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ORIGINAL RESEARCH

Inpatient and Outpatient Infection as a Trigger of Cardiovascular Disease: The ARIC Study

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Background—Acute infections are known cardiovascular disease (CVD) triggers, but little is known regarding how CVD risk varies following inpatient versus outpatient infections. We hypothesized that in- and outpatient infections are associated with CVD risk and that the association is stronger for inpatient infections.

Methods and Results—Coronary heart disease (CHD) and ischemic stroke cases were identified and adjudicated in the ARIC (Atherosclerosis Risk in Communities Study). Hospital discharge diagnosis codes and Medicare claims data were used to identify infections diagnosed in in- and outpatient settings. A case-crossover design and conditional logistic regression were used to compare in- and outpatient infections among CHD and ischemic stroke cases (14, 30, 42, and 90 days before the event) with corresponding control periods 1 and 2 years previously. A total of 1312 incident CHD cases and 727 incident stroke cases were analyzed. Inpatient infections (14-day odds ratio [OR]=12.83 [5.74, 28.68], 30-day OR=8.39 [4.92, 14.31], 42-day OR=6.24 [4.02, 9.67], and 90-day OR=4.48 [3.18, 6.33]) and outpatient infections (14-day OR=3.29 [2.50, 4.32], 30-day OR=2.69 [2.14, 3.37], 42-day OR=2.45 [1.97, 3.05], and 90-day OR=1.99 [1.64, 2.42]) were more common in all CHD case periods compared with control periods and inpatient infection was a stronger CHD trigger for all time periods ($P<0.05$). Inpatient infection was also a stronger stroke trigger with the difference borderline statistically significant ($P<0.10$) for the 42- and 90-day time periods.

Conclusions—In- and outpatient infections are associated with CVD risk. Patients with an inpatient infection may be at particularly elevated CVD risk and should be considered potential candidates for CVD prophylaxis. **(*J Am Heart Assoc*. 2018;7:e009683. DOI: 10.1161/JAHA.118.009683.)**

Key Words: cardiovascular disease • case-control study • coronary heart disease • infection • ischemic stroke

Population-based cohort studies have identified many chronic risk factors for cardiovascular disease (CVD) that are both modifiable, such as high blood pressure, elevated serum cholesterol, and smoking, and non-modifiable, such as male sex, nonwhite race, family history, and greater age.[1,2] Acute risk factors—or triggers—of CVD are less studied. Identifying and understanding CVD triggers offer potential new strategies for CVD prevention during vulnerable periods.

Previous research has provided evidence that acute infections triggers CVD events, including myocardial infarction[3–8] and stroke.[3,9,10] Although the results of these studies are informative, most previous studies only included hospitalized infections as their exposure of interest whereas studies that have considered the impact of outpatient infections on CVD risk are scarce. Furthermore, the magnitude and duration of increased cardiovascular risk has varied greatly between studies and remains under debate.

We expanded upon our previous work linking inpatient infection with stroke[9] by using longitudinal data from the ARIC (Atherosclerosis Risk in Communities) study, which have been linked to Centers for Medicare and Medicaid Services data, to examine the relationship between infections diagnosed in both in- and outpatient settings and coronary heart disease (CHD) and ischemic stroke. We hypothesized that infections among both in- and outpatients are independently associated with risk of CHD and ischemic stroke and that the association will be stronger among infections diagnosed in inpatient settings compared with infections diagnosed in outpatient

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Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009683

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Clinical Perspective

What Is New?

- Patients with infection have higher odds of coronary heart disease and ischemic stroke up to 90 days after infection.
- Inpatient infection appears to be a stronger coronary heart disease and ischemic stroke trigger compared with outpatient infection.

What Are the Clinical Implications?

- Patients with an inpatient infection may be potential candidates for cardiovascular disease prophylaxis.

settings given that they are likely more severe. We further hypothesized that the infection-CVD association is graded such that the association is strongest immediately following infection and decreases as the time after infection increases.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, the ARIC study data are publicly available through the database of Genotypes and Phenotypes and the National Heart, Lung, and Blood Institute Biological Specimen and Data Repository Information Coordinating Center.[11]

Study Design

The ARIC study is a multicenter, population-based, prospective cohort study designed to investigate the etiology and natural history of atherosclerosis in middle-aged Americans.[12] At baseline in 1987–1989 (visit 1), 15 792 mostly white and black men and women were selected from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[12] Subsequent exams took place during 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), 2011–2013 (visit 5), and 2016–2017 (visit 6). Institutional review board approval was obtained at each participating ARIC site, and informed consent was obtained from each ARIC study participant.

