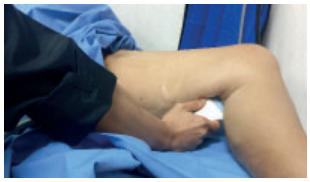
research



Thrombotic and bleeding outcomes post-covid p 59

Impact of interventions to reduce opioid use in non-cancer pain p 62

Thromboembolism and bleeding after covid-19

ORIGINAL RESEARCH Self-controlled cases series and matched cohort study

Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19

Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al

Cite this as: *BMJ* 2022;377:e069590
Find this at doi: 10.1136/bmj-2021-069590

Study question What is the risk of deep venous thrombosis (DVT), pulmonary embolism (PE), and bleeding after covid-19?

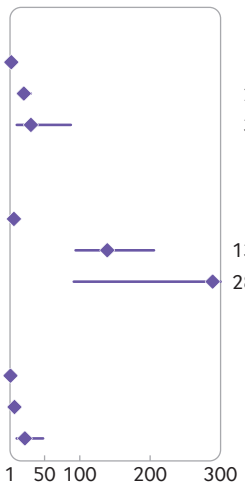
Methods The self-controlled case series (SCCS) and matched cohort study (MCS) were used to determine the incidence rate ratios for a first DVT, PE, and bleeding event after covid-19 in risk periods categorised from days 1-180, relative to the remaining time period (control), and risk ratios during days 1-30 of a first time event using registry data on all people who tested positive for SARS-CoV-2 (n=1 057 174) in Sweden, 1 February 2020 to 25 May 2021, and matched control participants (n=4 076 342).

Study answer and limitations Incidence rate ratios (SCCS) were significantly increased 70 days after covid-19 for DVT, 110 days for PE, and 60 days for bleeding, compared with the control period. Risk ratios (MCS) for days 1-30 after covid-19 were 4.98 (95% CI 4.96 to 5.01) for DVT, 33.05 (32.8 to 33.3) for PE, and 1.88 (1.71 to 2.07) for bleeding, after adjusting for confounders. Absolute risks for control participants versus patients with covid-19 were 0.007% (n=267) *v* 0.039% (n=401) for DVT, 0.004% (n=171) *v* 0.170% (n=1761) for PE, and 0.035 (n=1292) *v* 0.101 (n=1002) for bleeding. Registry information is at risk of incomplete or inaccurate data. As data for control participants were limited to 1997, events could have been falsely classified as first events.

What this study adds The findings suggest that covid-19 is a risk factor for DVT, PE, or bleeding.

Funding, competing interests, and data sharing
No additional funding or competing interests.
Study protocol and depersonalised and jittered data available from the corresponding author.

Outcome/ covid-19 severity	No of events (%)	Risk ratio (95% CI)	Risk ratio (95% CI)	P value
Deep vein thrombosis (n=4 967 398)				
Negative	267 (0.01)		1 (ref)	-
Mild	155 (0.02)		2.80 (2.26 to 3.47)	<0.001
Admitted to hospital	163 (0.36)		20.21 (13.07 to 31.25)	<0.001
Admitted to ICU	83 (1.18)		30.58 (10.57 to 88.46)	<0.001
Pulmonary embolism (n=4 967 398)				
Negative	171 (0.004)		1 (ref)	-
Mild	239 (0.02)		6.77 (5.43 to 8.45)	<0.001
Admitted to hospital	1037 (2.27)		139.16 (94.32 to 205.31)	<0.001
Admitted to ICU	485 (6.87)		289.38 (91.55 to 914.73)	<0.001
Bleeding (n=4 643 423)				
Negative	1 292 (0.04)		1 (ref)	-
Mild	349 (0.04)		1.03 (0.91 to 1.17)	0.64
Admitted to hospital	467 (1.18)		7.40 (6.00 to 9.12)	<0.001
Admitted to ICU	186 (2.85)		22.68 (10.67 to 48.2)	<0.001



Adjusted relative risks with 95% confidence intervals of a first deep vein thrombosis, pulmonary embolism, or bleeding event within 30 days after covid-19 in matched cohort study adjusted for weighted Charlson comorbidity index score, cancer, surgery, and long term anticoagulation treatment, and stratified according to disease severity using control participants who were not reported to the Public Health Agency of Sweden (test negative) as baseline. ICU=intensive care unit

FAST FACTS

The self-controlled case series method and covid-19

The self-controlled case series method is one of two approaches used to estimate the association between covid-19 and venous thromboembolism or bleeding. This article briefly describes the method, its assumptions, and how it was implemented in the study by Katsoularis et al, and offers some pointers to guide the interpretation of the results.

