Pneumonia and subsequent risk of dementia: Evidence from the Japan Gerontological Evaluation Study

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Abstract

Background: Recently, several studies reported that pneumonia might increase the risk of cognitive decline and dementia due to increased frailty.

Objectives: This study aims to examine the association between a history of pneumonia and subsequent dementia risk.

Methods: Participants were 9,952 aged 65 years or older Japanese men and women from the Japan Gerontological Evaluation Study (JAGES) prospective cohort study, followed up from 2013 to 2019. Dementia was identified by public long-term care insurance registration. A history of pneumonia contracted one year before the baseline questionnaire in 2013. A Cox regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia risk, adjusted for potential confounding variables. We conducted competing risk analyses using a cause-specific hazard model.

Results: During the follow-up period of 6 years, 939 persons developed dementia. There was no association between having a prior history of pneumonia with dementia risk (HR 1.20, 95% CI:0.81–1.78). However, we observed an increased risk of dementia in persons with pre-frailty and frailty; the multivariable HR (95%CI) was 1.75(1.48–2.07) and 2.42 (2.00–2.93) for pre-frailty and frailty, respectively. When pneumonia and frailty were combined, the risk of dementia was the highest for the persons with a history of pneumonia and frailty; the multivariable HR (95%CI) was 2.30 (1.47–3.62). The multivariable HR (95%CI) for those without pneumonia with frailty was 1.95 (1.66–2.28). Meanwhile, the multivariable HR (95%CI) for those with pneumonia without frailty was 1.64 (0.68–3.99).

Conclusion: Our findings imply that a prior history of pre-frailty and frailty with or without pneumonia, but not a history of pneumonia per se, was associated with an increased risk of dementia among population-based-cohort of older Japanese people.

Introduction

Dementia prevalence grew substantially from 1990 to 2016 and has been affected by the continuous increase of the aging population.[1] There was a steep increase of deaths due to dementia by 148% during that period, and it became the fifth leading cause of mortality in 2016 globally.[1] To date, the treatment of dementia has not shown an expected result; therefore, prevention strategies have become more critical,[2] focuses on the modifiable risk factors. Currently, there are twelve modifiable risk factors for dementia; less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution.[3] In addition, recently, frailty has been considered one of the critical risk factors for dementia.[4–6]

It is now well known that chronic inflammation involved in neuronal death, denervation, and acceleration of cognitive impairment could lead to dementia.[7,8] Newcombe et al. suggested that the accumulation effects of various inflammatory events during an individual's lifetime may lead to cumulative dementia risk.[7] Infectious disease has been proposed to have an essential role in the pathogenesis of dementia.[9,10] It is supported by several animal and population studies that found significant associations between infection with cognitive decline and dementia.[11–14] Valero et al. found that neurons' impairment leads to memory deficit and impairment of adult neurogenesis in mice after injection of lipopolysaccharide (LPS).[14] LPS injection also causes an elevation of neuronal cell death and acute cognitive dysfunction.[8,15]

Previous studies of older people showed that hospitalization due to pneumonia was associated with a higher risk of dementia.[16,17] The multicohort study using three Finland cohorts and the UK Biobank indicated that hospitalization for infectious diseases, including pneumonia, was associated with an increased risk of dementia.[18] A large UK population-based cohort study of adults aged 65 years and older showed that histories of common infections, including pneumonia, were associated with an increased risk of dementia.[19]

A cross-sectional study of 1,174 older Japanese patients found that the coexistence of cognitive impairment and oral frailty was associated with an increased prevalence of aspiration pneumonia.[20] The existence of frailty can increase pneumonia risk in elder populations.[21] Furthermore, frailty can also increase the risk of dementia[4,5,22]. Previous studies that investigated the association between pneumonia and the risk of dementia did not adjust for frailty[12,16,17], even though frailty is an important confounding factor in the association between pneumonia and dementia risk. Therefore, this study aims to investigate the effect of pneumonia and frailty on dementia development in healthy Japanese elder populations by adjusting for social and demographic, health behaviors, and health conditions.

