Title: Association of COVID-19 with major arterial and venous thrombotic diseases: a population-wide cohort study of 48 million adults in England and Wales

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Short Title: Vascular diseases after COVID-19

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Abstract

Background: Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces a pro-thrombotic state, but long-term effects of COVID-19 on incidence of vascular diseases are unclear.

Methods: We studied vascular diseases after COVID-19 diagnoses in population-wide anonymised linked English and Welsh electronic health records from 1st January to 7th December 2020. We estimated adjusted hazard ratios (aHRs) comparing the incidence of arterial thromboses and venous thromboembolic (VTE) events after diagnosis of COVID-19 with the incidence in people without a COVID-19 diagnosis. We conducted subgroup analyses by COVID-19 severity, demographic characteristics and prior history.

Results: Among 48 million adults, 125,985 were and 1,319,789 were not hospitalised within 28 days of COVID-19. In England, there were 260,279 first arterial thromboses and 59,421 first VTE events during 41.6 million person-years follow-up. aHRs for first arterial thrombosis compared with no COVID-19 declined from 21.7 (95% CI 21.0-22.4) in week 1 after COVID-19 to 1.34 (1.21-1.48) during weeks 27-49. aHRs for first VTE event declined from 33.2 (31.3-35.2) in week 1 to 1.80 (1.50-2.17) during weeks 27-49. aHRs were higher, for longer after diagnosis, after hospitalised versus non-hospitalised COVID-19, among people of Black and Asian versus White ethnicity and among people without versus with a previous event. The estimated whole-population increases in risk of arterial thromboses and VTE events 49 weeks after COVID-19 were 2.5% and 0.6% respectively, corresponding to 7,197 and 3,517 additional events respectively after 1.4 million COVID-19 diagnoses.

Conclusion: High relative incidence of vascular events soon after COVID-19 diagnosis declines more rapidly for arterial thromboses than VTEs. However, incidence remains

elevated up to 49 weeks after COVID-19. These results support policies to avoid severe COVID-19 with effective COVID-19 vaccines, early review after discharge, risk factor control and use of secondary preventive agents in high-risk patients.

Key words: COVID-19, thrombotic diseases, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, electronic health records.

Non-standard Abbreviations and Acronyms: N/A

Clinical Perspective

What is new?

- In a cohort study of 48 million adults in England and Wales, COVID-19 was associated with substantial excess incidence, which declined with time since diagnosis, of both arterial thromboses and venous thromboembolism.
- Excess incidence was higher, for longer, after hospitalised than non-hospitalised COVID-19.
- There were an estimated 10,500 excess arterial thromboses and venous thromboembolic events after 1.4 million COVID-19 diagnoses.

What are the clinical implications?

- Strategies to prevent vascular events after COVID-19 are particularly important after severe COVID-19 leading to hospitalisation, and should include an early review in primary care and risk factor management.
- Following severe COVID-19, individuals at high risk of vascular events should be prescribed preventive therapies and counselled about the importance of adherence to these.
- New simple treatment strategies to reduce infection-associated VTE and arterial thromboses are needed.

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, induces a pro-thrombotic and pro-inflammatory state that may increase the risk of serious thrombotic disorders.[1] Most previous studies suggest immediate marked increases in both arterial (largely myocardial infarction (MI) and stroke), and venous thromboembolic events (VTEs),[2–8] although these might have been exaggerated due to universal testing for COVID-19 in all hospital admissions (including those with thrombosis), surveillance for venous thrombosis in COVID-19 cohorts, or underuse of thromboprophylaxis. However, few studies have quantified long term vascular risks after diagnosis of COVID-19 or explored how these risks differ by key characteristics such as age, sex, ethnicity, or pre-existing comorbidities.

Anonymised population-scale linked primary and secondary care electronic health records (EHRs) for the whole population of England and Wales were analysed to compare the incidence of major arterial and venous thromboses in people with and without a diagnosis of COVID-19, accounting for multiple potential confounding factors. These comparisons were also made in men and women, different age groups, and different ethnic groups. We estimated the relative incidence of thrombotic events in people who were and were not hospitalised with COVID-19, compared with people without a diagnosis of COVID-19.

Methods

Procedures for accessing the data analysed in this paper are described at CVD-COVID-UK / COVID-IMPACT and SAIL Databank - The Secure Anonymised Information Linkage Databank. The analysis was performed according to a pre-specified protocol and analysis plan with phenotyping and analysis code, which is available at github.com/BHFDSC/CCU002_01. RK had full access to all the data in the study and takes responsibility for its integrity and that of the data analysis.

Data sharing

Data used in this study are available in NHS Digital's Trusted Research Environment (TRE) for England, but as restrictions apply they are not publicly available (https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/trusted-research-environment-service-for-england). The CVD-COVID-UK/COVID-IMPACT programme led by the BHF Data Science Centre (https://www.hdruk.ac.uk/helping-with-health-data/bhf-data-science-centre/) received approval to access data in NHS Digital's TRE for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/) subsequently granted approval to this project to access the data within NHS Digital's TRE for England and the Secure Anonymised Information Linkage (SAIL) Databank. The de-identified data used in

this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance.

Data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting data safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process.

Population

Pseudonymised data on adults alive and registered with a primary care general practice in England or Wales on 1st January 2020 were accessed and analysed via the British Heart Foundation Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium within NHS Digital's secure, privacy protecting Trusted Research Environment (TRE) Service for England and the SAIL Databank for Wales.[9,10] The TRE for England includes primary care data (GPES data for Pandemic Planning and Research, GDPPR) from 98% of general practices linked at individual-level to secondary care data including all NHS hospital admissions, critical care, emergency department and outpatient episodes (Hospital Episode Statistics and Secondary Uses Service data from 1997 onwards), COVID-19 laboratory testing data, national community drug dispensing data (NHS BSA Dispensed Medicines from 2018) and death registrations. The SAIL Databank includes data from hospital admissions, mortality registers,

primary care, COVID-19 test results, community dispensing, and critical care, enabled through the C19_Cohort20 platform.[11]

COVID-19 diagnosis

COVID-19 diagnosis was defined as a record of a positive COVID-19 polymerase chain reaction (PCR), or antigen test, or a confirmed COVID-19 diagnosis in primary care or secondary care hospital admission records and derived the earliest date on which COVID-19 was recorded (Supplementary Table 1). A confirmed COVID-19 diagnosis did not require documentation of a positive test for SARS-CoV-2, because widespread testing was not available in the UK until October 2020. 'Hospitalisation for COVID-19' was defined as a hospital admission record with confirmed COVID-19 diagnosis in the primary position of electronic hospital records within 28 days of first COVID-19 diagnoses and 'COVID-19 without hospitalisation' as a COVID-19 diagnosis without such hospitalisation. Hospitalisation for COVID-19 was further classified as with and without critical care within 28 days of COVID-19 diagnosis. COVID-19 critical care was defined based on receipt of non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation, or admission to an Intensive Care Unit.[12] Events following hospitalised COVID-19 were classified into those happening during the hospital admission and those post-discharge. We used the latest available discharge date for the admission: if no discharge date was available the latest episode end date relating to the admission was used. Rates of events during and after hospital admission were quantified as number of events per 1000 person-years.

Outcomes

Outcomes were defined using primary care, hospital admission and national death registry data (Supplementary Table 2, Supplementary Table 3). Specialist clinician-verified SNOMED-CT, Read code and ICD-10 rule-based phenotyping algorithms were used to define fatal or non-fatal: (i) arterial thromboses (MI, ischaemic stroke (ischaemic or unclassified stroke, spinal stroke or retinal infarction), and other non-stroke non-MI arterial thromboembolism); (ii) VTEs (pulmonary embolism (PE), lower limb deep venous thrombosis (DVT), other DVT, portal vein thrombosis and intracranial venous thrombosis (ICVT)); and (iii) other vascular events (transient ischaemic attack (TIA), haemorrhagic stroke (intracerebral or subarachnoid haemorrhage), heart failure and angina). An outcome event was defined as fatal if it was followed by death from any cause within 28 days. All remaining outcome events were defined as non-fatal. Patients with thromboembolic disease were treated according to national guidelines.[13-15]

Potential confounding variables

Primary and secondary care records up to 1st January 2020 were used to define ethnicity, deprivation, smoking status and region. A large number of potentially confounding variables were defined based on previous disease diagnoses, comorbidities and medications (Supplementary Table 4).

Statistical Analyses

We estimated hazard ratios (HRs) comparing the incidence of arterial thromboses, VTEs and other vascular events after a diagnosis of COVID-19 with the incidence of these events in people without a diagnosis of COVID-19 (the reference group, which was combined from people with no record of COVID-19 during follow up, and follow-up time before COVID-19 in

those who developed COVID-19 during follow-up). We estimated HRs in separate time periods after diagnosis of COVID-19 (0-6 days, 1-2 weeks, 3-4, 5-8, 9-12, 13-26 and 27-49 weeks since diagnosis). Analyses used Cox regression models with calendar time scale (starting on 1st January 2020), to account for rapid changes in the incidence of COVID-19, fitted separately by age group (categorised as <40, 40-59, 60-79 and ≥80 years on 1st January 2020) and by population (England and Wales). Censoring was at the earliest of the date of the outcome, death, or 7th December 2020 (the day before the UK COVID-19 vaccine rollout started). For computational efficiency, analyses included all people with the outcome of interest or with a record of COVID-19 infection, and a 10% randomly sampled subset of other people. Analyses incorporated inverse probability weights with robust standard errors to account for this sampling. Overall HRs were combined across age groups using inverse-variance weighted meta-analyses.

We estimated both age, sex and region-adjusted and maximally adjusted HRs: the latter controlled for all the potential confounders listed in Supplementary Table 4. Where necessary in subgroup analyses, potential confounders with ≤2 disease events at any level were excluded. In subgroup analyses for which there were no outcome events in one or more time periods post-COVID-19 diagnosis the time periods were collapsed into categories "1-4" and ">5" weeks since COVID-19.

Separate analyses were conducted to estimate HRs for hospitalised and non-hospitalised COVID-19, compared with no COVID-19. For the combined arterial thrombosis and VTE outcomes, additional subgroup analyses were conducted by sex, ethnicity and history of arterial thrombosis and VTE respectively. Because of the smaller population size, analyses of Welsh data excluded the <40 years age group, were restricted to all COVID-19 diagnoses

and the combined arterial thrombosis and VTE outcomes, and were conducted separately only by sex. These results were combined across the English and Welsh populations using inverse-variance weighted meta-analyses.