The self-controlled case series method is an epidemiological design for estimating the association between an exposure and a health outcome.[1 2] In the linked study, the exposure is covid-19 and the outcome is deep vein thrombosis, pulmonary embolism, or bleeding.[3]

Key features

The self-controlled case series method automatically adjusts for all multiplicative confounders that do not vary over the duration of the study—automatically meaning that such confounders need not be adjusted for explicitly, measured, or even known. This is because estimation is within individuals: individuals act as their own control (hence the term self-controlled). Time varying confounders (such as time, age, or other exposures), however, must be adjusted for explicitly. Also, cases (people who have experienced the outcome) only need be sampled as they contribute to the estimation (hence the term case series).

For these reasons, the method is well suited to the analysis of uncommon outcomes, using data from pre-existing databases with possibly incomplete information on potential confounders.

The method proceeds by specifying risk periods during which each individual is considered to be—potentially at least—at higher (or lower) risk of the outcome owing to the exposure of interest. In the linked study, we chose the period up to 180 days after the covid-19 date (the earliest recorded date of covid-19), subdivided into shorter segments. A peculiarity of the self-controlled case series, compared with other epidemiological techniques, is that time after the event is used. This is because the method derives from a conditional argument based on the question "Given that the outcome event occurred, how likely is it that it arose during a risk period?"; the answer to which involves all observation times at which the event could have occurred, including those after it actually did occur.

The self-controlled case series method requires two conditions stemming from this feature. The first is that the outcome event should not affect subsequent exposures, and the second is that the event should not censor subsequent observation.

KEY FEATURES OF SELF-CONTROLLED CASE SERIES

- Uses only cases
- Automatically controls for fixed multiplicative confounders
- Time varying confounders must be adjusted for explicitly
- Easy to check sensitivity to failure of key assumptions
- Provides relative and not absolute measures of risk

Paddy Farrington paddy.farrington@open.ac.uk
See bmj.com for author details

Application to covid-19 data

Are these two conditions met in our study? Strictly speaking, probably not (indeed, rare are the situations in which conditions required by any statistical method are strictly fulfilled). But simple work arounds exist. For the first condition, outcomes might affect subsequent exposures—for example, owing to nosocomial acquisition of SARS-CoV-2 after admission to hospital. But such an effect is time limited and may be circumvented by the inclusion of a dummy pre-exposure risk period. To take care of this, we chose a 30 day interval. Another mechanism resulting in inverse causality is the delay between SARS-CoV-2 infection and its identification, which is dealt with similarly by including the covid-19 date in the pre-risk period; this was the subject of a separate investigation.[4]

For the second condition, some events—notably pulmonary embolism, may result in the patient's death, at which point observation is censored. But a simple sensitivity analysis (repeating the analysis without the cases who died) can be used to determine whether this contravention actually affects the results in meaningful ways—and as it turns out, it does not.

Thus, in our study, departures from assumptions are not so serious as to invalidate the results, and the standard self-controlled case series model can be used. Had this not been the case, other (more complicated) self-controlled case series models could have been deployed that do not require these conditions to be met.[2-6]

Issues of interpretation

In our study, we used both the self-controlled case series method and a matched cohort method to estimate the incidence rate ratio associated with covid-19. In both cases, the incidence rate ratios represent the relative incidence of the event in a defined post-covid period, compared with the incidence in the absence of infection.

In the self-controlled case series method, all fixed confounders are adjusted for automatically, but time varying confounders must be adjusted for explicitly. We only adjusted for period effects, owing to difficulties in documenting other time varying confounders throughout the study period, such as cancer treatment. In the matched cohort study analysis, however, these concurrent treatments could be included. Nonetheless, fixed confounders also needed to be adjusted for explicitly, and only limited information on them was available. Thus, the two methods are to some extent complementary with respect to control of confounders. Obtaining similar results from similar analyses using different methods provides reassurance about the validity of the two approaches.

A shortcoming of the self-controlled case series method is that it only yields incidence rate ratios and not absolute measures of risk. An additional benefit of using both methods is that the matched cohort study yields absolute risks as well as incidence rate ratios. These estimates of absolute risk are essential to contextualise the associations. For example, in our study, the incidence of a first deep vein thrombosis, pulmonary embolism, and bleeding event in the population in the absence of covid-19 is low. Large incidence rate ratios such as those we obtained might represent low incidences, divided by very low incidences.