Methods

Study design and participants

The study design is a 6-year prospective cohort study using data drawn from the Japan Gerontological Evaluation Study (JAGES). This is a cohort study of the social determinants of health among physically and cognitively independent adults aged 65 years and over, identified from the public long-term care insurance (LTCI) database and official residents' registers of 30 municipalities in 13 prefectures in Japan. The complete explanation of JAGES had been explained elsewhere.[23,24] We used the 2013 baseline data set of JAGES. The questionnaire consists of a basic item module, and five other survey modules were distributed to every 20% of participants in each municipality. We used the questions on pneumonia and hospitalization included in module D, and identified 14,705 participants who completed the questionnaires. We excluded participants who did not answer the question about prior history of pneumonia (n =3327), who had the dependent status of basic daily living activity (n = 233), missing status of the activity daily living (n = 376), and participants with a history of stroke, dementia, depression, and cancer (n=817). Finally, the total number of participants was 9,952 **(Figure 1)**.

A history of stroke, dementia, depression, and cancer was ascertained from the questionnaire.

Ascertainment of exposure and outcome

Our study's exposure was pneumonia history determined by participant responses to a self-administered questionnaire. Prior history of pneumonia was defined as pneumonia experienced by participants within one year before the baseline questionnaire (2013).

Dementia onset was ascertained from the national standardized LTCI evaluation system's data that considers the physician's diagnosis, and it is managed by the local government, as explained in another study. [25] LTCI evaluation system collected information on physical, cognitive, and social conditions, including patient care resources availability. The committee recruited a panel of health and care professionals to evaluate the respondent's physical and mental status via home visit interviews and physical examination to determine the care-need levels' certification.[26]

The Japan Ministry of Health, Labour, and Welfare establish the Degree of Independency in Daily Lives of Dementia Individuals in Japan. This standard evaluates individual cognitive ability and categorizes them into eight levels: 0, I, IIa, IIb, IIIa, IIIb, IV, and M (0 = Independent, M = Needs constant treatment in a specialized medical facility). This scale was well-correlated with the Mini-Mental State Examination (MMSE) (Spearman's rank correlation $r = -0.73$, $p < 0.001$). [27,28] We defined participants who had individuals scoring IIa or above as having dementia development, as validated by the previous study. Level II indicates that the individuals had dementia-related symptoms, behavioral disturbance, and some communication difficulties that limited daily living outside the home but were capable of daily living under another person's care. [29]

Covariates

Demographic and socioeconomic covariates included age, which was categorized into five groups (65–69, 70–74, 75–79, 80–84, or ≥85 years), sex, body mass index [BMI (10

percentiles)], years of education (9 years or above, less than nine years/did not graduate from high school), marital status (single, married), and employment status (having occupation, no occupation). The frequency of meeting with friends (up to three times a month, more than three times a month) and frequency of going out was divided into two categories: three times a month or less and more than three times a month. Occupation, length of education, and marital status are essential socioeconomic factors associated with a higher risk of dementia.[30,31]

Health behaviors information was obtained on the alcohol drinking status (never, past, current), smoking status (never, past, current), the frequency of doing low-intensity physical activity, doing moderate-intensity physical activity, and doing high-intensity physical activity (divided into two categories: three times a month or less and more than three times a month). Health status that included frailty, history of diabetes mellitus, history of hypertension, hearing disease, tooth loss, and pneumonia vaccination were obtained from the questionnaire. Frailty was assessed using the Kihon Checklist (KCL), which consists of 25 questions classified into seven categories consists of instrumental activity of daily living (IADL), physical strength, nutritional status, oral function, home boundness, cognitive function, and depressive mood (Supplementary Table 1). According to KCL scores, frailty was classified into three groups: robust, 0–3; pre-frail, 4–7; and frail, ≥ 8. KCL was a score developed by the Japanese Ministry of Health, Labor, and Welfare to identify older adults requiring LTCI. KCL score was correlated well with the validated assessments of physical strength, nutritional state, cognitive function, depressive mood, and the number of frailty phenotypes defined by the Cardiovascular Health Study criteria (CHS).[32]

Statistical analysis

We calculated person-months of follow-up from baseline (2013) to the first endpoint: dementia, death, moving away from the registered resident area, loss to follow-up, or the end of the follow-up in December 2019. During the follow-up period, 699 (7.02%) participants died, and

197 (1.98 %) participants moved away and lost to follow-up.