We estimated hazard ratios using separate models for age group and, in the relevant analyses, for hospitalised and non-hospitalised COVID-19. Overall results were then derived by combining hazard ratios across age groups using inverse-variance meta-analysis. The same set of covariates was adjusted for in each age group before results were combined. In some analyses, limited numbers of outcome events after COVID-19 meant that the younger age groups had to be combined in order to fit maximally adjusted models. For some models examining outcomes after hospitalised COVID-19, all age groups had to be combined because small numbers of outcome events after hospitalised COVID-19 made it impossible to identify a set of covariates that could be adjusted for across all groups, and/or some regions had to be merged.

The average daily incidence of major arterial thromboses and VTEs before or in the absence of COVID-19 was calculated across the whole follow up period, separately in subgroups defined by age and sex. These were multiplied by the maximally adjusted age- and sex-specific HR for that day to derive the incidence on each day after COVID-19. A life table approach was used to calculate age- and sex-specific cumulative risks over time with and without COVID-19 and latter was subtracted from the former to derive the absolute excess risks over time after COVID-19, compared with no COVID-19 diagnosis. Overall absolute excess risk was estimated from a weighted sum of the age and sex-specific excess risks, weighted by the proportions of people in age and sex strata within the COVID-19 infected population in England during the follow-up period.

Study oversight

Approval for the CVD-COVID-UK/COVID-IMPACT research programme to access, within secure trusted research environments, unconsented, whole-population, de-identified data from electronic health records collected as part of patients' routine healthcare, was obtained from the Newcastle & North Tyneside 2 Research Ethics Committee (20/NE/0161), the NHS Digital Data Access Request Service (DARS-NIC 381078-Y9C5K) and the SAIL independent Information Governance Review Panel (IGRP) project number 0911.; and for this project from the British Heart Foundation Data Science Centre CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board. Analyses used SQL, Python and RStudio (Professional) Version 1.3.1093.1 driven by R Version 4.0.3 (2020-10-10).

Results

Among 44,964,486 people in the England population, 118,879 (264/100,000) were hospitalised with COVID-19 (22,992 of these patients received critical care) and 1,248,180 (2776/100,000) were not hospitalised within 28 days of their COVID-19 diagnosis (Table 1). Of 51,949 deaths from COVID-19 after a COVID-19 diagnosis, 37,908 were in those hospitalised with COVID-19: a further 6,764 COVID-19 deaths were recorded in people with no COVID-19 diagnosis. Among 2,615,854 people in the Wales population 7,106 (272/100,000) and 71,606 (2,737/100,000) respectively were hospitalised and not hospitalised after COVID-19 (Supplementary Table 5).

The risk of non-hospitalised COVID-19 was higher in women than men (3,110 versus 2,428/100,000), but the risk of hospitalised COVID-19 was higher in men than women (304 versus 226/100,000) (Table 1). As expected, the risk of hospitalised COVID-19 increased markedly with increasing age, from 28.3/100,000 at age 18-29 years to 1,944/100,000 at age 90+ years. By contrast the risk of non-hospitalised COVID-19 was higher (3,816 and 4,749/100,000) in these youngest and oldest age groups and lowest (1,450/100,000) in those aged 70-79 years. The risks of both hospitalised and non-hospitalised COVID-19 increased with increasing index of multiple deprivation.

Numbers of arterial thromboses, VTEs and other vascular events before COVID-19 and after hospitalised and non-hospitalised COVID-19, in the England population are shown in Table 2. Of 260,279 arterial thromboses, 2,241 were in the 118,879 patients hospitalised with COVID-19 (317 and 1924 with and without critical care respectively), and 5,180 were in the 1,248,180 patients who were not hospitalised with COVID-19. Corresponding figures for VTEs were 59,421 total events, 800 (114 and 686 with and without critical care) among

hospitalised patients and 1,808 among non-hospitalised patients. 1,726 (5.3%) of 32,622 fatal arterial thromboses were following a COVID-19 diagnosis, compared with 5,695 (2.5%) of 227,657 non-fatal arterial thromboses. 269 (4.7%) of 5,771 fatal VTEs were following a COVID-19 diagnosis, compared with 2,339 (4.4%) of 53,650 non-fatal VTEs.

The median (IQR) length of hospital admission was 11 days (IQR 6-19). Of 2,241 arterial thromboses among patients hospitalised with COVID-19, 1169 were during the hospital admission (rate 272/1000 person-years) and 1072 were after discharge (39.8/1000 person-years). Of 800 venous thromboses, 198 (44.4/1000 person-years) were during the hospital admission and 602 (21.8/1000 person-years) were after discharge.

Most arterial thromboses were either acute MI (129,799) or ischaemic stroke (128,539) and most VTEs were either PE (31,814) or lower limb deep vein thrombosis (DVT, 25,267). The proportion of strokes due to haemorrhage was as expected (9.3% after hospitalised COVID-19 and 15.1% after non-hospitalised COVID-19). The total person-years of follow up in the England population were 41,595,372 before COVID-19, 32,471 after hospitalised COVID-19 and 245,817 after non-hospitalised COVID-19. Corresponding figures in the Wales population were 2,383,967, 1,709 and 12,966.

Across outcomes and all time periods after COVID-19, maximally adjusted hazard ratios (aHRs) were attenuated compared with unadjusted hazard ratios (Figure 1, Table 3). aHRs for acute MI declined rapidly from 17.2 (95% CI 16.3-18.1) in week 1 to 1.21 (1.03-1.41) in weeks 27-49. They were higher, for longer after diagnosis, after hospitalised compared with non-hospitalised COVID-19: aHRs during weeks 27-49 were 1.39 (1.12-1.72) and 1.03 (0.83-1.28) respectively. aHRs for ischaemic stroke were higher than for MI: they declined from 28.1 (26.8-29.4) in week 1 to 1.62 (1.42-1.86) in weeks 27-49, at which time they were 1.62

(1.33-1.98) and 1.33 (1.10-1.59) after hospitalised and non-hospitalised COVID-19 respectively (Supplementary Figure 1).

Rates of DVT and PE were elevated for longer after diagnosis of COVID-19 than those for arterial thromboses: aHRs compared with no COVID-19 were 4.80 (95% CI 4.03-5.73) and 10.5 (9.44-11.8) respectively 3-4 weeks after diagnosis, declining to 1.62 (1.42-1.86) and 1.99 (1.49-2.65) in weeks 27-49, by which time aHRs were similar for hospitalised and non-hospitalised COVID-19. Overall aHRs for haemorrhagic stroke declined to below 2 by 3-4 weeks after diagnosis, but aHRs after hospitalised COVID-19 peaked again (aHR 4.85 [3.01-7.81]) 9-12 weeks after diagnosis. aHRs for angina and heart failure declined rapidly and were below 1.5 by 13-26 weeks after diagnosis.

For the first (of any) arterial thrombosis, aHRs compared with no COVID-19 declined rapidly from 21.7 (95% CI 21.0-22.4) to 3.87 (3.58-4.19) between the first and second weeks after COVID-19 to 2.80 (2.61-3.01) during weeks 3-4 and then more gradually to 1.34 (1.21-1.48) during weeks 27-49 (Figure 2, Table 4). aHRs were higher after hospitalised than non-hospitalised COVID-19 from week 2 (6.60 [5.85-7.44] versus 2.65 [2.37-2.96]) onwards declining to 1.46 (1.26-1.70) versus 1.21 (1.05-1.40) by weeks 27-49. From 4 weeks after diagnosis onwards, aHRs for arterial thromboses were substantially higher (compared with no COVID-19) in hospitalised patients who had received critical care than those who had not (Supplementary Figure 2, Supplementary Table 6). aHRs were higher for fatal arterial thromboses after COVID-19 (compared with no-COVID-19) than for non-fatal arterial thromboses (Supplementary Figure 3, Supplementary Table 6).

During weeks 1-4 aHRs were greater in those with no prior history of an arterial thrombosis (12.1 [11.5-12.8]), compared to those with a prior history (6.21 [5.30-7.27]), an effect that

attenuated with duration of follow up. There were no consistent differences between age groups. aHRs were marginally greater in males than females. aHRs were greater in people of Black or Black British ethnicity (10.4 [95% CI 8.70-12.5] and 1.96 [1.60-2.41] during weeks 1-4 and 5-49 respectively) and people of Asian or Asian British ethnicity (9.35 [8.48-10.30] and 1.64 [1.43-1.89] respectively) than those of White ethnicity (7.66 [7.42-7.92] and 1.47 [1.40-1.53] respectively).

For the first VTE, aHRs after COVID-19 compared with no COVID-19 declined more gradually than those for arterial thromboses, from 33.2 (95% CI 31.3-35.2) and 8.52 (7.59-9.58) in the first and second weeks to 7.95 (7.28-8.68) and 4.26 (3.86-4.69) during weeks 3-4 and 5-8, then more gradually to 2.20 (1.99-2.44) and 1.80 (1.50-2.17) during weeks 13-26 and 27-49 respectively (Figure 3, Table 5). aHRs for VTEs were substantial for the first 8 weeks following hospitalised COVID-19 (11.2 [9.72-12.9] during weeks 5-8 then 5.40 [4.31-6.77], 2.63 [2.19-3.14] and 1.57 [1.14-2.16] during weeks 9-12. 13-26 and 27-49 respectively. Following non-hospitalised COVID-19, aHRs were 2.56 (2.22-2.95), 2.22 (1.84-2.68), 1.98 (1.74-2.25) and 1.77 (1.38-2.27) during weeks 5-8, 9-12, 13-26 and 27-49 respectively. From 4 weeks after diagnosis onwards, aHRs for VTEs were initially higher (compared with no COVID-19) in hospitalised patients who had received critical care than those who had not, but there was little evidence that they differed from 13 weeks after diagnosis (Supplementary Figure 2). By contrast with the findings for arterial thromboses, aHRs for fatal VTEs after COVID-19 (compared with no-COVID-19) were lower than for non-fatal VTEs (Supplementary Figure 3, Supplementary Table 6).

aHRs were greater in those without than with a prior history of a VTE, but did not differ markedly between age groups. aHRs in males were greater than those in females during weeks 1-4 after COVID-19. aHRs were higher in people of Black or Black British ethnicity (18.0 [14.3-22.8] and 2.68 [1.94-3.70] during weeks 1-4 and 5-49 respectively) and people of Asian or Asian British ethnicity (17.6 [14.2-21.8] and 4.05 [3.09-5.31] respectively) than those of White ethnicity (10.1 [9.56-10.7] and 2.49 [2.32-2.66] respectively).

