Vaccinations, cardiovascular drugs, hospitalisation and mortality in COVID-19 and Long COVID.

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Highlights

- Hospitalisation and mortality rates in COVID-19 and Long COVID were comparable.
- Risk of mortality and hospitalisation were reduced with full COVID-19 vaccination.
- With influenza vaccination, mortality was reduced, but not hospitalisation.
- Mortality and hospitalisation were reduced by CVD prevention in those with CVD.
- Targeted COVID-19 vaccination and CVD prevention are priority interventions.

Vaccinations, cardiovascular drugs, hospitalisation and mortality in COVID-19 and Long COVID.

Running title: Vaccinations/cardiovascular drugs in COVID-19/Long COVID

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Abstract

Objective

To identify highest-risk subgroups for COVID-19 and Long COVID(LC), particularly in contexts of influenza and cardiovascular disease(CVD).

Methods

Using national, linked electronic health records for England(NHS England Secure Data Environment via CVD-COVID-UK/COVID-IMPACT Consortium), we studied individuals(of all ages) with COVID-19 and LC (2020-2023). We compared all-cause hospitalisation and mortality by prior CVD, high CV risk, vaccination status(COVID-19/influenza), and CVD drugs, investigating impact of vaccination and CVD prevention using population preventable fractions.

Results

Hospitalisation and mortality were 15.3% and 2.0% among 17,373,850 individuals with COVID-19(LC rate 1.3%), and 16.8% and 1.4% among 301,115 with LC.

Adjusted risk of mortality and hospitalisation were reduced with COVID-19 vaccination≥2 doses(COVID-19:HR 0.36 and 0.69; LC:0.44 and 0.90). With influenza vaccination, mortality was reduced, but not hospitalisation(COVID-19:0.86 and 1.01, and LC:0.72 and 1.05). Mortality and hospitalisation were reduced by CVD prevention in those with CVD, e.g. anticoagulants- COVID:19:0.69 and 0.92; LC:0.59 and 0.88; lipid lowering- COVID-19:0.69 and 0.86; LC:0.68 and 0.90. COVID-19 vaccination averted 245044 of 321383 and 7586 of 8738 preventable deaths after COVID-19 and LC, respectively.

Interpretation

Prior CVD and high CV risk are associated with increased hospitalisation and mortality in COVID-19 and LC. Targeted COVID-19 vaccination and CVD prevention are priority interventions.

Funding

NIHR. HDR UK.

INTRODUCTION

Healthcare challenges typically occur together, rather than in isolation, but have not tended to be investigated and modelled as “compound pressures”(1). In the UK, pressures due to COVID-19, influenza and impact on chronic disease risk and care(including cardiovascular disease, CVD) have been highlighted, especially during winter(2–4). COVID-19 and influenza can have direct(e.g. hospitalisation) and longer-term(e.g. Long COVID, LC) health effects. Moreover, chronic diseases can be both risk factors and outcomes in both COVID-19 and influenza(5). For example, high cardiovascular(CV) risk, even in absence of diagnosed CVD, is associated with high risk of respiratory and CVD events following acute respiratory infection(6). Respiratory viruses also carry a significant triggering effect for CVD. Risks for all-cause mortality, readmission, or death due to initial infection were higher for COVID-19-related than influenza-related hospital admissions(7). However, interplay of COVID-19 and influenza is poorly studied across direct and long-term COVID-19 effects.

Influenza and COVID-19 vaccinations have different mechanisms, respectively targeting the hemagglutinin surface protein(preventing viral attachment and entry into host cells) and the spike protein(generating neutralizing antibodies and stimulating T cell responses). Our parsimonious model to predict excess COVID-19 mortality has been validated(in overall and specific at-risk populations) and used to inform COVID-19 vaccination strategies, with potential utility in influenza vaccination(8). Different pandemic waves, concurrent influenza circulation and differing vaccination rates are not incorporated in this model. Vaccinations for COVID-19(9) and influenza(10)(to reduce infection mortality risk) and CVD prevention(to reduce baseline and post-infection CV risk by, for example, optimal hypertension management(11), lipid-lowering(12) and increased rates of anticoagulation for atrial fibrillation(13)) are major mitigation approaches but have not been studied together, nor has their potential impact been modelled in different subgroups. Interventions can be compared by use of measures such as the “averted” fraction of population(AFP), the proportion of reduction in mortality or hospitalisation attributable to a population-level intervention(14). Further research is required to understand optimal strategies to reduce morbidity and mortality in acute and chronic post-COVID-19 phases.

We examined how direct and long-term effects of COVID-19 are affected by underlying CV risk, influenza and COVID-19 vaccinations, and prior CVD prevention drugs.

Objectives

In individuals with COVID-19(direct effects) and individuals with LC(long-term effects) in the context of compound health pressures in England, we studied:

1. baseline characteristics by prior CVD and high CV risk
2. highest risk groups for hospitalisation and mortality
3. impact of COVID-19 and influenza vaccinations(individually and combined) and CVD prevention drugs on hospitalisation and mortality.

MATERIALS AND METHODS

Data resources

We conducted a population-based, matched cohort study using English linked national data accessed in NHS England's Secure Data Environment(SDE) service and made available via the British Heart Foundation(BHF) Data Science Centre's CVD-COVID-UK/COVID-IMPACT Consortium: primary care General Practice Extraction Service(GPES) Data for Pandemic Planning and Research(GDPPR), Hospital Episode Statistics Admitted Patient Care(HES APC), COVID-19 datasets(SGSS, CHESS, Pillar II, and HES APC), COVID-19 vaccination, and mortality(Office for National Statistics, ONS, Civil Registration of Deaths)(**Figure S1**). Data were linked at individual level by NHS England using pseudonymised transformation of the NHS number, a unique ten-digit patient identifier used in UK healthcare, assigned at birth or at first interaction. Ethical approval was by North-East-Newcastle and North Tyneside 2 research ethics committee(REC No 20/NE/0161)(15).

Study population:

We included general practice(GP)-registered individuals alive on study start date(1 Jan 2020) without age restrictions and: (i)COVID-19 by confirmed positive test(1 Jan 2020-1 Feb 2023), (ii)LC by coding(1 Apr 2020-1 Feb 2023). COVID-19 test status was extracted from HES data(Admitted Patient Care, Adult Critical Care, Outpatients, Emergency Care Data set, APC Maternity file), COVID-19 Second Generation Surveillance System(SGSS) Pillar 1 and Pillar 2; ONS death registration records, and COVID-19 Hospitalisation in England Surveillance System(CHESS). Unspecified COVID-19 diagnosis (e.g. unconfirmed records in Pillar II, and ICD-10 U04.9:unspecified SARS, excluding COVID-19) was excluded. LC was identified using SNOMED concepts(16) in primary care(**Table S1**), but did not require COVID-19 coding, due to changing availability of COVID-19 testing throughout the pandemic. Subgroups were CVD (composite of heart failure, acute myocardial infarction, cardiomyopathy, atrial fibrillation, deep vein thrombosis, peripheral arterial disease, coronary heart disease, and any stroke(non-specified, ischaemic,

haemorrhagic, transient ischaemic attack, or subarachnoid haemorrhagic) and “High CV risk”(by recorded QRISK-2 score ≥10, i.e. 10-year CVD risk≥10%)(17). There was no overlap between High-risk CV and CVD subgroups. The High-risk CV group did not have any history of CVD disease by the index date.

