BMJ Open

Short-term and long-term stroke risk following SARS-CoV-2 infection in relation to disease severity: a Danish national cohort study

Camilla Schade Skov ,[1,2] Anton Pottegård,[3] Jacob Harbo Andersen,[3] Grethe Andersen,[4,5] Annmarie Touborg Lassen [1,2]

To cite: Schade Skov C, Pottegård A, Harbo Andersen J, *et al*. Short-term and long-term stroke risk following SARS-CoV-2 infection in relation to disease severity: a Danish national cohort study. *BMJ Open* 2024;**14**:e083171. doi:10.1136/bmjopen-2023-083171

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-083171).

Received 13 December 2023
Accepted 26 June 2024

[1]Department of Emergency Medicine, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]Department of Public Health, Clinical Pharmacology Pharmacy and Environmental Medicine, University of Southern Denmark, Odense, Denmark
[4]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[5]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence to
Camilla Schade Skov;
camilla.schade.hansen@rsyd.dk

ABSTRACT

Objectives Studies have reported high incidences of stroke in patients hospitalised with SARS-CoV-2, but the impact of disease severity is unexplored. We aimed to estimate the risk of incident ischaemic stroke in SARS-CoV-2 test-positive individuals compared with test-negative individuals stratified by disease severity during acute infection and post infection.

Design A register-based cohort study.

Setting A Danish nationwide study.

Participants All Danish adults who had PCR tests for SARS-CoV-2 performed between 1 March 2020 and 30 November 2021. Test-positive individuals were included at their first positive test. For individuals tested prior to 30 November 2021, we randomly sampled an index date from the distribution of test dates among SARS-CoV-2 test-positive individuals. Test-positive individuals were followed during the acute phase of infection (days 0–14) and post infection (180 days after the acute phase). Test-negative individuals were followed in equivalent time periods.

Primary and secondary outcome measures Incident ischaemic stroke risk in SARS-CoV-2 test-positive individuals compared with test-negative individuals during acute infection and post infection. We calculated subdistribution HRs (SHR) with death as a competing risk using propensity score weighting as confounder control. The risk was stratified according to disease severity: community managed, hospitalised, or admission to the intensive care unit.

Results Among 3 910 219 SARS-CoV-2 PRC-tested individuals, 356 421 test-positive and 3 067 456 test-negative individuals were included. A positive SARS-CoV-2 test was associated with an SHR of 3.32 (95% CI 2.60 to 4.25) overall for stroke compared with test negative in the acute phase. In the postinfection period, the risk of stroke remained increased in individuals hospitalised during the acute phase (SHR 1.85, 95% CI 1.45 to 2.37). Individuals with community-managed SARS-CoV-2 had no increased long-term risk of stroke (SHR 1.01, 95% CI 0.88 to 1.16).

Conclusion SARS-CoV-2 infection is associated with increased stroke risk. Disease severity seems to be an important factor. Individuals with community-managed SARS-CoV-2 had no increased stroke risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Approximately 83% of the adult Danish population had one or more PCR tests performed within the study period which resulted in a large study cohort.
⇒ The used Danish national health registers allowed for extensive confounder control.
⇒ We used test date as index date for SARS-CoV-2 test-positive individuals, but the onset of COVID-19 was unknown.
⇒ Information of symptoms prior to testing was not available, and the fraction of individuals with other respiratory infections is unknown.

INTRODUCTION

Increasing evidence suggest that SARS-CoV-2 is associated with cardiovascular events such as ischaemic stroke.[1–3] It has been suggested that risk of stroke in patients with COVID-19 is mainly present in those who are already at risk of acute stroke due to conventional risk factors.[3 4]

In the beginning of the COVID-19 pandemic, studies reported in-hospital incidence of stroke among SARS-CoV-2 infected patients with great variability.[4–11] The highest incidence was reported among patients admitted to the intensive care unit (ICU) with an incidence of ischaemic stroke up to 7.0%.[12] The differences in stroke incidence among COVID-19 patients across studies probably reflect differences in study populations, and differences in healthcare systems across countries.

Since then, more studies have focused on the risk of ischaemic stroke in SARS-CoV-2-infected individuals. A Swedish self-controlled study found the risk of ischaemic stroke to be increased by three to six times in the first week following COVID-19 compared with each individual's baseline risk with an attenuating, but still increased, effect after 3–4 weeks.[2] Their findings of increased stroke

risk in SARS-CoV-2 infected individuals are consistent with other studies including a meta-analysis that found SARS-CoV-2 infection to be associated with an increased OR for ischaemic stroke (OR=3.58, 95% CI 1.43 to 8.92).[1]

It is important to improve knowledge of both short-term and long-term stroke risk in SARS-CoV-2-positive individuals as it is a prerequisite for potential preventive measures. Knowledge of the influence of disease severity will support clinicians in decision-making in post-COVID-19 care. In this study, we aimed to quantify the risk of stroke during acute infection with SARS-CoV-2 and post infection among all identified SARS-CoV-2-positive individuals at a Danish national level. The stroke risk was calculated overall and stratified by disease severity.

