Hospitalisation and mortality before and during the COVID-19 pandemic in individuals with cardiorenal–metabolic diseases in the UK: a retrospective cohort study

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Summary

Background Health-care access and use were considerably disrupted during the COVID-19 pandemic. This study assessed the sex-specific effect of the pandemic on hospitalisations and mortality among individuals in England with type 2 diabetes, cardiovascular disease, and chronic kidney disease.

Methods We conducted a retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD) GOLD primary care database in individuals with data linkage available to the Hospital Episode Statistics Admitted Patient Care (HES APC), the Office for National Statistics (ONS) death registry, and the patient-level Index of Multiple Deprivation (IMD) 2019. Individuals were eligible for inclusion if they were registered in CPRD GOLD on the study start date (ie, March 1, 2017); were aged 18 years or older; had up-to-standard registration in CPRD GOLD for at least 1 year before the study start date; and had linkage available to HES APC, ONS, and IMD data. Adults with type 2 diabetes, cardiovascular disease, or chronic kidney disease were identified and followed up for 2 years before (March 1, 2018, to Feb 29, 2020) and 1 year during (March 1, 2020, to Feb 28, 2021) the COVID-19 pandemic. We estimated sex-specific crude incidence rates of all-cause hospitalisations and mortality in both periods. We also estimated sex-stratified, age-adjusted incidence rate ratios (IRRs) for all-cause hospitalisations and mortality during March 1, 2020, to Feb 28, 2021 versus March 1, 2018, to Feb 29, 2020 using Poisson models. Excess deaths were estimated by comparing observed and expected mortality rates.

Findings Among 769 551 eligible individuals, 59 169 (7·7%) had type 2 diabetes, 49 754 (6·5%) had cardiovascular disease, and 39 803 (5·2%) had chronic kidney disease in 2018. From 2018–20 to 2020–21, all-cause hospitalisations declined across all disease cohorts, with the largest reduction observed in female participants with type 2 diabetes (from 568 [95% CI 561–575] to 394 [384–404] events per 1000 person-years; adjusted IRR [aIRR] 0·71 [95% CI 0·69–0·73]). From 2018–20 to 2020–21, all-cause mortality increased in all three cohorts and was highest among male participants (from 62 [95% CI 59–65] to 77 [71–83] events per 1000 person-years; aIRR 1·25 [95% CI 1·14–1·38]) and female participants (from 54 [95% CI 52–57] to 73 [67–79] events per 1000 person-years; aIRR 1·36 [95% CI 1·23–1·49]) with chronic kidney disease. In 2020 in England, there were approximately 24 500, 37 300, and 38 000 excess deaths in individuals with type 2 diabetes, cardiovascular disease, and chronic kidney disease, respectively.

Interpretation These findings show the effect of COVID-19 on male and female participants with three common chronic conditions in England. Prioritising care for groups at increased risk of severe outcomes and improving resilience are crucial for ensuring continuity of care during future public health crises.

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Introduction

The impact of the COVID-19 pandemic has been felt globally; as of January, 2025, an estimated 7·1 million deaths have been attributed to COVID-19.[1] Between March, 2020, and December, 2022, 167 355 excess deaths occurred in England and Wales compared with the previous 5-year averages, including 103 585 in male participants (13·9% increase) and 63 770 in female participants (8·4% increase).[2] The pandemic added a considerable burden to already overstretched health-care systems, leading to reductions in referrals, diagnoses, treatments, and hospitalisations.[3,4] Increasing delays, and waiting times and lists have led to fundamental changes in how health care is now delivered in England, including a reduction in in-person contact.[5,6] Particularly, the intersection of the pre-existing burden of chronic conditions with COVID-19 raised major concerns among health-care providers and policy makers.

Before the COVID-19 pandemic, chronic conditions such as type 2 diabetes, cardiovascular disease, and chronic kidney disease were consistently associated with poorer health outcomes (eg, quality of life, admission to hospital, and mortality) compared with individuals without these

Research in context

Evidence before this study

We searched PubMed for studies published from Jan 1, 2020, to Dec 31, 2024, using the search terms ("COVID-19" OR "pandemic") AND ("T2DM" OR "Diabetes" OR "CVD" OR "Cardiovascular disease" OR "CKD" OR "Chronic kidney disease") AND ("hospitalisation" OR "mortality"), with no restrictions on language. Previous studies separately reported worse outcomes, including hospitalisation and mortality, during the COVID-19 pandemic among people with chronic conditions than those without chronic conditions. Although most studies focused on overall population-level trends in hospitalisation and mortality, some also reported differences in these outcomes by sociodemographic groups. However, the intersectional inequalities in hospitalisation and mortality by chronic condition and sex have not been reported in large population-based studies comparing the outcomes before and during the pandemic.

Added value of this study

Our retrospective cohort study adds new understanding of the impact of the COVID-19 pandemic on hospitalisations and mortality among individuals with type 2 diabetes, cardiovascular disease, or chronic kidney disease in England by conducting a large-scale, sex-stratified analysis. Compared with male participants, hospitalisations declined more in female participants with type 2 diabetes in 2020–21 compared with 2018–20. Furthermore, male participants with type 2 diabetes or cardiovascular disease showed relatively higher increases in all-cause mortality than female participants with these conditions. However, for those with chronic kidney disease, female participants had a higher increase in all-cause mortality than male participants. Furthermore, we estimated substantial excess deaths in individuals with cardiovascular disease and chronic kidney disease during the pandemic, exceeding 37 000 in both cohorts. Our findings indicate which populations with type 2 diabetes, cardiovascular disease, or chronic kidney disease were most affected by health-care disruptions during the COVID-19 pandemic, addressing gaps in the existing literature.

Implications of all the available evidence

Our findings highlight clinical inequalities in the effects of the COVID-19 pandemic and reinforce the need for health-care systems to prioritise chronic condition management, essential treatments, and preventive care during public health crises. Future research should explore the drivers of sex differences and the impact of social factors on outcomes.

conditions.[7,8] During the pandemic, these conditions predisposed individuals to severe complications associated with COVID-19 and led to a higher rate of COVID-19-related deaths.[9] COVID-19 exacerbated these chronic conditions through systemic inflammation, endothelial dysfunction, and direct viral injury, leading to worsened disease prognosis.[10] Early reports also indicated that COVID-19 affected the delivery of guideline-recommended care to these patients, including reduced access to routine monitoring, and delays in medication reviews, referrals, and consultations.[10,11] There remains a need for a detailed analysis of people with chronic conditions to understand the extent of the effect of the pandemic on all-cause and cardiovascular disease-related outcomes, especially because cardiovascular disease-related outcomes are one of the leading causes of death in the UK.[12]

We aimed to address the research gap by comparing cardiovascular disease-related and all-cause hospitalisation and mortality before and during the COVID-19 pandemic in individuals with type 2 diabetes, cardiovascular disease, or chronic kidney disease using primary and secondary care records in England. We aim to provide crucial insights into how the pandemic changed health care for these vulnerable populations, with particular emphasis on sex-specific differences.