We used a case-crossover study design in which ARIC participants with incident CHD or ischemic stroke served as their own controls. Occurrence of infection immediately preceding CVD events was compared with preceding time intervals 1 and 2 years before the CVD event. The crossover study design is summarized in Figure 1. Additionally, we performed sensitivity analyses using nonoverlapping time intervals and using only 1 annual control period.

All ARIC participants with incident CHD or ischemic stroke events during follow-up were included. CHD and stroke analyses were done independently, thus study participants with both incident CHD and ischemic stroke events were included in both analyses. Within each analysis, participant cases were independent because only incident cases were included whereas recurrent events were not considered. CVD events were identified using information collected at each exam, annual telephone questionnaires, and hospitalizations. Hospitalizations were identified by surveillance of local hospital discharge lists for cohort members. Information obtained at study visits, during telephone questionnaires, and through review and abstraction of hospital and death records were used to adjudicate CVD outcomes and identify inpatient infections.[13] Additionally, Centers for Medicare and Medicaid Services claims data were used to identify both in- and outpatient infections in ARIC study participants. Centers for Medicare and Medicaid Services claims data for in- and outpatient services were available since 1991. We excluded individuals who were aged <67 years at the time of their CVD event because they were not Medicare eligible for both the case and control periods. We also excluded participants whose CVD events

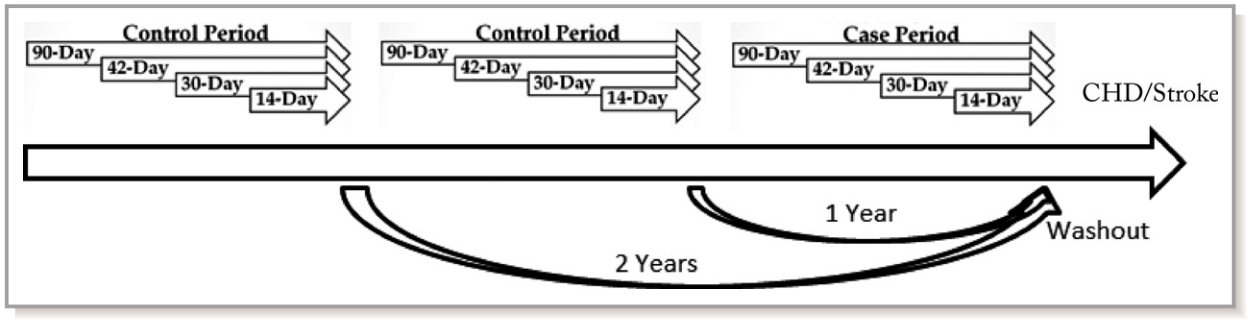

Figure 1. Case-crossover study design used to study infection as a cardiovascular disease trigger, the ARIC (Atherosclerosis Risk in Communities) Study. CHD indicates coronary heart disease.

occurred before 1993 to ensure that Centers for Medicare and Medicaid Services data were available for both case and control periods.

Infection Ascertainment

The exposure of interest was infection determined using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes. Inpatient hospitalization codes and outpatient visit codes were used to identify infections. Infections diagnosed in inpatient settings are referred to as inpatient infections whereas infections diagnosed in outpatient settings are termed outpatient infections throughout the article. Table 1 contains the infection types and corresponding *ICD-9* codes that were included in our exposure of interest. In the main analysis, codes in any position were counted. We also performed a sensitivity analysis in which only infection diagnosed primarily (first position) were counted. Given that some infection types may be associated with CVD through direct mechanisms, we also performed a sensitivity analysis only using the most common infection types (urinary tract infections, pneumonia, cellulitis, and blood infections). Table S1 contains the infection types and corresponding *ICD-9* codes that were included in the exposure of interest for this sensitivity analysis.

