COVID-19 infection and subsequent thromboembolism: A self-controlled case series analysis of a population cohort

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Key Points

Question: Does Covid-19 infection increase the risk of thromboembolism?

Findings: Among 1,449 individuals in Scotland who were tested positive of Covid-19 and had at least one thromboembolic events, the risk of thromboembolism was significantly elevated in the 7 days following the positive test (IRR 12.01, 95% CI 9.91-14.56). The risk of PE and DVT was particularly high and remained significantly elevated even 56 days following the test.

Meaning: Confirmed Covid-19 infection was associated with early elevated risk of MI, ischaemic stroke, and stronger and long elevations in risk with DVT and PE, reinforcing the need to consider monitoring and early diagnosis.
Abstract

Importance: An unexpectedly large number of people infected with Covid-19 appear to have experienced ischaemic stroke or thrombotic event.

Objective: This study aims to assess the risk associations between Covid-19 infection and thromboembolism.

Design: This is a self-controlled case-series study in Scotland. Their incidence rates during the risk interval (5 days before to 56 days after the positive test) and the control interval (the remaining periods) were compared intra-personally.

Setting: Population-based.

Participants: Individuals with confirmed (positive test) Covid-19 and at least one thromboembolic event between March 2018 and October 2020.

Exposure: Covid-19 test positive.

Main Outcomes and Measures: Myocardial infarction (MI), ischaemic stroke, deep-vein thrombosis (DVT), and pulmonary embolism (PE) hospital admissions and deaths.

Results: Across Scotland, 1,449 individuals tested positive for Covid-19 and experienced a thromboembolic event. The risk of thromboembolism was significantly elevated over the whole risk period but highest in the 7 days following the positive test (IRR 12.01, 95% CI 9.91-14.56), especially among people ≤75 years (IRR 22.78, 95% CI 17.58-29.53). Risk of MI, stroke, PE and DVT were all significantly higher in the week following a positive test. The risk of PE and DVT was particularly high and remained significantly elevated even 56 days following the test.

Conclusions and relevance: Confirmed Covid-19 infection was associated with early elevated risk of MI, ischaemic stroke, and stronger and long elevations in risk with DVT and PE, reinforcing the need to consider monitoring and early diagnosis. Treatment and prevention trials may need to be considered out of hospital on the basis of risk stratification.

Keywords: Covid-19; thromboembolism; stroke; self-controlled case series
Introduction

As of late January 2021, the Covid-19 pandemic has infected 100 million people and caused at least 2 million deaths globally. Increasing evidence suggests a potential link between Covid-19 infection and thromboembolism, which could affect a range of organs resulting in: myocardial infarction (MI), ischaemic stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT).

First indications of a potential link came from a case report that described pulmonary embolism in a patient infected with Covid-19 who had no relevant risk factors or past medical history, and a small case series that reported ischaemic stroke in five younger (33-49 years) patients who tested positive for Covid-19. These were supported by larger hospital-based case series. One reported that 31% of Covid-19 patients in intensive care units developed venous thromboembolism (VTE) and 4% had arterial thrombotic events. Another reported that 12% of hospitalised Covid-19 patients managed outside of intensive care developed DVTs. A recent meta-analysis of 3,487 Covid-19 patients from 30 studies produced a 26% pooled incidence of VTE, but concluded that the existing evidence was low-quality and heterogeneous. Similar findings were reported by another meta-analysis focused on PE and DVT. VTE has now been recognised as a relatively common complication of Covid-19 and clinical guidelines recommend the use of pharmaceutical prophylaxis following risk assessment, even though clinical trials have provided mixed evidence whether the anticoagulant use could lead to better outcomes.
The current evidence, however, is mainly based on crude incidence from hospitalised case series. Since hospitalised patients are a highly-selected minority of those infected with Covid-19, these studies are unrepresentative and not generalisable to the general population. Furthermore, the lack of comparison groups in most hospital studies meant they could not control for confounding whereby the high incidence of thromboembolic events among inpatients may simply reflect their high prevalence of comorbidity. To address these limitations, we conducted a self-controlled case series study using a national, general population cohort.

Methods

Data sources

We undertook individual-level record linkage of five health databases covering the whole of Scotland (5.5 million population): The Community Health Index (CHI) register; Electronic Communication of Surveillance in Scotland (ECOSS); Rapid Preliminary Inpatient Data (RAPID); Scottish Morbidity Record 01 (SMR01), and death certificates.

