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

Naoaki Nishimura[1)], Haruhisa Fukuda[2)*]

[1)] Kyushu University School of Medicine, Fukuoka, Kyushu, Japan
[2)] Kyushu University Graduate School of Medical Sciences, Fukuoka, Kyushu, Japan

*** Corresponding Author:**
Haruhisa Fukuda, MPH, PhD
Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences
3-1-1 Maidashi Higashi-ku Fukuoka 812-8582, Japan
Phone: +81-92-642-6956 Fax: +81-92-642-6961
Email address: h_fukuda@hcam.med.kyushu-u.ac.jp

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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

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

For this study, claims data from April 2014 to March 2020 were acquired from insurance enrollees who were residing in 3 municipalities (residential populations: 58,000, 121,600, and 305,200) in Fukuoka Prefecture.

Study subjects

First, patients with *S. pneumoniae* infections were identified through diagnosis codes developed by Japan's Ministry of Health, Labour and Welfare. The identification method was based on the approach described by Imai et al. [22]. The occurrence of subsequent cardiovascular events (coronary heart disease [CHD], HF, arrhythmia, and stroke) was identified using International Classification of Diseases, 10th revision (ICD-10) codes. We excluded patients with records of cardiovascular events before *S. pneumoniae* infection, patients with records of cardiovascular events during the index hospitalization for *S. pneumoniae* infection, and patients without any claims data ≥12 months before *S. pneumoniae* infection.

Next, we set each infected patient's index date as the last day of the month containing a recorded *S. pneumoniae* infection. The infected patients were then matched with a cohort of non-infected patients according to age (within 5 years), sex, and Charlson Comorbidity Index score at the index date using sampling without replacement. Charlson Comorbidity Index scores were calculated based on the following conditions: myocardial infarction, congestive HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with/without chronic complications, hemiplegia or paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS. The index date for each non-infected patient was set as the same date as his/her matched infected case. We excluded non-infected patients who had experienced cardiovascular events before their index dates.

Outcome measure

The outcome measure was the occurrence of a cardiovascular event that led to hospitalization after the *S. pneumoniae* infection date. Among inpatients, the infection date was set as the first date of admission for the in-hospital treatment of an *S. pneumoniae* infection. Among outpatients, the infection date was set as the first date of any medical treatment with a diagnosis code indicating an *S. pneumoniae* infection.

Next, we examined the subsequent occurrence of each of the following 4 cardiovascular events that led to hospitalization: (1) CHD (ICD-10 codes: I20-25), (2) HF

(I11, I50), (3) stroke (I60-69), and (4) arrhythmia (I47-49). The occurrence date of each cardiovascular event was set as the date of admission for the in-hospital treatment of that event.

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

Statistical analysis

Our analysis was designed to examine the possible effects of *S. pneumoniae* infection on the subsequent occurrence of cardiovascular events, and to determine if these effects differed among age groups. For each of the 4 target cardiovascular events, we calculated the number of events for the infected group and non-infected group during the observation period, and estimated the incidence rates per 1000 person-years. Cox proportional hazards models were constructed to estimate the hazard ratio (HRs) and 95% confidence interval (CIs) of each cardiovascular event in the infected group relative to the non-infected group. The Kaplan–Meier method was used to calculate the cumulative probability of cardiovascular event occurrence in the 2 groups. In addition, we analyzed the patients stratified according to the following age groups: 0–49 years, 50–64 years, and ≥65 years.

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

Ethical considerations

The study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 2019-406).

Patient and public involvement

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

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. pneumonia* 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. pneumonia* 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

patients. Our results showed that the experience of *S. pneumoniae* infection significantly elevates the risk of subsequent stroke and arrhythmia. Among patients aged 50–64 years, *S. pneumoniae* infection was associated with an increased risk of stroke. Furthermore, *S. pneumoniae* infection increased the risk of all 4 cardiovascular events among older patients aged ≥65 years. These findings may help to identify at-risk targets for expanded pneumococcal vaccination programs.

Recent studies have shown that patients with community-acquired pneumonia have a higher frequency of cardiovascular events [8, 10, 11, 16, 18, 21, 24, 25]. Our estimated incidence of arrhythmia after *S. pneumoniae* infection (9.0%) was slightly higher than that of a previous meta-analysis, which estimated an overall incidence of 7.2% among inpatients with community-acquired pneumonia [24]. This discrepancy may be explained by the fact that the meta-analysis had only included studies with short-term outcomes.

In our analysis, the estimated incidence of stroke after *S. pneumoniae* infection was considerably higher than those found in previous studies [11,16]. Perry et al. reported a stroke incidence of 0.17% in 40,979 patients during 90 days of admission for pneumonia, whereas Violi et al. reported a stroke incidence of 1.0% in 1,182 patients hospitalized for community-acquired pneumonia during in-hospital follow-up (median length of hospital stay: 11 days). Accordingly, those 2 studies had focused on the short-term incidence of stroke. However, the risk of stroke increases with age, and longer follow-up periods after *S. pneumoniae* infection would therefore provide a more accurate depiction of its risks. Furthermore, Perry et al. used ICD-9 codes to identify stroke, whereas Violi et al. identified stroke cases through clinical manifestations confirmed by computed tomography or magnetic resonance imaging [11,16]. Stroke diagnostic methods are generally reliant on imaging data, and many medical facilities in Japan are equipped with on-site computed tomography and/or magnetic resonance imaging scanners. This enables the accurate diagnosis of stroke, including cases of milder strokes, throughout Japan.

Among the studies that reported a high frequency of subsequent cardiovascular events in pneumonia patients, few have actually compared infected patients with non-infected controls. Eurich et al. performed a long-term prospective cohort study of both inpatients and outpatients with community-acquired pneumonia, and found that these infections substantially increased the risk of HF across different age groups and disease severity [18]. During a median follow-up period of 9.9 years, 11.9% of patients with pneumonia developed incident HF compared with 7.4% of the non-infected controls; furthermore, 13.3% of patients with pneumococcal bacteremia developed incident HF [18]. In contrast, 13.0% of our infected patients developed incident HF compared with 12.0% of their non-infected counterparts, with no significant difference between the groups. This discrepancy may be influenced by the fact that Eurich et al. used a control group that only controlled for age (five-year age bands) and sex, only investigated outpatients in emergency departments, and focused on severe pneumonia infections. In contrast, our study included outpatients from all types of medical

institutions, and our control group comprised patients without any *S. pneumoniae* infection. Our study also utilized a research design that differed from Eurich et al. [18], which only matched for age and sex, and adjusted for the effects for coexisting conditions by including them as covariates in analytical models. However, we matched infected patients and non-infected controls not only by age and sex, but also by coexisting conditions through Charlson Comorbidity Index scores.