Table 1. Infection Type and Corresponding *ICD-9* Codes Included in the Exposure of Interest

Infection	*ICD-9* Codes
Other infectious diseases	001 to 139
Thymus gland infection	254.1
Nervous system infections	320 to 326, 331.81
Eye infections	372 to 372.39, 373.0 to 373.2
Ear infections	382 to 382.4, 383, 386.33, 386.35, 388.60
Circulatory infections	390 to 393, 421 to 421.1, 422.0, 422.91 to 422.93
Respiratory infections	460 to 466, 472 to 474.0, 475 to 476.1, 478.21 to 478.24, 478.29, 480 to 490, 491.1, 494, 510 to 511, 513.0, 518.6, 519.01
Digestive infections	522.5, 522.7, 527.3, 528.3, 540 to 542, 566 to 567.9, 569.5, 572 to 572.1, 573.1 to 573.3, 575 to 575.12
Urinary tract infections	590 to 590.9, 595 to 595.4, 597 to 597.89, 598.0, 599.0
Male genital infections	601 to 601.9, 604 to 604.9, 607.1, 607.2, 608.0, 608.4
Breast infections	611.0
Female pelvic infections	614 to 616.1, 616.3 to 616.4, 616.8
Puerperal infections	670
Skin and subcutaneous infections	680 to 686.9, 706.0
Musculoskeletal infections	711 to 711.9, 730 to 730.3, 730.8 to 730.9,
Blood infections	790.7 to 790.8
Healthcare-acquired infections	996.60 to 996.69, 997.62, 998.5, 999.3

ICD-9 indicates *International Classification of Diseases, Ninth Revision*.

Cardiovascular Events

The outcomes of interest were CHD and ischemic stroke. The methods used for outcome ascertainment included: (1) participants were contacted annually by phone and interviewed about interim hospitalizations; (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses that were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were regularly surveyed. All discharge codes for cohort hospitalizations and listed causes of death from death certificates were recorded. CVD events were classified by a combination of computer algorithm and adjudicated physician review; disagreements were adjudicated by the ARIC Mortality and Morbidity Classification Committee using standardized ARIC criteria.[12,13]

CHD was defined as confirmed CHD death and definite or probably fatal and nonfatal myocardial infarction. CHD events were identified using symptoms, ECG tracing, and serum cardiac biomarkers. Methods for the adjudication of CHD events by a physician panel in the ARIC have been described in detail elsewhere.[13]

Ischemic stroke was identified and classified as thrombotic or cardioembolic stroke based on discharge codes, signs, symptoms, neuroimaging (computerized tomography/magnetic resonance imaging), and other diagnostic reports.[14] All events between study enrollment and end of year 2013 were included in the analysis.

Statistical Analysis

CHD and ischemic stroke were analyzed separately. In the primary analysis, prevalence of infection in the 14, 30, 42, and 90 days before each event was compared with the corresponding time periods exactly 1 and 2 years before the event. A washout period of 2 days between the CVD admission date and preceding infection date was used to exclude infections that may have been diagnosed secondarily at a CVD hospitalization. In addition to the overlapping exposure periods outlined above, we also performed a sensitivity analysis using nonoverlapping time intervals assessing the prevalence of infection 3 to 14, 15 to 30, 31

to 42, and 43 to 90 days before each event. We also performed a sensitivity analysis only using 1 control period 1 year before the event. Conditional logistic regression was used to estimate odds ratios (OR) of CVD events and 95% confidence intervals for each time period. Separate models were run using inpatient infections and outpatient infections to see whether the magnitude of the association differed between infection types. Differences between ORs for in- and outpatient infections for each outcome and time period were compared using multinomial logistic regression. Interactions between both in- and outpatient infection and race, sex, and diabetes mellitus status at most recent study visit were tested by adding interaction terms to the conditional logistic regression models.

Potential confounders that are stable within an individual are controlled in the case-crossover study design by having cases serve as their own controls. Confounding by overall health status related to age is possible because deteriorating health could be a common cause of both infection and CVD. As participants age and their health status decreases, their CVD risk and risk of infection may increase, suggesting potential positive confounding by health status.

To reduce potential confounding, only time periods proximal to the CVD event (1 and 2 years before) were included. We further controlled for the total number of hospitalizations for any cause in the 9 months preceding the start of each of the 3 exposure periods (case period and 2 control periods) to account for potential decline in overall health status. Finally, we performed a sensitivity analysis using only 1 control period 1 year before the CVD event to further reduce potential confounding related to overall health.

Results

Among the 15 792 ARIC study participants, 2356 (14.9%) experienced an incident CHD event. Those who were aged <67 years at the time of their event (n=1017) and those events that occurred before 1993 (n=27) were excluded to ensure that Centers for Medicare and Medicaid Services data were available for both case and control periods. Our final sample size was n=1312 CHD cases.