METHODS

Study design and selection of participants

This is a nationwide register-based cohort study including all adult Danish individuals (age ≥18 years) who were tested for SARS-CoV-2 with real-time PCR between 1 March 2020 to 30 November 2021. This date was chosen because at the end of November 2021, the first Danish citizens were infected with omicron B.1.1.529. Individuals with a positive PCR test result for SARS-CoV-2 performed on oropharyngeal and nasopharyngeal swabs and/or on respiratory-tract secretions and aspirate within the defined period were included as test-positive individuals with their first positive test date as the index date. Tested individuals who had no previous positive SARS-CoV-2 test were included as test-negative individuals. For each individual tested prior to 30 November 2021, we randomly sampled an index date from the distribution of test dates among SARS-CoV-2-positive-tested individuals. This proportional sampling was done to ensure a temporal match between test-negative and test-positive individuals. Test-negative individuals were excluded if they had an assigned index date before their first SARS-CoV-2 test, or if the assigned index date was after the first positive SARS-CoV-2 test. This ensured that all individuals who at some point in the inclusion period were test positive could only be included as such, while potential selection bias among test-negative individuals was handled.

Definition of acute SARS-CoV-2 and the postinfection period

The SARS-CoV-2-positive cohort was analysed in two steps: an analysis of all individuals with acute SARS-CoV-2 and an analysis of those who survived the acute phase of SARS-CoV-2 without stroke (postinfection period).

The acute phase of SARS-CoV-2 was defined as the first 2 weeks after a positive SARS-CoV-2 test. Patients hospitalised during the acute phase of infection remained in the acute phase until discharge from the hospital. For those with a long hospitalisation, we ended the acute phase 90 days after the index date. In the acute phase of infection, all individuals were followed until death, emigration (defined as the date when no longer registered with an address in the Danish Civil Registration System[13]), an event of stroke, or completion of the acute phase of the infection whichever came first. The postinfection period started when the acute phase of the infection ended and included all SARS-CoV-2-positive patients who survived the acute phase of the infection without an event of stroke. In the postinfection period, all individuals were followed until death, emigration, an event of stroke, or 180 days after entering the postinfection period whichever came first. The test-negative individuals were followed in parallel with the test-positive individuals in equivalent time periods.

Definition of stroke

Acute stroke was defined as incident ischaemic stroke. We used International Classification of Diseases 10th Revision (ICD-10) diagnoses to identify an acute event of stroke: I63 (I63.6 was excluded) or I64.9 (online supplemental eTable 1). Recent stroke was defined as a stroke occurring within 14 and until 1 day before a positive SARS-CoV-2 test (index date −14: −1). Previous stroke was defined as a stroke 15 days or more before study inclusion (ie, the date of positive SARS-CoV-2 test or assigned index date for the control individuals). Since the main outcome in this study was incident ischaemic stroke, we excluded previous and recent stroke in the main analysis.

Data sources

All Danish residents have a unique personal civil registration number, which allows cross-linkage at personal level between registers. We extracted data from several Danish registers. Data on all SARS-CoV-2 tested Danish residents are included in The Danish COVID-19 Cohort,[14] where results from the PCR tests were identified from the Danish Microbiology Database.[15] We linked these data to data from the Danish National Patient Registry[16] where stroke cases were identified and further information regarding comorbidities was obtained. Through The Danish Civil Registration System,[13] we obtained information regarding death or emigration. Stroke risk modifying medications were identified from the Danish National Prescription Registry.[17]

Analyses and statistics

We calculated the absolute risks and subdistribution HRs (SHRs) of incident ischaemic stroke in patients with SARS-CoV-2 compared with SARS-CoV-2 negative tested individuals. Absolute risks were reported based on the entire population. SHRs were calculated using the Fine-Gray model with death as a competing risk, and time to stroke was illustrated using the cumulative incidence function.[18] We used propensity score (PS) standardised mortality ratio weighting to control for potential confounding when calculating the SHR. The standardised mortality ratio weighting gives the average treatment effect among the treated, often referred to as the ATT. SARS-CoV-2-positive individuals were assigned a weight of 1, whereas the SARS-CoV-2 negative individuals were assigned a weight defined as the ratio of the

estimated PS to one minus the PS.[19] Covariates included in the PS model were age, sex, comorbidities, markers of smoking, alcohol-related disorders and prescribed drugs. These are defined in online supplemental eTable 1. To evaluate covariate balance, we calculated standardised mean differences (SMD), and a difference in SMD of less than 0.1 was accepted. All risk estimates were reported for the acute phase of SARS-CoV-2 and the analyses were repeated in the postinfection period. Incidence rates of incident stroke per 1000 person years at risk were calculated.

The analysis was performed overall and stratified by infection severity. In the acute phase of SARS-CoV-2, we stratified on hospitalised patients with no stay at the ICU and stay at the ICU (codes for identification of ICU admission are provided in online supplemental eTable 2). Patients hospitalised were followed from the day of admission and censored if later admitted to the ICU. Patients with stay at the ICU were followed from the day of admission to the ICU. In the postinfection period, we stratified on following: community managed, hospitalised with no stay at the ICU and hospitalised with an ICU stay—all three categories refer to the setting during the acute phase of infection. All Danish individuals with suspicion of an acute stroke (symptoms of stroke within the last 7 days) are acutely admitted to the hospital for diagnosis. This implies that no patients can have a community-managed acute stroke in the acute phase, because the diagnosis of stroke includes a hospital admission.