To our knowledge, few studies have shown the long-term risks of subsequent arrhythmia and stroke after *S. pneumoniae* infection (including non-hospitalized cases) relative to non-infected controls. Severe cases of pneumonia require hospital-based care, especially among older adults. Therefore, studies that focus on hospitalized pneumonia patients would overlook the risks associated with less severe cases. For example, although patients aged ≤65 years may have milder *S. pneumoniae* infections and a correspondingly lower risk of hospitalization than older patients, these infections could still elevate the risk of subsequent cardiovascular events in the younger age groups. As this study used insurance claims data that incorporated both inpatient and outpatient data, we were able to identify the risk of cardiovascular events after *S. pneumoniae* infection in patients regardless of whether they required hospitalization. Moreover, our study excluded patients who had subsequent cardiovascular events during the index hospital stay for *S. pneumoniae* infection. For patients who were admitted to hospital due to *S. pneumoniae* infection, we only monitored for cardiovascular events that occurred after discharge. Most studies have reported the short-term risks of cardiovascular events during or after acute infections, and the long-term impact of pneumonia on subsequent cardiovascular disease occurrence is less clear. Therefore, our study provides new insight into the mid-to long-term effects of milder *S. pneumoniae* infections treated in outpatient settings as well as severe *S. pneumoniae* infections that require hospitalization.

A previous study identified the major causative organisms of community-acquired pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several viral pathogens (including influenza A and B) [26]. *S. pneumoniae* reportedly reduces cardiac contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [27]. Many studies that seek to understand the pathogenesis of cardiovascular events following pneumonia focus on infections caused by *S. pneumoniae* [28]. Several studies have proposed that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-inflammatory mechanisms that ultimately result in cardiac damage [29-32]. Furthermore, the infection-mediated hyperactivation of platelets can create a pro-inflammatory and prothrombotic environment that facilitates the occurrence of cardiovascular events and cardiac damage [30]. Pneumonia and other infections can trigger fever, hypoxia, and hemodynamic disturbance in patients, which are all risk factors of atrial fibrillation and its associated cardiac damage [33].

The study limitations are as follows. First, *S. pneumoniae* infections and cardiovascular events were identified using diagnosis codes and ICD-10 codes, respectively. Therefore, our analysis may be vulnerable to coding errors. Second, our study could not account for patients' lifestyle factors (e.g., tobacco and alcohol consumption), socioeconomic factors, or pneumococcal vaccination statuses. Third, our study population was limited to enrollees of Japan's National Health Insurance and Latter-Stage Elderly Healthcare System, and the findings may not be extrapolatable to those enrolled in other insurance systems.

Conclusion

S. pneumoniae infections elevate the risk of subsequent stroke and arrhythmia occurrence. These findings indicate that pneumococcal infections do not only have short-term effects on patient health, but also increase the mid-to long-term susceptibility to serious cardiovascular events. With a greater understanding of *S. pneumoniae* infection's far-reaching impact, further studies are needed to explore the possible benefits of expanding current pneumococcal 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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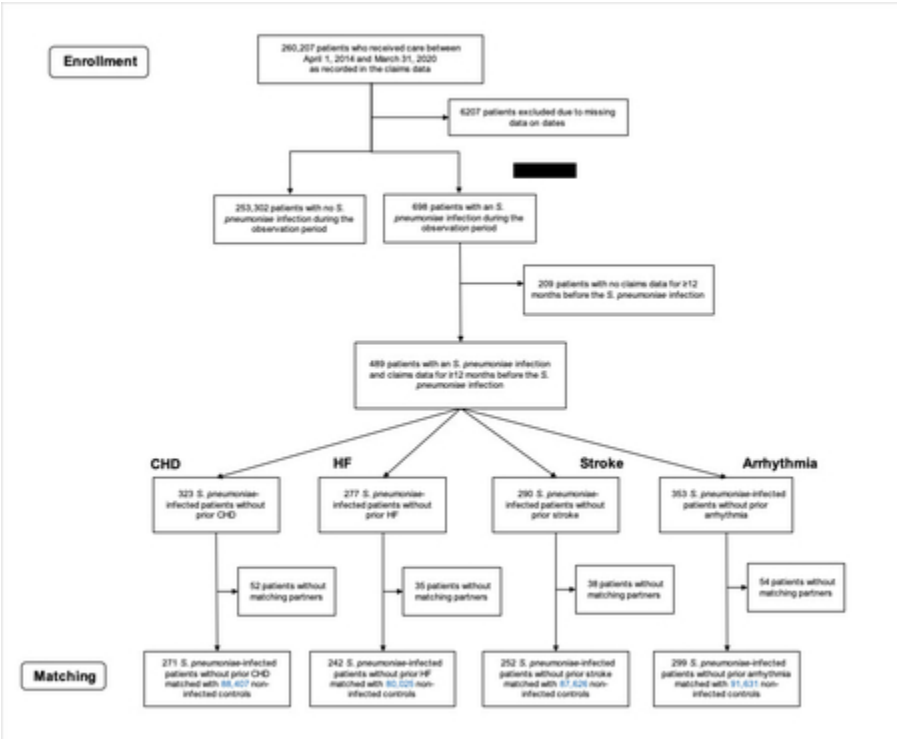

Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis. Abbreviations: CHD, coronary heart disease; HF, heart failure.

37x31mm (300 x 300 DPI)