A combined 1150 (7.3%) ARIC participants experienced an incident ischemic stroke event. We excluded those who were aged <67 years at the time of their event (n=410) and those events that occurred before 1993 (n=13) to ensure that CMS data were available for both case and control periods. Our final sample size was n=727 ischemic stroke cases. There were 144 ARIC participants who experienced an incident CHD and incident ischemic stroke event and were included in both analyses.

At-event characteristics of ARIC participants who developed CHD and ischemic stroke are provided in Table 2. Mean age at CVD event was 75 years. CHD was more common among men (57.4%) whereas ischemic stroke (54.1%) was more common among women. The majority of events occurred in white participants consistent with baseline enrollment.

Table 2. At-Event Characteristics of Participants of the ARIC Cohort Who Developed Cardiovascular Disease, 1987–2013

Characteristic	CHD (n=1312)	Ischemic Stroke (n=727)
Age, y, mean±SD	75.0 (5.3)	75.1 (5.1)
Sex, count (%)		
Male	753 (57.4)	334 (45.9)
Female	559 (42.6)	393 (54.1)
Race, count (%)		
White	949 (72.3)	492 (67.7)
Black	359 (27.4)	234 (32.2)
Other	4 (0.3)	1 (0.1)

ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease.

Coronary Heart Disease

Of the 1312 CHD cases, 119 (9.1%) had an inpatient infection and 366 (27.9%) had an outpatient infection in the 90 days preceding their CHD event. The most common infections preceding CHD events were urinary tract infections (≈29%), pneumonia/respiratory infections (≈27%), skin and subcutaneous infections (11%), and blood infections (8%).

Table 3 contains the conditional logistic regression model results for CHD. Both in- and outpatient infection were more common in all case periods compared with equivalent control periods. Inpatient infection was more common in all case periods compared with equivalent control periods: 14-day OR=12.83 (5.74, 28.68); 30-day OR=8.39 (4.92, 14.31); 42-day OR 6.24 (4.02, 9.67); and 90-day OR, 4.48 (3.18, 6.33). Outpatient infection was also more common in all case periods compared with control periods: 14-day OR=3.29 (2.50, 4.32); 30-day OR=2.69 (2.14, 3.37); 42-day OR 2.45 (1.97, 3.05); and 90-day OR, 1.99 (1.64, 2.42). Inpatient infection was a stronger CHD trigger compared with outpatient infection for all time periods ($P<0.05$). For both in- and outpatient infections, controlling for the number of hospitalizations in the 9-month period preceding each exposure period slightly attenuated the association between infection and CHD whereas the association was strongest in exposure periods closest to the CHD event and decreased as the time window before CHD increased. For CHD, no significant interactions between in- or outpatient infection and race, sex, or diabetes mellitus status were observed (data not shown). Infection was generally a stronger CHD trigger among nondiabetics, but the results were not statistically significant.

Table 3. Association Between Infection and Coronary Heart Disease in the ARIC Cohort, Odds Ratios and 95% Confidence Intervals

	Case (n)	Control (n)	Crude Model	Model 1
Inpatient infections				
14 d				
No infection	1265	2617	Ref	Ref
Infection	47	7	13.43 (6.07, 29.71)	12.83 (5.74, 28.68)
30 d				
No infection	1237	2605	Ref	Ref
Infection	75	19	8.66 (5.11, 14.67)	8.39 (4.92, 14.31)
42 d				
No infection	1224	2593	Ref	Ref
Infection	88	31	6.31 (4.10, 9.73)	6.24 (4.02, 9.67)
90 d				
No infection	1193	2558	Ref	Ref
Infection	119	66	4.52 (3.21, 6.36)	4.48 (3.18, 6.33)
Outpatient infections				
14 d				
No infection	1159	2517	Ref	Ref
Infection	153	107	3.35 (2.55, 4.50)	3.29 (2.50, 4.32)
30 d				
No infection	1084	2404	Ref	Ref
Infection	228	220	2.72 (2.17, 3.41)	2.69 (2.14, 3.37)
42 d				
No infection	1052	2333	Ref	Ref
Infection	260	291	2.47 (1.99, 3.06)	2.45 (1.97, 3.05)
90 d				
No infection	946	2109	Ref	Ref
Infection	366	515	2.02 (1.67, 2.46)	1.99 (1.64, 2.42)

Model 1: adjusted for total hospitalizations in the 9 months preceding each exposure period. ARIC indicates Atherosclerosis Risk in Communities.

