Neurology Publish Ahead of Print
DOI: 10.1212/WNL.00000000000013184

COVID-19 and Risk of Acute Ischemic Stroke Among Medicare Beneficiaries Aged 65 Years or Older: Self-Controlled Case Series Study

Author(s):

Quanhe Yang, PhD¹; Xin Tong, MPH¹; Mary G George, MD¹; Anping Chang, MS¹; Robert K Merritt, MA¹

Corresponding Author:

Quanhe Yang
qay0@cdc.gov

Affiliation Information for All Authors: 1. Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention (CDC), Atlanta, USA

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Contributions:

Quanhue Yang: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Xin Tong: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Mary G George: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Anping Chang: Analysis or interpretation of data

Robert K Merritt: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Number of characters in title: 130

Abstract Word count: 346

Word count of main text: 3766

References: 47

Figures: 2

Tables: 4

Supplemental: STROBE RECORD checklist

Statistical Analysis performed by: Xing Tong, MPH, senior statistician Anping Chang, MS, mathematical statistician

Search Terms: [2] All Cerebrovascular disease/Stroke, [6] Infarction, [59] Risk factors in epidemiology, [360] COVID-19, [324] Class IV

Acknowledgements: We thank Dr. Heather J Whitaker, Public Health England, an executive agency of the Department of Health and Social Care in the United Kingdom, for providing help with the self-controlled case series analysis of event-dependent observation periods using R package SCCS. We thank Eric Hong, Hamilton College, for his help with the literature review for this study during his summer student intern in 2020 at Division for Heart Disease and Stroke Prevention, CDC. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Study Funding: The authors report no targeted funding

Disclosures: The authors report no disclosures relevant to the manuscript.

Abstract

Background and Objectives: Findings of association between COVID-19 and stroke remain inconsistent, ranging from significant association, absence of association to less than expected ischemic stroke among hospitalized patients with COVID-19. The present study examined the association between COVID-19 and risk of acute ischemic stroke (AIS).

Methods: We included 37,379 Medicare fee-for-service (FFS) beneficiaries aged ≥ 65 years diagnosed with COVID-19 from April 1, 2020 through February 28, 2021 and AIS hospitalization from January 1, 2019 through February 28, 2021. We used a self-controlled case series design to examine the association between COVID-19 and AIS and estimated the incident rate ratios (IRR) by comparing incidence of AIS in risk periods (0–3, 4–7, 8–14, 15–28 days after diagnosis of COVID-19) vs. control periods.

Results: Among 37,379 Medicare FFS beneficiaries with COVID-19 and AIS, the median age at diagnosis of COVID-19 was 80.4 (interquartile range 73.5–87.1) years and 56.7% were women. When AIS at day of exposure (day=0) included in the risk periods, IRRs at 0–3, 4–7, 8–14, and 15–28 days following COVID-19 diagnosis were 10.3 (95% confidence interval 9.86–10.8), 1.61 (1.44–1.80), 1.44 (1.32–1.57), and 1.09 (1.02–1.18); when AIS at day 0 excluded in the risk periods, the corresponding IRRs were 1.77 (1.57–2.01) (day 1–3), 1.60 (1.43–1.79), 1.43 (1.31–1.56), and 1.09 (1.01–1.17), respectively. The association appeared to be stronger among younger beneficiaries and among beneficiaries without prior history of stroke but largely consistent across sex and race/ethnicities.

Discussion: Risk of AIS among Medicare FFS beneficiaries was ten times (day 0 cases in the risk period) as high during the first 3 days after diagnosis of COVID-19 as during the control

period and the risk associated with COVID-19 appeared to be stronger among those aged 65–74 years and those without prior history of stroke.

Classification of Evidence: This study provides Class IV evidence that SARS-CoV-2 infection, the virus that causes COVID-19, is associated with increased risk of AIS in the first three days after diagnosis in Medicare FFS beneficiaries ≥ 65 years age.

ACCEPTED

Introduction

Several studies suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the virus that causes coronavirus disease 2019 (COVID-19), has been associated with an increased risk of cerebrovascular events including acute ischemic stroke (AIS).¹⁻⁶ However, the findings of association between COVID-19 and stroke were not consistent, as studies reported the rates of stroke among patients with COVID-19 ranging from 0.4% to 8.0% with an average of 1.4%.² Two studies using similar study design suggested that risk of ischemic stroke increased significantly following diagnosis of COVID-19.^{3,6} One study suggested that the rates of stroke were similar between hospitalized patients with and without COVID-19,⁷ and another study showed that ischemic stroke occurred less often than expected among hospitalized patients with COVID-19.⁸ Differences in study designs, countries, inclusion criteria of patients and comparison groups, sample size and controlling for confounders may contribute to the inconsistent findings. Few studies focused on the older population where most stroke occurred.⁹ The objective of the present study is to examine the association between COVID-19 and risk of AIS among Medicare fee-for-service (FFS) beneficiaries aged 65 years or older. We used a self-controlled case series study design that is based on within-person comparisons and implicitly controls for all fixed confounding effects. Our study included more than 37,000 Medicare FFS beneficiaries who were diagnosed with COVID-19 during 04/01/2020–02/28/2021 and AIS hospitalizations during 01/01/2019–02/28/2021.

The primary research question of the present study is to determine the association between SARS-CoV-2 infection and risk of AIS among Medicare FFS beneficiaries ≥ 65 years or older.

