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Incidence of cognitive impairment and dementia after hospitalisation for pneumonia: a UK population-based matched cohort study

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ABSTRACT

Background

Survivors of common infections may develop cognitive impairment or dementia, however; the risk of these conditions in people hospitalised with pneumonia is not well-established.

Methods

A matched cohort study was conducted using Hospital Episode Statistics (HES) data linked to Clinical Practice Research Database (CPRD). Adults with the first ICD-10 code for pneumonia recorded in HES between 1 July 2002 and 30 June 2017 were included and up to four controls without hospitalisation for pneumonia in CPRD were matched by gender, age, and practice. Cognitive impairment and dementia incidence rates were calculated, and survival analysis was performed comparing those hospitalised with pneumonia to the general population.

Results

The incidence rates of cognitive impairment and dementia were 18 (95%CI 17.3 to 18.7) and 13.2 (95%CI 13 to 13.5) per 1,000 person-years among persons previously hospitalised with pneumonia and the matched cohort respectively. People previously hospitalised with pneumonia had 53% higher incidence of cognitive impairment and dementia (aHR 1.53; 95% CI 1.46 to 1.61) than their matched cohort. The highest incidence was observed within 1-year of hospitalisation for pneumonia compared to the general population (aHR = 1.89; 95%CI 1.75 to 2.05). Age modified the effect of hospitalisation for pneumonia on cognitive impairment and dementia such that the size of effect was stronger in people between 45 and 60 years old ($p_{interaction}<0.0001$).

Conclusion

Cognitive impairment and dementia are more likely to be diagnosed in people who have been hospitalised for pneumonia, especially in the first year after discharge, than in the general population.

INTRODUCTION

Pneumonia is a major cause of morbidity and mortality worldwide (1). Approximately 1% of the UK adult population develops pneumonia annually and it accounts for over 100,000 hospital admissions every year (2,3). Although pneumonia is an acute illness, substantial longer term associated risks are recognised; more than 50% mortality after a 5-year period and an almost 2-fold greater risk of subsequent pneumonia compared to those without previous pneumonia (1). Additionally, despite major advances in risk stratification and management, health sequelae in survivors of pneumonia have not significantly improved over the last years (4).

Common infections are an established risk factor for acute cognitive impairment in older adults (≥65 years) and increasing evidence from longitudinal studies suggests that they are also associated with an increased risk of dementia (5). Studies also report that survivors of critical illness are at increased risk of developing cognitive impairment even many years after discharge from the hospital and intensive care unit (ICU) (6–9). The current literature has mainly focused on outcomes such as mortality and cardiovascular diseases after pneumonia (1,10,11). A small number of studies focusing on older persons have reported that pneumonia survivors experience diminished cognition (12–14) however, these studies did not include adults across all ages.

The aim of this study was to address the gap in knowledge regarding the risk of incident cognitive impairment and dementia in people hospitalised with pneumonia when compared to the general population.

METHODS

Source population

A matched cohort study was conducted using hospitalisation data from Hospital Episode Statistics (HES) linked to the Clinical Practice Research Datalink (CPRD), a large longitudinal UK primary care database that provides anonymised electronic health records from general practices. HES admitted patient care data contained details of all admissions to NHS hospitals in England from 1 April 1997 to 30 November 2018, with diagnostic data coded using International Classification of Diseases, 10th Revision (ICD-10).

Study population and outcomes

Adults (≥18 years old) with the first hospitalisation for pneumonia (index date) recorded in HES between 1 July 2002 and 30 June 2017 were included. Pneumonia (ICD-10 codes; J12-J18) was defined as the primary code for the first episode of hospitalisation (Table S1). Patients were excluded if they a) had less than a year of time registered to the practice before admission (15), b) hospital-acquired pneumonia (admission for at least a day in the 10 days preceding the index admission) or c) if they had recorded pre-existing cognitive impairment or dementia. Up to four randomly selected people without hospitalisation with pneumonia in CPRD were matched with each people hospitalised with pneumonia based on gender, age (±1 yr.), and general practice. Controls were assigned the same index date as their matched people hospitalised for pneumonia. Participants were eligible for inclusion if their record was labelled as acceptable according to CPRD recommendations.

The outcomes of interest were the time from the index date to the first Read coded cognitive impairment and dementia, both combined and separately (Table S2 & S3). The used set of codes was based on previously published lists (7,16,17), augmented by a manual search of all

Read terms within CPRD. An expert geriatrician (R.H.H) was consulted to help identify all relevant Read codes of the outcomes.

Follow-up

All were followed up from day one after the date of discharge from hospital to either the date of outcome of interest, end of data collection (30 June 2017), date of transfer out of practice, date of last data collection for the practice or date of death, whichever came first.

Statistical analysis

The power of the study size was calculated to detect the increased risk of cognitive impairment and dementia when compared to the general population. The baseline characteristics between people hospitalised for pneumonia and controls were compared by performing conditional logistic regression using the matched set as the strata variable. Incidence rates of cognitive impairment and dementia were calculated by dividing the number of incident diagnosis by follow-up person-years for both groups. The probability of experiencing the outcomes during the follow-up time was presented with a plot using the Kaplan-Meier method and the log-rank test examined any difference between the groups. Performing a Cox regression analysis, stratified by matched set, we calculated the hazard ratio (HR) estimates and 95% confidence intervals (CI) comparing the cognitive impairment and dementia risk between hospitalised for pneumonia and control patients. Directed acyclic graphs (DAG) help in depicting the status of the covariates in a statistical model (confounders, mediators & colliders). DAG are based on a good understanding of the literature and are made prior to any analyses to determine which variables are appropriate to put in the adjust the model (18). Following a review of published literature (19), a DAG was used to identify the minimum sufficient adjustment set of confounders (Figure S1). This

included age at the index date, sex including only those clearly classified as male or female, smoking, body mass index (BMI), alcohol consumption, and comorbidities (depression, cerebrovascular diseases, type II diabetes, hypertension, traumatic brain injury). Comorbidities were also summarised using the Charlson comorbidity index score (20). Validated code lists were used for these confounders (21–23). The Cox model assumption was tested using Schoenfeld residuals. Incidence rates and HR by follow-up intervals were additionally determined; 0-1 year, >1-4 years, and >4-16 years. A new category was assigned to missing data for smoking, BMI, and alcohol consumption. In addition, two more analyses were conducted excluding those with missing data and imputed the missing data with multiple imputation. Five imputations were generated, and the imputed model consisted of age, gender, outcome, case and all confounders. A subgroup analysis by gender and age group was also performed. Age and gender were examined by fitting interaction terms (age*case & sex*case) and carrying out a likelihood ratio test whether they modified the effect of pneumonia on cognitive impairment and dementia. All data management and statistical analysis were performed using R v4.1.1.