Methods

Study design, data sources, and study population

For the **study protocol** see https://www.cprd.com/approved-studies/investigating-disruptions-primary-care-result-covid-19-pandemic-and-introduction

We conducted a retrospective cohort study using the UK's Clinical Practice Research Datalink (CPRD) GOLD database.[13] The study protocol (number 21_000431) was approved by CPRD's Independent Scientific Advisory Committee. CPRD GOLD is a primary care database in the UK maintained by the UK Medicines and Healthcare products Regulatory Agency (MHRA) containing anonymised longitudinal patient records including demographics, clinical diagnoses, prescriptions, laboratory test results, and referrals with robust data quality. CPRD GOLD generally reflects the characteristics of the broader population of England.[13] General practices across England opt into the CPRD database, and their data are automatically included in the CPRD database.

This study is based on data from CPRD GOLD obtained under licence from the UK MHRA. Data are provided by patients and collected by the UK National Health Service (NHS) as part of their care and support. The CPRD has ethics approval from the UK Health Research Authority to support research using anonymised patient data. Therefore, no additional ethical approval was needed for this study, provided it complied with the CPRD's data governance requirements. Because data were anonymised at source and collected as part of routine care, no oral or written informed consent was required from participants, nor were they directly informed of their inclusion in the study. However, patients can opt out of sharing their data for research purposes.

Individuals were eligible to be included in the cohort if they were registered in CPRD GOLD on the study start date (March 1, 2017), were aged 18 years or older, and had up-to-standard registration in CPRD GOLD for at least 1 year before the study start date. Individuals were also required to

have data linkage available to the Hospital Episode Statistics Admitted Patient Care (HES APC), the Office for National Statistics (ONS) death registry, and the patient-level Index of Multiple Deprivation (IMD) 2019 data in England. The study period was divided into two distinct phases: (1) 2 years before the pandemic, from March 1, 2018, to Feb 29, 2020 (referred to as 2018–20); and (2) 1 year after the start of the pandemic, from March 1, 2020, to Feb 28, 2021 (referred to as 2020–21). From the eligible individuals, three cohorts were identified at each period: those who were alive and registered at the start of the period with any previous diagnosis of (1) type 2 diabetes (excluding those with history of type 1 diabetes, gestational diabetes, or secondary diabetes), (2) cardiovascular disease (defined as having either coronary heart disease, stroke, peripheral arterial disease, or aortic disease), and (3) chronic kidney disease (stages 3–5). Cohorts could overlap, both by chronic condition (ie, patients could have more than one chronic condition) and timepoint. Regarding overlap across the two timepoints, this occurred because patients included in the first timepoint (2018–20) could still be alive by March 1, 2020, and were therefore included in the second timepoint (2020–21). Further details on the definition of variables and conditions are presented in the appendix (p 2).

Procedures

Conditions were identified from both CPRD and HES APC using Read codes (used in primary care in England) and ICD-10 codes (used in hospital records). Those with multiple conditions were included in all relevant cohorts. The follow-up period for each individual started from the beginning of each period until the earliest occurrence of death, transfer out of the practice, the practice's last collection of data, or the end of the period (appendix p 3). For each individual, at the start of each period, we obtained data on age (recorded as year of birth) and sex (recorded as self-reported male, female, or indeterminate; individuals recorded as indeterminate sex were not included due to their very small number) from CPRD patient data, ethnicity from HES and CPRD records, and area-level deprivation from the linked IMD records based on the individual's residential postcode (appendix p 2).

The study ran from March 1, 2018, to Feb 28, 2021; HES and ONS linkage were available up to March, 2021. Hospital admissions from HES and death records from ONS, if available, were obtained for each individual, separately for each study period phase. The two main outcomes of this study were all-cause hospitalisations and all-cause mortality; these outcomes were assessed in all eligible cohorts identified at each period. We also assessed six additional outcomes in all cohorts: (1) cardiovascular disease-related primary hospitalisations (admission or treatment, as required), for which a cardiovascular disease code was present in the primary diagnosis field; (2) cardiovascular disease-related (any) hospitalisations, for which a cardiovascular disease code was present in any position of diagnosis; (3) cardiovascular disease-related primary deaths, for which a cardiovascular disease code was present as the underlying cause of death; (4) cardiovascular disease-related (any) deaths, for which a cardiovascular disease code was present in either the underlying or associated cause of death fields; (5) COVID-19-related hospitalisations; and (6) COVID-19-related deaths (appendix p 2). COVID-19-related outcomes were assessed for the period of 2020–21 using ICD-10 codes U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus not identified), recorded as the primary diagnosis for hospitalisations or as the underlying cause of death. Non-COVID-19-related outcomes were estimated by subtracting COVID-19-related outcomes from all-cause outcomes. For hospitalisation outcomes, multiple admissions occurring within a 28-day period were counted as a single event. Cardiovascular disease-related outcomes were defined as events with ICD-10 diagnosis code related to stroke, peripheral artery disease, coronary heart disease, aortic disease, heart failure, acute myocardial infarction, or transient ischaemic attack. Exposures, outcomes, and covariates definitions were consistent throughout the periods and cohorts we analysed.

Statistical analysis

No formal sample size calculation was conducted due to the descriptive nature of the study. Characteristics of the included individuals in each cohort are presented for each period, overall, and by sex. Baseline cohort characteristics are described as frequency and percentages for categorical variables. Continuous normally distributed variables are presented as mean (SD) and non-normally distributed variables were reported as median (IQR). We also calculated total follow-up duration in person-years and number of events—overall and by age, sex, ethnicity, and deprivation.