We conducted a competing-risk analysis using the cause-specific hazard model with death as the competing event. A Cox-regression model was used to calculate multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for risk of dementia according to the history of pneumonia infection and hospitalization history. As for sensitivity analysis, we analyzed by excluding participants who developed dementia three years after baseline surveillance. P-values < 0.05 (two-tailed tests) were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participants' characteristics

The participants' average age at baseline was 73.2 years old (SD), and the mean follow-up was 6 years. Of the 9,552 older people, 939 (2.49%) developed dementia during the follow-up period. Those with a history of pneumonia were older than those without a history of pneumonia, had no occupation at the time of surveillance, mostly met with friends, or went out less than three times per month, and did physical activity less frequently than the participants who had no history of pneumonia infection (**Table 1**). As presented in Table 2, participants who did not graduate from junior high school, were single, did not work, met friends less than and equal to 3 times a month, had natural teeth less than and equal to 9, smoking, and had the hearing disease tended to have pre-frailty or frailty condition.

Of the 165 participants who had a history of pneumonia infection within one year before surveillance, 30 (18.2%) developed dementia. In model 1, adjusted for age and sex, HR was 1.75 (95% CI 1.22–2.52), *p*-value 0.005. This association was attenuated after adjusting for the other variables; HR was 1.30 (95% CI 0.89–1.89), *p*-value=0.17 (**Table 3**). No significant associations were observed in the sensitivity analysis (**Supplementary Table 2**), where we

excluded the participants who developed dementia less than three years after the surveillance. We observed similar associations using a cause-specific hazard model with death as the competing event (**Table 3**).

We observed an increased risk of dementia in participants with pre-frailty and frailty; the multivariable HR (95%CI) was 1.75 (1.49-2.07) and 1.54(1.41-1.69), respectively (**Table 4**). After employing a cause-specific hazard model competing risk analysis, the association was similar for pre-frailty but became stronger for frailty (**Table 4**). The associations were similar after excluding dementia cases with 3-year onset **(Supplementary Table 3)**. **Table 5** shows the association of pneumonia combined with frailty and the subsequent risk of dementia. The reference group had no history of pneumonia history or frailty. We found significant associations with dementia in participants who had no history of pneumonia but had frailty [HR and 95%CI: 1.94(1.66-2.27)], and in participants who had a history of both pneumonia and frailty [HR and 95%CI: 2.33(1.50-3.63)]. After the cause-specific hazard model competing risk analysis, the association with dementia was similar for the combinations of no pneumonia with frailty and pneumonia with frailty. However, the HRs became weaker and no longer statistically significant for the combination of pneumonia without frailty [HR and 95%CI: 1.64 (0.68-3.99)].

We observed no significant p-interaction between pneumonia and frailty (p=0.22) and a low Spearman's correlation coefficient (r=0.06).

Discussion

We observed no association between a history of pneumonia and the risk of dementia. On the other hand, we found an association between frailty and the risk of dementia, with or without a history of pneumonia. Our study results were inconsistent with the findings from previous cohort studies of people aged ≥18[18], ≥ 56[12], ≥ 65[17], and ≥75[16], which found an association between a history of pneumonia and an increased risk of dementia.[12,16,17] Our study strength is

that we adjusted for frailty in examining the association between pneumonia and the risk of dementia. To the best of the authors' knowledge, this is the first study to investigate the above association by adjusting for frailty. The null association between pneumonia and dementia risk could be caused by eliminating the effect of frailty on dementia risk. However, all those previous cohort studies had short or intermediate follow-up periods (3 to 8 years) except for the Finland three cohort study (15.4 years) and did not consider frailty[12,16–19], which could represent an important underlying mechanism that links pneumonia's prevalence with dementia risk.

A prospective study from UK Biobank found an increased risk of dementia among participants with pre-frailty [HR (95%CI): 1.21 (1.04-1.42)] and frailty [HR (95%CI): 1.98 (1.47-2.67)][4]. Similarly, the Screening Across the Lifespan Twin Study (SALT) showed that a 10% increase in the Rockwood frailty index was associated with a higher risk of dementia, independent of familial factors such as genetic predisposition [HR (95%CI): 1.17 (1.07-1.18).[33] Frailty is associated with a poor immune system causing a failure to sufficiently respond to acute inflammation.[34,35] Frailty could increase susceptibility and mortality from pneumonia.[21,36,37] A previous JAGES study found that the existence of pre-frailty and frailty was associated with a higher risk of pneumonia in older people [HR and 95%CI: 1.30 (1.14-1.48) and 1.92 (1.66-2.22) for pre-frailty and frailty, respectively][21]. A finding from the English Longitudinal Study of Ageing with approximately 9 years of follow-up showed that frailty was associated with subsequent risk of dementia.[38] Moreover, another JAGES study found that the risk scoring model using age, sex, Kihon checklist items, and health check-up data could predict dementia risk well in the older Japanese population.[22] Similarly, a significant association between frailty and risk of pneumonia was found in two prospective cohort studies from the USA[36] and Turkey[37]. The mechanisms for dementia in relation to frailty have not been clarified yet; however, there are common underlying mechanisms, including vascular dysregulation,