RESULTS

Baseline characteristics

The study cohort comprised 55,808 persons hospitalised with pneumonia and 206,108 age, sex and practice-matched controls without pneumonia (Table 1). The median age was 75 years (IQR 61 to 84) and 74 (IQR 59 to 83) for people hospitalised for pneumonia and controls, respectively. Median follow-up was 1.7 years (IQR 0.5 to 4) in people hospitalised for pneumonia and 3 (IQR 1.4 to 5.7) in controls. More persons hospitalised for pneumonia were current smokers than controls (21.1% vs 13.4%, $p < 0.0001$) and had more comorbid diseases (74.1% vs 51.5%, $p < 0.0001$).

Table 1. Baseline characteristics of those patients hospitalised for pneumonia and a matched comparison cohort of controls[1].

Characteristic	Hospitalisation for pneumonia (N = 55,808)	Controls (N = 206,168)
Follow-up yrs.		
Mean (SD)	2.7 (2.9)	3.9 (3.2)
Median (IQR)	1.7 (0.5 - 4)	3 (1.4 - 5.7)
Age, yrs.		
Mean (SD)	70.6 (17.8)	69.6 (17.8)
Median (IQR)	75 (61 - 84)	74 (59 - 83)
18-44	6125 (11)	24163 (11.7)
45-60	7633 (13.7)	30111 (14.6)
61-74	13452 (24.1)	51917 (25.2)
75-83	13461 (24.1)	50029 (24.3)
>83	15137 (27.1)	59948 (24.2)
Sex		
Male	27699 (49.6)	101638 (49.3)
Female	28109 (50.4)	104530 (50.7)
Body mass index, $\frac{kg}{m^2}$		
Mean (SD)	26.4 (6.4)	26.8 (5.3)
Median (IQR)	25.6 (22.1-29.8)	26.2 (23.3-29.7)
Underweight (<18.5)	3375 (6)	4876 (2.4)
Normal (18.5-24.9)	17377 (31.2)	58939 (28.6)
Overweight (25-29.9)	13721 (24.6)	60971 (29.6)
Obese (≥30)	11051 (19.8)	37990 (18.4)
Unknown	10273 (18.4)	43392 (21)
Smoking status		
Never	21887 (39.2)	106064 (51.5)
Ex	20474 (36.7)	59978 (29.1)
Current	11753 (21.1)	27695 (13.4)
Unknown	1694 (3)	12431 (6)
Alcohol status		
Never	11868 (21.3)	35326 (17.1)
Occasional	7658 (13.7)	29339 (14.2)
Current	26881 (48.2)	105996 (51.4)
Ex	2551 (4.6)	5403 (2.6)
Unknown	6850 (12.3)	30104 (14.6)
Charlson Comorbidity Index		
0	14469 (25.9)	100087 (48.5)
1	12007 (21.5)	37139 (18)
2	9708 (17.4)	30097 (14.6)
3	7558 (13.5)	18268 (8.9)
4	4852 (8.7)	9771 (4.7)
≥5	7220 (12.9)	10809 (5.2)
Comorbidities		
Depression	11367 (20.4)	28404 (13.8)
Hypertension	20218 (36.2)	69681 (33.8)
Diabetes mellitus	9149 (16.4)	22777 (11)
Cerebrovascular disease	5617 (10)	11606 (5.4)
Traumatic brain injury	377 (0.68)	969 (0.47)

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; IMD, Index of Multiple deprivation. Percentages have been rounded and might not total 100.

[1]P-value <.0001 for the baseline characteristics between the two groups except age and sex in which there are no significant differences.

Risk of cognitive impairment and dementia

During the whole study period the crude incidence of cognitive impairment and dementia was higher in people hospitalised for pneumonia than the controls (Figure S2) with the incidence rates equal to 18 (95% CI 17.3 to 18.7) and 13.2 (95% CI 13 to 13.5) per 1000 person-years, respectively (Table 2). The Kaplan–Meier plot also demonstrated a significantly higher probability of cognitive impairment and dementia during the follow-up in people who had recovered from pneumonia (log-rank test; $p<0.0001$) (Figure S3). Similarly, a significantly higher probability of cognitive impairment and dementia (as separate outcomes) was displayed in those with previous hospitalisation for pneumonia than in controls (log-rank test; $p<0.0001$) (Figure S3). An association between previous pneumonia and cognitive impairment and dementia was observed (aHR 1.53; 95% CI 1.46 to 1.61) (Table 2). Identical effect sizes were found from the complete case and multiple imputation analysis (Table S4). The higher risk for developing cognitive impairment and dementia was within 1-year after hospitalisation for pneumonia. During subsequent years, the risk decreased and remained almost stable. When cognitive impairment and dementia were examined separately, an increased risk was found for both conditions in people hospitalised for pneumonia; the effect was greater for dementia (aHR 2.04; 95% CI 1.74 to 1.95) than cognitive impairment (aHR 1.28; 95% CI 1.22 to 1.38).

Table 2. Incidence rates and hazard ratios (HR) for associations of cognitive impairment and/or dementia comparing people previously hospitalised for pneumonia and controls.

