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Risk of cardiovascular events after Streptococcus pneumoniae infection: A retrospective cohort LIFE study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059713
Article Type:	Original research
Date Submitted by the Author:	30-Nov-2021
Complete List of Authors:	Nishimura, Naoaki; Kyushu University Fukuda, Haruhisa; Kyushu University
Keywords:	Epidemiology < INFECTIOUS DISEASES, Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY

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BMJ Open**Risk of cardiovascular events after *Streptococcus pneumoniae* infection: A retrospective cohort LIFE study**Naoaki Nishimura¹), Haruhisa Fukuda²)*¹) Kyushu University School of Medicine, Fukuoka, Kyushu, Japan²) Kyushu University Graduate School of Medical Sciences, Fukuoka, Kyushu, Japan*** Corresponding Author:**

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*** Word count**

2615 words

Contributors NN and HF designed the study. HF provided the data. NN analyzed the data. NN prepared the first draft of the manuscript. HF made critical revisions to the manuscript. All authors reviewed and approved the final draft.

Funding The construction of the LIFE Study database was funded by a Grant-in-Aid for Scientific Research by the Japan Society for the Promotion of Science (Grant No. JP20H00563). Data analysis and publication were funded by an Investigator-Sponsored Research grant from Pfizer Japan Inc.

Competing interest HF received an Investigator-Sponsored Research grant from Pfizer Japan Inc.

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

Patient consent for publications Not required.

Data availability statement The data used in this study were acquired under agreements with the participating municipalities, which stipulate that the data can only be used by authorized research institutions and cannot be shared with third parties.

Abstract

Objectives: To elucidate the risk of cardiovascular event occurrence following *Streptococcus pneumoniae* infection.

Design: Retrospective cohort study using a LIFE Study database.

Setting: Three municipalities in Japan.

Participants: Municipality residents who were enrolled in either National Health Insurance or the Latter-Stage Elderly Healthcare System from April 2014 to March 2020.

Exposure: Occurrence of *S. pneumoniae* infection.

Primary Outcome Measures: Occurrence of one of the following cardiovascular events that led to hospitalization after *S. pneumoniae* infection: (1) coronary heart disease (CHD), (2) heart failure (HF), (3) stroke, or (4) arrhythmia.

Results: *S. pneumoniae*-infected patients were matched with non-infected patients for each cardiovascular event. We matched 271 infected patients and 88,407 non-infected patients for CHD, 242 infected patients and 80,025 non-infected patients for HF, 252 infected patients and 87,626 non-infected patients for stroke, and 299 infected patients and 91,631 non-infected patients for arrhythmia. During follow-up, the incidence rates for the matched infected and non-infected patients were, respectively, 59.2 (95% confidence interval: 37.5–88.8) and 53.5 (52.3–54.8) per 1000 person-years for CHD; 89.0 (60.9–125.7) and 64.7 (63.3–66.0) per 1000 person-years for HF; 95.7 (66.7–133.1) and 52.0 (50.8–53.2) per 1000 person-years for stroke; and 66.0 (43.5–96.0) and 40.0 (38.9–41.0) per 1000 person-years for arrhythmia. Infected patients were significantly more likely to develop stroke (adjusted hazard ratio: 1.86, 95% confidence interval: 1.26–2.76) and arrhythmia (1.58, 1.03–2.43) than their non-infected counterparts.

Conclusions: *S. pneumoniae* infections elevate the risk of subsequent stroke and arrhythmia occurrence. These findings indicate that pneumococcal infections not only have short-term effects on patients' health, but also increase their mid-to long-term susceptibility to serious cardiovascular events.

Keywords

Streptococcus pneumoniae infection; cardiovascular events; retrospective cohort study

Article Summary (Strengths and Limitations of this study)

- This study comparatively examined both *Streptococcus pneumoniae*-infected patients and non-infected controls to elucidate the association between pneumococcal infections and subsequent cardiovascular events.
- While prior studies mostly focused on short-term outcomes, our study period spanned from April 2014 to March 2020 to examine the mid-to long-term risks of cardiovascular events following pneumococcal infection.
- Despite a relatively large study sample and long study period, *S. pneumoniae* infections and cardiovascular events were identified using only diagnosis codes in the claims data.
- Our study did not account for patients' lifestyle factors (e.g., tobacco and alcohol consumption), socioeconomic factors, or pneumococcal vaccination statuses.

Introduction

Community-acquired pneumonia is a major infectious disease that frequently leads to hospitalization, and exhibits high morbidity and mortality rates across numerous countries [1, 2]. *Streptococcus pneumoniae* is the causal pathogen for a large proportion of pneumonia cases that require hospital-based care [3]. As older persons are more susceptible to pneumococcal pneumonia [4], this condition represents a particularly serious public health problem in countries with aging populations. In addition to its acute effects, pneumonia is also known to increase the mid-to long-term health risks of infected patients, thereby placing a heavy clinical and economic burden on patients and society [2, 5].

Previous cohort studies have reported that pneumonia is associated with an increased risk of the following conditions: overall cardiac events [6-14], acute coronary syndrome [6, 8, 9, 11, 12, 14-17], heart failure (HF) [6, 9-14, 16, 18], arrhythmia [6, 8-14, 16, 17, 19, 20], and stroke [11, 12, 17]. However, the majority of these studies focused on pneumonia patients without comparisons with non-infected controls, and generally used relatively short follow-up periods. Furthermore, only a few studies in the existing literature have explored the effects of pneumonia on subsequent cardiovascular disease [7, 18, 21].

In order to accurately evaluate the impact of *S. pneumoniae* infection on subsequent cardiovascular disease, there is a need for long-term cohort studies that compare infected patients with matched non-infected controls. This study aimed to elucidate the risk of cardiovascular event occurrence following *S. pneumoniae* infection using administrative claims data acquired from infected and non-infected patients in 3 Japanese municipalities. The study also examined if these risks differ among age groups.

Methods

Study data

Data were provided by the Longevity Improvement & Fair Evidence (LIFE) Study, which is managed by Kyushu University (Fukuoka, Japan). In the LIFE Study, participating municipalities voluntarily provide administrative claims data for research purposes. These claims data are acquired from the municipalities' residents who are enrolled in either National Health Insurance or the Latter-Stage Elderly Healthcare System, and encompass information on patient characteristics and reimbursement claims for all insurance-covered healthcare provided in the inpatient and outpatient settings. Enrollees in National Health Insurance include the self-employed, agricultural and fishery workers, part-time workers, retirees, and their dependents. Enrollees in the Latter-Stage Elderly Healthcare System include residents aged ≥ 75 years. The number of municipalities participating in the LIFE Study varies over time owing to differences in agreement contracts, with the earliest participant providing data from April 2014. The majority of the participating municipalities provide data from April

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3 2015 onward. As of 2021, the LIFE Study is able to conduct longitudinal studies with 5-year
4 follow-up periods.
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6 For this study, claims data from April 2014 to March 2020 were acquired from
7 insurance enrollees who were residing in 3 municipalities (residential populations: 58,000,
8 121,600, and 305,200) in Fukuoka Prefecture.
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12 13 *Study subjects* 14

15 First, patients with *S. pneumoniae* infections were identified through diagnosis codes
16 developed by Japan's Ministry of Health, Labour and Welfare. The identification method was
17 based on the approach described by Imai et al. [22]. The occurrence of subsequent
18 cardiovascular events (coronary heart disease [CHD], HF, arrhythmia, and stroke) was
19 identified using International Classification of Diseases, 10th revision (ICD-10) codes. We
20 excluded patients with records of cardiovascular events before *S. pneumoniae* infection,
21 patients with records of cardiovascular events during the index hospitalization for *S.*
22 *pneumoniae* infection, and patients without any claims data ≥ 12 months before *S. pneumoniae*
23 infection.
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29 Next, we set each infected patient's index date as the last day of the month containing
30 a recorded *S. pneumoniae* infection. The infected patients were then matched with a cohort of
31 non-infected patients according to age (within 5 years), sex, and Charlson Comorbidity Index
32 score at the index date using sampling without replacement. Charlson Comorbidity Index
33 scores were calculated based on the following conditions: myocardial infarction, congestive
34 HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary
35 disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with/without chronic
36 complications, hemiplegia or paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS.
37 The index date for each non-infected patient was set as the same date as his/her matched
38 infected case. We excluded non-infected patients who had experienced cardiovascular events
39 before their index dates.
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48 *Outcome measure* 49

50 The outcome measure was the occurrence of a cardiovascular event that led to hospitalization
51 after the *S. pneumoniae* infection date. Among inpatients, the infection date was set as the
52 first date of admission for the in-hospital treatment of an *S. pneumoniae* infection. Among
53 outpatients, the infection date was set as the first date of any medical treatment with a
54 diagnosis code indicating an *S. pneumoniae* infection.
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58 Next, we examined the subsequent occurrence of each of the following 4
59 cardiovascular events that led to hospitalization: (1) CHD (ICD-10 codes: I20-25), (2) HF
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3 (I11, I50), (3) stroke (I60-69), and (4) arrhythmia (I47-49). The occurrence date of each
4 cardiovascular event was set as the date of admission for the in-hospital treatment of that
5 event.
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8 Patients who had died during the observation period without developing any
9 cardiovascular event were followed-up until the last date of medical treatments in the claims
10 data. Patients who had died during the observation period after developing a cardiovascular
11 event were followed-up until the date of the cardiovascular event occurrence. All survivors
12 were followed-up until the end of their municipality's observation period. The ends of the
13 observation periods ranged from September 2019 to March 2020 among the municipalities.
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15 **Figure 1** shows an overview of the follow-up process.
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18 *Statistical analysis*

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21 Our analysis was designed to examine the possible effects of *S. pneumoniae* infection on the
22 subsequent occurrence of cardiovascular events, and to determine if these effects differed
23 among age groups. For each of the 4 target cardiovascular events, we calculated the number
24 of events for the infected group and non-infected group during the observation period, and
25 estimated the incidence rates per 1000 person-years. Cox proportional hazards models were
26 constructed to estimate the hazard ratio (HRs) and 95% confidence interval (CIs) of each
27 cardiovascular event in the infected group relative to the non-infected group. The Kaplan–
28 Meier method was used to calculate the cumulative probability of cardiovascular event
29 occurrence in the 2 groups. In addition, we analyzed the patients stratified according to the
30 following age groups: 0–49 years, 50–64 years, and ≥ 65 years.
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33 All statistical analyses were performed using R (version 4.1.0) and R Studio (version
34 1.4.1106) software. Two-tailed *P* values below 0.05 were considered statistically significant.
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38 *Ethical considerations*

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43 The study was approved by the Kyushu University Institutional Review Board for Clinical
44 Research (Approval No. 2019-406).
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49 *Patient and public involvement*

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52 Patients and the public were not involved in the design, conduct or reporting in our study.
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Results

We first identified 698 *S. pneumoniae*-infected patients and 253,302 non-infected patients between April 1, 2014 and March 31, 2020 (**Figure 2**). After applying the exclusion criteria, 489 eligible infected patients were included in the analysis. Among the infected patients that could be successfully matched with non-infected patients for each cardiovascular event, we identified 271 infected patients without prior CHD, 242 infected patients without prior HF, 252 infected patients without prior stroke, and 299 infected patients without prior arrhythmia. Using matching criteria of age, sex, and Charlson Comorbidity Index score, we matched 88,407, 80,025, 87,626, and 91,631 non-infected controls with the infected patients for CHD, HF, stroke, and arrhythmia, respectively. The non-infected patients were followed-up from the first *S. pneumoniae* infection date of their matched infected patients. **Table 1** shows the characteristics and comorbidities of the infected and non-infected patients.

Table 2 summarizes the risk of each cardiovascular event after *S. pneumoniae* infection. The observation periods of the infected and non-infected patients (weighted by the proportion of the infected patients) were, respectively, 389 and 141,705 person-years for CHD; 359 and 135,271 person-years for HF; 366 and 140,452 person-years for stroke; and 409 and 143,792 person-years for arrhythmia. During follow-up, the incidence rates for the infected and non-infected patients were, respectively, 59.2 (95% CI: 37.5–88.8) and 53.5 (95% CI: 52.3–54.8) per 1000 person-years for CHD; 89.0 (60.9–125.7) and 64.7 (63.3–66.0) per 1000 person-years for HF; 95.7 (66.7–133.1) and 52.0 (50.8–53.2) per 1000 person-years for stroke; and 66.0 (43.5–96.0) and 40.0 (38.9–41.0) per 1000 person-years for arrhythmia. The unadjusted HRs for cardiovascular event occurrence in infected patients (relative to non-infected patients) were 1.10 (95% CI: 0.71–1.72) for CHD, 1.37 (0.92–2.05) for HF, 1.84 (1.27–2.66) for stroke, and 1.64 (1.08–2.48) for arrhythmia. After adjusting for age, sex, and Charlson Comorbidity Index score, infected patients were significantly more likely to develop stroke (adjusted HR: 1.86, 95% CI: 1.26–2.76) and arrhythmia (adjusted HR: 1.58, 95% CI: 1.03–2.43) than their non-infected counterparts. In the age-stratified analysis, *S. pneumoniae* infections were significantly associated with a substantially higher risk of stroke occurrence in patients aged 50–64 years. Among older patients aged ≥ 65 years, *S. pneumoniae* infections were significantly associated with an increased risk for all 4 cardiovascular events.

Figure 3 presents the Kaplan–Meier curves of each cardiovascular event. When compared with non-infected patients, infected patients had a significantly higher risk of incident HF, stroke, and arrhythmia (all $P < 0.0001$); but not CHD ($P = 0.064$).

Discussion

Through an analysis of National Health Insurance and Latter-Stage Elderly Healthcare System enrollees residing in 3 Japanese municipalities, this study comparatively examined the incidence of cardiovascular events between *S. pneumoniae*-infected patients and non-infected

