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INFECTION HOSPITALIZATION INCREASES RISK OF DEMENTIA IN THE ELDERLY

Judith A Tate, PhD, Beth E Snitz, PhD, Karina A Alvarez, MA, Richard L Nahin, PhD, Lisa A Weissfeld, PhD, Oscar Lopez, MD, Derek C Angus, MD, Faraaz Shah, MD, Diane G Ives, MPH, Annette L Fitzpatrick, PhD, Jeffrey D Williamson, MD, Alice M Arnold, PhD, Steven T DeKosky, MD, and Sachin Yende, MD

University of Pittsburgh, Pittsburgh, Pennsylvania (Drs Tate, Snitz, Weissfeld, Lopez, Angus, Shah, Yende, Mss Alvarez and Ives); Wake Forest University, Winston-Salem, North Carolina (Dr Williamson); University of Washington, Seattle (Drs. Fitzpatrick and Arnold); National Center for Complementary and Alternative Medicine, Bethesda, Maryland (Dr Nahin); and University of Virginia, Charlottesville, Virginia (Dr DeKosky).

Abstract

Objectives—Severe infections, often requiring intensive care unit (ICU) admission, have been associated with persistent cognitive dysfunction. Less severe infections are more common and whether they are associated with an increased risk of dementia is unclear. We determined the association of pneumonia hospitalization with risk of dementia in well-functioning older adults.

Design—Secondary analysis of a randomized multicenter trial to determine the effect of Ginkgo biloba on incident dementia.

Setting and Subjects—Community volunteers (n=3069) with a median follow-up of 6.1 years.

Measurement and Main Results—We identified pneumonia hospitalizations using ICD-9CM codes and validated them in a subset. Less than 3% of pneumonia cases necessitated ICU admission, mechanical ventilation or vasopressor support. Dementia was adjudicated based on neuropsychological evaluation, neurological exam, and magnetic resonance imaging. Two hundred twenty one participants (7.2%) incurred at least one hospitalization with pneumonia (mean time to pneumonia=3.5 years). Of these, 38 (17%) developed dementia after pneumonia with half of these cases occurring 2 years after the pneumonia hospitalization. Hospitalization with pneumonia was associated with increased risk of time to dementia diagnosis (unadjusted hazard ratio [HR] = 2.3, CI: 1.6–3.2, p<0.0001). The association remained significant when adjusted for age, sex, race, study site, education, and baseline Mini-Mental Status Exam (HR=1.9, CI 1.4–2.8, p<.0001). Results were unchanged when additionally adjusted for smoking, hypertension, diabetes, heart disease, and pre-infection functional status. Results were similar using propensity analysis where participants with pneumonia were matched to those without pneumonia based on age, probability of developing pneumonia, and similar trajectories of cognitive and physical function prior to pneumonia (adjusted incidence rates: 91.7 vs. 65 cases per 1,000 person-years,

Address for correspondence: Judith Ann Tate, PhD, RN, 318 Victoria Building, School of Nursing, 3500 Victoria Street, Pittsburgh, PA 15260, 412-624-5872.

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adjusted incidence rate ratio=1.6, CI:1.06–2.7, $p=0.03$). Sensitivity analyses showed that the higher risk also occurred among those hospitalized with other infections.

Conclusion—Hospitalization with pneumonia is associated with increased risk of dementia.

Keywords

pneumonia; dementia; older adults

As the population ages, dementia represents an increasing burden to individuals, families, and the healthcare system worldwide. The number of dementia cases is expected to triple within the coming decades because of an expanding elderly population (1–2). Yet, causes of dementia remain poorly understood (3–7).