Methods

Study population

We used the real-time Medicare Geographic Variation (GV) files to identify the beneficiaries for this study. First, we identified all Medicare beneficiaries who had been diagnosed with COVID-19 from January 1, 2020 through February 28, 2021 from Part A (inpatient claims) and Part B (physician's office

claims). We used the *International Classification of Diseases, 10th revision clinical modification* (ICD-10-CM) code U07.1 to identify Medicare beneficiaries diagnosed with COVID-19. If the beneficiaries had more than one date for a COVID-19 diagnosis, the first diagnosed date was chosen. Second, we used the primary diagnosis code for AIS (ICD-10-CM code I63) to identify the beneficiaries with AIS hospitalizations from January 1, 2019 through February 28, 2021. The diagnosis of ischemic stroke in the administrative datasets are valid and the concordance between ICD-10-CM codes in administrative datasets and the clinical diagnosed stroke was shown to be generally high.^{10, 11} If the beneficiaries had more than one date of AIS hospitalization during the study period, the first hospitalization date was chosen. Third, we merged the above two datasets using the beneficiaries' IDs to create the dataset including all Medicare beneficiaries diagnosed with COVID-19 from January 1, 2020 through February 28, 2021 and incident AIS from January 1, 2019 through February 28, 2021. Fourth, we further identified all Medicare FFS beneficiaries with at least 11 months continuous enrollment in Medicare Parts A (hospitalization) and B (office-based care) in 2020 or at least one month enrollment in 2021, and those who were diagnosed with COVID-19 from April 1, 2020 through February 28, 2021. For the beneficiaries who died before March 1, 2021, they must have had continuous enrollment in Medicare Part A and B before death.

During January 1, 2019 through February 28, 2021, there were 2,297,300 beneficiaries diagnosed with COVID-19, and during January 1, 2019 through February 28, 2021, there were 428,105 beneficiaries hospitalized with incident or recurrent AIS. In the merged dataset, there were 43,188 beneficiaries diagnosed with COVID-19 and incident AIS, among which 41,631 met FFS criteria (≥ 11 months enrollment in both Part A and B in 2020, or ≥ 1 months enrollment in both Part A and B in 2021) and of these, 37,932 beneficiaries were aged ≥ 65 years. Of those Medicare FFS beneficiaries aged ≥ 65 years, 37,675 were diagnosed with COVID-19 during April 1, 2020 to February 28, 2021. After excluding the beneficiaries with missing information on race/ethnicities, the final analytical cohort had 37,379 Medicare FFS beneficiaries diagnosed with COVID-19 and AIS (Figure 1).

Exposure and outcome

The exposure variable was COVID-19, and the index date of COVID-19 diagnosis for each FFS beneficiary was identified through Medicare real-time GV Part A and Part B claims data for the period between April 1, 2020 and February 28, 2021. The outcome was AIS, and the index date of AIS was identified using primary diagnosis codes in Part A from January 1, 2019 through February 28, 2021. For Medicare FFS beneficiaries with more than one date of being diagnosed with COVID-19 or AIS during the study period, the first occurrence of events was chosen as the index date. If the Medicare FFS beneficiaries had a diagnosis of stroke (any type and including transient ischemic attack) based on the Chronic Conditions Warehouse definition used by Centers for Medicare and Medicaid Services¹² that occurred before January 1, 2019, they were classified as having a prior history of stroke.

Statistical Analysis

We calculated the median age and interquartile range (IQR) and the distribution of age group, sex, race/ethnicities, AIS with and without prior history of stroke and death before end of follow-up for all Medicare FFS beneficiaries. We used self-controlled case series study design to estimate incident rate ratio (IRR) and 95% confidence interval (CI) for risk of AIS between 0 to 28 days following a diagnosis of COVID-19. As shown in Figure 2, the self-controlled case series design is based on within-person comparisons (self-matched) after exposure during an observation period subdivided into risk and control periods, and this method implicitly controls for all fixed confounders during the period of study.¹³ The null hypothesis, $IRR=1.0$, implies that AIS event rates remained constant during the entire observation period and were not affected by having COVID-19. An $IRR>1.0$ or <1.0 implies an increased or reduced risk of AIS following diagnosis of COVID-19. The study observation period started on January 1, 2019 and ended on February 28, 2021 or the date of death for those who died before the end of follow-up. We categorized the risk periods after diagnosis of COVID-19 into 0–3, 4–7, 8–14, and 15–28 days and the remaining periods served as control periods.¹⁴ However, we observed a higher number of AIS at day 0 of COVID-19 ($n=1,924$) and more than expected number of AIS cases that occurred 7 days before the

COVID-19 index date. We could not determine if these AIS cases may have occurred after SARS-CoV-2 infection since the incubation period for COVID-19 may extend up to 14 days.¹⁵ Therefore, we conducted two analyses: one analysis had a pre-exposure period from day -7 to day -1, and the risk periods of 0–3, 4–7, 8–14, and 15–28 days (day 0 cases in the risk periods) and another analysis with a pre-exposure period from day -7 to day 0, and the risk periods of 1–3, 4–7, 8–14, and 15–28 days (day 0 cases not-in the risk periods) for total AIS analysis.^{6, 16} Other studies observed similar pattern of cases distribution around the COVID-19 index date^{3, 6} and suggested that most patients with the same date of ischemic stroke and COVID-19 were indeed infected with SARS-CoV-2 before stroke event.⁶ Therefore, we presented results of the risk periods including day 0 cases for the stratified and sensitivity analyses.

There are 2 key assumptions of the self-controlled case series design: 1. events do not influence subsequent exposures; 2. events do not influence the length of observation periods.¹⁷ Among FFS beneficiaries with AIS, 28.5% of them (n=10,663) died before March 1, 2021 and the assumption of event being independent of observation period was violated (due to increased mortality after AIS hospitalization), therefore we used the modified self-controlled case series method that takes into account the event-dependent observation period of time.^{17, 18} The IRRs were adjusted for age at diagnosis of COVID-19 from 65 to 90 years of age by 2-year age groups.

We conducted stratified analyses by age groups (65–74 years, 75–84 years and ≥ 85 years), sex, race/ethnicities (non-Hispanic White, non-Hispanic Black, Hispanic and All other race/ethnicities) and status of history of prior stroke (first vs. recurrent stroke). We tested for interaction to examine whether the IRRs for risk of AIS changed significantly across the subgroups in the stratified analyses based on the likelihood ratio tests and presented adjusted p-values by using Holm's method for multiple comparisons.^{13, 17, 19}