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3 patients. Our results showed that the experience of *S. pneumoniae* infection significantly
4 elevates the risk of subsequent stroke and arrhythmia. Among patients aged 50–64 years, *S.*
5 *pneumoniae* infection was associated with an increased risk of stroke. Furthermore, *S.*
6 *pneumoniae* infection increased the risk of all 4 cardiovascular events among older patients
7 aged ≥ 65 years. These findings may help to identify at-risk targets for expanded
8 pneumococcal vaccination programs.
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12 Recent studies have shown that patients with community-acquired pneumonia have a
13 higher frequency of cardiovascular events [8, 10, 11, 16, 18, 21, 24, 25]. Our estimated
14 incidence of arrhythmia after *S. pneumoniae* infection (9.0%) was slightly higher than that of
15 a previous meta-analysis, which estimated an overall incidence of 7.2% among inpatients with
16 community-acquired pneumonia [24]. This discrepancy may be explained by the fact that the
17 meta-analysis had only included studies with short-term outcomes.
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21 In our analysis, the estimated incidence of stroke after *S. pneumoniae* infection was
22 considerably higher than those found in previous studies [11,16]. Perry et al. reported a stroke
23 incidence of 0.17% in 40,979 patients during 90 days of admission for pneumonia, whereas
24 Violi et al. reported a stroke incidence of 1.0% in 1,182 patients hospitalized for community-
25 acquired pneumonia during in-hospital follow-up (median length of hospital stay: 11 days).
26 Accordingly, those 2 studies had focused on the short-term incidence of stroke. However, the
27 risk of stroke increases with age, and longer follow-up periods after *S. pneumoniae* infection
28 would therefore provide a more accurate depiction of its risks. Furthermore, Perry et al. used
29 ICD-9 codes to identify stroke, whereas Violi et al. identified stroke cases through clinical
30 manifestations confirmed by computed tomography or magnetic resonance imaging [11,16].
31 Stroke diagnostic methods are generally reliant on imaging data, and many medical facilities
32 in Japan are equipped with on-site computed tomography and/or magnetic resonance imaging
33 scanners. This enables the accurate diagnosis of stroke, including cases of milder strokes,
34 throughout Japan.
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42 Among the studies that reported a high frequency of subsequent cardiovascular events
43 in pneumonia patients, few have actually compared infected patients with non-infected
44 controls. Eurich et al. performed a long-term prospective cohort study of both inpatients and
45 outpatients with community-acquired pneumonia, and found that these infections substantially
46 increased the risk of HF across different age groups and disease severity [18]. During a
47 median follow-up period of 9.9 years, 11.9% of patients with pneumonia developed incident
48 HF compared with 7.4% of the non-infected controls; furthermore, 13.3% of patients with
49 pneumococcal bacteremia developed incident HF [18]. In contrast, 13.0% of our infected
50 patients developed incident HF compared with 12.0% of their non-infected counterparts, with
51 no significant difference between the groups. This discrepancy may be influenced by the fact
52 that Eurich et al. used a control group that only controlled for age (five-year age bands) and
53 sex, only investigated outpatients in emergency departments, and focused on severe
54 pneumonia infections. In contrast, our study included outpatients from all types of medical
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3 institutions, and our control group comprised patients without any *S. pneumoniae* infection.
4 Our study also utilized a research design that differed from Eurich et al. [18], which only
5 matched for age and sex, and adjusted for the effects for coexisting conditions by including
6 them as covariates in analytical models. However, we matched infected patients and non-
7 infected controls not only by age and sex, but also by coexisting conditions through Charlson
8 Comorbidity Index scores.
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12 To our knowledge, few studies have shown the long-term risks of subsequent
13 arrhythmia and stroke after *S. pneumoniae* infection (including non-hospitalized cases)
14 relative to non-infected controls. Severe cases of pneumonia require hospital-based care,
15 especially among older adults. Therefore, studies that focus on hospitalized pneumonia
16 patients would overlook the risks associated with less severe cases. For example, although
17 patients aged ≤ 65 years may have milder *S. pneumoniae* infections and a correspondingly
18 lower risk of hospitalization than older patients, these infections could still elevate the risk of
19 subsequent cardiovascular events in the younger age groups. As this study used insurance
20 claims data that incorporated both inpatient and outpatient data, we were able to identify the
21 risk of cardiovascular events after *S. pneumoniae* infection in patients regardless of whether
22 they required hospitalization. Moreover, our study excluded patients who had subsequent
23 cardiovascular events during the index hospital stay for *S. pneumoniae* infection. For patients
24 who were admitted to hospital due to *S. pneumoniae* infection, we only monitored for
25 cardiovascular events that occurred after discharge. Most studies have reported the short-term
26 risks of cardiovascular events during or after acute infections, and the long-term impact of
27 pneumonia on subsequent cardiovascular disease occurrence is less clear. Therefore, our study
28 provides new insight into the mid-to long-term effects of milder *S. pneumoniae* infections
29 treated in outpatient settings as well as severe *S. pneumoniae* infections that require
30 hospitalization.
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34 A previous study identified the major causative organisms of community-acquired
35 pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*,
36 *Chlamydomphila pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several
37 viral pathogens (including influenza A and B) [26]. *S. pneumoniae* reportedly reduces cardiac
38 contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [27]. Many
39 studies that seek to understand the pathogenesis of cardiovascular events following
40 pneumonia focus on infections caused by *S. pneumoniae* [28]. Several studies have proposed
41 that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-
42 inflammatory mechanisms that ultimately result in cardiac damage [29-32]. Furthermore, the
43 infection-mediated hyperactivation of platelets can create a pro-inflammatory and
44 prothrombotic environment that facilitates the occurrence of cardiovascular events and
45 cardiac damage [30]. Pneumonia and other infections can trigger fever, hypoxia, and
46 hemodynamic disturbance in patients, which are all risk factors of atrial fibrillation and its
47 associated cardiac damage [33].
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3 The study limitations are as follows. First, *S. pneumoniae* infections and
4 cardiovascular events were identified using diagnosis codes and ICD-10 codes, respectively.
5 Therefore, our analysis may be vulnerable to coding errors. Second, our study could not
6 account for patients' lifestyle factors (e.g., tobacco and alcohol consumption), socioeconomic
7 factors, or pneumococcal vaccination statuses. Third, our study population was limited to
8 enrollees of Japan's National Health Insurance and Latter-Stage Elderly Healthcare System,
9 and the findings may not be extrapolatable to those enrolled in other insurance systems.
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16 *Conclusion*

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18 *S. pneumoniae* infections elevate the risk of subsequent stroke and arrhythmia occurrence.
19 These findings indicate that pneumococcal infections do not only have short-term effects on
20 patient health, but also increase the mid-to long-term susceptibility to serious cardiovascular
21 events. With a greater understanding of *S. pneumoniae* infection's far-reaching impact, further
22 studies are needed to explore the possible benefits of expanding current pneumococcal
23 vaccination programs.
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Table 1. Characteristics and comorbidities of *Streptococcus pneumoniae*-infected and non-infected patients

	CHD		HF		Stroke		Arrhythmia	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
N	88,407	271	80,025	242	87,626	252	91,631	299
Cardiovascular event incidence	7,588 (8.6%)	23 (8.5%)	8,746 (11%)	32 (13%)	7,308 (8.3%)	35 (14%)	5,745 (6.3%)	27 (9.0%)
Age, mean (y)	77.4	77.6	75.9	76.2	76.5	76.8	77.9	78.1
Men	45,345 (51%)	139 (51%)	44,642 (56%)	135 (56%)	47,290 (54%)	136 (54%)	48,114 (53%)	157 (53%)
Women	43,062 (49%)	132 (49%)	35,383 (44%)	107 (44%)	40,336 (46%)	116 (46%)	43,517 (47%)	142 (47%)
Myocardial infarction	0 (0%)	0 (0%)	992 (1.2%)	3 (1.2%)	695 (0.8%)	2 (0.8%)	1,226 (1.3%)	4 (1.3%)
Congestive heart failure	13,375 (15%)	41 (15%)	4,299 (5.4%)	13 (5.4%)	11,127 (13%)	32 (13%)	11,952 (13%)	39 (13%)
Peripheral vascular disease	4,567 (5.2%)	14 (5.2%)	6,283 (7.9%)	19 (7.9%)	6,954 (7.9%)	20 (7.9%)	6,742 (7.4%)	22 (7.4%)
Cerebrovascular disease	17,290 (20%)	53 (20%)	15,542 (19%)	47 (19%)	7,998 (9.1%)	23 (9.1%)	19,307 (21%)	63 (21%)
Dementia	13,701 (15%)	42 (15%)	9,590 (12%)	29 (12%)	7,302 (8.3%)	21 (8.3%)	12,565 (14%)	41 (14%)
Chronic pulmonary disease	30,665 (35%)	94 (35%)	29,761 (37%)	90 (37%)	31,643 (36%)	91 (36%)	33,404 (36%)	109 (36%)
Rheumatic disease	2,610 (3.0%)	8 (3.0%)	3,637 (4.5%)	11 (4.5%)	3,477 (4.0%)	10 (4.0%)	3,677 (4.0%)	12 (4.0%)
Peptic ulcer disease	8,156 (9.2%)	25 (9.2%)	8,598 (11%)	26 (11%)	7,650 (8.7%)	22 (8.7%)	7,968 (8.7%)	26 (8.7%)
Mild liver disease	15,659 (18%)	48 (18%)	17,195 (21%)	52 (21%)	15,995 (18%)	46 (18%)	15,016 (16%)	49 (16%)
Diabetes without chronic complications	1,957 (2.2%)	6 (2.2%)	2,315 (2.9%)	7 (2.9%)	2,434 (2.8%)	7 (2.8%)	1,839 (2.0%)	6 (2.0%)
Diabetes with chronic complications	3,262 (3.7%)	10 (3.7%)	3,968 (5.0%)	12 (5%)	4,520 (5.2%)	13 (5.2%)	3,677 (4.0%)	12 (4.0%)
Hemiplegia or paraplegia	1,305 (1.5%)	4 (1.5%)	1,323 (1.7%)	4 (1.7%)	348 (0.4%)	1 (0.4%)	919 (1.0%)	3 (1.0%)
Renal disease	3,262 (3.7%)	10 (3.7%)	3,968 (5.0%)	12 (5%)	4,868 (5.6%)	14 (5.6%)	5,210 (5.7%)	17 (5.7%)
Malignancy	8,808 (10%)	27 (10%)	11,243 (14%)	34 (14%)	10,432 (12%)	30 (12%)	10,113 (11%)	33 (11%)
Moderate or severe liver disease	0 (0%)	0 (0%)	331 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)	306 (0.3%)	1 (0.3%)
Metastatic solid tumor	1,957 (2.2%)	6 (2.2%)	1,653 (2.1%)	5 (2.1%)	1,391 (1.6%)	4 (1.6%)	1,226 (1.3%)	4 (1.3%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Values are presented as number (percentage) unless stated otherwise. Abbreviations: CHD, coronary heart disease; HF, heart failure.

Table 2. Cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients

	CHD		HF		Stroke		Arrhythmia	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
Overall								
N	88,407	271	80,025	242	87,626	252	91,631	299
Incidence, n (%)	7,588 (8.6%)	23 (8.5%)	8,746 (11%)	32 (13%)	7,308 (8.3%)	35 (14%)	5,745 (6.3%)	27 (9.0%)
Person-years of follow-up	141,705	389	135,271	359	140,452	366	143,792	409
Incidence rate per 1000 person-years (95% CI)	53.5 (52.3-54.8)	59.2 (37.5-88.8)	64.7 (63.3-66.0)	89 (60.9-125.7)	52 (50.8-53.2)	95.7 (66.7 - 133.1)	40 (38.9-41.0)	66 (43.5-96.0)
Unadjusted Hazard ratio (95% CI)	-	1.10 (0.71-1.72)	-	1.37 (0.92-2.05)	-	1.84 (1.27-2.66)	-	1.64 (1.08-2.48)
Adjusted hazard ratio ^a (95% CI)	-	1.12 (0.71-1.78)	-	1.34 (0.88-2.06)	-	1.86 (1.26-2.76)	-	1.58 (1.03-2.43)
By age group								
N (%)								
0-49 years	3,674 (4.2%)	11 (4.1%)	3,729 (4.7%)	11 (4.5%)	3,574 (4.1%)	10 (4.0%)	3,459 (3.8%)	11 (3.7%)
50-64 years	7,730 (8.7%)	25 (9.2%)	7,256 (9.1%)	22 (9.1%)	7,661 (8.7%)	23 (9.1%)	7,639 (8.3%)	25 (8.4%)
≥65 years	77,003 (87%)	235 (87%)	69,039 (86%)	209 (86%)	76,390 (87%)	219 (87%)	80,533 (88%)	263 (88%)
Incidence rate per 1000 person-years (95% CI)								
0-49 years	4.6 (3.2-6.4)	0 (0-185.8)	3.7 (2.4-5.4)	0 (0-185.8)	4.6 (3.2-6.5)	0 (0-200.4)	8.3 (6.3-10.8)	0 (0-185.8)
50-64 years	29.5 (27.0-32.1)	18.9 (0.5-105.5)	11.8 (10.2-13.5)	20.9 (0.5-116.4)	7.4 (6.2-8.7)	60.0 (12.4-175.3)	15.0 (13.3-16.9)	19.1 (0.5-106.2)
≥65 years	60.3 (58.9-61.8)	69.6 (43.6-105.4)	76.9 (75.3-78.6)	106.3 (72.2-150.8)	62.2 (60.8-63.7)	107.6 (73.6-152.0)	45.5 (44.3-46.7)	77.1 (50.4-113.0)
Adjusted hazard ratio ^a (95% CI)								
0-49 years	-	0	-	0	-	0	-	0
50-64 years	-	0.75 (0.08-6.85)	-	2.34 (0.31-17.9)	-	7.97 (2.47-25.8)	-	1.85 (0.26-13.5)
≥65 years	-	1.17 (0.73-1.88)	-	1.34 (0.87-2.07)	-	1.73 (1.15-2.61)	-	1.60 (1.03-2.49)

^a Adjusted for age, sex, and Charlson Comorbidity Index score.

Abbreviations: CHD, coronary heart disease; HF, heart failure; CI, confidence interval.

Figure legends

Figure 1. Overview of the follow-up process for *Streptococcus pneumoniae*-infected and non-infected patients

Endpoints refer to the occurrence of a target cardiovascular event.

Figure 2. Selection of *Streptococcus pneumoniae*-infected and non-infected patients for analysis

Abbreviations: CHD, coronary heart disease; HF, heart failure.

Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients

(A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) arrhythmia

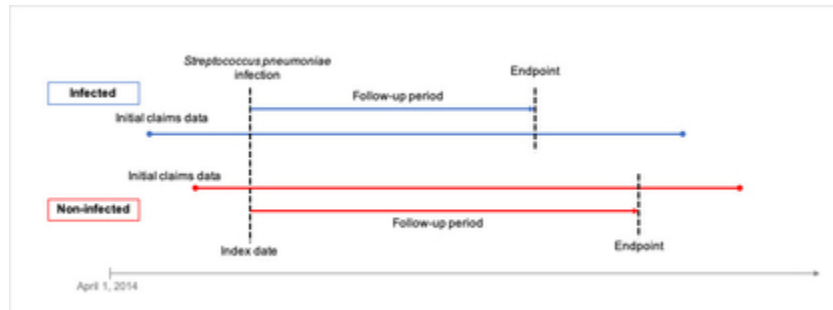


Figure 1. Overview of the follow-up process for Streptococcus pneumoniae-infected and non-infected patients
Endpoints refer to the occurrence of a target cardiovascular event.

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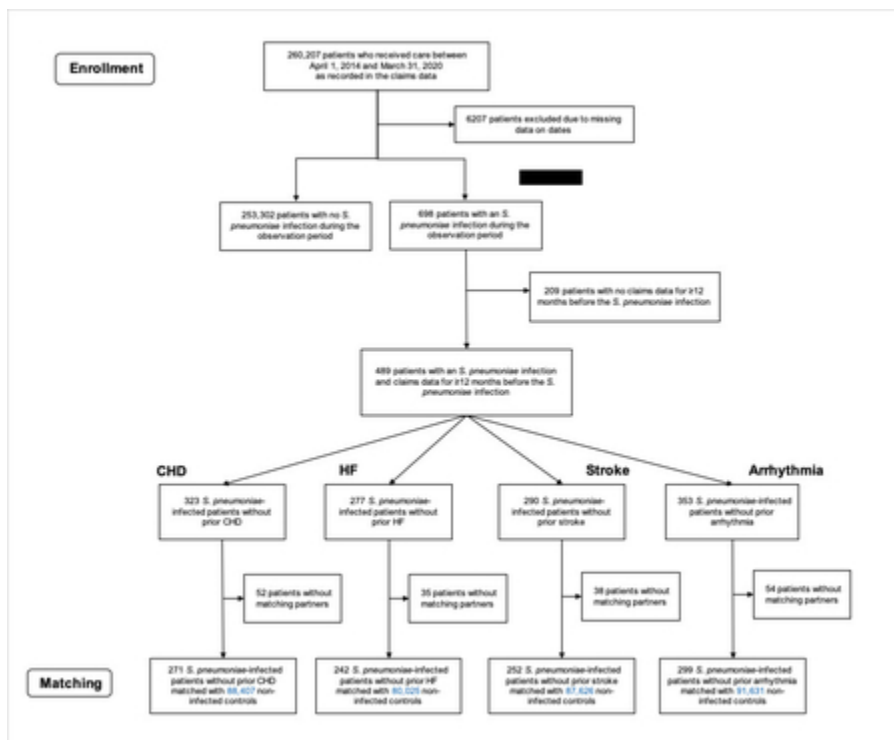


Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis. Abbreviations: CHD, coronary heart disease; HF, heart failure.