Animal and human studies suggest that infection may be an important risk factor for dementia, likely by increasing circulating inflammation and causing neuroinflammation (3–15). Prior studies examined the relationship between infection and cognitive dysfunction, and suggest that an episode of severe infection, especially if it requires admission to the intensive care unit (ICU), may worsen cognitive decline (16–20). Whether less severe infections increase risk of dementia is not known. These infections are more common and an association with increased risk of dementia would have important public health implications. Furthermore, prior studies that examined the relationship between infection and cognition had methodologic limitations. First, they conducted within-person analyses and examined trajectories of cognitive decline before and after infection. A limitation of this approach is that cognitive decline may be underway in the months preceding the infection and infection may merely be a marker for those that had started experiencing cognitive decline. Second, they examined the association between infection and persistent cognitive dysfunction and not dementia.

We addressed these limitations and determined the association between pneumonia hospitalizations and risk of dementia in a cohort of community dwelling older adults, where most cases did not require ICU admission, mechanical ventilation, or develop shock. We chose pneumonia because it is the most common infectious cause of hospitalization in developed countries (21–23).

MATERIALS AND METHODS

Study design, participants, and sample size

We conducted a secondary analysis of the Ginkgo Effect on Memory study (GEMs), a randomized double-blind clinical trial conducted at 5 academic medical centers to determine the effect of Ginkgo biloba on cognitive decline and incident dementia in older adults (24–25). Details of this study and the results of the trial where Ginkgo-biloba did not reduce risk of dementia are described elsewhere (24–25) and in the Supplemental Digital Content 1, which provides details of the methods in the GEM study.

Briefly, 3069 community-dwelling adults 75 years and older were followed between 2000–2008 (median follow-up = 6.1 years). Exclusion criteria were those with dementia and

conditions that might potentially affect cognitive function or place them at higher risk of development of dementia, such as Parkinson's disease and participants who were being treated with cognitive enhancers or cholinesterase inhibitors. Other eligibility criteria are included in Supplemental Digital Content 2, Table 1. Each site obtained approval from their local Institutional Review Board and informed consent from each participant.

We used 2 approaches to examine the risk of dementia after pneumonia. First, we used a cohort design and incorporated pneumonia as a time-varying covariate to determine whether pneumonia decreased time to dementia. Second, we compared incidence rates of dementia after pneumonia for participants with and without pneumonia hospitalization using propensity analysis to match participants. We conducted sensitivity analyses and assessed the effects of competing risk of death on the association between pneumonia and dementia. Additional details of these approaches are described below.

Outcomes

The primary outcome measure was diagnosis of dementia. An important strength of GEMs is that it used approaches to screen and diagnose dementia that were previously validated and based on consensus guidelines (26–29).

Because the primary outcome of GEMs was dementia, participants were screened with cognitive tests, including Teng's modified mini-mental status exam (3MSE)(30), the Alzheimer's Disease Assessment Scale (ADAS-Cog) (31), and the Clinical Dementia Rating (32), every 6 months during the course of the study. Participants were referred for a full neuropsychological battery (NPB) any time during the study if their scores declined to a pre-determined threshold on two of three cognitive screening tests. In addition, full NPB testing was conducted if the participant or proxy reported new onset memory difficulties, if the participant was prescribed medication for cognitive enhancement, or if the participant received a new diagnosis of dementia from their private physician.

An expert, centralized panel of neuropsychologists and neurologists blinded to treatment arm reviewed the results of the full NPB, proxy interview, functional status, depression scores, review of medications, and clinical neurologic exam and adjudicated the diagnosis of dementia. Participants diagnosed with dementia also underwent Magnetic Resonance Imaging (MRI), which were reviewed by a neuroradiologist.

The expert panel used the DSM-IV and National Institute of Neurological and Communication Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)(26) criteria. We used the NINCDS-ADRDA criteria in addition to the DSM-IV criteria because the DSM-IV criteria required the presence of memory deficits to diagnose dementia and epidemiologic studies suggest that some patients may have dementia in the absence of memory deficits (33–34). The panel first determined that dementia was present, and later the type of dementia using published diagnostic criteria (e.g., National Institute of Neurological Disorders and Stroke– Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (29–30), the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) (31) criteria for vascular and Alzheimer's dementia).