Phenotypes

Definitions were by reusable, validated algorithms in the CALIBER phenotyping library and GitHub(https://github.com/BHFDSC/CCU003_03/tree/main/phenotypes), using both ICD-10 codes(secondary care) and SNOMED concepts(primary care(18), and consistent with prior studies(15)16,18]. Having an underlying condition was defined by at least 1-year history prior to index date(earliest date of COVID-19 and LC diagnoses respectively). LC codes was recorded in primary care based on WHO and NICE guidelines, ensuring a minimum of 12 weeks had elapsed since a positive SARS-CoV-2 test result. Smoking status and NHS Integrated Care System(ICS) regions were by most recent record in 5 and 10 years prior to index date, respectively. Morbid obesity was body mass index>40 kg/m^2. Diabetes(all diabetes mellitus subtypes), cancer(skin and non-skin cancers) and chronic kidney disease(including stages 1-3) were as per prior studies(https://github.com/BHFDSC/CCU003_01/tree/main/phenotypes)(19).

Exposures and Controls

Standard definitions were used for full COVID-19(≥2 doses with 14-day window for vaccination effect) and influenza(≥1 doses within 1 year from index date) vaccination. Unvaccinated individuals received no vaccinations in the study period. Individuals receiving only 1 COVID-19 vaccination dose prior to index date and no other doses during the study period were excluded from relevant analyses. Antihypertensive, lipid-lowering, antiplatelet and anticoagulant drugs were recorded for ≥2 prescriptions in the last 2 years and ≥1 prescription in the year prior to index date. Dispensed data were unavailable. Control groups were unvaccinated/untreated for the relevant vaccination/drug.

Outcomes

All-cause(earliest) hospitalisation and mortality were recorded after index date.

Statistical Analysis

We conducted “exposed versus control” matched and adjusted analyses in cohorts(**Table S2**), using published methods(20,21)**.** Exact matching(with replacement) was based on covariates with highest standardised difference(>0.1) between exposed and control groups. Distributional plot, matching coverage rate, and differences between adjusted and unadjusted analyses were considered for quality of matching. In matched and adjusted analyses, we controlled for: history of relevant conditions(atrial fibrillation, cancer, hypertension and Type 1 or 2 diabetes), sociodemographic factors(including 9 NHS regions; age; sex; index of multiple deprivation, IMD, by five levels from least deprived to most deprived areas; and ethnicity-5 categories: White, Black/Black British, Asian/Asian British, Other, Mixed), influenza vaccination, full COVID-19 vaccination, and seasonal variation by index year(2020-2023). Where the exposure was one of 4 classes of CVD drugs, we included the other 3 drug classes in matching to ensure comparability of the exposed group(**Figures S5-S11**).

In COVID and LC cohorts(and subgroups) for vaccination(influenza, COVID-19, COVID-19 in addition to influenza) and four classes of CVD drugs(antihypertensive, lipid-lowering, antiplatelet and anticoagulant: individually, and those taking ≥1 and all 4 drugs)(**Figure S1**), we analysed:(a)baseline characteristics, (b)2-year all-cause mortality and hospitalisation: Kaplan-Meier estimates and adjusted/unadjusted hazard ratios(Cox proportional hazard models in matched and overall cohorts) incorporating clustering by individual ID to account for reinfection, and (c)AFP due to treatment(using population preventable risk[15] and relative risk (generalized linear model, GLM, with Poisson distribution, **Supplementary Methods**).

All analyses used complete data. Missing ethnicity was treated as "unknown". As a secondary objective, we investigated new diagnoses of common acute and chronic conditions following COVID-19 and LC diagnosis in individuals with incident and prevalent disease(at least one diagnosis within a year prior to index date). Pre-specified analyses were published(https://github.com/BHFDSC/CCU060_01).

Role of the funding source
Funders had no role in study design, data collection, analysis, interpretation, or writing. AD, CT, LP, and MAM had full data access. AB had final responsibility for submission.

RESULTS

Overall by pre-existing CVD and high CV risk

We identified 17,373,850 individuals(mean age 38.7 years; 54.4% female; mean follow-up 1.28 years, 95% CI 0.99-1.52) with COVID-19(pre-existing CVD:1,005,780 and high CV risk:370,160) and 301,115 individuals(mean age 46.0 years; 61.8% female; mean follow-up 1.1 years, 0.81-1.10) with LC(pre-existing CVD:26,775 and high CV risk:12,305). Overall, 22.4% and 7.6% of individuals with COVID-19 and LC were 0-19 years old. Overall, LC was more common in IMD1(most deprived) vs IMD5(least deprived), but not COVID-19(**Table 1**). There was geographic variation in the proportion of COVID-19 and LC, with highest in Northwest and London regions for overall, CVD and high CV risk populations(**Table S3**). Influenza vaccination rates were highest in high CV risk and CVD than the overall population in COVID-19(56.6% and 55.2% vs 27.8%) and LC groups(58.4% and 55.8% vs 33.1%), with similar patterns for COVID-19 vaccination(72.7% and 63.8% vs 50.0% in COVID-19; 78.4% and 70.5% vs 66.4% in LC)(**Table 1**). 5.8% and 8.9% of COVID-19 and LC groups, respectively, had CVD, most commonly atrial fibrillation, coronary heart disease and heart failure. In COVID-19 and LC groups, CV risk factors and other diseases were more common in those with CVD than those with high CV risk(**Table 1**).

Highest risk groups for hospitalisation and mortality

LC occurred in 1.3% of those with COVID-19(CVD:1.7%; high CV risk:2.1%). Hospitalisation and mortality were high in COVID-19(CVD:49.1% and 21.1%; high CV risk:27.1% and 3.6%) and LC(CVD:37.9% and 9.4%; high CV risk:21.7% and 1.8%). Time between first positive COVID-19 test and LC-related hospitalisation was a mean of 417 days(median 391, range 85-1070). Pre- and post-COVID-19 comorbidity burden was high in people with and without CVD. In people with LC, 8.3% and 4.2% of CVD and high CV risk groups, respectively, developed incident

CVD, corresponding to 8.5% and 4.0% in people with COVID-19. After COVID-19 and LC diagnosis, heart failure, atrial fibrillation and acute MI were most common in CVD and high CVD risk, respectively(**Table S4**).

