diseases such as chronic obstructive pulmonary disease, may have utility in the management of post-COVID syndrome.

Strengths and limitations

The strengths of our study include its size and completeness, with all individuals in England hospitalised with COVID-19 observed over a follow-up period of several months, exactly matched to general population controls using 10 years of clinical records. Like all observational studies, residual confounding is possible (for example, due to biomarkers or socio-economic exposures omitted from our

matching set). Limited events in the control group meant we could not disaggregate rate ratios stratified by age and ethnicity beyond '<70 years verses ≥70 years' and 'White versus Non-White' comparisons, despite likely heterogeneity in outcomes within these groups. Individuals with undiagnosed hypertension and diabetes were classified as not having these conditions as we did not consider blood pressure and HbA1c measurements when defining matching variables. However, due to the Quality and Outcomes Framework (pay for performance), primary care coding for hypertension and diabetes is generally of high quality. The hospital admission threshold may be lower among individuals with recent COVID-19 than in the general population, and rates of diagnoses in general may have decreased indirectly due to the pandemic, particularly among people not admitted to hospital with COVID-19.

We could not access testing data so some individuals with COVID-19 who did not require hospitalisation may have been matched in the control group. Moreover, our results are unlikely to fully capture lived experiences of individuals with post-COVID syndrome who were possibly asymptomatic and untested at time of infection. Multi-organ post-COVID manifestations have been identified in non-hospitalised individuals,[26] who were beyond the scope of our study. We did not capture symptoms such as fatigue, disturbance of taste and smell, and anxiety, widely reported in post-COVID syndrome.[24] Although we focussed on post-discharge outcomes following COVID-19 hospitalisation, a sizeable minority of individuals (38%) had not been discharged alive by the end of the study period, as reported globally.[34,35]

Choice of control group

We selected a matched control group from the general population of England, allowing estimation of the excess post-COVID morbidity following severe COVID-19. An alternative approach might have involved comparing outcomes following COVID-19 and other hospital admissions; indeed, such research has recently been conducted using similar data sources to those in our own study (though with a smaller COVID-19 cohort), finding comparable rates of organ dysfunction between discharged COVID-19 cases and individuals discharged from hospital with pneumonia in 2019.[33] We believe that our study design, whereby comparisons are made to the background rates that exist in the general population, is the more relevant to public health policy, and complementary to one using non-COVID hospital admissions as the comparison group. The latter does not allow estimation of excess morbidity since non-COVID admission does not necessarily represent an appropriate counterfactual situation to COVID-19 hospitalisation, and the size and direction of the inferences will clearly depend on the choice of control admissions.

Conclusions

Individuals discharged from hospital following acute COVID-19 face increased risk of mortality, readmission, and multi-organ dysfunction compared with similar individuals in the general population, and the relative increase in risk is neither confined to the elderly nor uniform across ethnic groups. Urgent research is required to understand risk factors for post-COVID syndrome, so that treatment provision can be better targeted to demographically and clinically at-risk populations.

References

[1] Ward H, Atchison C, Whitaker M, et al. Antibody prevalence for SARS-CoV-2 in England following first peak of the pandemic: REACT2 study in 100,000 adults. 2020. https://www.medrxiv.org/content/10.1101/2020.08.12.20173690v2

[2] Banerjee A, Pasea L, Harris S, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020;395:1715-25. doi: https://doi.org/10.1016/S0140-6736(20)30854-0

[3] Clift A, Coupland C, Keogh R, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020;371:m3731. doi: https://doi.org/10.1136/bmj.m3731

[4] Williamson E, Walker A, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;548:430-36. doi: https://doi.org/10.1038/s41586-020-2521-4

[5] World Health Organisation. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. 2020. https://apps.who.int/iris/handle/10665/331446

[6] Puntmann V, Ludovica Carer M, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265-73. doi: 10.1001/jamacardio.2020.3557

[7] Tabary M, Khanmohammadi S, Araghi F, et al. Pathologic features of COVID-19: A concise review. *Pathol Res Pract* 2020;216:153097. doi: 10.1016/j.prp.2020.153097

[8] Alqahtani S, Schattenberg J. Liver injury in COVID-19: The current evidence. *United European Gastroenterol J* 2020;8:509-19. doi: 10.1177/2050640620924157

[9] Somasundaram N, Ranathunga I, Ratnasamy V, et al. The Impact of SARS-Cov-2 Virus Infection on the Endocrine System. *J Endocr Soc* 2020;4:bvaa082. doi: 10.1210/jendso/bvaa082

[10] Farouk S, Fiaccadori E, Cravedi P, et al. COVID-19 and the kidney: what we think we know so far and what we don't. *J Nephrol* 2020;33:1213-18. doi: https://doi.org/10.1007/s40620-020-00789-y

[11] Ball S, Banerjee A, Berry C, et al. Monitoring indirect impact of COVID-19 pandemic on services for cardiovascular diseases in the UK. *Heart* 2020;106:1890-97. doi: 10.1136/heartjnl-2020-317870

[12] Lai A, Pasea L, Banerjee A, et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open* 2020;10:e043828. doi: 10.1136/bmjopen-2020-043828

[13] Katsoulis M, Gomes M, Lai A, et al. Estimating the effect of reduced attendance at emergency departments for suspected cardiac conditions on cardiac mortality during the COVID-19 pandemic. 2020. https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.120.007085

[14] National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020. https://www.nice.org.uk/guidance/ng188

[15] Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026. doi: 10.1136/bmj.m3026

[16] National Institute for Health Research. Themed Review: Living with Covid19. 2020. https://evidence.nihr.ac.uk/themedreview/living-with-covid19

[17] Herbert A, Wijlaars L, Zylbersztejn A, et al. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;46:1093. doi: 10.1093/ije/dyx015

[18] NHS Digital. General Practice Extraction Service (GPES) Data for pandemic planning and research: a guide for analysts and users of the data. 2020. https://digital.nhs.uk/coronavirus/gpes-data-for-pandemic-planning-and-research/guide-for-analysts-and-users-of-the-data

[19] Austin, P. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107. doi: 10.1002/sim.3697

[20] Iacus SM, King G, Porro G. Causal Inference without Balance Checking: Coarsened Exact Matching. *Political Analysis* 2017;20:1-24. doi: 10.1093/pan/mpr013

[21] Fraser, E. Long term respiratory complications of covid-19. *BMJ* 2020;370:m3001. doi: https://doi.org/10.1136/bmj.m3001

[22] Becker, R. Anticipating the long-term cardiovascular effects of COVID-19. *J Thromb Thrombolysis* 2020;50:512-24. doi: 10.1007/s11239-020-02266-6

[23] Rubino F, Amiel S, Zimmet P, et al. New-Onset Diabetes in Covid-19. *N Engl J Med* 2020;383:789-90. doi: 10.1056/NEJMc2018688

[24] Michelen M, Manoharan L, Elkheir N, et al. Characterising long-term covid-19: a rapid living systematic review. 2020. https://www.medrxiv.org/content/10.1101/2020.12.08.20246025v1

[25] Donnelly J, Qing Wang X, Iwashyna T. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. *JAMA* 2020;e2021465. doi: 10.1001/jama.2020.21465

[26] Dennis A, Wamil M, Kapur S, et al. Multi-organ impairment in low-risk individuals with long COVID. 2020. https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1

[27] McCarthy C, Murphy S, Jones-O'Connor M, et al. Early clinical and sociodemographic experience with patients hospitalized with COVID-19 at a large American healthcare system. *Lancet* 2020;26:100504. doi: 10.1016/j.eclinm.2020.100504

[28] Xie Y, Bowe B, Maddukuri G. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *BMJ* 2020;371:m4677. doi: 10.1136/bmj.m4677

[29] Liu D, Zhang W, Pan F, et al. The pulmonary sequalae in discharged patients with COVID-19: a short-term observational study. *Respir Res* 2020;21:125. doi: 10.1186/s12931-020-01385-1

[30] Rajpal S, Tong M, Borchers J, et al. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol* 2020;e204916. doi: 10.1001/jamacardio.2020.4916

[31] UK Government. Coronavirus (COVID-19) in the UK: daily update. https://coronavirus.data.gov.uk