Ascertainment of hospitalization with pneumonia

All inpatient admissions to hospital were recorded in GEMs participants. We used previously validated International Classification of Diseases, ninth edition- Coding Manual (ICD-9CM) codes (480–488) and textual search of discharge diagnoses to identify hospitalizations with pneumonia (35). We established validity of our approach by reviewing history and physical examination and discharge diagnoses of 75 randomly selected charts (50 and 25 cases with and without pneumonia recorded in the diagnoses fields). Of the 50 pneumonia cases, 92% were hospitalized *for* pneumonia and met both clinical and radiologic criteria for pneumonia as described by Fine et al (36). Less than 3% of pneumonia cases necessitated ICU admission, mechanical ventilation or vasopressor support. Of the 25 cases without pneumonia, pneumonia was not recorded in history and physical examination or discharge summary in a single participant.

Clinical risk factors

We examined clinical characteristics that were associated with the development of pneumonia (36) or dementia. These include demographic characteristics; specifically, age, race, sex, and years of education, self-reported chronic diseases, including history of heart disease (atrial fibrillation, angina, myocardial infarction, angioplasty, or cardiac surgery), lung disease (emphysema or asthma), neurovascular disease (transient ischemic attack [TIA] or stroke), diabetes, and hypertension, and health behaviors, including prior and current smoking history. Cognitive function was determined using the Teng's Modified Mini Mental Status Exam (3MSE) (32) and was measured at study entry and semi-annually during the course of the study (24). Physical function was determined by self-reported difficulty with at least one activity of daily living (ADL).

Statistical analysis

We conducted univariate analyses to compare clinical characteristics for participants who had been hospitalized with pneumonia and those who had not been hospitalized with pneumonia.

We used 2 approaches to determine the risk of dementia after pneumonia. First, we used a time-varying covariate analysis to determine whether pneumonia hospitalization is associated with time to dementia. Because pneumonia occurred at different time points for participants in the study, the time varying covariate model estimates the hazard ratio conditional upon occurrence of pneumonia and censors cases if dementia occurred prior to occurrence of pneumonia or the participant dies. We conducted unadjusted and adjusted analyses to account for potential confounders that may increase risk of pneumonia and dementia. We adjusted for demographics, site, baseline cognitive and physical function, smoking, hypertension, heart disease, and diabetes.

Second, we compared incidence rates of dementia among those with and without pneumonia using propensity matched analysis (37–40). Participants with pneumonia have lower survival and therefore may be less likely to be diagnosed with dementia. Thus, comparing incidence rates allowed us to compare dementia risk while accounting for differences in exposure time between the 2 groups. We matched each participant with pneumonia with a

participant who had never been hospitalized with pneumonia and was alive at that time point. Matching was based on age (within 2 years), probability or propensity of pneumonia hospitalization calculated at study entry (within 3% risk), and trajectories of 3MSE for cognitive function and ADL for physical function over time. Details of variables to calculate propensity score and model performance are described in Supplemental Digital Content 1. Finally, we also constructed trajectories of cognitive and physical function over time and details are described in the Supplemental Digital Content 1 and below.

We explored how well propensity score matching balanced covariates by estimating the absolute standardized differences before and after matching for covariates (38–39). An absolute standardized difference of less than 0.1 was chosen *a priori* as an indication of good covariate balance between groups (38). We calculated incidence of dementia for those with and without pneumonia using a Poisson model. We adjusted for those covariates where the absolute standardized differences were less than 0.1. We also explored the potential impact of hidden bias due to imbalances in unmeasured covariates using the approach outlined by Rosenbaum et al (41).