Three sensitivity analyses were done: one where individuals with a recent stroke were included, one where we restricted the inclusion period to 1 March 2020 to 31 October 2020 (introduction of antigen tests), and one where we included patients with transient ischaemic attack (TIA; ICD-10 code G45.9) in the outcome.

In Denmark, all patients with suspected stroke are admitted to a neurological department or a specific neurological section located in the emergency department. We did a post hoc analysis in which we excluded individuals who initially arrived at a neurological department and tested positive for SARS-CoV-2 on arrival (defined as −1:1 days of a positive test).

All analyses were performed using Stata V.17.0.

Patient and public involvement

Patients or public were not involved in the design, or conduct, or reporting, or dissemination of this research.

RESULTS

Baseline characteristics

From 1 March 2020 to 30 November 2021, 3 910 219 individuals had PCR tests for SARS-CoV-2 performed. After the proportional sampling, 3 423 877 individuals were included for analysis. Among the included individuals, 356 421 had a positive test. The largest proportion of SARS-CoV-2-positive tests was among younger people. In general, the population with a negative SARS-CoV-2 test had more comorbidities than the test-positive population (table 1).

Among the 356 421 individuals with a positive test result, 353 765 entered the postinfection period (table 2). The numbers of included individuals in both cohorts are shown in figure 1.

Stroke risk and SARS-CoV-2

Of the 356 421 individuals with a positive SARS-CoV-2 test, 90 had incident ischaemic stroke within the acute phase of infection, yielding an absolute risk of incident stroke of 0.025% corresponding to 6.6/1000 person years at risk. Among test-negative individuals, the absolute risk of ischaemic stroke was 0.010% (314 strokes in 3 067 456 individuals), 2.7/1000 person years at risk. In our PS-weighted analysis, we found a positive SARS-CoV-2 test to be associated with an SHR of 3.32 (95% CI 2.60 to 4.25) for stroke in the acute phase compared with SARS-CoV-2 test-negative individuals. The highest risk of stroke during acute SARS-CoV-2 was found in patients admitted to the ICU: SHR 36.4 (95% CI 22.6 to 58.5).

In the postinfection period, the overall SHR for stroke among SARS-CoV-2-positive patients was 1.12 (95% CI 0.99 to 1.26) compared with SARS-CoV-2 test-negative individuals (table 3). However, the risk of stroke remained increased among SARS-CoV-2-positive patients in the postinfection period if they had been admitted to the hospital during the acute phase of infection, SHR 1.85 (95% CI 1.45 to 2.37). In individuals with community-managed SARS-CoV-2 infection, we found no increased long-term risk of stroke, SHR 0.96 (95% CI 0.84 to 1.11). The cumulative incidence function for both periods is found in online supplemental eFigure 1.

Mortality

The highest mortality was seen among SARS-CoV-2-positive individuals in the acute phase of infection (2485 out of 356,421, 0.70% (95% CI 0.670 to 0.725)) and the corresponding mortality for SARS-CoV-2 test-negative individuals was 0.07% with 2080 deaths among 3 067 456 individuals (95% CI 0.065 to 0.071). This corresponded to a mortality rate of 181/1000 person years among test-positive individuals and 18/1000 person years among test-negative individuals. Among SARS-CoV-2-positive individuals, the mortality decreased in the postinfection period (1820 out of 353 765, 0.51% (95% CI 0.49 to 0.54), 11/1000 person years). The corresponding mortality for SARS-CoV-2 test-negative individuals was 0.49% (15 023 deaths among 3 047 919 individuals (95% CI 0.49 to 0.50)), 10/1000 person years.

Sensitivity analyses

When the analysis was time restricted (1 March 2020 to 31 October 2020), the absolute risks, SHRs and incidence rates were slightly increased in both SARS-CoV-2-positive and SARS-CoV-2-negative individuals in the two periods (online supplemental eTable 3). When individuals with a recent stroke were included, the incidences of stroke

Table 1 Baseline characteristics among SARS-CoV-2-positive individuals and test-negative controls in the acute phase of the infection