Risk of mortality and hospitalisation associated with vaccination and CVD prevention

In adjusted, matched analyses, COVID-19 vaccination was associated with reduced mortality(all:HR 0.36,0.34-0.38; CVD:0.39,0.36-0.43; and high CV risk:0.29,0.25-0.34) and hospitalisation(all:0.69,0.68-0.69; CVD:0.60,0.59-0.60; and high CV risk:0.55,0.54-0.56) in individuals with COVID-19. The same was true in LC for mortality(all:0.44,0.42-0.47; CVD:0.47,0.46-0.49; and high CV risk:0.49,0.44-0.56) and hospitalisation(all:0.90, 0.88-0.91; CVD:0.82,0.80-0.85; and high CV risk:0.85,0.80-0.90)(**Figures 1 and 2, Table S5**). Influenza vaccination was associated with reduced mortality in all groups(all:0.86,0.85-0.86; CVD:0.80,0.79-0.81; and high CV risk:0.83,0.80-0.86), and reduced hospitalisation in CVD and high CV risk groups(CVD:0.82,0.81-0.83; and high CV risk:0.92,0.91-0.93) in individuals with COVID-19. In individuals with LC, influenza vaccination was associated with reduced mortality, but not in high CV risk individuals(0.82,0.06-1.07) and reduced hospitalisation in those with CVD(0.84,0.81-0.87), but not in overall or high CV risk populations. Combined vaccination was associated with reduced mortality(all:0.35,0.35-0.36; CVD:0.41,0.40-0.41; and high CV risk:0.26,0.26-0.27) and hospitalisation(all:0.62,0.62-0.63; CVD:0.75,0.74-0.76; and high CV risk:0.56,0.55-0.56) in individuals with COVID-19. In LC, the same was true for mortality(all:HR 0.37,0.36-0.38; CVD:0.36,0.35-0.37; and high CV risk:0.31,0.28-0.35) and hospitalisation(all:0.43,0.42-0.44; CVD:0.47,0.45-0.49; and high CV risk:0.40,0.40-0.41)(**Figures 1 and 2, Table S5**).

In individuals with COVID-19 and CVD, mortality(anticoagulant:0.69,0.69-0.70; antiplatelet:0.87,0.86-0.88; antihypertensive:0.77,0.76-0.78; lipid-lowering:0.69,0.68-0.70) and hospitalisation(anticoagulant:0.92,0.91-0.93; antiplatelet:0.93,0.92-0.94; antihypertensive:0.90,0.90-0.90; lipid-lowering:0.86,0.86-0.87) were reduced with CVD drugs. In individuals with COVID-19 and high CV risk, anticoagulant, antihypertensive and lipid-lowering were associated with reduced mortality(0.62,0.59-0.66;0.86,0.83-0.88;and 0.84,0.82-0.87 respectively), but antiplatelet was associated with increased mortality(1.12,1.05-1.19). In the same group, antiplatelet drugs were associated with increased hospitalisation(1.16,1.08-1.23) but no change with other drugs(**Table S6, Figure 3 and 4**). The LC population had reduced mortality (anticoagulant:0.59,0.54-0.64;antiplatelet:0.73,0.66-0.80;antihypertensive:0.84,0.78-0.91; lipid-lowering:0.68,0.63-0.74) and hospitalisation (anticoagulant:0.88,0.84-0.92;antiplatelet:0.94,0.90-0.98;antihypertensive:0.93,0.90-0.96; and lipid-lowering:0.90,0.87-0.93) with CVD drugs in the CVD group. In the LC and high CV risk group, CVD drugs were not associated with mortality change, except lipid-lowering(0.68,0.51-0.91). In the same group, hospitalisation was increased with CVD drugs (anticoagulant:1.30,1.10-1.51; antiplatelet: 1.19,1.01-1.40 and antihypertensive: 1.07,1.01-1.15), except lipid-lowering(0.98,0.92-1.04)(**Table S6**).

Averted/preventable mortality and hospitalisation for vaccination and CVD prevention

In individuals with COVID-19, PPF(population preventable fraction) for COVID-19 vaccination was highest for mortality(all:67.1%; CVD:63.3%; high CV risk:74.2%) and hospitalisation(all:27.4%; CVD:38.7% and high CV risk:41.3%), compared with influenza vaccination(mortality: all 12.1%, CVD 12.3% and high CV risk 11.5%; and hospitalisation: all 3.6%, CVD 7.9% and high CV risk 5.6%). In individuals with LC, PPF was similar for COVID-19 vaccination(all: mortality 61.0%, hospitalisation 31.6%), and higher for combined influenza and COVID-19 vaccinations(all: mortality 73.1%; hospitalisation 57.0%). Due to low numbers in high CV risk individuals, PPF and AFP estimates had wide confidence intervals and were not calculated for CVD drugs. In those with COVID-19(mortality: CVD 16.5%, high CV risk 25.7%) and LC(mortality:CVD 33.4%), PPF was highest for anticoagulant(**Table S7**). Post-COVID-19, 245,044(89,505 and 34,928 in CVD and High CV risk groups) of 321,383 preventable deaths were averted, and 761,425(210,761 in CVD and 64,749 in high CV risk groups) of 888,426 preventable hospitalisations were averted with COVID-19 vaccination. In individuals with LC, 5,713(3,024 and 411 in CVD and high CV risk groups) of 6,103 preventable deaths were averted, and 7,856(2481 and 276 in CVD and high CV risk groups) of 8738 preventable hospitalisations were averted with COVID-19 vaccination. In individuals with COVID-19 that already received influenza vaccination, 2,138(1,362 and 79 in CVD and High CV risk groups) of 4,017 preventable deaths were averted, and 1,426(1,133 and 111 in CVD and high CV risk groups) of 2,800 preventable hospitalisations were averted with COVID-19 vaccination. In individuals with LC, 65(43 and 4 in CVD and high CV risk groups) of 127 preventable deaths were averted, and 1,375(1,098 and 2 in CVD and high CV risk groups) of 2,683 preventable hospitalisations were averted with influenza vaccination. In individuals with CVD within COVID-19 and LC, anticoagulant therapy averted 16,573 of 36,847 and 507 of 1,007 preventable deaths, respectively.