See Online for appendix

All individuals meeting eligibility criteria were included in this analysis and had complete data on age and sex. Sex-stratified incidence rates with 95% CIs per 1000 person-years were estimated for all outcomes for each cohort and during each period. We also estimated sex-stratified and age-stratified incidence rates for all outcomes. Overall incidence rates were estimated for the two main outcomes. Sex-stratified unadjusted and age-adjusted Poisson regression models, using logarithm of follow-up time as an offset term, were fitted to obtain incidence rate ratios (IRRs) with 95% CIs comparing 2020–21 with 2018–20 for all outcomes except for those related to COVID-19. Models were fitted separately for each of the three cohorts and for each outcome of interest. To estimate excess hospitalisation and deaths in 2020–21 compared with 2018–20, we first obtained the observed rates (the number of events occurring within the period divided by the total duration of follow-up years) of all-cause hospitalisation and deaths in 2018–20 for each stratum of age (ages <50, 50–59, 60–69, 70–79, and ≥80 years) and sex (male and female). We then estimated the expected number of events in 2020–21 (as observed event rates in 2018–20 multiplied by the total duration of follow-up years in 2020–21) for each stratum. The expected number of events was subtracted from the observed events in 2020–21 to estimate excess or reduced hospitalisation and

death (with 95% CIs estimated assuming a Poisson distribution) during the COVID-19 pandemic. We then converted the excess or reduced numbers to rates per 1000 person-years and extrapolated those rates to the population of England to obtain the corresponding total number for each chronic condition. The population in England in 2020 is based on Quality and Outcomes Framework prevalence data from 2020–2021.

For **Quality and Outcomes Framework prevalence data from 2020 to 2021** see https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2020-21

We performed a post-hoc sensitivity analysis exploring the effect of multiple long-term chronic conditions (MLTCs) at the start of each period on outcomes. We categorised all eligible individuals alive and registered at the start of each period into four groups based on the prevalence of the three chronic conditions at each period: (1) type 2 diabetes plus cardiovascular disease plus chronic kidney disease; (2) type 2 diabetes plus cardiovascular disease; (3) type 2 diabetes plus chronic kidney disease; and (4) cardiovascular disease plus chronic kidney disease; where plus indicates coexisting conditions. We estimated sex-stratified incidence rates of all-cause hospitalisations and mortality for each MLTC group. To address potential overlap between cohorts, we performed a further sensitivity analysis in which individuals were assigned to only one chronic condition (non-overlapping, mutually exclusive cohort) using the following order of priority based on clinical severity and risk of adverse outcomes during the COVID-19 pandemic: (1) chronic kidney disease, (2) cardiovascular disease, and (3) type 2 diabetes. The cohort with chronic kidney disease was unchanged; among those without chronic kidney disease, individuals with cardiovascular disease (with or without type 2 diabetes) were assigned to the cohort with cardiovascular disease. Individuals with type 2 diabetes and no history of chronic kidney disease or cardiovascular disease were assigned to the cohort with type 2 diabetes. We estimated and reported excess (or reduced) hospitalisations and deaths (with 95% CIs) for the newly constructed cohorts with cardiovascular disease and type 2 diabetes (using the same method as described before). We did not conduct this sensitivity analysis for the cohort with chronic kidney disease because the cohort remained unchanged.

All analyses were conducted using Python (version 3.11.5) and R (version 4.2.3). Results are reported using RECORD guidelines for the reporting of studies conducted using observational routinely collected health data (appendix pp 4–8) and the CRISP statement (appendix pp 9–12).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From a total 3 878 582 individuals registered on March 1, 2017, 3 151 412 (81·3%) were aged 18 years or older and 769 551 (19·8%) had linkage to HES APC, ONS, and IMD (figure 1). Among these 769 551 individuals, 113 018 (14·7%) had one or more chronic conditions in 2018–20; 59 169 (7·7%) had type 2 diabetes, 49 754 (6·5%) had cardiovascular disease, and 39 803 (5·2%) had chronic kidney disease in 2018. Individuals could be included in more than one cohort. Characteristics of these cohorts are presented in table 1.[14] In 2018–20, the mean age of individuals in the cohorts with type 2 diabetes, cardiovascular disease, and chronic kidney disease was 64·0 (SD 15·2), 71·9 (13·0), and 76·3 (11·4) years, respectively. Across both time periods, in the cohort with type 2 diabetes, 31 520 (48·6%) of 64 796 individuals were female and 33 276 (51·4%) were male; in the cohort with cardiovascular disease, 22 906 (41·9%) of 54 704 were female and 31 798 (58·1%) were male; and in the cohort with chronic kidney disease, 22 055 (53·0%) of 41 645 were female and 19 590 (47·0%) were male. In 2018–20, the mean duration of condition was higher in the cohort with cardiovascular disease (9·2 [SD 7·9] years) than in the cohorts with type 2 diabetes (8·0 [6·5]) and chronic kidney disease (7·7 [3·9]). In 2020–21, the mean duration of condition was 8·4 [6·7], 9·7 [8·2], and 8·7 [4·5] years for the cohorts with type 2 diabetes, cardiovascular disease, and chronic kidney disease, respectively.

In both 2018–20 and 2020–21, in all three cohorts, most individuals were White and from the least deprived areas, except for those with type 2 diabetes in 2020–21, most of whom were from the most deprived areas (table 1). Overall, the distribution of cohort demographics and comorbidities were similar between the 2018–20 and 2020–21 study periods (table 1). Sex-stratified baseline characteristics for each cohort are shown in the appendix (pp 13–15).

Figure 2 shows overall and sex-stratified crude event rates for all-cause hospitalisations and all-cause mortality in each cohort in 2018–20 and 2020–21, and figure 3 shows overall and sex-stratified unadjusted and age-adjusted IRRs for these outcomes in 2020–21 compared with 2018–20. The total number of individuals, median follow-up duration, total follow-up in person-years, and number of events—overall and by age, sex, ethnicity, and deprivation—are provided in table 1 and the appendix (pp 16–17).