Results from the sensitivity analysis in which only 1 control period was used were slightly attenuated, but did not differ substantially from the primary analysis, and are presented in Table S2. The results of the sensitivity analysis in which nonoverlapping time periods were used are presented in Table S3. Similar to the main analysis, inpatient infection was generally a stronger CHD trigger compared with outpatient infection and CHD risk was mostly highest immediately following an infection, although few infections made for imprecise estimates. Results from the sensitivity analysis in which only primarily diagnosed infections were included in our exposure of interest did not differ from the main analysis and are presented in Table S4. Table S5 contains the results of the sensitivity analysis in which the exposure of interest was limited to urinary tract infections, pneumonia, cellulitis, and blood infections. The results of this sensitivity analysis were also similar to the main analysis.

Stroke

Of the 727 ischemic stroke cases, 44 (6.1%) had an inpatient infection and 173 (23.8%) had an outpatient infection in the 90 days preceding the stroke event. The most common infections preceding stroke events were urinary tract infections (≈31%), pneumonia/respiratory infections (≈15%), skin and subcutaneous infections (≈6%), and blood infections (3%). Table 4 below contains the conditional logistic regression model results for infection and ischemic stroke. Inpatient infections were more common in all case periods compared with equivalent control periods: 14-day OR=5.96 (1.93,

Table 4. Association Between Infection and Ischemic Stroke in the ARIC Cohort, Odds Ratios and 95% Confidence Intervals

	Case (n)	Control (n)	Crude Model	Model 1
Inpatient infections				
14 d				
No infection	714	1450	Ref	Ref
Infection	13	4	6.50 (2.12, 19.34)	5.96 (1.93, 18.34)
30 d				
No infection	704	1440	Ref	Ref
Infection	23	14	3.29 (1.69, 6.39)	3.06 (1.56, 6.00)
42 d				
No infection	698	1436	Ref	Ref
Infection	29	18	3.46 (1.87, 6.39)	3.23 (1.74, 6.00)
90 d				
No infection	683	1419	Ref	Ref
Infection	44	35	2.98 (1.82, 4.89)	2.80 (1.71, 4.61)
Outpatient infections				
14 d				
No infection	659	1393	Ref	Ref
Infection	68	61	2.48 (1.71, 3.60)	2.42 (1.66, 3.53)
30 d				
No infection	634	1334	Ref	Ref
Infection	93	120	1.77 (1.29, 2.41)	1.69 (1.23, 2.31)
42 d				
No infection	614	1302	Ref	Ref
Infection	113	152	1.75 (1.31, 2.35)	1.68 (1.25, 2.26)
90 d				
No infection	554	1203	Ref	Ref
Infection	173	251	1.74 (1.34, 2.26)	1.69 (1.30, 2.20)

Model 1: adjusted for total hospitalizations in the 9 months preceding each exposure period. ARIC indicates Atherosclerosis Risk in Communities.

18.34); 30-day OR=3.06 (1.56, 6.00); 42-day OR=3.23 (1.74, 6.00); and 90-day OR=2.80 (1.71, 4.61). Similarly, outpatient infection was more common in all case periods compared with control periods: 14-day OR=2.42 (1.66, 3.53); 30-day OR=1.69 (1.23, 2.31); 42-day OR=1.68 (1.25, 2.26); and 90-day OR=1.69 (1.30, 2.20). Inpatient infection was a stronger stroke trigger compared with outpatient infection, with the difference being of borderline statistical significance ($P<0.10$) for the 42- and 90-day time periods. For both in- and outpatient infections, controlling for the number of hospitalizations in the 9-month period preceding each exposure period slightly attenuated the association between infection and ischemic stroke. The association between infection and stroke was generally stronger in the exposure periods closest to the stroke event and decreased as the time window before ischemic stroke increased. For stroke, no significant interactions between in- or outpatient infection and race, sex, or diabetes mellitus status were observed (data not shown). Results from the sensitivity analysis in which only 1 control period was used did not differ substantially from the primary analysis and are presented in Table S2. Table S3 contains the results of the sensitivity analysis in which nonoverlapping time periods were used. Like results from the primary analysis, inpatient infection was generally a stronger stroke trigger compared with outpatient infection and stroke risk was mostly highest immediately following an infection, although the estimates are imprecise. Similarly the sensitivity analyses in which only primary diagnosis infections were included and in which exposure infections were limited to urinary tract infections, pneumonia, cellulitis, and blood infections did not differ from the main analysis and are presented in Tables S4 and S5.

