

1 **Pneumonia hospitalizations and the subsequent risk of incident ischemic**
2 **cardiovascular disease in Chinese adults**

3

4 Yizhen Hu, MD¹, Canqing Yu, PhD^{1,2}, Yu Guo, MSc³, Zheng Bian, MSc³, Yuting Han, MD¹, Ling Yang, PhD^{4,5},
5 Yiping Chen, DPhil^{4,5}, Huaidong Du, PhD^{4,5}, Yuanjie Pang, DPhil¹, Dianjianyi Sun, PhD¹, Jianrong Jin, BA⁶,
6 Jun Zhang, BA⁷, Jingjia Wang, MD⁸, Chunli Shao, PhD⁸, Yi-Da Tang, PhD⁹, Junshi Chen, MD¹⁰, Zhengming
7 Chen, DPhil⁵, Jun Lv, PhD^{*1,2,11}, Liming Li, MPH^{1,2}, on behalf of the China Kadoorie Biobank Collaborative
8 Group[†]

9 1. Department of Epidemiology and Biostatistics, School of Public Health, Peking
10 University Health Science Center, Beijing, China

11 2. Peking University Center for Public Health and Epidemic Preparedness & Response,
12 Beijing, China

13 3. Chinese Academy of Medical Sciences, Beijing, China

14 4. Medical Research Council Population Health Research Unit at the University of Oxford,
15 Oxford, United Kingdom

16 5. Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department
17 of Population Health, University of Oxford, United Kingdom

18 6. Wuzhong District Center for Disease Control and Prevention, Jiangsu, China

19 7. Suzhou Center for Disease Control and Prevention, Jiangsu, China

20 8. Department of Cardiology, State Key Laboratory of Cardiovascular Disease, Fuwai
21 Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical
22 Sciences and Peking Union Medical College, Beijing, China

23 9. Department of Cardiology, Third Hospital, Peking University, Beijing, China

1 10. China National Center for Food Safety Risk Assessment, Beijing, China

2 11. Key Laboratory of Molecular Cardiovascular Sciences (Peking University), Ministry of
3 Education, Beijing, China

4 †The members of the steering committee and collaborative group are listed in the online-only supplemental
5 material.

6

7 ***Corresponding author:**

Jun Lv, MD, PhD

Department of Epidemiology and Biostatistics,

Peking University Health Science Center

38 Xueyuan Road, Beijing 100191, P. R. China

Fax number: 86-10-82801528

Phone: 86-10-82801528 ext.322

Email: lvjun@bjmu.edu.cn

8

9 **Running title:** Pneumonia and cardiovascular disease

10 **Word count:** Abstract 260, Main text 3543

11 (2 tables, 2 figures, and 5 supplementary tables/figure)

12

1 **Abstract**

2 **Background:** Acute respiratory infections have been associated with a transient increase in
3 cardiovascular risk. However, whether such an association persists beyond one month, and the
4 potential modifying effect of cardiovascular risk factors on such an association is less well
5 established.

6 **Methods:** The China Kadoorie Biobank enrolled 512 726 participants aged 30-79 years from
7 10 areas across China during 2004-08. By the end of 2017, a total of 5444 participants with
8 new-onset ischemic heart disease (IHD) and 4846 with ischemic stroke (IS) who also had at
9 least a record of hospitalization for pneumonia during follow-up were included. We used a
10 self-controlled case series method and calculated the age- and season-adjusted relative
11 incidences (RIs) and 95% confidence intervals (CIs) for ischemic cardiovascular disease
12 (CVD) after pneumonia.

13 **Results:** The risk of ischemic CVD increased during days 1-3 after pneumonia
14 hospitalization, with a RI (95% CI) of 4.24 (2.92-6.15) for IHD and 1.85 (1.02-3.35) for IS.
15 The risk gradually reduced with longer duration since pneumonia hospitalization but
16 remained elevated until days 92-365 for IHD (1.23, 1.12-1.35), and days 29-91 for IS (1.25,
17 1.05-1.48). Pre-existing cardiovascular risk factors amplified the associations between
18 pneumonia and ischemic CVD risks, such as chronic obstructive pulmonary disease for both
19 IHD and IS, and diabetes and smoking for IHD (all $P_{\text{interaction}} < 0.05$). Besides, the risk of
20 ischemic CVD was also higher among the participants aged ≥ 70 years ($P_{\text{interaction}} < 0.001$ for
21 IHD and =0.033 for IS).

22 **Conclusions:** Among middle-aged and older Chinese adults, pneumonia hospitalization was

1 associated with both short- and long-term increases in ischemic CVD risk for up to one year.

2

3 **Key words:** pneumonia, cardiovascular disease, ischemic heart disease, ischemic stroke, self-

4 controlled case series

5

1 **Key messages**

- 2 • Acute respiratory infections have been linked to a substantial but transient increase in the
3 risk of cardiovascular events, mostly within 30 days after infection.
- 4 • Only a few studies have addressed more lasting effects of respiratory infection on
5 cardiovascular disease risk. Most of the previous studies on the association of acute
6 respiratory infection with short- or long-term risk of cardiovascular disease were conducted in
7 Western populations and among older adults. Besides, the potential modifying effect of
8 cardiovascular risk factors on such association is less well established.
- 9 • Among middle-aged and older Chinese adults, pneumonia hospitalization was associated
10 with both short- and long-term increases in the risk of ischemic cardiovascular disease for up
11 to one year. Pre-existing cardiovascular risk factors amplified the associations between
12 pneumonia and ischemic cardiovascular disease risks.