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(A) CHD

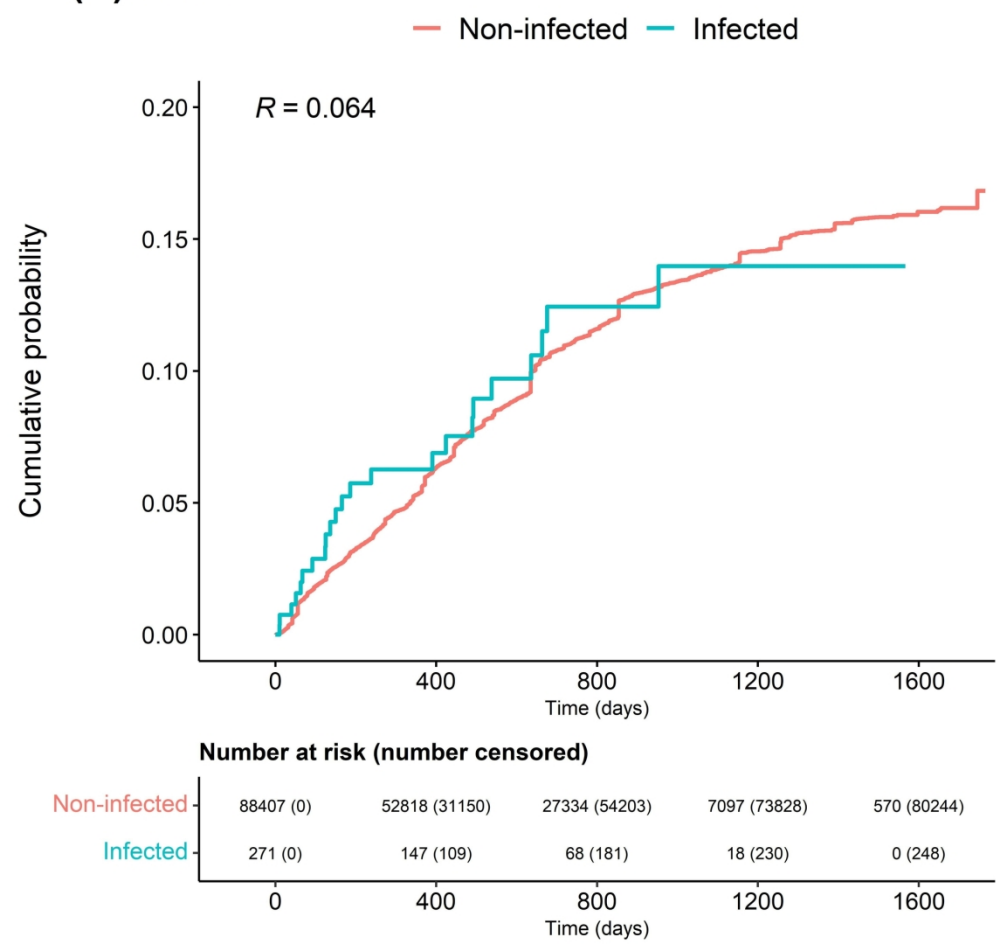


Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
(A) Coronary heart disease (CHD)

177x177mm (300 x 300 DPI)

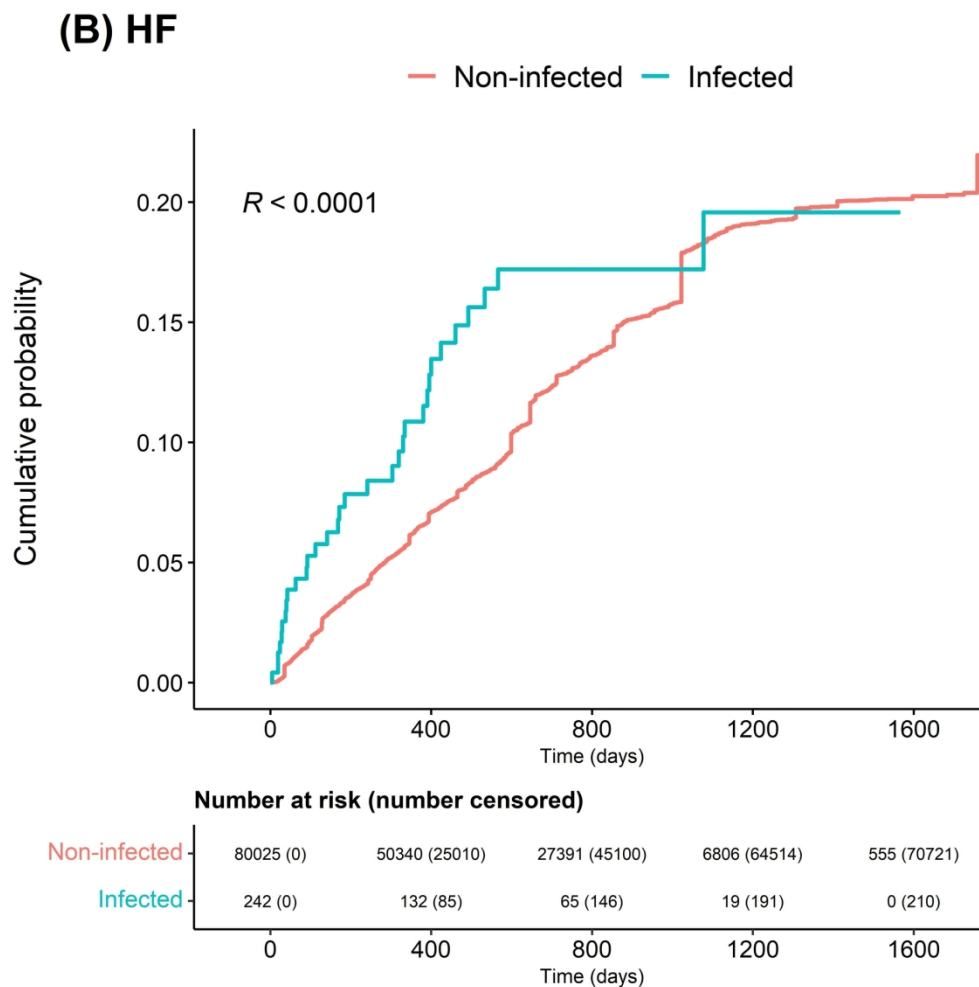


Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients
(B) heart failure (HF)

177x177mm (300 x 300 DPI)

(C) Stroke

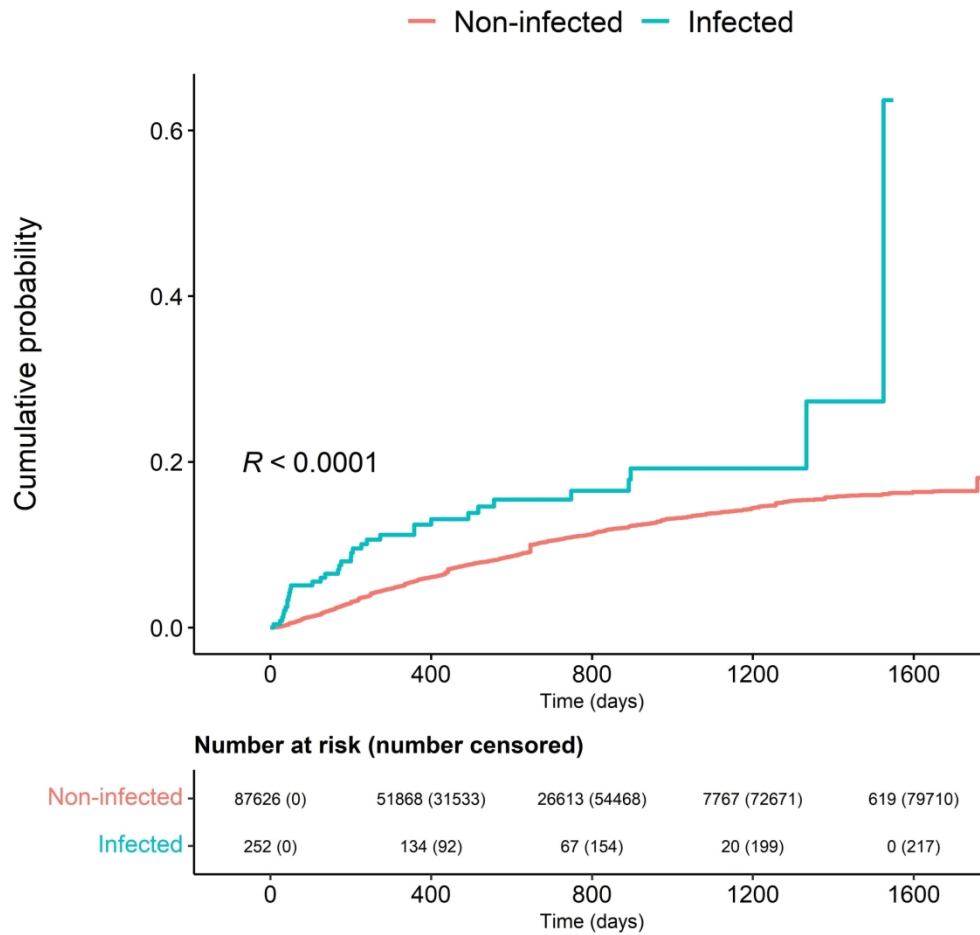


Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients
(C) stroke

177x177mm (300 x 300 DPI)

(D) Arrhythmia

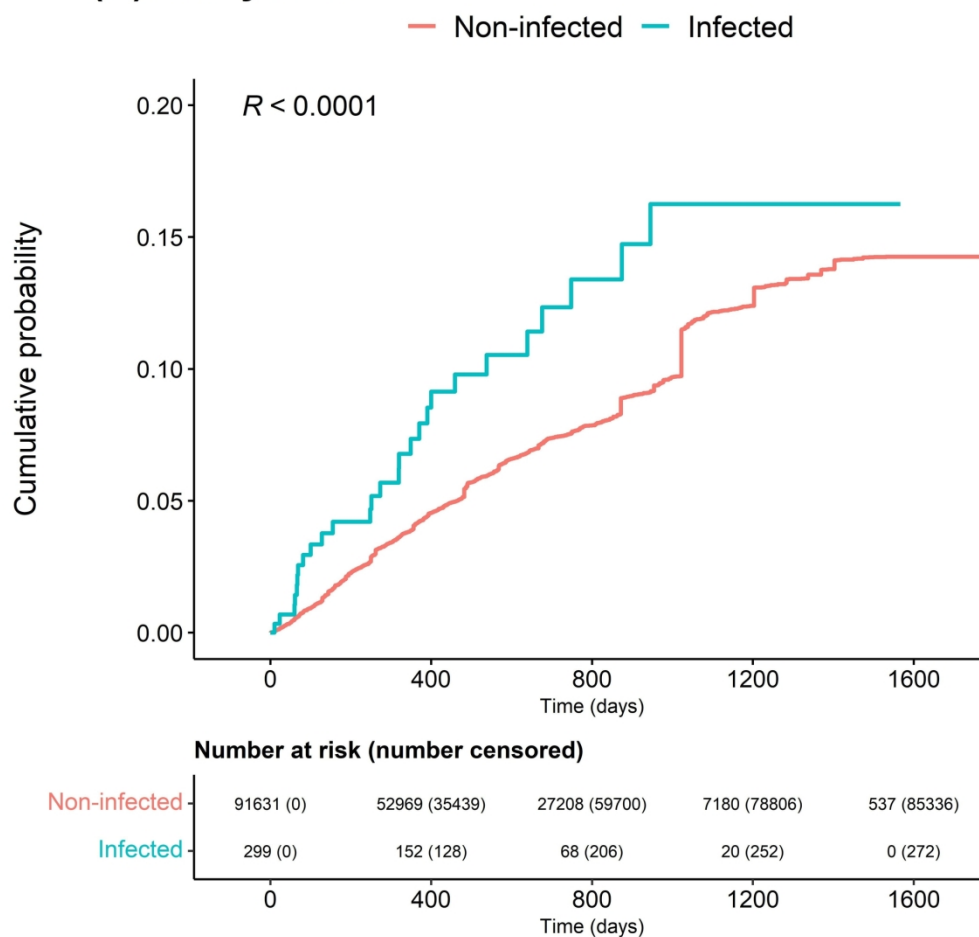


Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients (D) arrhythmia

177x177mm (300 x 300 DPI)

BMJ Open

Risk of cardiovascular events after *Streptococcus pneumoniae* infection: A retrospective cohort LIFE study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059713.R1
Article Type:	Original research
Date Submitted by the Author:	29-Jul-2022
Complete List of Authors:	Nishimura, Naoaki; Kyushu University School of Medicine, Fukuda, Haruhisa; Kyushu University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Health services research, Infectious diseases, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY

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4 1 ***BMJ Open***

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7 2 **Risk of cardiovascular events after *Streptococcus pneumoniae* infection: A retrospective**
8 3 **cohort LIFE study**

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1
2
3 31 **Abstract**

4 32 **Objectives:** To elucidate the risk of cardiovascular event occurrence following *Streptococcus*
5 33 *pneumoniae* infection.

6 34 **Design:** Retrospective cohort study using a LIFE Study database.

7 35 **Setting:** Three municipalities in Japan.

8 36 **Participants:** Municipality residents who were enrolled in either National Health Insurance
9 37 or the Latter-Stage Elderly Healthcare System from April 2014 to March 2020.

10 38 **Exposure:** Occurrence of *S. pneumoniae* infection.

11 39 **Primary Outcome Measures:** Occurrence of one of the following cardiovascular events that
12 40 led to hospitalization after *S. pneumoniae* infection: (1) coronary heart disease (CHD), (2)
13 41 heart failure (HF), (3) stroke, or (4) atrial fibrillation (AF).

14 42 **Results:** *S. pneumoniae*-infected patients were matched with non-infected patients for each
15 43 cardiovascular event. We matched 209 infected patients and 43,499 non-infected patients for
16 44 CHD, 179 infected patients and 44,148 non-infected patients for HF, 221 infected patients and
17 45 44,768 non-infected patients for stroke, and 241 infected patients and 39,568 non-infected
18 46 patients for AF. During follow-up, the incidence rates for the matched infected and non-
19 47 infected patients were, respectively, 38.6 (95% confidence interval: 19.9–67.3) and 30.4
20 48 (29.1–31.8) per 1000 person-years for CHD; 69.6 (41.9–108.8) and 50.5 (48.9–52.2) per 1000
21 49 person-years for HF; 75.4 (48.3–112.2) and 35.5 (34.1–36.9) per 1000 person-years for
22 50 stroke; and 34.7 (17.9–60.6) and 11.2 (10.4–12.0) per 1000 person-years for AF. Infected
23 51 patients were significantly more likely to develop stroke (adjusted hazard ratio: 2.05, 95%
24 52 confidence interval: 1.22–3.47; adjusted subdistribution hazard ratio: 1.94, 95% confidence
25 53 interval: 1.15–3.26) and AF (3.29, 1.49–7.26; 2.74, 1.24–6.05) than their non-infected
26 54 counterparts.

27 55 **Conclusions:** *S. pneumoniae* infections elevate the risk of subsequent stroke and AF
28 56 occurrence. These findings indicate that pneumococcal infections not only have short-term
29 57 effects on patients' health, but also increase their mid-to long-term susceptibility to serious
30 58 cardiovascular events.

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4 60 **Article Summary (Strengths and Limitations of this study)**

- 5 61 • This study comparatively examined both *Streptococcus pneumoniae*-infected patients and non-
6 62 infected controls to elucidate the association between pneumococcal infections and subsequent
7 63 cardiovascular events.
8
9 64 • While prior studies mostly focused on short-term outcomes, our study period spanned from April 2014
10 65 to March 2020 to examine the mid-to long-term risks of cardiovascular events following
11 66 pneumococcal infection.
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13 67 • Despite a relatively large study sample and long study period, *S. pneumoniae* infections and
14 68 cardiovascular events were identified using only diagnosis codes in the claims data.
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16 69 • Our study did not account for patients' lifestyle factors (e.g., tobacco and alcohol consumption),
17 70 socioeconomic factors, or pneumococcal vaccination statuses.
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72 Introduction

73 Community-acquired pneumonia is a major infectious disease that frequently leads to
74 hospitalization, and exhibits high morbidity and mortality rates across numerous countries [1,
75 2]. *Streptococcus pneumoniae* is the causal pathogen for a large proportion of pneumonia
76 cases that require hospital-based care [3]. As older persons are more susceptible to
77 pneumococcal pneumonia [4], this condition represents a particularly serious public health
78 problem in countries with aging populations. In addition to its acute effects, pneumonia is also
79 known to increase the mid-to long-term health risks of infected patients, thereby placing a
80 heavy clinical and economic burden on patients and society [2, 5].

81 Previous cohort studies have reported that pneumonia is associated with an increased
82 risk of the following conditions: overall cardiac events [6-14], acute coronary syndrome [6, 8,
83 9, 11, 12, 14-17], heart failure (HF) [6, 9-14, 16, 18], atrial fibrillation (AF) [6, 8-14, 16, 17,
84 19, 20], and stroke [11, 12, 17]. However, the majority of these studies focused on pneumonia
85 patients without comparisons with non-infected controls, and generally used relatively short
86 follow-up periods. Furthermore, only a few studies in the existing literature have explored the
87 effects of pneumonia on subsequent cardiovascular disease [7, 18, 21].

88 In order to accurately evaluate the impact of *S. pneumoniae* infection on subsequent
89 cardiovascular disease, there is a need for long-term cohort studies that compare infected
90 patients with matched non-infected controls. This study aimed to elucidate the risk of
91 cardiovascular event occurrence following *S. pneumoniae* infection using administrative
92 claims data acquired from infected and non-infected patients in 3 Japanese municipalities. The
93 study also examined if these risks differ among age groups.

95 Methods

96 Study data

97 Data were provided by the Longevity Improvement & Fair Evidence (LIFE) Study, which is
98 managed by Kyushu University (Fukuoka, Japan) [22]. In the LIFE Study, participating
99 municipalities voluntarily provide administrative claims data for research purposes. These
100 claims data are acquired from the municipalities' residents who are enrolled in either National
101 Health Insurance or the Latter-Stage Elderly Healthcare System, and encompass information
102 on patient characteristics and reimbursement claims for all insurance-covered healthcare
103 provided in the inpatient and outpatient settings. Enrollees in National Health Insurance
104 include the self-employed, agricultural and fishery workers, part-time workers, retirees, and
105 their dependents. Enrollees in the Latter-Stage Elderly Healthcare System include residents
106 aged ≥ 75 years. The number of municipalities participating in the LIFE Study varies over
107 time owing to differences in agreement contracts, with the earliest participant providing data

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3 108 from April 2014. The majority of the participating municipalities provide data from April
4 109 2015 onward. As of 2021, the LIFE Study is able to conduct longitudinal studies with 5-year
5 110 follow-up periods.

