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Bidirectional Relationship between Cognitive Function and Pneumonia

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***Rationale*: Relationships between chronic health conditions and acute infections remain poorly understood. Preclinical studies suggest crosstalk between nervous and immune systems.**

***Objectives*: To determine bidirectional relationships between cognition and pneumonia.**

***Methods*: We conducted longitudinal analyses of a population-based cohort over 10 years. We determined whether changes in cognition increase risk of pneumonia hospitalization by trajectory analyses and joint modeling. We then determined whether pneumonia hospitalization increased risk of subsequent dementia using a Cox model with pneumonia as a time-varying covariate.**

***Measurements and Main Results*: Of the 5,888 participants, 639 (10.9%) were hospitalized with pneumonia at least once. Most participants had normal cognition before pneumonia. Three cognition trajectories were identified: no, minimal, and severe rapid decline. A greater proportion of participants hospitalized with pneumonia were on trajectories of minimal or severe decline before occurrence of pneumonia compared with those never hospitalized with pneumonia (proportion with no, minimal, and severe decline were 67.1%, 22.8%, and 10.0% vs. 76.0%, 19.3%, and 4.6% for participants with and without pneumonia, respectively; $P < 0.001$). Small subclinical changes in cognition increased risk of pneumonia, even in those with normal cognition and physical function before pneumonia ($\beta = -0.02$; $P < 0.001$). Participants with pneumonia were subsequently at an increased risk of dementia (hazard ratio, 2.24 [95% confidence interval, 1.62–3.11]; $P = 0.01$). Associations were independent of demographics, health behaviors, other chronic conditions, and physical function. Bidirectional relationship did not vary based on severity of disease, and similar associations were noted for those with severe sepsis and other infections.**

***Conclusions*: A bidirectional relationship exists between pneumonia and cognition and may explain how a single episode of infection in well-appearing older individuals accelerates decline in chronic health conditions and loss of functional independence.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In this study, we demonstrate how changes in cognition over time, even small subclinical changes, are associated with an increased risk of pneumonia and within the same cohort we demonstrate that once participants develop pneumonia, they have an accelerated course to dementia. Similar patterns were seen in those with severe sepsis and when stratified by illness severity.

What This Study Adds to the Field

To our knowledge, we are the first to examine both aspects of this bidirectional relationship between cognitive function and pneumonia within the same study population. Future studies should examine mechanisms underlying this bidirectional relationship to develop interventions and explore the optimal timing to initiate these interventions to reduce infection and subsequent disability.

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Author Contributions: S.Y. and F.A.S. designed the study, requested relevant data from the Cardiovascular Health Study, assisted in the statistical analyses, and were responsible for compiling the manuscript. F.P. and K.A. performed all statistical analyses including trajectory modeling, joint modeling of cognitive function, and time varying covariate analyses. D.A., J.T., and A.W. helped refine the analyses and provided critical revisions for the manuscript. O.L. and A.B.N. provided data from the Cardiovascular Health Study and provided critical revisions for the manuscript. V.K., J.A.K., N.H., D.A., M.A., V.S.F., A.W., and R.G.B. are members of the Cardiovascular Health Study Lung working group who helped design the initial plan for our analyses and also reviewed the manuscript.

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Approximately half of all adults have a chronic health condition and these conditions are a leading cause of disability and death. A single episode of infection may also lead to a cascade of secondary illnesses, disability, and death (1–3). However, the relationship between chronic health conditions and infection remains poorly understood, particularly in community-dwelling individuals without major impairments in cognition or physical function.

We examined the relationship between pneumonia and cognition because pneumonia and dementia are common and

leading causes of death (4). We hypothesized that a bidirectional relationship exists whereby small, subclinical changes in cognition increase the risk of pneumonia hospitalization, and once pneumonia occurs, it accelerates underlying cognitive dysfunction and leads to dementia and loss of functional independence. Several preclinical studies support our hypothesis that a bidirectional relationship exists between the nervous and immune systems. For example, a cholinergic pathway by way of the vagus nerve inhibits release of proinflammatory mediators by the macrophages and may increase risk of infection (5). Increased systemic inflammation during an acute infection may persist, which may adversely affect the blood–brain barrier, cause persistent neuroinflammation, and cause changes in neuroimmune cells that are similar to those observed in neurodegenerative conditions, including Alzheimer disease (6–11). If a bidirectional relationship between cognition and acute infection exists, infections may play an important role in altering and accelerating trajectories of functional decline in older adults (12). Furthermore, it would underscore the need to develop early, effective preventive strategies for infections and identify a common set of mechanisms that play a role in cognitive decline and infection (13–15).