1 **Introduction**

2 Cardiovascular disease (CVD), chiefly ischemic heart disease (IHD) and ischemic stroke (IS),
3 remains the leading cause of death worldwide,¹ with a rising burden in China.² Pneumonia
4 also causes a substantial disease burden globally with an estimate of 6.8 million hospital
5 admissions with pneumonia among older adults in 2015.³

6 Acute respiratory infections have been linked to a substantial but transient increase in the
7 risk of cardiovascular events, mostly within 30 days after infection.^{4,5} Also, the systemic
8 inflammation and prothrombotic states may persist long after the infection has clinically
9 resolved,^{6,7} suggesting a prolonged cardiovascular impact of respiratory infection. A few
10 studies have addressed more lasting effects of respiratory infection on ischemic CVD risk, but
11 their results are inconsistent.⁸⁻¹³

12 Most of the previous studies on the association of acute respiratory infection with short-
13 or long-term risk of ischemic CVD were conducted in Western populations and among older
14 adults. Only a few studies, with conflicting findings, have examined whether such an
15 association holds among middle-aged adults, who are usually neglected by current prevention
16 and management strategies for respiratory infections.¹³⁻¹⁵ Also, whether ischemic CVD risk
17 after respiratory infections varies by pre-existing cardiovascular risk factors¹⁶ remains unclear.
18 Since there are cost-effective measures for CVD prevention, identifying people at high risk of
19 CVD event associated with pneumonia is critical in tailoring interventions to better prevent
20 CVD events in the population.¹⁷

21 In this study, we aimed to examine the association between pneumonia hospitalization

1 and subsequent one-year ischemic CVD risk using the self-controlled case series (SCCS)
2 method based on large-scale cohort data from the China Kadoorie Biobank (CKB) study. We
3 further investigated potential effect modifiers of the association.

4 **Methods**

5 **Study population**

6 Details of the design and implementation of CKB have been described previously.^{18, 19}
7 Briefly, a total of 512 726 participants aged 30 to 79 years were enrolled from five urban and
8 five rural areas of China during 2004-08 and have been followed up for nearly 15 years by the
9 end of 2017. All participants completed an interviewer-administered questionnaire and
10 physical measurements at baseline after signing a written informed consent. The vital status of
11 the participants was ascertained through the official Disease Surveillance Point death
12 registries.²⁰ Incident outcome cases were identified by electronic linkage, via a unique
13 personal identification number, to established registries of major diseases (including cancer,
14 CVD, and diabetes), and to health insurance (HI) claim database, which was renewed
15 annually. Participants who failed to be linked to the local HI database were actively followed
16 annually by local residential administrators. All fatal and nonfatal events were coded to the
17 10th revision of the International Classification of Diseases (ICD-10) by trained staff blinded
18 to the baseline information.

19 **Ascertainment of exposure**

20 Hospitalizations that occurred during the follow-up and had a discharge diagnosis of
21 pneumonia (ICD-10 codes J12-J18) were ascertained from the HI claim data. Complying with

1 previous studies, for each participant, records of multiple pneumonia hospitalizations dated
2 within 28 days of each other were regarded as part of a single episode of infection, with the
3 admission date taken from the earliest record.^{13, 14}

4 **Ascertainment of outcomes**

5 The primary outcomes were incident IHD (codes I20-I25) and IS (codes I63). We further
6 classified IHD into major coronary events (MCE; including fatal IHD and nonfatal
7 myocardial infarction [codes I21 to I23]) and IHD other than MCE. For IS, we classified it
8 into lacunar infarction (LACI) and non-lacunar infarction (non-LACI). LACI was defined as
9 stroke with neuroimaging evidence of an infarct <15 mm in diameter on the radiological
10 reports, while non-LACI was any other type of ischemic stroke other than LACI. Considering
11 that the occurrence of a cardiovascular event may affect the incidence of subsequent
12 outcomes, we restricted the analyses to the first event during the follow-up period. The
13 ongoing outcome adjudication process of IHD and IS cases have been initiated since 2014.
14 The medical records of incident cases were retrieved, and the diagnosis was confirmed by
15 cardiovascular specialists blinded to the study assay using standardize verification process. By
16 October 2018, of 33 515 incident IHD cases and 40 465 IS cases reported since baseline
17 survey whose medical records have been retrieved, 88% of IHD and 92% of stroke cases were
18 confirmed for diagnosis.

19 **Assessment of covariates**

20 While time-invariant factors are canceled out of the SCCS model, their potential modification
21 on the association of pneumonia with ischemic CVD deserves study. Covariate information

1 from the baseline questionnaire included sociodemographic characteristics (age, sex, urban or
2 rural residence, and educational attainment), lifestyle factors (tobacco smoking and alcohol
3 drinking), medical history and family history of CVD. A family history of CVD was defined
4 as having at least one first-degree relative (biological father, mother, and siblings) with heart
5 disease or stroke. Physical measurements taken by trained staff included height and weight
6 (further derived as body mass index, BMI), blood pressure, and lung function. Immediate on-
7 site testing for random plasma glucose was conducted. Prevalent hypertension, diabetes, and
8 chronic obstructive pulmonary disease (COPD) at baseline were defined based on self-
9 reported physician's diagnosis and baseline measurements. The disease status of hypertension,
10 diabetes, and COPD used in the present analyses were updated until the outcome of interest
11 occurred, integrating information from both at baseline and during the follow-up.

12 **Statistical analysis**

13 The present analysis included CKB participants who had both records of ischemic CVD and
14 hospitalization for pneumonia during the follow-up. Within-person comparison was
15 performed using the SCCS design, which can account for multiple hospitalization episodes
16 for pneumonia and automatically control for measured and unmeasured time-invariant
17 confounders such as genetic factors and underlying state of health over suitable time scales.^{21,}
18 ²² In the analysis of IHD, participants who reported a history of physician-diagnosed heart
19 disease at baseline were excluded (n=1046). In the analysis of IS, participants who reported a
20 prior diagnosis of stroke at baseline were excluded (n=455). We further excluded participants
21 who had an overlapping admission date for pneumonia and the first incidence of ischemic
22 CVD due to their unknown temporal relationship (n=1014 for IHD and n=305 for IS). We

1 also exclude records of pneumonia with missing admission date (n=35) or implausible length
2 of hospital stay (n=2).