Acute phase of SARS-CoV-2					
	SARS-CoV-2 positive (n=356 421)	SARS-CoV-2 negative (n=3 067 456)	Standardised mean difference	SARS-CoV-2 negative, PS-weighted (n=356 397)	Standardised mean difference, weighted
Demographics					
Sex, female, n%	182 770 (51)	1 619 362 (53)	0.03	182 769 (51)	0.00
Age					
18–50	246 986 (69)	1 723 629 (56)	0.27	245 676 (69)	0.01
51–69	80 483 (23)	899 064 (29)	0.15	81 450 (23)	0.01
70+	28 952 (8)	444 763 (14)	0.20	29 271 (8.2)	0.00
Comorbidities					
Charlson Comorbidity Index, n (%)					
CCI=0	310 799 (87)	2 572 424 (84)	0.09	312 217 (88)	0.01
CCI=1	10 050 (2.8)	119 385 (3.9)	0.06	10 430 (2.9)	0.01
CCI≥2	35 572 (10.0)	375 647 (12)	0.07	33 750 (9.5)	0.02
Hypertension	25 272 (7.1)	319 755 (10)	0.12	25 310 (7.1)	0.00
Atrial fibrillation or flutter	8648 (2.4)	110 716 (3.6)	0.07	8671 (2.4)	0.00
Congestive heart failure	4.328 (1.2)	52 125 (1.7)	0.04	4347 (1.2)	0.00
Ischaemic cardiac disease	13 424 (3.8)	165 360 (5.4)	0.08	13 431 (3.8)	0.00
Peripheral vascular disease	2939 (0.8)	42 398 (1.4)	0.05	2945 (0.8)	0.00
Venous thromboembolism	6459 (1.8)	70 198 (2.3)	0.03	6472 (1.8)	0.00
Diabetes mellitus	11 351 (3.2)	119 199 (3.9)	0.04	11 402 (3.2)	0.00
Chronic kidney disease	2882 (0.8)	30 437 (1.0)	0.02	2896 (0.8)	0.00
Dyslipidaemia	11 496 (3.2)	142 515 (4.6)	0.07	11 512 (3.2)	0.00
Cancer	14 267 (4.0)	196 123 (6.4)	0.11	14 276 (4.0)	0.00
Lifestyle-related diagnoses					
Alcohol-related disorders	3068 (0.9)	50 713 (1.7)	0.07	3076 (0.9)	0.00
Obesity	24 859 (7.0)	231 374 (7.5)	0.02	24 928 (7.0)	0.00
Markers of smoking	10 370 (2.9)	134 348 (4.4)	0.08	10 393 (2.9)	0.00
Prescription drug use					
Platelet inhibitor	28 249 (7.9)	369 535 (12)	0.14	28 284 (7.9)	0.00
Anticoagulants	14 024 (3.9)	176 364 (5.7)	0.08	14 057 (3.9)	0.00
Antidiabetic drugs	20 353 (5.7)	199 646 (6.5)	0.03	20 405 (5.7)	0.00
Antihypertensives	75 773 (21)	890 967 (29)	0.18	75 821 (21)	0.00
Loop diuretics	15 284 (4.3)	195 276 (6.4)	0.09	15 336 (4.3)	0.00
Lipid-lowering drugs	42 273 (12)	542 350 (18)	0.16	42 272 (12)	0.00

PS, propensity score.

in the acute phase of infection increased slightly among both test-positive and test-negative individuals (online supplemental eTable 4). In the post-hoc analysis, we identified 20 patients who initially arrived at a neurological department and tested positive for SARS-CoV-2 on arrival. Despite excluding these patients, the risk of stroke remained increased in SARS-CoV-2 infected individuals (online supplemental eTable 5). Results remained unchanged when individuals with diagnosis of TIA were included (online supplemental eTable 6).

DISCUSSION

In this Danish nationwide cohort study, we evaluated the risk of incident ischaemic stroke among 3 910 219 SARS-CoV-2 tested Danish individuals, corresponding to

Table 2 Baseline characteristics among SARS-CoV-2-positive individuals and test-negative individuals in the postinfection period

Postinfection period of SARS-CoV-2					
	SARS-CoV-2 positive (n=353 765)	SARS-CoV-2 negative (n=3 047 919)	Standardised mean difference	SARS-CoV-2 negative, PS weighted (n=353 760)	Standardised mean difference, weighted
Demographics					
Sex, female, n%	181 645 (51)	1 609 316 (53)	0.03	181 644 (51)	0.00
Age					
18–50	246 640 (70)	1 709 777 (56)	0.28	245 807 (69)	0.01
51–69	80 252 (23)	895 271 (29)	0.15	80 042 (23)	0.00
70+	26 873 (7.6)	442 871 (15)	0.22	27 911 (7.9)	0.01
Comorbidities					
Charlson Comorbidity Index, n (%)					
CCI=0	310 156 (88)	2 556 243 (84)	0.11	311 154 (88)	0.01
CCI=1	9793 (2.8)	118 799 (3.9)	0.06	10 110 (2.9)	0.01
CCI≥2	33 816 (9.6)	372 877 (12)	0.09	32 496 (9.2)	0.01
Hypertension	24 245 (6.9)	318 044 (10.0)	0.13	24 269 (6.9)	0.00
Atrial fibrillation or flutter	8080 (2.3)	110 187 (3.6)	0.08	8095 (2.3)	0.00
Congestive heart failure	3883 (1.1)	51 793 (1.7)	0.05	3896 (1.1)	0.00
Ischaemic cardiac disease	12 723 (3.6)	164 460 (5.4)	0.09	12 721 (3.6)	0.00
Peripheral vascular disease	2643 (0.7)	42 114 (1.5)	0.06	2647 (0.7)	0.00
Venous thromboembolism	6366 (1.8)	69 900 (2.3)	0.03	6376 (1.8)	0.00
Diabetes mellitus	11 053 (3.1)	118 444 (3.9)	0.04	11 098 (3.1)	0.00
Chronic kidney disease	2579 (0.7)	30 216 (1.0)	0.03	2586 (0.7)	0.00
Dyslipidaemia	11 012 (3.1)	141 847 (4.7)	0.08	11 022 (3.1)	0.00
Cancer	13 673 (3.9)	195 273 (6.4)	0.12	13 676 (3.9)	0.00
Lifestyle-related diagnoses					
Alcohol-related disorders	2942 (0.8)	50 478 (1.7)	0.07	2949 (0.8)	0.00
Obesity	24 714 (7.0)	230 517 (7.6)	0.02	24 786 (7.0)	0.00
Markers of smoking	9926 (2.8)	133 560 (4.4)	0.08	9944 (2.8)	0.00
Prescription drug use					
Platelet inhibitor	26 850 (7.6)	367 642 (12)	0.15	26 866 (7.6)	0.00
Anticoagulants	13 391 (3.8)	175 794 (5.8)	0.09	13 414 (3.8)	0.00
Antidiabetic drugs	19 805 (5.6)	199 104 (6.5)	0.04	19 849 (5.6)	0.00
Antihypertensives	73 811 (21)	887 538 (29)	0.19	73 837 (21)	0.00
Loop diuretics	14 082 (4.0)	194 454 (6.4)	0.11	14 116 (4.0)	0.00
Lipid-lowering drugs	40 833 (12)	540 631 (18)	0.18	40 816 (12)	0.00