We conducted several sensitivity analyses: 1. we restricted the starting time to January 1, 2020 to reduce the potential temporal changes in AIS before and after the COVID-19 pandemic (n=21,756); 2. we

excluded Medicare beneficiaries with I63.8 and I63.9 (less specific codes for AIS, n=17,251 after exclusion); 3. We excluded all beneficiaries who died before the end of observation period (n=26,716 after exclusion) and used the standard self-controlled case series analysis; 4. Studies suggested that pneumococcal vaccination was not associated with stroke.²⁰ We examined the association between pneumococcal vaccination and risk of AIS as a negative control to identify potential biases in using self-controlled case series design in Medicare claims data (first date of pneumococcal vaccination and AIS hospitalization, n=23,651). We changed the starting time to the date of pneumococcal vaccination because heart disease and stroke patients are advised to get vaccinated against pneumonia²¹ that may affect the probability of pneumococcal vaccination.²² We used the standard self-controlled case series analysis among stroke survivors. SAS, version 9.4 (SAS Institute) was used for analysis, and R package SCCS was used for self-controlled case series analyses.¹⁷

This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.ⁱ

Standard Protocol Approvals, Registrations, and Patient Consents

The Centers for Disease Control and Prevention Human Subjects Coordinator determined that this study did not require review for human subjects protections because the data did not contain personal identifiers and were not originally collected specifically for this study. Therefore, the requirement of informed consent was waived.

Data availability

Medicare data are available from Centers for Medicare & Medicaid Services, Department of Health and Human Services for any qualified investigator.

Results

Among 37,379 Medicare FFS beneficiaries diagnosed with COVID-19 and AIS, the median age was 80.4 years (IQR 73.5–87.1 years), 56.7% (95% confidence interval 56.2–57.2%) were women, and

75.9% (75.4–76.3%) were non-Hispanic White. Among the beneficiaries, 34.0% (33.5–34.5%) had prior history of stroke and 28.5% (28.1–29.0%) died before the end of observation period (Table 1).

When AIS at day of exposure (day=0) included in the risk period, IRRs at 0–3, 4–7, 8–14, and 15–28 days following COVID-19 diagnosis were 10.3 (9.86–10.8), 1.61 (1.44–1.80), 1.44 (1.32–1.57), and 1.09 (1.02–1.18), when AIS at day 0 excluded in the risk period, the corresponding IRRs were 1.77 (1.57–2.01) (day 1–3), 1.60 (1.43–1.79), 1.43 (1.31–1.56), and 1.09 (1.01–1.17), respectively (Table 2).

The association appeared to be stronger among younger (ages 65–74 years) beneficiaries and among beneficiaries without prior history of stroke. The age-adjusted IRRs at 0–3, 4–7, 8–14, and 15–28 days following the diagnosis of COVID-19 were 14.7 (13.6–15.8), 2.45 (2.02–2.92), 1.70 (1.46–1.98), and 1.06 (0.92–1.22) among those aged 65–74 years compared to 7.04 (6.46–7.66), 1.10 (0.89–1.35), 1.15 (0.98–1.34), and 1.05 (0.93–1.19) among those aged ≥ 85 years ($p < 0.001$); the corresponding comparisons for beneficiaries with and without prior history of stroke were 7.92 (7.26–8.63), 1.00 (0.78–1.27), 1.22 (1.03–1.43), and 1.10 (0.96–1.25) vs. 14.6 (13.9–15.4), 2.41 (2.13–2.73), 1.88 (1.70–2.08), and 1.24 (1.14–1.36) ($p < 0.001$). The pattern of association between COVID-19 and risk for AIS were largely consistent across sex, and race/ethnicities (Table 3) and for the sensitivity analyses (Table 4). The IRRs between pneumococcal vaccination and AIS were approximately 1.0 across the exposure period suggesting the validity of using self-controlled case series design in Medicare claims data (Table 4).

This study provides Class IV evidence that SARS-CoV-2 infection, the virus that causes COVID-19, is associated with increased risk of AIS in the first three days after diagnosis in Medicare FFS beneficiaries ≥ 65 years age.

Discussion

We found that the incidence of AIS hospitalizations was 10 times (day 0 cases in the risk periods) as high during the first 3 days after diagnosis of COVID-19 as during the control period among Medicare

FFS beneficiaries aged ≥ 65 years. There was a graded stronger association from older to younger beneficiaries. The association appeared to be stronger among the beneficiaries without prior history of stroke. We observed a higher number AIS (n=1,924) at day 0 of COVID-19 index date. A Swedish study using self-controlled case series design also found higher number of ischemic stroke and COVID-19 at day 0. The IRR for ischemic stroke was 6.18 (4.06–9.42) for the first week following diagnosis of COVID-19 (including day 0 cases in the risk periods) and IRR of 2.97 (1.71–5.15) excluding day 0 cases.⁶ With the mean incubation period for COVID-19 of 5.1 days (97.5% of patients developing symptoms within 12.5 days), the Swedish study suggested that the patients at day 0 were highly likely to be infected with SARS-CoV-2 before their stroke event. Most hospitals screen all patients for COVID-19 on hospital admissions in the United States, and some AIS patients may have had SARS-CoV-2 infection before hospitalizations and continue to have positive testing results after the initial infection. Those patients were likely to have the same date of AIS hospitalizations and COVID-19 diagnosis in the Medicare claims but also likely to have an AIS precipitated by SARS-CoV-2 infection. Our results of increased risk for AIS following diagnosis of COVID-19 were consistent with other studies.^{1-3, 5, 6} Modin, et. al. used the Danish nationwide registers data and self-controlled case series design to examine the association between COVID-19 and ischemic stroke and reported an IRR of 12.9 (7.1–23.5) during the first 14 days following diagnosis of COVID-19.³ However, using data extracted from the electronic medical records of 54 health care facilities in the United States, Qureshi et al, documented similar rates of AIS among patients hospitalized with and without COVID-19 (1.3% vs. 1.0%).⁷ Another retrospective cohort study of hospitalized COVID-19 patients within a major health system in the New York metropolitan area reported lower prevalence of imaging-confirmed AIS compared to the contemporary controls (patients without COVID-19) and historical controls (patients in 2019), but suggested that the rate of AIS may be underestimated due to the challenge of diagnosing stroke among critically ill patients with COVID-19.²³ A cross-sectional study of the hospital discharge data from a healthcare system in New York State with data collected from January to April 2020 found

that the prevalence of AIS was significantly less frequent among patients with diagnosed COVID-19 compared to those without COVID-19 (adjusted odds ratio 0.29 [0.18–0.48]).⁸ Residual confounding and uncertainties in coding of COVID-19 during the early phase of the pandemic may contribute to this observed association. The findings of our study support those of previous studies of a significant association between COVID-19 and stroke and provide further evidence of the association from a large Medicare cohort of beneficiaries aged 65 years or older.