3 The schematic of the present SCCS design is shown in Supplementary figure S1. The
4 observation period for each participant began from the date of baseline enrollment to the date
5 of death, loss to follow-up, or December 31, 2017, whichever came first. Because the dates of
6 infection and symptom onset were not available, the admission date for pneumonia served as
7 the index date for the exposure. We divided the risk period into days 1-3, 4-7, 8-28, 29-91,
8 and 92-365 following the index date. Each participant could have multiple risk periods if they
9 experienced more than one pneumonia hospitalization during the observation period. The
10 baseline period was the time of the observation period other than the risk periods.

11 We calculated relative incidences (RIs) and 95% confidence intervals (CIs) for the first
12 incidence of IHD or IS occurring in risk periods compared with the baseline period using a
13 conditional Poisson regression model. An additional adjustment was made for time-varying
14 confounders of age in 5-year groups and season in 3-month blocks (i.e., March-May, June-
15 August, September-November, and December-February). Sensitivity analyses were performed
16 to check the robustness of the results, including adjusting for age in 1-year bands and calendar
17 month, excluding cases that have died within 30 days of the ischemic CVD event. We
18 included unexposed cases, that is, ischemic CVD cases who were not hospitalized for
19 pneumonia in the observation period in the analysis to correct for potential confounding by
20 age. Considering that the occurrence of a CVD event may affect the subsequent risk of
21 pneumonia hospitalization (i.e., an episode of hospital-acquired pneumonia after CVD), we
22 applied a different length of pre-exposure period and excluded this time from the baseline

1 period.^{14, 21} We further examined the impacts of pneumonia on subtypes of IHD and IS,
2 separately. Allowing for smaller sample sizes in some subgroups, we merged the groups of
3 risk period into 1-28, 29-91, and 92-365 days after the index date.

4 Also, we conducted subgroup analyses to explore whether the association between
5 pneumonia hospitalization and ischemic CVD was consistent across subpopulations defined
6 by: age at CVD event (<60, 60-69, or ≥ 70 years), sex (male or female), region (rural or
7 urban), educational attainment (illiterate or primary school, or middle school or higher),
8 smoking (current or noncurrent smoker), alcohol drinking (weekly or non-weekly drinker),
9 BMI (18.5-24.9 kg/m²; or both <18.5 and ≥ 25.0 kg/m²), waist circumference (male: <85 or
10 ≥ 85 cm; female: <80 or ≥ 80 cm), and family history of CVD (presence or absence). Subgroup
11 analyses, according to the disease status updated until the outcome of interest occurred, were
12 also performed: diabetes, COPD, and hypertension (presence or absence). The tests for
13 interaction were examined using likelihood ratio tests, which involved comparing models
14 with and without interaction terms between hospitalization for pneumonia and the selected
15 variables. We used the SCCS package in R software (version 3.5.3) for analyses.

16 **Results**

17 **Participant characteristics**

18 The primary analysis included 5444 cases with first IHD and 4846 cases with first IS
19 (Supplementary figure S2), with a mean age (SD) of 68.6 (9.5) years and 69.3 (8.9) years on
20 the date the CVD newly developed, respectively (Table 1). The median duration of the
21 observation period (interquartile range) was 11.0 (9.9-12.1) years for IHD and 11.0 (10.0-

1 12.1) years for IS, during which 1432 (26.3%) IHD cases and 1145 (23.6%) IS cases had
2 died, and the median time to death was 3.7 (1.5- 6.5) years for IHD and 3.8 (1.7- 6.5) for IS.
3 IHD cases had records of 7337 separate episodes of pneumonia hospitalizations during the
4 observation period, with mean 1.3 (± 0.8) episodes per person. The corresponding figures for
5 IS cases were 6436 episodes, with mean 1.3 (± 0.9) episodes per person.

6 **Pneumonia hospitalization and subsequent risk of ischemic CVD**

7 The risk of new-onset IHD increased markedly for the first 1-3 days after pneumonia
8 hospitalization, with age- and season-adjusted RI (95% CI) of 4.24 (2.92-6.15) (Table 2). The
9 risk gradually reduced afterward but remained elevated until day 92-365, with a RI (95% CI)
10 of 1.23 (1.12-1.35). For IS, the risk after pneumonia increased but to a lesser degree than that
11 for IHD, with a RI (95% CI) of 1.85 (1.02-3.35) for days 1-3 and 3.44 (2.36-5.03) for days 4-
12 7. The increased risk of IS remained until days 29-91 after pneumonia hospitalization.

13 The patterns of the association of pneumonia hospitalization with subsequent risk of IHD
14 or IS across the 1-year risk period were robust in the sensitivity analyses (Supplementary
15 Table S1). Exclusion of cases who died within 30 days after the CVD event led to a moderate
16 reduction in the RIs for IHD and IS, but the association pattern was unchanged.

17 **Separate analysis for subtypes of IHD and IS**

18 Pneumonia hospitalization was associated with higher RIs for MCE than other IHD
19 ($P_{\text{interaction}} < 0.001$) (Figure 1). The adjusted RIs (95% CIs) for MCE associated with pneumonia
20 were 12.94 (9.91-16.89) for days 1-28, 4.14 (2.98-5.75) for days 29-91, and 2.64 (2.06-3.36)
21 for days 92-365. The effect estimates were similar for both IS subtypes ($P_{\text{interaction}} = 0.160$)

1 (Figure 2), despite wider confidence intervals for LACI due to the small number of cases.