inflammation, insulin resistance, and obesity.[39] In addition, hormonal factors such as low blood androgens and estrogens may be involved in the development or progression of frailty[40] and increased risk of cognitive impairment in older men[41]. Furthermore, the prevalence of frailty is higher in people with chronic diseases such as chronic obstructive pulmonary disease (COPD) than those without COPD.[42] A meta-analysis study showed that in people with Chronic obstructive pulmonary disease (COPD) or chronic heart failure, prone to contracted pneumonia, the prevalence of mild cognitive impairment(MCI) was higher than in the general population.[43] They assumed that hypoxemia, inflammation, and vascular disease might be involved in the development of MCI in those patients.[43]

Strength and Limitation

The strength of this study is that it used a large-scale nationwide cohort of Japanese older adults. In addition, we used well-ascertained dementia outcomes defined by a validated method combined with detailed and comprehensive data.

However, we also need to acknowledge several limitations. First, the diagnosis of pneumonia and hospitalization were attained from the questionnaire, not from the medical records. Therefore, recall bias may be occurred. Furthermore, it could represent an underdiagnosis and misclassification of pneumonia in our population. We also cannot confirm the frequency of contracting pneumonia in participants because there is no available data on the history of pneumonia before one year of the surveillance. Finally, the population in this study was mainly comprised of older Japanese cohort members; therefore, our findings might not be generalizable to other populations since there might be differences in age cohort effects, genetics, access to education and lifestyle.

Conclusion

In conclusion, the current study did not find enough evidence for an association between a history of pneumonia and subsequent dementia. However, pre-frailty and frailty with or without pneumonia were strongly linked with an increased risk of dementia in later life.

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Disclosure statement

The authors declare no conflict of interest.

Author Contributions

All authors contributed to the conception and design of this study. Data collection was primarily conducted by KK. Analyses were performed by PK and supported by KS, TS, HI. PK prepared the initial manuscript and KS, YS, DC, TS, KK, TS, and HI significantly contributed to revising it. All authors read and approved the final manuscript.

Data Accessibility Statement: Data are not open for public due to ethical concerns. Data were obtained from the JAGES study whose authors may be contacted at data management committee: dataadmin@ jages. net. The data set has ethical or legal restrictions because it includes human participants.

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Table 1. Mean values and proportions for participant characteristics according to the history of pneumonia during the past year

	No	Yes	*p*-value[a]
Number	9788	165	
Age, year [b]	73.1±6	75.6±6	<.0001
Sex			0.04
Male, n (%	4590 (46.1)	91 (0.91)	
Female, n (%)	5197 (52.2)	74 (0.74)	
BMI, kg/m^2 [b]	22.9±3	21.7±3	<.0001
Education			0.33
Did not graduate from high school, n (%)	3730 (38.1)	70 (42.4)	
Graduate from high school, n (%)	5690 (60.9)	94 (60.0)	
Missing, n (%)	97 (1.0)	1 (0.6)	
Marital status			0.67
Single, n (%)	2520 (25.8)	44 (26.7)	
Married, n (%)	7135 (72.9)	118 (71.5)	
Missing, n (%)	132 (1.4)	123 (1.8)	
Employment			0.05
Not working, n (%)	7015 (71.7)	116 (70.3)	
Working	2347 (24.0)	34 (20.6)	
Missing, n (%)	425 (4.3)	15 (0.2)	
Frequency of meeting friends			0.03
≤3 times a month, n (%)	5489 (46.9)	82 (49.7)	
>3 times a month, n (%)	4867 (49.7)	71 (43.0)	
Missing, n (%)	331 (3.4)	12 (7.3)	
Frequency of going out			0.6
≤3 times a month, n (%)	256 (2.7)	13 (8.0)	
>3 times a month, n (%)	9396 (97.4)	150 (92.0)	
Doing low-intensity physical activity			<.0001
≤ 3 times a month, n (%)	2125 (21.7	52 (31.5)	
>3 times a month, n (%)	7147 (73.0)	95 (57.6)	
Missing, n (%)	515 (5.3)	18 (10.9)	
Doing moderate-intensity physical activity			0.01
≤ 3 times a month, n (%)	3581 (36.6)	73 (44.2)	
>3 times a month, n (%)	5698 (58.2)	80 (48.5)	
Missing, n (%)	508 (5.2)	12 (7.3)	
Doing high-intensity physical activity			0.50
≤ 3 times a month, n (%)	7209 (73.7)	122 (73.9)	
>3 times a month, n (%)	1690 (17.3)	26 (15.8)	
Missing, n (%)	888 (8.9)	17 (0.2)	
History of hypertension			0.005
Yes, n (%)	4274 (43.7)	60 (36.4)	
No, n (%)	4972 (50.8)	101 (61.2)	
Missing, n (%)	541 (5.5)	4 (2.4)	