METHODS

Study Population and Design

We analyzed 5,888 participants from the Cardiovascular Health Study (CHS), a population-based observational cohort, over 10 years. CHS recruited community-dwelling, well-functioning participants who were 65 years of age or older from four US states in 1997–1998. The details of this cohort have been previously described and can be found in the online supplement (16, 17). Informed consent was obtained from all participants.

We used a cohort design and conducted longitudinal analyses to determine the bidirectional relationship between cognition and pneumonia in all CHS participants. We first determined whether decline in cognitive function over time increased risk of hospitalization with pneumonia using two approaches: trajectory analyses and joint modeling. We then determined whether pneumonia hospitalization accelerates time to dementia using a Cox proportional hazards model where pneumonia was included as a time-varying covariate in a subset (n = 3,602).

Cognitive Function

Annually the Teng Modified Mini-Mental State (3MS) examination was measured in CHS participants (18). 3MS is similar to the mini-mental state examination but is scored from 0–100 and is more sensitive to detect cognitive dysfunction in community-dwelling adults. A 3MS score below 79 is generally accepted as an indicator for severe cognitive impairment or dementia and a 5- to 10-point change in 3MS over a 5-year period is considered clinically significant (19).

Dementia was adjudicated based on neuropsychiatric testing and magnetic resonance imaging evaluations in 3,602 participants (17). In addition to annual testing with 3MS, the participants in this subgroup underwent extensive neuropsychiatric testing in Year 10 of the study to determine the presence of dementia. These tests were conducted on participants who were believed to be high risk (*see* online supplement) at three sites and in all participants at the Pittsburgh site, the latter served to validate screening methods for high-risk participants. Participants with abnormal testing on neuropsychiatric examination underwent physician assessment, magnetic resonance imaging, assessment for depression, and central adjudication of dementia. Time to dementia was determined in those for whom dementia was confirmed by retrospective review of 3MS scores.

Hospitalization with Pneumonia, Severe Sepsis, and Other Infections

Participants were asked about any major illnesses or hospitalizations at annual visits and in semiannual telephone contacts. Medical records were obtained for all hospitalizations and pneumonia was identified using previously validated International Classification of Diseases, 9th edition Clinical Modification codes (20–22). Independent review of 158 pneumonia hospitalizations showed that clinical and radiologic diagnoses of pneumonia were recorded in more than 85% and 80% of cases (*see* online supplement).

We also identified severe pneumonia (pneumonia with organ dysfunction), severe sepsis (infection with organ dysfunction), and infections alone using International Classification of Diseases, 9th edition Clinical Modification codes (23). These codes have been validated for severe sepsis previously (24). Severe sepsis cases included those hospitalized with pneumonia.

Clinical Variables

Clinical variables at study entry or baseline were obtained from participants and included demographics (age, sex, and race); level of education; income level; health behaviors (smoking, alcohol use, and exercise capacity as evidenced by blocks walked per week); and chronic health conditions (obtained by self-report and confirmed by review of medications and medical records). Chronic conditions included hypertension, coronary heart disease, diabetes mellitus, congestive heart failure, peripheral vascular disease, atrial fibrillation, and cerebrovascular accident. We used FEV_1 to assess lung function and estimated glomerular filtration rate using Modification of Diet in Renal Disease equation for kidney function. Additionally, we assessed physical function annually using activities of daily living (ADL) and instrumental ADL (IADL).

Statistical Analysis

We examined the association between baseline characteristics and risk of pneumonia hospitalization. Continuous variables were compared using Student *t* tests and categorical variables were compared using chi-square tests.