2 **Subgroup analyses**

3 The risk for both IHD and IS within one year after pneumonia hospitalization was generally
4 higher, or an increased risk in part of the risk period was seen only among participants aged
5 ≥ 70 years at the date of the cardiovascular event ($P_{\text{interaction}} < 0.001$ for IHD and $= 0.033$ for IS),
6 and COPD patients ($P_{\text{interaction}} = 0.012$ for IHD and < 0.001 for IS) (Figure 1 and 2).

7 Also, participants with diabetes ($P_{\text{interaction}} < 0.001$), current smokers ($P_{\text{interaction}} = 0.015$), and
8 those who were men ($P_{\text{interaction}} = 0.005$), lived in rural areas ($P_{\text{interaction}} = 0.001$), or who had low
9 levels of education ($P_{\text{interaction}} = 0.007$) showed a higher risk of developing IHD after
10 pneumonia hospitalization compared to their counterparts (Figure 1, Supplementary Table
11 S2). With regard to other characteristics including hypertension, alcohol drinking, BMI, waist
12 circumference, and family history of CVD, the association of pneumonia hospitalization with
13 IHD or IS was consistent across different sub-populations (all $P_{\text{interaction}} > 0.05$) (Figure 1 and 2,
14 Supplementary Table S2 and S3).

15 **Discussion**

16 Our study showed that pneumonia hospitalization was associated with an increased
17 subsequent risk of new-onset IHD and IS in Chinese adults. The ischemic CVD risk was
18 highest in the first month after pneumonia hospitalization, and gradually reduced with longer
19 duration since pneumonia hospitalization but remained elevated until one year for IHD and
20 three months for IS. Furthermore, pneumonia hospitalization was associated with higher RIs
21 for MCE than other IHD. Pre-existing cardiovascular risk factors amplified the associations

1 between pneumonia and ischemic CVD risks, such as COPD for both IHD and IS, and
2 diabetes and smoking for IHD. Besides, participants aged ≥ 70 years were at higher risk of
3 developing ischemic CVD associated with pneumonia.

4 **Comparison with other studies**

5 The short-term impacts of acute respiratory infections in triggering acute cardiovascular
6 events have been well documented in previous studies.^{4,5} Similar to our findings, two UK
7 studies, also based on SCCS design, found a four to five times higher risk of acute myocardial
8 infarction (MI) within the first three days after an acute respiratory infection, with a tapering
9 effect during the following weeks but an increased risk until 28 days after infection.^{12,13}
10 Another two SCCS studies, conducted in Ontario¹⁵ and Scottish populations¹⁴ respectively,
11 found a more transient elevated risk of MI within seven days after *Streptococcus pneumoniae*
12 or respiratory virus infection. For IS, we and the previous two UK studies consistently
13 observed an increased risk persisting to 28 days after an acute respiratory infection.^{12,14}
14 However, Warren-Gash et al. reported a higher estimates of stroke risk, with day 1-3 adjusted
15 RIs of 12.3 (95% CI: 5.48-27.7) and 6.79 (95% CI: 1.67-27.5) for *Streptococcus pneumoniae*
16 or respiratory virus infection, respectively; the stroke risk remained four times as high as that
17 during the baseline period to 28 days.¹⁴

18 In our study, the increased risks of IHD and IS after pneumonia hospitalization persisted
19 to one year and three months, respectively. Only two relevant UK studies using SCCS design
20 extended the risk period up to 91 days after an acute respiratory infection.^{12,13} Smeeth et al.
21 found that the elevated risk associated with respiratory infection remained until three months,

1 with day 29-91 RIs of 1.40 (1.33-1.48) for MI and 1.33 (1.26-1.40) for stroke.¹² However,
2 Warren-Gash et al. did not report an association between influenza infection and MI during
3 days 29-91 after infection.¹³ Another matched-cohort study nested within two population-
4 based cohorts showed that the risk of a composite endpoint of CVD events was highest (4-
5 fold) in the first 30 days after hospitalization for pneumonia, and progressively declined but
6 remained over day 91-1 year after infection (2-fold).⁸

7 The mechanisms underlying the role of acute respiratory infection in triggering a
8 cardiovascular event include both generalized inflammatory and thrombogenic changes, and
9 local effects on coronary arteries and atherosclerotic lesions.⁵ The persistence of
10 inflammation,⁷ prothrombotic state,⁶ and organ dysfunction after hospital discharge also
11 suggests a potential mechanism for the link between infection and long-term cardiovascular
12 risk. Two previous cohort studies showed that the elevated risk of CVD associated with
13 hospitalization for pneumonia extended to up to 10 years.^{8,9} Further studies are warranted to
14 elucidate the mechanisms by which acute infection affects the risk of CVD and identify
15 appropriate preventive measures.

16 The modifying effect of age on the risk of CVD following respiratory infection was less
17 clear, as the results were inconsistent.^{13-15, 23, 24} Findings of UK patients showed that the effect
18 of acute respiratory infection on MI was most marked in the oldest age group. The RI (95%
19 CI) for the first three days after infection was 5.94 (3.90-9.04) for adults aged ≥ 80 years and
20 1.46 (0.47-4.55) for adults aged < 60 years ($P_{\text{heterogeneity}}=0.023$).¹³ In contrast, findings of the
21 Scottish population found that adults aged < 65 years tended to have higher adjusted RIs for
22 MI and stroke after a respiratory infection, although the confidence intervals of effect

1 estimates were wide and overlapped between age groups.¹⁴ Our results showed that
2 participants aged ≥ 70 years had a higher risk of both IHD and IS after pneumonia
3 hospitalization, which persisted to one year for both outcomes. However, even for adults aged
4 < 60 years, we also observed an increased risk of IHD in the first month after pneumonia
5 hospitalization.