History of diabetes mellitus,			0.89
Yes, n (%)	1196 (12.2)	27 (16.4)	
No, n (%)	8050 (82.3)	134 (81.2)	
Missing, n (%)	541 (5.5)	4 (2.4)	
Tooth loss			0.002
Natural teeth ≤ 9, n (%)	2349 (24.0)	56 (33.9)	
Natural teeth > 9, n (%)	7237 (74.0)	104 (63.0)	
Missing, n (%)	201 (2.1)	5 (3.0)	
Pneumonia vaccination			<.0001
Yes, n (%)	769 (7.9)	35 (21.6)	
No, n (%)	8964 (92.1)	127 (78.4)	
Alcohol drinking			0.34
Current, n (%)	3658 (37.4)	56 (33.9)	
Past, n (%)	426 (4.4)	12 (7.3)	
Never, n (%)	5579 (57.0)	95 (57.6)	
Missing, n (%)	124 (1.3)	2 (1.2)	
Smoking			0.20
Current, n (%)	1033 (10.6)	15 (9.1)	
Past, n (%)	1487 (15.2)	37 (22.4)	
Never, n (%)	7154 (73.1)	111 (67.3)	
Missing, n (%)	113 (1.1)	2 (0.02)	
Hearing disease, n (%)			0.75
Yes, n (%)	583 (6.0)	4(10.3))	
No, n (%)	8663 (88.5)	144 (87.3)	
Missing, n (%)	541 (5.5)	4 (2.4)	
Frailty			<.0001
Robust/No frailty (KCL= 0-3)	5365 (54.8)	60 (36.4)	
Pre frailt and frailty (KCL ≥ 4)	4422 (45.2)	105 63.6)	

[a] chi-square test for qualitative variables, ANOVA for continuous variables.
[b] mean ± SD all such variable

Table 2. Mean values and proportions for participant characteristics according to frailty