The CHI register provides sociodemographic information (age, sex, area socioeconomic deprivation). Deprivation is measured using the Scottish Index of Multiple Deprivation (SIMD), derived from seven domains – income, education, health, employment, crime, housing, and access to services – and categorised into
general population quintiles. ECOSS collects laboratory data on infectious diseases, including test date and result. RAPID collects real-time data on hospitalisation, including dates of admission and discharge, and type of ward, and SMR01 records diseases using International Classification of Diseases (ICD-10) codes and procedures using Office of Population Censuses and Surveys (OPCS-4) codes. Death certificates provide the date and cause (using ICD-10) of all deaths, whether in hospital or the community. The Community Health Index (CHI), a unique identifier, is used across all databases enabling exact matching. We extracted records covering 1 March 2018 to 5 October 2020 inclusive for all databases except the ECOSS Covid-19 test data which covered 1 March 2020 to 5 October 2020. The Scottish data were accessed through the eDRIS, Public Health Scotland and have been utilised in several previous epidemiological studies. Approval for the study was provided by the Public Benefit and Privacy Panel for Health and Social Care (reference 2021-0064).

Outcomes

This study included five outcomes ascertained from SMR01 and death certificates: myocardial infarction (MI; ICD-10: I21), ischaemic stroke (I63-64), pulmonary embolism (PE; I26), and deep-vein thrombosis (DVT; I80.1-80.9, I82.8, I82.9), as well as thromboembolism (composite of all four). To test the specificity of any association between Covid-19 and thromboembolism, we also included a composite negative control outcome of elective surgery for hernia repair (OPCS-4 T19, T21-27), colonoscopy (OPCS-4 H22, H25, H28), cataract surgery (OPCS-4 C71-75, C77, C79), or hip/knee replacement (OPCS-4 W37-42, W93-95, O18).
Statistical Analyses

The self-controlled case series (SCCS) method was chosen to analyse the association between Covid-19 infection and outcomes (Supplementary Figure 1), in favour of a traditional cohort approach, because of its ability to control for intrapersonal time-invariant confounders, and the UK’s testing strategy. Frail individuals with long-term conditions were more likely both to be tested and experience adverse outcomes. These confounders may not be well recorded in the routine data. With a new condition, such as Covid-19, other unknown confounders may also exist. The SCCS method eliminates intrapersonal time-invariant confounders because each person acts as their own control.\(^\text{13}\) The method has been widely-used in epidemiological studies, including influenza and myocardial infarction.\(^\text{14}\)

The study population comprised everyone in Scotland who had confirmed (positive real-time PCR test) Covid-19 infection and had experienced one or more thromboembolic event over the study period. The incidence rate ratio (IRR) of thromboembolic outcomes was derived from the ratio of incidence rates in risk and control intervals. The risk interval was defined as between 5 days before and 54 days after the sample was taken for their first positive Covid-19 test. The risk interval was categorised into: 5 to 1 day before; 0 to 7 days after; 8 to 28 days after; and 29 to 56 days after. The five days prior to confirmed infection were included in the risk period to take account of lags in symptom development and testing. The control interval was defined as the remaining study period. Because the UK Covid-19
pandemic started in March 2020, the majority of the control interval occurred prior to infection.

Conditional Poisson regression was used adjusting for participant age in quintile groups, the main time-varying confounder. Deriving rates for both the risk and control intervals from the same individual obviated the need to control statistically for time-invariant confounders. Because standard SCCS cannot be applied to fatal events, the models were run initially for non-fatal hospitalisations. We then repeated the analyses for the composite outcome of hospitalisation or death using the extended SCCS for event-dependent observation periods, which was described elsewhere.15

Subgroup analyses were conducted by age (≤75 versus >75 years), sex, and socioeconomic deprivation (SIMD quintile 1-3 versus SIMD quintile 4-5). P-values for subgroup differences were calculated. Additional subgroup analysis was conducted for age (≤65, 66-80, >80 years) to explore any age trends, even though the number of events were not sufficient to conduct formal tests. Three sensitivity analyses were conducted. Firstly, seasonality, in three-month categories, were adjusted because cardiovascular diseases exhibit seasonal patterning. Secondly, we included an extended risk interval, 14 to 6 days prior to a positive test. If the elevated risk in this extended interval is lower than that in the immediate pre-test interval, reverse causation is less likely. Thirdly, as Covid-19 infection was not tested prior to the 2020 pandemic, we restricted the analysis to cases with events after 1 February 2020. Lastly, we calculated the E-values to investigate how robust our findings are regarding time-varying confounders.16 All analyses were conducted in R version 3.5.1 with the package SCCS.
Role of funding source

This study was conducted under the support of the Wellcome Trust ISSF COVID Rapid Response Fund in the University of Glasgow. The funder has no role in study design, analysis, interpretation of data, writing of the report, and decision to submit the paper for publication.