Absolute excess risks were generally greater in men and in older patients (Figure 4). Combining all arterial thromboses, the excess risk 49 weeks after diagnosis of COVID-19 ranged from 2.3% and 1.7% respectively in men and women aged ≥80 years to 0.03% and 0.01% respectively in men and women aged <40 years (Figure 4). Combining all VTE events, the excess risk at 49 weeks ranged from 0.6% in men and women aged ≥80 years to 0.1% in men and women aged <40 years. Excluding events in the first 28 days approximately halved these absolute excess risks (Supplementary Figure 4). Supplementary Figure 5 shows that 49 weeks after diagnosis the excess risks of both arterial thromboses and VTEs were higher for hospitalised COVID-19 (0.7% and 0.4% respectively) than for non-hospitalised COVID-19 (0.4% and 0.2% respectively). Across the whole population, the estimated absolute increases in the risk of arterial thromboses and VTEs were 0.5% and 0.25% respectively. This corresponds to 7,200 and 3,500 additional arterial thromboses and VTEs respectively after 1.4 million COVID-19 diagnoses.

Discussion

In this cohort of 48 million adults, a markedly higher incidence of arterial thromboses in the first weeks after COVID-19 diagnosis, relative to no COVID-19 diagnosis, declined rapidly with time since diagnosis. The excess incidence of VTEs in the first weeks after COVID-19 diagnosis declined less rapidly than for arterial thromboses and was 2-fold higher for up to 49 weeks after COVID-19 diagnosis. For both arterial thromboses and VTEs, relative incidence was higher, and remained elevated for longer, after hospitalised than non-hospitalised COVID-19. Associations between COVID-19 and thrombotic events did not vary markedly by age or sex, but were greater in people of Black or Asian ethnicity than those of White ethnicity, and in people without than with a prior history of vascular events. We estimate that by December 2020, COVID-19 led to over 10,500 additional arterial thromboses and VTEs in England and Wales.

Like other studies of vascular disease risk after COVID-19 infection, [4,7,8,16] this study found that incidence of arterial thromboses and VTEs was markedly elevated in the first 1-2 weeks after COVID-19 diagnosis, and declined with time from diagnosis. Two self-controlled case series studies found that excluding cases of arterial thromboses or VTEs recorded on the first day of COVID-19 diagnosis attenuated the early relative incidence associated with COVID-19.[4,7] This may have been due to ascertainment of COVID-19 at the time of hospitalisation for a vascular event, or to limited resolution of date coding of COVID and vascular events in the same hospital admission.

Incidence of arterial thromboses and VTEs is also elevated after non-COVID-19 infections. In general, the relative increases in these events are greatest soon after infection and fall within a month towards baseline, although elevated incidence of VTEs may persist for

longer. The mechanism for this may relate to persistence of a post-infection inflammatory response that predominantly affects the venous rather than arterial circulation, although whether this is predominantly driven by endothelial, leucocyte or other components of inflammation is not clear[17]. Relative increases after non-COVID infections have been shown to be similar to this study's estimates 2 weeks after COVID-19 diagnosis.[18–21] Hospital admissions due to MI[22] and stroke[23] fell during the height of the COVID-19 pandemic in England and Wales, which suggests that increases in hospitalisations for arterial thromboses or VTEs after COVID-19 were small compared with the substantial reductions in diagnoses and healthcare use at that time.

The large number of COVID-19 infections in England and Wales during 2020 and 2021 is likely to have caused a substantial additional burden of arterial thromboses and VTEs. Strategies to prevent vascular events after COVID-19 will therefore be important at a population level. These will include early review in primary care, risk factor management, ensuring adherence and preventative therapies in high-risk individuals. However, there have been significant reductions in primary care contacts for a number of conditions including cardiometabolic diseases and most health care professional have had an impact on primary care ability to provide routine health checks in people with chronic conditions[24,25]. The pandemic also led to reductions in prescriptions of antihypertensives and lipid lowering medication and many patients will have missed reviews of vascular risk modification after COVID-19 diagnosis[26].

Randomised trials of short courses of antithrombotic interventions with a low risk of harm might be the next step to reduce longer term risks after hospital discharge. Emerging evidence for this approach is promising[27], although its longer-term benefits are uncertain.

Observational studies suggest a protective effect of statins and blood pressure lowering against post-COVID vascular events[28,29]. The risks of arterial thromboses could be mitigated by review of known vascular risk factors soon after a COVID-19 diagnosis.

The excess incidence of thromboembolic events was higher in people of Black or Asian ethnicity than in those of White ethnicity. People of these ethnicities have had higher rates of COVID-19 mortality, which appears to be related to geography, deprivation, occupation, household composition, living arrangements, and pre-existing health conditions.[30] Pre-pandemic differences in control of vascular risk factors between ethnic groups may also explain these findings.[31]

Our study has a number of strengths. We included almost all of the adult English and Welsh populations, and so the results reflect the total population impact of COVID-19 on the incidence of major vascular events, and are generalisable to other settings with comprehensive healthcare. Linkage with primary care records and national COVID-19 testing data allowed us to study vascular diseases after both hospitalised and non-hospitalised COVID-19, and adjust for a wide range of potentially confounding factors. We used a widely agreed set of codes in EHRs to identify arterial thromboses and VTEs recorded in the first position in hospital and death records. The protocol was prespecified and all code lists are available.

This study has several limitations. First, the survival analyses allowed for variations in diagnoses with calendar time, so should control for the reductions in hospital attendance the period of maximum disruption (March and April 2020). However, some vascular events not have been recorded either because patients died in nursing homes with few diagnostic resources, or were so unwell that MI, stroke, PE or DVT diagnoses would have been difficult.

Second, patients may have avoided healthcare after minor vascular events because of fear of COVID-19. If this was more likely in people without COVID-19, then estimated hazard ratios would have been biased upwards. Third, because the English primary care dataset did not include information on PE and DVT, the incidence of milder non-hospitalised VTEs may have been underestimated.

Fourth, we had limited resolution to determine the date order of COVID diagnosis and arterial thromboses or VTE events for some hospitalised patients. Some patients hospitalised with a vascular event either developed a nosocomial infection or had a COVID-19 diagnosis after routine testing on admission. For some patients, a raised troponin with COVID-19 may have led to a diagnosis of MI.[31] Therefore the very high hazard ratios within one week of COVID-19 diagnosis may have been inflated by reverse causality. Fifth, there was under-ascertainment of COVID-19 infection before testing for SARS-CoV-2 became widely available for mild or asymptomatic infections. Such underdiagnosis would bias estimated post-COVID hazard ratios towards the null. Sixth, identification of exposures, covariates, and outcomes relies on the accuracy of data recorded in electronic health records during routine health care, and we were unable to validate these against fuller health records.

Seventh, unmeasured confounding may explain some findings, since there is a substantial overlap between risk factors for vascular disease and COVID-19. Risk factors for vascular events (e.g. body mass index) are not systematically recorded for all patients, and are subject to measurement error. The difference between adjusted and unadjusted hazard ratios was more marked longer after COVID-19 diagnosis: the hazard ratios for major arterial events more than 13 weeks (HR 1.3) after diagnosis could be due to unmeasured

confounding. However the higher hazard ratios for VTEs after 13 weeks are less plausibly explained by unmeasured confounding, and are consistent with the risk of VTEs after other infections.[18]

In conclusion, substantial increases in the relative incidence of arterial thromboses and VTE events 1-2 weeks after diagnosis of COVID-19 decline with time since diagnosis, although doubling of the incidence of VTE events persisted up to 49 weeks after diagnosis. These results support continued policies to avoid severe COVID-19 with effective COVID-19 vaccines, early review and management of vascular risks in COVID-19 patients and use of secondary preventive agents in patients at high-risk of vascular diseases. New simple treatment strategies to reduce infection associated VTE and arterial thromboses are needed.

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This study makes use of de-identified data held in NHS Digital's Trusted Research Environment for England and made available via the BHF Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make health relevant data available for research.

This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the de-identified data, which led to this output. The collaboration was led by the Swansea University Health Data Research UK team under the direction of the Welsh Government Technical Advisory Cell (TAC) and includes the following groups and organisations: the SAIL Databank, Administrative Data Research (ADR) Wales, Digital Health and Care Wales (DHCW), Public Health Wales, NHS Shared Services Partnership (NWSSP) and the Welsh Ambulance Service Trust (WAST). All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0911.

Author contributions

WW conceived the study. WW, AW, RD, JAC, CS and JACS drafted the protocol. JACS, AW, VW, JAC and RD designed the statistical analyses. RK, VW, SI, TB, SK, AA, HA, FT, EO, SH, SD, JHT and CT developed codelists and derived datasets. SD, JHT and CT created electronic health record phenotyping algorithms for hospitalised and non-hospitalised COVID-19. RK,

VW, SI, JAC, TB, SK, RD, AA, HA, FT, TLN, RT, SD, JHT, CT, XJ and AW conducted statistical analyses. JACS, WW, AW, VW, RK and SI produced the first draft of the manuscript. CS is Director of the BHF Data Science Centre and coordinated approvals for and access to data within the NHS Digital's TRE for England and the SAIL Databank TRE for CVD-COVID-UK/COVID-IMPACT. All authors critically appraised the manuscript for important intellectual content and contributed to the final draft of the manuscript.

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Conflicts of Interest Disclosures

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SUPPLEMENTAL MATERIAL

Tables S1-S6

Figures S1-S5

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Table 1: Number of patients analysed in the English Trusted Research Environment, and the numbers of people (risk per 100,000 during follow up) who were and were not hospitalised within 28 days of diagnosis of COVID-19.