	No-frailty	Pre-frailty	Frailty	*p*-value[a]
Number	5425	3073	1454	
Age, year [b]	71.9±5.2	73.9±6.1	76.4±7.1	<.0001
Sex				0.01
Male, n (%	2621 (48.3)	1383 (45.0)	677 (46.6)	
Female, n (%)	2804 (51.7)	1690 (55.0)	777 (53.4)	
BMI, kg/m^2 [b]	22.9±22.8	22.9±3.3	22.7±3.5	<.0001
Education				<.0001
Did not graduate from junior high school, n (%)	1783 (32.9)	1283 (41.8)	734 (50.5)	
Graduate from junior high school, n (%)	3604 (66.4)	1756 (57.1)	694 (47.7)	
Missing, n (%)	38 (0.7)	34 (1.1)	26 (1.8)	
Marital status				<.0001
Single, n (%)	1143 (21.1)	874 (28.4)	547 (37.6)	
Married, n (%)	4229 (78.0)	2147 (69.9)	877 (60.3)	
Missing, n (%)	53 (1.0)	52 (1.7)	30 (2.1)	
Employment				<.0001
Not working, n (%)	3744 (69.0)	2250 (73.2)	1137 (78.2)	
Working	1482 (27.3)	671 (21.8)	228 (15.7)	
Missing, n (%)	199 (3.7)	152 (5.0)	89 (6.1)	
Frequency of meeting friends				<.0001
≤3 times a month, n (%)	2212 (40.8)	1576 (51.3)	883 (60.7)	
>3 times a month, n (%)	3057 (56.4)	1376 (44.8)	505 (34.7)	
Missing, n (%)	156 (2.9)	121 (3.9)	66 (4.5)	
Frequency of going out				<.0001
≤3 times a month, n (%)	24 (0.5)	81 (2.7)	164 (11.4)	
>3 times a month, n (%)	5303 (99.5)	2965 (97.3)	1278 (88.6)	
Doing low-intensity physical activity				<.0001
≤ 3 times a month, n (%)	891 (16.4)	727 (23.7)	559 (38.5)	
>3 times a month, n (%)	4277 (78.8)	2168 (70.6)	797 (54.8)	
Missing, n (%)	257 (4.7)	178 (5.8)	98 (6.7)	
Doing moderate-intensity physical activity				<.0001
≤ 3 times a month, n (%)	1530 (28.2)	1296 (42.2)	828 (57.0)	
>3 times a month, n (%)	3670 (67.7)	1589 (51.7)	519 (35.7)	
Missing, n (%)	225 (4.2)	188 (6.1)	107 (7.4)	
Doing high-intensity physical activity				<.0001
≤ 3 times a month, n (%)	3799 (70.0)	2337 (76.1)	1195 (82.2)	
>3 times a month, n (%)	1188 (21.9)	412 (13.4)	116 (8.0)	
Missing, n (%)	438 (8.1)	324 (10.5)	143 (9.8)	
History of hypertension				0.15
Yes, n (%)	2281 (42.1)	1344 (43.7)	709 (48.8)	
No, n (%)	2797 (51.6)	1584 (51.6)	692 (47.6)	

Missing, n (%)	347 (6.4)	145 (4.7)	53 (3.7)	
History of diabetes mellitus,				0.86
Yes, n (%)	605 (11.2)	400 (13.0)	218 (15.0)	
No, n (%)	4473 (82.5)	2528 (82.3)	1183 (81.4)	
Missing, n (%)	347 (6.4)	145 (4.7)	53 (3.7)	
Tooth loss				<.0001
Natural teeth ≤ 9, n (%)	990 (18.3)	827 (26.9)	588 (40.4)	
Natural teeth > 9, n (%)	4343 (80.1)	2166 (70.5)	832 (57.2)	
Missing, n (%)	92 (1.7)	80 (2.6)	34 (2.3)	
Pneumonia vaccination				0.001
Yes, n (%)	392 (7.3)	269 (8.8)	143 (9.9)	
No, n (%)	5005 (92.7)	2787 (91.2)	1299 (90.1)	
Alcohol drinking				<.0001
Current, n (%)	2196 (40.5)	1080 (35.1)	438 (30.1)	
Past, n (%)	190 (3.5)	147 (4.8)	101 (7.0)	
Never, n (%)	2943 (54.3)	1821 (59.3)	910 (62.6)	
Missing, n (%)	96 (1.8)	25 (0.8)	5 (0.3)	
Smoking				<.0001
Current, n (%)	511 (9.4)	347 (11.3)	190 (13.1)	
Past, n (%)	815 (15.0)	470 (15.3)	239 (16.4)	
Never, n (%)	4016 (74.0)	2231 (72.6)	1018 (70.0)	
Missing, n (%)	83 (1.5)	25 (0.8)	7 (0.5)	
Hearing disease, n (%)				0.0006
Yes, n (%)	223 (4.1)	215 (7.0)	162 (11.1)	
No, n (%)	4855 (89.5)	2713 (88.3)	1239 (85.2)	
Missing, n (%)	347 (6.4)	145 (4.7)	53 (3.7)	

[a] chi-square test for qualitative variables, ANOVA for continuous variables.

[b] mean ± SD all such variable

Table 3. Hazard ratios and 95% CI of risk of dementia according to a history of pneumonia during the past year

A history of pneumonia during the past year			
	No	**Yes**	***p*-value**
Number at risk	9,787	165	
Person-months	21,066,350	319,016	
Case (n)	909	30	
HR1 (95% CI)[a]	1.00 (reference)	1.75 (1.22–2.52)	0.005
HR2 (95% CI)[b]	1.00 (reference)	1.66 (1.15–2.40)	0.007
HR3 (95% CI)[c]	1.00 (reference)	1.30 (0.89–1.89)	0.17
Competing risk analysis			
HR1 (95% CI)[a]	1.00 (reference)	1.62 (1.10–2.38)	0.01
HR2 (95% CI)[b]	1.00 (reference)	1.54 (1.05–2.26)	0.03
HR3 (95% CI)[c]	1.00 (reference)	1.20 (0.81–1.78)	0.36