Results

Of the 30,709 individuals who had at least one positive Covid-19 test (Figure 1) between 1 March 2020 and 5 October 2020, 29,260 were excluded because they did not have thromboembolic events. Of the 1,449 individuals who had thromboembolic events, 117 died out-of-hospital, 81 died in-hospital and 1,251 had non-fatal events. Less than two-third (62.59%) of the individuals had a Covid-19 diagnosis in hospital. The latter had a median age of 77 years (interquartile range [IQR] 65-85 years), half were male, and 26.46% lived in the most deprived quintile (Table 1). Median age was older for ischaemic stroke (82 years) and younger for PE (71 years) and DVT (73 years). Women accounted for a higher percentage (58.6%) of those with DVT.

The risk of non-fatal thromboembolism was significantly higher over the whole risk interval and highest within the seven days following the positive test (IRR 12.01, 95% CI 9.91-14.56) (Table 2). The associations were strongest for PE followed by DVT (Figure 2); which had similar risk patterns to overall thromboembolism.
associations with MI and ischaemic stroke were smaller in magnitude but nonetheless significant in the 7 days following a positive test, as well as the previous 5 days for MI only. Except for MI, all IRRs in the seven-day post-test interval were significantly stronger than those in the pre-test intervals (Ps <0.04). As expected, there was no significant change in the risk of elective surgery before or after a positive Covid-19 test. The findings for the composite outcome of fatal and non-fatal thromboembolism were similar to those for non-fatal thromboembolism, after accounting for censoring.

Adjusting for seasonality did not alter the findings (Supplementary Table 1). The extended pre-test risk interval generally had lower IRRs than the immediate pre-test interval, and were non-significant for MI, ischaemic stroke, and PE. Including only participants with thromboembolic events after February 2020 resulted in similar IRR estimates. The E-values ranged from 5.53 (MI) to 40.59 (PE) for the lower bound of 95% CIs within seven days of a positive test.

On subgroup analysis, a positive Covid-19 test was associated with higher risk of thromboembolism in both younger (≤75 years) and older (>75 years) people, but the magnitude of risk was significantly higher (P_{interaction} <0.0001) in the former. Compared with people aged older than 75 years, those younger had 23 and 47 times higher elevated thromboembolism and PE risk, respectively, within seven days of a positive Covid-19 test (Table 3). There appears to be a dose-response trend by age even though insufficient sample size inhibited formal testing (Supplementary Table 2). A positive Covid-19 test was associated with higher risk of overall thromboembolism, PE and DVT in both women and men, but the magnitude of risk
was higher in men \( (P_{\text{interaction}} < 0.006) \). The association between a positive Covid-19 test and ischaemic stroke was significant in men only. There was no consistent evidence of socioeconomic deprivation being an effect modifier.

Discussion

In this national, general population study we demonstrated an elevated risk of thromboembolism in temporal proximity to confirmed Covid-19 infection. In the week following a positive test, participants were at significantly increased risk of MI, ischaemic stroke, PE and DVT, with the increased risk of the latter two being marked (Day 0 to +7 IRRs of >27 and >17-fold, respectively) – with risk ratios substantially exceeding those previously associated with upper respiratory infections\(^{17}\) – and elevated risk continuing for some time thereafter. The risk ratios were even higher in younger people and in men.

The clear implication of this work is that PE/DVT is a broader problem not confined to hospitalised populations. At the present time unpublished results from ICU Covid-19 populations have led to early stopping of anticoagulant therapeutic arms because of signals suggestive of harm.\(^8\) Conversely the same collated international studies have intimated a significant decreased need for life support and improved results from less severe hospitalised patients.\(^9\) There is clearly ongoing confusion about who might benefit from more aggressive prophylaxis and treatment strategies. Given the potentially treatable nature of thrombotic events, urgent work needs to be
considered in prevention and treatment trial design to better stratify those at risk and consider community populations as well as the currently running hospitalised studies.