We conducted 2 sensitivity analyses for the time-varying covariate analysis. First, infection may be merely a marker for individuals who are frail and already declining in physical or cognitive function. We examined pre-pneumonia trajectories of cognitive and physical function over time. We examined whether pneumonia increases risk of dementia in participants who had no or minimal decline in cognitive and physical function prior to occurrence of pneumonia because pneumonia is less likely to be merely a marker for declining cognitive function in these subgroups. Trajectories were constructed using PROC TRAJ (see Supplemental Digital Content 3, Figure 1 which illustrates the trajectories), an unsupervised approach to identify discrete patterns of changes in longitudinal measures (42). Second, we sought to determine whether higher risk of dementia is unique to pneumonia hospitalization, or also observed in those hospitalized for other infections or hospitalized for other reasons.

Death competes with diagnosis of dementia. Participants hospitalized with pneumonia have higher mortality compared to those who are not hospitalized with pneumonia (43–44), thereby leading to unequal exposure time. We conducted 2 analyses to assess the effect of competing risk of death on the association between pneumonia and dementia. First, we compared risk of death and dementia for participants with pneumonia and propensity-matched controls over different time intervals to determine whether competing risk would over or under-estimate the association between pneumonia and dementia. Second, we repeated the time-varying covariate analyses with 2 assumptions: all subjects who died had dementia at the time of death and all subjects who died survived to end of study without a diagnosis of dementia. These analyses would allow us to determine range of hazard ratios (HR) for competing risk of death. All analyses were conducted using SAS 9.3 and EXCEL 2007.

RESULTS

Participant Characteristics

The average age in the GEMs cohort was 78.6 years, 54% of participants were male, and 4.5% were non-white. At study entry, most had normal cognitive function (average 3MSE score was 93.3) and 15.7% had mild cognitive deficit. Most participants had good physical function and only 17.7% reported difficulty with 1 or more ADL.

In longitudinal analyses using pre-pneumonia measures for those with pneumonia and all available measures for remaining participants, we identified 3 trajectories of cognitive and physical function, including no, minimal, or severe decline. Overall the group identified as no decline in 3MSE had an average score of 96.3 on study entry and changed very little during the course of the study (see Supplemental Digital Content 3, Figure 1 for illustration of trajectory groups). The group with minimal change had an average score of 91.7 on study entry and remained above 90 at study conclusion. The group with severe decline in cognitive function had an average score of 87.7 on study entry and demonstrated an appreciable decrement in 3MSE score by study conclusion. Most of the GEMs cohort (69.2%) experienced no or minimal decline in 3MSE during the study period. Similarly, 3 trajectories of physical function were observed and most participants (96.8%) experienced no or minimal decline in physical function during this study. Those in the group with no decline reported loss of less than 1 ADL, while those with minimal decline reported difficulty with more than 1 ADL by study conclusion. Those in the group with a severe decline reported difficulty with more than 2 ADL upon enrollment with declines in nearly all ADLs during the course of the study.

Of the 3069 participants, 523 (17%) developed dementia over median follow-up of 6.1 years (cumulative incidence of dementia= 23 cases per 1,000 person years) and the average time to diagnose dementia was 4.3 years (standard deviation [sd] = 1.6 years). We identified 221 (7.2%) participants hospitalized for pneumonia at least once and used the date of their first pneumonia hospitalization as the reference date. On average, pneumonia hospitalization occurred at 3.5 years post-enrollment (sd = 1.9 years, range =0.1–7.4 years). Of the 221 pneumonia hospitalizations, 68% of those hospitalizations occurred on the first or second hospitalization (first and second hospitalizations were for pneumonia in 44.3% and 23.5%). Only 6 cases (2.7%) of pneumonia occurred after dementia diagnosis. These cases were censored in the time-varying analysis.

The participants hospitalized with pneumonia were older, were more likely to be men, had less education, and were more likely to have a history of heart disease and smoking than the group without pneumonia (Table 1). However, both groups had similar cognitive and physical function at study entry.

