Review Article

A Systematic Review and Meta-Analysis Examining Pneumonia-Associated Mortality in Dementia

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Key Words

Alzheimer's disease · Cause of death · Epidemiology

Abstract

Background: Although it is generally accepted that deaths associated with pneumonia are more common in patients with dementia, no comprehensive reviews on the subject have previously been published. **Summary:** Relevant studies were identified through a literature search of the PubMed, EMBASE, Scopus, and ISI Web of Science databases for publications up to August 2013. Studies were included if (1) a group of adult subjects with dementia and a (comparison) group composed of subjects without dementia were included, (2) the cause(s) of death was/were reported, and (3) pneumonia was identified as one of the possible causes of death. The occurrence of death due to pneumonia associated with dementia was expressed as an odds ratio (OR) with 95% confidence interval (CI). Thirteen studies were included. The odds of death resulting from pneumonia were significantly increased for persons with any form of dementia compared with those without dementia (OR = 2.22, 95% CI 1.44–3.42, $p < 0.001$). In a subgroup analysis, using the results from 8 studies that restricted inclusion to persons with Alzheimer's disease, the odds of death resulting from pneumonia were also significantly higher (OR = 1.70, 95% CI 1.12–2.58, $p = 0.013$). **Key Messages:** The odds of pneumonia-associated mortality were increased more than 2-fold for patients with dementia.

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Introduction

Dementia is an umbrella term, which encompasses a group of related neurodegenerative disorders such as Alzheimer's disease (AD), Lewy body dementia, frontotemporal dementia, vascular dementia, and Parkinson's disease dementia. The disease is a progressive disorder that impairs memory, thinking, and the ability to perform activities of daily living and is associated with premature disability and death in developed countries [1, 2]. Persons with dementia tend to die at an earlier age and for different reasons compared with persons without dementia [3–5]. While cardiovascular diseases and neoplasms are more frequent causes of death in the general population, persons with dementia tend to die more often from infections, including pneumonia [6]. In fact, pneumonia has been cited as the most common cause of death in patients with AD [7–10]. Although it is generally accepted that deaths due to pneumonia are more common in patients with dementia, compared with those without dementia, there are contradictory reports [4, 11, 12], and no systematic reviews on the subject have been published. Therefore, the objectives of this study were to conduct a systematic review and meta-analysis to determine whether patients with dementia are more likely to die of pneumonia as the immediate or underlying cause, and if so, to estimate the magnitude of the increased risk.

Methods

Relevant studies were identified through a literature search encompassing the period from 1985 to August 2013. The following databases were searched: PubMed (MEDLINE), EMBASE, Scopus, and ISI Web of Science. Search terms varied slightly across databases but included the terms 'dementia' OR 'Alzheimer's dementia' AND 'pneumonia' OR 'aspiration pneumonia' AND mortality OR 'cause of death' as either MeSH terms, key words, or subject headings (see Appendix for details of the search terms used in each of the databases). Where possible, the searches were limited to 'Human', 'All adults; 19+ years', and the English language. Hand searching of the bibliographies of the included studies was conducted to identify potential articles not identified in the search. The inclusion criteria were broad to capture as many potentially relevant articles as possible.

Studies that included a group of patients with dementia and a control group, reporting the causes of death, were sought. The diagnosis of dementia could be made clinically before death (in population-based studies) or after death based on autopsy reports or death certificates (in studies that used hospital-based samples). Similarly, subjects in the control or the comparison group could include any group of individuals who did not have dementia.

Inclusion Criteria

Studies of any design were included if the following criteria were met: (1) the sample included a group of adult participants (≥ 19 years) who were identified with dementia (AD, vascular dementia, or non-specified dementia) and a (comparison) group composed of subjects without dementia; (2) the presence of dementia was identified through a standardized process that was described – or, following death, by autopsy – or it had been documented in the medical chart; (3) the cause of death, based on either death certificates or autopsy reports, was reported; (4) pneumonia, aspiration pneumonia, or bronchopneumonia was identified as one of the possible causes of death, and (5) the study was published in the English language.

Exclusion Criteria

Studies in which all, or a portion of the participants, suffered from Huntington's disease, Parkinson's disease, Creutzfeldt-Jakob disease, or AIDS-related dementia were excluded, as were studies in which vague terms such as chronic brain syndrome were used or where the results of the dementia subgroup were not reported separately when the study's sample included mixed diagnoses.