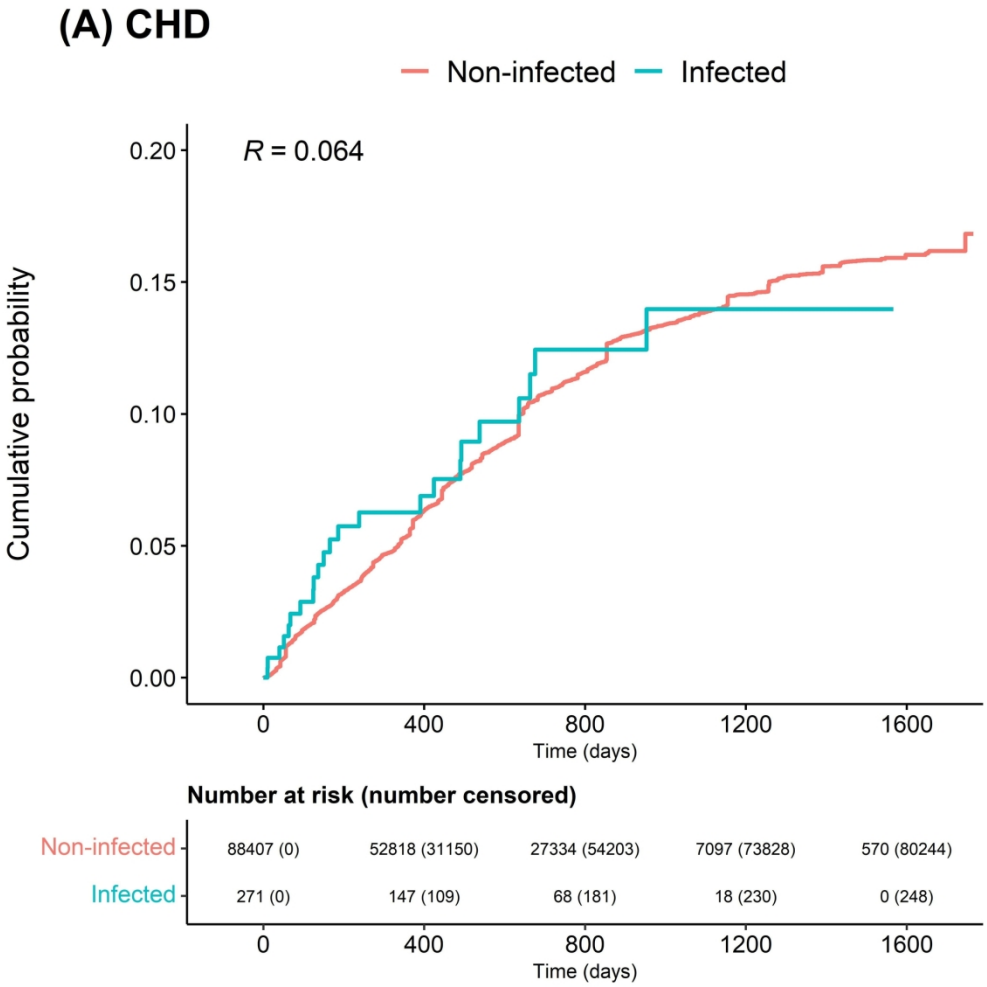

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
(A) Coronary heart disease (CHD)

177x177mm (300 x 300 DPI)

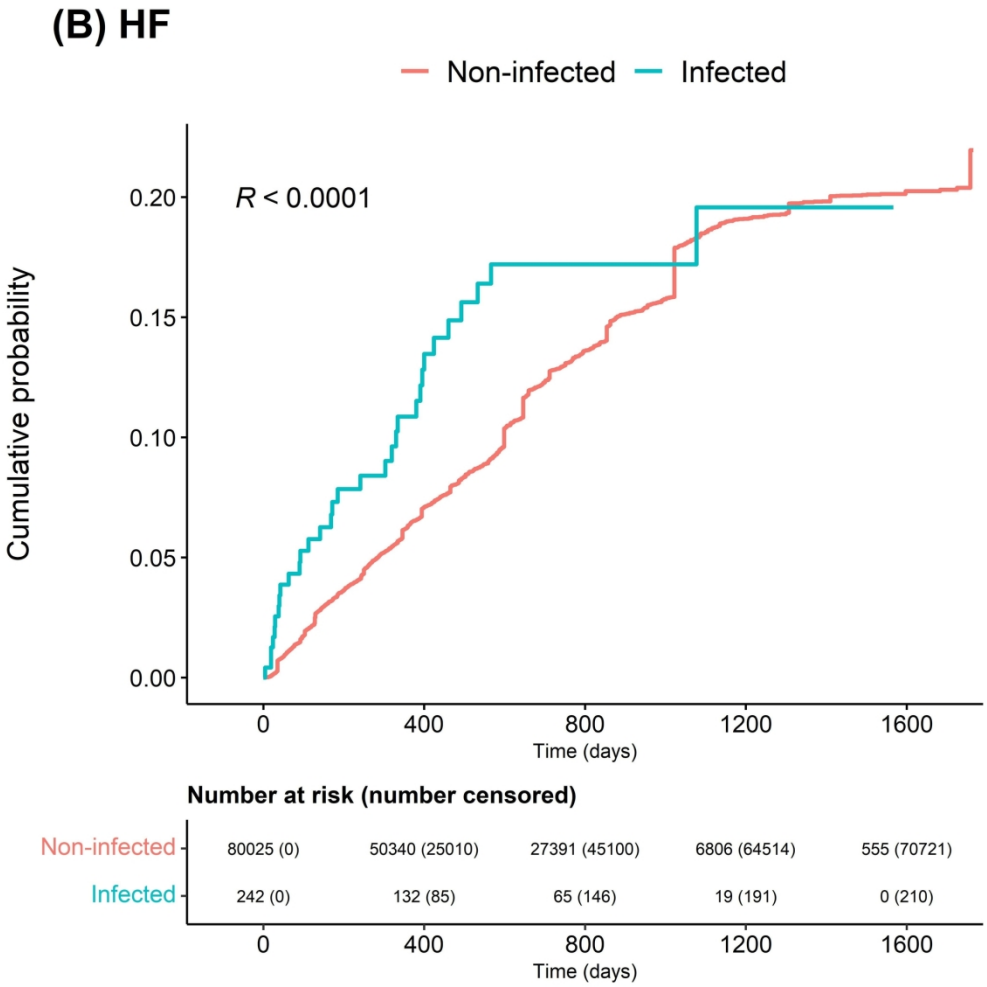

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
(B) heart failure (HF)

177x177mm (300 x 300 DPI)

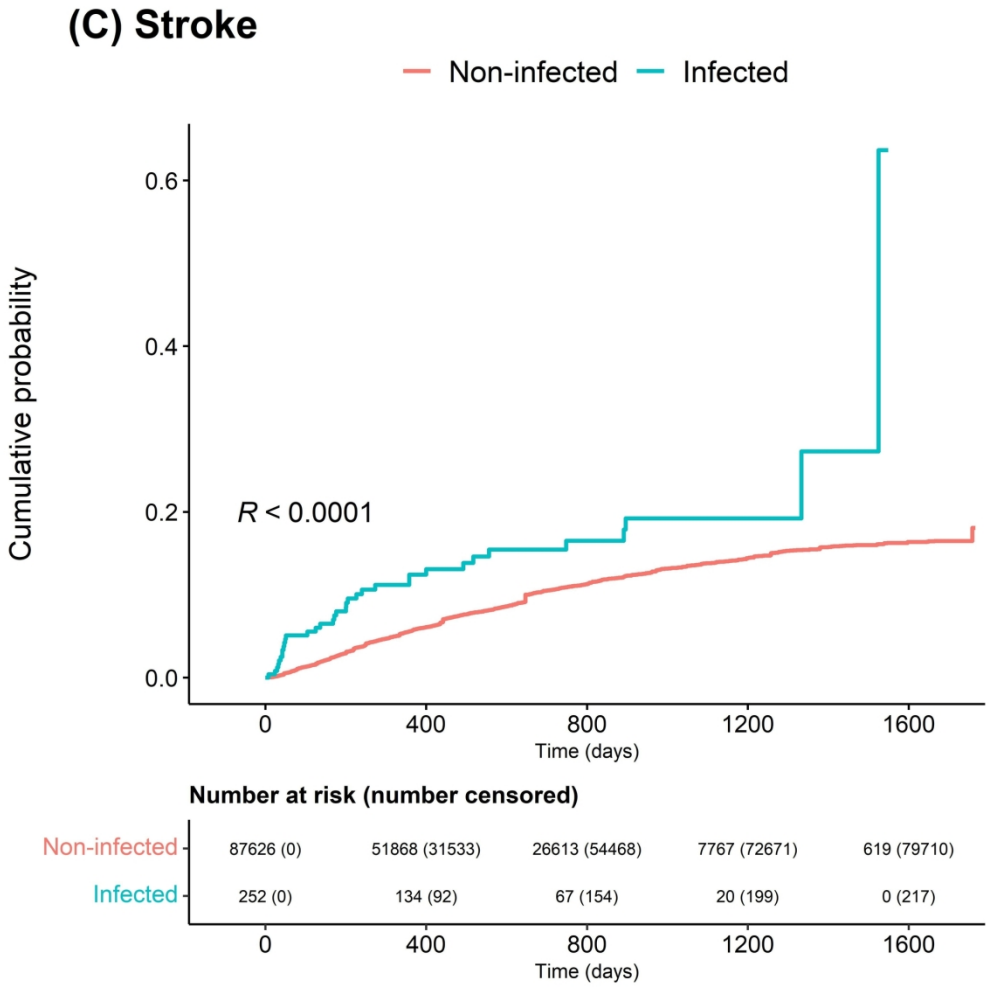

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
(C) stroke

177x177mm (300 x 300 DPI)