Association between pneumonia and development of dementia

Of the 221 participants hospitalized at least once with pneumonia, 38 (17%) developed dementia after their first pneumonia hospitalization. Of the 38 cases of dementia, 13 cases (34%) occurred within 1 year after pneumonia and 22 cases (58%) occurred within 2 years. Alzheimer's dementia was the most common type diagnosed in 34 of 38 cases (89%).

Although the absolute risk of developing dementia after pneumonia was similar to the entire cohort, the incidence rate of dementia was higher for participants who were hospitalized with pneumonia (91.7 cases per 1,000 person-years compared to 23 cases per 1,000 person-years). This difference in the absolute risk and incidence rate was due to lower survival after pneumonia.

In a time-varying covariate analysis, pneumonia was associated with increased risk of time to diagnosis of dementia (HR = 2.3, CI: 1.6–3.2, $p < 0.0001$, Table 2). The association remained significant when adjusted for age, sex, race, site, education, and baseline 3MSE (HR=1.9, CI: 1.4–2.89, $p < 0.0001$). Additionally adjusting for cardiovascular disease, smoking, and diabetes at baseline did not alter the HR (HR= 3.6, CI: 1.6–8.1, $p = 0.0018$).

For propensity analysis, we matched 217 participants who were hospitalized for pneumonia and did not have prior diagnosis of dementia to participants who were not hospitalized for pneumonia but had similar age, propensity to develop pneumonia, and cognitive and physical function trajectories. The weighted absolute conditional standardized differences for each covariate before and after matching are reported in Table 3 and 4 respectively. As expected matching on probability of pneumonia hospitalization, age and group membership for trajectories of cognitive and physical function were well balanced. In addition, the distributions for most of the baseline covariates were similar for the matched pairs. The weighted absolute conditional standardized differences exceeded 0.1 for 3 of the 19 baseline characteristics, specifically, history of lung disease, history of TIA and income, indicating a potential confounding influence for these three covariates. Results in propensity analysis were similar to time-varying covariate analysis and pneumonia hospitalization was associated with higher incidence of dementia (91.7 vs. 65 cases per 1,000 person-years; adjusted incidence rate ratio=1.66 [1.06–2.71], $p = 0.03$, adjusted for history of lung disease, history of TIA and income).

In the absence of hidden confounders, a sign-score test for matched data with censoring provides strong evidence ($p = 0.03$) that older adults hospitalized with pneumonia had an increased risk of dementia compared to those who were not hospitalized. While our matched cohort was well-balanced in almost all baseline covariates examined, it is possible that imbalances in unmeasured covariates have biased our results. This analysis reveals that an unmeasured binary covariate would both have to be a near-perfect predictor of dementia and would need to increase the odds of being hospitalized for pneumonia at least 6% to explain away our observed findings.

Sensitivity analysis

The association between pneumonia and risk of dementia persisted in the subset that was on a trajectory of no or minimal decline in cognition and physical function prior to occurrence of pneumonia (HR=2, CI: 1.1–3.6, Table 2). Thus, our results were unlikely to be confounded by the occurrence of pneumonia in participants who were frail or were experiencing large changes in cognitive function prior to pneumonia.

Of the 3069 participants, 1913 were hospitalized at least once. Of these 1913 participants, 221 were hospitalized with pneumonia, 287 were hospitalized with other infections, and

1405 were hospitalized for other reasons. The most common infections were urinary tract infection (n=136, 47%), cellulitis (n=55, 19%), bacteremia/septicemia (n=38, 13%), and cholecystitis (n=12, 4%). Compared to participants who were never hospitalized, those hospitalized with pneumonia and other infections had similar risk of dementia (HR=2.4, CI: 1.7–3.5 and 2.1, CI: 1.5–2.8, Table 2). We identified 136 subjects who were hospitalized more than once with an infection. The risk of dementia was similar to those hospitalized with pneumonia (HR=2.1, 95% CI=1.4–3.2, P=0.0003). In contrast, those hospitalized for other reasons did not have higher subsequent risk of dementia (HR=1.0, CI: 0.8–1.1). Thus, the higher risk of dementia observed after pneumonia hospitalization was observed among participants hospitalized for a broad range of infectious conditions.