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8 111 For this study, claims data from April 2014 to March 2020 were acquired from
9 112 insurance enrollees who were residing in 3 municipalities (residential populations: 58,000,
10 113 121,600, and 305,200) in Fukuoka Prefecture. The claims datasets contained records of
11 114 diagnoses (Japanese diagnosis codes and International Classification of Diseases, 10th
12 115 revision [ICD-10] codes), dates of treatments and admissions, and coexisting conditions
13 116 (Charlson Comorbidity Index scores). Charlson Comorbidity Index scores were generated
14 117 from ICD-10 codes recorded in both inpatient and outpatient claims.
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21 119 *Study subjects*

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23 120 First, patients with *S. pneumoniae* infections were identified through combinations of ICD-10
24 121 codes and/or Japanese diagnosis codes developed by the Ministry of Health, Labour and
25 122 Welfare. We used the combinations of codes proposed by Imai et al. [23]. In this study, we
26 123 considered all types of *S. pneumoniae* infections, including invasive pneumococcal diseases.
27 124 The occurrence of subsequent cardiovascular events (coronary heart disease [CHD], HF,
28 125 stroke, and AF) was identified using ICD-10 codes. We excluded patients with records of
29 126 previous in-hospital cardiovascular events from their earliest recorded dates within the
30 127 observation period until *S. pneumoniae* infection, patients with records of cardiovascular
31 128 events during the index hospitalization for *S. pneumoniae* infection, and patients without any
32 129 claims data ≥ 12 months before *S. pneumoniae* infection.

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35 130 Next, we set each infected patient's index date as the last day of the month containing
36 131 a recorded *S. pneumoniae* infection. The infected patients were then matched with a cohort of
37 132 non-infected patients according to age (within 5 years), sex, Charlson Comorbidity Index
38 133 score, and hospitalization at the index date using sampling without replacement. Using the
39 134 method proposed by Quan et al. [24], Charlson Comorbidity Index scores were calculated
40 135 based on the following conditions: myocardial infarction, congestive HF, peripheral vascular
41 136 disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease,
42 137 peptic ulcer disease, liver disease, diabetes with/without chronic complications, hemiplegia or
43 138 paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS. When examining the
44 139 occurrence of AF after *S. pneumoniae* infection, we included the comorbidity of AF as a
45 140 matching criterion. Infected patients who could not be matched with non-infected patients
46 141 were excluded. The index date for each non-infected patient was set as the same date as
47 142 his/her matched infected case. Each patient's Charlson Comorbidity Index score was
48 143 calculated using claims data for 30 days before the index date. We also excluded non-infected
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3 144 patients who had experienced cardiovascular events that led to hospitalization before their
4 index dates.
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8 147 *Outcome measure*

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11 148 The outcome measure was the occurrence of a cardiovascular event that led to hospitalization
12 149 after the *S. pneumoniae* infection date. Among inpatients, the infection date was set as the
13 150 first date of admission for the in-hospital treatment of an *S. pneumoniae* infection. Among
14 151 outpatients, the infection date was set as the first date of any medical treatment with a
15 152 diagnosis code indicating an *S. pneumoniae* infection. We focused on the first infection
16 153 episode for patients who had multiple infection episodes during the observation period.

17 154 Next, we examined the subsequent occurrence of each of the following 4
18 155 cardiovascular events that led to hospitalization: (1) CHD (ICD-10 codes: I20-25), (2) HF
19 156 (I50), (3) stroke (I61-63, 65-66), and (4) AF (I48). The occurrence date of each cardiovascular
20 157 event was set as the date of admission for the in-hospital treatment of that event.

21 158 Patients who had died during the observation period without developing any
22 159 cardiovascular event were followed-up until the last date of medical treatments in the claims
23 160 data. Patients who had died during the observation period after developing a cardiovascular
24 161 event were followed-up until the date of the cardiovascular event occurrence. All survivors
25 162 were followed-up until the end of their municipality's observation period. The ends of the
26 163 observation periods ranged from September 2019 to March 2020 among the municipalities.

27 164 **Figure 1** shows an overview of the follow-up process.
28 165

29 166 *Statistical analysis*

30 167 Our analysis was designed to examine the possible effects of *S. pneumoniae* infection on the
31 168 subsequent occurrence of cardiovascular events, and to determine if these effects differed
32 169 among age groups. For each of the 4 target cardiovascular events, we calculated the number
33 170 of events for the infected group and non-infected group during the observation period, and
34 171 estimated the incidence rates per 1000 person-years. Cox proportional hazards models were
35 172 constructed to estimate the hazard ratio (HRs) and 95% confidence interval (CIs) of each
36 173 cardiovascular event in the infected group relative to the non-infected group. Subdistribution
37 174 HRs were also estimated with Cox proportional hazards models using the Fine–Gray
38 175 competing risk approach in which death was regarded as a competing event. The Kaplan–
39 176 Meier method was used to calculate the cumulative probability of cardiovascular event
40 177 occurrence in the 2 groups. In addition, we analyzed the patients stratified according to the
41 178 following age groups: 0–49 years, 50–64 years, and ≥ 65 years.

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3 179 All statistical analyses were performed using R (version 4.1.0) and R Studio (version
4 180 1.4.1106) software. Two-tailed *P* values below 0.05 were considered statistically significant.
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8 182 *Patient and public involvement*

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10 183 Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans
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12 184 of this research.
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16 186 **Results**

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18 187 We first identified 698 *S. pneumoniae*-infected patients and 253,302 non-infected patients
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20 188 between April 1, 2014 and March 31, 2020 (**Figure 2**). After applying the exclusion criteria,
21 189 489 eligible infected patients were included in the analysis. There were 22 invasive
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23 190 pneumococcal disease cases (4.5%) and 467 non-invasive pneumococcal disease cases
24 191 (95.5%). Among the infected patients that could be successfully matched with non-infected
25 192 patients for each cardiovascular event, we identified 209 infected patients without prior CHD,
26 193 179 infected patients without prior HF, 221 infected patients without prior stroke, and 241
27 194 infected patients without prior AF. Using the various matching criteria, we matched 43,499,
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29 195 44,148, 44,768, and 39,568 non-infected controls with the infected patients for CHD, HF,
30 196 stroke, and AF, respectively. The non-infected patients were followed-up from the first *S.*
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32 197 *pneumoniae* infection date of their matched infected patients. **Table 1** shows the
33 198 characteristics and comorbidities of the infected and non-infected patients.
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199 **Table 1. Characteristics and comorbidities of *Streptococcus pneumoniae*-infected and non-infected patients**

	CHD		HF		Stroke		AF	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
N	43,499	209	44,148	179	44,768	221	39,568	241
Cardiovascular event incidence	2,090 (4.8%)	12 (5.7%)	3,790 (8.6%)	19 (11%)	2,502 (5.6%)	24 (11%)	703 (1.8%)	12 (5.0%)
Age, mean (y)	77.0	77.1	75.4	75.6	77.5	77.7	77.5	77.7
Men	22,062 (51%)	106 (51%)	24,417 (55%)	99 (55%)	22,890 (51%)	113 (51%)	20,523 (52%)	125 (52%)
Women	21,437 (49%)	103 (49%)	19,731 (45%)	80 (45%)	21,878 (49%)	108 (49%)	19,045 (48%)	116 (48%)
Hospital admission	30,595 (70%)	147 (70%)	29,103 (66%)	118 (66%)	31,804 (71%)	157 (71%)	29,224 (74%)	178 (74%)
Myocardial infarction	0 (0%)	0 (0%)	247 (0.6%)	1 (0.6%)	203 (0.5%)	1 (0.5%)	164 (0.4%)	1 (0.4%)
Congestive heart failure	4,787 (11%)	23 (11%)	987 (2.2%)	4 (2.2%)	4,051 (9.0%)	20 (9.0%)	4,433 (11%)	27 (11%)
Peripheral vascular disease	1,249 (2.9%)	6 (2.9%)	1,233 (2.8%)	5 (2.8%)	1,418 (3.2%)	7 (3.2%)	1,149 (2.9%)	7 (2.9%)
Cerebrovascular disease	6,036 (14%)	29 (14%)	5,179 (12%)	21 (12%)	4,254 (9.5%)	21 (9.5%)	5,254 (13%)	32 (13%)
Dementia	6,244 (14%)	30 (14%)	4,933 (11%)	20 (11%)	5,267 (12%)	26 (12%)	4,761 (12%)	29 (12%)
Chronic pulmonary disease	12,488 (29%)	60 (29%)	14,305 (32%)	58 (32%)	12,762 (29%)	63 (29%)	11,000 (28%)	67 (28%)
Rheumatic disease	624 (1.4%)	3 (1.4%)	1,233 (2.8%)	5 (2.8%)	810 (1.8%)	4 (1.8%)	985 (2.5%)	6 (2.5%)
Peptic ulcer disease	2,914 (6.7%)	14 (6.7%)	3,453 (7.8%)	14 (7.8%)	2,633 (5.9%)	13 (5.9%)	2,134 (5.4%)	13 (5.4%)
Mild liver disease	6,868 (16%)	33 (16%)	7,399 (17%)	30 (17%)	6,685 (15%)	33 (15%)	4,925 (12%)	30 (12%)
Diabetes without chronic complications	624 (1.4%)	3 (1.4%)	493 (1.1%)	2 (1.1%)	405 (0.9%)	2 (0.9%)	328 (0.8%)	2 (0.8%)
Diabetes with chronic complications	1,249 (2.9%)	6 (2.9%)	1,726 (3.9%)	7 (3.9%)	1,215 (2.7%)	6 (2.7%)	1,149 (2.9%)	7 (2.9%)
Hemiplegia or paraplegia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal disease	416 (1.0%)	2 (1.0%)	493 (1.1%)	2 (1.1%)	810 (1.8%)	4 (1.8%)	657 (1.7%)	4 (1.7%)
Malignancy	3,538 (8.1%)	17 (8.1%)	4,686 (11%)	19 (11%)	4,051 (9.0%)	20 (9.0%)	3,284 (8.3%)	20 (8.3%)
Moderate or severe liver disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Metastatic solid tumor	833 (1.9%)	4 (1.9%)	987 (2.2%)	4 (2.2%)	608 (1.4%)	3 (1.4%)	657 (1.7%)	4 (1.7%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AF							328 (0.8%)	2 (0.8%)

200 Values are presented as number (percentage) unless stated otherwise. Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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3 201 **Table 2** summarizes the risk of each cardiovascular event after *S. pneumoniae*
4 202 infection. The observation periods of the matched infected and non-infected patients
5 203 (weighted by the proportion of the infected patients) were, respectively, 311 and 68,706
6 204 person-years for CHD; 273 and 74,999 person-years for HF; 318 and 70,454 person-years for
7 205 stroke; and 346 and 62,986 person-years for AF. The median observation periods of the
8 206 matched infected and non-infected patients were 823 days for CHD, 827 days for HF, 820
9 207 days for stroke, and 797 days for AF. During follow-up, the incidence rates for the infected
10 208 and non-infected patients were, respectively, 38.6 (95% CI: 19.9–67.3) and 30.4 (95% CI:
11 209 29.1–31.8) per 1000 person-years for CHD; 69.6 (41.9–108.8) and 50.5 (48.9–52.2) per 1000
12 210 person-years for HF; 75.4 (48.3–112.2) and 35.5 (34.1–36.9) per 1000 person-years for
13 211 stroke; and 34.7 (17.9–60.6) and 11.2 (10.4–12.0) per 1000 person-years for AF. The
14 212 unadjusted HRs for cardiovascular event occurrence in infected patients (relative to non-
15 213 infected patients) were 1.27 (95% CI: 0.72–2.24) for CHD, 1.38 (0.88–2.16) for HF, 2.12
16 214 (1.42–3.17) for stroke, and 3.11 (1.76–5.50) for AF. After adjusting for age, sex, Charlson
17 215 Comorbidity Index score, and coexisting AF (only for the outcome of AF), infected patients
18 216 were significantly more likely to develop stroke (adjusted HR: 2.05, 95% CI:1.22–3.47) and
19 217 AF (adjusted HR: 3.29, 95% CI: 1.49–7.26) than their non-infected counterparts. When death
20 218 was regard as a competing event, infected patients were still significantly more likely to
21 219 develop stroke (adjusted subdistribution HR: 1.94, 95% CI: 1.15–3.26) and AF (2.74, 1.24–
22 220 6.05) than their non-infected counterparts.

221 **Table 2. Cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients**

	CHD		HF		Stroke		AF	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
Overall								
N	43,499	209	44,148	179	44,768	221	39,568	241
Incidence, n (%)	2,090 (4.8%)	12 (5.7%)	3,790 (8.6%)	19 (11%)	2,502 (5.6%)	24 (11%)	703 (1.8%)	12 (5.0%)
Person-years of follow-up	68,706	311	74,999	273	70,454	318	62,986	346
Incidence rate per 1000 person-years (95% CI)	30.4 (29.1-31.8)	38.6 (19.9-67.3)	50.5 (48.9-52.2)	69.6 (41.9-108.8)	35.5 (34.1-36.9)	75.4 (48.3-112.2)	11.2 (10.4-12.0)	34.7 (17.9-60.6)
Unadjusted hazard ratio (95% CI)	-	1.27 (0.72-2.24)	-	1.38 (0.88-2.16)	-	2.12 (1.42-3.17)	-	3.11 (1.76-5.50)
Adjusted hazard ratio ^a (95% CI)	-	1.20 (0.60-2.39)	-	1.18 (0.58-2.37)	-	2.05 (1.22-3.47)	-	3.29 (1.49-7.26)
Adjusted subdistribution hazard ratio ^a (95% CI)	-	1.19 (0.63-2.26)	-	1.13 (0.60-2.13)	-	1.94 (1.15-3.26)	-	2.74 (1.24-6.05)
By age group								
N (%)								
0-49 years	1,958 (4.5%)	9 (4.3%)	2,304 (5.2%)	9 (5.0%)	1,895 (4.2%)	9 (4.1%)	1,533 (3.9%)	9 (3.7%)
50-64 years	3,963 (9.1%)	21 (10%)	4,080 (9.2%)	18 (10%)	3,620 (8.1%)	19 (8.6%)	3,305 (8.4%)	22 (9.1%)
≥65 years	37,578 (86%)	179 (86%)	37,765 (86%)	152 (85%)	39,253 (88%)	193 (87%)	34,730 (88%)	210 (87%)
Incidence rate per 1000 person-years (95% CI)								
0-49 years	8.0 (5.6-11.0)	0 (0-200.4)	15.0 (11.8-18.7)	0 (0-200.4)	3.0 (1.6-5.1)	0 (0-200.4)	1.2 (0.3-3.0)	0 (0-200.4)
50-64 years	5.4 (4.0-7.0)	21.8 (0.6-121.5)	29.4 (26.1-33.1)	24.3 (0.6-135.1)	35.1 (31.3-39.3)	69.7 (14.4-203.6)	6.2 (4.6-8.2)	21.4 (0.5-119.2)
≥65 years	36.7 (35.1-38.3)	44.5 (22.2-79.7)	57.1 (55.2-59.0)	84.4 (50.0-133.4)	38.0 (36.5-39.7)	81.8 (50.6-125.0)	12.6 (11.7-13.6)	39.2 (19.6-70.1)
Adjusted hazard ratio ^a (95% CI)								
0-49 years	-	0	-	0	-	0	-	0
50-64 years	-	4.06 (0.56-29.38)	-	0.82 (0.12-5.86)	-	1.98 (0.64-6.19)	-	3.47 (0.48-25.02)
≥65 years	-	1.21 (0.64-2.10)	-	1.48 (0.78-1.97)	-	2.15 (1.29-3.04)	-	3.11 (1.58-5.20)

222 ^a Adjusted for age, sex, Charlson Comorbidity Index score, and coexisting AF (only for the outcome of AF).

223 Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; CI, confidence interval

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3 224 In the age-stratified analysis, *S. pneumonia* infections were not significantly associated
4 225 with a higher risk of the 4 cardiovascular events in patients aged 50–64 years. Among older
5 226 patients aged ≥ 65 years, *S. pneumonia* infections were significantly associated with
6 227 substantially higher risks of stroke and AF occurrence.

9 228 **Figure 3** presents the Kaplan–Meier curves of each cardiovascular event. When
10 229 compared with non-infected patients, infected patients had a significantly higher risk of
11 230 incident HF, stroke, and AF (all $P < 0.0001$); but not CHD ($P = 0.046$).

14 231 **Figure 4** presents the cumulative incidence curves for cardiovascular events where
15 232 death was regarded as a competing event.

18 233 Discussion

19 234 Through an analysis of National Health Insurance and Latter-Stage Elderly Healthcare
20 235 System enrollees residing in 3 Japanese municipalities, this study comparatively examined the
21 236 incidence of cardiovascular events between *S. pneumoniae*-infected patients and non-infected
22 237 patients. Our results showed that the experience of *S. pneumoniae* infection significantly
23 238 elevates the risk of subsequent stroke and AF. *S. pneumoniae* infection increased the risk of
24 239 these cardiovascular events among older patients aged ≥ 65 years. While *S. pneumonia*
25 240 infections were not significantly associated with a higher risk of these cardiovascular events
26 241 in patients aged 50–64 years, the ratios were relatively high and more studies should be
27 242 conducted. These findings may help to identify at-risk targets for expanded pneumococcal
28 243 vaccination programs.