	Number of events	Rate/1000 person-years	Unadjusted[1] HR (95% CI)	Adjusted[2] HR (95%CI)	p value
Overall; 0 to 16-years after hospitalisation					
Either cognitive impairment or dementia					
Controls	10650	13.2 (13.0 – 13.5)	1.00	1.00	
People hospitalised for pneumonia	2727	18.0 (17.3 – 18.7)	1.65 (1.57 – 1.73)	1.53 (1.46 – 1.61)	<.0001
Cognitive impairment					
Controls	7014	8.7 (8.5 – 8.9)	1.00	1.00	
People hospitalised for pneumonia	1547	10.2 (9.7 – 10.7)	1.38 (1.30 – 1.47)	1.28 (1.22 – 1.38)	<.0001
Dementia					
Controls	3636	4.5 (4.3 – 4.7)	1.00	1.00	
People hospitalised for pneumonia	1180	7.8 (7.4 – 8.3)	2.22 (2.05 – 2.41)	2.04 (1.74 – 1.95)	<.0001
Within 1-year after hospitalisation					
Either cognitive impairment or dementia					
Controls	2396	11.2 (10.8 – 11.7)	1.00	1.00	
People hospitalised for pneumonia	1071	22.9 (21.6 – 24.4)	2.04 (1.89 – 2.20)	1.89 (1.75 – 2.05)	<.0001
Cognitive impairment					
Controls	1561	7.6 (7.3 – 8)	1.00	1.00	
People hospitalised for pneumonia	507	11.2 (10.3 – 12.3)	1.49 (1.34 – 1.65)	1.39 (1.25 – 1.55)	<.0001
Dementia					
Controls	835	4.3 (4 – 4.6)	1.00	1.00	
People hospitalised for pneumonia	564	12.9 (11.9 – 14)	3.12 (2.77 – 3.51)	2.88 (2.56 – 3.26)	<.0001
Within >1 to 4-years after hospitalisation					
Either cognitive impairment or dementia					
Controls	4665	8.4 (8.2 – 8.6)	1.00	1.00	
People hospitalised for pneumonia	1073	9.7 (9.1 – 10.3)	1.43 (1.33 – 1.54)	1.33 (1.24 – 1.4)	<.0001
Cognitive impairment					
Controls	3075	5.6 (5.4 – 5.8)	1.00	1.00	
People hospitalised for pneumonia	646	5.8 (5.4 – 6.3)	1.26 (1.15 – 1.39)	1.19 (1.08 – 1.32)	<.001
Dementia					
Controls	1590	2.9 (2.8 – 3)	1.00	1.00	
People hospitalised for pneumonia	427	3.9 (3.5 – 4.3)	1.79 (1.58 – 2.03)	1.62 (1.43 – 1.84)	<.0001
Within >4 to 16-years after hospitalisation					
Either cognitive impairment or dementia					
Controls	3589	4.5 (4.3 – 4.6)	1.00	1.00	
People hospitalised for pneumonia	589	3.9 (3.6 – 4.2)	1.42 (1.31 – 1.63)	1.35 (1.20 – 1.50)	<.0001
Cognitive impairment					
Controls	2378	2.9 (2.8 – 3.1)	1.00	1.00	
People hospitalised for pneumonia	394	2.6 (2.4 - 2.9)	1.47 (1.29 – 1.68)	1.35 (1.18 – 1.55)	<.0001
Dementia					
Controls	1211	1.5 (1.4 – 1.6)	1.00	1.00	
People hospitalised for pneumonia	189	1.2 (1.1 – 1.4)	1.45 (1.18 – 1.79)	1.31 (1.06 – 1.63)	.013

[1] *Cox model accounting for matched set (age, sex, and practice).*

[2] *Cox model accounting for matched set (age, sex, and practice) and adjusting for smoking, body mass index, alcohol consumption, depression, cerebrovascular diseases, type II diabetes, traumatic brain injury, and hypertension.*

Stratified risk of cognitive impairment and dementia

Age modified the effect of previous pneumonia on cognitive impairment and dementia. Although younger people were at t lowest absolute risk of incident cognitive impairment and dementia, the effect of previous pneumonia was larger in younger people ($p_{interaction}$<0.0001) with the size of the effect to be similar for both age groups (18 to 44 & 45 to 60 yrs. old) but statistical significance was only retained in the 45-to-60-year group (aHR 2.19; 95% CI 1.65–2.90) (Table 3). Results were similar when the incidence of both conditions was examined separately. The aHR stratified by gender and age groups for each outcome are reported in Table S5.

Table 3. Incidence rates and hazard ratios (HR) for associations of cognitive impairment and/or dementia comparing people hospitalised for pneumonia and controls.