From 2018–20 to 2020–21, rates of all-cause hospitalisations declined from 565 (95% CI 560–570) to 403 (396–410) events per 1000 person-years in those with type 2 diabetes, 734 (728–740) to 552 (543–562) in those with cardiovascular disease, and 762 (755–769) to 608 (595–620) in those with chronic kidney disease. Age-adjusted IRRs for hospitalisations in 2020–21 compared with 2018–20 were 0·73 (95% CI 0·72–0·75) for the cohort with type 2 diabetes, 0·76 (0·75–0·78) for the cohort with cardiovascular disease, and 0·80 (0·78–0·82) for the cohort with chronic kidney disease. All-cause mortality increased between 2018–20 and 2020–21, from 27 (95% CI 26–28) to 31 (29–33) events per 1000 person-years in those with type 2 diabetes, 50 (49–52) to 57 (54–60) in those with cardiovascular disease, and 58 (56–60) to 75 (71–80) in those with chronic kidney disease. The age-adjusted IRRs for all-cause mortality in 2020–21 compared with 2018–20 were 1·22 (95% CI 1·13–1·31) for individuals with type 2 diabetes, 1·17 (1·10–1·24) for individuals with cardiovascular

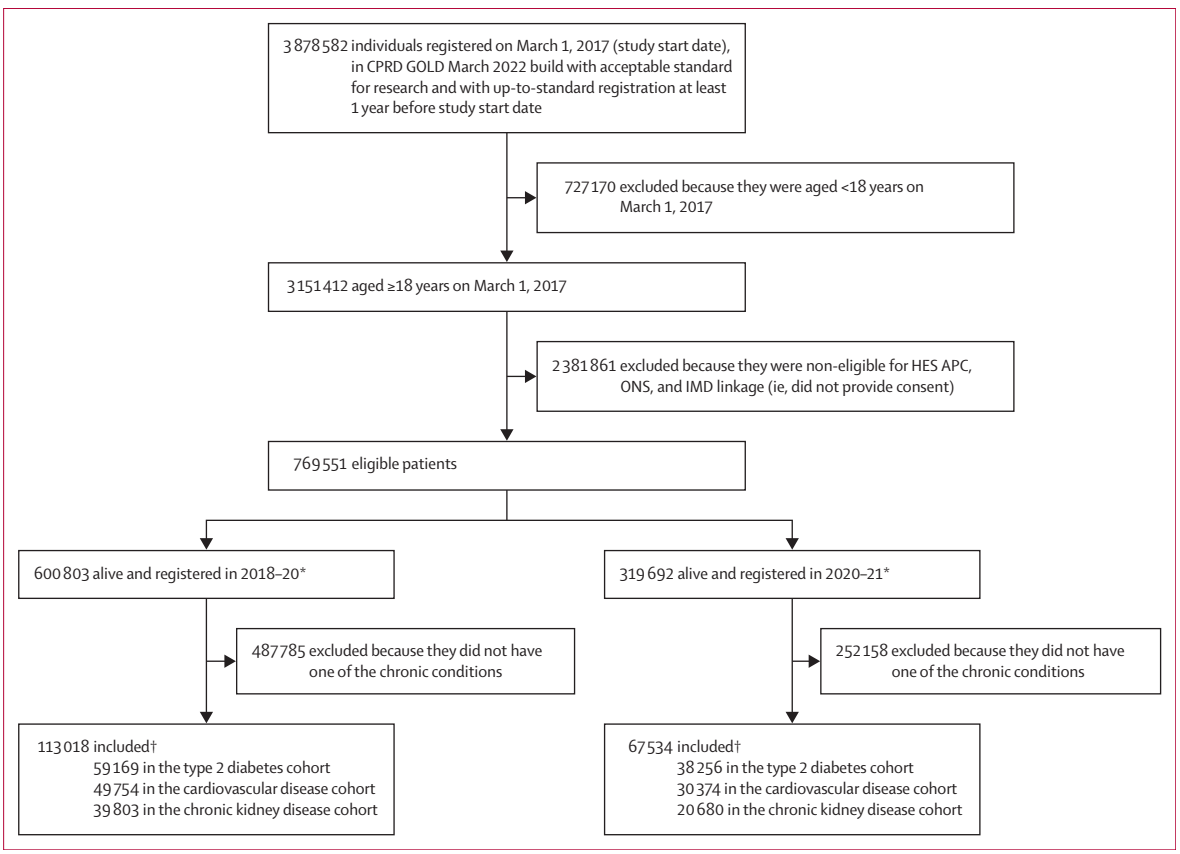

Figure 1: **Study population flow diagram**
CPRD=Clinical Practice Research Datalink. HES APC=Hospital Episode Statistics Admitted Patient Care. IMD=Index of Multiple Deprivation. ONS=Office for National Statistics. *Some patients (n=151 944) contributed data to both periods; therefore, the subgroup totals are not mutually exclusive and do not sum to the overall total. †Groupings were non-exclusive.

disease, and 1·31 (1·22–1·40) for individuals with chronic kidney disease.

From 2018–20 to 2020–21, in the cohort with type 2 diabetes, all-cause hospitalisation rates reduced from 562 (95% CI 555–569) to 413 (403–423) events per 1000 person-years in male participants (adjusted IRR [aIRR] 0·76 [95% CI 0·74–0·78) and from 568 (561–575) to 394 (384–404) events per 1000 person-years in female participants (aIRR 0·71 [0·69–0·73]). All-cause mortality rates, however, increased from 28 (95% CI 27–30) to 33 (30–35) events per 1000 person-years in male participants (aIRR 1·23 [95% CI 1·11–1·36]) and from 26 (25–28) to 29 (27–32) events per 1000 person-years in female participants (aIRR 1·20 [1·08–1·34]; figures 2, 3).

From 2018–20 to 2020–21, in the cohort with cardiovascular disease, all-cause hospitalisations decreased from 704 (95% CI 696–711) to 539 (527–552) events per 1000 person-years in male participants (aIRR 0·78 [95% CI 0·76–0·80]) and from 777 (95% CI 767–787) to 570 (556–586) events per 1000 person-years in female participants (aIRR 0·74 [0·72–0·76]). All-cause mortality rates, however, increased from 46 (95% CI 44–48) to 54 (50–58) events per 1000 person-years in male participants (aIRR 1·22 [95% CI 1·12–1·32]) and from 57 (54–59) to 61 (57–66) events per 1000 person-years in female participants (aIRR 1·12 [1·02–1·22]; figures 2, 3).

From 2018–20 to 2020–21, in the cohort with chronic kidney disease, all-cause hospitalisations also decreased from 815 (95% CI 804–826) to 654 (636–673) events per 1000 person-years in male participants (aIRR 0·80 [95% CI 0·78–0·83) and from 718 (709–727) to 561 (544–578) events per 1000 person-years in female participants (aIRR 0·78 [95% CI 0·76–0·81]). All-cause mortality rates, however, increased from 62 (95% CI 59–65) to 77 (71–84) events per 1000 person-years in male participants (aIRR 1·25 [95% CI 1·14–1·38]) and from 54 (52–57) to 73 (67–79) events per 1000 person-years in female participants (aIRR 1·36 [1·23–1·49]; figures 2, 3).