The interval between occurrence of pneumonia and the last available 3MS measure varied. We incorporated all 3MS measures before pneumonia in an extended Cox model (*see* online supplement) and estimated the 3MS immediately before the occurrence of pneumonia.

We examined the relationship between longitudinal changes in cognitive function over time and risk of pneumonia using two approaches (*see* online supplement). First, we constructed trajectories of cognitive function over time using Proc Traj, an unsupervised learning tool that clusters participants with similar trajectories into groups (25). For participants who were hospitalized with pneumonia, we used all 3MS measurements before the development of pneumonia, and for the remaining participants, all available 3MS measures either until the end of the study or until they died. The distribution of trajectories was compared between participants who were and were not hospitalized with pneumonia using chi-square test.

Second, we used a joint model to determine the relationship between decline in cognition over time and risk of pneumonia. Joint modeling fits a longitudinal model for 3MS scores over time to determine cognitive function at the time of pneumonia (26, 27). We chose joint modeling because it allowed us to simultaneously model associations between baseline cognition, changes in cognition over time, cognitive function immediately before the onset of pneumonia, and risk of time to pneumonia. We initially performed unadjusted joint modeling and then adjusted for demographics, income, educational status, health behaviors (smoking history, alcohol use, and blocks walked per week), lung (percent predicted FEV_1) and kidney function (estimated glomerular filtration rate), history of hypertension, atrial fibrillation, stroke, coronary heart disease, congestive heart failure, and diabetes because these factors may increase risk of pneumonia (28–32). We also adjusted for longitudinal changes in physical function by constructing trajectories of ADLs and IADLs and including group membership for these trajectories as a covariate. We adjusted for physical function to account for participants undergoing decline in physical function that may increase risk for pneumonia.

We performed a subset analysis using the joint model for the participants who were on trajectories of no or minimal cognitive decline for two reasons. First, most of these participants had normal cognitive and physical function before pneumonia hospitalization and would represent well-appearing participants. Second, change in cognitive function over time in these individuals would be small, thereby allowing us to

examine the relationship between small subclinical changes and pneumonia susceptibility.

We modeled pneumonia as a time-varying covariate in a Cox proportional hazards model and determined whether pneumonia accelerated time to dementia. This model allowed us to examine the risk of dementia conditional on occurrence of pneumonia. Unadjusted and adjusted analyses were performed. The adjusted analyses included the same covariates used to assess the relationship between 3MS and pneumonia. Trajectories of cognitive function before pneumonia hospitalization were also included as a covariate in this analysis because these trajectories were associated with higher risk of pneumonia and may confound the association between pneumonia and subsequent risk of dementia.

We examined whether the bidirectional relationship is also observed with different types of infection (pneumonia alone or with any infection) and severity as evidenced by presence or absence of organ dysfunction. We analyzed the following groups: participants hospitalized with severe sepsis, infection alone, and never hospitalized with infection; and those hospitalized with severe pneumonia, pneumonia without organ dysfunction, and never hospitalized with pneumonia. Finally, we assessed whether the bidirectional relationship was observed only in participants hospitalized with pneumonia or was also seen among participants hospitalized for any reason. Frequency of missing data and additional analyses performed assessing impact of mortality on the bidirectional relationship are included in the online supplement. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) or PAWS Statistics version 18 (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Of the 5,888 community-dwelling well-functioning older participants, 639 (10.9%) were hospitalized with pneumonia at least once over 10 years. The median time to pneumonia hospitalization was 5.8 years (interquartile range, 3.2–7.9 yr). Of the 639 hospitalized with pneumonia, 159 (24.9%) participants incurred organ dysfunction. Of these, 71 required mechanical ventilation and had shock during their hospitalization.