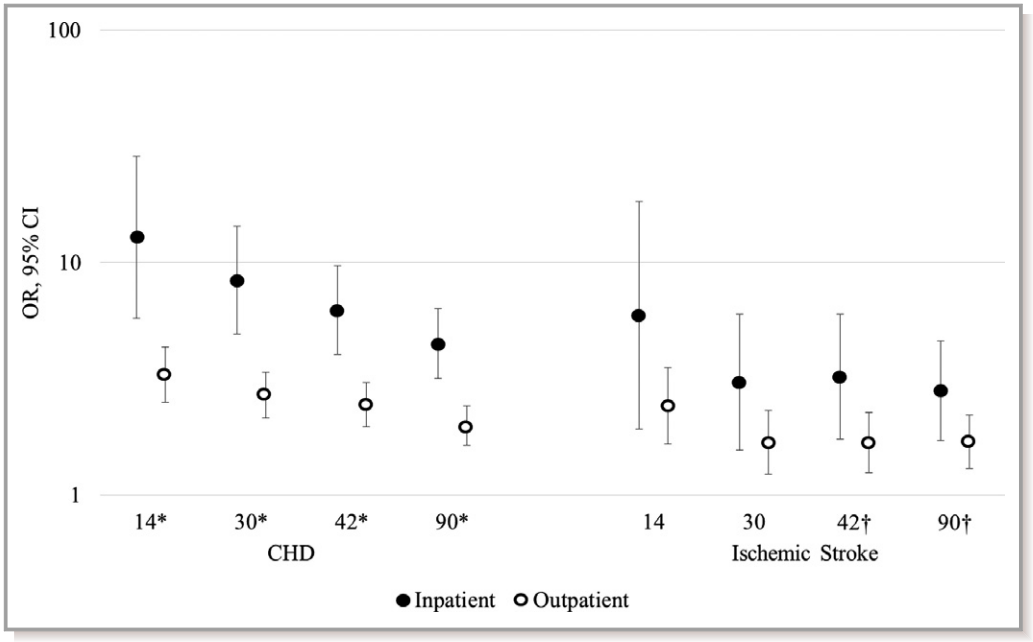

Figure 2. Associations between inpatient and outpatient infection and coronary heart disease and ischemic stroke in the ARIC (Atherosclerosis Risk in Communities) Cohort. *P<0.05; †P<0.10. CHD indicates coronary heart disease; CI, confidence interval; OR, odds ratio.

In- and outpatient results for both CHD and ischemic stroke are presented side by side in Figure 2.

Whereas outpatient infections were more common, inpatient infections were generally stronger CVD triggers compared with outpatient infections. It is worth considering the attributable risk percent (AR%) of out- and inpatient infections for both CHD and stroke. Using the approach used by Vlak et al,[15] AR%=[(OR−1/OR)×100]. The 90-day AR of CHD for outpatient infections is 50% whereas the AR for inpatient infection is 78%. Similarly, the 90-day AR of stroke for outpatient infections is 41% whereas the AR for inpatient infection is 64%. Among those with an infection, between 41% and 78% of their CVD risk is attributable to their infection.

Discussion

This case-crossover study nested within a population-based cohort demonstrated that CHD and ischemic stroke risk is higher after both in- and outpatient infection. Patients with infection had higher odds of CHD and ischemic stroke up to 90 days after infections compared with equivalent control periods 1 and 2 years before the event. This provides evidence in support of our hypothesis that infection is associated with higher acute CVD risk and that infection is a CVD trigger. Inpatient infection was consistently a stronger CHD and ischemic stroke trigger compared with outpatient infection whereas the association between infection and CVD was weaker when only considering outpatient infections, as we hypothesized. Inpatient infections may be more severe and trigger a stronger inflammatory response that results in higher CVD risk. It is also possible that inpatient infections may be stronger CVD triggers as a result of the "hospitalization effect" or changes in health resulting from hospitalization itself, including immobilization or change in medications as a result of being hospitalized that may increase CVD risk. The association between infection and CVD was also graded such that the infection-CVD association was highest in the exposure periods most proximal to the event and generally decreased as the time window before the event increased.