[32] Campbell H, Hotchkiss R, Bradshaw N, et al. Integrated care pathways. *BMJ* 1998;316:133-37. doi: 10.1136/bmj.316.7125.133

[33] Tazare J, Walker AJ, Tomlinson L, et al. Rates of serious clinical outcomes in survivors of hospitalisation with COVID-19: a descriptive cohort study within the OpenSAFELY platform. 2021. https://www.medrxiv.org/content/10.1101/2021.01.22.21250304v2

[34] Wang Z, Deng H, Ou C, et al. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. *Medicine (Baltimore)* 2020;99:e23327. doi: 10.1097/MD.0000000000023327

[35] Li L-Q, Huang T, Wang Y-Q, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020;92:577-83. doi: 10.1002/jmv.25757

Tables and figures

Table 1. Baseline characteristics of individuals in hospital with COVID-19 in England compared with those of a random sample from the general population and in the matched control group

Table 2. Counts and rates of death, readmission and respiratory disease contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

Figure 1. Study population flow diagram

Figure 2. Rates of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

Figure 3. Rate ratios of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls, stratified by demographic factors

Table 1. Baseline characteristics of individuals in hospital with COVID-19 in England compared with those of a random sample from the general population and in the matched control group

Characteristic	Category	COVID-19 cases (*n* = 47,780)	General population, before matching (*n* = 239,380)		Matched control group, after matching (*n* = 47,780)	
		Sample distribution	Sample distribution	Standardised difference vs. cases (%)	Sample distribution	Standardised difference vs. cases (%)
Age	<30 years	2,255 (4.7%)	75,700 (31.6%)	-74.5	1,190 (2.5%)	11.9
	30-49 years	7,760 (16.2%)	61,430 (25.7%)	-23.3	8,820 (18.5%)	-5.9
	50-69 years	15,945 (33.4%)	61,500 (25.7%)	16.9	15,945 (33.4%)	0.0
	≥70 years	21,825 (45.7%)	35,715 (14.9%)	71.0	21,825 (45.7%)	0.0
Sex	Male	26,245 (54.9%)	107,890 (45.1%)	19.8	26,245 (54.9%)	0.0
	Female	21,535 (45.1%)	126,450 (52.8%)	-15.5	21,535 (45.1%)	0.0
Ethnicity	White	34,355 (71.9%)	151,180 (63.2%)	18.8	34,355 (71.9%)	0.0
	Asian	4,320 (9.0%)	15,150 (6.3%)	10.2	4,320 (9.0%)	0.0
	Black	2,565 (5.4%)	6,840 (2.9%)	12.7	2,565 (5.4%)	0.0
	Mixed/Other	1,430 (3.0%)	7,010 (2.9%)	0.4	1,430 (3.0%)	0.0
	Unknown	5,110 (10.7%)	59,205 (24.7%)	-37.4	5,110 (10.7%)	0.0
IMD quintile	1 (most deprived)	11,510 (24.1%)	48,555 (20.3%)	9.2	11,510 (24.1%)	0.0
	2	10,970 (23.0%)	47,680 (19.9%)	7.4	10,970 (23.0%)	0.0
	3	9,265 (19.4%)	47,125 (19.7%)	-0.8	9,265 (19.4%)	0.0
	4	8,315 (17.4%)	46,040 (19.2%)	-4.7	8,315 (17.4%)	0.0
	5 (least deprived)	7,695 (16.1%)	44,795 (18.7%)	-6.9	7,695 (16.1%)	0.0
	Unknown	25 (<0.1%)	5,185 (2.2%)	-20.3	25 (<0.1%)	0.0
Smoking status	Current	4,000 (8.4%)	38,040 (15.9%)	-23.2	4,000 (8.4%)	0.0
	Former	19,560 (40.9%)	56,210 (23.5%)	38.0	19,560 (40.9%)	0.0
	Never	20,295 (42.5%)	93,750 (39.2%)	6.7	22,000 (46.0%)	-7.2
	Unknown	3,920 (8.2%)	51,375 (21.5%)	-38.0	2,215 (4.6%)	14.6
BMI	<25 kg/m^2	9,415 (19.7%)	60,140 (25.1%)	-13.0	12,345 (25.8%)	-14.7
	25 to <30 kg/m^2	12,140 (25.4%)	48,290 (20.2%)	12.5	12,140 (25.4%)	0.0
	≥30 kg/m^2	15,390 (32.2%)	40,795 (17.0%)	35.8	15,390 (32.2%)	0.0
	Unknown	10,835 (22.7%)	90,155 (37.7%)	-33.1	7,905 (16.5%)	15.5
Previous hospitalisation		39,575 (82.8%)	150,510 (62.9%)	46.0	37,930 (79.4%)	8.8
Hypertension		24,720 (51.7%)	43,170 (18.0%)	75.6	24,720 (51.7%)	0.0
Respiratory disease		19,440 (40.7%)	38,695 (16.2%)	56.5	19,440 (40.7%)	0.0
Asthma		8,695 (18.2%)	27,345 (11.4%)	19.2	9,270 (19.4%)	-3.1
COPD		6,565 (13.7%)	7,090 (3.0%)	39.7	5,900 (12.4%)	4.1
Other		11,890 (24.9%)	20,405 (8.5%)	45.0	10,124 (21.2%)	8.8
Diabetes		11,680 (24.4%)	16,670 (7.0%)	49.5	11,680 (24.4%)	0.0
Type 1		1,235 (2.6%)	1,770 (0.7%)	14.5	920 (1.9%)	4.4
Type 2		11,530 (24.1%)	15,810 (6.6%)	50.1	11,475 (24.0%)	0.3

MACE	11,650 (24.4%)	13,385 (5.6%)	54.6	11,650 (24.4%)	0.0
Heart failure	5,255 (11.0%)	4,150 (1.7%)	38.7	4,595 (9.6%)	4.5
Stroke	3,040 (6.4%)	3,100 (1.3%)	26.6	2,580 (5.4%)	4.1
Myocardial infarction	2,265 (4.7%)	3,160 (1.3%)	20.1	2,635 (5.5%)	-3.5
Arrhythmia	7,170 (15.0%)	7,540 (3.1%)	42.2	7,060 (14.8%)	0.6
Cancer	9,820 (20.5%)	22,090 (9.2%)	32.2	9,820 (20.5%)	0.0
CKD stages 3-5	6,075 (12.7%)	7,930 (3.3%)	35.1	6,075 (12.7%)	0.0
Chronic liver disease	1,380 (2.9%)	3,005 (1.3%)	11.5	1,380 (2.9%)	0.0

Table notes: BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; IMD: Index of Multiple Deprivation; MACE: major adverse cardiovascular event. Baseline characteristics extracted from primary care records and hospital episodes over the period 1 January 2010 to 31 December 2019. The general population is a random 0.5% sample of individuals with primary care records between 1 January 2019 and 30 September 2020. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer).

Table 2. Counts and rates of death, readmission and respiratory disease contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

Adverse event (sample size per group)	COVID-19 cases		Control group	
	Events (n, %)	Rate per 1,000 person-years (95% CI)	Events (n, %)	Rate per 1,000 person-years (95% CI)
Death (*n* = 47,780)	5,875 (12.3%)	320.0 (311.9 to 328.3)	830 (1.7%)	41.3 (38.6 to 44.3)
Readmission to hospital (*n* = 47,780)	14,060 (29.4%)	766.0 (753.4 to 778.8)	4,385 (9.2%)	218.9 (212.4 to 225.4)
Respiratory disease (all events) (*n* = 47,780)	14,140 (29.6%)	770.5 (757.8 to 783.3)	2,585 (5.4%)	129.1 (124.2 to 134.2)
Respiratory disease (new onset) (*n* = 28,335)	6,085 (21.5%)	538.9 (525.5 to 552.6)	240 (0.8%)	19.7 (17.3 to 22.4)

Table notes: CI: confidence interval. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission to hospital' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer).