DISCUSSION

In a large population-level, electronic health record study of COVID-19 and LC, we had three major findings. First, CVD was a common risk factor and outcome in people with COVID-19 and LC, associated with high hospitalisation and mortality over two years, with nearly half of people with COVID-19 and CVD hospitalised and 2 in 5 dying within two years. Second, in individuals with COVID-19 and LC, there were intervention-specific(COVID-19/influenza vaccination and CVD drugs) and risk-specific(CVD or high CV risk) differences in risk reduction for hospitalisation and mortality, although COVID-19 vaccination was associated with the most consistent and greatest risk reduction, particularly in those with underlying CVD. Third, full COVID-19 vaccination has averted the greatest number of deaths and hospitalisations, compared with influenza vaccination and CVD prevention drugs.

CVD is a risk factor, comorbidity and outcome of both COVID-19 and LC(22). For example, in 153,760 US individuals there was increased risk of all CVD, including heart failure(HR 1.72,1.65-1.80), coronary artery disease(HR 1.72,1.56-1.90)(23). This population is neither representative of UK nor US general populations by age, gender or ethnicity. Using national English EHR, risk of arterial and venous events was shown to be increased one year post-COVID-19 but highest in the first two weeks post-COVID-19, with an estimated additional 7,200 and 3,500 arterial and venous thrombotic events, respectively, after 1.4 million COVID-19 diagnoses(24).

Similarly, high short- and long-term CV risk after COVID-19 have been shown in UK Biobank(25). However, these studies have not identified people with LC with long-term prospective follow-up and comparison with individuals after initial COVID-19 illness. Using an inclusive CVD definition, we now show the scale of effect of high CV risk over two years on outcomes in COVID-19 *and* LC. Compared with the general population, individuals with CVD and high CV risk had higher hospitalisation and mortality at two years after COVID-19 and LC, respectively. Although higher age in CVD and high CV risk groups is likely to be contributory, other studies have highlighted that individuals at high CV risk are more likely to experience adverse COVID-19 outcomes, even after age-adjusting(26). Pathophysiology of high post-COVID-19 CV risk is unclear with postulated immune, inflammatory, endothelial, and thrombotic dysfunction, as well as indirect health system effects, including reduced CVD diagnosis, prevention, and treatment during the pandemic(27).

We show that COVID-19 vaccination was associated with substantial reductions in mortality and hospitalisation in both COVID-19 and LC populations, whereas there were clear differences by risk of baseline CVD, hospitalisation and mortality in the smaller reductions with influenza vaccination. Full COVID-19 vaccination was associated with 60-70% reduced mortality and 30-45% reduced hospitalisation after COVID-19, as well as 50-55% reduced mortality and 10-15% reduced hospitalisation after LC. Our findings align with recent literature (28–30) on the effectiveness of vaccination against severe outcomes of SARS-CoV-2 infection. However, our results demonstrate a significantly lower efficacy compared to the effectiveness reported for non-infected individuals. Recent studies have shown 74%-90% efficacy (30) in preventing mortality and 64%-84% efficacy in preventing hospitalization among non-infected individuals. This discrepancy may be attributed to the partial immunity conferred by prior infection, which could have already established a long-term baseline immune response in those individuals. Influenza vaccination was associated with 15-20% reduced mortality, and 10-20% reduced hospitalisation in CVD and high CV risk groups after COVID-19, and in individuals with LC, 35% reduced mortality and 16% reduced hospitalisation in the CVD group. The limited observed effect of influenza vaccination on mortality may be due to confounding, higher baseline risk of hospitalisation due to underlying health conditions or mis-coding of vaccinated individuals as unvaccinated. In people post-COVID-19, each of the four classes of CVD drugs was associated with 20-30% reduced mortality and 5-15% reduced hospitalisation after COVID-19, and there was 15-40% reduced mortality and 5-15% reduced hospitalisation after LC in the CVD group. We add comparative data to observational studies suggesting benefit in mortality and hospitalisation in COVID-19(31) and LC, but trials and guideline recommendations for the latter are lacking. Influenza vaccination is indicated in primary and secondary CVD prevention(6,32,33), and emerging data support COVID-19 vaccination[(34). CVD management, including drugs, declined during the pandemic(17). We show that four CVD drug classes, especially anticoagulants and lipid lowering drugs, were associated with mortality and hospitalisation reductions in people with CVD and COVID-19 or LC.

We showed that approximately 250000 and 6000 deaths and 750000 and 8000 hospitalisations were averted by COVID-19 vaccination in people with COVID-19 and LC, respectively, with greatest effect in those receiving annual influenza vaccination. Prioritising those at-risk of influenza and CVD may yield highest impact.

The UK government issued guidance in August 2023(35), supporting COVID-19 vaccination in high-risk groups, including those with CVD, but recommendations in LC or those at high CV risk, as supported by our analyses, are lacking.

Implications for future research

There are four research implications. First, our matched cohort analyses and modelling of averted and preventable deaths using national, near-real-time data, represent a pragmatic way to develop targeted preventive strategies beyond pandemics. Second, there is a gap in trial data to recommend COVID-19 vaccination for people with LC. Third, we have emphasised CVD, but other chronic diseases are high-risk COVID-19 conditions(e.g. diabetes, chronic kidney disease), where impact of vaccination and disease-specific treatments should be assessed. Fourth, hospitalisation and mortality are measurable and available, but future research may address broader outcomes, including health economic and patient-reported.

Implications for future policy and practice

There are three policy and practice ramifications. First, large-scale EHR can be mobilised to inform, compare, support and update policy recommendations for interventions during public health emergencies. Second indirect and long-term impact should be incorporated in pandemic planning and implementation. Third, underlying diseases are a major driver of mortality and hospitalisation in COVID-19, but also in LC, and their diagnosis and treatment should be protected during pandemics. Fourth, considering interventions together may simplify policy recommendations, such as COVID-19 vaccination in those who are eligible for influenza vaccination.

Strengths and Limitations

This is one of the largest studies in LC and COVID-19 to consider strategies in people with LC, CVD, and at high-risk of CVD with two years of follow-up. We used standardised, validated EHR phenotypes and methods in national EHR but biases are possible. Use of all-cause hospitalisation and mortality enabled comparison across interventions, as well as across COVID-19 and LC. Our methods for matched cohort analyses and estimation of averted and preventable outcomes enabled the most reliable and feasible evidence base for pandemic era interventions. However, there are several limitations. First, we only investigated all-cause mortality and hospitalisation, which may overlook heterogeneity of more specific health outcomes,.and neither health economic impact nor patient-reported outcomes nor indirect pandemic effects. Future research should prioritise cause-specific endpoints. Second, further studies are needed to investigate comorbidity clusters and progression of LC and outcomes. Third, we only studied four classes of CVD drugs and did not investigate their combined impact on deaths and hospitalisations, but analyses by “any” or “all” of the four drug classes suggests similar results(**Tables S8** and **S9**). Fourth, we only considered CVD but expect similar effects in other at-risk conditions for COVID-19, which need to be investigated in future research. Fifth, we are likely to have underestimated both COVID-19 and LC, due to unavailable symptom data, phenotyping based on SNOMED-CT and ICD-10 codes and under-utilisation of LC coding. Moreover, COVID-19 testing was not widely available after April 2022, but sensitivity analyses did not suggest major differences between tested and untested individuals with

LC(**Table S10**). Finally, we did not investigate within-year or between-year effectiveness of different COVID-19 and influenza vaccines and had insufficient power to investigate effect of booster doses.