34 244 Recent studies have shown that patients with community-acquired pneumonia have a
35 245 higher frequency of cardiovascular events [8, 10, 11, 16, 18, 21, 25, 26]. Our estimated
36 246 incidence of AF after *S. pneumoniae* infection was 5.0%. The incidence of arrhythmia (ICD-
37 247 10 codes: I47-49) in this study was estimated to be 9.0%, which is slightly higher than that of
38 248 a previous meta-analysis that estimated an overall incidence of 7.2% among inpatients with
39 249 community-acquired pneumonia [25]. This discrepancy may be explained by the fact that the
40 250 meta-analysis had only included studies with short-term outcomes.

45 251 In our analysis, the estimated incidence of stroke after *S. pneumoniae* infection was
46 252 considerably higher than those found in previous studies [11,16]. Perry et al. reported a stroke
47 253 incidence of 0.17% in 40,979 patients during 90 days of admission for pneumonia, whereas
48 254 Violi et al. reported a stroke incidence of 1.0% in 1,182 patients hospitalized for community-
49 255 acquired pneumonia during in-hospital follow-up (median length of hospital stay: 11 days).
50 256 Accordingly, those 2 studies had focused on the short-term incidence of stroke. However, the
51 257 risk of stroke increases with age, and longer follow-up periods after *S. pneumoniae* infection
52 258 would therefore provide a more accurate depiction of its risks. Furthermore, Perry et al. used
53 259 ICD-9 codes to identify stroke, whereas Violi et al. identified stroke cases through clinical
54 260 manifestations confirmed by computed tomography or magnetic resonance imaging [11,16].

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3 261 Stroke diagnostic methods are generally reliant on imaging data, and many medical facilities
4 262 in Japan are equipped with on-site computed tomography and/or magnetic resonance imaging
5 263 scanners. This enables the accurate diagnosis of stroke, including cases of milder strokes,
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7 264 throughout Japan.

9 265 Among the studies that reported a high frequency of subsequent cardiovascular events
10 266 in pneumonia patients, few have actually compared infected patients with non-infected
11 267 controls. Eurich et al. performed a long-term prospective cohort study of both inpatients and
12 268 outpatients with community-acquired pneumonia, and found that these infections substantially
13 269 increased the risk of HF across different age groups and disease severity [18]. During a
14 270 median follow-up period of 9.9 years, 11.9% of patients with pneumonia developed incident
15 271 HF compared with 7.4% of the non-infected controls; furthermore, 13.3% of patients with
16 272 pneumococcal bacteremia developed incident HF [18]. In contrast, 13.0% of our infected
17 273 patients developed incident HF compared with 12.0% of their non-infected counterparts, with
18 274 no significant difference between the groups. This discrepancy may be influenced by the fact
19 275 that Eurich et al. used a control group that only controlled for age (five-year age bands) and
20 276 sex, only investigated outpatients in emergency departments, and focused on severe
21 277 pneumonia infections. In contrast, our study included outpatients from all types of medical
22 278 institutions, and our control group comprised patients without any *S. pneumoniae* infection.
23 279 Our study also utilized a research design that differed from Eurich et al. [18], which only
24 280 matched for age and sex, and adjusted for the effects for coexisting conditions by including
25 281 them as covariates in analytical models. However, we matched infected patients and non-
26 282 infected controls not only by age and sex, but also by coexisting conditions through Charlson
27 283 Comorbidity Index scores.

28 284 To our knowledge, few studies have shown the long-term risks of subsequent stroke
29 285 and AF after *S. pneumoniae* infection (including non-hospitalized cases) relative to non-
30 286 infected controls. Severe cases of pneumonia require hospital-based care, especially among
31 287 older adults. Therefore, studies that focus on hospitalized pneumonia patients would overlook
32 288 the risks associated with less severe cases. For example, although patients aged ≤ 65 years
33 289 may have milder *S. pneumoniae* infections and a correspondingly lower risk of hospitalization
34 290 than older patients, these infections could still elevate the risk of subsequent cardiovascular
35 291 events in the younger age groups. As this study used insurance claims data that incorporated
36 292 both inpatient and outpatient data, we were able to identify the risk of cardiovascular events
37 293 after *S. pneumoniae* infection in patients regardless of whether they required hospitalization.
38 294 Moreover, our study excluded patients who had subsequent cardiovascular events during the
39 295 index hospital stay for *S. pneumoniae* infection. For patients who were admitted to hospital
40 296 due to *S. pneumoniae* infection, we only monitored for cardiovascular events that occurred
41 297 after discharge. Most studies have reported the short-term risks of cardiovascular events

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3 298 during or after acute infections, and the long-term impact of pneumonia on subsequent
4 299 cardiovascular disease occurrence is less clear. Therefore, our study provides new insight into
5 300 the mid-to long-term effects of milder *S. pneumoniae* infections treated in outpatient settings
6 301 as well as severe *S. pneumoniae* infections that require hospitalization.

7
8 302 A previous study identified the major causative organisms of community-acquired
9 303 pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*,
10 304 *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several
11 305 viral pathogens (including influenza A and B) [27]. *S. pneumoniae* reportedly reduces cardiac
12 306 contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [28]. Many
13 307 studies that seek to understand the pathogenesis of cardiovascular events following
14 308 pneumonia focus on infections caused by *S. pneumoniae* [29]. Several studies have proposed
15 309 that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-
16 310 inflammatory mechanisms that ultimately result in cardiac damage [30-33]. Furthermore, the
17 311 infection-mediated hyperactivation of platelets can create a pro-inflammatory and
18 312 prothrombotic environment that facilitates the occurrence of cardiovascular events and
19 313 cardiac damage [31]. Pneumonia and other infections can trigger fever, hypoxia, and
20 314 hemodynamic disturbance in patients, which are all risk factors of AF and its associated
21 315 cardiac damage [34].

22
23 316 The study limitations are as follows. First, *S. pneumoniae* infections and
24 317 cardiovascular events were identified using diagnosis codes and ICD-10 codes, respectively.
25 318 Therefore, our analysis may be vulnerable to coding errors. Second, our study could not
26 319 account for patients' lifestyle factors (e.g., tobacco and alcohol consumption), socioeconomic
27 320 factors, or pneumococcal vaccination statuses. In addition, we also could not account for
28 321 differences in medications and treatments (especially at discharge) among the patients. Third,
29 322 our study population was limited to enrollees of Japan's National Health Insurance and
30 323 Latter-Stage Elderly Healthcare System, and the findings may not be extrapolatable to those
31 324 enrolled in other insurance systems. Fourth, our study excluded patients with previous in-
32 325 hospital cardiovascular events. However, the real-world population of patients would include
33 326 those with such events. This approach could introduce selection bias and affect the
34 327 comparability of our findings with real-world scenarios. Fifth, we excluded infected patients
35 328 who were not matched with non-infected controls. With consideration to the relatively low
36 329 number of infected patients, the exclusion of these non-matched patients could potentially
37 330 reduce the power of our statistical analyses. Sixth, our study outcomes focused on
38 331 cardiovascular events that resulted in hospitalization, and did not consider events without in-
39 332 hospital care. Therefore, our study may overlook the impact of *S. pneumoniae* infection on
40 333 subsequent occurrences of mild cardiovascular disease. Seventh, previous outpatient
41 334 treatments were not included in the analysis, which could result in selection bias. Eighth, the

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3 335 index date for matching was set as the last day of the month with *S. pneumoniae* infection
4 336 instead of the claims date, which could result in lead-time bias. Finally, we did not consider
5 337 the random effects of hospitals or municipalities in our multivariate analyses. Patients treated
6 338 in the same hospital or municipality may be similar to one another. However, all the study
7 339 municipalities were located in the same prefecture, and there were no major differences in
8 340 characteristics at the regional or hospital level. Additionally, pneumonia is a common disease
9 341 that hospitals regularly treat, and it is unlikely that there would be a large bias at the hospital
10 342 level.
11 343

17 344 *Conclusion*

19 345 *S. pneumoniae* infections elevate the risk of subsequent stroke and AF occurrence. These
20 346 findings indicate that pneumococcal infections do not only have short-term effects on patient
21 347 health, but also increase the mid-to long-term susceptibility to serious cardiovascular events.
22 348 With a greater understanding of *S. pneumoniae* infection's far-reaching impact, further studies
23 349 are needed to explore the possible benefits of expanding current pneumococcal vaccination
24 350 programs.
25 351

26 352
27 353 **Contributors** NN and HF designed the study. HF provided the data. NN analyzed the data. NN
28 354 prepared the first draft of the manuscript. HF made critical revisions to the manuscript. All authors
29 355 reviewed and approved the final draft.

30 356 **Funding** The construction of the LIFE Study database was funded by a Grant-in-Aid for Scientific
31 357 Research by the Japan Society for the Promotion of Science (Grant No. JP20H00563). Data analysis
32 358 and publication were funded by an Investigator-Sponsored Research grant from Pfizer Japan Inc.

33 359 **Competing interest** HF received an Investigator-Sponsored Research grant from Pfizer Japan Inc.

34 360 **Ethical considerations** The study was approved by the Kyushu University Institutional Review
35 361 Board for Clinical Research (Approval No. 2019-406).

36 362 **Patient consent for publications** Not required.

37 363 **Data availability statement** The data used in this study were acquired under agreements with the
38 364 participating municipalities, which stipulate that the data can only be used by authorized research
39 365 institutions and cannot be shared with third parties.
40 366

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3 445 **Figure 1. Overview of the follow-up process for *Streptococcus pneumoniae*-infected and non-infected**
4 446 **patients**

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6 447 Endpoints refer to the occurrence of a target cardiovascular event.

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10 450 **Figure 2. Selection of *Streptococcus pneumoniae*-infected and non-infected patients for analysis**

11 451 Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments. Abbreviations: CHD,
12 452 coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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15 455 **Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and**
16 456 **non-infected patients**

17 457 (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

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20 460 **Figure 4. Cumulative incidence curves for cardiovascular events in *Streptococcus pneumoniae*-infected**
21 461 **and non-infected patients**

22 462 (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

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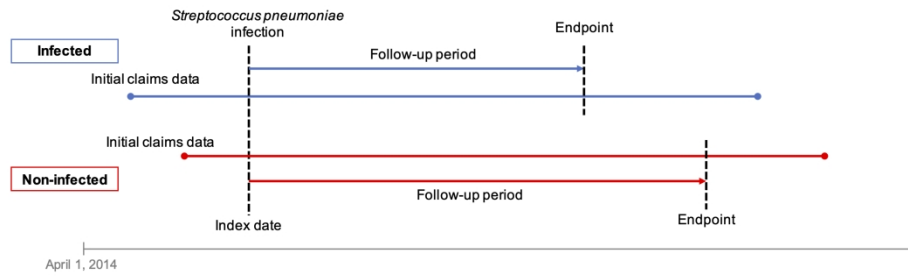
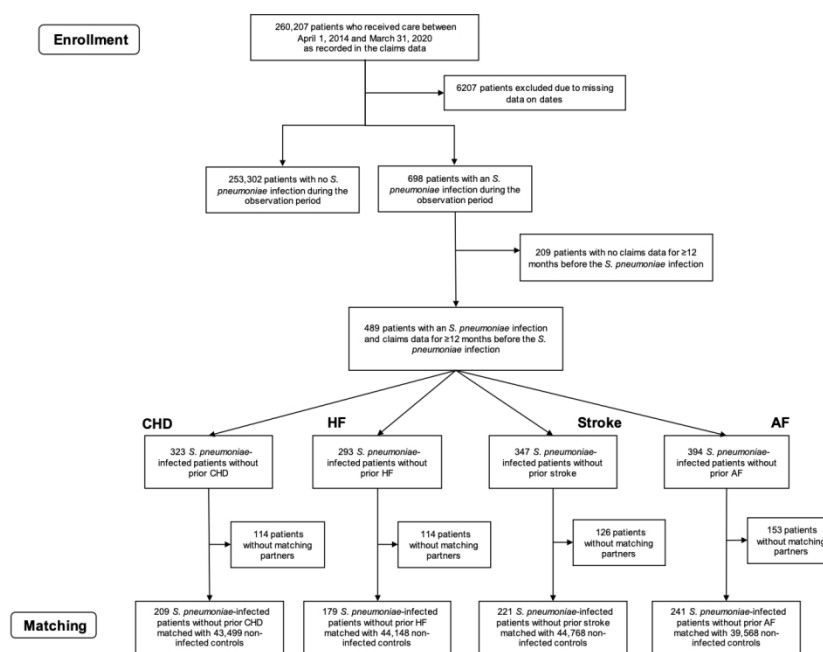


Figure 1. Overview of the follow-up process for Streptococcus pneumoniae-infected and non-infected patients.

Legend: Endpoints refer to the occurrence of a target cardiovascular event.

1028x342mm (72 x 72 DPI)



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Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis
Legend: Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments.
Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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579x403mm (72 x 72 DPI)

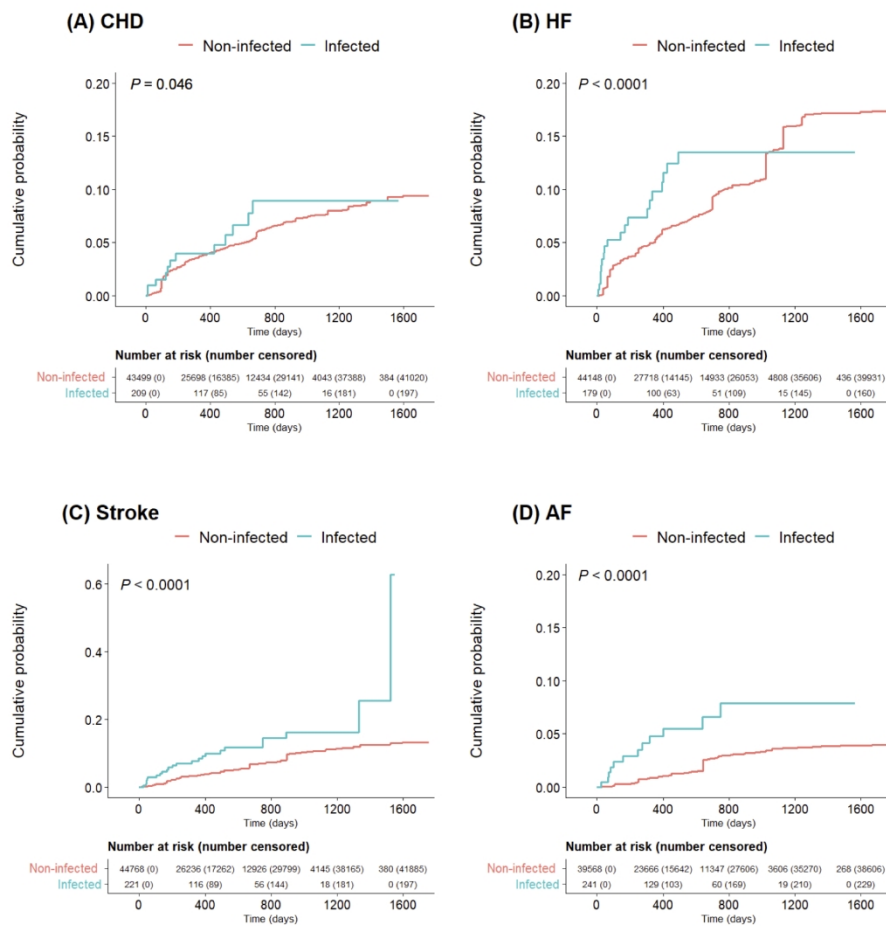
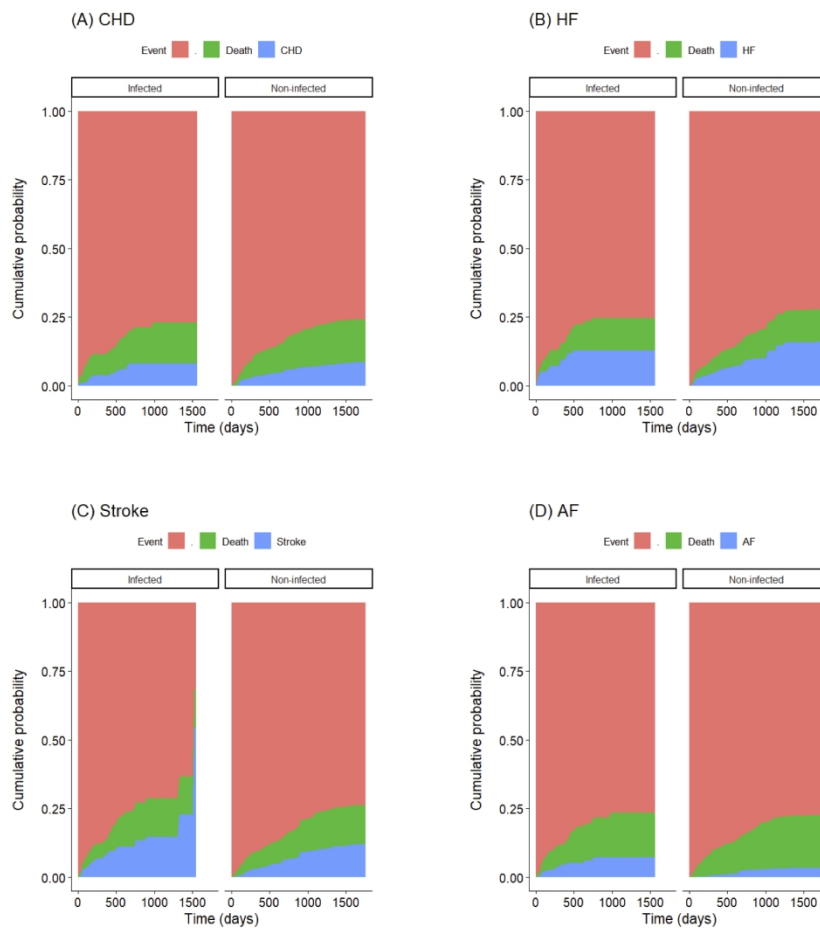


Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients

Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

624x666mm (72 x 72 DPI)



Caption : Figure 4. Cumulative incidence curves for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients

Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

624x666mm (72 x 72 DPI)

BMJ Open

Risk of cardiovascular events leading to hospitalization after *Streptococcus pneumoniae* infection: A retrospective cohort LIFE study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059713.R2
Article Type:	Original research
Date Submitted by the Author:	07-Oct-2022
Complete List of Authors:	Nishimura, Naoaki; Kyushu University School of Medicine, Fukuda, Haruhisa; Kyushu University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Health services research, Infectious diseases, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY

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7 2 **Risk of cardiovascular events leading to hospitalization after *Streptococcus pneumoniae***
8 3 **infection: A retrospective cohort LIFE study**
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3 16 **Abstract**

4 17 **Objectives:** To elucidate the risk of cardiovascular event occurrence following *Streptococcus*
5 18 *pneumoniae* infection.