Titles and abstracts identified by the literature search were first screened for eligibility by two authors (N.C.F. and R.H.A.). If the eligibility remained in question, the full article was retrieved and reviewed. Disagreements were resolved through consensus. Data pertaining to participant characteristics, criteria used to

identify/diagnose dementia, and deaths associated with pneumonia, aspiration pneumonia, or broncho-pneumonia were extracted from each eligible trial by one reviewer (N.C.F.) and verified for accuracy by a second author (R.H.A.). The odds ratio (OR) and 95% confidence interval (CI) of pneumonia-associated mortality given the presence of dementia were estimated for each study using the software Comprehensive Meta-Analysis (version 2, 2007; Biostat Inc., Englewood, N.J., USA), and the results were pooled. The pre-planned subgroup analysis included AD and sample origin (population or hospital based). When provided, the most adjusted estimates of risks and odds of death reported in the individual studies were used in pooled analyses; otherwise, the raw proportions of persons with and those without dementia who died due to pneumonia were used. A random-effects model was used to account for true variation in effect size and sampling error (i.e., between- and within-study variability).

Results

Literature Search Results

The literature search results and the reasons for exclusions are presented in figure 1. The initial search returned 568 results, after the removal of duplicates. Following the review of titles and abstracts, 23 potentially relevant studies remained for detailed examination, 12 of which met all inclusion criteria. One additional study was retrieved through hand searching, leaving 13 studies in total for review [3, 4, 6, 11–20].

A summary of the details of all included studies is presented in tables 1 and 2. The reporting details in one study, an extension of a previous study [10] and reported in abstract form, were limited [15]. Eight of these studies included participants who were selected from the general population. In these studies, incident cases of dementia were identified based on standardized criteria. Participants with and those without dementia were followed up over time, and the cause(s) of death was/were established during the course of the study's follow-up period or after all the study participants had died [3, 4, 11, 16–20]. The average lengths of follow-up varied between studies from 4 to 10 years. In 5 studies, the samples were composed of groups of patients with and patients without dementia who had died following admission to the hospital [6, 12–15]. In 4 of these studies, both the cases and the controls were drawn from the same institution; in the fifth study, persons from the general population formed the comparison group [6]. With one exception [14], the confirmation of dementia was verified post mortem based on brain pathology, and the cause(s) of death also was/were established based on autopsy.

Participants diagnosed with AD exclusively composed the dementia group in 4 studies [3, 4, 14, 16]. In the remaining studies, participants with AD represented >50% (n = 5 studies) [11, 13, 17, 18, 20] or <50% (n = 2 studies) [6, 12] of the dementia cases, or the breakdown of dementia types was not reported [15, 19]. Other types of dementia included vascular dementia, mixed dementia, and unspecified, 'other' dementia. In 5 of the population-based studies, the participants' mean age at baseline was reported for both the dementia and the comparison group, and in all cases, those with dementia were significantly older [4, 11, 17, 18, 20]. In the 2 hospital-based studies where age was reported, those with dementia were significantly older at the time of hospital death [12, 13]. There was no difference in the sex distribution between groups in 2 studies [11, 19], while significantly more females were included in the dementia group in 4 studies [4, 13, 17, 18]. The severity/stage of dementia at study entry was reported in 2 population-based studies [11, 18]. In one case, the majority of participants suffered from mild or very mild disease [11], while most participants in the other study had moderate or severe forms of dementia [18].

Most of the studies classified mortality into general categories, which included cardiovascular disease, cerebrovascular diseases, neoplasm (cancer), accident, pulmonary disorders, digestive tract disorders, other neurological disorders, pneumonia, and 'other'. Immediate,

Fig. 1. Literature search results.

underlying, *and* contributory significant conditions of death were reported in 2 studies [4, 16], while immediate *or* underlying *or* contributory causes of death were reported in 1 study [3]. The immediate cause of death only was reported in 3 studies [12, 17, 19], while the underlying cause of death was reported in 3 other studies [6, 18, 20]. It was unclear whether the immediate or the underlying cause of death was reported in the remaining studies.