Competing risk

We compared the risk of dementia and death at intervals following pneumonia hospitalizations (within 6 months, 6 months–1 year, 1–3 years and over 3 years) for the cases and propensity-matched control groups (See Figure 1). Consistent with prior studies, this exploratory analysis demonstrates that the risk of death is higher during the first 6 months following pneumonia compared to controls (22.3% vs. 1.9%). Furthermore, the risk for dementia increased over time in both cases and controls, albeit at different rates. Thus, competing risk of death may underestimate the association between pneumonia and dementia. Furthermore, the association between pneumonia and dementia remained significant when we assumed that all participants had dementia on the date of death (HR=3.70, CI: 3.05–4.5) and deaths were censored at the end of study (HR=1.65, CI 1.18–2.3).

DISCUSSION

We showed that pneumonia hospitalization is associated with at least a 1.4-fold higher risk of dementia in well-functioning older adults. The higher risk of dementia was observed across a broad range of infections, including pneumonia, urinary tract infection, bacteremia, and cellulitis. Our results were independent of risk factors that increase risk of pneumonia and dementia, including demographic characteristics, education, smoking, heart disease, diabetes, and hypertension. We also adjusted for pre-infection cognition and physical function trajectories; thus pneumonia is less likely to be merely a marker for those already experiencing cognitive decline. Our results were robust and persisted when pneumonia was modeled as a time-varying covariate and in propensity analyses, and are not confounded by competing risk of death. Collectively, these results suggest that hospitalization for infections not severe enough to require intensive interventions, such as mechanical ventilation or vasopressor support, is associated with acceleration in time to dementia diagnosis.

Dementia is a chronic degenerative disease and the pathophysiologic changes of dementia were likely to be underway prior to the occurrence of pneumonia in our study. Our results suggest that an episode of infection accelerates dementia. A potential mechanism to explain this association could be persistent inflammation in the systemic circulation or in the brain or due to activation of other aspects of the innate immune response, as evidenced in observational human studies (4–9, 13–15) and in animal models (10–12, 45). For example, a single lipopolysaccharide injection in animals causes chronic neuroinflammation, long-term

cognitive deficits, and accelerates neurodegenerative conditions (10–12). Epidemiologic studies in individuals without an infection have shown that a small increase in circulating inflammatory mediators was associated with dementia (7), and in those with an infection have shown increased and in some cases persistent circulating inflammation.

Although our study primarily focused on less severe infections, recent work by our group suggests that the risk of dementia is similar regardless of the severity of infection (46). Furthermore, the risk of dementia in this study was similar to the risk of dementia observed in patients with severe pneumonia and severe sepsis. Thus, our results could be generalized to patients hospitalized with infection in different countries, whose illness severity may be different from those in the United States.

Our study has several strengths compared to prior studies. We had detailed measures of cognitive function and physical function annually. We considered 2 important reasons that may confound the association between pneumonia and dementia. First, participants with rapidly declining cognitive function over time may be at higher risk for pneumonia and subsequently develop dementia. Second, prior to the diagnosis of dementia, many individuals experience frailty (47–48), which may place them at higher risk for pneumonia (49–50). In the time-varying covariate analyses, we adjusted for baseline and longitudinal measures of cognitive function and physical function prior to the occurrence of pneumonia using trajectory analyses. Thus, pneumonia is less likely to be merely a marker for patients who would develop dementia. Prior studies that assessed the association between infection and cognitive dysfunction examined changes in cognitive function alone rather than diagnosis of dementia (16–20). Our primary endpoint was all-cause dementia, and was adjudicated based on detailed neuropsychological assessment, neurological and medical evaluation, and MRI of the brain using previously validated approaches (26–29). Finally, prior studies used either a case-control design or conducted a within-person analysis of infection patients alone (16–20). In contrast, we used a cohort design and propensity-matched analysis, and compared risk among several different groups, including those hospitalized with pneumonia, other infections, and for other reasons.