Our results suggest that the risk of AIS following diagnosis of COVID-19 was higher among beneficiaries aged 65–74 years compared to those aged ≥ 85 years (IRR in 0–3 days 14.7 (13.6–15.8) vs. 7.04 (6.46–7.66), $p < 0.001$). We are not aware of any study that provided age-stratified analysis of risk of COVID-19–associated AIS. The reasons for stronger association among younger Medicare beneficiaries are not clear. Studies have reported increased incidence of large vessel stroke among younger patients with COVID-19.^{4, 24} Other studies observed that patients with COVID-19 and stroke were significantly younger than stroke patients without COVID-19,^{23, 25–27} with a pooled age difference of 6 years.² In the general population, the incidence of stroke increases rapidly with age.^{9, 28} If COVID-19 disproportionately affects younger patients with respect to risk of stroke, it might partly explain the stronger association between COVID-19 and AIS among younger Medicare beneficiaries because of relatively lower baseline risk among younger beneficiaries. On the other hand, the higher risk among younger beneficiaries might be due to inclusion bias because older beneficiaries with severe COVID-19 might have not survived to get tested for COVID-19 or evaluated for stroke. Further studies are needed to examine the incidence of stroke subtypes by age group.

The risk of AIS following diagnosis of COVID-19 appeared to be higher among beneficiaries without a history of stroke compared to those with a history of stroke (IRR in 0–3 days 14.6 (13.9–15.4) vs. 7.92 (7.26–8.63), $p < 0.001$). The reasons for the stronger association among the beneficiaries without history of stroke are not clear. Medicare beneficiaries with history of stroke may be more likely on the

medications for secondary prevention of stroke.^{29, 30} The beneficiaries who had a history of stroke were older than the beneficiaries without a history of stroke (median age 82.1 years vs. 79.2 years, $p<0.05$) and this might partly contribute to the stronger association because of the stronger association between COVID-19 and AIS among younger Medicare beneficiaries. The association between COVID-19 and AIS appeared to be stronger among men compared to women ($p=0.011$). The detailed analysis suggested that the difference was mainly driven by the IRRs 8-14 days after diagnosis of COVID-19 (1.70 (1.50–1.93) among men vs. 1.25 (1.11–1.41) among women. The association between COVID-19 and AIS appeared to be different across race/ethnic group ($p=0.010$). There is no difference between non-Hispanic White and non-Hispanic Black ($p=0.293$) and between Mexican American and Other ($p=0.268$) but the risk appeared to be stronger among Mexican American and Other compared to non-Hispanic White and non-Hispanic Black. However, the pattern of association remained largely consistent across race/ethnic group, and these statistically significant differences by sex and race/ethnicities may not be clinically significant. Further study is warranted to determine the sex and race/ethnic-specific association between COVID-19 and AIS.

Many studies provided evidence showing the presence of systemic infection, such as influenza, systemic respiratory tract infection, and herpes zoster, as a trigger of stroke.³¹⁻³⁶ The mechanisms underlying the association between COVID-19 and risk of stroke are not yet fully understood but are considered complex and may involve multiple pathways. The key proposed mechanisms suggested that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors of epithelial and endothelial cells where the immunological activation occurs that can lead to development of cytokine storm and hypercoagulability, and an increased tendency of blood clots formation, leading to increased risk of AIS.^{2, 37} SARS-CoV-2 infection may also have direct viral injury causing viral-induced endotheliitis, potentially leading to angioathic thrombosis.³⁸ The analysis of endothelial cells from the human brain suggested that SARS-CoV-2 can directly affect the brain endothelial cells triggering a unique gene expression profile in brain endothelia and increase the risk of stroke.³⁹

Studies suggested that COVID-19 associated ischemic strokes are more severe, with worse functional outcomes and significantly higher mortality, than non-COVID-19 ischemic strokes.^{2, 27, 40, 41} Although the overall incidence of COVID-19 associated AIS is not clear, emerging evidence suggested that the incidence of large vessel stroke may increase in patients with COVID-19 who might not have the typical risk factors for stroke.^{2, 4, 24} Timely diagnosis of COVID-19 associated stroke, and providing recommended treatment might play important roles in reducing the morbidity and mortality in patients with temporally COVID-19 associated stroke during the pandemic. In addition, further studies are warranted to examine the long-term effects of COVID-19-associated stroke.

The main strength of this study is the use of the self-controlled case series study design. This study design is based on within-person comparisons and implicitly controls for all fixed confounders.⁴² Also, the self-controlled case series is more efficient than other observational study designs and provide more precise estimates of the exposure effects on risk of outcomes.¹³

Our study had several limitations. First, we used Medicare real time GV preliminary data that is updated on monthly basis. We might have missed some beneficiaries with diagnosed COVID-19 and AIS or have misclassified some beneficiaries who died before end of follow-up as alive because of delayed reporting. However, Centers for Medicare & Medicaid Services indicated that more than 95% of Medicare FFS in-hospital claims were received within 3 months.⁴³ Second, Medicare beneficiaries with COVID-19 were identified through the administrative claims data and might be subject to misclassification. However, one study suggested that the physicians and hospitals were likely to follow the recommendations and guidelines regarding COVID-19 diagnosis because of the seriousness of the COVID-19 pandemic.⁴⁴ Third, the dates of diagnosed COVID-19 and AIS in Medicare data might be subject to error. The diagnostic testing for COVID-19 in the outpatient settings, especially during the early phase of the pandemic, was limited and types of tests used to confirm COVID-19 and turnaround time from the onset of symptoms to return a positive test varied. In addition, the beneficiaries without

COVID-19 symptoms were unlikely to get tested in the outpatient settings. We observed higher number of AIS and COVID-19 at day 0 and more than the expected AIS hospitalizations within 7 days before the index date of diagnosed COVID-19. Screening all patients for COVID-19 on the hospital admissions including some patients who may continue to have positive testing results after the initial infection might contribute to the higher number of AIS and COVID-19 at day 0. These factors may affect the accurate timing of exposure to SARS-CoV-2 among Medicare beneficiaries. Fourth, the self-controlled case series methods assume that the other confounders affecting the outcome remain largely unchanged during the study period. However, COVID-19 pandemic affected all hospitals and health care systems, including changes in emergency department visits and hospitalizations for stroke or stroke-like symptoms, care of acute stroke, and access to preventive care.^{5, 27, 45-47} These changes may affect the assumption of unchanged confounders during the study period. In the sensitivity analyses, we restricted the starting time of the study to January 1, 2020 and pattern of association remained largely consistent. Fifth, we restricted our study to Medicare FFS beneficiaries, which included about 60% of Medicare beneficiaries, thus our findings are not generalizable to non-FFS beneficiaries.