	People hospitalised for pneumonia		Controls				
Variables	**Number of events**	**Rate/1000 person-years**	**Number of events**	**Rate/1000 person-years**	**Unadjusted[1] HR (95%CI)**	**Adjusted[2] HR (95%CI)**	***p*-value**
Either cognitive impairment or dementia							
Gender							.256[4]
Male	1209	16.2 (15.3 – 17.1)	4612	11.4 (11.1 – 11.8)	1.68 (1.57 – 1.81)	1.51 (1.40 – 1.66)	<.0001
Female	1518	19.8 (18.8 – 20.8)	6038	15 (14.6 – 15.4)	1.62 (1.52 – 1.73)	1.48 (1.36 – 1.59)	<.0001
Age[3]							<.0001[4]
18-44	40	1.4 (1 – 1.9)	74	0.6 (0.5 – 0.7)	2.25 (1.50 – 3.74)	1.84 (0.96 – 3.52)	.0.063
45-60	142	4.6 (3.9 - 5.4)	278	1.9 (1.7 – 2.1)	2.66 (2.13 – 3.33)	2.19 (1.65 – 2.90)	<.0001
61-74	560	13.6 (12.5 – 14.8)	1905	8.3 (7.9 – 8.6)	1.85 (1.66 – 1.98)	1.69 (1.50 – 1.92)	<.0001
75-83	976	33 (31 – 35.2)	4167	22.8 (22.1 – 23.5)	1.65 (1.52 – 1.79)	1.46 (1.33 – 1.61)	<.0001
>83	1009	47.2 (44.4 – 50.2)	4226	32.9 (31.9 – 33.9)	1.43 (1.31 – 1.55)	1.48 (1.27 – 1.41)	<.0001
Cognitive impairment							
Gender							.588[4]
Male	695	9.3 (8.6 – 10)	3216	8 (7.7 – 8.3)	1.38 (1.26 – 1.51)	1.29 (1.17 – 1.45)	<.0001
Female	852	11.1 (10.4 – 11.9)	3798	9.5 (10.4 – 11.9)	1.39 (1.28 – 1.51)	1.28 (1.20 – 1.38)	<.0001
Age[3]							<.0001[4]
18-44	38	1.4 (1-1.8)	74	0.6 (0.5 – 0.8)	2.14 (1.42 – 3.23)	1.73 (0.90 – 3.33)	.103
45-60	124	4 (3.4 – 4.8)	256	1.8 (1.6 – 2)	2.49 (1.97 – 3.15)	2.01 (1.57 – 2.82)	<.0001
61-74	402	9.8 (8.9 – 10.8)	1531	6.6 (6.3 – 7)	1.62 (1.43 – 1.83)	1.55 (1.35 – 1.78)	<.0001
75-83	568	19.2 (17.7 – 20.8)	2834	15.5 (14.9 – 16.1)	1.33 (1.20 – 1.48)	1.19 (1.06 – 1.35)	.004
>83	415	19.4 (17.6 – 21.4)	2319	18.1 (17.3 – 18.8)	1.04 (0.92 – 1.18)	0.98 (0.85 – 1.14)	.842
Dementia							
Gender							.001[4]
Male	514	6.9 (6.3 – 7.5)	1396	3.5 (3.3 – 3.7)	2.46 (2.17 – 2.78)	2.12 (1.81 – 2.48)	<.0001
Female	666	8.7 (8.1 – 9.4)	2240	5.6 (5.4 – 5.8)	2.08 (1.88 – 2.31)	1.91 (1.67 – 2.18)	<.0001
Age[a]							<.0001[4]
18-44	2	0.1 (0.02 – 0.2)	0	0	NA	NA	NA
45-60	18	0.6 (0.4 – 0.9)	22	0.2 (0.1 – 0.3)	5.21 (2.44 – 11.1)	2.10 (1.56 – 2.82)	<.0001
61-74	158	3.8 (3.3 – 4.5)	374	1.6 (1.5 – 1.8)	2.94 (2.35 – 3.68)	2.39 (1.80 – 3.18)	<.0001
75-83	408	13.8 (12.5 – 15.2)	1333	7.3 (6.9 – 7.6)	2.44 (2.12 – 2.80)	2.18 (1.85 – 2.60)	<.0001
>83	594	27.8 (25.6 – 30.1)	1907	14.5 (14.2 – 15.5)	1.90 (1.70 – 2.13)	1.67 (1.43 – 1.95)	<.0001

[1] *Cox model accounting for matched set (age, sex, and practice).*

[2] Cox model accounting for matched set (age, sex, and practice) and adjusting for smoking, body mass index, alcohol consumption, depression, traumatic brain injury, cerebrovascular diseases, type II diabetes, and hypertension. [3] Age at the index date. [4] P-value for interaction

DISCUSSION

Our study highlights that people are significantly at increased risk of developing cognitive impairment and dementia after hospitalisation for pneumonia across all age groups. The highest risk of incident cognitive impairment and dementia was observed within a year of hospitalisation. Age modified the effect of pneumonia on cognitive impairment and dementia; although the absolute risk was highest in the older age groups, the size of the effect of increased risk was strongest in those aged 45 to 60 years.

Our results are in accordance with the limited current literature. Three previous studies which included older patients examined whether patients hospitalised for pneumonia have an increased risk of a decline in cognition or developing dementia. Davydow et al found increased odds (aOR = 2.46; 95%CI 1.60 to 3.79) of moderate to severe cognitive impairment in people aged 50 years or older who were hospitalised with pneumonia (12). Similarly, a study which included people aged 65 or more years found that participants with pneumonia were at increased risk of developing dementia (aHR = 1.57; 95%CI 1.11 to 2.22) (13). Tate et al reported that pneumonia hospitalization was associated with a 1.9-fold (95%CI 1.40 to 2.80) increase in the hazard of dementia in older people (14). Finally, a small study (n=58) found that 23% of patients developed moderate to severe cognitive impairment within a year of hospitalisation for community-acquired pneumonia (24). Our study extends the literature by providing estimates for the risk of cognitive impairment and dementia, which are lacking, while stratifying by follow-up interval, gender, and age groups.

The mechanisms by which pneumonia may increase the risk of cognitive impairment and dementia are multifactorial. Systemic infection including pneumonia is a well-recognised risk factor for delirium (25). Activation of microglia is key for the mediation of the behavioural effects of systemic infections. Although the microglial response is usually tightly regulated to prevent deleterious effects, the self-propelling defensive features could turn neurotoxic,

reducing the threshold for delirium. Despite initial recovery from delirium, findings from follow-up studies confirm an association between delirium and long-term cognitive impairment and dementia, suggesting longer-lasting cognitive impacts may occur. (26,27). Studies are emerging regarding the longer-term effects of severe COVID-19 on cognitive function. Cognitive impairment can still be observed after 1 year from hospital discharge due to COVID-19 (28). Whether the underlying mechanisms behind longer-term cognitive impairment from pneumonia and from COVID-19 are similar awaits further investigation.

Alternatively, it is possible that hospitalisation with pneumonia is a marker for subclinical or undiagnosed cognitive impairment or dementia (29). Pneumonia-related hypoxia (30) and inflammation (31,32) may contribute to subsequent cognitive impairment and dementia. These different reasons for the observed association may all contribute in part and may be differentially important across different ages.

We found stronger associations between pneumonia, cognitive decline, and dementia in the short term than in the long term. Reverse causation and ascertainment bias can contribute to short-term associations, but infection might also accelerate or exacerbate existing neuropathology (13,33,34). Robust, but weaker, long-term associations suggest that pneumonia infection might also trigger early stages of neurodegeneration.

Cognitive impairment and dementia in older people are well recognised and confirmed in our data. That the risk was also observed in people aged 45 to 60 years hospitalised for pneumonia is also important as they are not typically regarded as being at high risk of cognitive impairment or dementia. Awareness of this propensity in this age group following pneumonia may enable more timely appropriate clinical management, such as preventative measures, or earlier diagnosis.

This is the first large study to observe that the risk of cognitive impairment following pneumonia is greater for younger persons than for older persons. Possible reasons for this

observation include i) younger persons who develop pneumonia severe enough to require hospital care have host characteristics that also place them at higher risk of developing cognitive impairment which has not been measured in the current dataset (residual confounding), ii) the degree of systemic inflammation may have been higher in these younger patients than in older patients, and the degree of systemic inflammation may be associated with future cognitive impairment, iii) the pathogens causing pneumonia in younger persons may have been different and different pathogens may be associated differentially with subsequent cognitive impairment. These explanations are speculative until further investigation.