Our findings corroborate previous work that has identified a triggering association between infection and CVD and that the risk varies by time after infection. Considering infection as a trigger of CHD, our results are similar to those found by Warren-Gash et al (incidence ratio=4.19),[4] Corrales-Medina et al (hazard ratio=4.07),[7] Chew et al (OR=7.5),[16] Kwong et al (incidence ratio=6.05),[8] and Dalager-Pedersen et al using hospital controls (relative risk=2.32), but slightly smaller than their analysis using population controls (30-day relative risk=17.70).[3]

Our reported associations between infection and ischemic stroke are similar in magnitude compared with those shown by Elkind et al (OR=7.3)[10] and Fullerton et al (OR=6.3).[17] Notably, our group has previously published on the association between inpatient infections and ischemic stroke, also using ARIC data.[9]

Previous investigators have suggested possible mechanisms by which infection may trigger CVD events. The primary mechanism linking infection and CVD is through systemic inflammation, which acutely leads to platelet aggregation and hypercoagulability and chronically leads to atherosclerotic development.[18] Corrales-Medina et al posited mechanisms by which infection may trigger coronary events, including by inflammation, prothrombosis, increased biomechanical stress on coronary arteries, variations in the coronary arterial tone, disturbed hemodynamic homoeostasis, and altered myocardial metabolic balance.[19] Epaulard et al summarized existing studies that showed that the inflammatory response to infection and the coagulation and fibrinolysis processes likely share common pathways, explaining why infection is associated with thrombosis and CVD.[20] Considering stroke, specifically, Elkind et al suggest that infection may trigger stroke events through hypercoagulability, platelet activation, and impaired endothelial function.[10] They further hypothesize that infection may contribute to dehydration and immobility, which may contribute to CVD risk. Finally, infection-induced fever and activation of the sympathetic nervous system leading to tachycardia may increase CVD risk.[21]

Our study has several clinical implications. Infection information, particularly inpatient infections, should be considered in assessing CVD risk. Identification of infection as a CVD trigger may prompt more-aggressive treatment with standard preventive strategies, including antiplatelet agents and statins, during and immediately after infection to reduce the increased CVD. This time period immediately after infection has been referred to as a treatable moment.[10] Patients suffering from an inpatient infection may be particularly good candidates for CVD preventive therapies. Evidence-based vaccinations may be considered because of their ability to not only reduce infection, but also CVD.[22]

Our study has a number of strengths, including a large sample size from a community cohort, ascertainment of both in- and outpatient infection exposure data, a rigorous methodology to adjudicate CVD events, and a crossover design to control for potential confounding. It also has limitations. Like all case-crossover studies, our study may suffer from survival bias given that we did not consider infections in participants who did not have a CVD event. Our study only considered the relationship between infection and CVD among those who survived any infections and later had a CVD event. Confounding by age is possible because as participants age their risk of both CVD and infection increase. However, to reduce potential confounding by age, only control periods 1 and 2 years preceding CVD events were examined. We also adjusted for possible confounding by the total number of hospitalizations in the 9-month period preceding each exposure period. We also performed a sensitivity analysis in which only 1 control period 1 year before the CVD event was used to further verify that confounding by age was absent. Other confounders that may vary between the exposure and control periods were not included. Analyses to assess whether the infection-CVD relationship differed by diabetes mellitus status used diabetes mellitus status measured at the most recent study visit, which may not accurately reflect a person's diabetes mellitus status at the time of their CVD event. Because we used the hospital admission date as the CVD event date, dates for patients who do not seek immediate medical attention may be inaccurate, but we think that this is rare because most patients immediately seek care. We may be underascertaining infections, especially minor ones that did not require care, given that exposure data were collected using hospital and Medicare claims data. This would most likely lead to nondifferential misclassification of the exposure that would typically bias ORs toward the null.

Conclusion

CVD patients had higher odds of infection within 90 days preceding their CVD event compared with equivalent control periods 1 and 2 years previous. Although the risk of CHD and stroke is higher following an inpatient infection, the higher prevalence of outpatient infections suggests that the proportion of events attributable to each infection type is more similar. Consideration should thus be given to CVD prevention following all infections.

Previous research on CVD triggers has referred to the time period immediately following an infection as a "treatable moment" that may hold an opportunity for CVD prevention.[10] Given that inpatient infections appear to be stronger CVD triggers compared with outpatient infections, patients with an inpatient infection may be of particular interest for CVD prophylaxis. There may be a role for infection in CVD prevention decision making, though clinical trials and a cost-benefit analysis should be considered.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Infection type and corresponding ICD-9 codes included in the infection exposure of interest of the sensitivity analysis.