Conclusions

Incidence of AIS hospitalizations was ten times (including day 0 cases in the risk periods) as high during the 3 days after diagnosis of COVID-19 as during the control periods and risk associated with COVID-19 appeared to be stronger among younger Medicare FFS beneficiaries and among beneficiaries without history of stroke.

Appendix 1. Authors

Name	Location	Contribution
Quanhe Yang, PhD	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, USA	Designed and conceptualized study; conducted statistical analysis; drafted the manuscript for intellectual content
Xin Tong, MPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, USA	Validated, generated analytical datasets, and conducted statistical analyses
Mary G. George, MD, MSPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, USA	Interpreted the data; revised the manuscript for intellectual content
Anping Chang, MPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, USA	Generated the analytical datasets
Robert Merritt, MS	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, USA	Interpreted the data; revised the manuscript for intellectual content

References

1. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, Lantos J, Schenck EJ, Goyal P, Bruce SS, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (covid-19) vs patients with influenza. *JAMA Neurol.* 2020;77:1-7
2. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in covid-19: A systematic review and meta-analysis. *Int J Stroke.* 2021;16:137-149
3. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, Fralick M, Schou M, Lamberts M, Gerds T, et al. Acute covid-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation.* 2020;142:2080-2082
4. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med.* 2020;382:e60
5. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, Turc G, Romoli M, Sharma VK, Mavridis D, et al. The impact of sars-cov-2 on stroke epidemiology and care: A meta-analysis. *Ann Neurol.* 2021;89:380-388
6. Katsoularis I, Fonseca-Rodriguez O, Farrington P, Lindmark K, Fors Connolly AM. 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
7. Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, Lobanova I, Suri MFK, Naqvi SH, French BR, et al. Acute ischemic stroke and covid-19: An analysis of 27 676 patients. *Stroke.* 2021;52:905-912
8. Bekelis K, Missios S, Ahmad J, Labropoulos N, Schirmer CM, Calnan DR, Skinner J, MacKenzie TA. Ischemic stroke occurs less frequently in patients with covid-19: A multicenter cross-sectional study. *Stroke.* 2020;51:3570-3576
9. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2021 update: A report from the american heart association. *Circulation.* 2021:CIR00000000000000950
10. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of diagnostic codes for acute stroke in administrative databases: A systematic review. *PLoS One.* 2015;10:e0135834
11. Chang TE, Tong X, George MG, Coleman King SM, Yin X, O'Brien S, Ibrahim G, Liskay A, Paul Coverdell National Acute Stroke Program t, Wiltz JL. Trends and factors associated with concordance between international classification of diseases, ninth and tenth revision, clinical modification codes and stroke clinical diagnoses. *Stroke.* 2019;50:1959-1967
12. Centers for Medicare & Medicaid Services. Chronic conditions data warehouse. Available from: <https://www2.ccwdata.org/web/guest/condition-categories> Accessed September 1, 2021.
13. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: The self-controlled case series method. *Stat Med.* 2006;25:1768-1797

14. Kwong JC, Schwartz KL, Campitelli MA. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378:2540-2541
15. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (covid-19). Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html> Accessed September 1, 2021.
16. Fonseca-Rodriguez O, Fors Connolly AM, Katsoularis I, Lindmark K, Farrington P. Avoiding bias in self-controlled case series studies of coronavirus disease 2019. *Stat Med* 2021 Sep 1. doi: 10.1002/sim.9179. Online ahead of print
17. Farrington P, Whitaker H, Ghebremichael Weldeselassie Y. *Self-controlled case series studies : A modelling guide with r*. Boca Raton: CRC Press, Taylor & Francis Group; 2018.
18. Farrington CP, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-controlled case series analysis with event-dependent observation periods. *J Am Stat Assoc*. 2011;106:417-426
19. Holm SA. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65-70
20. Kaczorowski J. Pneumococcal vaccination and cardiovascular events in men. *JAMA*. 2010;304:742; author reply 743
21. Centers for Disease Control and Prevention. Heart disease, stroke, or other cardiovascular disease and adult vaccination. Available from: <https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/heart-disease.html> Accessed September 1, 2021.
22. Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. *Epidemiol Infect*. 2011;139:1805-1817
23. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, et al. Sars-cov-2 and stroke in a new york healthcare system. *Stroke*. 2020;51:2002-2011
24. Fifi JT, Mocco J. Covid-19 related stroke in young individuals. *Lancet Neurol*. 2020;19:713-715
25. Majidi S, Fifi JT, Ladner TR, Lara-Reyna J, Yaeger KA, Yim B, Dangayach N, Oxley TJ, Shigematsu T, Kummer BR, et al. Emergent large vessel occlusion stroke during new york city's covid-19 outbreak: Clinical characteristics and paraclinical findings. *Stroke*. 2020;51:2656-2663
26. Sweid A, Hammoud B, Bekelis K, Missios S, Tjoumakaris SI, Gooch MR, Herial NA, Zarzour H, Romo V, DePrince M, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. *Int J Stroke*. 2020;15:733-742
27. Srivastava PK, Zhang S, Xian Y, Xu H, Rutan C, Alger HM, Walchok J, Williams J, de Lemos JA, Decker-Palmer MR, et al. Acute ischemic stroke in patients with covid-19: An analysis from get with the guidelines-stroke. *Stroke*. 2021:STROKEAHA121034301

28. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781-1787
29. Dalli LL, Kim J, Thrift AG, Andrew NE, Sanfilippo FM, Lopez D, Grimley R, Lannin NA, Wong L, Lindley RI, et al. Patterns of use and discontinuation of secondary prevention medications after stroke. *Neurology*. 2021;96:e30-e41
30. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockcroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the american heart association/american stroke association. *Stroke*. 2021;52:e364-e467
31. Fugate JE, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. *Lancet Infect Dis*. 2014;14:869-880
32. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a stroke risk factor and determinant of outcome after stroke. *Stroke*. 2020;51:3156-3168
33. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611-2618
34. Kulick ER, Canning M, Parikh NS, Elkind MSV, Boehme AK. Seasonality of influenza-like-illness and acute cardiovascular events are related regardless of vaccine effectiveness. *Journal of the American Heart Association*. 2020;9:e016213
35. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: A self-controlled case-series study. *Clin Infect Dis*. 2014;58:1497-1503
36. Yang Q, George MG, Chang A, Tong X, Merritt R, Hong Y. Effect of herpes zoster vaccine and antiviral treatment on risk of ischemic stroke. *Neurology*. 2020;95:e708-e717
37. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in covid-19-positive patients: An overview of sars-cov-2 and thrombotic mechanisms for the neurointerventionalist. *J Neurointerv Surg*. 2021;13:202-206
38. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in covid-19. *Lancet*. 2020;395:1417-1418
39. Kaneko N, Satta S, Komuro Y, Muthukrishnan SD, Kakarla V, Guo L, An J, Elahi F, Kornblum HI, Liebeskind DS, et al. Flow-mediated susceptibility and molecular response of cerebral endothelia to sars-cov-2 infection. *Stroke*. 2021;52:260-270
40. Jain R, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, Bilaloglu S, Hochman K, Raz E, Galetta S, et al. Covid-19 related neuroimaging findings: A signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. *J Neurol Sci*. 2020;414:116923

41. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, Calleja P, Ostos F, González-Ortega G, Fuentes B, et al. Characteristics and outcomes in patients with covid-19 and acute ischemic stroke: The global covid-19 stroke registry. *Stroke*. 2020;51:e254-e258
42. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: An alternative to standard epidemiological study designs. *BMJ (Online)*. 2016;354:i4515
43. Centers for Medicare & Medicaid Services. Preliminary medicare covid-19 data snapshot: Medicare claims and encounter data: January 1, 2020 to june 19, 2021, received by july 16, 2021. Available from: <https://www.cms.gov/files/document/medicare-covid-19-data-snapshot-fact-sheet.pdf> Accessed September 1, 2021.
44. Izurieta HS, Graham DJ, Jiao Y, Hu M, Lu Y, Wu Y, Chillarige Y, Wernecke M, Menis M, Pratt D, et al. Natural history of covid-19: Risk factors for hospitalizations and deaths among >26 million u.S. Medicare beneficiaries. *J Infect Dis*. 2020
45. Yang Q, Tong X, Coleman King S, Olivari BS, Merritt RK. Stroke hospitalizations before and during covid-19 pandemic among medicare beneficiaries in the united states. *Stroke*. 2021:STROKEAHA121034562
46. Tong X, King SMC, Asaithambi G, Odom E, Yang Q, Yin X, Merritt RK. Covid-19 pandemic and quality of care and outcomes of acute stroke hospitalizations: The paul coverdell national acute stroke program. *Prev Chronic Dis*. 2021;18:E82
47. Lange SJ, Ritchey MD, Goodman AB, Dias T, Twentyman E, Fuld J, Schieve LA, Imperatore G, Benoit SR, Kite-Powell A, et al. Potential indirect effects of the covid-19 pandemic on use of emergency departments for acute life-threatening conditions - united states, january-may 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:795-800

Figure Legends

Figure 1. Flowchart of Medicare FFS beneficiaries with diagnosed COVID-19 and acute ischemic stroke, Medicare 2019-2021 — United States

Figure 2. Graphic representation of self-controlled case series study design

Table 1. Characteristics of Medicare Fee-For-Service Beneficiaries with Diagnosed COVID-19 and Acute Ischemic Stroke, Medicare 2019-2021 — United States

Characteristics	Number of Medicare FFS beneficiaries	Median/percent (95% CI)
Age, median (IQR)	37,379	80.4 (73.5–87.1)
Age group		
65–74 years	11,305	30.2 (29.8–30.7)
75–84 years	13,873	37.1 (36.6–37.6)
≥85 years	12,201	32.6 (32.2–33.1)
Sex		
Men	16,199	43.3 (42.8–43.8)
Women	21,180	56.7 (56.2–57.2)
Race/ethnicities		
Non-Hispanic White	28,361	75.9 (75.4–76.3)
Non-Hispanic Black	5,030	13.5 (13.1–13.8)
Hispanic	2,560	6.9 (6.6–7.1)
All other race/ethnicities	1,428	3.8 (3.6–4.0)
History of stroke^a		
Yes	12,715	34.0 (33.5–34.5)
No	24,664	66.0 (65.5–66.5)
Death before end of follow-up		
Yes	10,663	28.5 (28.1–29.0)
No	26,716	71.5 (71.0–71.9)

Abbreviation: CI = confidence interval; FFS = fee-for-service; IQR = interquartile range

a Medicare FFS beneficiaries who had stroke before January 1, 2019.

Table 2. Incidence Rate Ratio (95% CI) of Acute Ischemic Stroke Among Medicare Fee-For-Service Beneficiaries Diagnosed with COVID-19, Medicare 2019-2021 — United States

Risk Period	Number of events	Crude IRR (95% CI)	Age adjusted IRR (95% CI)^a
Day 0 cases in the risk period			
-7 to -1 days	789	1.82 (1.69-1.95)	1.91 (1.78-2.05)
0–3 days	2,173	9.82 (9.40-10.3)	10.3 (9.86-10.8)
4–7 days	322	1.53 (1.37-1.71)	1.61 (1.44-1.80)
8–14 days	523	1.37 (1.25-1.49)	1.44 (1.32-1.57)
15–28 days	735	1.04 (0.96-1.12)	1.09 (1.02-1.18)
Baseline ^b	32,837	1.0	1.0
Day 0 cases not-in the risk period			
-7 to 0 days	2,713	5.34 (5.13-5.55)	5.60 (5.37-5.83)
1–3 days	249	1.69 (1.49-1.91)	1.77 (1.57-2.01)
4–7 days	322	1.52 (1.36-1.70)	1.60 (1.43-1.79)
8–14 days	523	1.36 (1.25-1.49)	1.43 (1.31-1.56)
15–28 days	735	1.04 (0.96-1.12)	1.09 (1.01-1.17)
Baseline ^b	32,837	1.0	1.0

Abbreviation: CI = confidence interval; IRR = incidence rate ratio.

a Adjusted by age at diagnosis of COVID-19 of 65 to 90 years of age by 2-year age group.

b All time from observation start on January 1, 2019 to seven days before date of COVID-19 diagnoses and after 28 days of diagnosis of COVID-19.