A key strength of this study is the large sample size that is representative of the population in England. We captured the cognitive impairment and dementia diagnoses for the general pneumonia population, not limited to a specific subset, such as older people. There are a few study limitations that warrant discussion. Firstly, although considerable efforts were taken to ensure data quality, we cannot fully exclude the possibility of any diagnosis misclassification as we were reliant on how accurately GPs recorded these conditions. Historically, dementia has been underdiagnosed by 50% or more, but that has improved since the National Dementia Strategy in 2009, and especially since 2015 when diagnosis and dementia registers have been incentivised. In many places dementia ascertainment rates are over 80% of that expected epidemiologically. In this study, no differential bias is expected as both patients with pneumonia and controls were identified using the same methodology. Secondly, a significant proportion of people hospitalised with pneumonia consult primary care after discharge. This may increase the opportunities for a diagnosis of cognitive impairment and dementia in those people compared to controls. Thirdly, owing to the nature of the data, we were unable to assess the degree of severity of the diseases. Finally, the absence of education as a variable in the model is a recognised limitation although it is unlikely that this single variable would

dramatically alter the main study findings given the very large size of the sample, together with adjustment for all major confounders.

Our findings suggest post-discharge care plans by clinicians, in partnership with patients, aimed at preventative measures are warranted. These could include active screening and primary prevention strategies targeted at modifiable risk factors for cognitive impairment and dementia. Major risk factors for dementia are identified in early life (low level education), midlife (hypertension, obesity, hearing loss, traumatic brain injury, alcohol misuse) and later life (smoking, depression, physical inactivity, social isolation, diabetes, air pollution) can contribute to decreased dementia risk (35). Additionally, increased attention to the prevention of pneumonia, both as the first consideration and following a first episode, are also justified, particularly in those patients at higher risk of pneumonia. These measures include pneumococcal, seasonal influenza, and COVID-19 vaccinations (when indicated).

In conclusion, adults who recover following hospitalisation for pneumonia have an increased risk of a new diagnosis of cognitive impairment or dementia particularly in the subsequent 12 months, compared to the general population. Further research is needed to better understand the underlying pathophysiological mechanisms for this association and this information will be important in identifying appropriate future interventions. In the meantime, evidence-based preventative measures against dementia should be promoted in patients recovering from pneumonia, particularly for younger men who may not perceive themselves to be at higher risk.

CONTRIBUTORS

C.V.C. had full access to all the study data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: C.V.C., V.B, W.S.L, T.M.M.; acquisition of data: C.V.C., V.B; analysis of data: C.V.C.; interpretation of data:

C.V. C., R.H.H, W.S.L, T.M.M.; drafting the article: C.V.C.; revision for important intellectual content and approval of the version to be published: C.V.C., V.B, R.H.H, W.S.L, T.M.M.

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COMPETING INTERESTS

C.V.C., V.B, R.H.H, T.M.M. declare no competing interests. W.S.L reports grants from National Institute for Health Research and Pfizer outside the submitted work. W.S.L is the Chair of COVID-19 Immunisation (unpaid) and the National Lead of British Thoracic Society community acquired pneumonia audit programme (unpaid).

DATA AVAILABILITY

This study is based on CPRD linked HES data and is subject to a full license agreement which does not permit data sharing outside of the research team. However, data can be obtained by applying to CPRD (enquiries@cprd.com) for any replication of the study. The diagnostic codes used are available from the corresponding author upon a reasonable request.

ETHICAL APROVAL STATEMENT

The study was approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 18_178A).

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Incidence of cognitive impairment and dementia after hospitalisation for pneumonia: a UK population-based matched cohort study

Christos V. Chalitsios, Vadsala Baskaran, Rowan H. Harwood, Wei Shen Lim, Tricia M. McKeever.

Table of Contents

SUPPLEMENTS

Diagnostic codes

Table S1. ICD-10 codes for pneumonia.

ICD-10 code	Description
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism

Table S2. Medcodes for cognitive impairment.

Medcode	Description
1993	memory loss - amnesia
3639	amnesia symptom
5777	memory loss symptom
2908	memory disturbance
27788	temporary loss of memory
103453	short-term memory loss
39507	poor visual sequential memory
40821	poor auditory sequential memory
67163	disturbance of memory for order of events
110307	memory impairment
7674	cognitive decline
107282	mild cognitive impairment
107482	moderate cognitive impairment
107402	severe cognitive impairment
108266	cognitive impairment
52947	memory: own age not known
53146	memory: present time not known
53014	memory: present place not known
52948	memory: present year not known
53125	memory: own dob not known
52825	memory: present month not known
52800	memory: important event not known
52801	memory: important person not known
52805	memory: count down unsuccessful
53016	memory: address recall unsuccessful
65856	gds level 2 - very mild cognitive decline
60263	gds level 3 - mild cognitive decline
60726	gds level 4 - moderate cognitive decline
70057	gds level 5 - moderately severe cognitive decline

94717	gds level 6 - severe cognitive decline
72520	gds level 7 - very severe cognitive decline
6387	mild memory disturbance
6061	organic memory impairment
11936	[x]mild cognitive disorder
110729	[x]cognitive communication disorder
31572	visual disorientation syndrome
7711	[d]memory deficit
20683	[d]disorientation, unspecified
112378	[x]symptoms/signs involving cognition, percept, emotion state & behaviour
52939	[x]other & unspecified symptom/signs involving cognitive function/awareness
52811	[x]disorientation, unspecified
10822	impaired cognition
61639	unable to recognise surroundings
47279	mistakes people's identity
67565	does not recognise self
61869	does not recognise photographs of self
92635	unable to recognise parts of own body
101458	unable to recognise objects
100788	unable to recognise faces
91516	unable to recognise familiar people
59539	unable to reason
52550	difficulty reasoning
46554	unable to use verbal reasoning
46320	difficulty using verbal reasoning
99474	difficulty using visuospatial reasoning
48506	unable to process information
50446	difficulty processing information
61308	unable to process information accurately
57609	difficulty processing information accurately
109311	unable to process information at normal speed
99588	difficulty processing information at normal speed
56044	unable to analyse information
57608	difficulty analysing information
50843	difficulty performing logical sequencing
66172	isolated memory skills
19719	orientation confused
64219	orientation poor
66012	disorientation for person
55460	spatial disorientation
51379	memory disturbance (& amnesia (& symptom))
67838	memory loss symptom
103375	memory loss - amnesia