6 Only three prior studies have examined the effect modification by pre-existing
7 cardiovascular risk factors, and the conclusions were inconsistent, partly because of the
8 limited number of cases.^{10, 23, 24} Findings of UK studies showed that the risk of MI after
9 respiratory infection did not vary with prior cardiovascular risk factors, including smoking,
10 BMI, and history of asthma.^{23, 24} However, the impact of respiratory infection on stroke was
11 less in those with more cardiovascular risk factors.²³ Another study of American older adults
12 aged ≥ 65 years found that the risk of IS after infection did not vary by diabetes.¹⁰ However, in
13 the present study, the impact of pneumonia on ischemic CVD was amplified in adults with
14 pre-existing cardiovascular risk factors, such as COPD for both IHD and IS, and diabetes and
15 smoking for IHD. Previous studies have indicated that a low-grade chronic inflammatory state
16 is present in patients with diabetes or COPD.²⁵⁻²⁷ An acute lung infection may induce
17 activation of inflammatory cells and further increases the inflammatory response,
18 exacerbating the risk of developing cardiovascular events in patients with diabetes or COPD.

19 Unlike previous studies that did not find sex heterogeneity in the association between
20 acute respiratory infection and MI,^{13, 15, 23, 24} our findings suggested that men had a higher
21 pneumonia-associated IHD risk than women, especially in the first three months after
22 infection. Likewise, the effect estimates were greater in current smokers than their

1 counterparts during the first trimester of the risk period. Such sex heterogeneity in our study
2 might relate to the fact that the smoking prevalence in Chinese men is much higher than that
3 in women.^{28, 29} We also found that patients who lived in rural areas or had lower education
4 showed a higher risk of developing IHD after pneumonia hospitalization than their
5 counterparts, which is not reported by previous studies. As surrogates for socioeconomic
6 status, rural residence and low educational attainment are long being recognized as risk
7 factors for developing infectious diseases and IHD.^{30, 31} Some researchers also found that
8 timely diagnosis and prompt treatment improve the prognosis of patients with pneumonia.^{32, 33}
9 For rural residents or those with lower education, lack of access to quality care and a delay in
10 seeking health care may be associated with a more severe and persistent inflammatory
11 response, which in turn may promote the development of IHD.

12 **Strengths and limitations**

13 The present study, nested in a large-scale population-based cohort, provides solid evidence
14 that pneumonia could not only trigger new-onset IHD or IS in the first month after
15 hospitalization, but also contribute to a longer-term increase in the CVD risk up to one year
16 among Chinese adults. The inclusion of a large number of cases from diverse populations and
17 the collection of extensive information on potential risk factors for CVD allow us to examine
18 whether the pneumonia-associated risks were consistent across sub-populations. The SCCS
19 design and the inclusion of a large number of cases enable us to quantify the RIs of multiple
20 exposure risk periods within one year after pneumonia hospitalization.

21 Several limitations also merit consideration. First, we only included pneumonia that

1 required inpatient admission. Episodes of pneumonia not requiring hospitalization were not
2 included, so its association with the subsequent risk of CVD cannot be investigated. Second,
3 we did not have information on infectious agents. However, previous studies suggested that
4 the association between acute respiratory infection and cardiovascular risk was not limited to
5 specific infectious agents, although the RIs are slightly different.^{14, 15} Third, our study was
6 unable to distinguish community-acquired pneumonia from hospital-acquired pneumonia.
7 However, the prevalence of hospital-acquired pneumonia among inpatient was less than 2% in
8 China and thus should have little impact on our results.^{34, 35} Furthermore, participants who
9 had an overlapping admission date for pneumonia and ischemic CVD have been excluded
10 from our analysis, further minimizing the potential of hospital-acquired cases. Fourth,
11 pneumonia hospitalization events were collected through electronic linkage with HI claim
12 database, and we did not perform adjudication as what we did for vascular events. However,
13 pneumonia events diagnosed in an outpatient setting were not included, which may reduce the
14 potential bias coming from misclassification to some extent.

15 **Conclusion**

16 Based on a large-scale SCCS study of the Chinese population, we found that pneumonia
17 hospitalization was associated with an elevated risk of new-onset IHD and IS for up to one
18 year. The risk was highest during the initial days following pneumonia, but remained elevated
19 for one year and three months for IHD and IS, respectively. Pre-existing cardiovascular risk
20 factors may amplify the association between pneumonia and CVD. Recognition of such an
21 association calls for more intensive efforts to identify people at high risk of pneumonia and
22 CVD events associated with pneumonia, and to avoid respiratory infection through

1 vaccination and other hygiene measures. The use of preventive medications for those at high
2 risk of CVD after an acute infection could be one such strategies,^{36, 37} once the biological
3 pathways underlying the association between acute infection and CVD are elucidated. Also,
4 our findings add to previous reports pertaining to cardiovascular considerations related to
5 coronavirus disease 2019 (COVID-19)³⁸ by raising the concern of the long-term CVD health
6 for survivors who recovered from COVID-19.

7

1 **Ethics approval**

2 Ethics approval was obtained from the Ethical Review Committee of the Chinese Center for
3 Disease Control and Prevention (Beijing, China) (Ethics ID number of approval: 005/2004)
4 and the Oxford Tropical Research Ethics Committee, University of Oxford (UK) (Ethics ID
5 number of approval: OXTREC 025-04).