Cite this as: *BMJ* 2022;377:o625
Find the full version with references at http://dx.doi.org/10.1136/bmj.o625

COMMENTARY

Risks are increased even after mild infections

It is now clear from meta-analyses of case series,[1 2] cohort studies,[3] and self-controlled case series[4 5] that the risk of venous thromboembolism is increased after SARS-CoV-2 infection. However, two important questions remain: for how long post-infection is the risk increased, and does mild infection also increase risk? In this issue, Katsoularis and colleagues address these questions by applying two complementary study designs to data from several Swedish registries.[6]

The authors identified more than one million people with laboratory confirmed SARS-CoV-2 infection from the start of the pandemic to mid-2021, matched on age, sex, and county of residence to more than four million people who had not had a positive SARS-CoV-2 test result. After adjustment for a wide range of potential confounders, the authors reported a fivefold increase in risk of deep vein thrombosis (relative incidence 4.98, 95% confidence interval 4.96 to 5.01), 33-fold increase in risk of pulmonary embolism (33.05, 32.8 to 33.3), and an almost twofold increase in risk of bleeding (1.88, 1.71 to 2.07) in the 30 days after infection.

The results were largely consistent in alternative analyses using a self-controlled case series approach comparing risk 1-30 days after the infection with a control period. The advantage of this approach is that comparing two periods in the same individual eliminates confounding by factors that are stable over time, such as genetics.[7]

Frederick K Ho
Frederick.Ho@glasgow.ac.uk
Jill P Pell
See bmj.com for author details

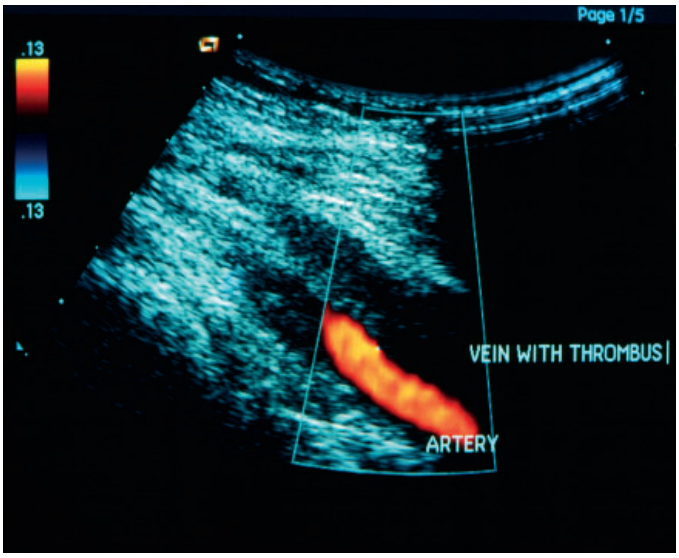
Finer detail

The large study population enabled novel, granular analyses. Previous studies have already shown that the association between SARS-CoV2-2 and thromboembolic events is much stronger for pulmonary embolism than for deep vein thrombosis.[8] Katsoularis and colleagues were able to show that the increased risk of thromboembolism also lasts longer for pulmonary embolism than for deep vein thrombosis; six and two months, respectively.

These authors also report an increased risk of bleeding after SARS-CoV-2 infection that is consistent with previous studies. Use of thromboprophylaxis after SARS-CoV-2 infection clearly carries a risk of bleeding. However, covid-19 has also been associated with coagulopathy and disseminated intravascular coagulation.[9] Although unable to identify the underlying mechanism, the authors show that the association with bleeding is independent of anticoagulation before SARS-CoV-2 infection and lasts for two weeks after infection.

As risks of thromboembolism and bleeding were highest among participants with more severe covid-19, vaccination could reduce the overall risk both by preventing infection and by reducing its severity when it does occur. While risk of thromboembolic events is increased after vaccination,[5 10] the magnitude of risk remains smaller and persists for a shorter period that that associated with infection.

Are the new study findings still relevant now that nearly 65% of the world's population has received at least one vaccine dose [11]? Yes—current vaccines are highly effective against severe covid-19 but confer only moderate protection against infection with the omicron variant.[12 13] Breakthrough infections are common, even after a third dose,[14] and effectiveness against symptomatic disease appears to decrease to less than 50% 10 weeks after vaccination.[13]



JAMES KING-HOLMES/SPL

There is a need to remain vigilant to the complications associated with even mild SARS-CoV-2 infection

Although many infections with the omicron variant are mild, the new study confirms an increased risk of venous thromboembolism even among those with milder infections who do not require admission to hospital.[4] The association was much weaker (relative incidence 5.87, 95% confidence interval 4.88 to 7.05 for pulmonary embolism) than that among patients admitted to hospital (64.49, 53.91 to 77.15) and those admitted to intensive care (196.98, 128.71 to 301.46), but mild disease accounts for a much larger proportion of infections (94.5% in this study). This patient group may therefore contribute a substantial number of thromboembolic events.