PS, propensity score.

approximately 83% of the adult Danish population.[20] We included 356 421 individuals with a positive SARS-CoV-2 test, which is the largest number of individuals in a study quantifying the association between incident ischaemic stroke and SARS-CoV-2. We found an overall increased risk of incident ischaemic stroke in SARS-CoV-2-positive patients compared with test-negative individuals in the acute phase of infection. However, we found no increased risk in individuals with community-managed SARS-CoV-2.

In the postinfection period, the risk remained increased among individuals who had been admitted to the hospital during the acute phase. The incidences of stroke among test-negative individuals in both periods corresponded to incidences of stroke in the general Danish population, but were slightly lower than the incidence found in the USA.[21 22]

In a previous Danish study, researchers found an absolute stroke risk of 0.9% in patients with COVID-19,

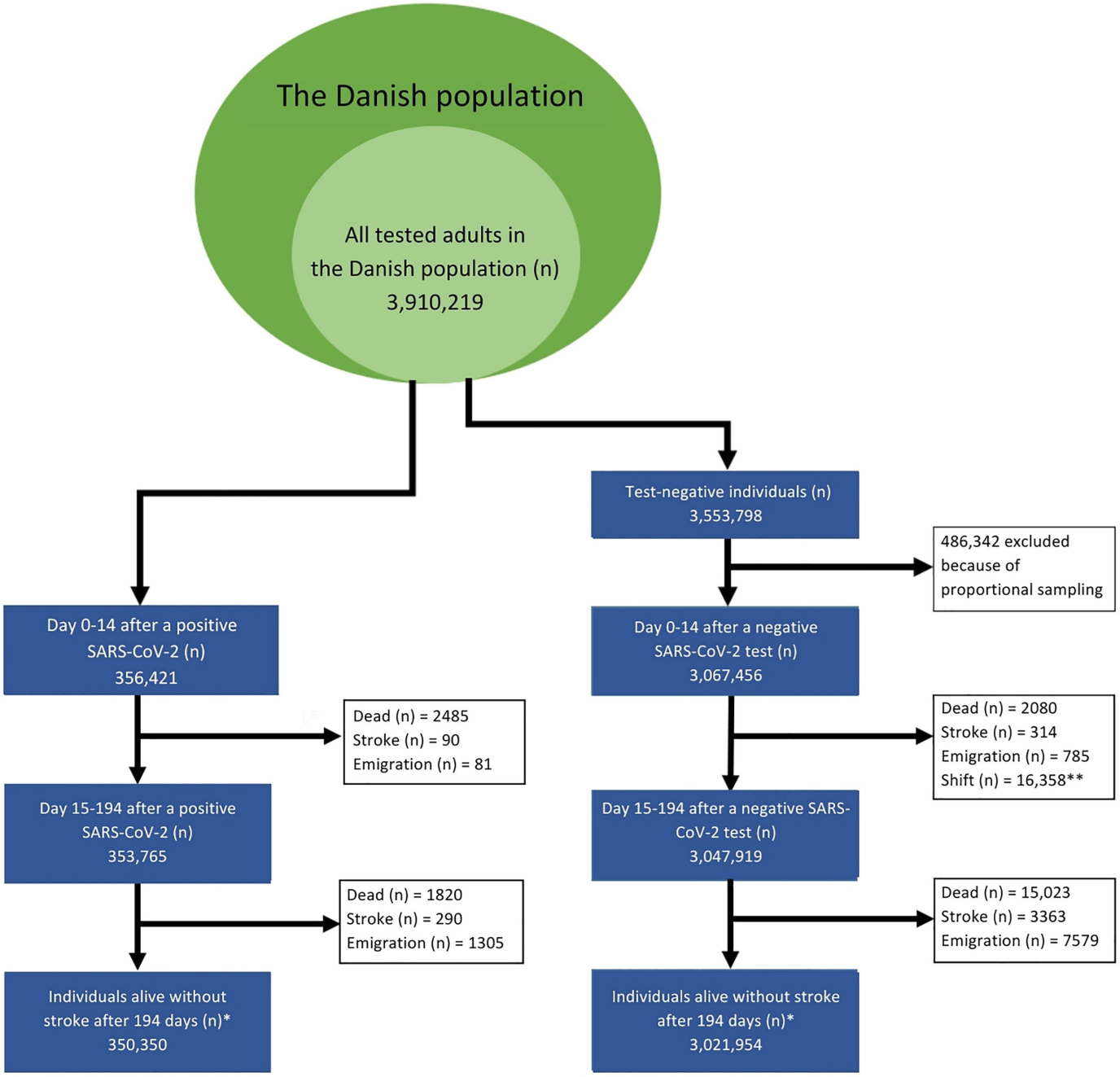

Figure 1 The study cohort. Acute phase of infection: days 0–14 after a positive test result. For patients hospitalised within the first 14 days after index, the acute phase lasted until discharge. Postinfection period: first 180 days after the acute phase of infection corresponding to days 15–194 from the test result. *Migrated individuals are excluded. **Number of individuals who initially are included at a negative SARS-CoV-2 test and later have a positive test and therefore are shifting to the acute phase of SARS-CoV-2.

which is twice as high as the absolute risk we found.[23] Their results are based on data from patients diagnosed with COVID-19 at the hospital in the beginning of the pandemic and are based on relatively few individuals. Another Danish study by Lund *et al* reported an absolute risk of 0.1% of ischaemic stroke or TIA among SARS-CoV-2-positive tested individuals who were not hospitalised. Their results are based on postacute data from 2 weeks to 6 months after a positive SARS-CoV-2 test.[24] This risk is corresponding to the risk of stroke in the general population and supports our findings from the postinfection period.[21]