6 19 **Design:** Retrospective cohort study using a LIFE Study database.

7 20 **Setting:** Three municipalities in Japan.

8 21 **Participants:** Municipality residents who were enrolled in either National Health Insurance
9 22 or the Latter-Stage Elderly Healthcare System from April 2014 to March 2020.

10 23 **Exposure:** Occurrence of *S. pneumoniae* infection.

11 24 **Primary Outcome Measures:** Occurrence of one of the following cardiovascular events that
12 25 led to hospitalization after *S. pneumoniae* infection: (1) coronary heart disease (CHD), (2)
13 26 heart failure (HF), (3) stroke, or (4) atrial fibrillation (AF).

14 27 **Results:** *S. pneumoniae*-infected patients were matched with non-infected patients for each
15 28 cardiovascular event. We matched 209 infected patients and 43,499 non-infected patients for
16 29 CHD, 179 infected patients and 44,148 non-infected patients for HF, 221 infected patients and
17 30 44,768 non-infected patients for stroke, and 241 infected patients and 39,568 non-infected
18 31 patients for AF. During follow-up, the incidence rates for the matched infected and non-
19 32 infected patients were, respectively, 38.6 (95% confidence interval: 19.9-67.3) and 30.4 (29.1-
20 33 31.8) per 1000 person-years for CHD; 69.6 (41.9-108.8) and 50.5 (48.9-52.2) per 1000
21 34 person-years for HF; 75.4 (48.3-112.2) and 35.5 (34.1-36.9) per 1000 person-years for stroke;
22 35 and 34.7 (17.9-60.6) and 11.2 (10.4-12.0) per 1000 person-years for AF. Infected patients
23 36 were significantly more likely to develop stroke (adjusted hazard ratio: 2.05, 95% confidence
24 37 interval: 1.22–3.47; adjusted subdistribution hazard ratio: 1.94, 95% confidence interval: 1.15-
25 38 3.26) and AF (3.29, 1.49-7.26; 2.74, 1.24-6.05) than their non-infected counterparts.

26 39 **Conclusions:** *S. pneumoniae* infections elevate the risk of subsequent stroke and AF
27 40 occurrence. These findings indicate that pneumococcal infections not only have short-term
28 41 effects on patients' health, but also increase their mid-to long-term susceptibility to serious
29 42 cardiovascular events.
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4 44 **Article Summary (Strengths and Limitations of this study)**

- 5 45 • This study comparatively examined both *Streptococcus pneumoniae*-infected patients and non-
6 46 infected controls to elucidate the association between pneumococcal infections and subsequent
7 47 cardiovascular events.
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9 48 • While prior studies mostly focused on short-term outcomes, our study period spanned from April 2014
10 49 to March 2020 to examine the mid-to long-term risks of cardiovascular events following
11 50 pneumococcal infection.
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13 51 • Despite a relatively large study sample and long study period, *S. pneumoniae* infections and
14 52 cardiovascular events were identified using only diagnosis codes in the claims data.
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16 53 • Our study did not account for patients' lifestyle factors (e.g., tobacco and alcohol consumption),
17 54 socioeconomic factors, or pneumococcal vaccination statuses.
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56 Introduction

57 Community-acquired pneumonia is a major infectious disease that frequently leads to
58 hospitalization, and exhibits high morbidity and mortality rates across numerous countries [1,
59 2]. *Streptococcus pneumoniae* is the causal pathogen for a large proportion of pneumonia
60 cases that require hospital-based care [3]. As older persons are more susceptible to
61 pneumococcal pneumonia [4], this condition represents a particularly serious public health
62 problem in countries with aging populations. In addition to its acute effects, pneumonia is also
63 known to increase the mid-to long-term health risks of infected patients, thereby placing a
64 heavy clinical and economic burden on patients and society [2, 5].

65 Previous cohort studies have reported that pneumonia is associated with an increased
66 risk of the following conditions: overall cardiac events [6-14], acute coronary syndrome [6, 8,
67 9, 11, 12, 14-17], heart failure (HF) [6, 9-14, 16, 18], atrial fibrillation (AF) [6, 8-14, 16, 17,
68 19, 20], and stroke [11, 12, 17]. However, the majority of these studies focused on pneumonia
69 patients without comparisons with non-infected controls, and generally used relatively short
70 follow-up periods. Furthermore, only a few studies in the existing literature have explored the
71 effects of pneumonia on subsequent cardiovascular disease [7, 18, 21].

72 In order to accurately evaluate the impact of *S. pneumoniae* infection on subsequent
73 cardiovascular disease, there is a need for long-term cohort studies that compare infected
74 patients with matched non-infected controls. This study aimed to elucidate the risk of
75 cardiovascular event occurrence following *S. pneumoniae* infection using administrative
76 claims data acquired from infected and non-infected patients in 3 Japanese municipalities. The
77 study also examined if these risks differ among age groups.

79 Methods

80 Study data

81 Data were provided by the Longevity Improvement & Fair Evidence (LIFE) Study, which is
82 managed by Kyushu University (Fukuoka, Japan) [22]. In the LIFE Study, participating
83 municipalities voluntarily provide administrative claims data for research purposes. These
84 claims data are acquired from the municipalities' residents who are enrolled in either National
85 Health Insurance or the Latter-Stage Elderly Healthcare System, and encompass information
86 on patient characteristics and reimbursement claims for all insurance-covered healthcare
87 provided in the inpatient and outpatient settings. Enrollees in National Health Insurance
88 include the self-employed, agricultural and fishery workers, part-time workers, retirees, and
89 their dependents. Enrollees in the Latter-Stage Elderly Healthcare System include residents
90 aged ≥ 75 years. The number of municipalities participating in the LIFE Study varies over
91 time owing to differences in agreement contracts, with the earliest participant providing data
92 from April 2014. The majority of the participating municipalities provide data from April

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3 93 2015 onward. As of 2021, the LIFE Study is able to conduct longitudinal studies with 5-year
4 94 follow-up periods.

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6 95 For this study, claims data from April 2014 to March 2020 were acquired from
7
8 96 insurance enrollees who were residing in 3 municipalities (residential populations: 58,000,
9 97 121,600, and 305,200) in Fukuoka Prefecture. The claims datasets contained records of
10 98 diagnoses (Japanese diagnosis codes and International Classification of Diseases, 10th
11 99 revision [ICD-10] codes), dates of treatments and admissions, and coexisting conditions. For
12
13 100 the coexisting conditions, we analyzed the list of comorbidities included in the Charlson
14 101 comorbidity index using ICD-10 codes recorded in both inpatient and outpatient claims.
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17 18 19 103 *Study subjects*

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21 104 First, patients with *S. pneumoniae* infections were identified through combinations of ICD-10
22 105 codes and/or Japanese diagnosis codes developed by the Ministry of Health, Labour and
23 106 Welfare. We used the combinations of codes proposed by Imai et al. [23]. In this study, we
24 107 considered all types of *S. pneumoniae* infections, including invasive pneumococcal diseases.
25 108 The occurrence of subsequent cardiovascular events leading to hospitalization (coronary heart
26 109 disease [CHD], HF, stroke, and AF) was identified using ICD-10 codes. We excluded patients
27 110 with records of previous in-hospital cardiovascular events from their earliest recorded dates
28 111 within the observation period until *S. pneumoniae* infection, patients with records of
29 112 cardiovascular events during the index hospitalization for *S. pneumoniae* infection, and
30 113 patients without any claims data ≥ 12 months before *S. pneumoniae* infection.
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33 114 Next, we set each infected patient's index date as the last day of the month containing
34 115 a recorded *S. pneumoniae* infection. The infected patients were then exactly matched with a
35 116 cohort of non-infected patients according to age (within 5 years), sex, comorbidities, and
36 117 hospitalization at the index date using sampling without replacement. The comorbidities
37 118 included the following conditions: myocardial infarction, congestive HF, peripheral vascular
38 119 disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease,
39 120 peptic ulcer disease, liver disease, diabetes with/without chronic complications, hemiplegia or
40 121 paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS [24]. When examining the
41 122 occurrence of AF after *S. pneumoniae* infection, we also included the comorbidity of AF as a
42 123 matching criterion. Infected patients who could not be matched with non-infected patients
43 124 were excluded. The index date for each non-infected patient was set as the same date as
44 125 his/her matched infected case. Each patient's comorbidities were identified using claims data
45 126 for 30 days before the index date. We also excluded non-infected patients who had
46 127 experienced cardiovascular events that led to hospitalization before their index dates.
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129 *Outcome measure*

130 The outcome measure was the occurrence of a cardiovascular event that led to hospitalization
131 after the *S. pneumoniae* infection date. Among inpatients, the infection date was set as the
132 first date of admission for the in-hospital treatment of an *S. pneumoniae* infection. Among
133 outpatients, the infection date was set as the first date of any medical treatment with a
134 diagnosis code indicating an *S. pneumoniae* infection. We focused on the first infection
135 episode for patients who had multiple infection episodes during the observation period.

136 Next, we examined the subsequent occurrence of each of the following 4
137 cardiovascular events that led to hospitalization: (1) CHD (ICD-10 codes: I20-25), (2) HF
138 (I50), (3) stroke (I61-63, 65-66), and (4) AF (I48). The occurrence date of each cardiovascular
139 event was set as the date of admission for the in-hospital treatment of that event.

140 Patients who had died during the observation period without developing any
141 cardiovascular event were followed-up until the last date of medical treatments in the claims
142 data. Patients who had died during the observation period after developing a cardiovascular
143 event were followed-up until the date of the cardiovascular event occurrence. All survivors
144 were followed-up until the end of their municipality's observation period. The ends of the
145 observation periods ranged from September 2019 to March 2020 among the municipalities.
146 **Figure 1** shows an overview of the follow-up process.

148 *Statistical analysis*

149 Our analysis was designed to examine the possible effects of *S. pneumoniae* infection on the
150 subsequent occurrence of cardiovascular events, and to determine if these effects differed
151 among age groups. For each of the 4 target cardiovascular events, we calculated the number
152 of events for the infected group and non-infected group during the observation period, and
153 estimated the incidence rates per 1000 person-years. Cox proportional hazards models were
154 constructed to estimate the hazard ratio (HRs) and 95% confidence interval (CIs) of each
155 cardiovascular event in the infected group relative to the non-infected group. Subdistribution
156 HRs were also estimated with Cox proportional hazards models using the Fine–Gray
157 competing risk approach in which death was regarded as a competing event. The Kaplan–
158 Meier method was used to calculate the cumulative probability of cardiovascular event
159 occurrence in the 2 groups. In addition, we analyzed the patients stratified according to the
160 following age groups: 0–49 years, 50–64 years, and ≥ 65 years.

161 All statistical analyses were performed using R (version 4.1.0) and R Studio (version
162 1.4.1106) software. Two-tailed *P* values below 0.05 were considered statistically significant.

164 *Patient and public involvement*

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

167

168 **Results**

169 We first identified 698 *S. pneumoniae*-infected patients and 253,302 non-infected patients
170 between April 1, 2014 and March 31, 2020 (**Figure 2**). After applying the exclusion criteria,
171 489 eligible infected patients were included in the analysis. There were 22 invasive
172 pneumococcal disease cases (4.5%) and 467 non-invasive pneumococcal disease cases
173 (95.5%). Among the infected patients that could be successfully matched with non-infected
174 patients for each cardiovascular event, we identified 209 infected patients without prior CHD,
175 179 infected patients without prior HF, 221 infected patients without prior stroke, and 241
176 infected patients without prior AF. Using the various matching criteria, we matched 43,499,
177 44,148, 44,768, and 39,568 non-infected controls with the infected patients for CHD, HF,
178 stroke, and AF, respectively. The non-infected patients were followed-up from the first *S.*
179 *pneumoniae* infection date of their matched infected patients. **Table 1** shows the
180 characteristics and comorbidities of the infected and non-infected patients. The covariate
181 balance summaries before and after matching for the target cardiovascular events are
182 presented in **Supplementary Tables 1–4**.

183 **Table 2** summarizes the risk of each cardiovascular event after *S. pneumoniae*
184 infection. The observation periods of the matched infected and non-infected patients
185 (weighted by the proportion of the infected patients) were, respectively, 311 and 68,706
186 person-years for CHD; 273 and 74,999 person-years for HF; 318 and 70,454 person-years for
187 stroke; and 346 and 62,986 person-years for AF. The median observation periods of the
188 matched infected and non-infected patients were 823 days for CHD, 827 days for HF, 820
189 days for stroke, and 797 days for AF. During follow-up, the incidence rates for the infected
190 and non-infected patients were, respectively, 38.6 (95% CI: 19.9–67.3) and 30.4 (95% CI:
191 29.1–31.8) per 1000 person-years for CHD; 69.6 (41.9–108.8) and 50.5 (48.9–52.2) per 1000
192 person-years for HF; 75.4 (48.3–112.2) and 35.5 (34.1–36.9) per 1000 person-years for
193 stroke; and 34.7 (17.9–60.6) and 11.2 (10.4–12.0) per 1000 person-years for AF. The
194 unadjusted HRs for cardiovascular event occurrence in infected patients (relative to non-
195 infected patients) were 1.27 (95% CI: 0.72–2.24) for CHD, 1.38 (0.88–2.16) for HF, 2.12
196 (1.42–3.17) for stroke, and 3.11 (1.76–5.50) for AF. After adjusting for age, sex,
197 comorbidities, and coexisting AF (only for the outcome of AF), infected patients were
198 significantly more likely to develop stroke (adjusted HR: 2.05, 95% CI: 1.22–3.47) and AF
199 (adjusted HR: 3.29, 95% CI: 1.49–7.26) than their non-infected counterparts. When death was
200 regard as a competing event, the adjusted subdistribution HRs were 1.19 (95% CI: 0.63–2.26)

201 **Table 1. Characteristics and comorbidities of *Streptococcus pneumoniae*-infected and non-infected patients**