Characteristic		All	Number diagnosed with COVID-19 (risk per 100,000)	
			Hospitalised	Non-hospitalised
All		44,964,486	118,879 (264)	1,248,180 (2776)
Sex	Male	22,003,234	66,954 (304)	534,198 (2428)
	Female	22,961,252	51,925 (226)	713,982 (3110)
Age	18 - 29	8,185,993	2,315 (28.3)	312,359 (3,816)
	30 - 39	8,088,594	4,754 (58.8)	230,993 (2,856)
	40 - 49	7,384,405	8,951 (121)	215,874 (2,923)
	50 - 59	7,709,556	15,806 (205)	218,836 (2,839)
	60 - 69	5,920,117	18,755 (317)	117,140 (1,979)
	70 - 79	4,723,368	26,205 (555)	68,469 (1,450)
	80 - 89	2,374,255	30,852 (1,299)	57,048 (2,403)
	90+	578,198	11,241 (1,944)	27,461 (4,749)
Ethnicity	Asian or Asian British	3,594,845	13,761 (383)	160,479 (4,464)
	Black or Black British	1,540,990	5,748 (373)	37,625 (2,442)
	Mixed	678,232	1,504 (222)	19,121 (2,819)
	Other Ethnic Groups	1,455,251	2,795 (192)	25,466 (1,750)
	White	36,131,134	93,871 (260)	980,990 (2,715)
	Unknown	1,254,798	929 (74.0)	19,377 (1544)
	Missing	309,236	271 (87.6)	5,122 (1656)
Index of Multiple Deprivation	1 – 2 (most deprived)	8,817,841	33,170 (376)	316,779 (3,592)
	3 - 4	9,173,504	26,553 (289)	261,364 (2,849)
	5 - 6	9,035,766	21,500 (238)	231,658 (2,564)
	7 – 8	8,825,196	19,793 (224)	226,234 (2,564)
	9 – 10 (least deprived)	8,571,714	16,850 (197)	199,733 (2,330)
	Missing	540,465	1,013 (187)	12,412 (2,297)
Smoking status	Current	7,746,609	8,776 (113)	151,693 (1,958)
	Former	10,440,342	46,595 (446)	278,105 (2,664)
	Never	24,875,152	61,968 (249)	755,621 (3,038)
	Missing	1,902,383	1,540 (81)	62,761 (3,299)
Medical history	Arterial thrombosis	1,877,562	25,629 (1,365)	54,636 (2,910)
	Venous thromboembolism	629,769	7,573 (1,203)	20,049 (3,184)
Number of medications	0	22,262,206	15,724 (70.6)	591,154 (2,655)
	1 - 5	20,399,092	64,583 (317)	571,391 (2,801)
	6+	2,303,188	38,572 (1,675)	85,635 (3,718)
Number of diagnoses	0	32,831,142	50,791 (155)	864,717 (2,634)
	1 - 5	11,941,404	63,667 (533)	374,473 (3,136)
	6+	191,940	4,421 (2,303)	8,990 (4,684)
Region	North West	5,782,507	22,632 (391)	244,767 (4,233)
	South East	6,742,942	12,550 (186)	115,639 (1,715)
	London	7,266,911	19,524 (269)	135,530 (1,865)
	East of England	4,184,375	8,774 (210)	67,173 (1,605)
	South West	3,629,924	5,066 (140)	57,517 (1,585)
	Missing	3,422,062	6,441 (188)	67,141 (1,962)
	Yorkshire and the Humber	4,390,661	14,733 (336)	184,983 (4,213)
	East Midlands	3,236,271	8,701 (269)	110,496 (3,414)
	West Midlands	4,588,617	14,796 (322)	195,674 (4,264)
	North East	1,720,216	5,662 (329)	69,260 (4,026)

Table 2. Numbers* of arterial thrombotic, venous thromboembolic and other vascular events in the English Trusted Research Environment before and after diagnosis of COVID-19.

	No COVID-19	After hospitalised COVID-19 (118,879 patients)	After non-hospitalised COVID-19 (1,248,180 patients)	Total
Arterial thromboses				
First arterial thrombosis	252,858	2,241	5,180	260,279
Acute myocardial infarction	126,581	1,001	2,217	129,799
Ischaemic stroke	124,360	1,273	2,906	128,539
Other arterial embolism	5,510	63	229	5,802
Venous thromboembolic events				
First venous thromboembolism	56,813	800	1,808	59,421
Pulmonary embolism	30,021	569	1,224	31,814
Lower limb deep vein thrombosis	24,531	210	526	25,267
Other deep vein thrombosis	1,883	23	62	1,968
Portal vein thrombosis	516	<10	18	534
Intracranial venous thrombosis	671	<10	21	692
Other vascular events				
Heart failure	242,717	2,279	3,733	248,729
Angina	193,915	807	1,905	196,627
Transient ischaemic attack	62,371	278	788	63,437
Subarachnoid or intracranial haemorrhage	16,292	131	516	16,939

* Numbers reported are of the first occurrence of each outcome. We did not censor when events other than the outcome of interest occurred.

Table 3. Hazard ratios (95% CI) compared with no COVID-19 for different arterial thromboses (acute myocardial infarction and ischaemic stroke), venous thromboembolism events (pulmonary embolism and deep vein thrombosis) and other vascular events, according to time since diagnosis of COVID-19. All results are maximally adjusted unless otherwise stated.

	Weeks since diagnosis of COVID-19						
	1	**2**	**3-4**	**5-8**	**9-12**	**13-26**	**27-49**
Acute myocardial infarction							
All	17.2 (16.3-18.1)	3.37 (2.99-3.80)	2.37 (2.12-2.64)	1.57 (1.41-1.76)	1.44 (1.26-1.65)	1.17 (1.07-1.29)	1.21 (1.03-1.41)
All, age/sex/region adjusted	22.1 (21.0-23.2)	4.31 (3.82-4.87)	2.99 (2.68-3.34)	2.03 (1.82-2.27)	1.97 (1.72-2.26)	1.68 (1.53-1.84)	1.75 (1.50-2.05)
Hospitalised COVID-19	13.7 (12.3-15.3)	6.64 (5.58-7.89)	4.28 (3.60-5.09)	2.42 (2.00-2.92)	1.70 (1.32-2.19)	1.44 (1.23-1.68)	1.39 (1.12-1.72)
Non-hospitalised COVID-19	17.9 (16.9-19.0)	2.19 (1.85-2.60)	1.79 (1.55-2.06)	1.31 (1.15-1.51)	1.37 (1.16-1.61)	1.06 (0.94-1.19)	1.03 (0.83-1.28)
Ischaemic stoke							
All	23.0 (22.0-24.1)	4.22 (3.78-4.72)	3.17 (2.88-3.50)	2.47 (2.25-2.70)	1.92 (1.70-2.17)	1.58 (1.45-1.71)	1.62 (1.42-1.86)
All, age/sex/region adjusted	28.1 (26.8-29.4)	5.08 (4.54-5.67)	3.78 (3.42-4.16)	3.02 (2.75-3.31)	2.43 (2.15-2.74)	2.03 (1.87-2.21)	2.15 (1.88-2.47)
Hospitalised COVID-19	15.3 (13.9-16.9)	6.84 (5.79-8.09)	5.87 (5.07-6.80)	4.10 (3.54-4.75)	2.47 (2.01-3.04)	1.64 (1.42-1.90)	1.62 (1.33-1.98)
Non-hospitalised COVID-19	23.2 (22.1-24.4)	2.86 (2.46-3.32)	2.10 (1.84-2.39)	1.74 (1.54-1.95)	1.50 (1.30-1.74)	1.35 (1.22-1.49)	1.33 (1.10-1.59)
Deep vein thrombosis							
All	10.8 (9.32-12.5)	4.00 (3.10-5.15)	4.80 (4.03-5.73)	3.20 (2.68-3.82)	2.55 (2.01-3.25)	1.95 (1.65-2.32)	1.99 (1.49-2.65)
All, age/sex/region adjusted	12.3 (10.6-14.3)	4.56 (3.54-5.88)	5.47 (4.59-6.52)	3.71 (3.11-4.43)	3.12 (2.45-3.97)	2.48 (2.09-2.94)	2.61 (1.96-3.48)
Hospitalised COVID-19	6.44 (4.28-9.70)	5.03 (3.03-8.35)	6.20 (4.33-8.88)	7.29 (5.56-9.56)	4.20 (2.83-6.22)	2.42 (1.81-3.22)	1.89 (1.19-3.00)
Non-hospitalised COVID-19	11.3 (9.65-13.2)	3.50 (2.61-4.69)	4.23 (3.46-5.17)	2.18 (1.73-2.75)	1.95 (1.44-2.64)	1.64 (1.33-2.03)	1.88 (1.31-2.71)
Pulmonary embolism							
All	33.2 (30.7-35.9)	9.97 (8.57-11.6)	10.5 (9.44-11.8)	5.55 (4.91-6.27)	3.22 (2.66-3.90)	2.41 (2.10-2.76)	1.61 (1.23-2.12)
All, age/sex/region adjusted	39.7 (36.7-42.9)	11.7 (10.1-13.7)	12.5 (11.2-14.0)	6.76 (5.98-7.63)	4.11 (3.39-4.97)	3.17 (2.76-3.63)	2.22 (1.69-2.92)
Hospitalised COVID-19	19.3 (15.7-23.6)	16.6 (13.1-21.1)	21.0 (17.8-24.9)	14.4 (12.2-17.0)	5.67 (4.23-7.60)	2.76 (2.19-3.48)	1.40 (0.90-2.18)
Non-hospitalised COVID-19	34.5 (31.7-37.5)	7.06 (5.80-8.58)	7.16 (6.21-8.26)	3.07 (2.57-3.67)	2.27 (1.76-2.92)	2.08 (1.76-2.47)	1.60 (1.13-2.27)
Haemorrhagic stroke (intracerebral or subarachnoid haemorrhage)							
All	31.7 (28.6-35.2)	2.83 (1.97-4.05)	1.92 (1.39-2.67)	1.86 (1.41-2.45)	1.99 (1.43-2.76)	1.57 (1.27-1.95)	1.80 (1.29-2.50)
All, age/sex/region adjusted	40.2 (37.3-43.3)	3.51 (2.71-4.54)	2.43 (1.93-3.07)	2.28 (1.87-2.78)	2.78 (2.19-3.52)	2.09 (1.79-2.44)	2.54 (2.01-3.20)
Hospitalised COVID-19	12.4 (8.94-17.2)	3.97 (1.78-8.84)	2.41 (1.21-4.83)	2.22 (1.23-4.01)	4.85 (3.01-7.81)	1.81 (1.19-2.75)	1.17 (0.59-2.35)
Non-hospitalised COVID-19	37.3 (33.4-41.6)	2.46 (1.60-3.78)	1.74 (1.18-2.56)	1.64 (1.18-2.28)	1.21 (0.76-1.92)	1.46 (1.13-1.89)	2.25 (1.55-3.27)
Transient ischaemic attack							
All	7.79 (6.99-8.68)	2.05 (1.64-2.56)	1.44 (1.18-1.76)	1.41 (1.19-1.66)	1.39 (1.15-1.69)	1.17 (1.03-1.34)	1.38 (1.13-1.69)
All, age/sex/region adjusted	9.23 (8.54-9.97)	2.43 (2.08-2.85)	1.68 (1.46-1.94)	1.71 (1.51-1.92)	1.79 (1.56-2.05)	1.53 (1.39-1.67)	1.80 (1.56-2.08)
Hospitalised COVID-19	5.82 (4.54-7.45)	1.97 (1.22-3.17)	1.75 (1.15-2.67)	2.02 (1.47-2.77)	1.85 (1.27-2.70)	1.24 (0.97-1.58)	1.60 (1.19-2.16)
Non-hospitalised COVID-19	8.44 (7.48-9.52)	2.07 (1.61-2.66)	1.34 (1.06-1.69)	1.27 (1.04-1.54)	1.32 (1.05-1.66)	1.13 (0.97-1.32)	1.20 (0.91-1.58)