Figure 1. Study population flow diagram

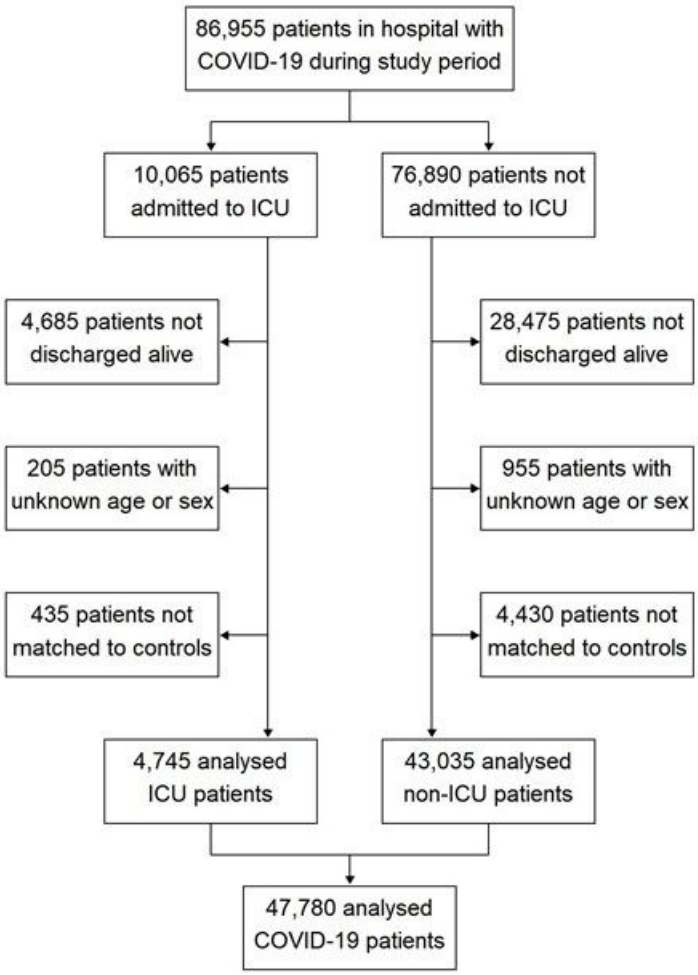

Figure 2. Rates of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

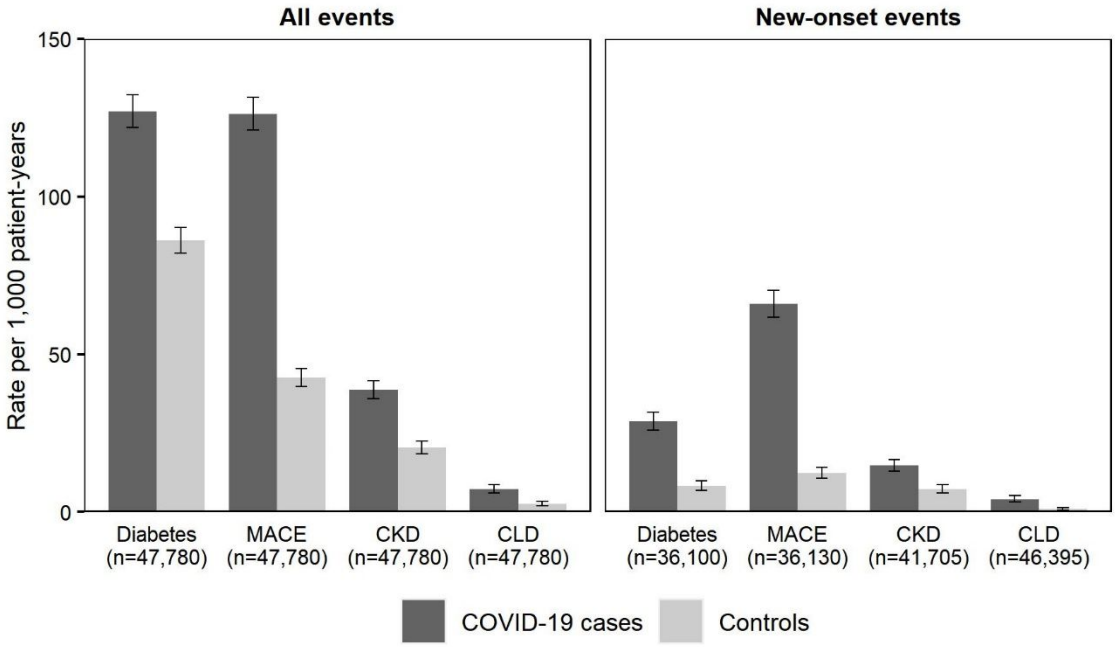

Figure notes: CKD: chronic kidney disease stages 3-5; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer).

Figure 3. Rate ratios of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls, stratified by demographic factors

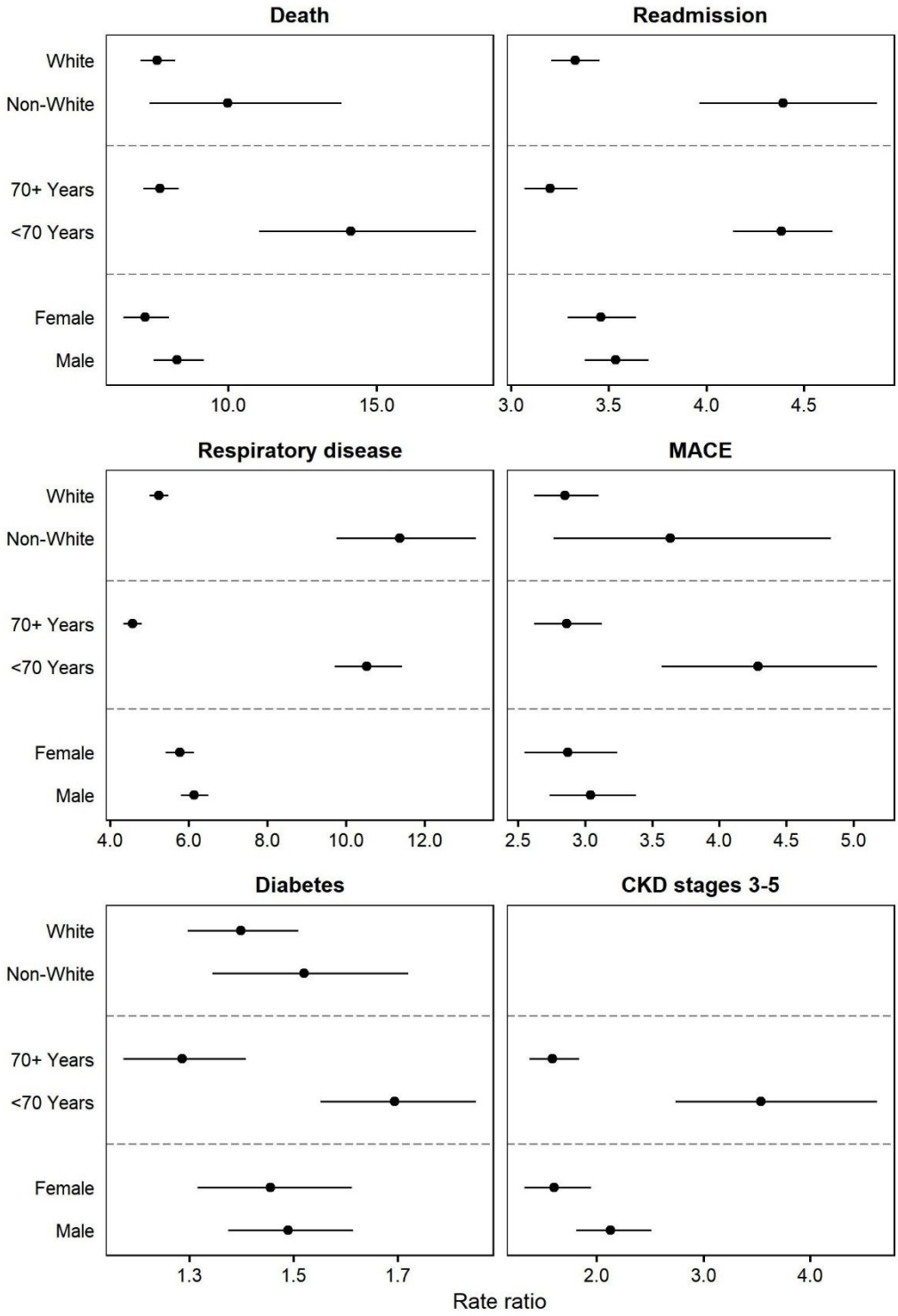

Figure notes: CKD: chronic kidney disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission to hospital' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer). Rate ratios for CKD could not be stratified by ethnic group due to insufficient event counts in the control group.

