Supplementary Online Content

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eTable 5. Sensitivity analysis of risk of cardiovascular disease after hospitalization for pneumonia in CHS including participants hospitalized for pneumonia, where pneumonia was recorded as the primary discharge diagnosis, and controls not hospitalized for pneumonia

eTable 6. Sensitivity analysis of risk of cardiovascular disease after hospitalization for pneumonia in CHS including participants hospitalized for pneumonia without a concomitant diagnosis of heart failure in the hospitalization and controls not hospitalized for pneumonia

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Description of Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) Study.

Cardiovascular Health Study (CHS) is a prospective cohort study to determine risk factors for cardiovascular disease (CVD) in adults 65 years or older recruited in four US communities: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Allegheny County, Pennsylvania. Eligible participants were sampled from Medicare eligibility lists in each area. A total of 5,201 predominantly European Americans were recruited in 1989-1990, followed by recruitment of an additional 687 African Americans in 1992-1993 (total n=5,888). Exclusion criteria included being wheelchair bound in the home, unable to participate in the examination at the field center, plans to leave the area, or undergoing active treatment for cancer.

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort study to determine the etiology and natural history of atherosclerosis. ARIC used probability-based sampling of persons aged 45–64 years from four US communities: Forsyth County, North Carolina; Jackson, Mississippi (black participants only); northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. In addition to age and residence, eligibility criteria included no definitive plans to leave the area, mentally and physically able to attend the clinic examination, and no language barrier.

eTable 1. Procedures for adjudication of myocardial infarction (MI) and stroke events in CHS and ARIC.

Cohort	Identification and retrieval of potential cases	Operational diagnosis of MI	Operational diagnosis of stroke
CHS	Medical records of all potential MI and stroke events identified through surveillance procedures (per-protocol examinations, semiannual participant contacts, notification by participants and proxies, and review of Medicare hospitalization records) are retrieved and directed to the CHS Events Subcommittees (Cardiovascular Adjudication Committee for MI and the Cerebrovascular Adjudication Committee for stroke) for final adjudication.[1,2]	Potential MI events are discussed and adjudicated by the Cardiovascular Adjudication Committee based on a algorithm that includes symptoms, cardiac enzymes, and electrocardiographic evidence. When there is discrepancy between the discharge diagnoses coded and adjudication of an event by the committee, the cases are reviewed again to resolve the discrepancy. [1]	Potential stroke cases are discussed and adjudicated by the Cerebrovascular Adjudication Committee based on clinical findings, duration of neurologic deficits, and radiographic (CT and MRI) evidence.[2] When there is discrepancy between the discharge diagnoses coded and adjudication of an event by the committee, the cases are reviewed again to solve the discrepancy.[2]
ARIC	Medical records associated with all potentials MI and stroke events identified through surveillance procedures (per-protocol examinations, annual phone contacts, review of discharge lists of local hospitals and death certificates from state vital statistics offices) are retrieved and submitted to the ARIC Morbidity and Mortality Classification	MI events are diagnosed by a computer algorithm using symptoms, cardiac enzymes, and electrocardiographic evidence. When there is discrepancy between the discharge-diagnoses codes and the computer diagnosis, cases are reviewed by the Mortality and Morbidity Classification Committee to solve the discrepancy.[4]	Stroke cases are diagnosed by a computer algorithm using criteria adopted from the National Survey of Stroke, and by a study physician-reviewer based on documented clinical and radiographic (CT and MRI) findings. A final event diagnosis was determined by agreement of the

	Committee for final adjudication.[3]		computer and reviewer diagnoses. Disagreements were adjudicated by a second study physician-reviewer.[5]

Abbreviations: CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk in Communities; CT, computed tomography; MRI, magnetic resonance imaging.

eTable 2. Covariates used for adjusted analyses. The covariates were updated annually or every 3 years during the first 10 years for CHS. For ARIC, we used only covariates obtained at study entry.