	Weeks since diagnosis of COVID-19						
	1	**2**	**3-4**	**5-8**	**9-12**	**13-26**	**27-49**
Angina							
All	6.37 (5.94-6.83)	1.97 (1.73-2.25)	1.72 (1.55-1.92)	1.45 (1.32-1.60)	1.22 (1.07-1.38)	1.08 (1.00-1.18)	1.07 (0.93-1.23)
All, age/sex/region adjusted	8.12 (7.73-8.53)	2.47 (2.25-2.72)	2.14 (1.98-2.31)	1.84 (1.72-1.98)	1.62 (1.48-1.77)	1.50 (1.41-1.59)	1.53 (1.39-1.69)
Hospitalised COVID-19	5.31 (4.58-6.15)	3.01 (2.42-3.73)	2.58 (2.13-3.12)	1.61 (1.32-1.96)	1.45 (1.14-1.83)	1.13 (0.98-1.31)	0.98 (0.79-1.21)
Non-hospitalised COVID-19	6.72 (6.20-7.28)	1.48 (1.24-1.77)	1.44 (1.26-1.64)	1.40 (1.25-1.56)	1.15 (0.99-1.34)	1.06 (0.96-1.18)	1.17 (0.98-1.41)
Heart failure							
All	9.40 (8.99-9.84)	2.01 (1.81-2.24)	2.04 (1.89-2.21)	1.98 (1.85-2.11)	1.89 (1.74-2.04)	1.42 (1.35-1.50)	1.27 (1.15-1.39)
All, age/sex/region adjusted	13.8 (13.4-14.3)	2.86 (2.65-3.08)	2.87 (2.71-3.04)	2.85 (2.72-2.99)	2.96 (2.79-3.12)	2.31 (2.22-2.40)	2.19 (2.05-2.34)
Hospitalised COVID-19	8.21 (7.56-8.93)	2.50 (2.10-2.97)	3.27 (2.89-3.70)	3.03 (2.72-3.37)	2.62 (2.30-2.97)	1.86 (1.71-2.02)	1.45 (1.28-1.66)
Non-hospitalised COVID-19	9.92 (9.39-10.5)	1.73 (1.51-1.98)	1.57 (1.41-1.74)	1.62 (1.49-1.76)	1.59 (1.44-1.76)	1.22 (1.13-1.31)	1.10 (0.96-1.26)

Table 4. Hazard ratios (95% CI) compared with no COVID-19 for first arterial thrombosis, according to time since diagnosis of COVID-19. All results are maximally adjusted unless otherwise stated.

	Weeks since diagnosis of COVID-19						
	1	**2**	**3-4**	**5-8**	**9-12**	**13-26**	**27-49**
All	21.7 (21.0-22.4)	3.87 (3.58-4.19)	2.80 (2.61-3.01)	2.00 (1.87-2.14)	1.58 (1.45-1.73)	1.34 (1.27-1.43)	1.34 (1.21-1.48)
All, age/sex/region adjusted	27.9 (27.0-28.8)	4.90 (4.53-5.30)	3.50 (3.27-3.76)	2.57 (2.40-2.75)	2.14 (1.96-2.34)	1.88 (1.77-2.00)	1.92 (1.73-2.12)
Hospitalised COVID-19	14.2 (13.2-15.3)	6.60 (5.85-7.44)	4.97 (4.43-5.56)	3.25 (2.90-3.66)	2.00 (1.70-2.36)	1.50 (1.35-1.68)	1.46 (1.26-1.70)
Non-hospitalised COVID-19	22.0 (21.2-22.9)	2.65 (2.37-2.96)	2.03 (1.84-2.23)	1.58 (1.45-1.73)	1.42 (1.27-1.59)	1.24 (1.15-1.34)	1.21 (1.05-1.40)
Prior history of event		5.68 (5.40-5.98)			1.42 (1.34-1.51)		
No prior history of event		10.6 (10.2-11.0)			1.72 (1.63-1.82)		
Age <40 years	16.7 (12.7-22.0)	3.30 (1.77-6.16)	1.31 (0.62-2.75)	1.07 (0.53-2.14)	0.90 (0.33-2.40)	1.56 (0.93-2.61)	0.94 (0.30-2.93)
Age 40-59 years	19.3 (17.8-21.0)	3.36 (2.75-4.12)	2.72 (2.30-3.22)	1.92 (1.62-2.28)	1.77 (1.41-2.22)	1.39 (1.18-1.64)	1.86 (1.48-2.35)
Age 60-79 years	26.8 (25.6-28.2)	4.61 (4.09-5.19)	3.03 (2.71-3.39)	2.20 (1.98-2.45)	1.61 (1.38-1.87)	1.38 (1.25-1.53)	1.39 (1.18-1.64)
Age 80+ years	18.1 (17.2-19.0)	3.40 (3.00-3.85)	2.67 (2.39-2.98)	1.89 (1.70-2.10)	1.54 (1.35-1.75)	1.30 (1.19-1.42)	1.12 (0.96-1.31)
Females	20.5 (19.5-21.5)	3.36 (2.97-3.81)	2.61 (2.35-2.91)	1.91 (1.72-2.11)	1.55 (1.36-1.77)	1.27 (1.16-1.38)	1.19 (1.02-1.39)
Males	22.9 (21.9-23.8)	4.33 (3.92-4.79)	3.00 (2.73-3.29)	2.10 (1.91-2.30)	1.64 (1.45-1.86)	1.43 (1.32-1.55)	1.50 (1.31-1.71)
White		7.66 (7.42-7.92)			1.47 (1.40-1.53)		
Black or Black British		10.4 (8.70-12.5)			1.96 (1.60-2.41)		
Asian or Asian British		9.35 (8.48-10.3)			1.64 (1.43-1.89)		
Other ethnic groups		9.04 (6.84-12.0)			1.97 (1.39-2.79)		
Mixed ethnicity		8.27 (5.88-11.6)			1.24 (0.77-1.99)		

Table 5. Hazard ratios (95% CI) compared with no COVID-19 for first venous thromboembolism, according to time since diagnosis of COVID-19. All results are maximally adjusted unless otherwise stated.

	Weeks since diagnosis of COVID-19						
	1	**2**	**3-4**	**5-8**	**9-12**	**13-26**	**27-49**
All	33.2 (31.3-35.2)	8.52 (7.59-9.58)	7.95 (7.28-8.68)	4.26 (3.86-4.69)	2.96 (2.58-3.41)	2.20 (1.99-2.44)	1.80 (1.50-2.17)
All, age/sex/region adjusted	40.3 (38.0-42.7)	10.1 (9.03-11.4)	9.44 (8.65-10.3)	5.19 (4.71-5.72)	3.79 (3.29-4.36)	2.92 (2.64-3.23)	2.49 (2.07-3.00)
Hospitalised COVID-19	14.5 (12.2-17.4)	11.5 (9.22-14.2)	14.3 (12.3-16.7)	11.2 (9.72-12.9)	5.40 (4.31-6.77)	2.63 (2.19-3.14)	1.57 (1.14-2.16)
Non-hospitalised COVID-19	24.4 (22.7-26.3)	5.46 (4.66-6.40)	6.05 (5.39-6.78)	2.56 (2.22-2.95)	2.22 (1.84-2.68)	1.98 (1.74-2.25)	1.77 (1.38-2.27)
Prior history of event		6.21 (5.30-7.27)			1.72 (1.45-2.05)		
No prior history of event		12.1 (11.5-12.8)			2.87 (2.68-3.08)		
Age <40 years	18.6 (14.9-23.1)	5.95 (4.04-8.76)	5.62 (4.16-7.58)	2.94 (2.06-4.18)	2.09 (1.21-3.61)	2.98 (2.17-4.11)	2.85 (1.61-5.05)
Age 40-59 years	31.8 (28.3-35.7)	11.8 (9.80-14.3)	9.61 (8.26-11.2)	3.68 (3.00-4.52)	2.44 (1.78-3.36)	2.18 (1.76-2.70)	1.68 (1.11-2.53)
Age 60-79 years	42.2 (38.5-46.2)	9.27 (7.64-11.2)	9.06 (7.88-10.4)	5.07 (4.34-5.91)	3.57 (2.86-4.45)	2.40 (2.03-2.84)	2.10 (1.56-2.82)
Age 80+ years	27.9 (24.7-31.5)	3.75 (2.76-5.10)	4.81 (3.90-5.93)	4.23 (3.53-5.06)	2.91 (2.29-3.71)	1.81 (1.51-2.17)	1.38 (0.97-1.96)
Females	29.7 (27.3-32.3)	6.84 (5.77-8.12)	6.87 (6.04-7.81)	4.22 (3.70-4.82)	3.00 (2.49-3.63)	2.08 (1.81-2.39)	1.91 (1.49-2.44)
Males	38.2 (35.2-41.5)	11.0 (9.41-12.9)	9.50 (8.43-10.7)	4.40 (3.81-5.09)	3.08 (2.49-3.79)	2.41 (2.08-2.80)	1.76 (1.32-2.34)
White		10.1 (9.56-10.7)			2.49 (2.32-2.66)		
Black or Black British		18.0 (14.2-22.8)			2.68 (1.94-3.70)		
Asian or Asian British		17.6 (14.1-21.8)			4.05 (3.09-5.31)		
Other ethnic groups		15.9 (9.13-27.8)			5.62 (3.28-9.63)		
Mixed ethnicity		15.7 (9.78-25.1)			2.52 (1.29-4.93)		

Figure 1. Age/sex/region adjusted and maximally adjusted hazard ratios (log scale) for different arterial thrombotic, and venous thromboembolic and other vascular events by time since diagnosis of COVID-19. All results are maximally adjusted unless otherwise stated.