6 **Funding**

7 This work was supported by the National Natural Science Foundation of China [81941018].
8 The CKB baseline survey and the first re-survey were supported by a grant from the Kadoorie
9 Charitable Foundation in Hong Kong. The long-term follow-up is supported by grants from
10 the National Key R&D Program of China [2016YFC0900500, 2016YFC1303904], National
11 Natural Science Foundation of China [81390540], and Chinese Ministry of Science and
12 Technology [2011BAI09B01]. The funders had no role in the study design, data collection,
13 data analysis and interpretation, writing of the report, or the decision to submit the article for
14 publication.

15 **Acknowledgments**

16 The most important acknowledgment is to the participants in the study and the members of
17 the survey teams in each of the 10 regional centres, as well as to the project development and
18 management teams based at Beijing, Oxford and the 10 regional centres. JL conceived and
19 designed the paper. LL, ZC, and JC, as the members of CKB steering committee, designed
20 and supervised the conduct of the whole study, obtained funding, and together with JL, YG,
21 ZB, LY, YC, CY, JJ, JZ and DS acquired the data. YHu and YHan analyzed the data. YHu

1 drafted the manuscript. JL, LL, YP, JW, CS, YT contributed to the interpretation of the results.

2 JL critically reviewed and revised the manuscript for important intellectual content. All

3 authors reviewed and approved the final manuscript. JL is the guarantor.

4 **Conflict of interest**

5 None declared.

6 **Data sharing**

7 The access policy and procedures are available at www.ckbiobank.org.

1 **References**

- 2 1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282
3 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of
4 Disease Study 2017. *Lancet* 2018; **392**: 1736-88.
- 5 2. Hu S, Gao R, Liu L, et al. Summary of the 2018 Report on Cardiovascular Diseases in China [in Chinese].
6 *Chinese Circulation Journal* 2019; **34**: 209-20.
- 7 3. Shi T, Denouel A, Tietjen AK, et al. Global and Regional Burden of Hospital Admissions for Pneumonia
8 in Older Adults: A Systematic Review and Meta-Analysis. *J Infect Dis* 2019.
- 9 4. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet*
10 *Neurol* 2008; **7**: 341-53.
- 11 5. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary
12 syndromes. *Lancet Infect Dis* 2010; **10**: 83-92.
- 13 6. Yende S, D'Angelo G, Mayr F, et al. Elevated hemostasis markers after pneumonia increases one-year
14 risk of all-cause and cardiovascular deaths. *PLoS One* 2011; **6**: e22847.
- 15 7. Kaptoge S, Seshasai SR, Gao P, et al. Inflammatory cytokines and risk of coronary heart disease: new
16 prospective study and updated meta-analysis. *Eur Heart J* 2014; **35**: 578-89.
- 17 8. Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for
18 pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015; **313**: 264-74.
- 19 9. Bergh C, Fall K, Udumyan R, Sjoqvist H, Frobert O, Montgomery S. Severe infections and subsequent
20 delayed cardiovascular disease. *Eur J Prev Cardiol* 2017; **24**: 1958-66.
- 21 10. Elkind MS, Carty CL, O'Meara ES, et al. Hospitalization for infection and risk of acute ischemic stroke:
22 the Cardiovascular Health Study. *Stroke* 2011; **42**: 1851-6.
- 23 11. Chen LF, Chen HP, Huang YS, Huang KY, Chou P, Lee CC. Pneumococcal pneumonia and the risk of
24 stroke: a population-based follow-up study. *PLoS One* 2012; **7**: e51452.
- 25 12. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and
26 stroke after acute infection or vaccination. *N Engl J Med* 2004; **351**: 2611-8.
- 27 13. Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza infection and risk of acute myocardial
28 infarction in England and Wales: a CALIBER self-controlled case series study. *J Infect Dis* 2012; **206**: 1652-
29 9.
- 30 14. Warren-Gash C, Blackburn R, Whitaker H, McMenamin J, Hayward AC. Laboratory-confirmed
31 respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series
32 analysis of national linked datasets from Scotland. *Eur Respir J* 2018; **51**.
- 33 15. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute Myocardial Infarction after Laboratory-Confirmed
34 Influenza Infection. *N Engl J Med* 2018; **378**: 345-53.
- 35 16. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report
36 From the American Heart Association. *Circulation* 2019; **139**: e56-e528.
- 37 17. Davidson JA, Warren-Gash C. Cardiovascular complications of acute respiratory infections: current
38 research and future directions. *Expert Rev Anti Infect Ther* 2019; **17**: 939-42.
- 39 18. Chen Z, Lee L, Chen J, et al. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC).
40 *Int J Epidemiol* 2005; **34**: 1243-9.
- 41 19. Chen Z, Chen J, Collins R, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline
42 characteristics and long-term follow-up. *Int J Epidemiol* 2011; **40**: 1652-66.
- 43 20. Yang G, Hu J, Rao KQ, Ma J, Rao C, Lopez AD. Mortality registration and surveillance in China: History,