Table 3. Incidence Rate Ratio (95% CI) for Acute Ischemic Stroke Among Medicare Fee-For-Service Beneficiaries with Diagnosed COVID-19 by Selected Characteristics, Medicare 2019-2021 — United States (Table 3 continued)

Characteristics	No. events	Crude IRR (95% CI)	Age adjusted IRR (95% CI) ^a	p-value ^b
Age group				
65-74 years				
-7 to -1 days	228	2.06 (1.80-2.35)	2.14 (1.88-2.45)	
0-3 days	794	14.1 (13.1-15.1)	14.7 (13.6-15.8)	
4-7 days	128	2.35 (1.97-2.79)	2.45 (2.05-2.92)	
8-14 days	168	1.63 (1.40-1.90)	1.70 (1.46-1.98)	
15-28 days	204	1.02 (0.89-1.17)	1.06 (0.92-1.22)	
Baseline ^c	9,783	1.0	1.0	
75-84 years				
-7 to -1 days	277	1.80 (1.60-2.03)	1.87 (1.66-2.11)	
0-3 days	790	10.1 (9.41-10.9)	10.5 (9.78-11.4)	
4-7 days	107	1.44 (1.19-1.74)	1.50 (1.24-1.81)	
8-14 days	196	1.43 (1.24-1.65)	1.49 (1.30-1.72)	
15-28 days	277	1.09 (0.96-1.23)	1.13 (1.00-1.28)	
Baseline ^c	12,226	1.0	1.0	
≥85 years				
-7 to -1 days	284	1.71 (1.52-1.93)	1.79 (1.59-2.02)	
0-3 days	589	6.72 (6.18-7.31)	7.04 (6.46-7.66)	
4-7 days	87	1.05 (0.85-1.29)	1.10 (0.89-1.35)	
8-14 days	159	1.09 (0.94-1.28)	1.15 (0.98-1.34)	
15-28 days	254	1.00 (0.88-1.14)	1.05 (0.93-1.19)	
Baseline ^c	10,828	1.0	1.0	<0.001
Sex				
Men				
-7 to -1 days	369	1.96 (1.77-2.18)	2.10 (1.89-2.33)	
0-3 days	990	10.4 (9.78-11.1)	11.2 (10.5-11.9)	
4-7 days	147	1.64 (1.39-1.93)	1.75 (1.49-2.07)	
8-14 days	259	1.59 (1.40-1.80)	1.70 (1.50-1.93)	
15-28 days	285	0.95 (0.84-1.07)	1.02 (0.91-1.15)	
Baseline ^c	14,149	1.0	1.0	
Women				
-7 to -1 days	420	1.77 (1.61-1.95)	1.83 (1.66-2.02)	
0-3 days	1,183	9.57 (9.01-10.2)	9.87 (9.29-10.5)	
4-7 days	175	1.47 (1.26-1.70)	1.52 (1.31-1.76)	
8-14 days	264	1.21 (1.07-1.37)	1.25 (1.11-1.41)	
15-28 days	450	1.11 (1.01-1.22)	1.15 (1.04-1.26)	
Baseline ^c	18,688	1.0	1.0	0.011
Race/ethnicities				
Non-Hispanic White				
-7 to -1 days	601	1.82 (1.68-1.97)	1.90 (1.76-2.07)	
0-3 days	1,613	9.51 (9.04-10.0)	9.97 (9.46-10.5)	
4-7 days	239	1.48 (1.30-1.68)	1.55 (1.37-1.76)	
8-14 days	398	1.36 (1.23-1.50)	1.43 (1.29-1.58)	
15-28 days	560	1.04 (0.96-1.13)	1.09 (1.00-1.19)	
Baseline ^c	24,950	1.0	1.0	

Characteristics	No. events	Crude IRR (95% CI)	Age adjusted IRR (95% CI) ^a	p-value ^b
Age group				
Non-Hispanic Black				
-7 to -1 days	99	2.01 (1.65-2.46)	2.11 (1.72-2.57)	
0-3 days	268	11.0 (9.76-12.5)	11.6 (10.2-13.1)	
4-7 days	39	1.68 (1.23-2.30)	1.76 (1.28-2.41)	
8-14 days	62	1.42 (1.11-1.83)	1.49 (1.16-1.91)	
15-28 days	100	1.16 (0.95-1.42)	1.22 (1.00-1.49)	
Baseline ^c	4,462	1.0	1.0	
Hispanic				
-7 to -1 days	59	2.11 (1.63-2.74)	2.20 (1.70-2.86)	
0-3 days	190	13.1 (11.2-15.2)	13.6 (11.7-15.9)	
4-7 days	30	2.12 (1.48-3.04)	2.22 (1.54-3.19)	
8-14 days	36	1.38 (0.99-1.93)	1.45 (1.04-2.02)	
15-28 days	56	1.16 (0.89-1.51)	1.21 (0.93-1.59)	
Baseline ^c	2,189	1.0	1.0	
All other				
-7 to -1 days	30	1.74 (1.21-2.51)	1.86 (1.29-2.69)	
0-3 days	102	11.9 (9.71-14.6)	12.8 (10.4-15.8)	
4-7 days	14	1.74 (1.03-2.96)	1.87 (1.10-3.18)	
8-14 days	27	1.83 (1.25-2.69)	1.96 (1.34-2.89)	
15-28 days	19	0.71 (0.45-1.12)	0.76 (0.48-1.20)	
Baseline ^c	1,236	1.0	1.0	0.010
History of stroke				
Yes				
-7 to -1 days	238	1.52 (1.34-1.73)	1.69 (1.48-1.92)	
0-3 days	566	7.13 (6.55-7.76)	7.92 (7.26-8.63)	
4-7 days	67	0.90 (0.70-1.14)	1.00 (0.78-1.27)	
8-14 days	147	1.09 (0.93-1.28)	1.22 (1.03-1.43)	
15-28 days	243	0.98 (0.86-1.12)	1.10 (0.96-1.25)	
Baseline ^c	11,454	1.0	1.0	
No				
-7 to -1 days	551	2.45 (2.25-2.66)	2.48 (2.28-2.70)	
0-3 days	1607	14.4 (13.7-15.2)	14.6 (13.9-15.4)	
4-7 days	255	2.38 (2.10-2.69)	2.41 (2.13-2.73)	
8-14 days	376	1.85 (1.67-2.05)	1.88 (1.70-2.08)	
15-28 days	492	1.23 (1.12-1.34)	1.24 (1.14-1.36)	
Baseline ^c	21,383	1.0	1.0	<0.001