Co-variable	CHS	ARIC
Age	Yes	Yes
Race	Yes	Yes
Gender	Yes	Yes
Hypertension	Yes	Yes
Diabetes Mellitus	Yes	Yes
Atrial Fibrillation	Yes	Yes
Body mass index	Yes	Yes
Smoking	Yes	Yes
Alcohol Abuse	Yes	Yes
Glomerular Filtration Rate [a]	Yes	Yes
Serum LDL Cholesterol	Yes	Yes
Serum HDL Cholesterol	Yes	Yes
Serum Total Cholesterol	Yes	Yes
Serum C-reactive protein	Yes	No
Percentage of the Predicted FEV1 using spirometry	Yes	Yes
Subclinical Cardiovascular Disease (combined index) [b]	Yes	No
Diagnostic Q waves in electrocardiogram	No	Yes
Peripheral arterial disease as defined by ankle-brachial index <0.9	No	Yes
Carotid artery wall thickness	No	Yes
Carotid atherosclerotic plaque by ultrasound	No	Yes
Activities of Daily Living (ADL) Scale	Yes	No
Instrumental Activities of Daily Living (IADL) scale	Yes	No
Mini Mental State Examination (MMSE)	Yes	No

Abbreviations: CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk in Communities, LDL, low-density lipoproteins; HDL, high-density lipoproteins; forced expiratory volume in 1st second.
Data missingness was <5% for all available variables.

[a] Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) Study equation. [7]

[b] The subclinical cardiovascular disease index was defined as the presence of any 1 of the following: (1) major electrocardiogram abnormalities based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) increased carotid or internal carotid artery wall thickness (>80th percentile of the CHS distribution) or stenosis of >25 percent (based on ultrasonographic findings), (4) echocardiogram wall motion abnormality or low ejection fraction, or (5) positive responses to the Rose Questionnaire for angina or intermittent claudication (without clinical history of these diagnoses). [6]

eMethods 2. Trajectories for activities of daily living (ADL), independent ADL (IADL), and cognition analysis.

We constructed trajectories of longitudinal changes in ADL, IADL, and cognition and included them as covariates. We chose trajectory analysis because changes over time are more important than a single value for these covariates. ADL and IADLs were coded as the number of ADLs and IADLs requiring assistance. We used the Teng's mini-mental (3MS) status score to assess cognition (scale of 0-100).[8] Trajectory analysis identified 3 groups for each variable: no, minimal, and rapid decline. The group membership ADL, IADL, and cognition was included as a covariate in the adjusted models.

We used Proc Traj, an unsupervised learning tool that clusters participants with similar trajectories into groups.[9] For participants who were hospitalized with pneumonia, we used all available measurements prior to the development of pneumonia, and for the remaining participants, all available 3MS measures either until the end of the study or until they died.

Proc Traj uses a discrete mixture model to model longitudinal data. This model allows for data grouping using different parameter values for each group distribution. Model fit is assessed by BIC values. Each participant is assigned a group membership for each trajectory. Additional details to construct these trajectories have been described previously.[10]

eTable 3. Baseline characteristics of all participants in CHS and ARIC and the analysis cohorts, which were nested within CHS and ARIC and included participants with pneumonia and matched controls.