Across all three cohorts, cardiovascular disease-related hospitalisation (both in primary and any position of diagnosis) declined during 2020–21 compared with 2018–20 (appendix pp 18–19). However, the highest relative increase in cardiovascular disease-related deaths (in any position of diagnosis) was observed in in male and female participants with chronic kidney disease (appendix p 20). Incidence rates of COVID-19-related and non-COVID-19-related

	Eligible cohort on March 1, 2018			Eligible cohort on March 1, 2020		
	Type 2 diabetes (n=59 169)	Cardiovascular disease (n=49 754)	Chronic kidney disease (n=39 803)	Type 2 diabetes (n=38 256)	Cardiovascular disease (n=30 374)	Chronic kidney disease (n=20 680)
Age at start date, years	64·0 (15·2)	71·9 (13·0)	76·3 (11·4)	64·4 (14·9)	72·0 (12·8)	77·0 (11·1)
Age group at start date, years						
18–44	6341 (10·7%)	1324 (2·7%)	384 (1·0%)	3835 (10·0%)	742 (2·4%)	168 (0·8%)
45–64	22 307 (37·7%)	12 004 (24·1%)	5460 (13·7%)	14 587 (38·1%)	7357 (24·2%)	2678 (12·9%)
65–74	14 786 (25·0%)	13 741 (27·6%)	9731 (24·4%)	9470 (24·8%)	8321 (27·4%)	4724 (22·8%)
≥75	15 735 (26·6%)	22 685 (45·6%)	24 228 (60·9%)	10 364 (27·1%)	13 954 (45·9%)	13 110 (63·4%)
Sex						
Male	30 419 (51·4%)	28 994 (58·3%)	18 097 (45·5%)	19 550 (51·1%)	17 637 (58·1%)	10 150 (49·1%)
Female	28 750 (48·6%)	20 760 (41·7%)	21 706 (54·5%)	18 706 (48·9%)	12 737 (41·9%)	10 530 (50·9%)
Age at diagnosis, years	55·7 (14·7)	62·4 (14·0)	68·4 (11·5)	55·7 (14·6)	62·0 (13·9)	67·9 (11·3)
Duration of condition, years	8·0 (6·5)	9·2 (7·9)	7·7 (3·9)	8·4 (6·7)	9·7 (8·2)	8·7 (4·5)
Follow-up duration, years	2·0 (1·3–2·0)	2·0 (1·2–2·0)	2·0 (1·2–2·0)	1·0 (0·5–1·0)	1·0 (0·5–1·0)	1·0 (0·5–1·0)
Race or ethnicity*						
White	47 717 (80·6%)	45 426 (91·3%)	35 101 (88·2%)	30 797 (80·5%)	27 633 (91·0%)	18 091 (87·5%)
South Asian	3459 (5·8%)	1441 (2·9%)	825 (2·1%)	2310 (6·0%)	905 (3·0%)	455 (2·2%)
Black	1895 (3·2%)	683 (1·4%)	970 (2·4%)	1019 (2·7%)	348 (1·1%)	407 (2·0%)
Mixed or other	2567 (4·3%)	1147 (2·3%)	746 (1·9%)	1686 (4·4%)	761 (2·5%)	425 (2·1%)
Missing	3531 (6·0%)	1057 (2·1%)	2161 (5·4%)	2444 (6·4%)	727 (2·4%)	1302 (6·3%)
IMD quintile						
1 (least deprived)	13 645 (23·1%)	12 544 (25·2%)	10 908 (27·4%)	7900 (20·7%)	6637 (21·9%)	4981 (24·1%)
2	11 696 (19·8%)	10 333 (20·8%)	8945 (22·5%)	7209 (18·8%)	5996 (19·7%)	4465 (21·6%)
3	11 903 (20·1%)	10 121 (20·3%)	8118 (20·4%)	7889 (20·6%)	6395 (21·1%)	4416 (21·4%)
4	10 579 (17·9%)	8480 (17·0%)	6458 (16·2%)	7169 (18·7%)	5414 (17·8%)	3595 (17·4%)
5 (most deprived)	11 330 (19·1%)	8264 (16·6%)	5369 (13·5%)	8083 (21·1%)	5926 (19·5%)	3222 (15·6%)
Missing	16 (<0·0%)	12 (<0·0%)	5 (<0·0%%)	6 (<0·0%)	6 (<0·0%)	1 (<0·0%)
Smoking status						
Smoker	8721 (14·7%)	7819 (15·7%)	3674 (9·2%)	6053 (15·8%)	5255 (17·3%)	2322 (11·2%)
Non-smoker	19 116 (32·3%)	12 117 (24·4%)	11 177 (28·1%)	12 100 (31·6%)	7524 (24·8%)	6072 (29·4%)
Ex-smoker	14 578 (24·6%)	13 872 (27·9%)	10 013 (25·2%)	9337 (24·4%)	8295 (27·3%)	5245 (25·4%)
Missing	16 754 (28·3%)	15 946 (32·0%)	14 939 (37·5%)	10 766 (28·1%)	9300 (30·6%)	7041 (34·0%)
Comorbidities						
Cardiovascular disease	14 839 (25·1)	..	14 322 (36·0)	10 076 (26·3)	..	8113 (39·2)
Chronic kidney disease	11 872 (20·1)	14 322 (28·8)	..	6955 (18·2)	8113 (26·7)	..
Type 2 diabetes	..	14 839 (29·8)	11 872 (29·8)	..	10 076 (33·2)	6955 (33·6)
Hypertension	36 262 (61·3)	36 732 (73·8)	31 032 (78·0)	23 220 (60·7)	22 689 (74·7)	16 384 (79·2)

Data are mean (SD), n (%), or median (IQR). IMD=Index of Multiple Deprivation. *Categories defined as per previous literature.[14]

Table 1: **Characteristics of people with type 2 diabetes, cardiovascular disease, and chronic kidney disease, by study period**

hospitalisations and deaths varied by cohort and sex in 2020–21, with the highest COVID-19-related rates observed among individuals with chronic kidney disease (appendix p 21). The lowest COVID-19-related rates were seen in the cohort with type 2 diabetes, particularly among female participants. Within-subgroup data are shown in the appendix and similar results were observed (pp 22–24).

Baseline characteristics of the cohorts in the sensitivity analysis of individuals with MLTCs are shown in the appendix (p 25). All-cause mortality was highest in male and female participants with a combination of type 2 diabetes, cardiovascular disease, and chronic kidney disease, followed by individuals with both cardiovascular disease and chronic kidney disease in both study periods. Declines in hospitalisation rates between 2018–20 and 2020–21 were observed within all groups, but remained highest in those with all three chronic conditions (appendix p 26).