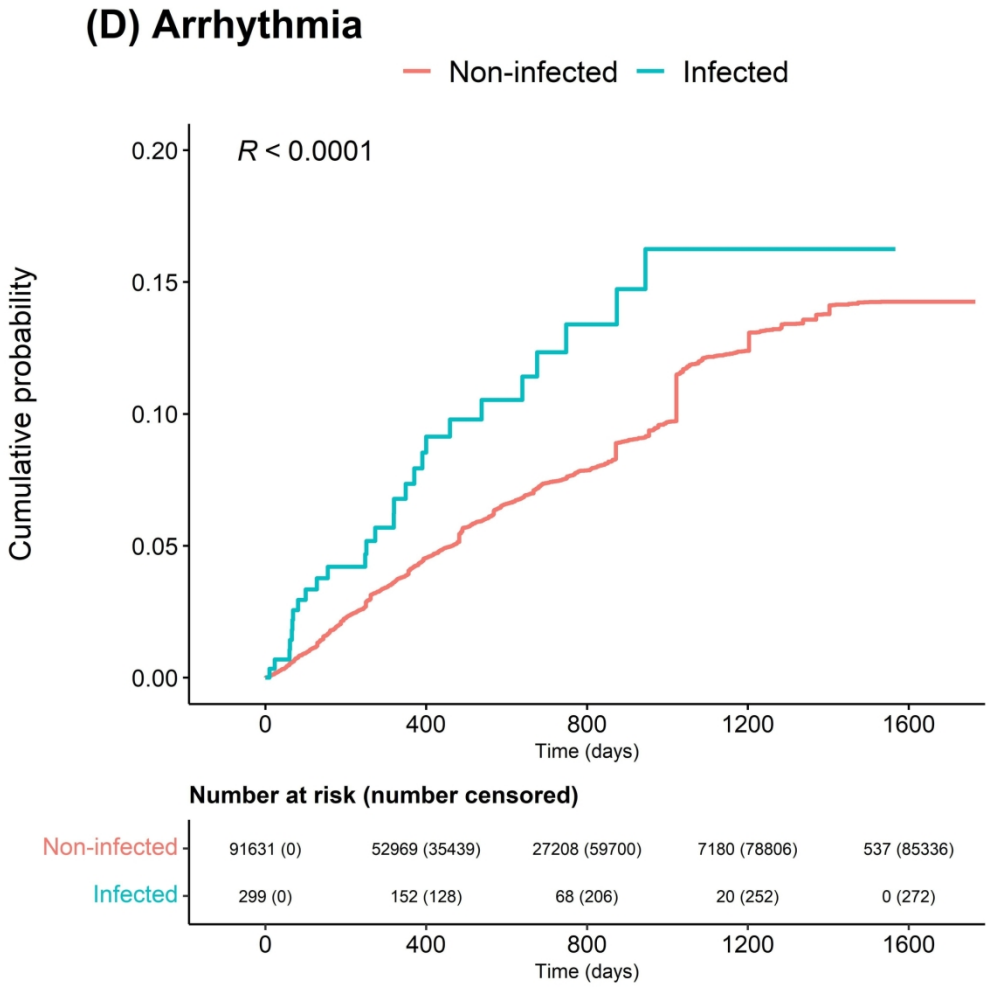

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
(D) arrhythmia

177x177mm (300 x 300 DPI)

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

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

Naoaki Nishimura[1)], Haruhisa Fukuda[2)*]

[1)] Kyushu University School of Medicine, Fukuoka, Kyushu, Japan
[2)] Kyushu University Graduate School of Medical Sciences, Fukuoka, Kyushu, Japan

*** Corresponding Author:**
Haruhisa Fukuda, MPH, PhD
Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences
3-1-1 Maidashi Higashi-ku Fukuoka 812-8582, Japan
Phone: +81-92-642-6956 Fax: +81-92-642-6961
Email address: fukuda.haruhisa.977@m.kyushu-u.ac.jp

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) atrial fibrillation (AF).

Results: *S. pneumoniae*-infected patients were matched with non-infected patients for each cardiovascular event. We matched 209 infected patients and 43,499 non-infected patients for CHD, 179 infected patients and 44,148 non-infected patients for HF, 221 infected patients and 44,768 non-infected patients for stroke, and 241 infected patients and 39,568 non-infected patients for AF. During follow-up, the incidence rates for the matched infected and non-infected patients were, respectively, 38.6 (95% confidence interval: 19.9–67.3) and 30.4 (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 person-years for HF; 75.4 (48.3–112.2) and 35.5 (34.1–36.9) per 1000 person-years for stroke; and 34.7 (17.9–60.6) and 11.2 (10.4–12.0) per 1000 person-years for AF. Infected patients were significantly more likely to develop stroke (adjusted hazard ratio: 2.05, 95% confidence interval:1.22–3.47; adjusted subdistribution hazard ratio: 1.94, 95% confidence interval: 1.15–3.26) and AF (3.29, 1.49–7.26; 2.74, 1.24-6.05) than their non-infected counterparts.

Conclusions: *S. pneumoniae* infections elevate the risk of subsequent stroke and AF 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.

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], atrial fibrillation (AF) [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) [22]. 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 2015 onward. As of 2021, the LIFE Study is able to conduct longitudinal studies with 5-year follow-up periods.

For this study, claims data from April 2014 to March 2020 were acquired from insurance enrollees who were residing in 3 municipalities (residential populations: 58,000, 121,600, and 305,200) in Fukuoka Prefecture. The claims datasets contained records of diagnoses (Japanese diagnosis codes and International Classification of Diseases, 10th revision [ICD-10] codes), dates of treatments and admissions, and coexisting conditions (Charlson Comorbidity Index scores). Charlson Comorbidity Index scores were generated from ICD-10 codes recorded in both inpatient and outpatient claims.