- 1 current situation and challenges. *Popul Health Metr* 2005; **3**: 3.
- 2 21. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard
3 epidemiological study designs. *BMJ* 2016; **354**: i4515.
- 4 22. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case
5 series method. *Stat Med* 2006; **25**: 1768-97.
- 6 23. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease:
7 case-control study through a general practice database. *Eur Heart J* 2008; **29**: 96-103.
- 8 24. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time
9 acute myocardial infarction. *Lancet* 1998; **351**: 1467-71.
- 10 25. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary
11 disease. *Lancet* 2011; **378**: 1015-26.
- 12 26. Masters SL, Latz E, O'Neill LA. The inflammasome in atherosclerosis and type 2 diabetes. *Sci Transl*
13 *Med* 2011; **3**: 81ps17.
- 14 27. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011; **11**: 98-
15 107.
- 16 28. Chen Z, Peto R, Zhou M, et al. Contrasting male and female trends in tobacco-attributed mortality in
17 China: evidence from successive nationwide prospective cohort studies. *Lancet* 2015; **386**: 1447-56.
- 18 29. Yang G, Fan L, Tan J, et al. Smoking in China: findings of the 1996 National Prevalence Survey. *JAMA*
19 1999; **282**: 1247-53.
- 20 30. Concepción-Zavaleta MJ, Coronado-Arroyo JC, Zavaleta-Gutiérrez FE, Concepción-Urteaga LA. Does
21 level of education influence mortality of SARS-CoV-2 in a developing country? *Int J Epidemiol* 2020.
- 22 31. Hamad R, Penko J, Kazi DS, et al. Association of Low Socioeconomic Status With Premature Coronary
23 Heart Disease in US Adults. *JAMA Cardiol* 2020; **5**: 899-908.
- 24 32. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients
25 with pneumonia. *JAMA* 1997; **278**: 2080-4.
- 26 33. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection
27 reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of
28 care and resource utilization. *Arch Intern Med* 2002; **162**: 682-8.
- 29 34. Ren N, Wen X, Wu A. Study on the changing trends in national nosocomial infection transection
30 investigation results [in Chinese]. *Chinese Journal of Infection Control* 2007: 16-8.
- 31 35. Liu Y, CAO B, Wang H, et al. Adult hospital acquired pneumonia: a multicenter study on microbiology
32 and clinical characteristics of patients from 9 Chinese cities [in Chinese]. *Chinese Journal of Tuberculosis*
33 *and Respiratory Diseases* 2012: 739-46.
- 34 36. Cheng HH, Tang TT, He Q, et al. Beneficial effects of statins on outcomes in pneumonia: a systematic
35 review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2014; **18**: 2294-305.
- 36 37. Winning J, Reichel J, Eisenhut Y, et al. Anti-platelet drugs and outcome in severe infection: clinical
37 impact and underlying mechanisms. *Platelets* 2009; **20**: 50-7.
- 38 38. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care
39 Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol* 2020; **75**: 2352-71.

40

1 **Table 1** Characteristics of participants who had both records of new-onset ischemic
 2 cardiovascular disease and pneumonia hospitalization during the observation period

| | Ischemic heart disease | Ischemic stroke |
|--|-------------------------------|------------------------|
| No. of participants | 5444 | 4846 |
| Age at baseline, years (SD) | 62.1 (9.2) | 62.8 (8.9) |
| Age groups at baseline | | |
| <60 years | 2047 (37.6) | 1715 (35.4) |
| 60-69 years | 2147 (39.4) | 1916 (39.5) |
| ≥70 years | 1250 (23.0) | 1215 (25.1) |
| Age at CVD event, years (SD) | 68.6 (9.5) | 69.3 (8.9) |
| Age groups at CVD event | | |
| <60 years | 1037 (19.1) | 781 (16.1) |
| 60-69 years | 1668 (30.6) | 1496 (30.9) |
| ≥70 years | 2739 (50.3) | 2569 (53.0) |
| Male | 2357 (43.3) | 2266 (46.8) |
| Urban resident | 2384 (43.8) | 2795 (57.7) |
| Middle school or higher | 1912 (35.1) | 2013 (41.5) |
| Current smoker^a | | |
| Male | 1597 (67.8) | 1436 (63.4) |
| Female | 251 (8.1) | 218 (8.5) |
| Regular alcohol drinker^b | | |
| Male | 658 (27.9) | 685 (30.2) |

| | Ischemic heart disease | Ischemic stroke |
|--|------------------------|-----------------|
| Female | 92 (2.98) | 65 (2.5) |
| BMI | | |
| <18.5 kg/m ² | 421 (7.7) | 270 (5.6) |
| 18.5-24.9 kg/m ² | 3034 (55.7) | 2722 (56.2) |
| 25.0-29.9 kg/m ² | 1678 (30.8) | 1572 (32.4) |
| ≥30.0 kg/m ² | 311 (5.7) | 282 (5.8) |
| Waist circumference | | |
| Male<85 cm, female<80 cm | 2718 (49.9) | 2377 (49.1) |
| Male≥85 cm, female≥80 cm | 2726 (50.1) | 2469 (50.9) |
| Having disease before CVD event^c | | |
| Diabetes | 850 (15.6) | 879 (18.1) |
| COPD | 1447 (26.6) | 1030 (21.3) |
| Hypertension | 3092 (56.8) | 2991 (61.7) |
| Family history of CVD^d | 1161 (21.3) | 1175 (24.2) |

1 Abbreviations: BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

2 Data are presented as n or n (%), and all variables were measured at baseline unless indicated otherwise.

3 ^a Participant who quit smoking because of illness was classified as a current smoker.

4 ^b Regular alcohol drinkers were those who drank alcohol at least weekly.

5 ^c The disease status of diabetes, COPD, and hypertension were updated until the occurrence of the study outcome.

6 ^d A family history of CVD was defined as having at least one first-degree relative (biological father, mother, and siblings) with

7 heart disease or stroke.