Footnotes

Acknowledgements

The authors thank staff at NHS Digital for facilitating access to the data and providing valuable guidance as to its quality and usage, and Neil Bannister and Myer Glickman at the Office for National Statistics (ONS) for their input throughout the study. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).

Contributors

DA, KK, VN, BH and AB conceptualised and designed the study. DA and TM prepared the study data and performed statistical analysis. All authors contributed to interpretation of the results. KK, VN, BH, ID and AB contributed to critical revision of the manuscript. All authors approved the final manuscript. DA is the guarantor for the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KK is Chair of the Ethnicity Subgroup of the Independent Scientific Advisory Group for Emergencies (SAGE), a member of Independent SAGE, a Trustee of the South Asian Health Foundation (SAHF), and Director of the University of Leicester Centre for Black Minority Ethnic Health; and AB is a Trustee of the SAHF, and has received a research grant unrelated to the current work from AstraZeneca.

Dissemination declaration

The size of the study population precludes direct dissemination to participants.

Data sharing

In accordance with NHS Digital's Information Governance (IG) requirements, it is not possible for the study data to be shared.

Ethics approval

NHS Digital approved access to the data for this study following a favourable recommendation from its Independent Group Advising on the Release of Data (IGARD). Ethical approval was obtained from the National Statistician's Data Ethics Advisory Committee [NSDEC(20)12].

Transparency statement

The manuscript's guarantor affirms that this 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 (and, if relevant, registered) have been explained.

Funding source

There was no external funding for this study.

Supplementary Table 1. Description of variables used to match COVID-19 and control patients

Variable	Categorisation
Age group	<50 years, 50-69 years, ≥70 years
Sex	Female, male
Ethnic group	Asian, Black, White, Mixed/Other, Unknown
Region of residence	North (North East, North West, Yorkshire and the Humber), South (East of England, London, South East, South West), Midlands (East Midlands, West Midlands), Unknown
IMD quintile	1 (most deprived), 2, 3, 4, 5 (least deprived), Unknown
Smoking status	Current, Former, Never/Unknown
BMI group	<25 kg/m^2 or Unknown, 25 kg/m^2 to <30 kg/m^2, ≥30 kg/m^2
History of hypertension	Yes, No
History of MACE	Yes, No
History of respiratory disease	Yes, No
History of CKD stages 3-5	Yes, No
History of CLD	Yes, No
History of diabetes	Yes, No
History of cancer	Yes, No

Table notes: BMI: body mass index; CKD: chronic kidney disease; CLD: chronic liver disease; IMD: Index of Multiple Deprivation; MACE: major adverse cardiovascular event (a composite of heart failure, myocardial infarction, stroke, and arrhythmia).

Supplementary Table 2. Counts and rates of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

Adverse event (sample size per group)	COVID-19 cases		Control group	
	Events (n, %)	Rate per 1,000 person-years (95% CI)	Events (n, %)	Rate per 1,000 person-years (95% CI)
Death (*n* = 47,780)	5,875 (12.3%)	320.0 (311.9 to 328.3)	830 (1.7%)	41.3 (38.6 to 44.3)
Readmission to hospital (*n* = 47,780)	14,060 (29.4%)	766.0 (753.4 to 778.8)	4,385 (9.2%)	218.9 (212.4 to 225.4)
Respiratory disease (all events) (*n* = 47,780)	14,140 (29.6%)	770.5 (757.8 to 783.3)	2,585 (5.4%)	129.1 (124.2 to 134.2)
Respiratory disease (new onset) (*n* = 28,335)	6,085 (21.5%)	538.9 (525.5 to 552.6)	240 (0.8%)	19.7 (17.3 to 22.4)
Diabetes (all events) (*n* = 47,780)	2,330 (4.9%)	126.9 (121.8 to 132.2)	1,725 (3.6%)	86.0 (82.0 to 90.2)
Diabetes (new onset) (*n* = 36,100)	400 (1.1%)	28.7 (26.0 to 31.7)	125 (0.3%)	8.2 (6.9 to 9.8)
MACE (all events) (*n* = 47,780)	2,315 (4.8%)	126.1 (121.0 to 131.4)	855 (1.8%)	42.6 (39.8 to 45.5)
MACE (new onset) (*n* = 36,130)	945 (2.6%)	65.9 (61.8 to 70.3)	190 (0.5%)	12.3 (10.6 to 14.1)
CKD (all events) (*n* = 47,780)	710 (1.5%)	38.7 (35.9 to 41.6)	410 (0.9%)	20.4 (18.5 to 22.5)
CKD (new onset) (*n* = 41,705)	240 (0.6%)	14.6 (12.8 to 16.6)	125 (0.3%)	7.2 (6.0 to 8.5)
CLD (all events) (*n* = 47,780)	135 (0.3%)	7.2 (6.1 to 8.6)	50 (0.1%)	2.5 (1.9 to 3.3)
CLD (new onset) (*n* = 46,395)	70 (0.2%)	4.0 (3.2 to 5.1)	15 (0.04%)	0.9 (0.5 to 1.4)

Table notes: CI: confidence interval; CKD: chronic kidney disease stages 3-5; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission to hospital' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer).

Supplementary Table 3. Counts and rates of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls, stratified by ICU versus non-ICU admission

Group (sample size)	Adverse event	COVID-19 cases		Control group	
		Events (n, %)	Rate per 1,000 person-years (95% CI)	Events (n, %)	Rate per 1,000 person-years (95% CI)
ICU patients (*n* = 4,745)	Death	420 (8.8%)	237.9 (215.7 to 261.8)	20 (0.5%)	11.4 (7.2 to 17.3)
	Readmission	1,235 (26.0%)	701.2 (662.6 to 741.4)	260 (5.5%)	134.8 (118.9 to 152.2)
	Respiratory disease	1,620 (34.1%)	918.6 (874.4 to 964.5)	100 (2.1%)	53.1 (43.3 to 64.4)
	Diabetes	335 (7.1%)	190.2 (170.4 to 211.7)	175 (3.6%)	90.0 (77.1 to 104.5)
	MACE	175 (3.6%)	98.2 (84.1 to 114.0)	30 (0.6%)	15.1 (10.1 to 21.7)
	CKD	65 (1.3%)	35.8 (27.5 to 45.8)	20 (0.4%)	9.4 (5.6 to 14.8)
Non-ICU patients (*n* = 43,035)	Death	5,455 (12.7%)	328.8 (320.1 to 337.6)	805 (1.9%)	44.5 (41.5 to 47.7)
	Readmission	12,825 (29.8%)	772.9 (759.5 to 786.4)	4,125 (9.6%)	227.8 (220.9 to 234.8)
	Respiratory disease	12,525 (29.1%)	754.7 (741.6 to 768.1)	2,485 (5.8%)	137.2 (131.8 to 142.7)
	Diabetes	1,995 (4.6%)	120.2 (115.0 to 125.6)	1,550 (3.6%)	85.6 (81.4 to 90.0)
	MACE	2,140 (5.0%)	129.1 (123.7 to 134.7)	825 (1.9%)	45.5 (42.4 to 48.7)
	CKD	645 (1.5%)	39.0 (36.0 to 42.1)	390 (0.9%)	21.6 (19.5 to 23.8)

Table notes: CI: confidence interval; CKD: chronic kidney disease stages 3-5; ICU: intensive care unit; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer).