A Swedish self-controlled and matched cohort study, including 86 742 patients with COVID-19, estimated incidence rate ratios (IRR) of acute incident stroke up to 4 weeks after exposure. They found an IRR of 2.97 (95% CI 1.71 to 5.15) in the first week when excluding the day of exposure, and an IRR of 6.18 (95% CI 4.06 to 9.42) when

Table 3 Absolute and relative risk estimations for incident ischaemic stroke in SARS-CoV-2-positive-tested individuals compared with SARS-CoV-2 negative tested individuals in the acute phase of infection, and in the postinfection period

	Events (n)	Absolute risk (%)	Incident rate (95% CI)*	Unweighted SHR (95% CI)	PS-weighted SHR (95% CI)
Acute phase of SARS-CoV-2					
SARS-CoV-2 test-negative (n=3 067 456)					
Ischaemic stroke	314	0.010	2.7 (2.4 to 3.0)	1.0 (ref.)	1.0 (ref.)
SARS-CoV-2 test-positive (n=356421)					
Overall					
Ischaemic stroke	90	0.025	6.6 (5.3 to 8.0)	3.11 (2.42 to 4.00)	3.32 (2.60 to 4.25)
Hospitalised, no ICU stay (n=14852)					
Ischaemic stroke	67	0.451	155 (122 to 192)	16.5 (12.0 to 22.7)	16.6 (12.4 to 22.3)
Hospitalised, ICU stay (n=1837)					
Ischaemic stroke	23	1.252	215 (141 to 305)	30.4 (14.0 to 66.1)	36.4 (22.6 to 58.5)
Postinfection period after a positive SARS-CoV-2					
SARS-CoV-2 test-negative (n=3 047 919)					
Ischaemic stroke	3363	0.110	2.3 (2.2 to 2.4)	1.0 (ref.)	1.0 (ref.)
SARS-CoV-2 test-positive (n=353765)					
Overall					
Ischaemic stroke	290	0.082	1.7 (1.5 to 1.9)	1.10 (0.97 to 1.24)	1.12 (0.99 to 1.26)
Community managed (n=339713)					
Ischaemic stroke	219	0.064	1.3 (1.1 to 1.5)	0.96 (0.84 to 1.11)	1.01 (0.88 to 1.16)
Hospitalised, no ICU stay (n=12819)					
Ischaemic stroke	66	0.515	11 (8.5 to 14)	1.93 (1.51 to 2.46)	1.85 (1.45 to 2.37)
Hospitalised, ICU stay (n=1233)					
Ischaemic stroke	5	0.406	8.8 (2.8 to 20)	1.91 (0.79 to 4.59)	1.64 (0.67 to 3.99)

*Incident rate per 1000 person years at risk.
ICU, intensive care unit; PS, propensity score; SHR, subdistribution HR.