Table 1. Details of the included population-based studies

Study (type)	Sample and screening/assessment methods to establish dementia	Participants with/without dementia	Length of follow-up and outcomes	Results
Kukull et al. [20], 1994 (retrospective study)	654 persons with suspected dementing illness included in the Washington Alzheimer's Disease Patient Registry Screening/assessment: the diagnosis of dementia was established using the DSM-III-R; the diagnosis of AD was based on the NINCDS-ADRDA criteria	At the time of the study, there were 104 deaths: possible AD (n = 10), probable AD (n = 55), and other dementia (n = 22); 17 persons who were initially identified with potential dementia symptoms, but who did not fulfil the dementia criteria following standardized testing, formed the comparison group	The mean time from diagnosis to death in persons with probable AD ranged from 3.7–5.3 years, depending on the level of cognitive impairment at death, based on MMSE scores (severe: 0–14, 15–20; moderate, ≥21: mild) Pneumonia as the underlying cause of death, based on results from death certificates, was reported	Death resulting from pneumonia was not significantly increased in the participants with dementia (n = 9, 10.3%) compared with those without dementia (n = 1, 5.9%; $\chi^2 = 0.015$, p = 0.904); among patients with possible/probable AD, the rates of death from pneumonia were not significantly increased compared with subjects without dementia (12.3 vs. 5.9%; $\chi^2 = 0.102$, p = 0.750)
Morgan and Clarke [19], 1995 (prospective cohort study)	A random sample of 1,042 persons aged ≥65 years selected from general practitioners' lists during a 5-month period in 1985 Screening/assessment: a score of ≤7 on the 12-item CAPE-IO indicated dementia; at two additional follow-up points, the CAPE-IO and a clinical interview using the DSM-III-R were used to identify new cases of dementia	Over 8 years, 81 participants were diagnosed with dementia; 29 prevalent cases were identified at baseline, and 52 incident cases in 1989 and 1993	The participants were followed from 1985 to 1994 Bronchopneumonia as the primary cause of death, based on results from death certificates, was reported; no other causes of death were reported	Over the study period, there were 512 deaths, of which 44 occurred in persons with dementia; an additional 22 persons were identified with dementia, based on death certificates; death resulting from bronchopneumonia was more common in participants with dementia (n = 42, 65.6%) than in those without dementia (n = 113, 25.2%; $\chi^2 = 43.3$, p < 0.0001)
Beard et al. [16], 1996 (case-control study)	959 incident cases of AD that were identified over 15 years (1960–1984) from the Rochester Epidemiological Project who had died The diagnosis of AD was based on established clinical criteria (dementia + insidious onset + slow progression + other causes ruled out, or autopsy, if available); the severity of the AD cases was not reported	The controls were 703 participants, age and sex-matched, who had attended the Mayo clinic during the year of onset of dementia in the case patients, with no evidence of dementia reported in the medical chart, who had died	The mean length of follow-up prior to death was not reported Immediate causes of death (death due to, or as a consequence of pneumonia, and other significant conditions) were reported, based on death certificates	The most common immediate cause of death for both cases and controls was cardiovascular disease (46.0 and 37.2%); bronchitis/pneumonia was more often the immediate cause of death in cases than in controls (26.6 vs. 14.5%; p < 0.001); death as a consequence of bronchitis/pneumonia was reported in 4.4% of cases compared with 2.6% of controls
Tschanz et al. [17], 2004 (Cache County Study on Memory in Aging; cohort study)	5,677 residents of Cache County aged ≥65 years Screening: 5,092 (90%) underwent cognitive screening using the modified MMSE (scores <87 indicated a need for additional assessment) Assessment: 4,683 participants were assessed; the diagnosis of dementia was established using the DSM-III; the stage of dementia was established using the DRS; the diagnosis of AD was based on the NINCDS-ADRDA criteria	355 participants were diagnosed with dementia (AD: n = 207, 58.3%; VaD: n = 54, 15.2%; AD/VaD: n = 31, 8.7%; other dementia: n = 63, 17.7%) and 4,328 subjects did not have dementia; compared with the participants who had dementia, those without dementia were significantly younger (mean age: 74.7 vs. 83.3 years, p < 0.0001) and more likely to be male (44 vs. 36%, p = 0.007) and to be living in a nursing home at study entry (<1 vs. 28%, p < 0.0001); the mean duration of dementia at study entry was 4.1 years	Deaths were monitored over 5 years using vital statistics records The primary cause of death was reported Pneumonia	Over the follow-up period, a total of 1,238 participants (26.4%) died; the most common cause of death for both cases with dementia and for controls was cardiovascular disease (18 and 33%); death was more common in participants with dementia (n = 291, 82%) than in those without (n = 947, 22%; $\chi^2 = 606.1$, p < 0.0001); death due to pneumonia was more common in cases with dementia and in the subset of participants with AD than in cases without AD (n = 39, 13% and n = 18, 11% vs. n = 45, 5%; $\chi^2 = 26.3$, p < 0.0001 and $\chi^2 = 8.43$, p = 0.0037); across 3 age groups, in adjusted analysis, the risk of death was highest for persons with severe dementia (65–74 years: RR = 18.6, 95% CI 8.5–40.5; 75–84 years: RR = 7.04, 95% CI 4.8–10.4; ≥85 years: RR = 3.45, 95% CI 2.04–5.84); the median survival time after screening for prevalent cases of dementia was 3.3 years; the estimated survival time for incident cases of dementia was 7.6 years