105538	memory disturbance
102880	loss of memory
10123	memory loss
68230	memory gone
12805	memory loss - amnesia
19297	loss of memory
12277	lom - loss of memory
32367	impairment of working memory
65696	impairment of primary memory
37191	poor memory for remote events
9786	loss of memory for recent events
67802	no memory for recent events
67998	temporary loss of memory
47882	transient memory loss
10514	memory impairment
39915	memory dysfunction
50418	memory deficit
26434	bad memory
12057	memory problem
12583	poor memory
19073	memory lapses
51739	distortion of memory
64892	invents experiences to compensate for loss of memory
11410	poor short-term memory
10571	short-term memory loss
53978	poor long-term memory
47581	long-term memory loss
98798	delayed verbal memory
46860	difficulty making plans
46564	difficulty making decisions
53388	unable to use decision-making strategies
107021	difficulty using decision-making strategies
65319	unable to make considered choices
43204	difficulty making considered choices
59242	difficulty solving problems
40002	language-related cognitive disorder

Table S3. Medcodes for dementia diagnosis.

Medcode	Description
1916	Senile dementia
1350	Senile/presenile dementia
7323	Uncomplicated senile dementia
15165	Presenile dementia
42602	Uncomplicated presenile dementia
30032	Presenile dementia with paranoia
27677	Presenile dementia with depression
38438	Presenile dementia NOS
44674	Senile dementia with depressive or paranoid features
18386	Senile dementia with paranoia
21887	Senile dementia with depression
41089	Senile dementia with depressive or paranoid features NOS
37015	Senile dementia with delirium
19477	Arteriosclerotic dementia
43089	Uncomplicated arteriosclerotic dementia
55467	Arteriosclerotic dementia with paranoia
43292	Arteriosclerotic dementia with depression
42279	Arteriosclerotic dementia NOS
25386	Dementia in conditions EC
4951	Chronic confusional state
7664	[X]Dementia in Alzheimer's disease
49263	[X]Dementia in Alzheimer's disease with early onset
25704	[X]Presenile dementia,Alzheimer's type
60059	[X]Primary degen dementia, Alzheimer's type, presenile onset
61528	[X]Alzheimer's disease type 2
38678	[X]Dementia in Alzheimer's disease with late onset
46762	[X]Alzheimer's disease type 1
11379	[X]Senile dementia,Alzheimer's type
43346	[X]Primary degen dementia of Alzheimer's type, senile onset
30706	[X]Dementia in Alzheimer's dis, atypical or mixed type
29386	[X]Dementia in Alzheimer's disease, unspecified
8195	[X]Alzheimer's dementia unspec
6578	[X]Vascular dementia
9565	[X]Arteriosclerotic dementia
46488	[X]Vascular dementia of acute onset
55838	[X]Predominantly cortical dementia
8934	[X]Subcortical vascular dementia
31016	[X]Mixed cortical and subcortical vascular dementia
55313	[X]Other vascular dementia
19393	[X]Vascular dementia, unspecified
12621	[X]Dementia in other diseases classified elsewhere

28402	[X]Dementia in Pick's disease
26270	[X]LEWY BODY DEMENTIA
64267	[X]Dementia in other specified diseases classif elsewhere
4693	[X] Unspecified dementia
48501	[X] Presenile dementia NOS
34944	[X] Primary degenerative dementia NOS
4357	[X] Senile dementia NOS
27759	[X] Senile dementia, depressed or paranoid type
1917	ALZHEIMER'S DISEASE
16797	ALZHEIMER'S DISEASE WITH EARLY ONSET
32057	ALZHEIMER'S DISEASE WITH LATE ONSET
11136	pick's disease
29512	senile degeneration of brain
7572	lewy body disease
59122	[x]other alzheimer's disease
8634	Multi infarct dementia
11175	[X]Multi-infarct dementia
9509	[X]Dementia in Parkinson's disease
68125	[x]delirium not superimposed on dementia, so described
112783	[x]delirium of mixed origin
25066	[x]delirium, not induced by alcohol+other psychoactive subs
53924	[x]delirium, unspecified
52394	[x]other delirium
22466	delirium - acute organic
24077	delirium - subacute organic
5367	o/e - delirious
49513	presenile dementia with delirium
53446	[x]delirium superimposed on dementia
56912	arteriosclerotic dementia with delirium

Methods

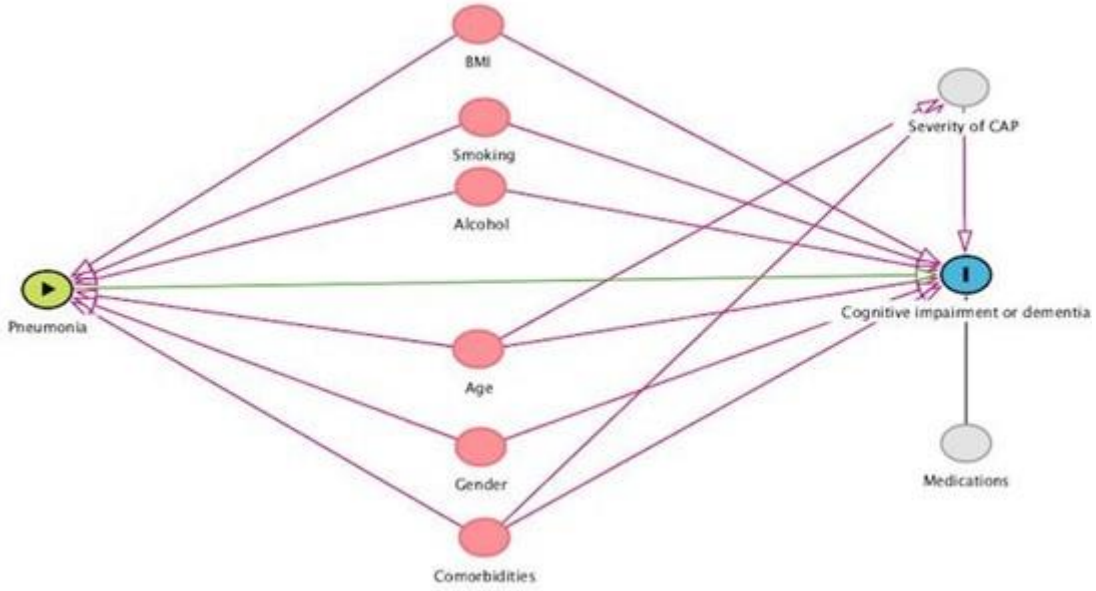

Figure S1. Directed acyclic graph illustrating the association between admission for pneumonia (exposure) and developing cognitive impairment and dementia (outcome).