Supplementary Table 4. Rates and rate ratios of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls, stratified by demographic factors

Group (sample size)	Adverse event	Rate per 1,000 person-years (95% CI)		Rate ratio (95% CI)
		COVID-19 cases	Control group	
Sex: Male (*n* = 26,245)	Death	318.4 (307.5 to 329.6)	38.5 (34.9 to 42.3)	8.3 (7.5 to 9.2)
	Readmission	757.5 (740.7 to 774.7)	214.3 (205.8 to 223.1)	3.5 (3.4 to 3.7)
	Respiratory	780.9 (763.8 to 798.3)	127.3 (120.7 to 134.1)	6.1 (5.8 to 6.5)
	Diabetes	142.4 (135.2 to 150.0)	95.6 (90.0 to 101.6)	1.5 (1.4 to 1.6)
	MACE	130.7 (123.7 to 137.9)	43.0 (39.2 to 47.1)	3.0 (2.7 to 3.4)
	CKD	43.7 (39.7 to 48.0)	20.5 (17.9 to 23.4)	2.1 (1.8 to 2.5)
Sex: Female (*n* = 21,535)	Death	322.0 (309.9 to 334.5)	44.8 (40.6 to 49.4)	7.2 (6.5 to 8.0)
	Readmission	776.4 (757.5 to 795.7)	224.5 (214.8 to 234.5)	3.5 (3.3 to 3.6)
	Respiratory	757.6 (738.9 to 776.6)	131.4 (124.0 to 139.1)	5.8 (5.4 to 6.1)
	Diabetes	107.9 (101.0 to 115.3)	74.2 (68.6 to 80.0)	1.5 (1.3 to 1.6)
	MACE	120.6 (113.2 to 128.3)	42.0 (37.9 to 46.5)	2.9 (2.5 to 3.2)
	CKD	32.5 (28.8 to 36.7)	20.3 (17.5 to 23.5)	1.6 (1.3 to 1.9)
Age group: <70 years (*n* = 25,955)	Death	86.2 (80.7 to 91.9)	6.1 (4.7 to 7.7)	14.1 (11.0 to 18.3)
	Readmission	556.6 (542.6 to 570.8)	127.0 (120.5 to 133.8)	4.4 (4.1 to 4.6)
	Respiratory	615.8 (601.1 to 630.8)	58.5 (54.1 to 63.1)	10.5 (9.7 to 11.4)
	Diabetes	123.9 (117.4 to 130.7)	73.2 (68.2 to 78.4)	1.7 (1.6 to 1.8)
	MACE	55.7 (51.4 to 60.4)	13.0 (11.0 to 15.3)	4.3 (3.6 to 5.2)
	CKD	24.4 (21.6 to 27.5)	6.9 (5.4 to 8.6)	3.5 (2.7 to 4.6)
Age group: ≥70 years (*n* = 21,825)	Death	658.4 (640.1 to 677.0)	85.6 (79.6 to 91.9)	7.7 (7.1 to 8.3)
	Readmission	1,069.0 (1,045.7 to 1,092.6)	334.2 (322.3 to 346.5)	3.2 (3.1 to 3.3)
	Respiratory	994.2 (971.7 to 1,017.0)	217.8 (208.2 to 227.7)	4.6 (4.3 to 4.8)
	Diabetes	131.3 (123.2 to 139.8)	102.1 (95.6 to 109.0)	1.3 (1.2 to 1.4)
	MACE	227.9 (217.3 to 239.0)	79.7 (74.0 to 85.8)	2.9 (2.6 to 3.1)
	CKD	59.3 (53.9 to 65.1)	37.4 (33.5 to 41.6)	1.6 (1.4 to 1.8)
Ethnic group: White (*n* = 34,355)	Death	403.4 (392.5 to 414.5)	53.1 (49.4 to 57.0)	7.6 (7.0 to 8.2)
	Readmission	876.8 (860.7 to 893.2)	263.6 (255.3 to 272.2)	3.3 (3.2 to 3.5)
	Respiratory	861.1 (845.1 to 877.3)	164.5 (157.9 to 171.3)	5.2 (5.0 to 5.5)
	Diabetes	119.6 (113.6 to 125.7)	85.5 (80.8 to 90.4)	1.4 (1.3 to 1.5)
	MACE	153.4 (146.7 to 160.3)	53.9 (50.2 to 57.9)	2.8 (2.6 to 3.1)
Ethnic group: Non-White (*n* = 8,315)	Death	126.6 (115.0 to 139.0)	12.7 (9.3 to 16.9)	10.0 (7.3 to 13.8)
	Readmission	553.7 (529.2 to 579.0)	126.1 (114.8 to 138.2)	4.4 (4.0 to 4.9)
	Respiratory	567.8 (543.0 to 593.4)	49.9 (42.9 to 57.8)	11.4 (9.8 to 13.3)
	Diabetes	184.1 (170.1 to 198.9)	121.1 (110.1 to 133.0)	1.5 (1.3 to 1.7)
	MACE	68.2 (59.8 to 77.4)	18.8 (14.6 to 23.8)	3.6 (2.8 to 4.8)

Table notes: CI: confidence interval; CKD: chronic kidney disease stages 3-5; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer). Rates and rate ratios for CKD could not be stratified by ethnic group due to insufficient event counts in the control group.

Supplementary Appendix: Sensitivity analyses

1. Comparison of matched and unmatched COVID-19 cases, and the impact of excluding unmatched cases from the main analysis

Of 86,955 individuals in hospital with COVID-19 during the study period, 53,795 (61.9%) had been discharged alive by end-of-study. After excluding individuals with unknown age or sex and those who could not be matched to a control, 47,780 COVID-19 cases were included in the analysis, representing 90.8% of those discharged alive with known age and sex. Compared with those in the matched population, the 9.2% of individuals who remained unmatched were more likely to belong to an ethnic minority group, live in a deprived area, currently smoke, have been admitted to hospital during the baseline period, and have comorbidities (Table 1).

Table 1. Baseline characteristics of matched and unmatched COVID-19 cases

Characteristic	Category	Matched cases (*n* = 47,780)	Unmatched cases (*n* = 4,865)	P-value	Standardised difference (%)
Age	<30 years	2,255 (4.7%)	135 (2.8%)	<0.0001	10.1
	30-49 years	7,760 (16.2%)	1,020 (20.9%)	<0.0001	-12.1
	50-69 years	15,945 (33.4%)	1,700 (34.9%)	0.0292	-3.3
	≥70 years	21,825 (45.7%)	2,010 (41.3%)	<0.0001	8.8
Sex	Male	26,245 (54.9%)	2,540 (52.3%)	0.0004	5.3
	Female	21,535 (45.1%)	2,325 (47.7%)	0.0004	-5.3
Ethnicity	White	34,355 (71.9%)	2,115 (43.5%)	<0.0001	60.1
	Asian	4,320 (9.0%)	975 (20.1%)	<0.0001	-31.7
	Black	2,565 (5.4%)	865 (17.8%)	<0.0001	-39.5
	Mixed/Other	1,430 (3.0%)	545 (11.2%)	<0.0001	-32.3
	Unknown	5,110 (10.7%)	365 (7.5%)	<0.0001	11.2
Index of Multiple Deprivation quintile	1 (most deprived)	11,510 (24.1%)	1,435 (29.5%)	<0.0001	-12.3
	2	10,970 (23.0%)	1,270 (26.1%)	<0.0001	-7.4
	3	9,265 (19.4%)	850 (17.5%)	0.0015	4.9
	4	8,315 (17.4%)	710 (14.6%)	<0.0001	7.7
	5 (least deprived)	7,695 (16.1%)	535 (11.0%)	<0.0001	15.1
	Unknown	25 (<0.1%)	65 (1.3%)	<0.0001	-15.3
Smoking status	Current	4,000 (8.4%)	685 (14.1%)	<0.0001	-18.1
	Former	19,560 (40.9%)	1,730 (35.6%)	<0.0001	10.9
	Never	20,295 (42.5%)	2,095 (43.1%)	0.4301	-1.2
	Unknown	3,920 (8.2%)	355 (7.2%)	0.0175	3.7
Body mass index	<25 kg/m^2	9,415 (19.7%)	1,050 (21.6%)	0.0019	-4.6
	25 to <30 kg/m^2	12,140 (25.4%)	1,165 (23.9%)	0.0248	3.4
	≥30 kg/m^2	15,390 (32.2%)	1,745 (35.9%)	<0.0001	-7.7
	Unknown	10,835 (22.7%)	905 (18.6%)	<0.0001	10.1
Previous hospitalisation		39,575 (82.8%)	4,720 (97.1%)	<0.0001	-48.8
Hypertension		24,720 (51.7%)	3,440 (70.7%)	<0.0001	-39.7
Respiratory disease		19,440 (40.7%)	3,325 (68.4%)	<0.0001	-57.9
Asthma		8,695 (18.2%)	1,320 (27.2%)	<0.0001	-21.6
COPD		6,565 (13.7%)	915 (18.8%)	<0.0001	-13.7
Other		11,890 (24.9%)	2,285 (47.0%)	<0.0001	-47.3
Diabetes		11,680 (24.4%)	2,770 (57.0%)	<0.0001	-70.2
Type 1		1,235 (2.6%)	490 (10.1%)	<0.0001	-31.1
Type 2		11,530 (24.1%)	2,710 (55.7%)	<0.0001	-68.2
Major adverse cardiovascular event		11,650 (24.4%)	2,370 (48.8%)	<0.0001	-52.4
Heart failure		5,255 (11.0%)	1,190 (24.5%)	<0.0001	-35.9
Stroke		3,040 (6.4%)	640 (13.1%)	<0.0001	-23.0
Myocardial infarction		2,265 (4.7%)	530 (10.9%)	<0.0001	-23.0
Arrhythmia		7,170 (15.0%)	1,180 (24.3%)	<0.0001	-23.6
Cancer		9,820 (20.5%)	1,930 (39.7%)	<0.0001	-42.7
Chronic kidney disease stages 3-5		6,075 (12.7%)	1,830 (37.7%)	<0.0001	-60.0
Dementia		5,010 (10.5%)	540 (11.1%)	0.1580	-2.1
Osteoporosis		4,390 (9.2%)	530 (10.9%)	0.0001	-5.8
Rheumatoid arthritis		1,890 (4.0%)	265 (5.5%)	<0.0001	-7.1
Chronic liver disease		1,380 (2.9%)	1,440 (29.6%)	<0.0001	-77.8