Observed, expected, and excess or reduced rates of all-cause hospitalisations and deaths in 2018–20 and 2020–21 for the three cohorts are reported in table 2 and the appendix (pp 27–28). In 2020–21, compared with 2018–20, there were 214 (95% CI 185–243) excess deaths in the cohort with type 2 diabetes (rate increase 7·0 events per 1000 person-years [95% CI 6·1–7·9]), 267 (235–299) excess deaths in the cohort with cardiovascular disease (rate increase 11·3 events per 1000 person-years [95% CI 9·9–12·6]), and 296 (262–330) excess deaths in the cohort with chronic kidney disease (rate increase 19·8 events per

1000 person-years [17·6–22·1]; table 2). Hospitalisation declined across all three cohorts, with the highest rate of reduction observed in individuals with cardiovascular disease (table 2). Extrapolating from our CPRD cohort in England to the whole population of England with these conditions—and acknowledging that, due to the overlap between these cohorts, the excess deaths could not be summed to give an accurate overall estimate for the study population—we estimated that the number of excess deaths were 24 443 (95% CI 21 300–27 586), 37 304 (32 682–41 595), and 37 959 (33 741–42 368) in the cohorts with type 2 diabetes, cardiovascular disease, and chronic kidney disease, respectively, in 2020–21 (table 2). In our sensitivity analysis restricting to a single chronic condition (non-overlapping, mutually exclusive cohort), there were 24 593 individuals in the cohort with type 2 diabetes and 22 261 individuals in the cohort with cardiovascular disease in 2020–21. There were no changes to the cohort chronic kidney disease. Baseline characteristics were broadly similar with the original cohorts, except for age, which was lower in the restricted cohorts with type 2 diabetes and cardiovascular disease than in the original cohorts (appendix p 29). Estimated excess all-cause deaths were 8380 (95% CI 5936–10 476) in the restricted cohort with type 2 diabetes and 20 467 (16 506–24 099) in the restricted cohort with cardiovascular disease in 2020–21 (appendix p 30).

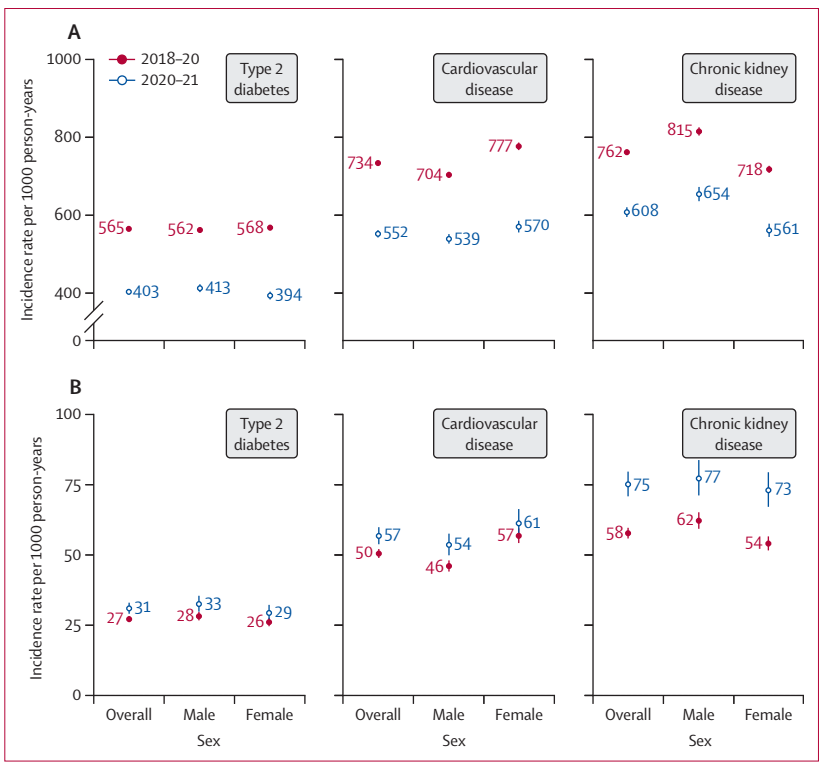

Figure 2: **Sex-stratified crude incidence rates of all-cause hospitalisation (A) and all-cause mortality (B) for cohorts with type 2 diabetes, cardiovascular disease, and chronic kidney disease in 2018–20 and 2020–21**
Incidence rates are reported per 1000 person-years for the study periods 2018–20 and 2020–21. Bars indicate 95% CIs, with point estimates provided on each datapoint.

Discussion

This study examined overall and sex-specific differences in all-cause hospitalisations and mortality across three cohorts of people with type 2 diabetes, cardiovascular disease, or chronic kidney disease, comparing 2020–21 (COVID-19 pandemic period) with 2018–20 (pre-pandemic period), with several findings: (1) a general decrease in hospitalisations across all cohorts and in both male and female individuals, whereas mortality rates generally increased, particularly all-cause mortality; (2) the largest reductions in all-cause hospitalisation rates during 2020–21 were in female individuals with type 2 diabetes or cardiovascular disease; (3) among individuals with chronic kidney disease, increases in all-cause mortality in both male and female participants were most substantial compared with the other chronic conditions, with the highest relative increase observed in female participants during the pandemic years; and (4) in 2020–21, substantial excess mortality was observed across all three cohorts, with estimated total excess all-cause deaths (after extrapolation to the general English population) in two cohorts (with cardiovascular disease and chronic kidney disease) both exceeding 37 000 compared with pre-pandemic mortality.

The observed reduction in hospitalisation rates alongside increased mortality is consistent with previously published evidence on the effects of the COVID-19 pandemic.[15–19] For example, a study in Spain reported a decline in hospital admissions for acute myocardial infarction, possibly due to delays in seeking care followed by increased in-hospital mortality during the pandemic.[19] However, most previous studies have focused primarily on the overall population or single disease states.[15–19] Our study expands on these findings by examining sex-specific differences across three predominant chronic conditions that were major risk factors for COVID-19. Our sensitivity analysis examining individuals with MLTCs also revealed that all-cause mortality was highest among those with coexisting type 2 diabetes, cardiovascular disease, and chronic kidney disease for both study periods, followed by those with both cardiovascular disease and chronic kidney disease. This gradient of mortality risk highlights the cumulative burden of chronic conditions, particularly during periods of health-care system strain such as during the COVID-19 pandemic.