Abbreviation: CI = confidence interval, IRR = incidence rate ratio.

a Adjusted by age at diagnosis of COVID-19 of 65 to 90 years of age by 2-year age group.

b p-value for interaction was calculated using likelihood ratio test and adjusted for multiple comparison based on Holm methods.

c All time from observation start on January 1, 2019 to seven days before date of COVID-19 diagnoses and after 28 days of diagnosis of COVID-19.

ACCEPTED

Table 4. Sensitivity Analyses of Incidence Rate Ratio (95% CI) of Acute Ischemic Stroke Among Medicare Fee-For-Service Beneficiaries, Medicare 2019-2021 — United States

Risk Period	Number of events	Crude IRR (95% CI)	Age adjusted IRR (95% CI)^a
Restricted the starting time of the study period to January 1, 2020 ^c			
-7 to -1 days	789	1.90 (1.77-2.05)	1.93 (1.80-2.08)
0-3 days	2,173	10.2 (9.76-10.7)	10.4 (9.92-10.9)
4-7 days	322	1.58 (1.42-1.77)	1.61 (1.44-1.80)
8-14 days	523	1.40 (1.28-1.52)	1.42 (1.30-1.55)
15-28 days	735	1.05 (0.97-1.13)	1.07 (0.99-1.15)
Baseline ^b	17,214	1.0	1.0
Excluding AIS with I63.8 and I63.9 diagnosis codes ^d			
-7 to -1 days	403	1.95 (1.76-2.15)	2.00 (1.81-2.21)
0-3 days	1,108	10.3 (9.63-10.9)	10.5 (9.89-11.2)
4-7 days	186	1.81 (1.57-2.09)	1.86 (1.61-2.16)
8-14 days	299	1.61 (1.44-1.81)	1.66 (1.48-1.86)
15-28 days	392	1.15 (1.04-1.27)	1.18 (1.07-1.31)
Baseline ^b	14,863	1.0	1.0
Deleted Medicare FFS beneficiaries who died before the end of observation period ^e			
-7 to -1 days	505	2.26 (2.17-2.34)	2.25 (2.16-2.34)
0-3 days	1,487	11.7 (11.6-11.7)	11.6 (11.6-11.7)
4-7 days	204	1.61 (1.47-1.75)	1.61 (1.47-1.75)
8-14 days	353	1.61 (1.51-1.72)	1.61 (1.50-1.71)
15-28 days	459	1.07 (0.98-1.17)	1.07 (0.98-1.17)
Baseline ^b	23,708	1.0	1.0
Medicare FF beneficiaries who had pneumococcal vaccination and AIS from January 1, 2019 to February 28, 2021 ^f			
0-3 days	256	1.13 (0.99-1.25)	1.13 (0.99-1.28)
4-7 days	254	1.12 (0.99-1.25)	1.12 (0.98-1.27)
8-14 days	447	1.13 (1.03-1.23)	1.13 (1.03-1.23)
15-28 days	841	1.07 (0.99-1.14)	1.07 (0.99-1.14)
Baseline ^b	21,853	1.0	1.0

Abbreviation: CI = confidence interval; IRR = incidence rate ratio.

a Adjusted by age at diagnosis of COVID-19 of <65 to 90 years by 2-year age group.

b All time from observation start on January 1, 2019 to seven days before date of COVID-19 diagnoses and after 28 days of diagnosis of COVID-19.

c The starting time of the observation period was January 1, 2020 and ended on February 28, 2021 (n=21,756).

d Excluded AIS cases that had I63.8 and I63.9 ICD-10 diagnosis codes (n=17,251).

e Medicare FFS beneficiaries who died before the end of follow-up were excluded (n=26,716).

f Included Medicare FFS beneficiaries who had pneumococcal vaccination and AIS from January 1, 2019 to February 28, 2021. If the Medicare beneficiaries had more than one pneumococcal vaccination or AIS hospitalizations, the first date was chosen for the analysis. The date of pneumococcal vaccination was the starting time of the study period and ended on February 28, 2021. Standard self-controlled case series was used among stroke survivors (n=23,651).

ⁱ See e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

Neurology®

COVID-19 and Risk of Acute Ischemic Stroke Among Medicare Beneficiaries Aged 65 Years or Older: Self-Controlled Case Series Study

Quanhe Yang, Xin Tong, Mary G George, et al.

Neurology published online February 3, 2022

DOI 10.1212/WNL.00000000000013184

This information is current as of February 3, 2022

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/early/2022/02/02/WNL.00000000000013184.full
Citations	This article has been cited by 2 HighWire-hosted articles: http://n.neurology.org/content/early/2022/02/02/WNL.00000000000013184.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Cerebrovascular disease/Stroke http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke Class IV http://n.neurology.org/cgi/collection/class_iv COVID-19 http://n.neurology.org/cgi/collection/covid_19 Infarction http://n.neurology.org/cgi/collection/infarction Risk factors in epidemiology http://n.neurology.org/cgi/collection/risk_factors_in_epidemiology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.