Taken together, the aforementioned differences in characteristics between the matched and unmatched populations mean that the adverse event rates presented in the main analysis, which are based on only the matched population, may slightly underestimate the rates in the full population of discharged COVID-19 cases (Table 2). The estimates presented in the main results may therefore be considered conservative.

Table 2. Counts and rates of adverse events contrasting matched and all COVID-19 cases

Adverse event	**Matched COVID-19 cases (*n* = 47,780)**		**All COVID-19 cases (*n* = 52,645)**	
	Events (n, %)	**Rate per 1,000 person-years (95% CI)**	**Events (n, %)**	**Rate per 1,000 person-years (95% CI)**
Death	5,875 (12.3%)	320.0 (311.9 to 328.3)	6,555 (12.5%)	324.7 (316.9 to 332.6)
Readmission to hospital	14,060 (29.4%)	766.0 (753.4 to 778.8)	16,065 (30.5%)	795.5 (783.2 to 807.9)
Respiratory disease (all events)	14,140 (29.6%)	770.5 (757.8 to 783.3)	15,910 (30.2%)	787.8 (775.6 to 800.1)
Respiratory disease (new onset)	6,085 (21.5%)	538.9 (525.5 to 552.6)	6,435 (21.5%)	541.0 (527.8 to 554.4)
Diabetes (all events)	2,330 (4.9%)	126.9 (121.8 to 132.2)	2,805 (5.3%)	138.8 (133.7 to 144.0)
Diabetes (new onset)	400 (1.1%)	28.7 (26.0 to 31.7)	425 (1.1%)	28.9 (26.2 to 31.8)
MACE (all events)	2,315 (4.8%)	126.1 (121.0 to 131.4)	2,655 (5.0%)	131.4 (126.5 to 136.5)
MACE (new onset)	945 (2.6%)	65.9 (61.8 to 70.3)	1,030 (2.7%)	67.2 (63.1 to 71.4)
CKD (all events)	710 (1.5%)	38.7 (35.9 to 41.6)	1,055 (2.0%)	52.3 (49.2 to 55.6)
CKD (new onset)	240 (0.6%)	14.6 (12.8 to 16.6)	270 (0.6%)	15.6 (13.8 to 17.5)
CLD (all events)	135 (0.3%)	7.2 (6.1 to 8.6)	205 (0.4%)	10.1 (8.7 to 11.5)
CLD (new onset)	70 (0.2%)	4.0 (3.2 to 5.1)	80 (0.2%)	4.1 (3.3 to 5.1)

Table notes: CI: confidence interval; CKD: chronic kidney disease stages 3-5; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer).

2. Impact of conducting regression adjustment after matching

We investigated the possibility of residual confounding by age after matching, since we had to use coarse age groups to ensure a sufficient match rate. The age distributions were well balanced between COVID-19 cases and controls within all three matching groups, with mean ages of: 36.2 and 36.7, respectively, in the <50 years group; 59.4 and 59.4, respectively, in the 50-69 years group; and 81.4 and 79.4, respectively, in the ≥70 years group. The proportion of individuals in the <30 years age group was slightly greater among COVID-19 cases (4.7%) than in the matched control group (2.5%).

We also found imbalance between COVID-19 cases and controls in terms of unknown smoking status (8.2% and 4.6%, respectively) and BMI (22.7% and 16.5%, respectively). As with age, this imbalance was due to use of coarsened versions of the smoking status and BMI variables during matching, in which individuals with unknown smoking status were grouped with non-smokers, and individuals with unknown BMI were grouped with those with BMI <25 kg/m^2.

We therefore assessed the robustness of our main results by adjusting for a second-order polynomial of age and non-coarsened versions of smoking status and BMI (each including a separate 'Unknown' category) in a Poisson regression of outcome counts, including the natural logarithm of person-years as an offset term. This analysis revealed very little change in the estimated rate ratios of adverse events between cases and controls (Figure 1), including when the analysis was stratified by demographic characteristics (Figure 2), indicating the absence of residual confounding by age, smoking status, or BMI after matching.

Figure 1. Rate ratios contrasting COVID-19 cases with matched controls, with and without regression adjustment for age, smoking status, and BMI

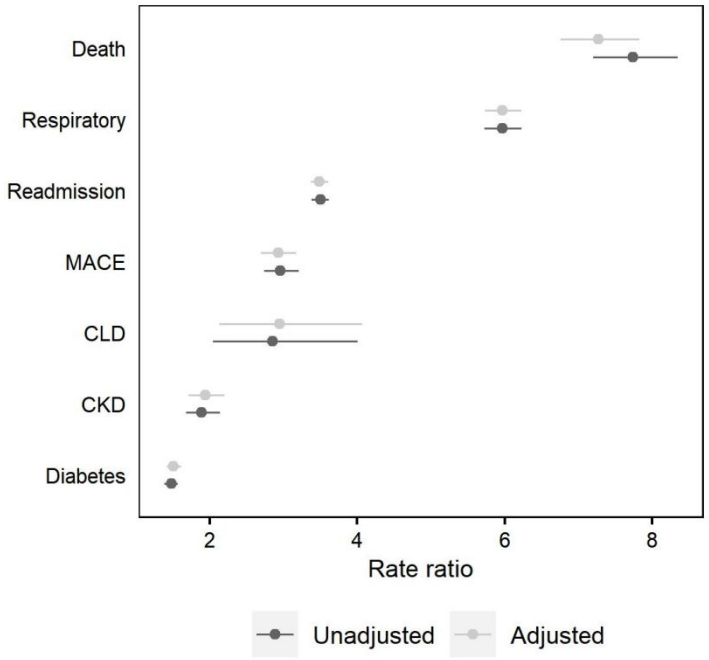

Figure notes: CKD: chronic kidney disease; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls.COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer). Adjusted estimates were obtained from a Poisson regression of outcome counts on group (case or control), a second-order polynomial of age, smoking status, and BMI category, including log-exposure as an offset term.