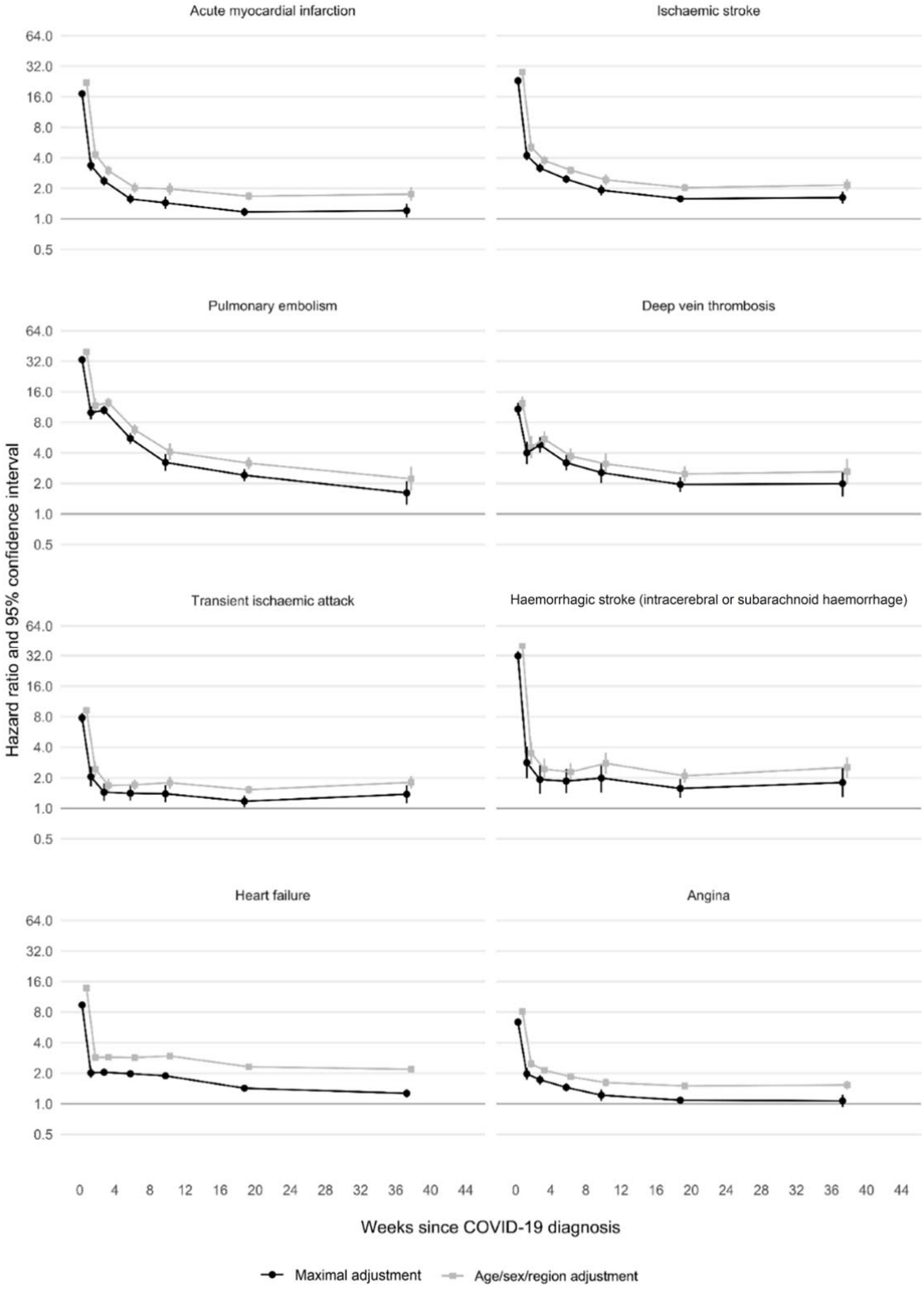


Figure 2 Hazard ratios (log scale) for first arterial event after COVID-19 by time since diagnosis, overall and stratified by whether hospitalised with COVID-19, prior history of an arterial event, age, sex and ethnicity. All results are maximally adjusted unless otherwise stated.

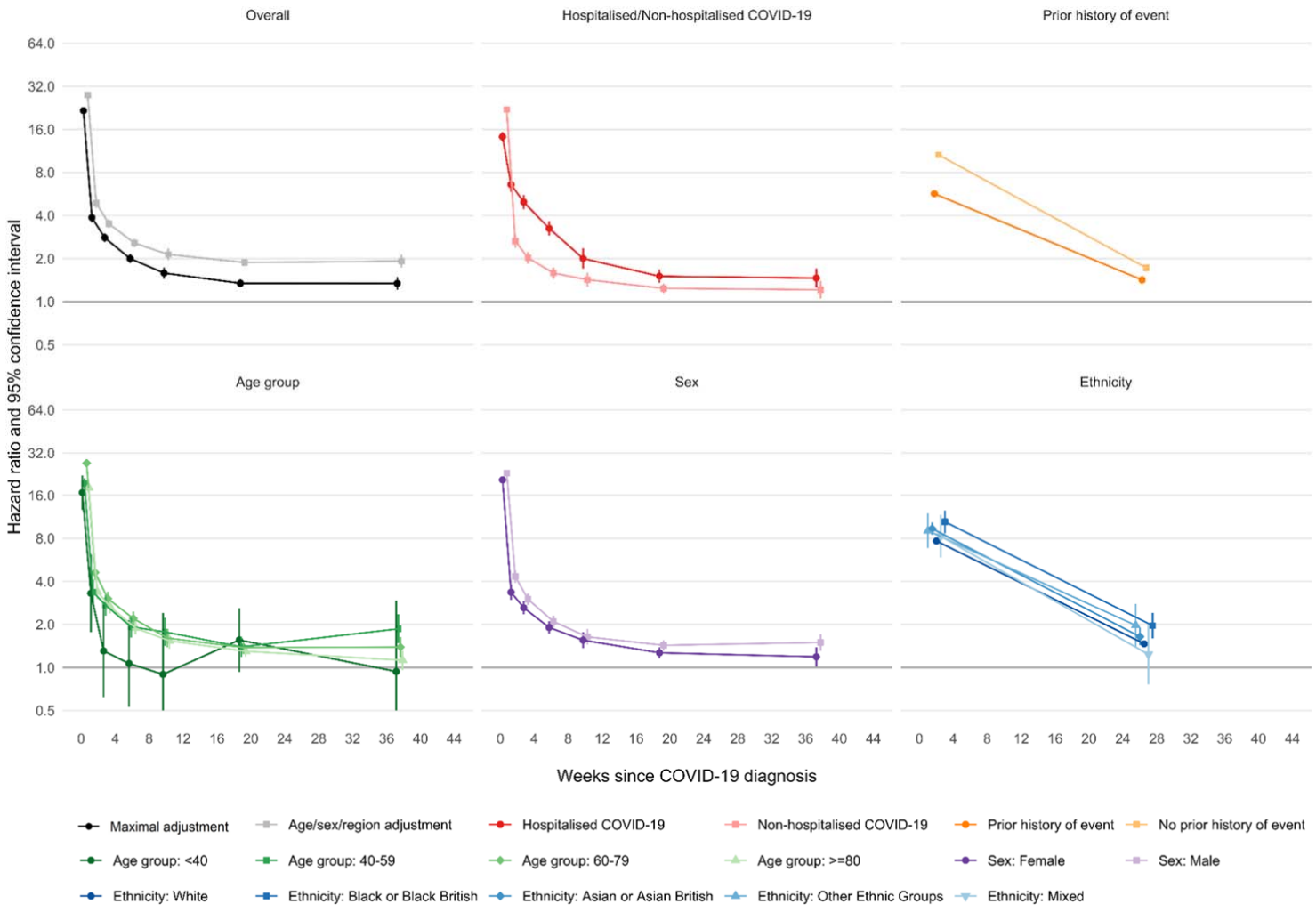


Figure 3 Hazard ratios for first venous thromboembolism after COVID-19 by time since diagnosis, overall and stratified by whether hospitalised with COVID-19, prior history of an venous thromboembolism, age, sex and ethnicity. All results are maximally adjusted unless otherwise stated.