Defining smoking status

Smoking status was divided into three categories: never smokers, ex-smokers, and current smokers. If patients had more than one record for smoking status, the most recent record of smoking status was used. Never smokers were reclassified to ex-smokers if they had any record of smoking recorded in their entire clinical record entered on CPRD prior to study entry. Read code lists for smoking status were developed using validated medical Read codes.

Defining alcohol status

Self-reported alcohol consumption was collected prospectively and coded by general practitioners or practice nurses on the consultation date in CPRD. The most recent alcohol consumption record prior the index date was used to classify participants drinking behaviour. Four categories were defined including: (1) non-drinkers (Read codes such as "Non-drinker alcohol"), (2) former drinkers (Read codes such as "stopped drinking alcohol"), (3) occasional drinkers (Read codes such as "drinks rarely"), and (4) current drinkers (Read codes such as “drinks wine”, and “alcohol misuse”). Data based on the alcohol status and the alcohol units per week from the additional file of CPRD were also extracted to define patients in the above categories, where available. The information about the alcohol status helped to include more patients as “non-drinkers” or “former-drinkers”, and if a patient had more than 0 alcohol units per week classified as “current drinker”. Non-drinkers were reclassified as former drinkers if they had any record of drinking

recorded in their entire clinical record entered on CPRD prior to study entry, otherwise their category remained the same.

Power study calculation

Outcome: Dementia/Cognitive impairment	Ratio of unexposed to exposed	Hazard ratio (unexposed v. Exposed)	Exposed patients	Unexposed patients
Exposure: Hospitalisation for pneumonia	4	1.10	2,617	10,468

Standard assumptions:

Powered at 90% with a type 1 error probability of 0.05

Median survival time in unexposed cases is assumed to be 6 years (based on previous work in this topic area) with the ratio of unexposed to exposed subjects 4:1; accrual time of 5 years and follow-up of 1 year

Hazard ratios based on previous point estimates obtained from scientific literature and consultation with study collaborators considering the clinical significance

Results

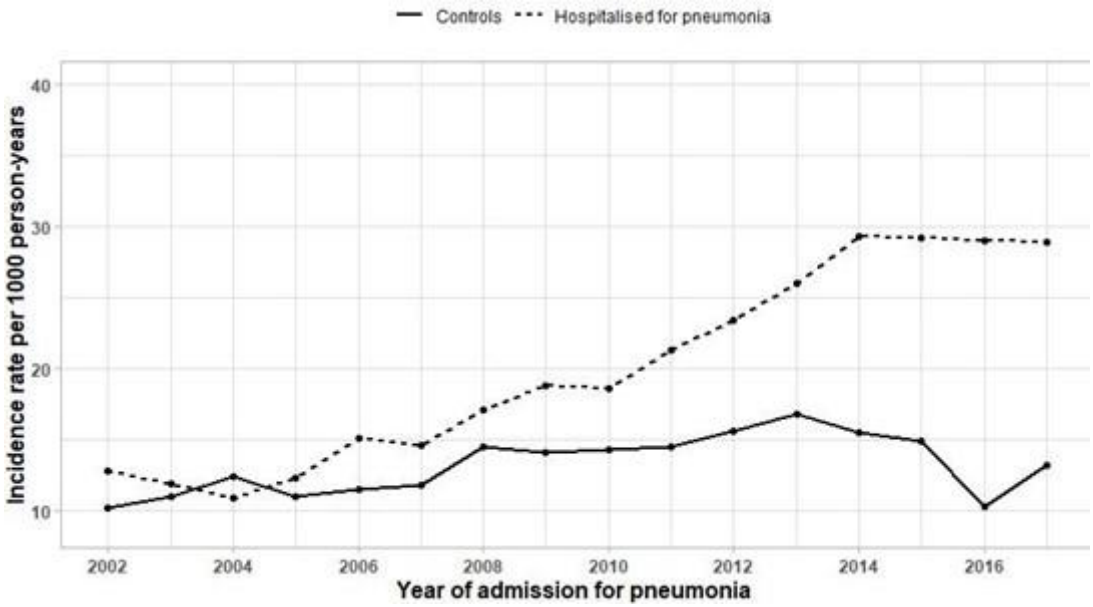

Figure S2. Incidence rate for cognitive impairment and dementia events by year of admission for pneumonia.