Figure 2. Rate ratios contrasting COVID-19 cases with matched controls, with and without regression adjustment for age, smoking status, and BMI, stratified by demographic factors

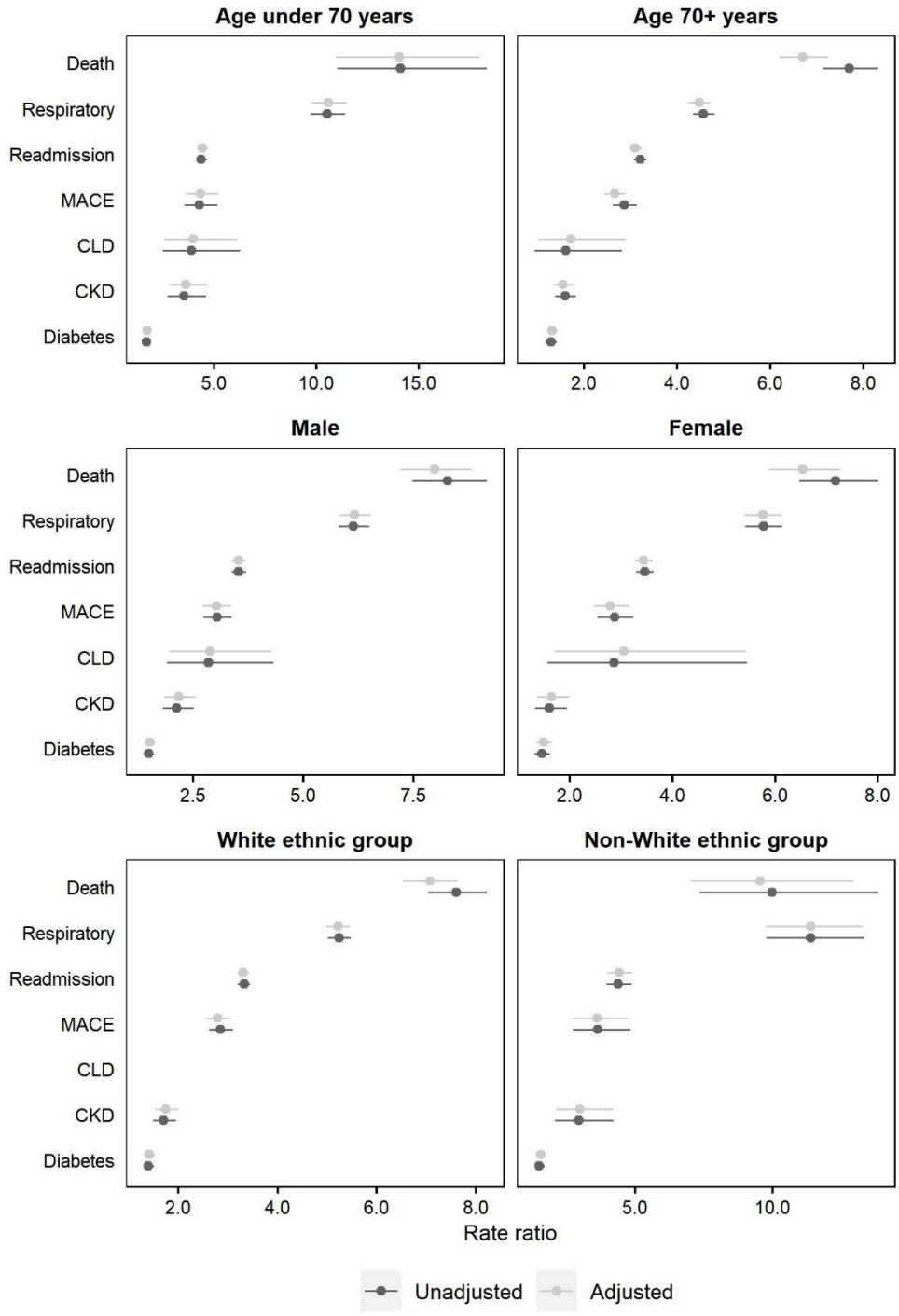

Figure notes: CKD: chronic kidney disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer). Adjusted estimates were obtained from a Poisson regression of outcome counts on group (case or control), a second-order polynomial of age, smoking status, and BMI category, including log-exposure as an offset term. Rate ratios for CKD could not be stratified by ethnic group due to insufficient event counts in the control group.

3. Impact of including only laboratory-confirmed cases of COVID-19 in the study

Individuals with COVID-19 were included in the study if they had a hospital episode starting from 1 January 2020 and ending by 31 August 2020 with a primary diagnosis of COVID-19, identified using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes U07.1 (virus identified) and U07.2 (virus not identified); that is, by a positive laboratory test or clinical diagnosis. We included cases coded to U07.2 to recognise that not all patients with COVID-19 would have received a test during their hospital episode, particularly during the early weeks of the pandemic, and we wanted to recognise the importance of professional judgement on the part of clinicians. In sensitivity analysis, we restricted the case definition to diagnoses coded to U07.1 only (representing 80.2% of COVID-19 cases included in the main analysis), finding that comparisons between event rates of cases and controls were robust to this restriction (Table 3).

Table 3. Counts and rates of adverse events contrasting laboratory-confirmed COVID-19 cases with matched controls

Adverse event	COVID-19 cases		Control group	
	Events (n, %)	Rate per 1,000 person-years (95% CI)	Events (n, %)	Rate per 1,000 person-years (95% CI)
Death	4,935 (12.9%)	334.1 (324.8 to 343.5)	705 (1.8%)	43.5 (40.4 to 46.9)
Readmission to hospital	11,135 (29.1%)	753.8 (739.8 to 767.9)	3,615 (9.4%)	223.0 (215.8 to 230.4)
Respiratory disease (all events)	10,820 (28.2%)	732.6 (718.9 to 746.6)	2,120 (5.5%)	130.9 (125.4 to 136.6)
Respiratory disease (new onset)	4,710 (20.7%)	517.8 (503.1 to 532.8)	205 (0.9%)	21.0 (18.2 to 24.1)
Diabetes (all events)	1,965 (5.1%)	133.1 (127.3 to 139.1)	1,435 (3.8%)	88.7 (84.2 to 93.4)
Diabetes (new onset)	330 (1.2%)	29.7 (26.6 to 33.1)	105 (0.4%)	8.5 (6.9 to 10.3)
MACE (all events)	1,810 (4.7%)	122.5 (117.0 to 128.3)	685 (1.8%)	42.3 (39.2 to 45.6)
MACE (new onset)	725 (2.5%)	63.0 (58.5 to 67.8)	150 (0.5%)	12.2 (10.3 to 14.3)
CKD (all events)	590 (1.5%)	39.9 (36.8 to 43.3)	345 (0.9%)	21.2 (19.1 to 23.6)
CKD (new onset)	195 (0.6%)	15.1 (13.0 to 17.3)	105 (0.3%)	7.4 (6.0 to 8.9)
CLD (all events)	105 (0.3%)	7.2 (5.9 to 8.7)	35 (0.1%)	2.3 (1.6 to 3.2)
CLD (new onset)	60 (0.2%)	4.3 (3.3 to 5.5)	15 (<0.1%)	0.8 (0.4 to 1.4)

Table notes: CI: confidence interval; CKD: chronic kidney disease stages 3-5; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission to hospital' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, major adverse cardiovascular event, respiratory disease, chronic kidney disease, chronic liver disease, diabetes, cancer). Laboratory-confirmed cases of COVID-19 were those with a primary diagnosis code of U07.1 during the hospital spell.

Supplementary Appendix: Code lists for outcome variables

1. ICD-10 codes for defining outcome variables from HES data

Condition	Codes
Heart failure	I50
Stroke	I60-64
Myocardial infarction	I21-22
Arrhythmia	I47-49
Respiratory illness	J00-99
Chronic kidney disease stages 3-5	N18.3-18.5, Z94.0, Z99.2
Chronic liver disease	K70-77
Type 1 diabetes mellitus	E10
Type 2 diabetes mellitus	E11