In our study, hospitalisations (all-cause or cardiovascular-related) generally decreased less in individuals with chronic kidney disease than in those with type 2 diabetes and cardiovascular disease, yet mortality was substantially higher in the cohort with chronic kidney disease, suggesting that individuals with chronic kidney disease were disproportionately vulnerable during the pandemic. However, the increase in mortality rates during the pandemic was largely attributable to COVID-19 being recorded as the underlying cause of death, which suggests that direct effects of COVID-19 illness played a major role in excess mortality. Several factors could explain the higher COVID-19-related mortality and excess all-cause mortality in the cohort with chronic kidney disease. Although chronic kidney disease

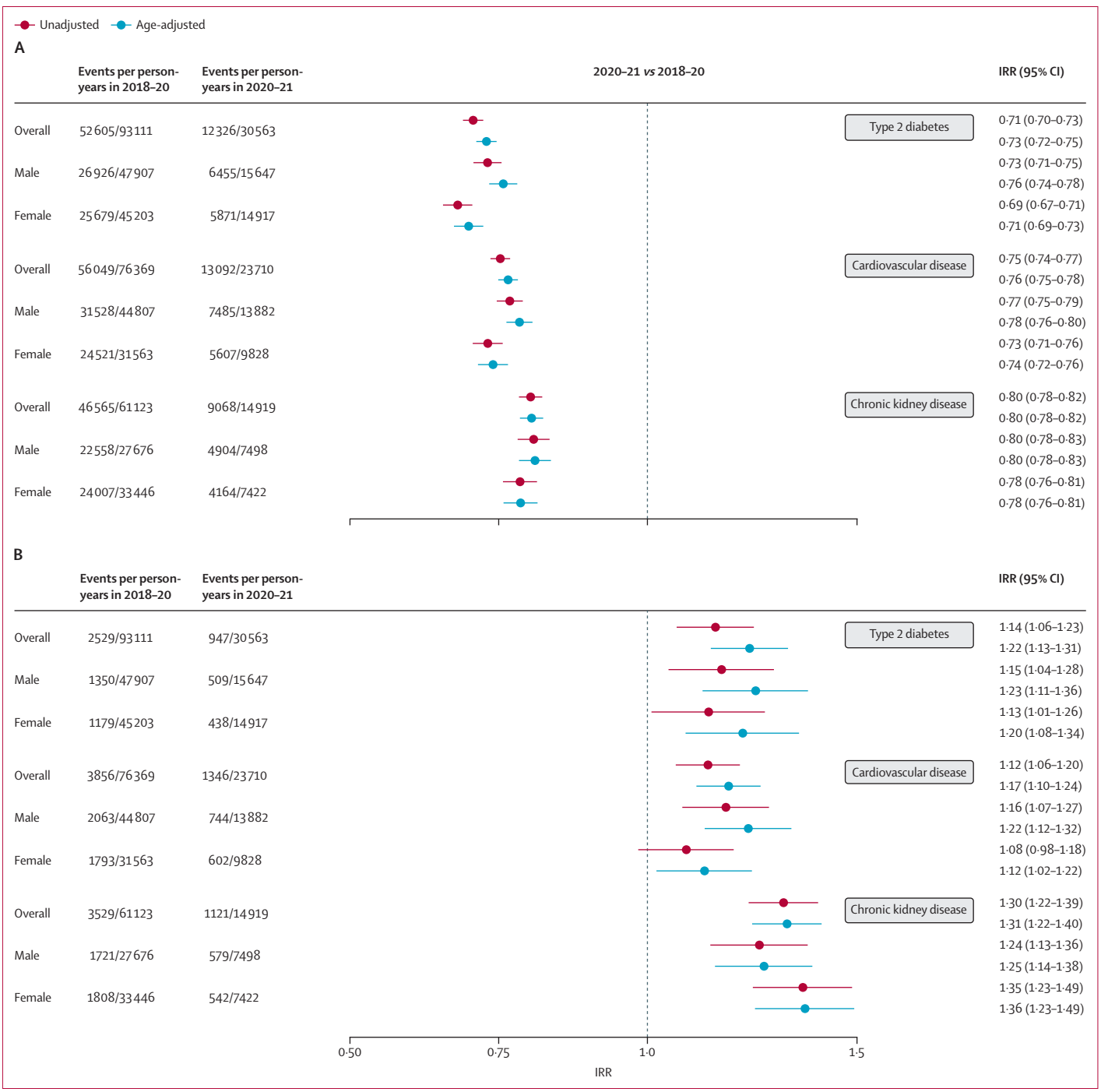

***Figure 3*: Unadjusted and age-adjusted IRRs of all-cause hospitalisation (A) and all-cause mortality (B) in 2020–21 compared with 2018–20 for cohorts with type 2 diabetes, cardiovascular disease, and chronic kidney disease, overall and stratified by sex**

Poisson models were used to estimate IRRs and 95% CIs of all-cause hospitalisations and mortality. Rate ratios were adjusted for the age of the patients included in the cohort and presented on a log scale on the x axis. IRR=incidence rate ratio.

includes a wide spectrum of severity, even a moderately severe stage is associated with poor outcomes after COVID-19 illness.[20] Unlike type 2 diabetes or cardiovascular disease, chronic kidney disease often requires in-person care, particularly for people on dialysis, increasing exposure risk to SARS-CoV-2.[21] Moreover, individuals with chronic kidney disease have impaired adaptive immunity and chronic inflammation, which further increases their

	Number of patients	Total follow-up, person-years	Follow-up duration, median years (IQR)	Number of reduced hospital admissions in 2020–21 *vs* 2018–20 (95% CI)	Rate reduction of hospital admissions in 2020–21 *vs* 2018–20 per 1000 person-years (95% CI)	Number of excess deaths in 2020–21 *vs* 2018–20 (95% CI)	Excess death rate in 2020-21 *vs* 2018-20 per 1000 person-years (95% CI)	Population in England in 2020*	Estimated total excess deaths in England in 2020 (95% CI)
Type 2 diabetes	38 256	30 563	1·0 (0·5–1·0)	4303 (4181–4438)	141 (137–145)	214 (185–243)	7·0 (6·1–7·9)	3 491 868	24 443 (21 300–27 586)
Cardiovascular disease	30 374	23 710	1·0 (0·5–1·0)	3881 (3766–4011)	164 (159–169)	267 (235–299)	11·3 (9·9–12·6)	3 301 208	37 304 (32 682–41 595)
Chronic kidney disease	20 680	14 919	1·0 (0·5–1·0)	2258 (2160–2346)	151 (145–157)	296 (262–330)	19·8 (17·6–22·1)	1 917 102	37 959 (33 741–42 368)

*Population with type 2 diabetes represents number of patients aged 17 years or older with diabetes recorded on practice disease register; population with cardiovascular disease represents number of patients with coronary heart disease, peripheral arterial disease, stroke, or transient ischaemic attack recorded on practice disease register; and population with chronic kidney disease represents number of patients aged 18 years or older with chronic kidney disease with classification of categories G3a to G5 (previously stage 3 to 5).