Study subjects

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

Next, we set each infected patient's index date as the last day of the month containing a recorded *S. pneumoniae* infection. The infected patients were then matched with a cohort of non-infected patients according to age (within 5 years), sex, Charlson Comorbidity Index score, and hospitalization at the index date using sampling without replacement. Using the method proposed by Quan et al. [24], Charlson Comorbidity Index scores were calculated based on the following conditions: myocardial infarction, congestive HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with/without chronic complications, hemiplegia or paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS. When examining the occurrence of AF after *S. pneumoniae* infection, we included the comorbidity of AF as a matching criterion. Infected patients who could not be matched with non-infected patients were excluded. The index date for each non-infected patient was set as the same date as his/her matched infected case. Each patient's Charlson Comorbidity Index score was calculated using claims data for 30 days before the index date. We also excluded non-infected

patients who had experienced cardiovascular events that led to hospitalization before their index dates.

Outcome measure

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

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

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

Statistical analysis

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

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

Patient and public involvement

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

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. There were 22 invasive pneumococcal disease cases (4.5%) and 467 non-invasive pneumococcal disease cases (95.5%). Among the infected patients that could be successfully matched with non-infected patients for each cardiovascular event, we identified 209 infected patients without prior CHD, 179 infected patients without prior HF, 221 infected patients without prior stroke, and 241 infected patients without prior AF. Using the various matching criteria, we matched 43,499, 44,148, 44,768, and 39,568 non-infected controls with the infected patients for CHD, HF, stroke, and AF, 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 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%)

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

Table 2 summarizes the risk of each cardiovascular event after *S. pneumoniae* infection. The observation periods of the matched infected and non-infected patients (weighted by the proportion of the infected patients) were, respectively, 311 and 68,706 person-years for CHD; 273 and 74,999 person-years for HF; 318 and 70,454 person-years for stroke; and 346 and 62,986 person-years for AF. The median observation periods of the matched infected and non-infected patients were 823 days for CHD, 827 days for HF, 820 days for stroke, and 797 days for AF. During follow-up, the incidence rates for the infected and non-infected patients were, respectively, 38.6 (95% CI: 19.9–67.3) and 30.4 (95% CI: 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 person-years for HF; 75.4 (48.3–112.2) and 35.5 (34.1–36.9) per 1000 person-years for stroke; and 34.7 (17.9–60.6) and 11.2 (10.4–12.0) per 1000 person-years for AF. The unadjusted HRs for cardiovascular event occurrence in infected patients (relative to non-infected patients) were 1.27 (95% CI: 0.72–2.24) for CHD, 1.38 (0.88–2.16) for HF, 2.12 (1.42–3.17) for stroke, and 3.11 (1.76–5.50) for AF. After adjusting for age, sex, Charlson Comorbidity Index score, and coexisting AF (only for the outcome of AF), infected patients were significantly more likely to develop stroke (adjusted HR: 2.05, 95% CI:1.22–3.47) and AF (adjusted HR: 3.29, 95% CI: 1.49–7.26) than their non-infected counterparts. When death was regard as a competing event, infected patients were still significantly more likely to develop stroke (adjusted subdistribution HR: 1.94, 95% CI: 1.15–3.26) and AF (2.74, 1.24–6.05) than their non-infected counterparts.

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, Charlson Comorbidity Index score, and coexisting AF (only for the outcome of AF).
Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; CI, confidence interval

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

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 AF (all $P < 0.0001$); but not CHD ($P = 0.046$).

Figure 4 presents the cumulative incidence curves for cardiovascular events where death was regarded as a competing event.

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 patients. Our results showed that the experience of *S. pneumoniae* infection significantly elevates the risk of subsequent stroke and AF. *S. pneumoniae* infection increased the risk of these cardiovascular events among older patients aged ≥65 years. While *S. pneumonia* infections were not significantly associated with a higher risk of these cardiovascular events in patients aged 50–64 years, the ratios were relatively high and more studies should be conducted. These findings may help to identify at-risk targets for expanded pneumococcal vaccination programs.

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

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

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

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

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

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

A previous study identified the major causative organisms of community-acquired pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several viral pathogens (including influenza A and B) [27]. *S. pneumoniae* reportedly reduces cardiac contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [28]. Many studies that seek to understand the pathogenesis of cardiovascular events following pneumonia focus on infections caused by *S. pneumoniae* [29]. Several studies have proposed that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-inflammatory mechanisms that ultimately result in cardiac damage [30-33]. Furthermore, the infection-mediated hyperactivation of platelets can create a pro-inflammatory and prothrombotic environment that facilitates the occurrence of cardiovascular events and cardiac damage [31]. Pneumonia and other infections can trigger fever, hypoxia, and hemodynamic disturbance in patients, which are all risk factors of AF and its associated cardiac damage [34].

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

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

Conclusion

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

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.

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

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

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.

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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

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.

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) AF (Atrial fibrillation)

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

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

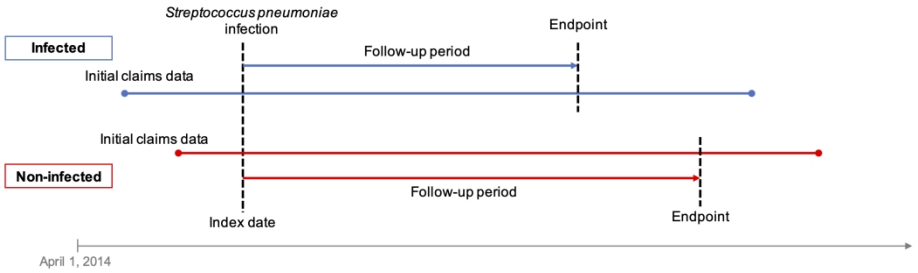

Figure 1. Overview of the follow-up process for Streptococcus pneumoniae-infected and non-infected patients.
Legend: Endpoints refer to the occurrence of a target cardiovascular event.

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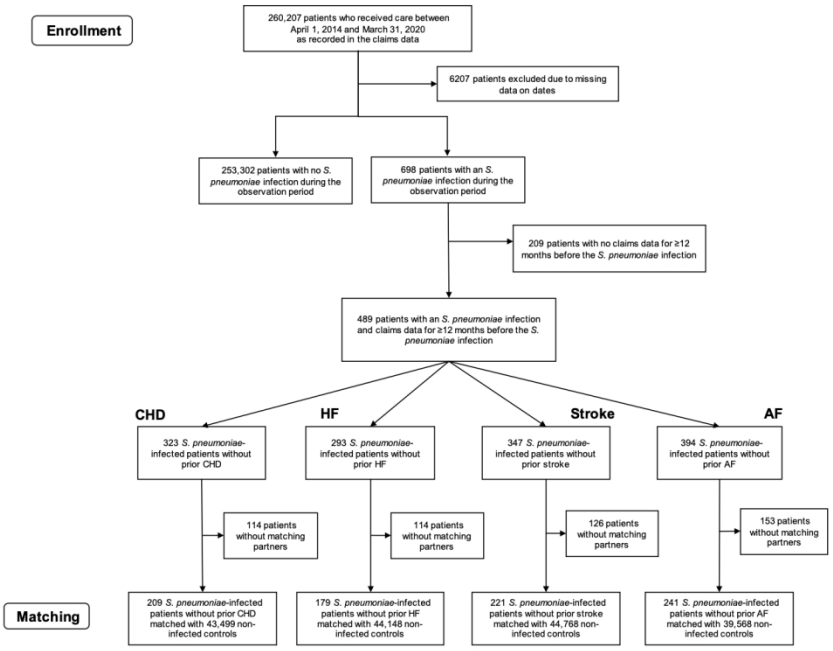

Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis
Legend: Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments.
Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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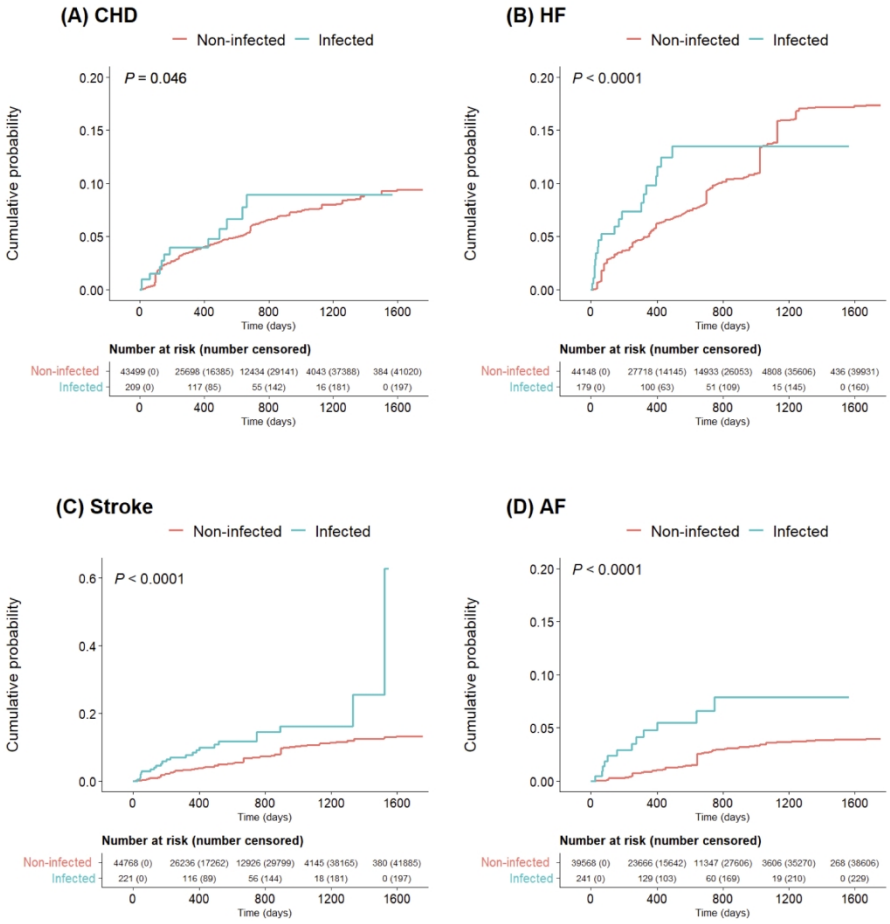

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients

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

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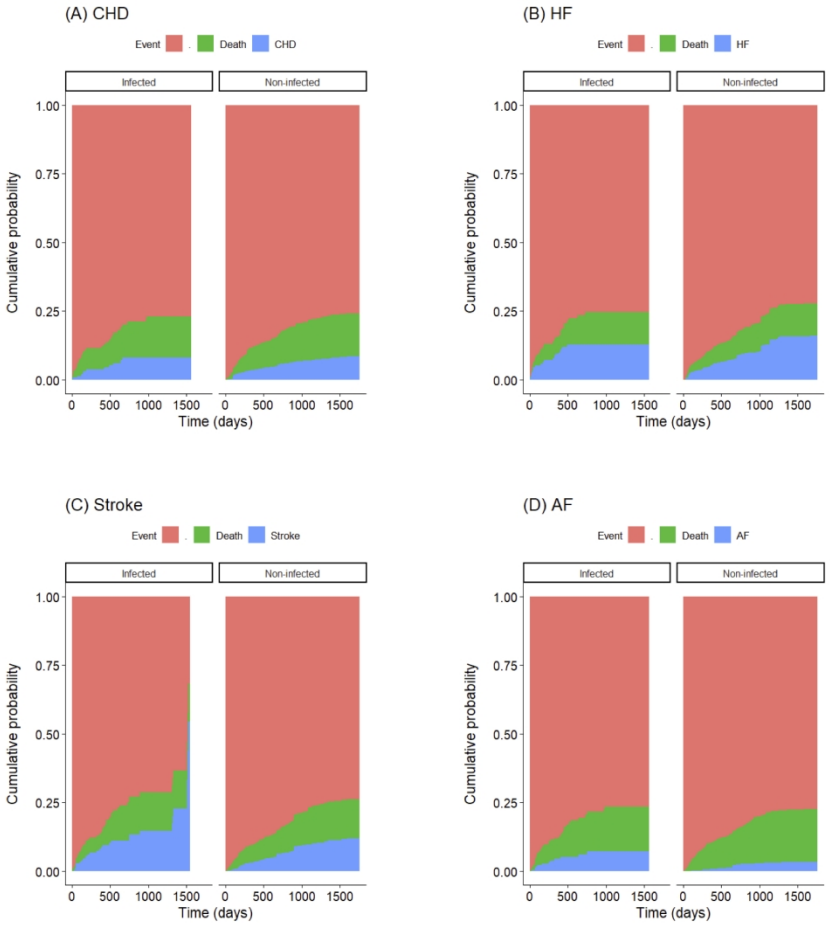

Caption : Figure 4. Cumulative incidence curves for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

624x666mm (72 x 72 DPI)

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

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

Naoaki Nishimura[1)], Haruhisa Fukuda[2)*]

[1)] Kyushu University School of Medicine, Fukuoka, Kyushu, Japan

[2)] Kyushu University Graduate School of Medical Sciences, Fukuoka, Kyushu, Japan

*** Corresponding Author:**

Haruhisa Fukuda, MPH, PhD

Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences

3-1-1 Maidashi Higashi-ku Fukuoka 812-8582, Japan

Phone: +81-92-642-6956 Fax: +81-92-642-6961

Email address: fukuda.haruhisa.977@m.kyushu-u.ac.jp

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) atrial fibrillation (AF).

Results: *S. pneumoniae*-infected patients were matched with non-infected patients for each cardiovascular event. We matched 209 infected patients and 43,499 non-infected patients for CHD, 179 infected patients and 44,148 non-infected patients for HF, 221 infected patients and 44,768 non-infected patients for stroke, and 241 infected patients and 39,568 non-infected patients for AF. During follow-up, the incidence rates for the matched infected and non-infected patients were, respectively, 38.6 (95% confidence interval: 19.9-67.3) and 30.4 (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 person-years for HF; 75.4 (48.3-112.2) and 35.5 (34.1-36.9) per 1000 person-years for stroke; and 34.7 (17.9-60.6) and 11.2 (10.4-12.0) per 1000 person-years for AF. Infected patients were significantly more likely to develop stroke (adjusted hazard ratio: 2.05, 95% confidence interval:1.22–3.47; adjusted subdistribution hazard ratio: 1.94, 95% confidence interval: 1.15-3.26) and AF (3.29, 1.49-7.26; 2.74, 1.24-6.05) than their non-infected counterparts.