Conclusions
Using national, linked electronic health records in 17 million individuals with COVID-19 and 300,000 individuals with LC, we showed that CVD and high CV risk are major risk factors for mortality and hospitalization. COVID-19 vaccination is likely to be associated with greatest impact, compared with influenza vaccination and CVD drugs, although we could not demonstrate causation. Policy strategies should prioritise COVID-19 vaccination to as wide a high-risk population as possible.

Contributors
AB conceived the research question, obtained funding, and designed the study. AD was responsible for development and execution of the analysis plan, cohort preparation. MAM guided implementation of EHR disease phenotypes. LP contributed to quality control of the statistical analysis. AB and AD drafted the initial manuscript and all authors critically reviewed early and final versions of the manuscript. CS is Director of the BHF Data Science Centre and coordinated approvals for and access to data within NHS England's Secure Data Environment service for England for the CVD-COVID-UK/COVID-IMPACT research programme.

Declaration of interests
KK is chair of the ethnicity subgroup of the UK Scientific Advisory Group for Emergencies(SAGE) and is a member of SAGE. KK(Chair) and AB are members of the LC Research Group that reports to the Chief Medical Officer for England. All other authors declare no competing interests.

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Ethical approval and data availability

The North East-Newcastle and North Tyneside 2 research ethics committee provided approval for the CVD-COVID-UK/COVID-IMPACT research programme(20/NE/0161). Further details regarding data availability are in **Supplementary methods**.

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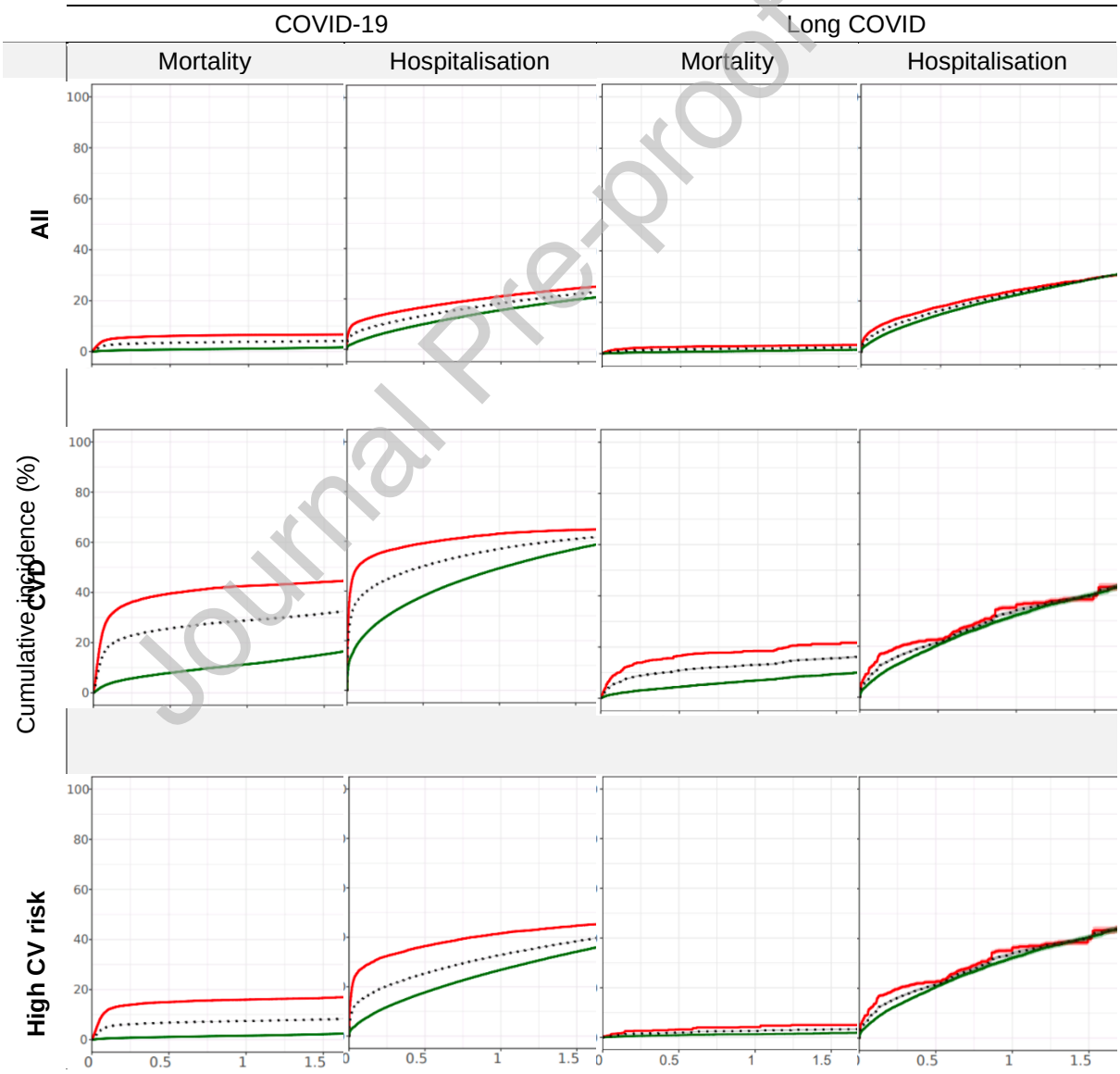
Table 1. Baseline Characteristics and outcomes in COVID-19 and Long COVID, stratified by cardiovascular disease and high cardiovascular risk