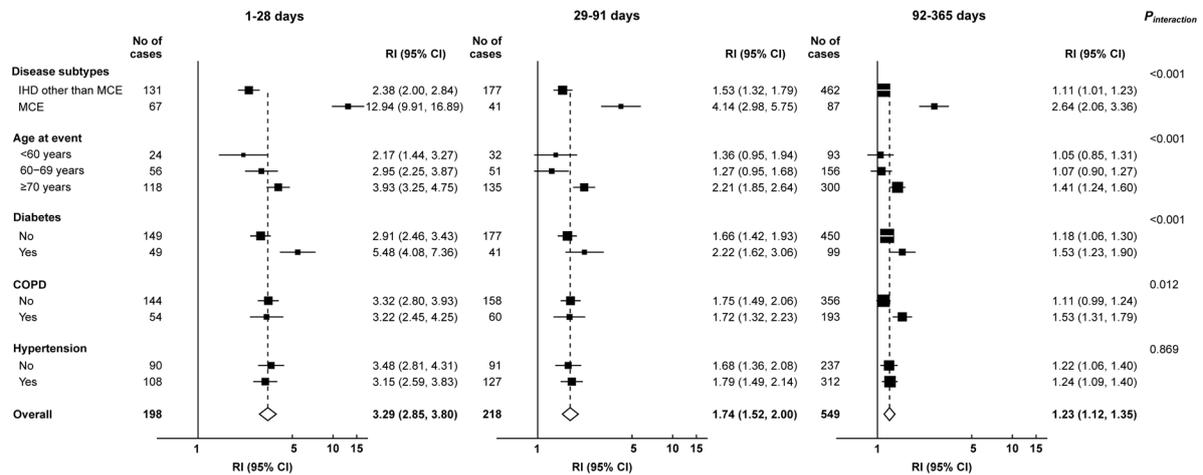
1 **Table 2** Age- and season-adjusted RIs (95% CIs) for new-onset ischemic cardiovascular disease in risk
 2 periods after pneumonia hospitalization compared with the baseline period

| Time period after the index date | Ischemic heart disease | | | Ischemic stroke | | |
|-------------------------------------|------------------------|-------|-------------------|-----------------|-------|-------------------|
| | PYs | Cases | RIs (95% CIs) | PYs | Cases | RIs (95% CIs) |
| Baseline period | 52 296.4 | 4479 | 1.00 | 47 112.6 | 4193 | 1.00 |
| 1-3 days | 60.0 | 28 | 4.24 (2.92, 6.15) | 52.6 | 11 | 1.85 (1.02, 3.35) |
| 4-7 days | 79.5 | 32 | 3.66 (2.59, 5.19) | 69.6 | 27 | 3.44 (2.36, 5.03) |
| 8-28 days | 409.9 | 138 | 3.08 (2.59, 3.65) | 358.7 | 64 | 1.59 (1.24, 2.04) |
| 29-91 days | 1152.1 | 218 | 1.74 (1.52, 2.00) | 1002.2 | 139 | 1.25 (1.05, 1.48) |
| 92-365 days | 4190.5 | 549 | 1.23 (1.12, 1.35) | 3611.5 | 412 | 1.04 (0.94, 1.15) |

3 Abbreviations: PY, person-year; RI, relative incidence; CI, confidence interval.

4

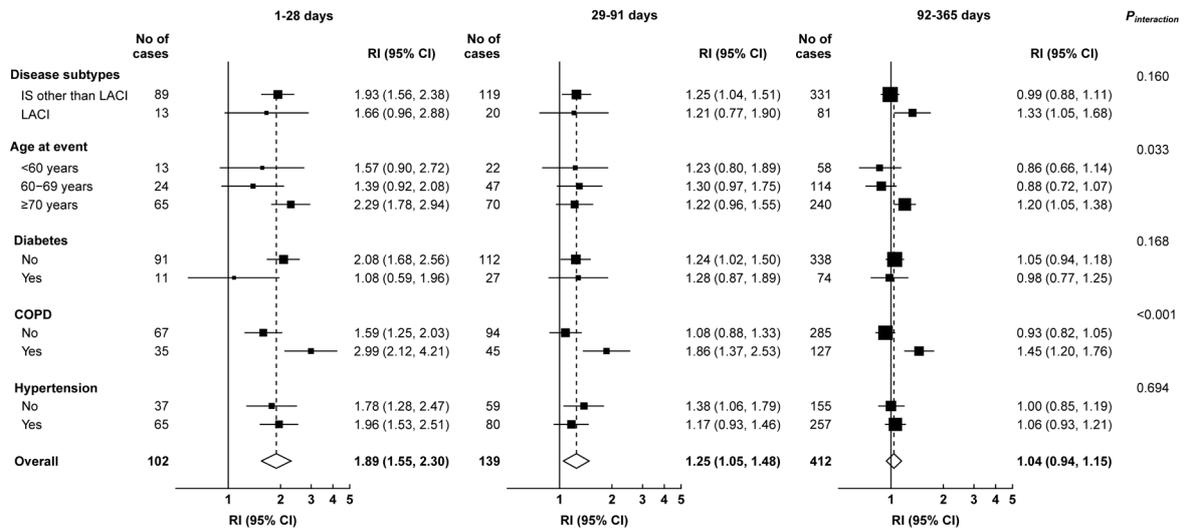
1 **Figure 1 Subgroup analyses for association between pneumonia hospitalization and ischemic heart**
 2 **disease**



3
 4 Abbreviations: RI, relative incidence; CI, confidence interval; IHD, ischemic heart disease; MCE, major
 5 coronary events; COPD, chronic obstructive pulmonary disease.
 6 The model was adjusted for age and season. The disease status of diabetes, COPD, and hypertension were
 7 updated until the occurrence of the study outcome. We tested multiplicative interaction by using a likelihood
 8 ratio test comparing models with and without a cross-product term.

9

1 **Figure 2 Subgroup analyses for association between pneumonia hospitalization and ischemic stroke**



2

3 Abbreviations: RI, relative incidence; CI, confidence interval; IS, ischemic stroke; LACI, lacunar infarction;

4 COPD, chronic obstructive pulmonary disease.

5 The model was adjusted for age and season. The disease status of diabetes, COPD, and hypertension were

6 updated until the occurrence of the study outcome. We tested multiplicative interaction by using a likelihood

7 ratio test comparing models with and without a cross-product term.

8