Compared with participants never hospitalized with pneumonia, those who were hospitalized were older, more likely to be male, and had a higher prevalence of chronic conditions (Table 1). At baseline, 3MS scores were slightly lower for those who were hospitalized with pneumonia compared with those never hospitalized with pneumonia, but these differences were small (86.4 vs. 89.9; $P < 0.001$). Most participants required minimal assistance in ADLs and IADLs, and there were small differences in physical function between those ever and never hospitalized with pneumonia. Compared with those never hospitalized with pneumonia, participants who were hospitalized had higher baseline number of ADLs and IADLs requiring assistance (average number of ADLs requiring assistance was 0.36 vs. 0.16 and average IADLs was 0.63 vs. 0.33; $P < 0.001$). Furthermore, most participants did not incur new impairments before pneumonia (*see* Figure E1 in the online supplement). Anticholinesterase inhibitors were used in fewer than 2% of cases throughout the study period.

Of the 5,888 CHS participants, dementia was adjudicated in 3,602 (61.1%) participants. Baseline characteristics of those in whom dementia was adjudicated are described in Table E1. In general, baseline characteristics and cognition for the subgroup in whom dementia was adjudicated was similar to all CHS participants, except for slightly lower frequency of chronic health conditions.

Cognitive Function before Pneumonia

Three distinct trajectories of 3MS scores were identified for cognitive function: (*1*) no decline, (*2*) minimal decline, and (*3*) severe rapid decline in the entire cohort (Figure 1). The same three trajectories were observed when only 3MS scores before pneumonia were used. These trajectories differed based on 3MS scores at enrollment and change in scores over time. Participants on trajectories of no decline had an average 3MS score of 93.5 at enrollment and subsequently experienced no change

TABLE 1. CHARACTERISTICS OF ALL PARTICIPANTS ON ENTRY TO THE CARDIOVASCULAR HEALTH STUDY AND STRATIFIED BY OCCURRENCE OF PNEUMONIA

Variable	All Participants (*n = 5,888*)	Participants Never Hospitalized with Pneumonia (*n = 5,249*)	Participants Hospitalized with Pneumonia (*n = 639*)	*P* Value*
Demographics				
Age at enrollment in the study, mean (SD)	72.8 (5.6)	72.5 (5.5)	75.3 (6.2)	<0.001
Sex, female, n (%)	3,393 (57.6)	3,090 (58.9)	336 (52.6)	<0.001
Race, black, n (%)	924 (15.7)	825 (15.7)	99 (15.5)	0.883
Body mass index, mean (%)	26.69 (4.7)	26.76 (4.7)	26.1 (4.8)	<0.001
Smoking (ever vs. never), n (%)	3,144 (53. 5)	2,748 (52.4)	396 (62.1)	<0.001
Comorbid conditions				
Congestive heart failure, n (%)	275 (4. 7)	209 (4.0)	66 (10.3)	<0.001
Coronary heart disease, n (%)	1,154 (19.6)	977 (18.6)	177 (27.7)	<0.001
Stroke, n (%)	249 (4.2)	198 (3.8)	51 (8.0)	<0.001
Diabetes, n (%)	956 (16.4)	824 (15.9)	132 (20.9)	0.001
Chronic kidney disease,† n (%)	764 (13.2)	650 (12.6)	114 (18.2)	<0.001
Percent predicted FEV_1, mean (SD)	92.3 (22.3)	91.1 (21.7)	80.5 (24.9)	<0.001
Percent predicted $FEV_1 < 80\%$, n (%)	1,574 (28.3)	1,321 (25.2)	253 (39.6)	<0.001
Cognitive function‡				
Modified Mini-Mental State examination, mean (SD)	89.6 (7.3)	89.91 (9.0)	86.5 (12.7)	<0.001
Physical function				
Activities of daily living requiring assistance, mean (SD)	0.12 (0.54)	0.16 (0.58)	0.36 (0.91)	<0.001
Instrumental activities of daily living requiring assistance, mean (SD)	0.36 (0.75)	0.33 (0.71)	0.63 (1.04)	<0.001
15-foot walk test in seconds, mean (SD)	5.8 (2.3)	5.7 (2.1)	6.3 (2.6)	<0.001

* *P* values are calculated for independent sample *t* tests for continuous variables (age at enrollment, body mass index, percent predicted FEV_1) and chi-squared analysis for dichotomous variables (sex, race, tobacco use, and prevalence of comorbid conditions).