	COVID-19			Long-COVID		
	All	**CVD**	**High CV risk**	**All**	**CVD**	**High CV risk**
N	17373850	1005780	370160	301115	26775	12305
Age **mean (SD)**	38.8 (21.1)	71.6 (16.4)	65.1 (9.3)	46.0 (17.8)	65.0 (17.1)	63.6 (9.0)
median [IQR]	37.1 [22.0, 53.7]	74.1 [61.6, 84.0]	65.1 [58.8, 71.9]	46.4 [33.4, 58.1]	66.3 [55.8, 77.3]	63.3 [57.5, 69.8]
Age bands						
<10	1266095 (7.3)	3000 (0.3)	0	6380 (2.1)	185 (0.7)	0
10-19	2618710 (15.1)	4430 (0.4)	0	16470 (5.5)	415 (1.6)	0
20-29	2625775 (15.1)	11355 (1.1)	0	35490 (11.8)	500 (1.9)	0
30-39	2923295 (16.8)	25575 (2.5)	1850 (0.5)	52280 (17.4)	1090 (4.1)	60 (0.5)
40-49	2655115 (15.3)	52155 (5.2)	18885 (5.1)	61720 (20.5)	2075 (7.7)	715 (5.8)
50-59	2347645 (13.5)	125370 (12.5)	85930 (23.2)	64020 (21.3)	4900 (18.3)	3505 (28.5)
60-69	1442415 (8.3)	186010 (18.5)	144490 (39.0)	37730 (12.5)	6370 (23.8)	5005 (40.7)
>70	1494795 (8.6)	597880 (59.4)	119015 (32.2)	27030 (9.0)	11240 (42.0)	3025 (24.6)
Female	9459525 (54.4)	440935 (43.8)	155885 (42.1)	186075 (61.8)	12380 (46.2)	5615 (45.6)
IMD Quantile						
1	3335390 (19.2)	207210 (20.6)	78730 (21.3)	61980 (20.6)	7260 (27.1)	3250 (26.4)
2	3463680 (19.9)	198355 (19.7)	76485 (20.7)	62885 (20.9)	5405 (20.2)	2815 (22.9)
3	3490530 (20.1)	200905 (20.0)	72890 (19.7)	59775 (19.9)	4900 (18.3)	2275 (18.5)
4	3517245 (20.2)	203495 (20.2)	72280 (19.5)	59705 (19.8)	4785 (17.9)	2170 (17.6)
5	3567000 (20.5)	195810 (19.5)	69775 (18.9)	56765 (18.9)	4430 (16.5)	1795 (14.6)
Ethnicity						
White	14135880 (81.4)	905955 (90.1)	310305 (83.8)	249375 (82.8)	23350 (87.2)	10150 (82.5)
Black, Black British	508165 (2.9)	20005 (2.0)	9950 (2.7)	10040 (3.3)	790 (2.9)	385 (3.1)
Asian, Asian British	1336515 (7.7)	52740 (5.2)	37130 (10.0)	26025 (8.6)	1930 (7.2)	1430 (11.6)
Other Ethnics	434525 (2.5)	10725 (1.1)	4920 (1.3)	6720 (2.2)	320 (1.2)	195 (1.6)
Mixed	362140 (2.1)	6865 (0.7)	2785 (0.8)	6170 (2.0)	310 (1.2)	115 (1.0)
Unknown	596620 (3.4)	9490 (0.9)	5065 (1.4)	2790 (0.9)	75 (0.3)	30 (0.3)
Intervention						
Influenza vaccination	4827660 (27.8)	555410 (55.2)	209630 (56.6)	99680 (33.1)	14940 (55.8)	7190 (58.4)
COVID-19 vaccination >=2 doses	8687540 (50.0)	641280 (63.8)	269065 (72.7)	199920 (66.4)	18880 (70.5)	9655 (78.4)
Anticoagulant	401150(2.3)	337950(33.6)	2305(6.3)	12130(4.03)	7910(29.5)	955(7.75)
Antiplatelet	678890(3.9)	420645(41.8)	23765(6.4)	16705(5.5)	10580(39.5)	870(7.1)
Antihypertensive	2237370(12.9)	734675(73.1)	213940(57.8)	59905(19.9)	18545(69.3)	6985(56.8)
Lipid Lowering	1733860(9.97)	614360(61.1)	190335(51.5)	45190(15.0)	15795(59.0)	6465(52.5)
Cardiovascular Disease	1005780 (5.8)	1005780 (100.0)	45345 (12.2)	26775 (8.9)	26775 (100.0)	1810 (14.7)
Acute Myocardial Infarction	257750 (1.5)	257750 (25.6)	4605 (1.2)	6310 (2.1)	6310 (23.6)	155 (1.3)
Heart Failure	287645 (1.7)	287645 (28.6)	11390 (3.1)	6955 (2.3)	6955 (26.0)	430 (3.5)
Atrial Fibrillation	428760 (2.5)	428760 (42.6)	23980 (6.5)	11555 (3.8)	11555 (43.1)	980 (8.0)
Coronary Heart Disease	377000 (2.2)	377000 (37.5)	9385 (2.5)	9985 (3.3)	9985 (37.3)	415 (3.4)
Stroke	205550 (1.2)	205550 (20.4)	4455 (1.2)	4470 (1.5)	4470 (16.7)	140 (1.1)
Cardiomyopathy	31745 (0.2)	31745 (3.2)	1360 (0.4)	925 (0.3)	925 (3.4)	55 (0.4)
Deep vein thrombosis	50600 (0.3)	50600 (5.0)	2550 (0.7)	1805 (0.6)	1805 (6.7)	115 (0.9)
Peripheral artery disease	43730 (0.3)	43730 (4.3)	2540 (0.7)	1070 (0.4)	1070 (4.0)	105 (0.9)
Cardiovascular Risk Factors						
Diabetes mellitus	1145280 (6.6)	320515 (31.9)	123330 (33.3)	32275 (10.7)	10140 (37.9)	4445 (36.1)
Hypertension	1257975 (7.2)	303350 (30.2)	144930 (39.2)	35815 (11.9)	8400 (31.4)	5005 (40.7)
Morbid Obesity	357785 (2.1)	53420 (5.3)	26565 (7.2)	10875 (3.6)	1840 (6.9)	990 (8.1)

Current Smoker	894675 (5.1)	36120 (3.6)	14230 (3.8)	12920 (4.3)	745 (2.8)	410 (3.3)
Ex-Smoker	1604520 (9.2)	189635 (18.9)	50315 (13.6)	31020 (10.3)	3545 (13.2)	1435 (11.7)
High CVD risk	370160 (38.1)	45345 (76.6)	-	12305 (35.1)	1810 (63.1)	-
Other Diseases						
Cancer	2619845 (15.1)	193720 (19.3)	47755 (12.9)	61110 (20.3)	4850 (18.1)	1545 (12.5)
Chronic Kidney Disease	416200 (2.4)	220390 (21.9)	26335 (7.1)	9910 (3.3)	4755 (17.8)	950 (7.7)
Asthma	1957375 (11.3)	179180 (17.8)	55910 (15.1)	54740 (18.2)	6435 (24.0)	2510 (20.4)
COPD	1054760 (6.1)	255165 (25.4)	43685 (11.8)	36090 (12.0)	8245 (30.8)	2200 (17.9)
Depression	1765110 (10.2)	179465 (17.8)	44765 (12.1)	56925 (18.9)	6380 (23.8)	2375 (19.3)
Dementia	258070 (1.5)	135595 (13.5)	6855 (1.9)	2215 (0.7)	1215 (4.5)	145 (1.2)
Influenza	4105 (0.0)	1960 (0.2)	170 (0.0)	80 (0.0)	25 (0.1)	< 10 (0.0)
Outcomes						
Outcome – Long COVID	231415 (1.3)	16625 (1.7)	7775 (2.1)	-	-	-
Outcome – Hospitalisation	2665755 (15.3)	493605 (49.1)	100465 (27.1)	50530 (16.8)	10160 (37.9)	2665 (21.7)
Outcome – Mortality	353930 (2.0)	212165 (21.1)	13280 (3.6)	4090 (1.4)	2505 (9.4)	220 (1.8)