Our findings are in line but meaningfully extend previous Covid-19 studies. A meta-analysis of over 100,000 Covid-19 patients reported that 1.2% developed ischaemic stroke,\(^{18}\) a large proportion even considering their age and vascular risk profile. A hospital-based case-control study of 123 patients found an association (odds ratio 3.9) between Covid-19 infection and acute ischemic stroke, after controlling for age, sex, and vascular risk factors.\(^{19}\) Similarly, two meta-analyses reported high rates of PE and DVT in patients with Covid-19.\(^{5,6}\) Of note, traditional thromboembolic risk factors were not significantly associated with PE in Covid-19 patients suggesting the pathways may be different.\(^{20}\)

This study’s association pattern for MI is similar to that for influenza, with 5-6 times higher risk in the first 7 days after a test positive.\(^{14}\) However, the association of Covid-19 with VTE appeared to be much stronger than that of other infections. For example, a study using the same SCCS method found the elevated risk of DVT was much lower (IRR 1.91 in the first 2 weeks) for upper respiratory infections.\(^{17}\) The same study also found that the risk of PE elevated (IRR 2.11 in the first 4 weeks) following urinary tract infection. These suggest that Covid-19 may have either different mechanisms, or a much more marked inflammatory hit (in keeping with the cytokine storm), leading to an exponential difference in the risk of PE/DVT compared to other infections.
Our study demonstrated that the association with ischaemic stroke was significantly stronger in younger (≤75 years) individuals. This is consistent with previous reports of relatively young people (mean age 53-60 years) with Covid-19 requiring thrombectomy.\textsuperscript{21-23} In addition, among stroke patients, those who tested positive for Covid-19 were on average 7-15 years younger than those tested negative.\textsuperscript{24, 25} The underlying mechanism warrants further investigation but could relate to cytokine storm, at least to some people.\textsuperscript{26} Historical reports showed healthy young people were more likely to experience cytokine storm following viral infections,\textsuperscript{26} and cytokine storm in Covid-19 patients leading to hypercoagulable was a hypothesised mechanism for thromboembolism.\textsuperscript{27} The finding that Covid-19 is associated with a higher risk of thromboembolism in men than women may partially explain our previous finding that men have worse case-fatality following Covid-19 infection.\textsuperscript{28} This hypothesis requires further study.

Our study has several strengths. Firstly, it was unselective; covering the whole of Scotland and all confirmed Covid-19 cases regardless of whether they were hospitalised. This avoided the selection bias intrinsic to hospital-based studies. Since both Covid-19 infection and thromboembolism increase the chance of hospitalisation, selecting only hospital cases inevitably results in collider bias.\textsuperscript{10} Secondly, time-invariant confounders, including unknown and unmeasured confounders, were perfectly controlled by using participants as their own controls.\textsuperscript{13} The key time-varying confounders, age and seasonality, were adjusted for in the model.\textsuperscript{13} The use of E-values showed that the elevated risk within seven days of test positive would only be meaningfully nullified if there were very strong time-varying confounders that could increase/decrease the risk of test positive and thromboembolic events by 5 to 20
times. Thirdly, we were able to separately analyse non-fatal events, using the standard SCCS method, and all events, using a specific method designed for censored data, and the two approaches produced consistent findings.

However, the findings of this study are still subject to the following limitations. To ensure internal validity, this study opted for the SCCS method, which only included patients with at least one thromboembolism during the study period. However, this may limit the generalisability of the findings to people with lower risk of these events. It should be noted that, if the elevated risk of PE is truly causal, the estimates that we provided could be an underestimate. The IRR for the latest categories in the risk interval was still significantly greater than one, suggesting a long tail of risk elevation and thus some of the pre- and post-infection control interval could be misspecified. Patients with no or mild symptoms from Covid-19 infection are less likely to have been tested, especially at the beginning of the pandemic when testing capacity was lower. The increased risk of thromboembolism demonstrated in the days prior to confirmed infection is likely to reflect the time lag between actual date of infection and our proxy measure of it; date of specimen collection. Reverse causation is possible in some patients; for example, nosocomial infection of patients hospitalised for thromboembolic events. However, the lack of an association with elective surgery suggests that any reverse causation is unlikely to fully explain our findings. The lowered risk in extended pre-test interval for outcomes except MI also does not support strong reverse causation. It is highly likely that there was underreporting of events from the first wave. Even though there was no role for routine CT scanning in Covid-19 and data on rates of advanced imaging are not yet clear, it is our
expectation that more extensive imaging in subsequent waves is highly likely to increase pick-up of thrombus.