Clinical Characteristics	CHS Whole cohort (n=5,888)	CHS Nested cohort (n=1,773)	ARIC Whole cohort (n=15,792)	ARIC Nested cohort (n=2,040)
Age	72.84 ± 5.62	73.01 ± 5.67	54.16 ± 5.76	55.52 ± 5.86
Females - no. (%)	2,495 (42.4)	1,120 (63.2)	8,710 (55.2)	1,139 (55.8)
African Americans - no. (%)	924 (15.7)	242 (13.7)	4,266 (27.1)	548 (26.9)
Atrial fibrillation- no. (%)	397 (6.7)	106 (6.0)	25 (0.2)	2 (0.1)
Diabetes - no. (%)	1,171 (20.0)	269 (15.2)	1,870 (12.0)	239 (11.9)
Hypertension - no. (%)	4,646 (78.9)	1,334 (75.2)	5,277 (35.3)	686 (33.8)
Chronic kidney disease [a] - no. (%)	1,845 (31.6)	494 (28.0)	3,428 (22.0)	451 (22.4)
Body mass index	26.7 ± 4.8	26.7 ± 5.0	27.7 ± 5.4	27.4 ± 5.6
Ever smoke - no. (%)	3,629 (61.6)	1,045 (58.9)	9,204 (58.3)	1,242 (60.9)
Pack-years, Median	1.60	0.0	5.0	7.0
(Interquartile range)	(0.0, 30.0)	(0.0, 26.0)	(0.0,28.0)	(0.0, 30.0)
Alcohol abuse - no. (%)	325 (5.5)	89 (5.0)	1560 (10.0)	215 (10.6)
Serum LDL cholesterol in mg/dL				
≤ 130 - no. (%)	3,227 (55.8)	979 (55.9)	6,452 (44.2)	891 (45.2)
>130 - no. (%)	2,559 (44.2)	773 (44.1)	8,135 (55.8)	1,079 (54.8)
Serum HDL cholesterol in mg/dL				
≤ 60 - no. (%)	4,170 (71.4)	1,167 (66.2)	10,946 (73.9)	1,452 (72.5)
>60 - no. (%)	1,669 (28.6)	597 (33.8)	3,859 (26.1)	550 (27.5)
Total serum cholesterol in mg/dL				
≤ 240 - no. (%)	4,816 (82.2)	1,445 (81.8)	11,104 (75.0)	1,503 (75.0)
>240- no. (%)	1,043 (17.8)	321 (18.2)	3,700 (25.0)	499 (25.0)
Serum C-reactive protein in mg/L				
Median	2.4	2.4	--	--
(Interquartile range)	(1.2, 4.8)	(1.2, 4.3)	--	--
Percentage of predicted FEV1	90.0 ± 22.3	91.5 ±22.1	93.3 ± 17.4	90.9 ± 19.8
Subclinical CVD [b] – no. (%)	4,131 (70.2)	1,126 (63.6)	--	--
Diagnostic Q waves in electrocardiogram – no. (%)	--	--	188 (1.2)	5 (0.3)
Ankle-brachial index <0.9 – no. (%)	--	--	660 (4.2)	85 (4.2)
Carotid artery wall thickness in mm	--	--	0.73 ± 0.19	0.73 ± 0.19
Carotid atherosclerotic plaque on ultrasound – no. (%)	--	--	10,172 (64.4)	994 (48.7)
Longitudinal trajectories in the performance of Activities of Daily Living [c]	4,238 (72.0)	1,323 (74.6)	--	--

No decline - no. (%)	1,232 (20.9)	357 (20.1)	--	--
Minimal decline- no. (%)	418 (7.1)	93 (5.3)	--	--
Rapid decline - no. (%)				
Longitudinal trajectories in the performance of Independent Activities of Daily Living [c]				
No decline - no. (%)	4,034 (68.5)	1,304 (73.6)	--	--
Rapid decline - no. (%)	1,854 (31.5)	469 (26.5)	--	--
Longitudinal trajectories in Cognition based on Mini-mental Status Score [c]	4,420 (75.1)	1,369 (77.2)	--	--
	1,161 (19.7)	319 (18.0)	--	--
No decline - no. (%)	307 (5.2)	85 (4..8)	--	--
Minimal decline- no. (%)				
Rapid decline - no. (%)				

Abbreviations: CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk in Communities, LDL, low-density lipoproteins; HDL, high-density lipoproteins; CRP, C-reactive protein; FEV1, forced expiratory volume in 1st second; CVD, cardiovascular disease.

[a] Chronic kidney disease is defined as glomerular filtration rate of GFR <60 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease (MDRD) Study equation.[7]

[b] Subclinical disease was defined as having any 1 of the following: (1) major electrocardiogram abnormalities based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) increased carotid or internal carotid artery wall thickness (>80th percentile of the CHS distribution) or stenosis of >25 percent (based on ultrasonographic findings), (4) echocardiogram wall motion abnormality or low ejection fraction, or (5) positive responses to the Rose Questionnaire for angina or intermittent claudication (without clinical history of these diagnoses).[6]

[c] Iinformation on the calculation of these trajectories is provided in Section IV of these supplementary materials.

eTable 4. Sensitivity analysis of risk of cardiovascular disease after hospitalization for pneumonia in CHS including participants hospitalized for pneumonia and controls hospitalized for other reasons (n=1,228, 614 pneumonia cases and 614 controls).