† Chronic kidney disease was defined as glomerular filtration rate less than 60 ml/min/1.73 m^2.

‡ Cognitive function was assessed using the Teng Modified Mini-Mental State examination, a screening tool for cognitive impairment in community-dwelling older adults. The typical cut-off used to indicate the presence of cognitive impairment is a score below 79.

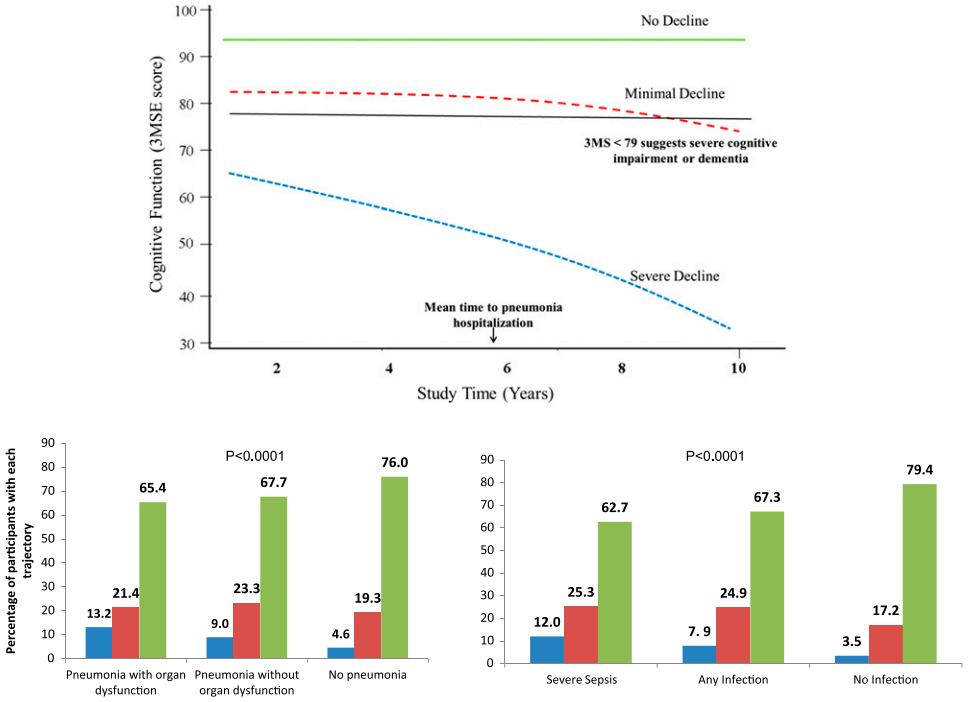

Figure 1. Representative trajectories of cognitive function over 10 years in all participants (*top panel*). Trajectories were constructed using Teng Modified Mini-Mental State (3MS) examination status scores for all participants, and before the index event and using all available data for those never hospitalized with pneumonia. Three trajectories were identified in the study population: no, minimal, and severe decline based on baseline scores and change in scores over time (4,420 [75.1%], 1,161 [19.7%], and 307 [5.2%], participants respectively). Distribution of the trajectories among those with and without pneumonia and severe sepsis is stratified by illness severity in the *bottom panels*. Participants hospitalized with pneumonia were more likely to be on trajectory of severe and minimal decline compared with no decline. Similar patterns were seen in those with sepsis and when stratified by illness severity.

in cognition throughout the ascertainment period (average score at 10 yr was 95.3). Those on trajectories of minimal decline had an average 3MS score of 82.3 at enrollment with a small decline over 10 years (mean score was 75.9 at 10 yr). Those on a trajectory of severe decline had a low 3MS score at enrollment (average score, 62) and incurred large changes over 10 years. Most CHS participants (72.7%) were on trajectories of no decline. Twenty-one percent of participants experienced minimal decline in cognitive function over time and 5.8% experienced severe rapid decline.