Table 2: **Age-adjusted and sex-adjusted differences in all-cause hospitalisations and all-cause deaths in 2020–21 compared with 2018–20 for type 2 diabetes, cardiovascular disease, and chronic kidney disease cohorts**

risk of severe COVID-19 complications.[22] Overall, our findings highlight the complexity of managing chronic kidney disease care and the need for targeted protection of these individuals during public health emergencies.

Increases in all-cause mortality and cardiovascular disease-related mortality rates appeared to be slightly higher in male participants with type 2 diabetes or cardiovascular disease than in female participants with these conditions. However, the reductions in all-cause hospitalisation rates were greater in female individuals than in male individuals with these conditions. This difference could reflect differences in health-care-seeking behaviour during the pandemic, with some evidence suggesting that female individuals were more likely to defer or avoid hospital care due to concerns about COVID-19 exposure or caregiving responsibilities.[23] Evidence also suggests that male individuals are more likely to have severe outcomes from COVID-19 than female individuals in the UK.[24] The increased mortality risk in male individuals could be partly attributed to differential risk exposure and immune response (eg, due to sex hormones).[25]

Our findings of higher crude rates of cardiovascular disease-related mortality in male individuals with chronic kidney disease than in female individuals, both before and after the COVID-19 pandemic, align with previous studies.[26] However, in our age-adjusted analysis, female participants with chronic kidney disease had the highest relative increase in all-cause mortality during the pandemic. This finding highlights a crucial vulnerability in this subgroup during a public health crisis and adds to the limited literature exploring sex-specific outcomes in chronic kidney disease. Generally, female individuals face disparities in chronic kidney disease diagnosis, treatment, and transplant access, despite reporting a higher symptom burden and poorer quality of life than male individuals.[27] This disparity in baseline care could have been exacerbated during the pandemic, leading to more severe outcomes for female participants.

Our study estimates notably high rates of excess deaths during 2020–21. By comparison, two previous studies reported 85 000 and 62 000 excess deaths in England and Wales, equating to 1·5 and 1·0 deaths per 1000 person-years, respectively.[28,29] The studies represent the broader population (ie, individuals with or without chronic conditions), whereas our analysis focuses on those with cardiorenal–metabolic conditions who are inherently at increased risk of severe COVID-19 outcomes including mortality and had substantial health-care disruptions during the pandemic. A previous study in England estimated that excess deaths in individuals with cardiovascular disease during the pandemic could range from 31 205 to 62 410, depending on the severity of disruptions to health-care services.[30] Similarly, another study in England predicted 28 746 and 24 546 (using the NHS Digital Trusted Research Environment national dataset and CPRD data, respectively) excess deaths compared with 34 265 observed excess deaths among individuals with chronic kidney disease.[31] These findings align closely with our excess death estimates (ie, extrapolation to the full English population) in the cohorts with cardiovascular disease and chronic kidney disease, emphasising the substantial burden in these groups. Our study adds to the existing literature by providing a comprehensive picture of the pandemic's impact on populations with chronic diseases by sex. Our findings could help inform forecasting the direct and indirect impacts of overwhelmed health systems during crises such as pandemics, seasonal viral surges such as respiratory syncytial virus or influenza, and similar disruptions. There is an urgent need for investing in preparedness strategies and resilient health systems that can safeguard continuity of care for vulnerable individuals with chronic conditions during future pandemics.

The strengths of our study include a large cohort, which improves the precision of our estimates and allows for robust subgroup analyses by sex and disease type. Furthermore, the CPRD GOLD database, alongside linked hospital admissions and mortality data, are highly representative of the English population, which strengthens the completeness and validity of our findings. Although the results are largely applicable to the context of England, their generalisability to other countries might vary depending on health-care systems, chronic disease burdens, and pandemic-response strategies.

Several limitations should also be noted. First, hospitalisation data in HES could be incomplete if patients received care outside the typical NHS settings or if hospital admission records were missed due to system delays or reporting issues. Second, we analysed the first year of the COVID-19 pandemic as a single study period, although the pandemic had distinct waves that varied over time and by region. These differences could have influenced access to care and mortality outcomes. Third, we did not have data on gender; sex data were self-reported, and we assumed that this referred to sex assigned at birth. We were also not able to account for differences in disease severity due to the absence of these data in primary care records. Finally, our study was largely descriptive and therefore cannot establish causation. Nonetheless, our findings were consistent and are informative.

Overall, our study showed the major and differential effect of the COVID-19 pandemic on hospitalisation and mortality in male and female participants with type 2 diabetes, cardiovascular disease, and chronic kidney disease. To improve resilience in future crises, health policies should focus on ensuring uninterrupted access to essential care for those most vulnerable to both direct and indirect health risks.

Contributors

SSh contributed to study design, data collection and cleaning, statistical analysis, and writing of the manuscript. CLG, FZ, NI, and KK contributed to study design, statistical analysis, writing of the manuscript, and critical revision for important content. All authors contributed to interpretation of the data, critical review, and final approval of the manuscript. CLG and SSh had full access to all data, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

KK has been a consultant for Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Novo Nordisk, Sanofi, Servier, Pfizer, Roche, Daiichi-Sankyo, Embecta, and Nestle Health Science; has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Lilly, Merk, Novo Nordisk, Roche, Sanofi, Servier, Oramed Pharmaceuticals, Roche, Daiichi-Sankyo, and Applied Therapeutics; and was in a speakers bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Merk, Novo Nordisk, Sanofi, Servier, and Roche. All other authors declare no competing interests.

Data sharing

The data controller for the UK Clinical Practice Research Datalink (ie, the Department of Health and Social Care) does not allow sharing of raw data with third parties. Researchers can apply for data access online (https://www.cprd.com/research-applications). The statistical code is available on request from the first author (SSh; ss1279@leicester.ac.uk). Phenotypes used to define the cohort, medical conditions, and ethnicity are available online (https://github.com/shabnam-shbd/risk_factor_control_during_covid19).

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