Our study has limitations. First, we used ICD-9 codes and text field searches to identify pneumonia hospitalization. Prior studies suggest that these approaches have good accuracy (35), and chart review of participants in our study showed that over 90% of cases met clinical and radiologic criteria for pneumonia. Second, we did not have data regarding outpatient infections, and whether infections occurring in the outpatient setting have a similar effect on dementia is not known. Third, we do not know the percentage of participants who experienced delirium or received psychoactive medications, factors that may contribute to increased risk of dementia. Finally, we did not utilize a formal index of frailty. Instead, we used decline in physical and cognitive function scores over time as an approximation for frailty.

In conclusion, episodes of pneumonia are associated with higher risk of dementia diagnosis. Future studies should examine mechanisms underlying this association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Risk of dementia and death are shown for each interval (e.g. within 6 months, 6 months –1 year, 1–3 years, > 3 years)

Table 1

Clinical characteristics at enrollment

Variables	All participants (n=3069)	Hospitalized with pneumonia (n=221)	Never hospitalized with pneumonia (n=2848)	p-value
Demographics				
Age at enrollment, mean (sd)	78.6	79.5	78.5	< 0.0001
Sex, female, (%)	1418 (46.2)	81 (36.7)	1337 (46.9)	0.003
Race, non-white (%)	139 (4.5)	10 (4.5)	129 (4.5)	0.998
Education, mean	14.3	13.9	14.4	0.02
Common risk factors for pneumonia at enrollment				
Smoking ever (%)	1787 (58.2)	154 (69.7)	1636 (58.3)	0.001
Lung disease (%)	278 (9.1)	30 (13.6)	248 (8.7)	0.02
Heart disease (%)	888 (28.9)	88 (40.2)	800 (28.7)	< 0.0001
Stroke (%)	88 (2.9)	10 (4.5)	78 (2.8)	0.15
Transient Ischemic Attacks (%)	221 (7.2)	28 (12.7)	193(6.8)	0.005
Diabetes (%)	277 (9.0)	23 (10.4)	254 (9.0)	0.47
Hypertension, (%)	1306 (42.6)	102 (46.2)	1204 (42.7)	0.36
Baseline cognitive measures				
Modified Mini-mental Status Exam (32)	93.36 (4.7)	92.90 (4.8)	93.39 (4.7)	0.13
Alzheimer's Disease Assessment Scale – Cognitive Subscale (46)	6.48 (2.7)	6.80 (2.9)	6.46 (2.7)	0.07
Baseline physical function				
Difficulty with at least one activity of daily living	542 (17.7)	36(16.3)	506 (17.8)	0.58
Difficulty with at least one Instrumental activity of daily living	919 (29.9)	75(33.9)	844(29.6)	0.18

Table 2

Association between pneumonia hospitalization and time to dementia using time-varying covariate analyses

All participants	Hazard ratios (95% confidence limits)	p-value
Unadjusted risk (n=3069)	2.4 (1.7–3.3)	<0.0001
Adjusted risk (n=3069)		
For demographics *, site, education, and baseline cognitive function **	1.9 (1.4 – 2.8)	<0.0001
For demographics, baseline cognitive function, heart disease, hypertension, diabetes, ever smoked	3.6 (1.6–8.1)	0.0018
For demographics and functional status using Activity of Daily Living (ADL) and Instrumental Activity Daily Living (IADL) trajectories ***	3.5 (1.5–8.6)	0.005
Unadjusted risk for participants who had no or mild decline in functional and cognitive status prior to pneumonia hospitalization (n=2425)	2.0 (1.1–3.6)	0.01
Unadjusted risk stratified by reasons for infection type and hospitalization (n=3069)	2.0 (1.1–3.6)	<0.0001
Hospitalizations with pneumonia	2.4 (1.7–3.5)	<0.0001
Hospitalizations with infections other than pneumonia	2.1 (1.5–2.8)	<0.0001
Hospitalizations where infection was not recorded	1.0 (0.8–1.1)	0.83