A greater proportion of those with pneumonia had trajectories of minimal or severe rapid cognitive decline and fewer had trajectories of no decline compared with participants never hospitalized with pneumonia (participants with pneumonia, no decline 67.1%, minimal decline 22.8%, severe rapid decline 10.0% vs. participants who were never hospitalized with pneumonia, no decline 76.0%, minimal decline 19.3%, severe rapid decline 4.6%; $P < 0.001$).

3MS scores were measured on average 208 days (interquartile range, 112–285 d) before pneumonia hospitalization. Despite the association between cognitive decline and pneumonia, more than two-thirds of participants who were hospitalized with pneumonia had normal cognition before pneumonia. Using extended Cox model, we estimated that the average 3MS score immediately before pneumonia was 90.2 (SD = 10). Most subjects (73%) who were on trajectories of no and minimal decline had few physical impairments before pneumonia (average number of ADLs requiring assistance = 0.21; *see* Figure E1), indicating that participants with pneumonia were well-appearing and without major cognitive or physical impairments before pneumonia.

Association between Cognition and Pneumonia

Only 9.7% of those on trajectories of no cognitive decline were hospitalized with pneumonia, but 12.6% of those on trajectories of minimal decline and 20.8% of participants on trajectories of severe decline were hospitalized with pneumonia ($P < 0.001$). The association between cognitive function and risk of pneumonia observed in the trajectory analyses was also observed with the joint modeling. We fit joint models in a stepwise manner for the univariate analyses to determine how cognitive function affects the risk of time to pneumonia hospitalization. We first estimated the effect of baseline cognition by assessing the effect of 3MS score at study entry alone on risk of time to pneumonia hospitalization ($\beta = -0.02$ for one-point decrease in 3MS score; $P < 0.0001$). This implies a 2% increase in the hazard of pneumonia hospitalization for a one-point lower 3MS score at baseline. We next added rate of change in 3MS over time to the model, and in this model 3MS at baseline and rate of change were significantly associated with risk of time to pneumonia hospitalization ($\beta = -0.02$ for one-point decrease in baseline 3MS score, $P = 0.01$; and association estimate is -0.24 for one-point decrease in 3MS annually, $P < 0.0001$). Finally, when we added cognitive score immediately before pneumonia to the model, neither baseline 3MS nor the rate of change were significant, only cognitive score immediately before the pneumonia hospitalization was associated with increased risk of pneumonia ($\beta = -0.02$ for one-point decrease in 3MS; $P < 0.001$). Thus, a 1-, 5-, and 10-point change would increase the hazard of pneumonia by 2.4%, 11.6%, and 21.9%, respectively. Similar results were seen in adjusted analyses, although the estimates were attenuated ($\beta = -0.009$; $P < 0.001$). In the adjusted analyses, a 10-point lower 3MS score would increase hazards of pneumonia by 8.4%.

Excluding participants on trajectories of severe decline because they had major cognitive and physical impairment before pneumonia, we focused on the subset with trajectories of no or minimal decline and considered to be well-appearing (n = 5,581). We fit joint models with three parameters in a stepwise fashion, similar to the joint models for the entire cohorts. Results were similar and only 3MS scores before pneumonia were significant (adjusted $\beta = -0.008$; $P < 0.0001$). Thus, a 10-point lower 3MS score would increase hazards of pneumonia by 7.7%.

Association between Pneumonia and Subsequent Dementia

Of the 3,602 participants in whom dementia was assessed, 707 developed dementia over 10 years. Median time to dementia diagnosis was 5.2 years. Of the 3,602 participants, 320 (8.8%)

were hospitalized with pneumonia, and of these, 39 (12.2%) developed dementia after their pneumonia hospitalization. On average, participants developed dementia 2 years after their pneumonia episode. Type of dementia was adjudicated in 37 of these cases: 17 had Alzheimer dementia, 6 had vascular dementia, and 14 had both. Hospitalization with pneumonia was associated with increased hazard for subsequent development of dementia in unadjusted analyses (hazard ratio [HR], 2.24; 95% confidence interval [CI], 1.62–3.11; $P < 0.001$). This relationship remained significant even after adjusting for demographics, health behaviors, other chronic health conditions, and for trajectories of physical and cognitive decline before pneumonia hospitalization (HR, 1.57; 95% CI, 1.11–2.22; $P = 0.01$). We also adjusted for atrial fibrillation, blocks walked, and income but did so separately because greater than 5% data was missing for these variables, but results remained significant (HR, 1.83; 95% CI, 1.17–2.86; $P = 0.007$).