[a]HR1= adjusted for sex and age

[b]HR2= adjusted further for BMI, history of hypertension, history of diabetes

[c]HR3= adjusted further for the length of education, marital status, employment status, frequency of meeting friends, low-intensity of physical activity, moderate-intensity of physical activity, tooth loss, the status of pneumonia vaccination, smoking status, alcohol drinking, history of hearing disease, and frailty

Table 4. Hazard ratios and 95% CI of risk of dementia according to frailty

	No Frailty	Pre-frailty	*p*-value	Frailty	*p*-value
Number at risk	5,425	3,073		1,454	
Person-months	12,032,593	6,529,342		2,823,431	
Case (n)	264	362		313	
HR1 (95% CI)[a]	1.00 (reference)	1.96 (1.67–2.30)	<.0001	1.72 (1.58–1.87)	<.0001
HR2 (95% CI)[b]	1.]00 (reference)	1.92 (1.63–2.25)	<.0001	1.70 (1.56–1.85)	<.0001
HR3 (95% CI)[c]	1.00 (reference)	1.75 (1.49–2.07)	<.0001	1.54 (1.41–1.69)	<.0001
p-value				<.0001	
Competing risk analysis					
HR1 (95% CI)[a]	1.00 (reference)	1.96 (1.66–2.30)	<.0001	3.01 (2.53–3.57)	<.0001
HR2 (95% CI)[b]	1.00 (reference)	1.92 (1.63–2.26)	<.0001	2.93 (2.46–3.49)	<.0001
HR3 (95% CI)[c]	1.00 (reference)	1.75 (1.48–2.07)	<.0001	2.42 (2.00–2.93)	<.0001

[a]HR1= adjusted for sex and age

[b]HR2= adjusted further for BMI, history of hypertension, history of diabetes

[c]HR3= adjusted further for the length of education, marital status, employment status, frequency of meeting friends, low-intensity of physical activity, moderate-intensity of physical activity, tooth loss, the status of pneumonia vaccination, smoking status, alcohol drinking, and history of hearing disease

Table 5. Hazard ratios and 95% CI of risk of dementia according to a history of pneumonia during the past year and frailty

	Pneumonia (-) Frailty*(-)	Pneumonia (+) Frailty*(-)		Pneumonia (-) Frailty*(+)		Pneumonia (+) Frailty*(+)	
			p value		p value		p value
Total population							
Number at risk	5365	60		4422		105	
Person-months	11,909,026	123,567		9,157,324		195,449	
Case (n)	257	7		652		23	
HR1 (95% CI)[a]	1.00 (reference)	2.35(1.11–4.98)	0.03	2.30(1.98–2.67)	<.0001	3.24(2.11–4.98)	<.0001
HR2 (95% CI)[b]	1.00 (reference)	2.25(1.06–4.78)	0.03	2.25(1.94–2.61)	<.0001	3.02(1.96–4.64)	<.0001
HR3 (95% CI)[c]	1.00 (reference)	2.17(1.02–4.63)	0.04	1.94(1.66–2.27)	<.0001	2.33(1.50–3.63)	0.0002
Competing risk analysis							
HR1 (95% CI)[a]	1.00 (reference)	1.72(0.24–1.41)	0.23	2.30(1.80–2.68)	<.0001	3.20 (2.07–4.96)	<.0001
HR2 (95% CI)[b]	1.00 (reference)	1.65(0.68–4.00)	0.27	2.25(1.94–2.62)	<.0001	2.97 (1.91–4.61)	<.0001
HR3 (95% CI)[c]	1.00 (reference)	1.64(0.68–3.99)	0.27	1.95(1.66–2.28)	<.0001	2.30 (1.47–3.62)	0.0003

[a]HR1= adjusted for sex and age

[b]HR2= adjusted further for BMI, history of hypertension, history of diabetes

[c]HR3= adjusted further for the length of education, marital status, employment status, frequency of meeting friends, low-intensity of physical activity, moderate-intensity of physical activity, tooth loss, the status of pneumonia vaccination, smoking status, alcohol drinking, history of hearing disease

*Frailty included pre-frailty and frailty.