Conclusions: *S. pneumoniae* infections elevate the risk of subsequent stroke and AF 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.

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], atrial fibrillation (AF) [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) [22]. 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

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

For this study, claims data from April 2014 to March 2020 were acquired from insurance enrollees who were residing in 3 municipalities (residential populations: 58,000, 121,600, and 305,200) in Fukuoka Prefecture. The claims datasets contained records of diagnoses (Japanese diagnosis codes and International Classification of Diseases, 10th revision [ICD-10] codes), dates of treatments and admissions, and coexisting conditions. For the coexisting conditions, we analyzed the list of comorbidities included in the Charlson comorbidity index using ICD-10 codes recorded in both inpatient and outpatient claims.

Study subjects

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

Next, we set each infected patient's index date as the last day of the month containing a recorded *S. pneumoniae* infection. The infected patients were then exactly matched with a cohort of non-infected patients according to age (within 5 years), sex, comorbidities, and hospitalization at the index date using sampling without replacement. The comorbidities included the following conditions: myocardial infarction, congestive HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes with/without chronic complications, hemiplegia or paraplegia, malignancy, metastatic solid tumor, and HIV/AIDS [24]. When examining the occurrence of AF after *S. pneumoniae* infection, we also included the comorbidity of AF as a matching criterion. Infected patients who could not be matched with non-infected patients were excluded. The index date for each non-infected patient was set as the same date as his/her matched infected case. Each patient's comorbidities were identified using claims data for 30 days before the index date. We also excluded non-infected patients who had experienced cardiovascular events that led to hospitalization before their index dates.

Outcome measure

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

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

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

Statistical analysis

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

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

Patient and public involvement

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

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. There were 22 invasive pneumococcal disease cases (4.5%) and 467 non-invasive pneumococcal disease cases (95.5%). Among the infected patients that could be successfully matched with non-infected patients for each cardiovascular event, we identified 209 infected patients without prior CHD, 179 infected patients without prior HF, 221 infected patients without prior stroke, and 241 infected patients without prior AF. Using the various matching criteria, we matched 43,499, 44,148, 44,768, and 39,568 non-infected controls with the infected patients for CHD, HF, stroke, and AF, 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. The covariate balance summaries before and after matching for the target cardiovascular events are presented in **Supplementary Tables 1–4**.

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

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%)

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

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.

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. Infected patients were still significantly more likely to develop stroke and AF than their non-infected counterparts.

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

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 AF (all $P < 0.0001$); but not CHD ($P = 0.046$).

Figure 4 presents the cumulative incidence curves for cardiovascular events where death was regarded as a competing event.

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 leading to hospitalization between *S. pneumoniae*-infected patients and non-infected patients. Our results showed that the experience of *S. pneumoniae* infection significantly elevates the risk of subsequent stroke and AF. *S. pneumoniae* infection increased the risk of these cardiovascular events among older patients aged ≥65 years. While *S. pneumonia* infections were not significantly associated with a higher risk of these cardiovascular events in patients aged 50–64 years, the ratios were relatively high and more studies should be conducted. These findings may help to identify at-risk targets for expanded pneumococcal vaccination programs.

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

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

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

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

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

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

A previous study identified the major causative organisms of community-acquired pneumonia to be *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, and several viral pathogens (including influenza A and B) [27]. *S. pneumoniae* reportedly reduces cardiac contractility by increasing cardiomyocyte uptake of bacterial cell wall antigens [28]. Many studies that seek to understand the pathogenesis of cardiovascular events following pneumonia focus on infections caused by *S. pneumoniae* [29]. Several studies have proposed that *S. pneumoniae* cell wall components and pneumolysin (a pore-forming toxin) trigger pro-inflammatory mechanisms that ultimately result in cardiac damage [30-33]. Furthermore, the infection-mediated hyperactivation of platelets can create a pro-inflammatory and prothrombotic environment that facilitates the occurrence of cardiovascular events and cardiac damage [31]. Pneumonia and other infections can trigger fever, hypoxia, and hemodynamic disturbance in patients, which are all risk factors of AF and its associated cardiac damage [34]. In our analysis, *S. pneumonia* infections were significantly associated with higher risks of stroke and AF, but not CHD and HF. These differences may be due to the presence of multiple mechanisms that differentially contribute to each type of cardiovascular event. Further studies are needed to explore these differences in greater depth.

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

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

Conclusion

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

Contributorship statament 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.

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

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Data sharing 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.

Ethics Approval

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

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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

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.

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) AF (Atrial fibrillation)

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

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

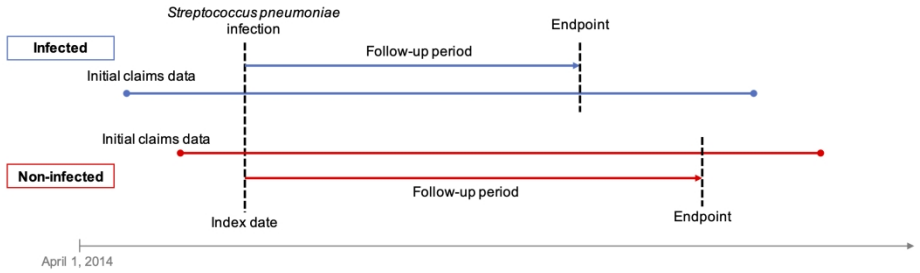

Figure 1. Overview of the follow-up process for Streptococcus pneumoniae-infected and non-infected patients
Legend: Endpoints refer to the occurrence of a target cardiovascular event.

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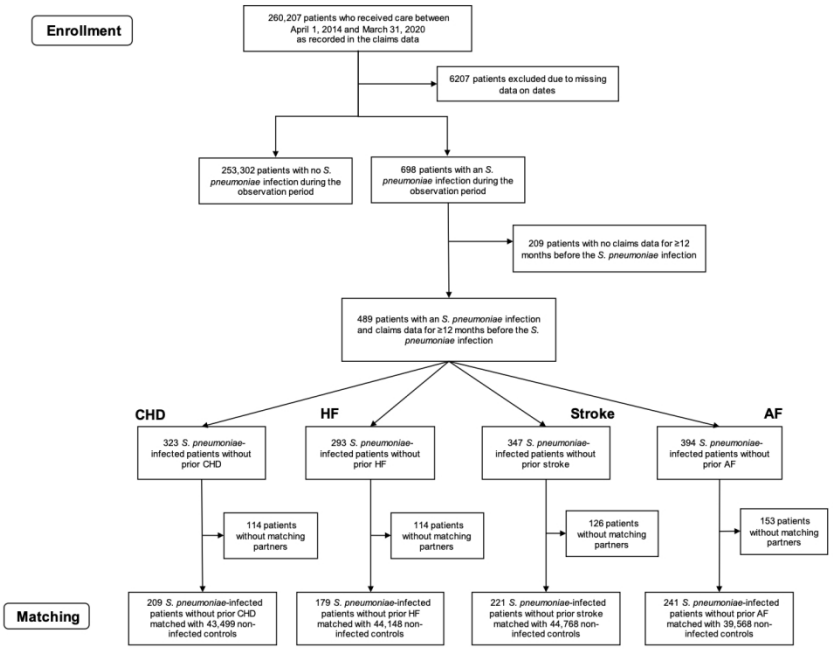

Figure 2. Selection of Streptococcus pneumoniae-infected and non-infected patients for analysis
Legend: Prior CHD, HF, stroke, and AF refer only to previous events with in-hospital treatments.
Abbreviations: CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation.