Time intervals after pneumonia	Number at risk		Number of events		Adjusted HR [a] (95% CI)
	Cases	Controls	Cases	Controls	
0 to 30 days	506	512	34	5	3.11 (1.94 to 4.29)
31 to 90 days	404	484	11	3	2.70 (1.79 to 3.61)
91 days to 1 year	365	470	20	13	2.25 (1.55 to 2.95)
1 to 2 years	299	431	29	26	1.95 (1.38 to 2.52)
2 to 3 years	235	383	9	14	1.87 (1.34 to 2.41)
3 to 4 years	207	348	16	12	1.82 (1.28 to 2.36)
4 to 5 years	167	320	12	13	1.74 (1.20 to 2.29)
5 to 6 years	137	298	10	12	1.62 (1.08 to 2.16)
6 to 7 years	112	267	5	18	1.73 (1.11 to 2.36)
7 to 8 years	98	227	7	6	1.75 (1.06 to 2.44)
8 to 9 years	76	198	6	9	1.71 (0.98 to 2.43)
9 to 10 years	51	176	4	12	1.71 (0.98 to 2.43)

Abbreviations: CHS, Cardiovascular Health Study; HR, hazard ratio; CI, confidence interval.

[a] Covariables included in the analyses were age, sex, race, hypertension, diabetes mellitus, serum total, high-density lipoproteins, and low-density lipoproteins cholesterol, smoking (pack-years history), alcohol abuse,[11] atrial fibrillation, chronic kidney disease,[7] serum C-reactive protein,[12] subclinical cardiovascular disease,[6] percentage of predicted forced expiratory volume in 1st second (FEV1) measured by spirometry,[13] trajectories of activities of daily living and independent activities of daily living over time,[10] and trajectories of modified mini-mental status exam scores over time.[10] Subclinical disease was defined as having any 1 of the following: (1) major electrocardiogram abnormalities based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) increased carotid or internal carotid artery wall thickness (>80th percentile of the CHS distribution) or stenosis of >25 percent (based on ultrasonographic findings), (4) echocardiogram wall motion abnormality or low ejection fraction, or (5) positive responses to the Rose Questionnaire for angina or intermittent claudication (without clinical history of these diagnoses).[6] Chronic kidney disease is defined as glomerular filtration rate of GFR <60 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease (MDRD) Study equation.[7] The analysis was carried using the most recently available measurement of the covariables before inclusion in the nested analysis cohort.

eTable 5. Sensitivity analysis of risk of cardiovascular disease after hospitalization for pneumonia in CHS including participants hospitalized for pneumonia, where pneumonia was recorded as the primary discharge diagnosis, and controls not hospitalized for pneumonia (n=1,137, 379 pneumonia cases and 758 controls).

Time intervals after pneumonia	Number at risk		Number of events		Adjusted HR [a] (95% CI)
	Cases	Controls	Cases	Controls	
0 to 30 days	327	700	19	5	2.65 (1.67 to 3.63)
31 to 90 days	274	694	8	4	2.21 (1.48 to 2.93)
91 days to 1 year	248	682	15	40	1.70 (1.18-2.21)
1 to 2 years	196	625	16	32	1.63 (1.17 to 2.10)
2 to 3 years	161	565	7	25	1.59 (1.15 to 2.03)
3 to 4 years	141	518	10	21	1.72 (1.23 to 2.21)
4 to 5 years	112	470	11	18	1.83 (1.29 to 2.37)
5 to 6 years	86	427	9	23	1.77 (1.21 to 2.33)
6 to 7 years	70	380	2	23	1.66 (1.10 to 2.23)
7 to 8 years	61	323	5	19	1.80 (1.13 to 2.47)
8 to 9 years	47	269	5	8	2.01 (1.20 to 2.82)
9 to 10 years	31	231	4	9	2.10 (1.20 to 2.99)

Abbreviations: CHS, Cardiovascular Health Study; HR, hazard ratio; CI, confidence interval.

[a] Covariables included in the analyses were age, sex, race, hypertension, diabetes mellitus, serum total, high-density lipoproteins, and low-density lipoproteins cholesterol, smoking (pack-years history), alcohol abuse,[11] atrial fibrillation, chronic kidney disease,[7] serum C-reactive protein,[12] subclinical cardiovascular disease,[6] percentage of predicted forced expiratory volume in 1st second (FEV1) measured by spirometry,[13] trajectories of activities of daily living and independent activities of daily living over time,[10] and trajectories of modified mini-mental status exam scores over time.[10] Subclinical disease was defined as having any 1 of the following: (1) major electrocardiogram abnormalities based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) increased carotid or internal carotid artery wall thickness (>80th percentile of the CHS distribution) or stenosis of >25 percent (based on ultrasonographic findings), (4) echocardiogram wall motion abnormality or low ejection fraction, or (5) positive responses to the Rose Questionnaire for angina or intermittent claudication (without clinical history of these diagnoses).[6] Chronic kidney disease is defined as glomerular filtration rate of GFR <60 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease (MDRD) Study equation.[7] The analysis was carried using the most recently available measurement of the covariables before inclusion in the nested analysis cohort.

eTable 6. Sensitivity analysis of risk of cardiovascular disease after hospitalization for pneumonia in CHS including participants hospitalized for pneumonia without a concomitant diagnosis of heart failure in the same hospitalization and controls not hospitalized for pneumonia (n=1,548, 516 pneumonia cases and 1,032 controls).