including the day of exposure.[2] This demonstrates the risk of test bias to drive overestimation of the association between SARS-CoV-2 and stroke. Through the COVID-19 pandemic, all patients admitted to a Danish hospital were PCR tested for SARS-CoV-2. Therefore, patients may be admitted because they suffer from stroke and by coincidence have a positive SARS-CoV-2 test without any symptoms of COVID-19. This potential bias was handled in our study using proportional sampling and further highlighted in the post-hoc analysis. The increased risk of stroke among patients hospitalised, and especially those in the ICU, may reflect a general vulnerability or frailty in these patients which one might suspect makes them more susceptible to stroke. Further, these patients may have more severe COVID-19 infection. Contrary, one would expect less morbidity and a less severe COVID-19 infection in community-managed SARS-CoV-2 test-positive individuals. The fact that we found no increased risk of stroke among community-managed SARS-CoV-2 infected individuals underlines that the patients' general condition when infected with SARS-CoV-2 is of importance. A study from the USA found an increased risk of stroke 12 months after COVID-19 infection. They reported an increased risk of stroke, both among non-hospitalised individuals (HR=1.30, 95% CI 1.22 to 1.37), hospitalised individuals (HR=2.92, 95% CI 2.53 to 3.37) and ICU-admitted individuals (HR=4.00, 95% CI 3.19 to 5.02).[25] These risk estimates are all higher than those from the postinfection period in our study.

Other infectious diseases and sepsis have been associated with increased risk of short-term and long-term stroke.[26–28] An incidence rate of 25.5 (95% CI 14.2 to 45.8) following respiratory infection has been demonstrated, but the rate varies according to follow-up time and microbiological aetiology.[29] Boehme *et al* found sepsis to be associated with an increased short-term risk of ischaemic stroke (OR of 28.4 (95% CI 20.0 to 40.1)), which remains increased up to a year after sepsis, OR 2.59 (95% CI 7.54 to 19.42).[28] Compared with influenza, SARS-CoV-2 is associated with a 7.6-fold increased risk of stroke.[30] Despite this knowledge, the complexity of the association between infection and stroke is not fully understood. The association is considered bidirectional, because infection increases the risk of stroke whereas stroke induces immune suppression which increases the risk of infection.[31]

During our inclusion period, the test strategy in Denmark changed. Before 12 March 2020, SARS-CoV-2 PCR test was only offered to individuals with suspected COVID-19 and a relevant travel history or close contact with a confirmed SARS-CoV-2-positive individual. From 12 March 2020 until 21 April 2020, test of individuals requiring hospital admission or with moderate-to-severe symptoms were prioritised. Screening of healthcare worker were introduced. At the end of May 2020, all Danish citizens had free access to SARS-CoV-2 PCR test without requisition.[14] From December 2020, antigen test has been a part of the public health services with free availability. However, as some antigen tests are provided by private companies, some of the results might not have been registered in the Danish COVID-19 cohort. Thus, an unknown number of SARS-CoV-2-positive individuals may be categorised as SARS-CoV-2 negative in our dataset. We do believe that this potential bias is rather small as Danish citizens with a positive antigen test were strongly advised to get a confirming PCR test. Further, individuals with severe symptoms requiring hospital admission always have a SARS-CoV-2 PCR test performed. This potential bias was investigated in a time-restricted sensitivity analysis and resulted in slightly higher SHRs, which can be explained by the test strategy.

Strengths and limitations

The completeness of Danish nationwide registers provides strong data for health research, and cross linkage between the registers allows merging of multiple confounders and strengthening the confounder control in our study. The free access to PCR tests for the Danish population during the pandemic (except at the beginning) has resulted in PCR test results for most of the Danish citizens, providing strong data for COVID-19 research.

Our study also has several limitations. Despite extensive confounder control, residual confounding cannot be excluded. The date of onset of COVID-19 is not precisely known, but the date of a positive test is considered as the onset of infection. Therefore, an individual can be diagnosed with a stroke before diagnosed with COVID-19, although COVID-19 was present in that person before the stroke. Individuals who were tested, later had a stroke without being admitted to the hospital and afterwards died at home, were only included as 'dead'. The number of such events was not available in this study. Information regarding potential symptoms on PCR testing was not available. Possible reinfection(s) with SARS-CoV-2 were not handled in this study. The COVID-19 vaccines were launched on 27 December 2020 in Denmark[32] with a gradual vaccination of the Danish population and an expected decrease in the number of seriously ill patients, which may have influenced our results. The use of setting (community-managed, hospitalised or ICU admission) as a marker of disease severity should be interpreted with the limitations inherent in it. However, severity of the disease assessed at a personal level in this population-based study was not possible, and therefore we used setting as a proxy. Due to limited number of events in the subgroups, we did not stratify the postinfection period into shorter time periods. Finally, the diagnosis of stroke is limited to discharge diagnoses which include a risk of misclassification.

Conclusion

Individuals with community-managed SARS-CoV-2 had no increased long-term risk of stroke compared with SARS-CoV-2 negative tested individuals. SARS-CoV-2 seems to be an independent risk factor of stroke for those

who were hospitalised during acute SARS-CoV-2 infection. Among hospitalised individuals, the risk of incident stroke was highest in the acute phase of infection, especially in ICU patients, and remained increased up to half a year in patients hospitalised during the acute phase.