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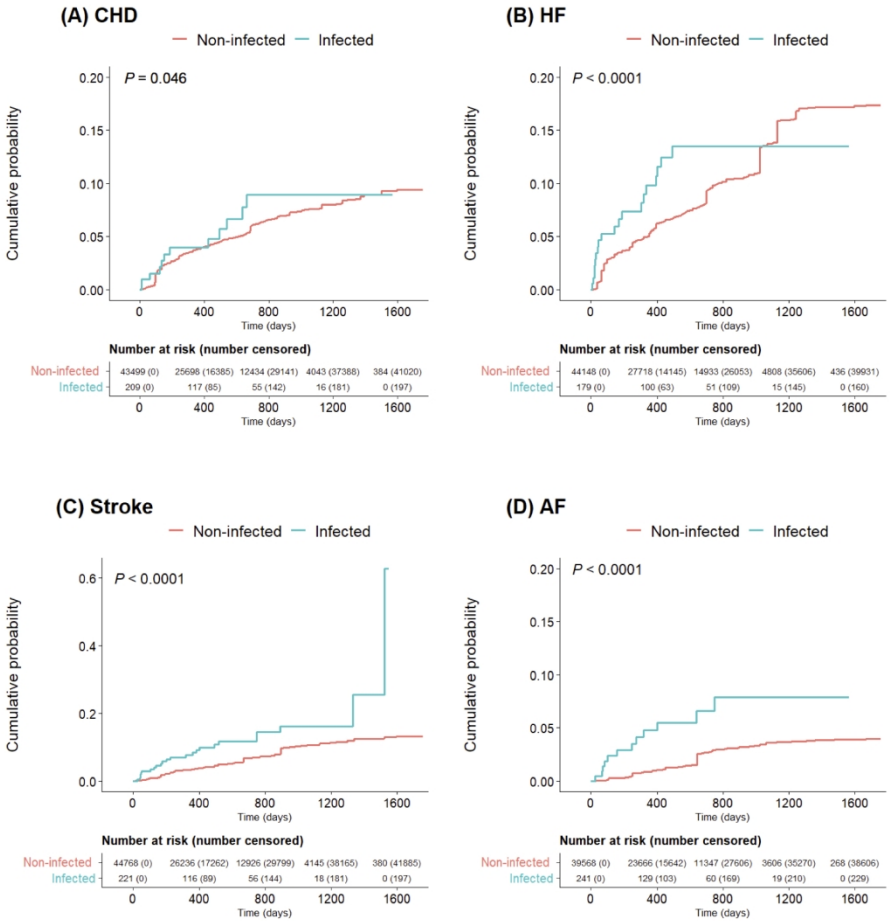

Figure 3. Kaplan–Meier estimates for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients

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

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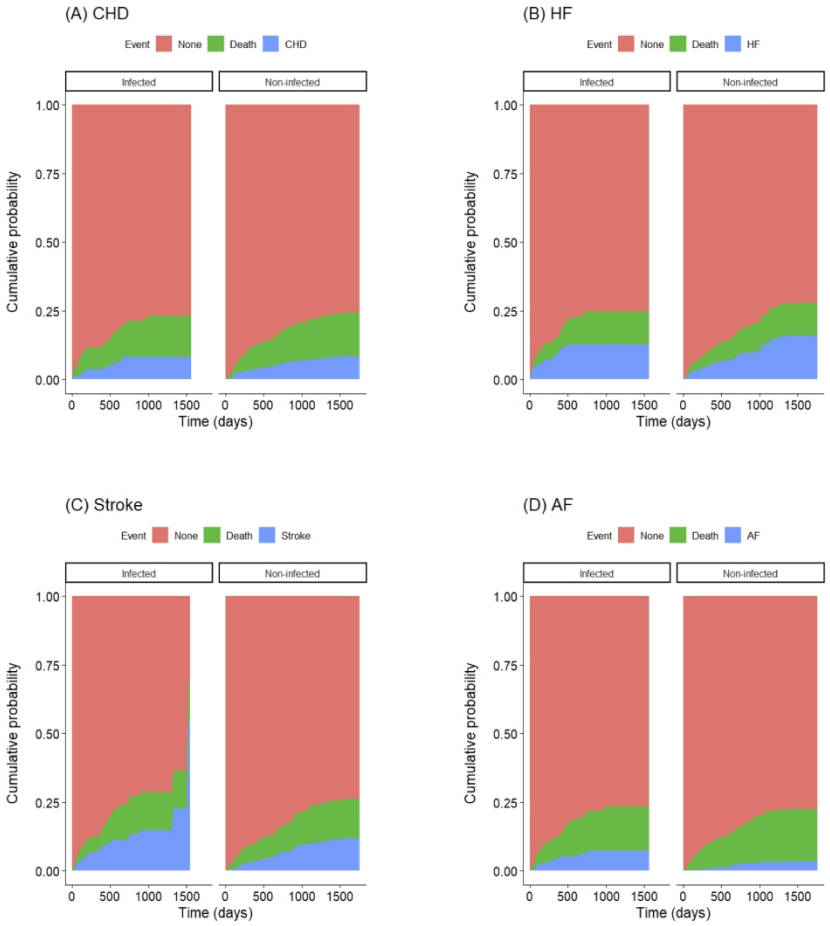

Figure 4. Cumulative incidence curves for cardiovascular events in Streptococcus pneumoniae-infected and non-infected patients
Legend: (A) Coronary heart disease (CHD), (B) heart failure (HF), (C) stroke, and (D) AF (Atrial fibrillation)

624x666mm (72 x 72 DPI)

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

	Coronary heart disease					
	Unmatched			Matched		
	Mean		Standardized mean differences	Mean		Standardized mean differences
	Infected	Non-infected		Infected	Non-infected	
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		Standardized mean differences	Mean		Standardized mean differences
	Infected	Non-infected		Infected	Non-infected	
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		Standardized mean differences	Mean		Standardized mean differences
	Infected	Non-infected		Infected	Non-infected	
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		Standardized mean differences	Mean		Standardized mean differences
	Non-infected	Infected		Non-infected	Infected	
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