* Age, sex, race

** Modified Mini-Mental Status Exam (30)

*** Trajectories constructed using ADL and IADL measures before hospitalization for pneumonia and all available longitudinal measures for the remaining participants. Trajectories constructed using Proc TRAJ function (see Supplemental Digital Content 1, which provides details of our methods).

Table 3

Standardized differences of unmatched sample for selected variables

Variables	Hospitalized with pneumonia (n=217)	Not hospitalized with pneumonia (n=2848)	Absolute Standardized Differences
Age at enrollment mean, (sd)	79.5 (3.8)	78.6 (3.2)	0.28
Sex, female (%)	36.7	46.9	0.21
Race, non-white (%)	4.5	4.5	0
Education, mean years completed(sd)	13.9 (3)	14.4 (3)	0.16
Smoking ever (%)	69.7	58.3	0.24
Lung Disease (%)	13.6	8.7	0.16
Heart Disease (%)	40.2	28.7	0.24
Stroke (%)	4.5	2.8	0.09
Transient ischemic attack (%)	12.7	6.8	0.20
Diabetes (%)	10.4	9	0.05
Hypertension (%)	46.2	42.7	0.07
Modified Mini-Mental Status Exam (32)	92.9 (4.8)	93.4 (4.7)	0.11
Difficulty with 1+ Activity of Daily Living (%)	16.3	17.8	0.04
Difficulty with 1+ Instrumental Activity of Daily Living(%)	33.9	29.6	0.09

Table 4

Clinical characteristics at enrollment with standardized difference for matched sample

	Hospitalized with pneumonia (n=217)	Not hospitalized with pneumonia (n=217)	Absolute Standardized Difference
Probability of pneumonia hospitalization	0.09 (0.04)	0.09 (0.04)	0
Membership in Mini-mental Status Exam trajectory group, no or minimal decline (%)	52.5	69.1	0
Membership in Activity of Daily Living trajectory group, no or minimal decline (%)	91.7	90.8	0
Membership in Instrumental Activity Daily Living trajectory group, no or minimal decline (%)	85.7	84.7	0
Demographic Variables			
Age at enrollment mean, (sd)	79.6 (4)	79.6 (4)	0
Sex, female (%)	63.6	63.6	0
Race, non white(%)	4.6	5.1	0.02
Education, mean years completed (sd)	13.9 (3)	14 (3)	0
Smoking ever (%)	29.9	32.7	0.06
Lung Disease (%)	12.0	7.0	0.17
Heart Disease (%)	41.5	42.4	0.02
Stroke (%)	4.6	4.1	0.02
Transient ischemic attack (%)	12.4	7.8	0.15
Diabetes (%)	10.6	10.1	0.01
Hypertension (%)	45.6	43.8	0.04
Modified Mini-mental Status Exam (32)	92.9 (4.8)	92.6 (4.7)	0.07
Difficulty with 1+ Instrumental Activity Daily Living	0.34	0.32	0
Difficulty with 1+ Activity Daily Living	0.17	0.18	0
Income (\$10,000)	4.5 (1.2)	4.1 (1.2)	0.33
Creatinine	1.0 (0.3)	1.0 (0.2)	0.08
Thyroid stimulating hormone	2.4 (2.3)	2.2 (2.3)	0.09
Body mass index	27.5 (4. 9)	27.7 (3.9)	0.03
Alcohol drink/wk	3.7(7.0)	3.6 (6.2)	0.01