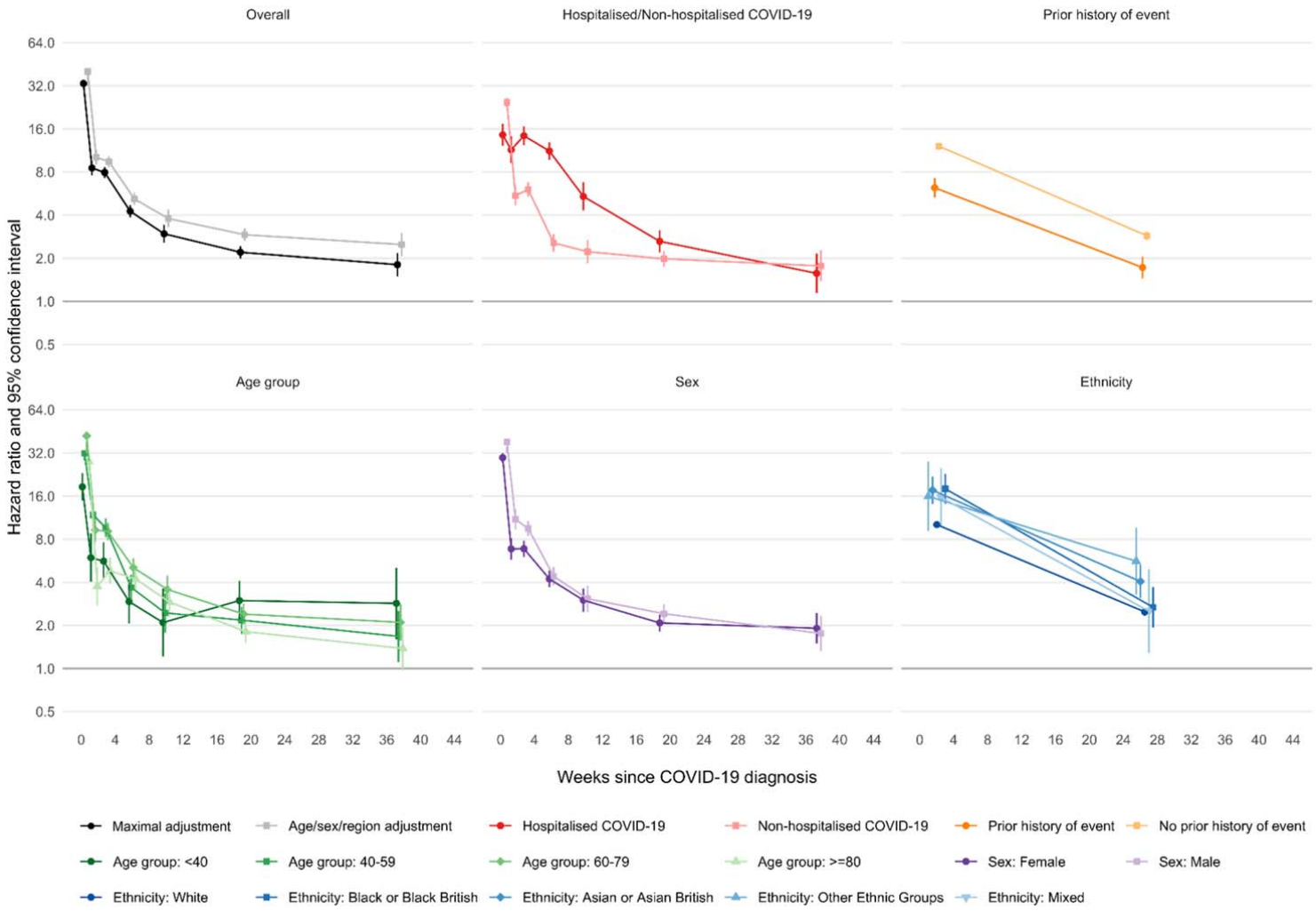
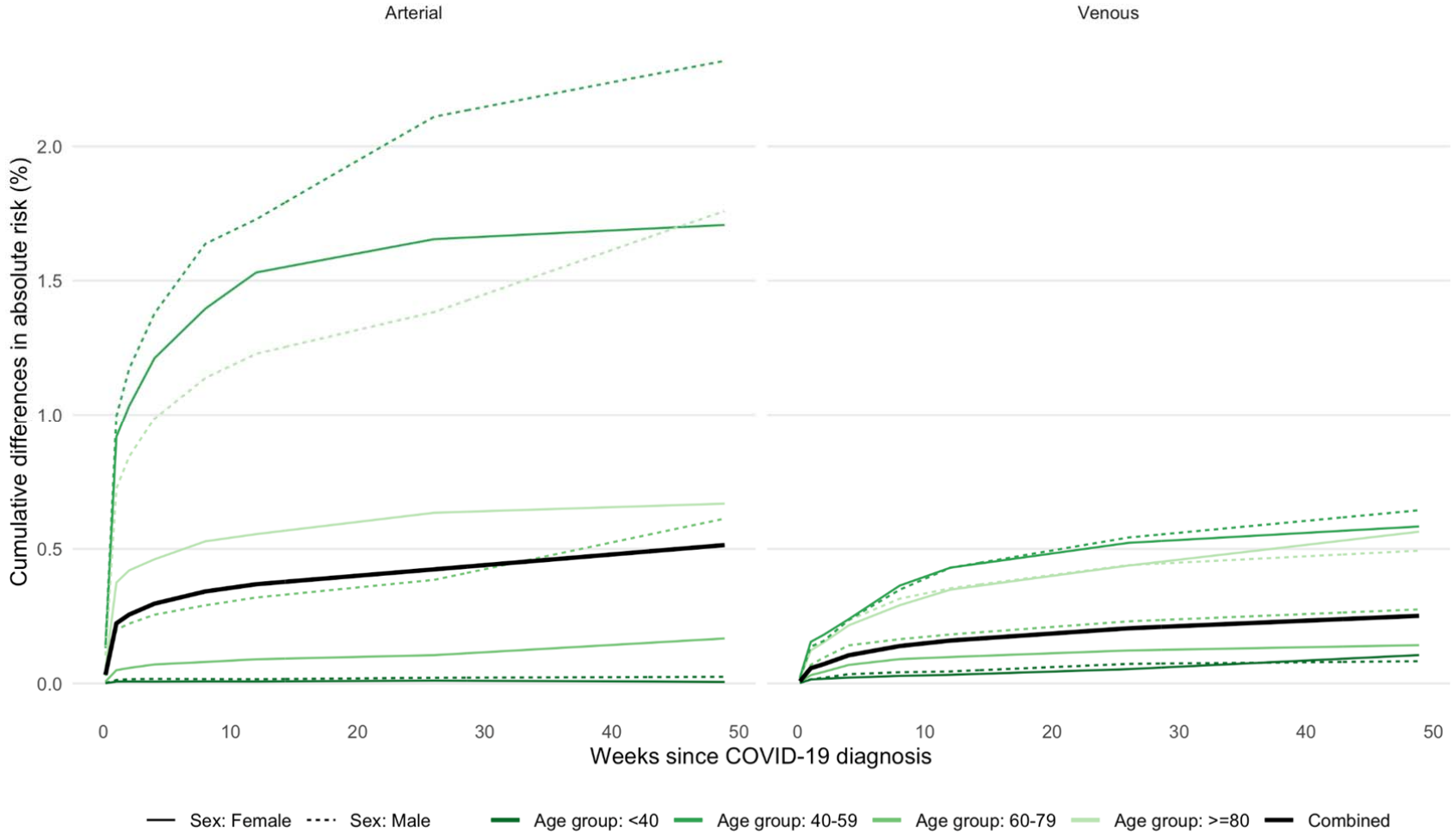
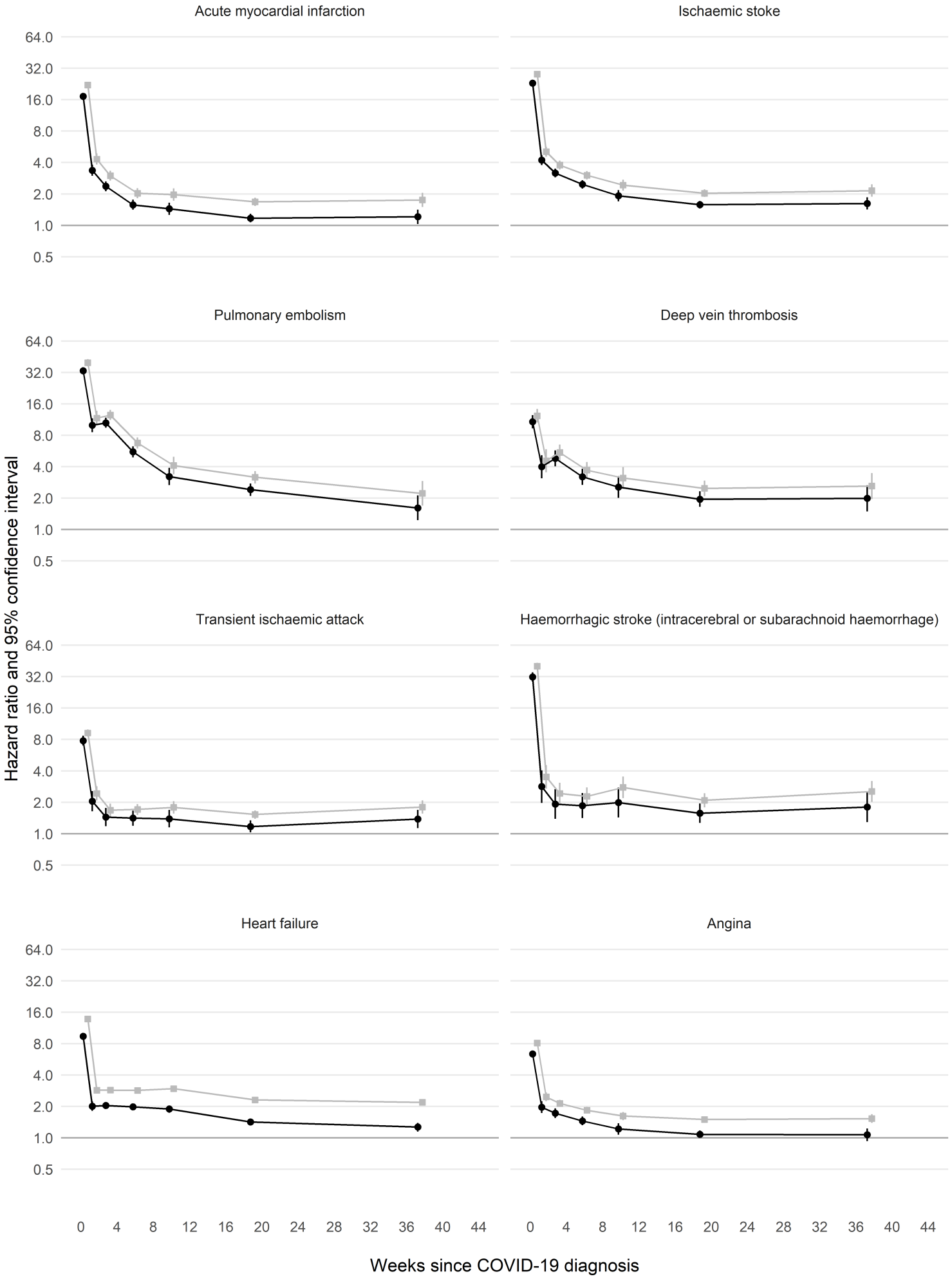
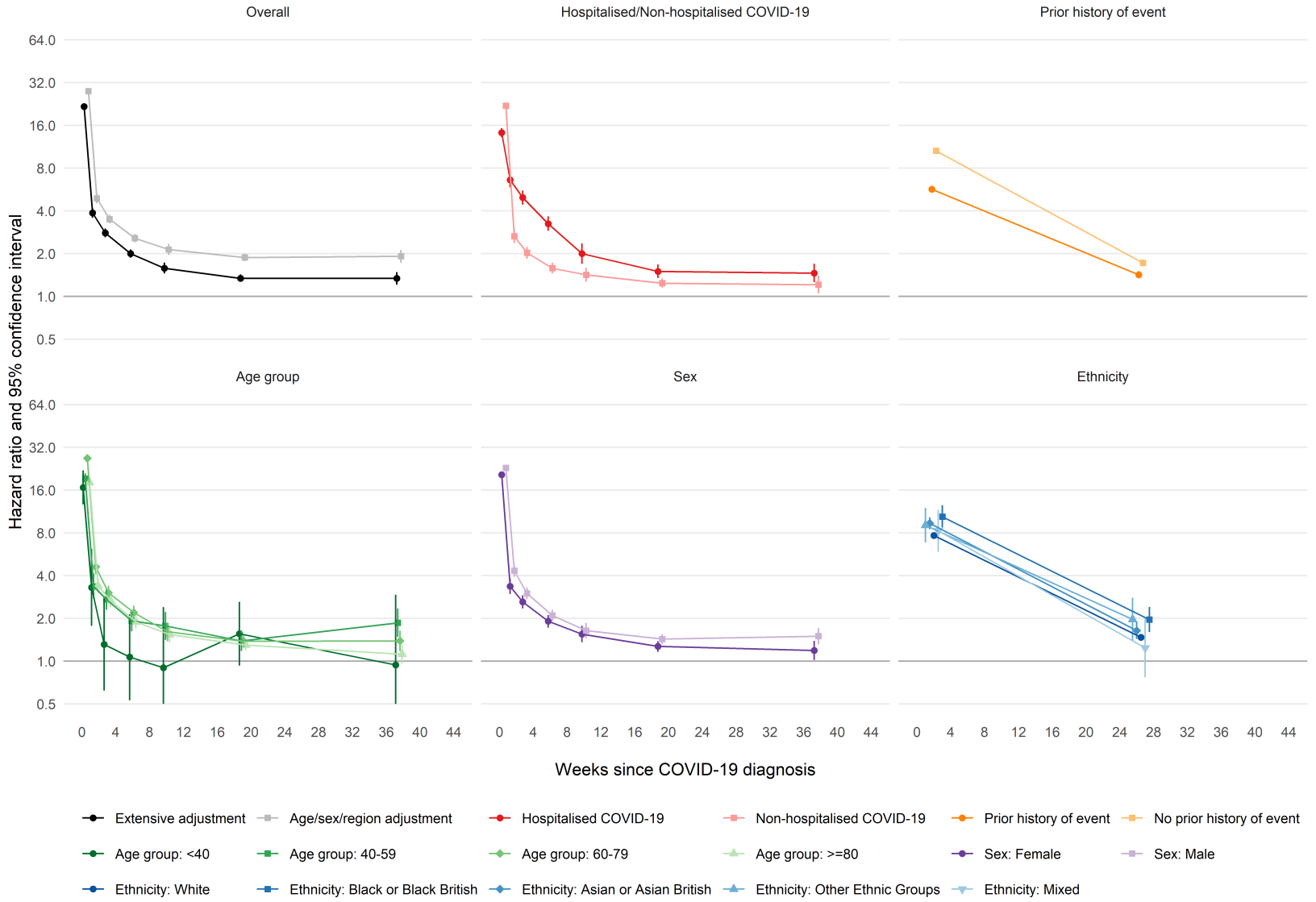
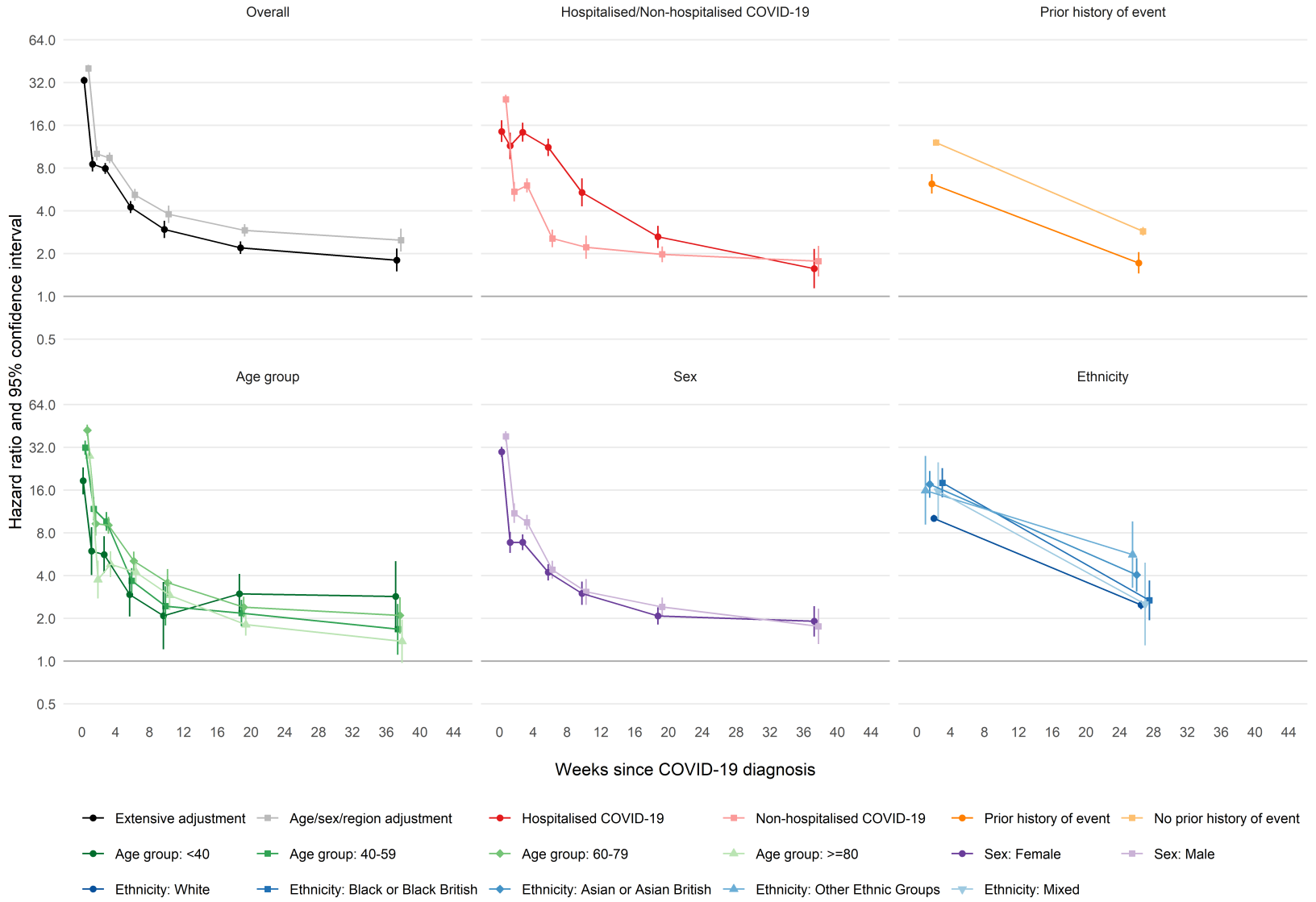