Effect of Severity of Infection and Type of Infection on Bidirectional Relationship

Of the 5,888 participants, 399 (6.8%) and 1,932 (32.8%) were hospitalized with severe sepsis and infection alone. Similar to pneumonia hospitalization, those hospitalized with severe sepsis and those hospitalized with other infections were more likely to be on trajectories of severe and minimal cognitive decline rather than trajectories of no decline (Figure 1). The distribution of trajectories seemed to be similar regardless of illness severity among those with pneumonia and those with severe sepsis.

In the subset in whom dementia was ascertained, 198 (5.5%) and 1,049 (40.4%) were hospitalized with severe sepsis and infection. The HR for the risk of dementia was similar regardless of illness severity and type of infection (Table 2). For instance, the HR for those with severe sepsis and with infection was 2.28 and 1.98 compared with those never hospitalized with infection. Additionally, the HR was similar in participants hospitalized with pneumonia in those with and without organ dysfunction (HR, 2.06 and 2.19).

Other Hospitalizations

Of the 5,888 participants, 3,799 were hospitalized at least once during the 10-year period. We estimated the associations between cognition for subjects hospitalized with pneumonia and those hospitalized for other reasons. Longitudinal changes in 3MS were associated with both higher risk of hospitalization with pneumonia and other reasons (association estimate = −0.24 and −0.02 for one-point change in 3MS score over time for hospitalizations with pneumonia and other reasons, respectively; $P < 0.001$ for both). The higher risk of dementia was observed only after hospitalization with pneumonia and not after hospitalization for other reasons (HR, 1.47; 95% CI, 1.03–2.10; $P = 0.03$ for pneumonia hospitalization; and HR, 1.13; 95% CI, 0.94–1.35; $P = 0.17$ for hospitalization for other reasons). Thus, the bidirectional relationship between cognition and pneumonia in our cohort does not seem to be an effect of hospitalization alone.

TABLE 2. RISK OF DEMENTIA DID NOT VARY BASED ON SEVERITY OF INFECTION*

Variable	Number of Cases	Hazard Ratio	95% Confidence Interval	*P* Value
Pneumonia	320	2.24	1.62–3.11	<0.0001
Pneumonia with organ dysfunction†	82	2.06	0.92–4.61	0.07
Pneumonia without organ dysfunction	240	2.19	1.52–3.16	<0.0001
Severe sepsis	198‡	2.28	1.38–3.77	0.001
Other infections	1,049§	1.98	1.61–2.43	<0.0001

Time-varying covariate approach used and analyses conducted in the subset in whom dementia was adjudicated (n = 3,602).

* International Classification of Diseases, 9th edition Clinical Modification codes to define severe sepsis, organ dysfunction, and infection based on criteria by Weycker and coworkers (23).

† Pneumonia with organ dysfunction includes 40 cases of pneumonia with acute respiratory failure and shock. The hazard ratio for dementia was 1.94 (95% confidence interval, 0.62–6.05; $P = 0.25$).

‡ Includes 80 cases hospitalized with pneumonia.

§ Includes 313 cases hospitalized with pneumonia.

DISCUSSION

Our results suggest a bidirectional relationship between cognitive function and pneumonia. We showed that small subclinical changes in cognition over time increased risk of pneumonia hospitalization. Pneumonia hospitalization also accelerated time to clinical presentation of dementia. The bidirectional associations between cognition and pneumonia were independent of demographic characteristics, health behaviors, education, income, and detailed measures of chronic diseases and physical function. Although our primary analysis was conducted for pneumonia, we observed a similar bidirectional relationship between those hospitalized with other infections, but not in those hospitalized for other reasons. Furthermore, the bidirectional relationship was observed regardless of illness severity. These findings explain in part why well-appearing older adults progress to functional dependence after infection and how a single episode of infection may play an important role in functional decline in older adults.