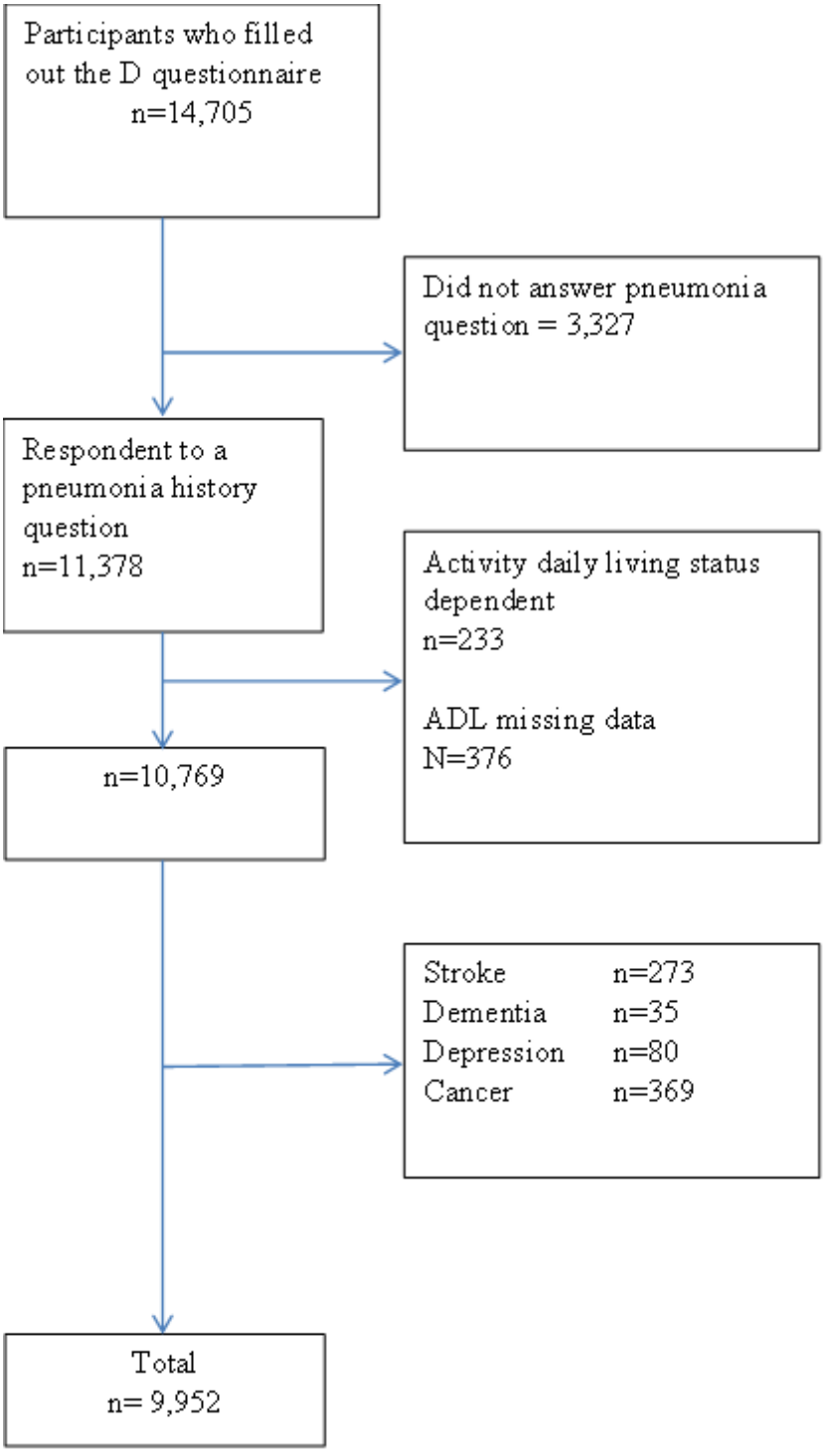

Figure 1. Flow chart of participants selection from JAGES

[a]HR1= adjusted for sex and age

[b]HR2= adjusted further for BMI, history of hypertension, history of diabetes

[c]HR3= adjusted further for the length of education, marital status, employment status, frequency of meeting friends, low-intensity of physical activity, moderate-intensity of physical activity, tooth loss, the status of pneumonia vaccination, smoking status, alcohol drinking, history of hearing disease, and frailty