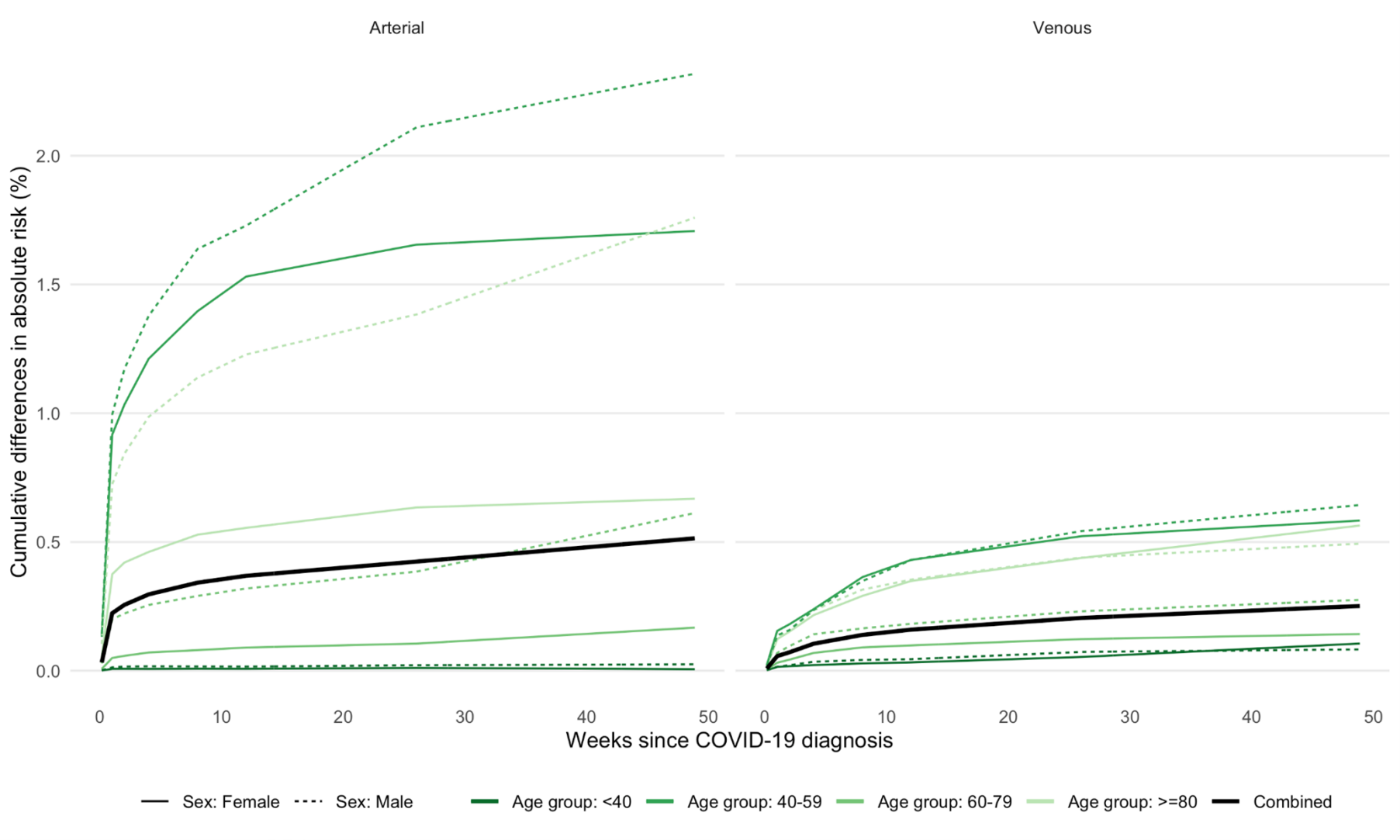
Figure 4. Estimated absolute increase in risk of arterial thrombosis and venous thromboembolism over time since diagnosis of COVID-19, compared with no COVID-19 diagnosis.




Acute myocardial infarction
Ischaemic stoke
Pulmonary embolism
Deep vein thrombosis
Transient ischaemic attack
Haemorrhagic stroke (intracerebral or subarachnoid haemorrhage)
Heart failure
Angina
Hazard ratio and 95% confidence interval
64.0
32.0
16.0
8.0
4.0
2.0
1.0
0.5
0
4
8
12
16
20
24
28
32
36
40
44
Weeks since COVID-19 diagnosis
Extensive adjustment
Age/sex/region adjustment


Overall
Hospitalised/Non-hospitalised COVID-19
Prior history of event
Age group
Sex
Ethnicity
Hazard ratio and 95% confidence interval
64.0
32.0
16.0
8.0
4.0
2.0
1.0
0.5
0 4 8 12 16 20 24 28 32 36 40 44
Weeks since COVID-19 diagnosis
Extensive adjustment
Age/sex/region adjustment
Hospitalised COVID-19
Non-hospitalised COVID-19
Prior history of event
No prior history of event
Age group: <40
Age group: 40-59
Age group: 60-79
Age group: >=80
Sex: Female
Sex: Male
Ethnicity: White
Ethnicity: Black or Black British
Ethnicity: Asian or Asian British
Ethnicity: Other Ethnic Groups
Ethnicity: Mixed


Overall
Hospitalised/Non-hospitalised COVID-19
Prior history of event
Age group
Sex
Ethnicity
Hazard ratio and 95% confidence interval
64.0
32.0
16.0
8.0
4.0
2.0
1.0
0.5
0 4 8 12 16 20 24 28 32 36 40 44
Weeks since COVID-19 diagnosis
Extensive adjustment
Age/sex/region adjustment
Hospitalised COVID-19
Non-hospitalised COVID-19
Prior history of event
No prior history of event
Age group: <40
Age group: 40-59
Age group: 60-79
Age group: >=80
Sex: Female
Sex: Male
Ethnicity: White
Ethnicity: Black or Black British
Ethnicity: Asian or Asian British
Ethnicity: Other Ethnic Groups
Ethnicity: Mixed


Arterial
Venous
Cumulative differences in absolute risk (%)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
Weeks since COVID-19 diagnosis
Sex: Female
Sex: Male
Age group: <40
Age group: 40-59
Age group: 60-79
Age group: >=80
Combined