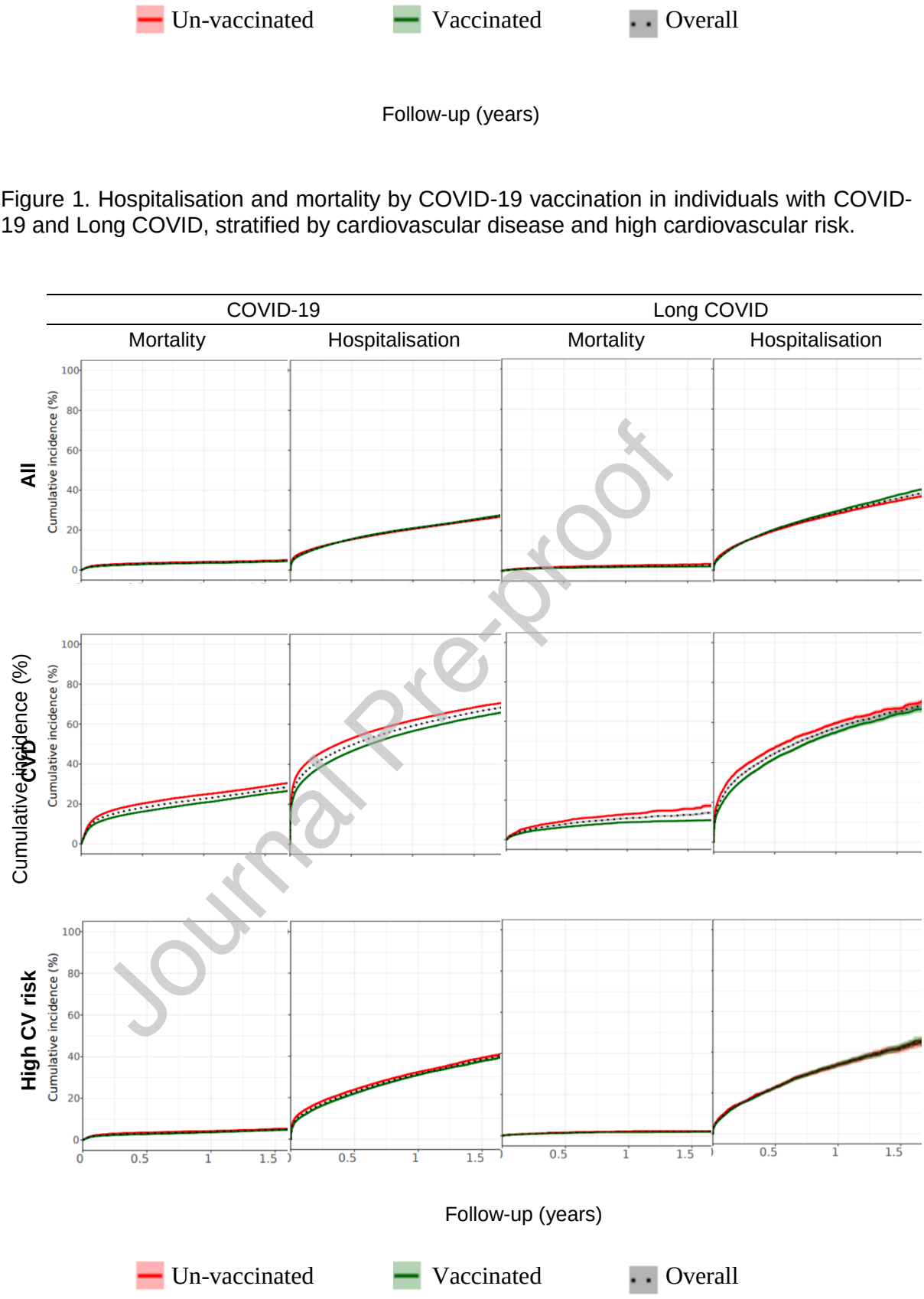


Figure 1. Hospitalisation and mortality by COVID-19 vaccination in individuals with COVID-19 and Long COVID, stratified by cardiovascular disease and high cardiovascular risk.

Figure 2. Hospitalisation and mortality by influenza vaccination in individuals with COVID-19 and Long COVID, stratified by cardiovascular disease and high cardiovascular risk.]