2. SNOMED codes for defining outcome variables from GDPPR data

GDPPR code lists.xlsx

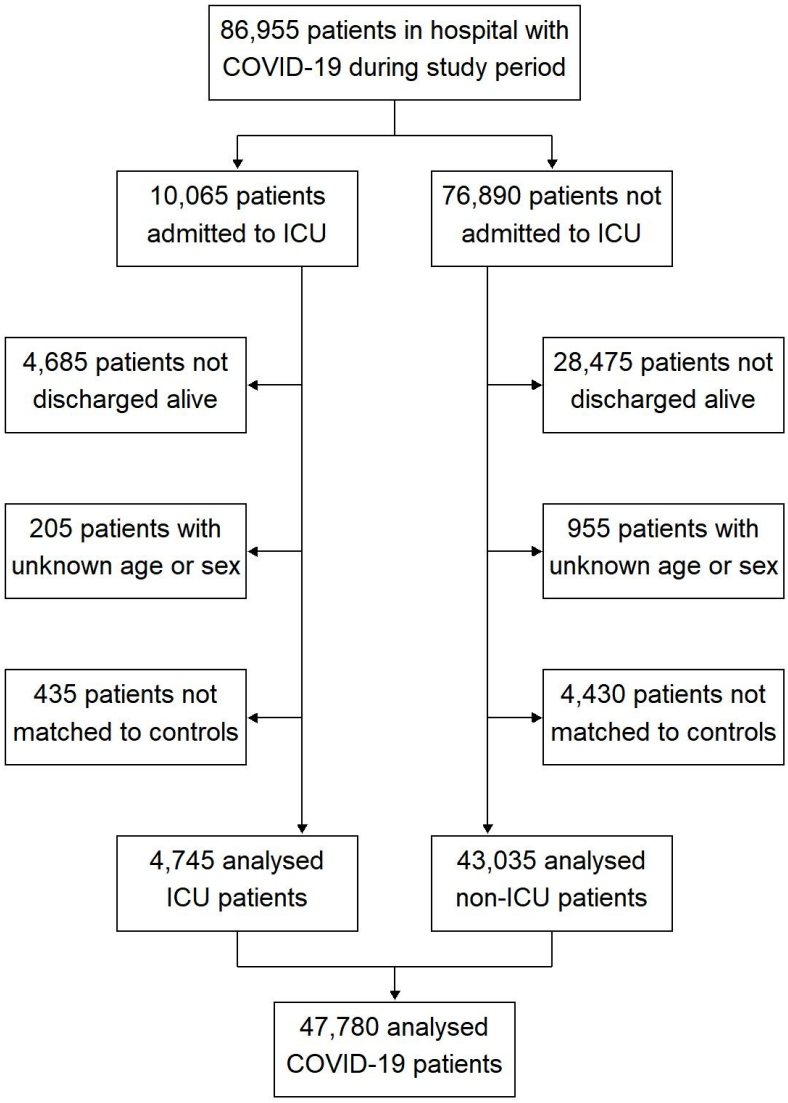

Figure 1. Study population flow diagram

99x139mm (300 x 300 DPI)

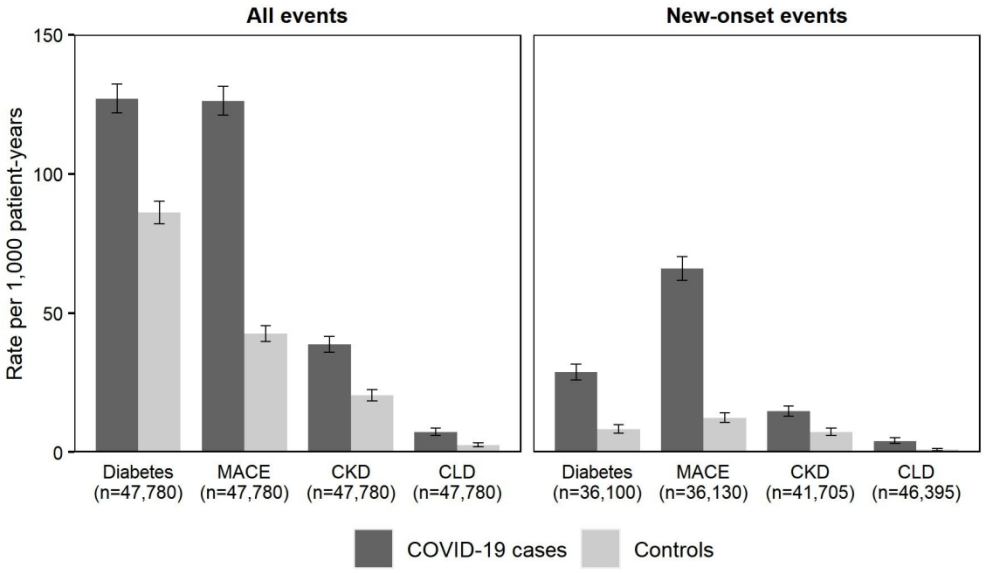

Figure 2. Rates of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls

Figure notes: CKD: chronic kidney disease stages 3-5; CLD: chronic liver disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer).

149x89mm (300 x 300 DPI)

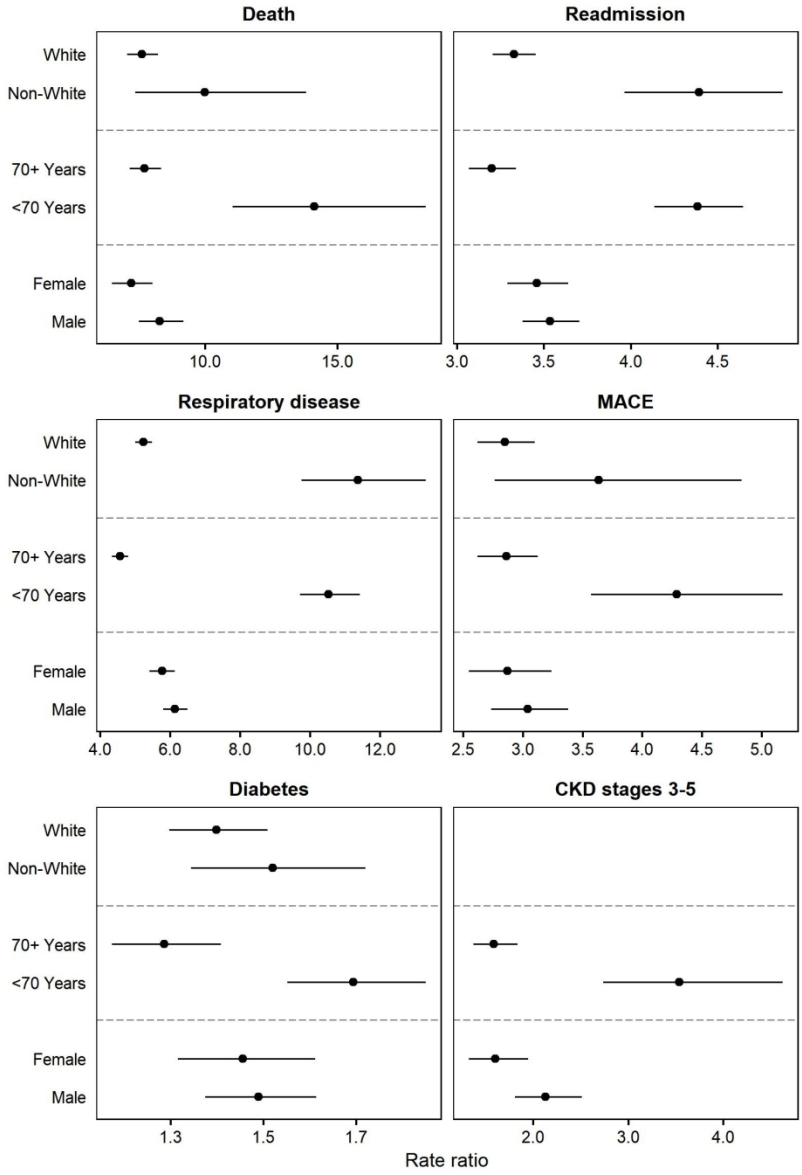

Figure 3. Rate ratios of adverse events contrasting individuals with COVID-19 in England discharged from hospital by 31 August 2020 with matched controls, stratified by demographic factors

Figure notes: CKD: chronic kidney disease; MACE: major adverse cardiovascular event. Adverse events calculated from hospital episodes to 31 August 2020, and primary care records and deaths registrations to 30 September 2020. 'Readmission to hospital' represents any admission after discharge for COVID-19 cases, and any post-index admission for controls. COVID-19 cases were matched to controls on baseline demographic characteristics (age, sex, ethnicity, region, Index of Multiple Deprivation quintile, smoking status) and clinical histories (hypertension, MACE, respiratory disease, CKD, CLD, diabetes, cancer). Rate ratios for CKD could not be stratified by ethnic group due to insufficient event counts in the control group.

139x199mm (300 x 300 DPI)