Time intervals after pneumonia	Number at risk		Number of events		Adjusted HR [a] (95% CI)
	Cases	Controls	Cases	Controls	
0 to 30 days	446	955	34	4	3.65 (2.42 to 4.87)
31 to 90 days	342	949	9	6	2.77 (1.95 to 3.58)
91 days to 1 year	309	936	18	42	2.03 (1.48 to 2.57)
1 to 2 years	244	871	22	47	1.79 (1.34 to 2.25)
2 to 3 years	190	781	9	32	1.67 (1.30 to 2.04)
3 to 4 years	164	718	10	33	1.63 (1.22 to 2.04)
4 to 5 years	133	652	12	29	1.61 (1.19 to 2.03)
5 to 6 years	103	590	8	38	1.65 (1.19 to 2.10)
6 to 7 years	82	512	3	23	1.56 (1.09 to 2.02)
7 to 8 years	69	438	4	21	1.54 (1.05 to 2.04)
8 to 9 years	57	364	4	11	1.75 (1.08 to 2.42)
9 to 10 years	39	311	4	10	1.83 (1.09 to 2.57)

Abbreviations: CHS, Cardiovascular Health Study; HR, hazard ratio; CI, confidence interval.

[a] Covariables included in the analyses were age, sex, race, hypertension, diabetes mellitus, serum total, high-density lipoproteins, and low-density lipoproteins cholesterol, smoking (pack-years history), alcohol abuse,[11] atrial fibrillation, chronic kidney disease,[7] serum C-reactive protein,[12] subclinical cardiovascular disease,[6] percentage of predicted forced expiratory volume in 1st second (FEV1) measured by spirometry,[13] trajectories of activities of daily living and independent activities of daily living over time,[10] and trajectories of modified mini-mental status exam scores over time.[10] Subclinical disease was defined as having any 1 of the following: (1) major electrocardiogram abnormalities based on the Minnesota Code, (2) an ankle-arm–systolic BP ratio of 0.9 or less, (3) increased carotid or internal carotid artery wall thickness (>80th percentile of the CHS distribution) or stenosis of >25 percent (based on ultrasonographic findings), (4) echocardiogram wall motion abnormality or low ejection fraction, or (5) positive responses to the Rose Questionnaire for angina or intermittent claudication (without clinical history of these diagnoses).[6] Chronic kidney disease is defined as glomerular filtration rate of GFR <60 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease (MDRD) Study equation.[7] The analysis was carried using the most recently available measurement of the covariables before inclusion in the nested analysis cohort.

eReferences.

1. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann. Epidemiol.* 1995;5(4):278-285.
2. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. *Ann Epidemiol.* 1993;3(5):504-507.
3. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129(4):687-702.
4. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol.* 1996;49(2):223-233.
5. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke.* 1999;30(4):736-743.
6. Kuller L, Borhani N, Furberg C, et al. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol.* 1994;139(12):1164-1179.
7. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354(23):2473-2483.
8. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry.* 1987;48(8):314-318.
9. Jones B, Nagin D. Advances in Group-Based Trajectory Modeling and an SAS Procedure for Estimating Them. *Sociol Methods Res.* 2007;35(4):542-571.
10. Shah FA, Pike F, Alvarez K, et al. Bidirectional relationship between cognitive function and pneumonia. *Am J Respir Crit Care Med.* 2013;188(5):586-592.
11. Town M, Naimi TS, Mokdad AH, Brewer RD. Health care access among U.S. adults who drink alcohol excessively: missed opportunities for prevention. *Prev Chronic Dis.* 2006;3(2):A53.
12. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol.* 1997;17(6):1121-1127.
13. Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of loss of lung function in the elderly: the Cardiovascular Health Study. *Am J Respir Crit Care Med.* 2001;163(1):61-68.