A study from England [15] reported a doubling in the incidence of, and mortality from, thromboembolism since the start of the pandemic in 2020 compared with the same periods in 2018 and 2019. The same study reported comparable increases among individuals without positive SARS-CoV-2 test results. Some of those without a positive test result will have been infected before widespread testing was available, but others will have had mild or asymptomatic infections.[16]

Living with covid

Despite the potential for new variants of concern, most governments are removing restrictions and shifting their focus to determining how best to "live with covid."[17] Katsoularis and colleagues' study reminds us of the need to remain vigilant to the complications associated with even mild SARS-CoV-2 infection, including thromboembolism.

Cite this as: *BMJ* 2022;377:o817
Find the full version with references at http://dx.doi.org/10.1136/bmj.o817

Efficacy of interventions to reduce long term opioid treatment for chronic non-cancer pain

Avery N, McNeilage AG, Stanaway F, et al

Cite this as: *BMJ* 2022;377:e066375
Find this at doi: 10.1136/bmj-2021-066375

ED ROONEY/ALAMY

Study questions What is the efficacy of clinical interventions to support people with chronic non-cancer pain receiving long term opioid treatment to reduce or discontinue opioid treatments; what are the effects of these interventions on patients' opioid doses and their own pain, function, and quality of life; and are these interventions associated with any adverse events, withdrawal symptoms, or incidents of substance use?

Methods This systematic review and meta-analysis of randomised controlled trials and non-randomised studies included searches of Medline, Embase, PsycINFO, CINAHL, and the Cochrane Library from inception to July 2021 for original research published in English. Case reports and cross sectional studies were excluded. Studies at better than critical risk of bias were included in the evidence synthesis. Interventions were grouped into five categories: pain self-management, complementary and alternative medicine, pharmacological and biomedical devices and interventions, opioid replacement treatment, and deprescription methods.

Study answer and limitations Of 166 studies that met inclusion criteria, 130 were considered at critical risk of bias. Of the 36 remaining studies, few were similar enough to contribute to pooled findings, and sample sizes were generally small. As such, the certainty in the evidence was low or very low for most outcomes, including for all non-opioid patient outcomes. Despite these limitations, interventions to support prescribers' adherence to guidelines could have increased patients' likelihood of opioid discontinuation (adjusted odds ratio 1.5, 95% confidence interval 1.0 to 2.1), and both these interventions and pain self-management programmes could have reduced opioid dose more than controls (prescriber intervention *v* control, mean difference −6.8 mg (standard error 1.6 mg) daily oral morphine equivalent, P<0.001; pain self-management programme *v* control, mean difference −14.31 mg daily oral morphine equivalent, 95% confidence interval −21.57 to −7.05).

What this study adds Interventions supporting prescribers' adherence to opioid guidelines and participation in pain self-management programmes are probably effective in reducing opioids by small and moderate amounts, respectively. However, an absence of evidence on patient outcomes remains. Agreed standards for designing and reporting studies on the reduction of opioids are urgently needed.

Funding, competing interests, and data sharing Funded by the Salteri Family Foundation, Perpetual Foundation, Pain Foundation, and Ernest Heine Family Foundation.
Competing interests listed in full on bmj.com. All data available in online appendices.
Review registration PROSPERO CRD42020140943.

Interventions to reduce long term opioid treatment in people with chronic non-cancer pain

Category	Explanation	Examples
Pain self-management	Aims to reduce over-reliance on prescription opioids through behaviour change by increasing tolerance to pain and withdrawal symptoms; usually adopts a bio-psychosocial framework for pain management or has a focus on improving function	A three week outpatient multidisciplinary pain management programme based on cognitive behavioural therapy principles and including exercise, goal setting, pain education, and opioid discontinuation
Complementary and alternative medicine	Complementary and or alternative to mainstream medicine; seeks to decrease pain intensity or withdrawal symptoms through different mechanisms that might include biomedical and psychosocial elements	Acupuncture as an additional treatment to opioid discontinuation in an outpatient pain clinic; medical cannabis; herbal medicine
Pharmacological and biomedical devices and interventions	Aims to reduce over-reliance on prescription opioids by decreasing the intensity of pain or withdrawal symptoms through drug treatments, implantation of medical devices, or provision of interventional procedures	Clonidine for the management of withdrawal symptoms; spinal cord stimulation; total knee arthroplasty
Opioid replacement treatment	Also known as opioid maintenance treatment; patients are transitioned from long term opioid treatment to methadone or buprenorphine; most often recommended for patients with chronic pain and comorbid opioid use disorder or other substance use disorder	Transition to methadone maintenance; transition and stabilisation on buprenorphine or buprenorphine/naloxone, and then weaning off these substances
Deprescription methods	An emphasis on drug treatment management that might occur alongside or in the absence of alternative pain management techniques; these include patient focused and prescriber focused interventions	Treatment in primary care where opioids are reduced by 10% per week; an electronic decision tool that helps prescribers adhere to a new opioid prescription safety policy