In conclusion, confirmed Covid-19 infection was associated with elevated risk of thromboembolic events, including MI, ischaemic stroke, DVT, and PE. Whilst, the elevated risk of MI and ischaemic stroke was transient, the increased risk of DVT and PE was marked and persisted longer. These complications of Covid-19, particularly in younger people, should be addressed through a combination of prophylaxis and early detection. Clinical trials to prevent thrombotic events should include younger non-hospitalised individuals with Covid-19.

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Declaration of interests

All authors completed the ICMJE conflict of interest form and declare no potential conflicts of interests.

Data sharing

Relevant data can be requested via eDRIS, Public Health Scotland (https://www.isdscotland.org/products-and-services/edris/).
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Table 1. Patients characteristics for analysis of non-fatal admissions

|                      | Composite | Myocardial infarction | Ischaemic stroke | Pulmonary embolism | Deep-vein thrombosis | Elective surgery* |
|----------------------|-----------|-----------------------|------------------|-------------------|----------------------|------------------|
| N for all events     | 1449      | 376                   | 560              | 417               | 179                  | 123              |
| N for admissions only| 1332      | 337                   | 505              | 391               | 174                  | 123              |
| N for non-fatal admissions only | 1251 | 319                   | 473              | 359               | 169                  | 116              |
| Covid-19 hospitalisation | 783 (62.59) | 205 (64.26) | 295 (62.37) | 235 (65.46) | 94 (55.62) | 60 (51.72) |
| Median (IQR) age, years | 77 (65-85) | 78 (67-85) | 82 (73-87) | 71 (59-81) | 73 (59-82) | 78 (70-85) |
| Sex                  |           |                       |                  |                   |                      |                  |
| Female               | 626 (50.04) | 128 (40.13) | 246 (52.01) | 180 (50.14) | 99 (58.58) | 45 (38.79) |
| Male                 | 625 (49.96) | 191 (59.87) | 227 (47.99) | 179 (49.86) | 70 (41.42) | 71 (61.21) |
| SIMD quintile        |           |                       |                  |                   |                      |                  |
| 1st (Most deprived)  | 331 (26.46) | 91 (28.53) | 124 (26.22) | 84 (23.40) | 47 (27.81) | 34 (29.31) |
| 2nd                  | 282 (22.54) | 79 (24.76) | 100 (21.14) | 88 (24.51) | 32 (18.93) | 21 (18.10) |
| 3rd                  | 230 (18.39) | 55 (17.24) | 94 (19.87) | 65 (18.11) | 33 (19.53) | 21 (18.10) |
| 4th                  | 230 (18.39) | 53 (16.61) | 95 (20.08) | 68 (18.94) | 27 (15.98) | 25 (21.55) |
| 5th (Least deprived) | 178 (14.23) | 41 (12.85) | 60 (12.68) | 54 (15.04) | 30 (17.75) | 15 (12.93) |

Numbers (%) are presented unless otherwise specified.

*Elective surgery included hernia repair, colonoscopy, cataract surgery, and hip and knee replacement, and is a negative control outcome.
Table 2. Associations between COVID-19 and outcomes