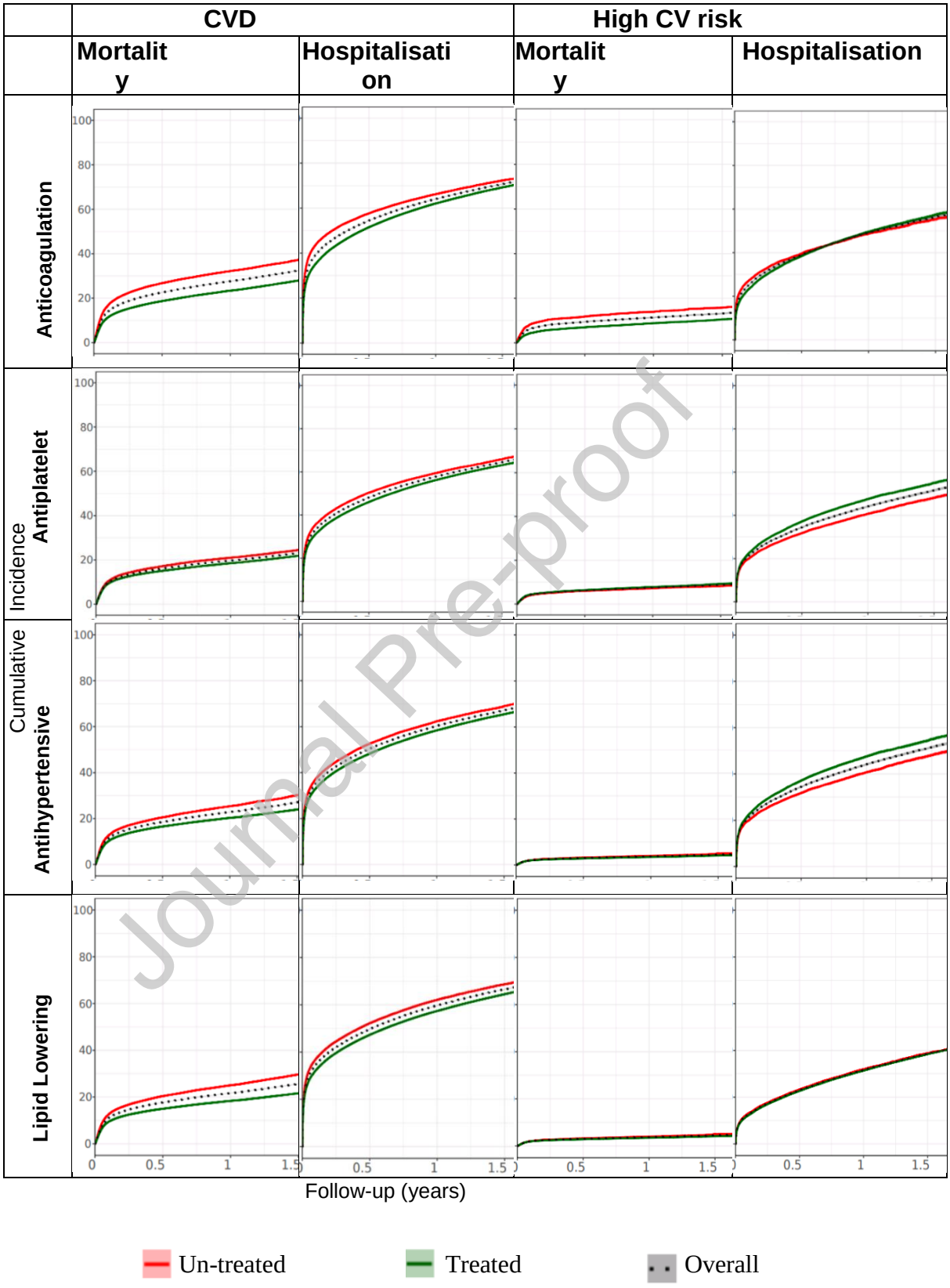


Figure 3. Mortality and hospitalisation in individuals with COVID-19 and cardiovascular disease or high cardiovascular risk, stratified by drugs (Anticoagulant, Antiplatelet, Antihypertensive, and Lipid lowering)

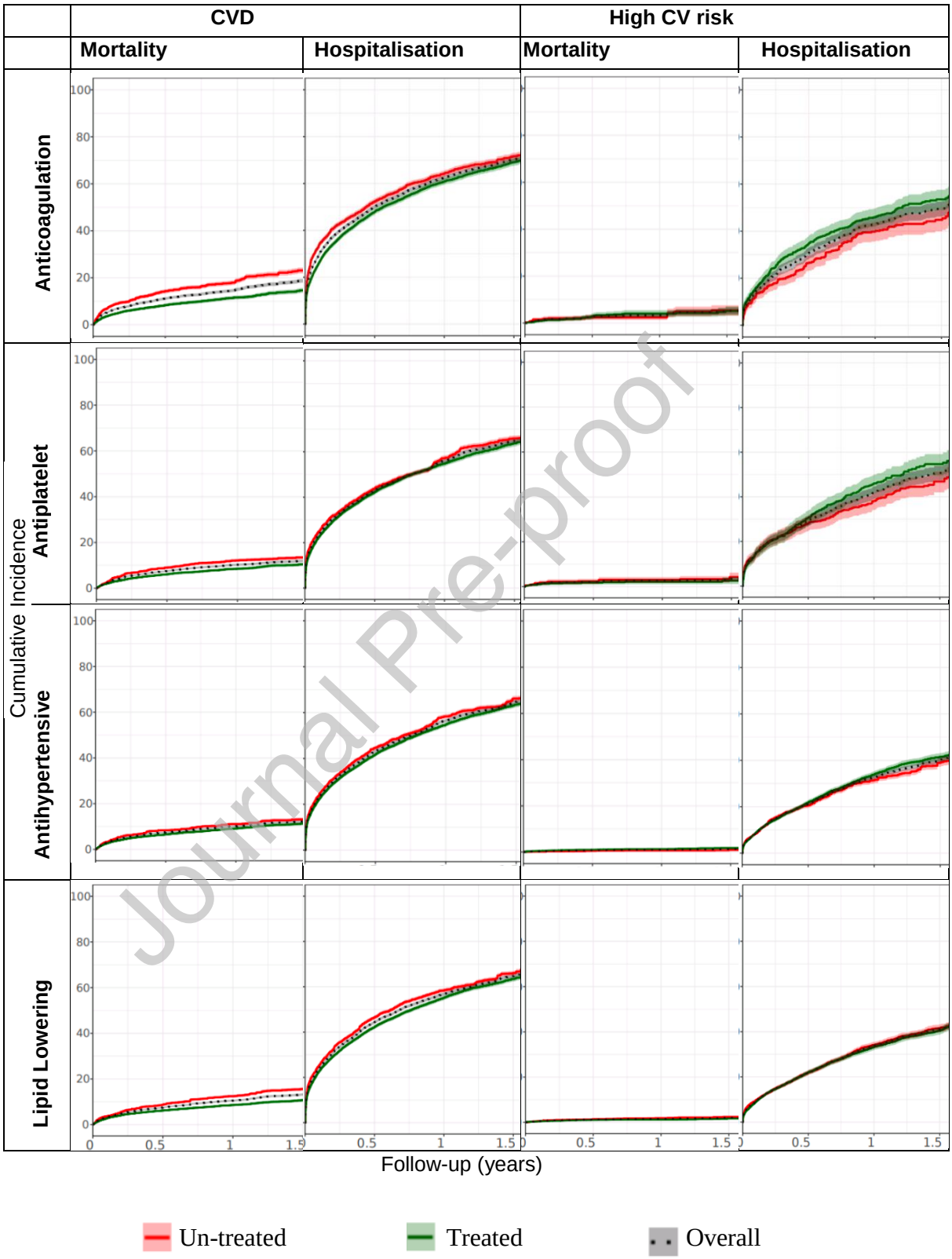


Figure 4. Mortality and hospitalisation in individuals with Long COVID and cardiovascular disease or high cardiovascular risk, stratified by drugs (Anticoagulant, Antiplatelet, Antihypertensive, and Lipid lowering)

Declaration of interests

KK is chair of the ethnicity subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and is a member of SAGE. KK (Chair) and AB are members of the LC Research Group that reports to the Chief Medical Officer for England. All other authors declare no competing interests.