Table 1 (continued)

Study (type)	Sample and screening/assessment methods to establish dementia	Participants with/without dementia	Length of follow-up and outcomes	Results
Chamandy and Wolfson [18], 2005 (cohort study)	10,263 (9,008 community-dwelling and 1,255 institutionalized participants) ≥65 years randomly selected from 36 urban areas and their surrounding rural areas in 10 Canadian provinces from 1991–1992 Screening was performed with the modified MMSE; a score <78 indicated a positive screen; 8,949 participants were screened; of these, 1,614 failed the screen and 508 refused further assessment Assessment: the diagnosis of dementia was established using the DSM-III-R and the ICD-10; possible or probable cases of AD were diagnosed using the NINCDS-ADRDA criteria	Based on the screening results, 71.6% of the participants did not have dementia (59 persons were not screened); 2,420 participants were assessed for dementia; of these, 1,295 (53.5%) did not have dementia and 1,125 (46.5%) had dementia	The underlying cause of death was ascertained from death certificates Mortality at 5 years was assessed	2,982 participants died during the study period; the most common cause of death for participants with dementia and those without was ischemic heart disease (19.2 and 24.7%); of the 823 participants with dementia who died, death certificates were available for 754 (AD: n = 499; VaD: n = 151; other: n = 104); 670 participants without dementia died during the study period; death certificates were available for 618 of them; 1,431 participants (1,302) with death certificates were presumed non-demented; death due to pneumonia as an underlying cause of death was more common for participants with dementia (n = 93, 12.3% vs. n = 34, 5.5%; $\chi^2 = 18.1$, $p < 0.0001$); in adjusted analysis, participants with AD and VaD had higher odds of death due to pneumonia as an underlying cause compared with non-demented participants (OR = 1.88, 95% CI 1.18–3.01 and OR = 1.98, 95% CI 1.06–3.68, respectively)
Ganguli et al. [3], 2005 (cohort study)	1,670 participants were randomly selected from the voter registration lists in rural Pennsylvania and volunteers from the same area Screening included the MMSE, the modified Centre for Epidemiological Studies Depression Scale, and the Older Americans Resources and Services Scale (the numbers of those who failed cognitive screening were not reported) Assessment: the diagnosis of AD was established with both the DSM-III and the NINCDS-ADRDA criteria; DRS scores ≥0.5 also indicated possible/probable AD	1,322 (79.2%) without AD, 348 (20.8%) with AD	The duration of follow-up ranged from 0.02 to 15.8 years (mean ± SD: 10.3 ± 4.6 years) Immediate, underlying, and contributory causes of death were established from death certificates Pneumonia	951 participants (57%) had died during follow-up; of these, 262 (27.5%) had AD; the mean duration of survival for the participants with AD was 5.9 ± 3.7 years; the adjusted hazard ratio for mortality given AD was 1.4 (95% CI 1.2–1.8, $p < 0.05$); death certificates were available for 782 (99.1%) of the 789 participants with/without dementia (immediate, underlying, and contributory cause of death); pneumonia was listed as the cause of death more frequently for AD participants (12.3 vs. 6.4%; unadjusted: $p = 0.006$; adjusted for age and sex: $p = 0.04$)
Andersen et al. [11], 2010 (cohort study)	5,237 participants who were aged 65–84 years living in the community and in nursing homes were randomly selected from a central register Screening was done by the CAMCOG; the cut-off score was based on a difference of 4.41 between the actual and the predicted score Assessment: the diagnosis of dementia was based on DSM-III-R criteria; the diagnosis of AD was based on the NINCDS-ADRDA criteria; the severity of dementia was assessed using the DRS; assessments were conducted on 3 occasions: at baseline, to identify prevalent cases, and again at 2 and 5 years, to identify incident cases	At the last follow-up at 5 years, there were 503 incident/prevalent cases of dementia; of these, 339 (67.4%) had AD, 96 (19.1%) had VaD, and 68 (13.5%) had mixed dementia; the severity of dementia was classified as mild or very mild in 80.7% of the cases; 3,065 participants did not have dementia; there was no difference in the proportion of cardiovascular disease, depression, or alcohol/tobacco use between the groups	The mean duration of follow-up was 14 years The cause of death was established using death certificates (unclear whether the immediate or the underlying cause of death was reported) Pneumonia	It is unclear what percentage of the participants in each group died during the study period; a cause of death was reported for 286 participants with dementia and for 884 without dementia; the most common cause of death for the participants with and those without dementia was cardiovascular disease (32.4 and 33.2%); 102 participants without dementia (11.5%) died of pneumonia during the study period compared with 41 participants with dementia (14.3%); the difference was not statistically significant ($\chi^2 = 1.326$, $p = 0.250$)