| Outcome by | Non-fatal events | All events† |
|-----------|------------------|-------------|
|           | IRR (95% CI)     | P           | IRR (95% CI) | P   |
| **Composite** |                  |             |              |
| 5-1 days before | 4.77 (3.20, 7.10) | <0.0001     | 3.71 (2.50, 5.49) | <0.0001 |
| 0-7 days after  | 12.01 (9.91, 14.56) | <0.0001    | 5.70 (4.72, 6.89) | <0.0001 |
| 8-28 days after | 2.82 (2.16, 3.67)  | <0.0001    | 1.54 (1.22, 1.94) | 0.0003  |
| 28-56 days after | 2.30 (1.77, 3.00)  | <0.0001    | 1.51 (1.21, 1.88) | 0.0002  |
| **Myocardial infarction** |                |             |              |
| 5-1 days before | 5.15 (2.54, 10.46) | <0.0001     | 3.79 (1.86, 7.71) | 0.0002  |
| 0-7 days after  | 5.16 (3.04, 8.73)  | <0.0001    | 1.98 (1.23, 3.18) | 0.005   |
| 8-28 days after | 1.51 (0.77, 2.95)  | 0.23        | 0.85 (0.50, 1.44) | 0.55    |
| 28-56 days after | 1.15 (0.56, 2.35)  | 0.70        | 0.90 (0.53, 1.50) | 0.67    |
| **Ischaemic stroke** |                |             |              |
| 5-1 days before | 2.12 (0.88, 5.13)  | 0.10        | 1.58 (0.65, 3.84) | 0.31    |
| 0-7 days after  | 7.22 (5.02, 10.38) | <0.0001    | 3.25 (2.34, 4.50) | <0.0001 |
| 8-28 days after | 0.75 (0.35, 1.58)  | 0.45        | 0.69 (0.42, 1.12) | 0.14    |
| 28-56 days after | 1.11 (0.63, 1.94)  | 0.72        | 0.94 (0.63, 1.41) | 0.77    |
| **Pulmonary embolism** |              |             |              |
| 5-1 days before | 9.95 (5.42, 18.27) | <0.0001     | 7.47 (4.13, 13.51) | <0.0001 |
| 0-7 days after  | 27.55 (20.55, 36.95) | <0.0001    | 16.81 (12.46, 22.69) | <0.0001 |
| 8-28 days after | 7.27 (5.07, 10.43) | <0.0001    | 4.52 (3.21, 6.35)  | <0.0001 |
| 28-56 days after | 5.59 (3.87, 8.07)  | <0.0001    | 3.54 (2.54, 4.93)  | <0.0001 |
| **Deep vein thrombosis** |            |             |              |
| 5-1 days before | 4.67 (1.48, 14.72) | 0.008       | 4.23 (1.34, 13.32) | 0.01    |
| 0-7 days after  | 17.44 (11.00, 27.66) | <0.0001    | 11.51 (7.30, 18.16) | <0.0001 |
| 8-28 days after | 3.64 (1.90, 7.01)  | 0.0001     | 2.43 (1.27, 4.67)  | 0.008   |
| 28-56 days after | 1.98 (0.91, 4.29)  | 0.08        | 1.77 (0.92, 3.42)  | 0.09    |
| **Elective surgeries**† |       |             |              |
| 5-1 days before | -                | -           | -             | -      |
| 0-7 days after  | 1.69 (0.41, 6.88)  | 0.47        | 1.28 (0.40, 4.06) | 0.67    |
| 8-28 days after | 1.78 (0.65, 4.90)  | 0.26        | 0.94 (0.34, 2.59) | 0.91    |
| 28-56 days after | 2.28 (0.98, 5.32)  | 0.06        | 1.19 (0.51, 2.76) | 0.68    |

Patients' age quintile was adjusted

IRR: incidence rate ratio

*Elective surgery included hernia repair, colonoscopy, cataract surgery, and hip/knee replacement, and is a negative control outcome

†Including both fatal and non-fatal events, with event dependent observation handled using specialised method
Table 3. Subgroup analysis for non-fatal events