Earlier studies that examined risk factors for pneumonia conducted cross-sectional analyses at a single time point (28–32). We examined the role of baseline and longitudinal changes in cognitive function. The results of trajectory analyses and joint modeling to examine effect of longitudinal changes were consistent. These results and our subgroup analysis in well-appearing participants underscore the importance of small changes that may not be clinically apparent.

Previous studies that suggested an association between infection or critical illness and cognitive dysfunction have experienced challenges in estimating cognition immediately before the acute illness (14, 33–37). For example, studies that recruited subjects once infection occurs had to rely on informant questionnaires (34, 38). Population-based studies that identified infectious illnesses, similar to our study, have cognition measures collected months or years before the illness occurs (14, 35). We used trajectory analysis, extended Cox model, and joint modeling to estimate the cognitive function at the time of pneumonia hospitalization. These approaches suggest that approximately two-thirds had normal cognition and were not experiencing any changes in cognition before pneumonia. A smaller subset had normal cognition at baseline, but was experiencing small subclinical changes in cognition before the illness. Once pneumonia occurred, they were at higher risk of dementia. Thus, an infectious illness may accelerate decline in cognition that may be underway before occurrence of the infection. Based on results in animal models and our prior work, a potential mechanism to explain this relationship may be inflammation (8, 39). For instance, small changes in cognitive function may impair inflammatory response to infection caused by stimulation of the vagus nerve and increase susceptibility to pneumonia. During an episode of pneumonia, systemic inflammatory marker levels increase (40), and higher levels may persist during

recovery and accelerate time to dementia by causing neuroinflammation (41, 42). Other mechanisms, such as occurrence of delirium, hypoxemia, and fluid management, may also explain why pneumonia may worsen cognition.

Our study has several strengths. This is the first study to assess the bidirectional relationship between cognition and infection within the same cohort. To account for potential confounding factors, we adjusted for detailed measures of chronic diseases, including lung and kidney function, education, income, and longitudinal measures of physical function. Our results can be generalized because subjects were recruited from a multicenter population-based study from four geographic regions in the United States. Finally, we used validated approaches to diagnose dementia.

Our study has limitations. First, although we posit a bidirectional relationship, we are only able to prove associations and not causation. Second, we considered but were unable to adjust for other confounders, including professional qualification; presence of swallowing dysfunction; and characteristics of the hospitalizations with pneumonia, such as the development of delirium or degree of hypoxemia. Third, although all participants were well-appearing community-dwelling participants, the group that developed pneumonia was slightly older, required more assistance at baseline, and had a slightly worse 3MS score on enrollment. Our results could be confounded by these factors or small differences in cognitive function that occurred before the development of pneumonia that were not identified by 3MS testing but might be detected by an alternative method. Fourth, the care of patients at risk for dementia may have changed since these data were collected. For example, use of acetylcholinesterase inhibitors, a commonly prescribed therapy for dementia currently, occurred in fewer than 2% of participants during the study period.

Recent work has transformed how the impact of acute illness is understood by demonstrating that patients suffering from severe sepsis or acute respiratory distress syndrome may have some cognitive decline before their acute illness and incur long-term cognitive deficits (13, 14, 33, 38, 43). Our results are consistent with those of prior studies but have some important additions to the understanding of the relationship between acute illness and chronic health. First, we were able to demonstrate a bidirectional relationship between infection and cognitive function, not just a unidirectional effect. Second, we have examined the impact of pneumonia hospitalization on cognitive function using dementia, instead of the results of cognitive testing. Our study highlights that some will have an accelerated course to dementia after their pneumonia episode. Lastly, our study shows no evidence that the bidirectional relationship between cognitive function and infection varies based on severity of illness, and demonstrated that robust effects are present even among the participants who were not critically ill. These findings suggest that insults or interventions occurring in the intensive care unit alone may not solely worsen long-term cognition. Future studies should examine mechanisms underlying this bidirectional relationship to develop interventions and explore the optimal timing to initiate these interventions to reduce infection and subsequent disability.

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