	CHD		HF		Stroke		AF	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
N	43,499	209	44,148	179	44,768	221	39,568	241
Cardiovascular event incidence	2,090 (4.8%)	12 (5.7%)	3,790 (8.6%)	19 (11%)	2,502 (5.6%)	24 (11%)	703 (1.8%)	12 (5.0%)
Age, mean (y)	77.0	77.1	75.4	75.6	77.5	77.7	77.5	77.7
Men	22,062 (51%)	106 (51%)	24,417 (55%)	99 (55%)	22,890 (51%)	113 (51%)	20,523 (52%)	125 (52%)
Women	21,437 (49%)	103 (49%)	19,731 (45%)	80 (45%)	21,878 (49%)	108 (49%)	19,045 (48%)	116 (48%)
Hospital admission	30,595 (70%)	147 (70%)	29,103 (66%)	118 (66%)	31,804 (71%)	157 (71%)	29,224 (74%)	178 (74%)
Myocardial infarction	0 (0%)	0 (0%)	247 (0.6%)	1 (0.6%)	203 (0.5%)	1 (0.5%)	164 (0.4%)	1 (0.4%)
Congestive heart failure	4,787 (11%)	23 (11%)	987 (2.2%)	4 (2.2%)	4,051 (9.0%)	20 (9.0%)	4,433 (11%)	27 (11%)
Peripheral vascular disease	1,249 (2.9%)	6 (2.9%)	1,233 (2.8%)	5 (2.8%)	1,418 (3.2%)	7 (3.2%)	1,149 (2.9%)	7 (2.9%)
Cerebrovascular disease	6,036 (14%)	29 (14%)	5,179 (12%)	21 (12%)	4,254 (9.5%)	21 (9.5%)	5,254 (13%)	32 (13%)
Dementia	6,244 (14%)	30 (14%)	4,933 (11%)	20 (11%)	5,267 (12%)	26 (12%)	4,761 (12%)	29 (12%)
Chronic pulmonary disease	12,488 (29%)	60 (29%)	14,305 (32%)	58 (32%)	12,762 (29%)	63 (29%)	11,000 (28%)	67 (28%)
Rheumatic disease	624 (1.4%)	3 (1.4%)	1,233 (2.8%)	5 (2.8%)	810 (1.8%)	4 (1.8%)	985 (2.5%)	6 (2.5%)
Peptic ulcer disease	2,914 (6.7%)	14 (6.7%)	3,453 (7.8%)	14 (7.8%)	2,633 (5.9%)	13 (5.9%)	2,134 (5.4%)	13 (5.4%)
Mild liver disease	6,868 (16%)	33 (16%)	7,399 (17%)	30 (17%)	6,685 (15%)	33 (15%)	4,925 (12%)	30 (12%)
Diabetes without chronic complications	624 (1.4%)	3 (1.4%)	493 (1.1%)	2 (1.1%)	405 (0.9%)	2 (0.9%)	328 (0.8%)	2 (0.8%)
Diabetes with chronic complications	1,249 (2.9%)	6 (2.9%)	1,726 (3.9%)	7 (3.9%)	1,215 (2.7%)	6 (2.7%)	1,149 (2.9%)	7 (2.9%)
Hemiplegia or paraplegia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal disease	416 (1.0%)	2 (1.0%)	493 (1.1%)	2 (1.1%)	810 (1.8%)	4 (1.8%)	657 (1.7%)	4 (1.7%)
Malignancy	3,538 (8.1%)	17 (8.1%)	4,686 (11%)	19 (11%)	4,051 (9.0%)	20 (9.0%)	3,284 (8.3%)	20 (8.3%)
Moderate or severe liver disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Metastatic solid tumor	833 (1.9%)	4 (1.9%)	987 (2.2%)	4 (2.2%)	608 (1.4%)	3 (1.4%)	657 (1.7%)	4 (1.7%)
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AF							328 (0.8%)	2 (0.8%)

202 Values are presented as number (percentage) unless stated otherwise. Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

203 **Table 2. Cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients**

	CHD		HF		Stroke		AF	
	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected
Overall								
N	43,499	209	44,148	179	44,768	221	39,568	241
Incidence, n (%)	2,090 (4.8%)	12 (5.7%)	3,790 (8.6%)	19 (11%)	2,502 (5.6%)	24 (11%)	703 (1.8%)	12 (5.0%)
Person-years of follow-up	68,706	311	74,999	273	70,454	318	62,986	346
Incidence rate per 1000 person-years (95% CI)	30.4 (29.1-31.8)	38.6 (19.9-67.3)	50.5 (48.9-52.2)	69.6 (41.9-108.8)	35.5 (34.1-36.9)	75.4 (48.3-112.2)	11.2 (10.4-12.0)	34.7 (17.9-60.6)
Unadjusted hazard ratio (95% CI)	-	1.27 (0.72-2.24)	-	1.38 (0.88-2.16)	-	2.12 (1.42-3.17)	-	3.11 (1.76-5.50)
Adjusted hazard ratio ^a (95% CI)	-	1.20 (0.60-2.39)	-	1.18 (0.58-2.37)	-	2.05 (1.22-3.47)	-	3.29 (1.49-7.26)
Adjusted subdistribution hazard ratio ^a (95% CI)	-	1.19 (0.63-2.26)	-	1.13 (0.60-2.13)	-	1.94 (1.15-3.26)	-	2.74 (1.24-6.05)
By age group								
N (%)								
0-49 years	1,958 (4.5%)	9 (4.3%)	2,304 (5.2%)	9 (5.0%)	1,895 (4.2%)	9 (4.1%)	1,533 (3.9%)	9 (3.7%)
50-64 years	3,963 (9.1%)	21 (10%)	4,080 (9.2%)	18 (10%)	3,620 (8.1%)	19 (8.6%)	3,305 (8.4%)	22 (9.1%)
≥65 years	37,578 (86%)	179 (86%)	37,765 (86%)	152 (85%)	39,253 (88%)	193 (87%)	34,730 (88%)	210 (87%)
Incidence rate per 1000 person-years (95% CI)								
0-49 years	8.0 (5.6-11.0)	0 (0-200.4)	15.0 (11.8-18.7)	0 (0-200.4)	3.0 (1.6-5.1)	0 (0-200.4)	1.2 (0.3-3.0)	0 (0-200.4)
50-64 years	5.4 (4.0-7.0)	21.8 (0.6-121.5)	29.4 (26.1-33.1)	24.3 (0.6-135.1)	35.1 (31.3-39.3)	69.7 (14.4-203.6)	6.2 (4.6-8.2)	21.4 (0.5-119.2)
≥65 years	36.7 (35.1-38.3)	44.5 (22.2-79.7)	57.1 (55.2-59.0)	84.4 (50.0-133.4)	38.0 (36.5-39.7)	81.8 (50.6-125.0)	12.6 (11.7-13.6)	39.2 (19.6-70.1)
Adjusted hazard ratio ^a (95% CI)								
0-49 years	-	0	-	0	-	0	-	0
50-64 years	-	4.06 (0.56-29.38)	-	0.82 (0.12-5.86)	-	1.98 (0.64-6.19)	-	3.47 (0.48-25.02)
≥65 years	-	1.21 (0.64-2.10)	-	1.48 (0.78-1.97)	-	2.15 (1.29-3.04)	-	3.11 (1.58-5.20)

^a Adjusted for age, sex, comorbidities, and coexisting AF (only for the outcome of AF).

Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; CI, confidence interval.

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3 206 for CHD, 1.13 (0.60–2.13) for HF, 1.94 (1.15–3.26) for stroke, and 2.74 (1.24–6.05) for AF.
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5 207 Infected patients were still significantly more likely to develop stroke and AF than their non-
6
7 208 infected counterparts.

8 209 In the age-stratified analysis, *S. pneumonia* infections were not significantly associated
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10 210 with a higher risk of the 4 cardiovascular events in patients aged 50–64 years. Among older
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12 211 patients aged ≥ 65 years, *S. pneumonia* infections were significantly associated with
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14 212 substantially higher risks of stroke and AF occurrence.

15 213 **Figure 3** presents the Kaplan–Meier curves of each cardiovascular event. When
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17 214 compared with non-infected patients, infected patients had a significantly higher risk of
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19 215 incident HF, stroke, and AF (all $P < 0.0001$); but not CHD ($P = 0.046$).

20 216 **Figure 4** presents the cumulative incidence curves for cardiovascular events where
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22 217 death was regarded as a competing event.

23 218 Discussion

24 219 Through an analysis of National Health Insurance and Latter-Stage Elderly Healthcare
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26 220 System enrollees residing in 3 Japanese municipalities, this study comparatively examined the
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28 221 incidence of cardiovascular events leading to hospitalization between *S. pneumoniae*-infected
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30 222 patients and non-infected patients. Our results showed that the experience of *S. pneumoniae*
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32 223 infection significantly elevates the risk of subsequent stroke and AF. *S. pneumoniae* infection
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34 224 increased the risk of these cardiovascular events among older patients aged ≥ 65 years. While
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36 225 *S. pneumonia* infections were not significantly associated with a higher risk of these
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38 226 cardiovascular events in patients aged 50–64 years, the ratios were relatively high and more
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40 227 studies should be conducted. These findings may help to identify at-risk targets for expanded
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42 228 pneumococcal vaccination programs.

43 229 Recent studies have shown that patients with community-acquired pneumonia have a
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45 230 higher frequency of cardiovascular events [8, 10, 11, 16, 18, 21, 25, 26]. Our estimated
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47 231 incidence of AF after *S. pneumoniae* infection was 5.0%. The incidence of arrhythmia (ICD-
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49 232 10 codes: I47-49) in this study was estimated to be 9.0%, which is slightly higher than that of
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51 233 a previous meta-analysis that estimated an overall incidence of 7.2% among inpatients with
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53 234 community-acquired pneumonia [25]. This discrepancy may be explained by the fact that the
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55 235 meta-analysis had only included studies with short-term outcomes.

56 236 In our analysis, the estimated incidence of stroke after *S. pneumoniae* infection was
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58 237 considerably higher than those found in previous studies [11,16]. Perry et al. reported a stroke
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60 238 incidence of 0.17% in 40,979 patients during 90 days of admission for pneumonia, whereas
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62 239 Violi et al. reported a stroke incidence of 1.0% in 1,182 patients hospitalized for community-
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64 240 acquired pneumonia during in-hospital follow-up (median length of hospital stay: 11 days).
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66 241 Accordingly, those 2 studies had focused on the short-term incidence of stroke. However, the
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68 242 risk of stroke increases with age, and longer follow-up periods after *S. pneumoniae* infection
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70 243 would therefore provide a more accurate depiction of its risks. Furthermore, Perry et al. used

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3 244 ICD-9 codes to identify stroke, whereas Violi et al. identified stroke cases through clinical
4 245 manifestations confirmed by computed tomography or magnetic resonance imaging [11,16].
5 246 Stroke diagnostic methods are generally reliant on imaging data, and many medical facilities
6 247 in Japan are equipped with on-site computed tomography and/or magnetic resonance imaging
7 248 scanners. This enables the accurate diagnosis of stroke, including cases of milder strokes,
8 249 throughout Japan.

12 250 Among the studies that reported a high frequency of subsequent cardiovascular events
13 251 in pneumonia patients, few have actually compared infected patients with non-infected
14 252 controls. Eurich et al. performed a long-term prospective cohort study of both inpatients and
15 253 outpatients with community-acquired pneumonia, and found that these infections substantially
16 254 increased the risk of HF across different age groups and disease severity [18]. During a
17 255 median follow-up period of 9.9 years, 11.9% of patients with pneumonia developed incident
18 256 HF compared with 7.4% of the non-infected controls; furthermore, 13.3% of patients with
19 257 pneumococcal bacteremia developed incident HF [18]. In contrast, 13.0% of our infected
20 258 patients developed incident HF compared with 12.0% of their non-infected counterparts, with
21 259 no significant difference between the groups. This discrepancy may be influenced by the fact
22 260 that Eurich et al. used a control group that only controlled for age (five-year age bands) and
23 261 sex, only investigated outpatients in emergency departments, and focused on severe
24 262 pneumonia infections. In contrast, our study included outpatients from all types of medical
25 263 institutions, and our control group comprised patients without any *S. pneumoniae* infection.
26 264 Our study also utilized a research design that differed from Eurich et al. [18], which only
27 265 matched for age and sex, and adjusted for the effects for coexisting conditions by including
28 266 them as covariates in analytical models. However, we matched infected patients and non-
29 267 infected controls not only by age and sex, but also by comorbidities.

39 268 To our knowledge, few studies have shown the long-term risks of subsequent stroke
40 269 and AF after *S. pneumoniae* infection (including non-hospitalized cases) relative to non-
41 270 infected controls. Severe cases of pneumonia require hospital-based care, especially among
42 271 older adults. Therefore, studies that focus on hospitalized pneumonia patients would overlook
43 272 the risks associated with less severe cases. For example, although patients aged ≤ 65 years
44 273 may have milder *S. pneumoniae* infections and a correspondingly lower risk of hospitalization
45 274 than older patients, these infections could still elevate the risk of subsequent cardiovascular
46 275 events in the younger age groups. As this study used insurance claims data that incorporated
47 276 both inpatient and outpatient data, we were able to identify the risk of cardiovascular events
48 277 after *S. pneumoniae* infection in patients regardless of whether they required hospitalization.
49 278 Moreover, our study excluded patients who had subsequent cardiovascular events during the
50 279 index hospital stay for *S. pneumoniae* infection. For patients who were admitted to hospital
51 280 due to *S. pneumoniae* infection, we only monitored for cardiovascular events that occurred
52 281 after discharge. Most studies have reported the short-term risks of cardiovascular events
53 282 during or after acute infections, and the long-term impact of pneumonia on subsequent

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3 283 cardiovascular disease occurrence is less clear. Therefore, our study provides new insight into
4 284 the mid-to long-term effects of milder *S. pneumoniae* infections treated in outpatient settings
5 285 as well as severe *S. pneumoniae* infections that require hospitalization.

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8 286 A previous study identified the major causative organisms of community-acquired
9 287 pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*,
10 288 *Chlamydia pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several
11 289 viral pathogens (including influenza A and B) [27]. *S. pneumoniae* reportedly reduces cardiac
12 290 contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [28]. Many
13 291 studies that seek to understand the pathogenesis of cardiovascular events following
14 292 pneumonia focus on infections caused by *S. pneumoniae* [29]. Several studies have proposed
15 293 that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-
16 294 inflammatory mechanisms that ultimately result in cardiac damage [30-33]. Furthermore, the
17 295 infection-mediated hyperactivation of platelets can create a pro-inflammatory and
18 296 prothrombotic environment that facilitates the occurrence of cardiovascular events and
19 297 cardiac damage [31]. Pneumonia and other infections can trigger fever, hypoxia, and
20 298 hemodynamic disturbance in patients, which are all risk factors of AF and its associated
21 299 cardiac damage [34]. In our analysis, *S. pneumoniae* infections were significantly associated
22 300 with higher risks of stroke and AF, but not CHD and HF. These differences may be due to the
23 301 presence of multiple mechanisms that differentially contribute to each type of cardiovascular
24 302 event. Further studies are needed to explore these differences in greater depth.

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33 303 The study limitations are as follows. First, *S. pneumoniae* infections and
34 304 cardiovascular events were identified using diagnosis codes and ICD-10 codes, respectively.
35 305 Therefore, our analysis may be vulnerable to coding errors. Second, our study could not
36 306 account for patients' lifestyle factors (e.g., tobacco and alcohol consumption), socioeconomic
37 307 factors, or pneumococcal vaccination statuses. In addition, we also could not account for
38 308 differences in medications and treatments (especially at discharge) among the patients. Third,
39 309 our study population was limited to enrollees of Japan's National Health Insurance and
40 310 Latter-Stage Elderly Healthcare System, and the findings may not be extrapolatable to those
41 311 enrolled in other insurance systems. Fourth, our study excluded patients with previous in-
42 312 hospital cardiovascular events. However, the real-world population of patients would include
43 313 those with such events. This approach could introduce selection bias and affect the
44 314 comparability of our findings with real-world scenarios. Fifth, we excluded infected patients
45 315 who were not matched with non-infected controls. With consideration to the relatively low
46 316 number of infected patients, the exclusion of these non-matched patients could potentially
47 317 reduce the power of our statistical analyses. Sixth, our study outcomes focused on
48 318 cardiovascular events that resulted in hospitalization, and did not consider events without in-
49 319 hospital care. Therefore, our study may overlook the impact of *S. pneumoniae* infection on
50 320 subsequent occurrences of mild cardiovascular disease. Seventh, previous outpatient
51 321 treatments were not included in the analysis, which could result in selection bias. Eighth, the

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3 322 index date for matching was set as the last day of the month with *S. pneumoniae* infection
4 323 instead of the claims date, which could result in lead-time bias. Finally, we did not consider
5 324 the random effects of hospitals or municipalities in our multivariate analyses. Patients treated
6 325 in the same hospital or municipality may be similar to one another. However, all the study
7 326 municipalities were located in the same prefecture, and there were no major differences in
8 327 characteristics at the regional or hospital level. Additionally, pneumonia is a common disease
9 328 that hospitals regularly treat, and it is unlikely that there would be a large bias at the hospital
10 329 level.
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331 *Conclusion*

332 *S. pneumoniae* infections elevate the risk of subsequent stroke and AF occurrence. These
333 findings indicate that pneumococcal infections do not only have short-term effects on patient
334 health, but also increase the mid-to long-term susceptibility to serious cardiovascular events.
335 With a greater understanding of *S. pneumoniae* infection's far-reaching impact, further studies
336 are needed to explore the possible benefits of expanding current pneumococcal vaccination
337 programs.
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339 **Contributorship statement** NN and HF designed the study. HF provided the data. NN analyzed the
340 data. NN prepared the first draft of the manuscript. HF made critical revisions to the manuscript. All
341 authors reviewed and approved the final draft.

342 **Competing interests** HF received an Investigator-Sponsored Research grant from Pfizer Japan Inc.