| Outcome by risk intervals | Age ≤75 years | Age >75 years | Sex Female | Sex Male | SIMD ≤2nd quintile | SIMD >2nd quintile |
|--------------------------|--------------|--------------|-----------|---------|-------------------|-------------------|
|                          | IRR (95% CI) | P_interaction | IRR (95% CI) | P_interaction | IRR (95% CI) | P_interaction |
| Composite                |              |              |            |          |                  |                  |
| 5-1 days before          | 3.80 (2.44, 5.93) | 0.19 | 2.22 (1.41, 3.47) | 0.03 | 3.26 (2.24, 4.76) | 0.67 |
| 0-7 days after           | 22.78 (17.58, 29.53) | <0.0001 | 6.36 (4.47, 9.04) | <0.0001 | 11.04 (8.38, 14.56) | 0.55 |
| 8-28 days after          | 5.79 (4.16, 8.07) | <0.0001 | 2.64 (1.83, 3.82) | 0.50 | 2.23 (1.48, 3.35) | 0.15 |
| 28-56 days after         | 4.27 (3.03, 6.03) | <0.0001 | 2.28 (1.59, 3.27) | 0.79 | 2.38 (1.66, 3.42) | 0.72 |
| Myocardial infarction    |              |              |            |          |                  |                  |
| 5-1 days before          | 4.14 (2.00, 8.54) | 0.67 | 4.29 (2.15, 8.58) | 0.66 | 4.38 (2.21, 8.66) | 0.69 |
| 0-7 days after           | 6.19 (2.85, 13.42) | 0.28 | 3.35 (1.22, 9.18) | 0.11 | 6.46 (3.14, 13.30) | 0.51 |
| 8-28 days after          | 2.49 (1.08, 5.77) | 0.89 | 1.58 (0.57, 4.39) | 0.67 | 1.92 (0.78, 4.75) | 0.57 |
| 28-56 days after         | 1.01 (0.32, 3.23) | 0.96 | 1.41 (0.51, 3.92) | 0.60 | 1.31 (0.48, 3.59) | 0.80 |
| Ischaemic stroke         |              |              |            |          |                  |                  |
| 5-1 days before          | 1.70 (0.54, 5.39) | 1.00 | 1.21 (0.50, 2.96) | 0.18 | 2.47 (1.31, 4.68) | 0.22 |
| 0-7 days after           | 17.81 (10.67, 29.72) | <0.0001 | 2.05 (0.84, 5.00) | 0.0002 | 6.50 (3.87, 10.91) | 0.54 |
| 8-28 days after          | 0.45 (0.06, 3.27) | 1.00 | 0.75 (0.28, 2.03) | 0.96 | 0.76 (0.28, 2.07) | 0.89 |
| 28-56 days after         | 1.46 (0.53, 4.02) | 0.96 | 1.20 (0.59, 2.45) | 0.75 | 0.61 (0.22, 1.64) | 0.12 |
| Pulmonary embolism       |              |              |            |          |                  |                  |
| 5-1 days before          | 5.36 (2.60, 11.08) | 0.39 | 1.98 (0.73, 5.37) | 0.02 | 4.72 (2.39, 9.32) | 0.89 |
| 0-7 days after           | 46.94 (23.21, 98.12) | <0.0001 | 15.22 (9.30, 24.90) | 0.001 | 25.44 (16.80, 38.54) | 0.49 |
| 8-28 days after          | 12.64 (8.20, 19.49) | 0.20 | 5.77 (3.42, 9.71) | 0.57 | 4.32 (2.32, 8.07) | 0.22 |
| 28-56 days after         | 8.13 (5.16, 12.81) | 0.0009 | 4.98 (3.02, 8.21) | 0.32 | 6.66 (4.17, 10.85) | 0.32 |
| Deep vein thrombosis     |              |              |            |          |                  |                  |
| 5-1 days before          | 2.20 (0.54, 9.04) | 1.00 | 3.18 (1.16, 8.73) | 0.80 | 1.79 (0.44, 7.36) | 0.19 |
| 0-7 days after           | 24.21 (13.13, 46.64) | 0.09 | 8.04 (3.49, 18.57) | 0.006 | 15.80 (8.23, 30.33) | 0.55 |
| 8-28 days after          | 5.30 (2.38, 11.80) | 0.13 | 4.89 (2.33, 10.26) | 0.33 | 4.27 (1.83, 9.97) | 0.74 |
| 28-56 days after         | 2.85 (1.11, 7.28) | 0.19 | 1.41 (0.44, 4.50) | 0.26 | 2.30 (0.83, 6.41) | 0.92 |

Patients’ age quintile was adjusted

IRR: incidence rate ratio; SIMD: Scottish Index of Multiple Deprivation
Figure 1. Participant flowchart

Figure 2. Associations between Covid-19 and non-fatal outcomes
30,714 COVID-19 test positive episodes

30,709 unique COVID-19 episodes

1449 COVID-19 episodes with composite outcome based on hospital admission and death certificate (All events)

1332 COVID-19 episodes with hospital admission composite outcome

1251 COVID-19 episodes with hospital admission composite outcome who were alive at discharge (Non-fatal events)

5 excluded due to being the same COVID-19 episodes

29,260 excluded due to not having the outcome

117 excluded due to event ascertained from death certificate only

81 excluded due to in-hospital death