Contributors CSS and ATL invented the study. All authors contributed to the study design and the applied methods. JHA performed the analysis. CSS drafted the manuscript with support from all coauthors. All authors approved the final version. CSS is the guarantor of this study.

Funding This study was founded by the University of Southern Denmark and Odense University Hospital.

Competing interests ATL was supported by an unrestricted grant to the University of Southern Denmark from TrygFoundation. All other authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. According to Danish law, data from the Danish national health registers is not allowed to be shared. However, any researcher can apply the Danish health authorities for access to data.

ORCID iDs
Camilla Schade Skov http://orcid.org/0000-0002-2207-8883
Annmarie Touborg Lassen http://orcid.org/0000-0003-4942-6152

REFERENCES

1 Katsanos AH, Palaiodimou L, Zand R, *et al*. The impact of SARS-Cov-2 on stroke epidemiology and care: a meta-analysis. *Ann Neurol* 2021;89:380–8.
2 Katsoularis I, Fonseca-Rodríguez O, Farrington P, *et al*. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet* 2021;398:599–607.
3 Nannoni S, de Groot R, Bell S, *et al*. Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke* 2021;16:137–49.
4 Qureshi AI, Baskett WI, Huang W, *et al*. Acute ischemic stroke and COVID-19: an analysis of 27 676 patients. *Stroke* 2021;52:905–12.
5 Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683–90.
6 Perry RJ, Smith CJ, Roffe C, *et al*. Characteristics and outcomes of COVID-19 associated stroke: a UK Multicentre case-control study. *J Neurol Neurosurg Psychiatry* 2021;92:242–8.
7 Tan BK, Mainbourg S, Friggeri A, *et al*. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax* 2021;76:970–9.
8 Siepmann T, Sedghi A, Simon E, *et al*. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. *Eur J Neurol* 2021;28:238–47.
9 Yaghi S, Ishida K, Torres J, *et al*. SARS-Cov-2 and stroke in a New York healthcare system. *Stroke* 2020;51:2002–11.
10 Travi G, Rossotti R, Merli M, *et al*. Neurological manifestations in patients hospitalized with COVID-19: a retrospective analysis from a large cohort in northern Italy. *Eur J Neurosci* 2021;53:2912–22.
11 Cantador E, Núñez A, Sobrino P, *et al*. Incidence and consequences of systemic arterial thrombotic events in COVID-19 patients. *J Thromb Thrombolysis* 2020;50:543–7.
12 Fan S, Xiao M, Han F, *et al*. Neurological manifestations in critically ill patients with COVID-19: a retrospective study. *Front Neurol* 2020;11:806.
13 Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
14 Pottegård A, Kristensen KB, Reilev M, *et al*. Existing data sources in clinical epidemiology: the Danish COVID-19 cohort. *Clin Epidemiol* 2020;12:875–81.
15 Voldstedlund M, Haarh M, Mølbak K, *et al*. The Danish Microbiology database (MiBa) 2010 to 2013. *Euro Surveill* 2014;19:20667.
16 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
17 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, *et al*. Data resource profile: the Danish national prescription Registry. *Int J Epidemiol* 2017;46:798–798f.
18 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133:601–9.
19 Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019;367:l5657.
20 Denmark S. Befolkningstal. 2023. Available: https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal [Accessed 18 Oct 2023].
21 Yafasova A, Fosbøl EL, Christiansen MN, *et al*. Time trends in incidence, comorbidity, and mortality of ischemic stroke in Denmark (1996-2016). *Neurol (ECronicon)* 2020;95:e2343–53.
22 Koton S, Schneider ALC, Rosamond WD, *et al*. Stroke incidence and mortality trends in US communities. *JAMA* 2014;312:259.
23 Modin D, Claggett B, Sindet-Pedersen C, *et al*. Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation* 2020;142:2080–2.
24 Lund LC, Hallas J, Nielsen H, *et al*. Post-acute effects of SARS-Cov-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. *Lancet Infect Dis* 2021;21:1373–82.
25 Xie Y, Xu E, Bowe B, *et al*. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28:583–90.
26 Smeeth L, Thomas SL, Hall AJ, *et al*. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;351:2611–8.
27 Elkind MSV, Carty CL, O'Meara ES, *et al*. Hospitalization for infection and risk of acute ischemic stroke: the cardiovascular health study. *Stroke* 2011;42:1851–6.
28 Boehme AK, Ranawat P, Luna J, *et al*. Risk of acute stroke after hospitalization for sepsis: a case-crossover study. *Stroke* 2017;48:574–80.
29 Ohland J, Warren-Gash C, Blackburn R, *et al*. Acute myocardial Infarctions and stroke triggered by laboratory-confirmed respiratory infections in Denmark, 2010 to 2016. *Euro Surveill* 2020;25:17.
30 Merkler AE, Parikh NS, Mir S, *et al*. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol* 2020;77:1–7.
31 Elkind MSV, Boehme AK, Smith CJ, *et al*. Infection as a stroke risk factor and determinant of outcome after stroke. *Stroke* 2020;51:3156–68.
32 Patel S, Ershad F, Zhao M, *et al*. Wearable electronics for skin wound monitoring and healing. *Soft Sci* 2022;2:9.