343 **Funding** The construction of the LIFE Study database was funded by a Grant-in-Aid for Scientific
344 Research by the Japan Society for the Promotion of Science (Grant No. JP20H00563). Data analysis
345 and publication were funded by an Investigator-Sponsored Research grant from Pfizer Japan Inc.

346 **Data sharing statement** The data used in this study were acquired under agreements with the
347 participating municipalities, which stipulate that the data can only be used by authorized research
348 institutions and cannot be shared with third parties.

349 **Ethics Approval**

350 The study was approved by the Kyushu University Institutional Review Board for Clinical Research
351 (Approval No. 2021-423).

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4 **Figure 1. Overview of the follow-up process for *Streptococcus pneumoniae*-infected and non-infected**
5 **patients**
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9 Endpoints refer to the occurrence of a target cardiovascular event.
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13 **Figure 2. Selection of *Streptococcus pneumoniae*-infected and non-infected patients for analysis**
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16 Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments. Abbreviations: CHD,
17 coronary heart disease; HF, heart failure; AF, atrial fibrillation.
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24 **Figure 3. Kaplan–Meier estimates for cardiovascular events in *Streptococcus pneumoniae*-infected and**
25 **non-infected patients**
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30 (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)
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36 **Figure 4. Cumulative incidence curves for cardiovascular events in *Streptococcus pneumoniae*-infected**
37 **and non-infected patients**
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42 (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)
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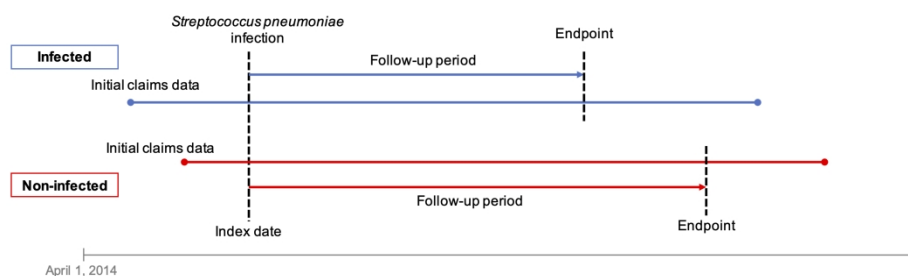
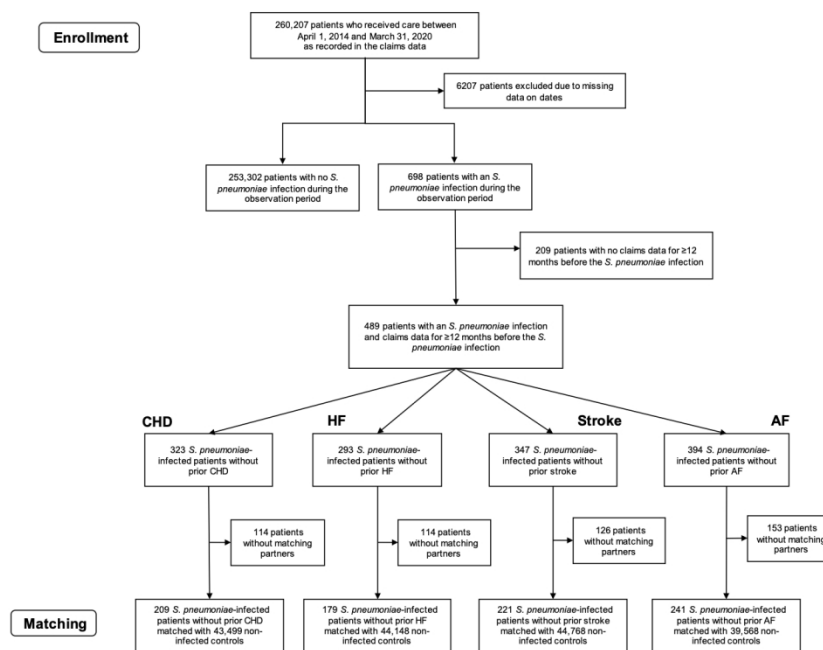


Figure 1. Overview of the follow-up process for Streptococcus pneumoniae-infected and non-infected patients

Legend: Endpoints refer to the occurrence of a target cardiovascular event.

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Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis
Legend: Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments.
Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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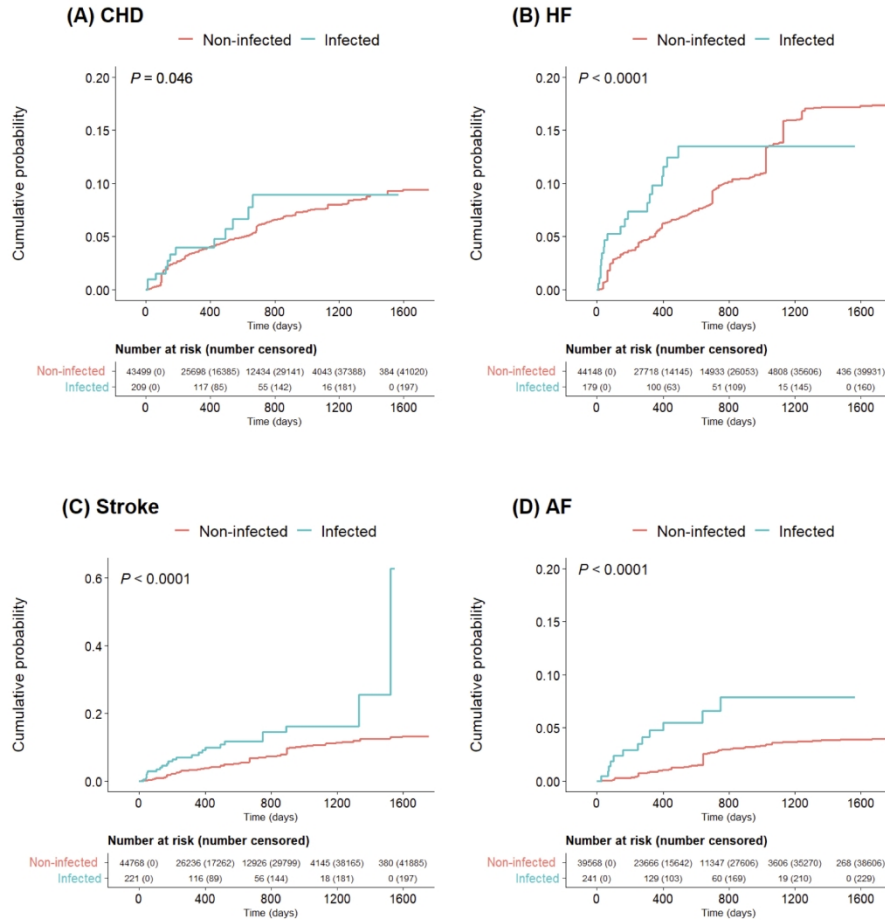


Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients

Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

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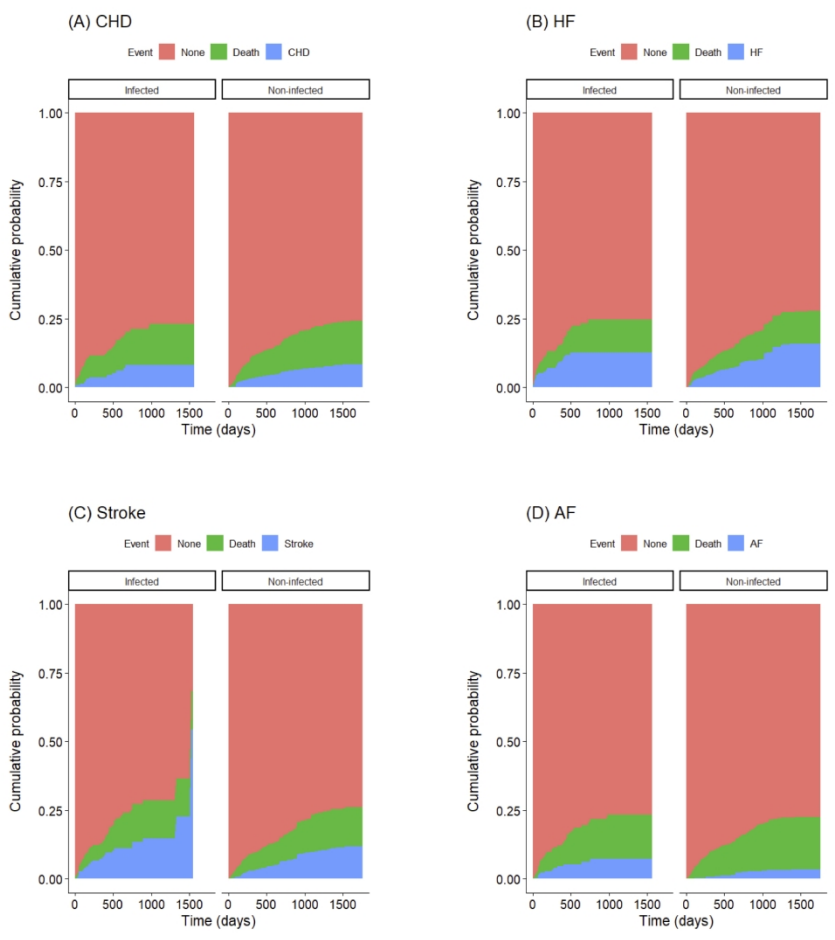


Figure 4. Cumulative incidence curves for cardiovascular events in *Streptococcus pneumoniae*-infected and non-infected patients
 Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

624x666mm (72 x 72 DPI)

Supplementary Table 1. Covariate balance before and after matching for coronary heart disease

	Coronary heart disease					
	Unmatched			Matched		
	Mean Infected	Non- infected	Standardized mean differences	Mean Infected	Non- infected	Standardized mean differences
Age	77.84	68.41	0.48	77.08	77.03	0.0043
Sex	0.48	0.60	0.25	0.49	0.49	0.00
Hospital admission	0.79	0.02	5.58	0.70	0.70	0.00
Myocardial infarction	0.01	0.01	0.02	0.00	0.00	0.00
Congestive heart failure	0.20	0.06	0.60	0.11	0.11	0.00
Peripheral vascular disease	0.08	0.05	0.14	0.03	0.03	0.00
Cerebrovascular disease	0.25	0.12	0.43	0.14	0.14	0.00
Dementia	0.21	0.05	0.68	0.14	0.14	0.00
Chronic pulmonary disease	0.37	0.10	0.89	0.29	0.29	0.00
Rheumatic disease	0.06	0.02	0.32	0.01	0.01	0.00
Peptic ulcer disease	0.13	0.04	0.40	0.07	0.07	0.00
Mild liver disease	0.20	0.12	0.25	0.16	0.16	0.00
Diabetes without chronic complications	0.06	0.01	0.68	0.01	0.01	0.00
Diabetes with chronic complications	0.05	0.03	0.12	0.03	0.03	0.00
Hemiplegia or paraplegia	0.02	0.01	0.19	0.00	0.00	0.00
Renal disease	0.07	0.03	0.26	0.01	0.01	0.00
Malignancy	0.15	0.05	0.42	0.08	0.08	0.00
Moderate or severe liver disease	0.00	0.00	0.05	0.00	0.00	0.00
Metastatic solid tumor	0.03	0.01	0.25	0.02	0.02	0.00
HIV/AIDS	0.00	0.00	0.01	0.00	0.00	0.00

Supplementary Table 2. Covariate balance before and after matching for heart failure

	Heart failure					
	Unmatched			Matched		
	Mean Infected	Non- infected	Standardized mean differences	Mean Infected	Non- infected	Standardized mean differences
Age	77.08	68.42	0.45	75.56	75.36	0.016
Sex	0.43	0.59	0.34	0.45	0.45	0.00
Hospital admission	0.78	0.02	5.40	0.66	0.66	0.00
Myocardial infarction	0.02	0.01	0.13	0.01	0.01	0.00
Congestive heart failure	0.10	0.05	0.22	0.02	0.02	0.00
Peripheral vascular disease	0.12	0.05	0.29	0.03	0.03	0.00
Cerebrovascular disease	0.25	0.12	0.42	0.12	0.12	0.00
Dementia	0.19	0.05	0.64	0.11	0.11	0.00
Chronic pulmonary disease	0.39	0.10	0.95	0.32	0.32	0.00
Rheumatic disease	0.06	0.02	0.31	0.03	0.03	0.00
Peptic ulcer disease	0.15	0.05	0.51	0.08	0.08	0.00
Mild liver disease	0.23	0.12	0.33	0.17	0.17	0.00
Diabetes without chronic complications	0.06	0.01	0.65	0.01	0.01	0.00
Diabetes with chronic complications	0.06	0.03	0.18	0.04	0.04	0.00
Hemiplegia or paraplegia	0.02	0.01	0.18	0.00	0.00	0.00
Renal disease	0.08	0.03	0.33	0.01	0.01	0.00
Malignancy	0.18	0.05	0.54	0.11	0.11	0.00
Moderate or severe liver disease	0.01	0.00	0.09	0.00	0.00	0.00
Metastatic solid tumor	0.02	0.01	0.11	0.02	0.02	0.00
HIV/AIDS	0.00	0.00	0.01	0.00	0.00	0.00

Supplementary Table 3. Covariate balance before and after matching for stroke

	Stroke					
	Unmatched			Matched		
	Mean Infected	Non- infected	Standardized mean differences	Mean Infected	Non- infected	Standardized mean differences
Age	78.20	68.57	0.50	77.66	77.53	0.011
Sex	0.46	0.60	0.29	0.49	0.49	0.00
Hospital admission	0.80	0.02	5.41	0.71	0.71	0.00
Myocardial infarction	0.03	0.01	0.11	0.00	0.00	0.00
Congestive heart failure	0.20	0.07	0.52	0.09	0.09	0.00
Peripheral vascular disease	0.11	0.05	0.24	0.03	0.03	0.00
Cerebrovascular disease	0.20	0.10	0.31	0.10	0.10	0.00
Dementia	0.17	0.05	0.53	0.12	0.12	0.00
Chronic pulmonary disease	0.37	0.11	0.88	0.29	0.29	0.00
Rheumatic disease	0.05	0.02	0.28	0.02	0.02	0.00
Peptic ulcer disease	0.11	0.05	0.31	0.06	0.06	0.00
Mild liver disease	0.19	0.12	0.21	0.15	0.15	0.00
Diabetes without chronic complications	0.04	0.01	0.42	0.01	0.01	0.00
Diabetes with chronic complications	0.05	0.03	0.16	0.03	0.03	0.00
Hemiplegia or paraplegia	0.02	0.01	0.18	0.00	0.00	0.00
Renal disease	0.10	0.03	0.39	0.02	0.02	0.00
Malignancy	0.15	0.06	0.41	0.09	0.09	0.00
Moderate or severe liver disease	0.00	0.00	0.05	0.00	0.00	0.00
Metastatic solid tumor	0.01	0.01	0.07	0.01	0.01	0.00
HIV/AIDS	0.00	0.00	0.01	0.00	0.00	0.00

Supplementary Table 4. Covariate balance before and after matching for atrial fibrillation

	Atrial fibrillation					
	Unmatched			Matched		
	Mean Non- infected	Mean Infected	Standardized mean differences	Mean Non- infected	Mean Infected	Standardized mean differences
Age	78.70	68.92	0.51	77.67	77.52	0.012
Sex	0.45	0.60	0.29	0.48	0.48	0.00
Hospital admission	0.83	0.02	5.42	0.74	0.74	0.00
Myocardial infarction	0.02	0.01	0.09	0.00	0.00	0.00
Congestive heart failure	0.20	0.07	0.52	0.11	0.11	0.00
Peripheral vascular disease	0.10	0.05	0.21	0.03	0.03	0.00
Cerebrovascular disease	0.26	0.12	0.42	0.13	0.13	0.00
Dementia	0.19	0.06	0.55	0.12	0.12	0.00
Chronic pulmonary disease	0.38	0.11	0.90	0.28	0.28	0.00
Rheumatic disease	0.06	0.02	0.32	0.02	0.02	0.00
Peptic ulcer disease	0.12	0.05	0.36	0.05	0.05	0.00
Mild liver disease	0.18	0.12	0.18	0.12	0.12	0.00
Diabetes without chronic complications	0.05	0.01	0.53	0.01	0.01	0.00
Diabetes with chronic complications	0.06	0.03	0.19	0.03	0.03	0.00
Hemiplegia or paraplegia	0.02	0.01	0.16	0.00	0.00	0.00
Renal disease	0.10	0.03	0.41	0.02	0.02	0.00
Malignancy	0.17	0.06	0.50	0.08	0.08	0.00
Moderate or severe liver disease	0.01	0.00	0.05	0.00	0.00	0.00
Metastatic solid tumor	0.02	0.01	0.17	0.02	0.02	0.00
HIV/AIDS	0.00	0.00	0.01	0.00	0.00	0.00
Atrial fibrillation	0.03	0.03	0.02	0.01	0.01	0.00