Infection	ICD-9 Codes
Pneumonia	480*-486*
Urinary Tract Infections	590*, 595.0, 595.1, 595.2, 595.3, 595.4, 597*, 598.0*, 599.0, 601*, 604*, 607.1, 607.2, 608.0, 608.4
Bloodstream Infections	038*, 790.7
Cellulitis	681*, 682*

Table S2. Association between infection and cardiovascular disease in the Atherosclerosis Risk in Communities Cohort using only 1 annual crossover control period, odds ratios* and 95% confidence intervals.

CHD	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	8.73 (3.46, 22.03)	5.84 (3.17, 10.78)	4.62 (2.77, 7.69)	3.11 (2.12, 4.56)
Outpatient Infection	3.14 (2.23, 4.43)	2.58 (1.96, 3.40)	2.27 (1.75, 2.93)	1.85 (1.47, 2.33)
Stroke	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	3.98 (1.13, 14.02)	2.41 (1.11, 5.24)	2.83 (1.32, 6.04)	2.64 (1.43, 4.88)
Outpatient Infection	3.61 (2.12, 6.13)	2.04 (1.37, 3.02)	1.88 (1.30, 2.74)	1.72 (1.25, 2.37)

*Adjusted for total hospitalizations in the 9 months preceding each exposure period

Table S3. Association between infection and cardiovascular disease in the Atherosclerosis Risk in Communities Cohort by time since the infection, odds ratios* and 95% confidence intervals.

CHD	**3-14 Days**	**15-30 Days**	**31-42 Days**	**43-90 Days**
Inpatient Infection	12.83 (5.74, 28.68)	4.75 (2.39, 9.45)	2.54 (1.09, 5.94)	1.89 (1.14, 3.11)
Outpatient Infection	3.29 (2.50, 4.32)	1.40 (1.02,1.93)	0.94 (0.61, 1.44)	0.91 (0.71, 1.18)
Stroke	**3-14 Days**	**15-30 Days**	**31-42 Days**	**43-90 Days**
Inpatient Infection	5.96 (1.93, 18.34)	1.86 (0.76, 4.55)	2.76 (0.78, 9.83)	1.85 (0.88, 3.90)
Outpatient Infection	2.42 (1.66, 3.53)	0.77 (0.47, 1.27)	1.26 (0.70, 2.25)	1.28 (0.89, 1.82)

*Adjusted for total hospitalizations in the 9 months preceding each exposure period

Table S4. Association between primary diagnosis infection and cardiovascular disease in the Atherosclerosis Risk in Communities Cohort, odds ratios* and 95% confidence intervals.

CHD	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	5.42 (2.05, 14.30)	3.93 (1.94, 7.96)	3.02 (1.65, 5.50)	2.18 (1.38, 3.44)
Outpatient Infection	2.75 (1.99, 3.79)	2.44 (1.88, 3.16)	2.03 (1.59, 2.59)	1.78 (1.45, 2.19)
Stroke	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	N/A	3.49 (0.64, 19.09)	5.22 (1.05, 25.92)	3.11 (1.12, 8.60)
Outpatient Infection	3.02 (0.98, 9.31)	1.89 (0.79, 4.47)	2.41 (1.12, 5.22)	1.69 (0.93, 3.06)

*Adjusted for total hospitalizations in the 9 months preceding each exposure period

Table S5. **Association between urinary tract infections, pneumonia, cellulitis, and blood infections and cardiovascular disease in the Atherosclerosis Risk in Communities Cohort, odds ratios* and 95% confidence intervals.**

CHD	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	14.56 (5.64, 37.60)	9.64 (5.14, 18.08)	7.23 (4.32, 12.11)	447 (3.04, 6.56)
Outpatient Infection	5.45 (3.47, 8.55)	3.41 (2.48, 4.70)	3.22 (2.39, 4.33)	2.54 (1.98, 3.26)
Stroke	**14-Days**	**30 Days**	**42 Days**	**90 Days**
Inpatient Infection	19.62 (2.51, 153.47)	5.67 (2.04, 15.78)	6.61 (2.65, 16.49)	2.75 (1.53, 4.95)
Outpatient Infection	2.72 (1.58, 4.67)	1.80 (1.14, 2.83)	1.71 (1.14, 2.58)	1.46 (1.04, 2.04)

*Adjusted for total hospitalizations in the 9 months preceding each exposure period