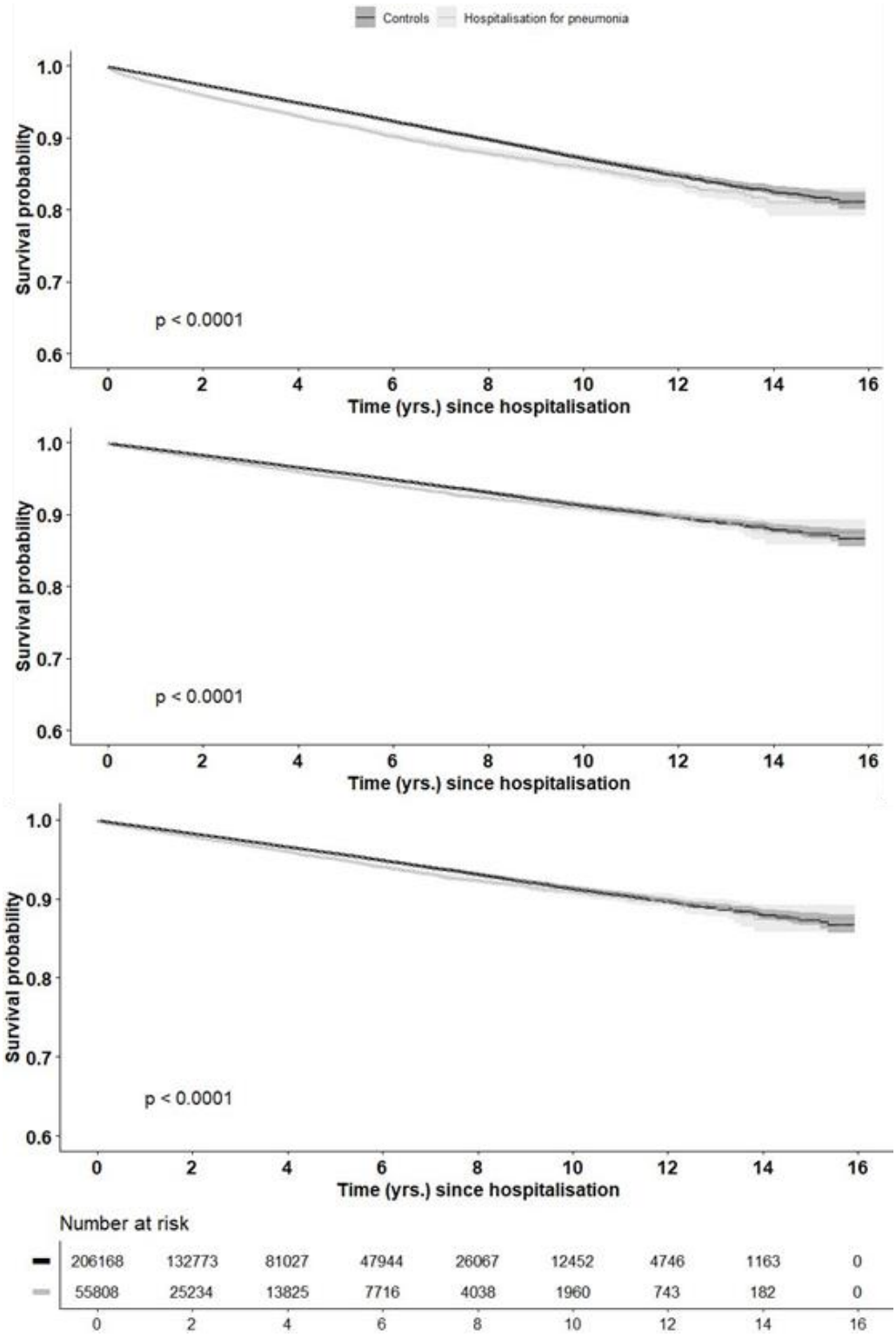

Figure S3. Kaplan-Meier plot with 95%CI and the log-rank test of incidence of time post hospitalisation to first either cognitive impairment or dementia episode (top), first cognitive impairment episode (middle), first dementia episode (bottom) in people previously hospitalised for pneumonia and controls.

Table S4. Adjusted hazard ratios (aHR) for the association of cognitive impairment and/or dementia comparing people previously hospitalised for pneumonia and controls after a complete case and multiple imputation analysis.

	Either cognitive impairment or dementia		Cognitive impairment	
Variables	**Adjusted HR[1] (95%CI)**	**P value**	**Adjusted HR[1] (95%CI)**	**P value**
Either cognitive impairment or dementia Males				
Controls	1.00		1.00	
People hospitalised for pneumonia	1.49 (1.41-1.58)	<.0001	1.55 (1.48-1.63)	<.0001
Cognitive impairment				
Controls	1.00		1.00	
People hospitalised for pneumonia	1.29 (1.20-1.38)	<.0001	1.32 (1.24-1.40)	<.0001
Dementia				
Controls	1.00		1.00	
People hospitalised for pneumonia	2.01 (1.81-2.22)	<.0001	2.07 (1.91-2.25)	<.0001

[2] *Cox model accounting for matched set (age, sex, and practice) and adjusting for smoking, body mass index, alcohol consumption, depression, cerebrovascular diseases, type II diabetes, traumatic brain injury, and hypertension*

Table S5. Hazard ratios (HR) for association of cognitive impairment and dementia with exposure to hospitalisation for pneumonia stratified by gender and age groups.

	Either cognitive impairment or dementia		Cognitive impairment		Dementia	
Variables	**Adjusted HR (95%CI)**	**P value**	**Adjusted HR (95%CI)**	**P value**	**Adjusted HR (95%CI)**	**P value**
			Males			
Age[1]						
18-44	0.98 (0.25-3.88)	.98	0.89 (0.22-3.55)	.867	NA	
45-60	2.42 (1.61-3.63)		2.18 (1.41-3.38)	<.001	2.03 (0.51-8.32)	.323
61-74	1.65 (1.41–1.92)	<.0001	1.46 (1.22-1.75)	<.0001	2.60 (1.86-3.66)	<.0001
75-83	1.52 (1.33-1.72)	<.0001	1.27 (1.09-1.50)	.002	2.15 (1.73-2.68)	<.0001
>83	1.35 (1.17-1.55)	<.0001	0.89 (0.72-1.09)	.254	1.98 (1.64-2.41)	<.0001
Age[1]						
18-44	2.84 (1.24-6.47)	.014	2.65 (1,15-6.10)	.022	NA	
45-60	1.97 (1.32-2.94)	<.001	1.97 (1.30-2.98)	.001	1.29 (0.90-1.86)	.851
61-74	1.74 (1.47-2.05)	<.0001	1.53 (1.27-1.85)	<.0001	2.60 (1.82-3.70)	<.0001
75-83	1.54 (1.33-1.70)	<.0001	1.26 (1.10-1.47)	.002	2.11 (1.75-2.57)	<.0001
>83	1.38 (1.25-1.54)	<.0001	1.08 (0.92-1.26)	.347	1.74 (1.50-2.01)	<.0001

[1] *Age at the index date.*

[2] *Cox model accounting for matched set (age, sex, and practice) and adjusting for smoking, body mass index, alcohol consumption, depression, cerebrovascular diseases, type II diabetes, traumatic brain injury, and hypertension*