Table 1 (continued)

Study (type)	Sample and screening/assessment methods to establish dementia	Participants with/without dementia	Length of follow-up and outcomes	Results
Todd et al. [4], 2013 (cohort study)	202 predominantly community-dwelling participants with probable AD were recruited from a single regional hospital that accepted referrals from primary care providers in the area from 2002–2006. Screening: not stated. Assessment: the diagnosis of AD was based on the NINCDS-ADRDA criteria	Controls (n = 194) were recruited from day hospital and orthogeriatric rehabilitation units and senior's clubs; the control participants also included the spouses of AD participants; the inclusion criterion was an MMSE score ≥ 28	The participants were followed up until death or termination of the study (2010); the mean duration of the follow-up was 4.3 years. Immediate, underlying, and contributory causes of death were reported, based on death certificates and regional databases. Pneumonia	145 patients (36.4%) died during the study period; 92 (63.4%) in the AD group and 53 (36.6%) in the control group; there was no difference in the percentage of those who died of pneumonia as an underlying cause of death between the participants with and those without AD (17.6 vs. 25.0%, p = 0.383); compared with expected deaths, using age and sex population norms, the observed deaths of persons with AD were significantly higher in number (5.8 vs. 15); the standardized mortality ratio was 2.59 (95% CI 1.45–4.27); the rates of death due to pneumonia as an immediate, underlying, or contributory cause of death were similar between persons with AD and controls (38.8 vs. 44.2%, p = 0.593)

CAMCOG = Cambridge Cognitive Mental Disorders of the Elderly Examination; CAPE-IO = Clifton Assessment Procedure for the Elderly, information/orientation subscale; DRS = Dementia Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; VaD = vascular dementia.

Table 2. Details of the included hospital-based studies

Study (type)	Sample and screening/assessment methods to establish dementia	Participants with/without dementia	Length of follow-up and outcomes	Results
Kammoun et al. [12], 2000 (retrospective study)	342 patients who had died following admission to a single university-based hospital, over a 15-year period from 1989 to 1996; cases of major psychiatric illness, alcoholism, head trauma, and Parkinson's disease were excluded. Dementia was identified based on the DSM-IV following admission; on autopsy, the diagnosis of AD was based on the NIA-Reagan Institute criteria; VaD and mixed dementia were also identified based on neuropathology	There were 120 cases of dementia and 222 cases without evidence of dementia; of the cases with dementia, 21 had AD, 34 had VaD, and 65 had mixed dementia	The immediate cause of death was reported, based on autopsy results. Pneumonia	Bronchopneumonia was identified as the immediate cause of death more commonly in cases with dementia than in those without dementia, but the difference was not statistically significant (n = 49, 40.8% vs. n = 76, 34.2%, p = 0.226); bronchopneumonia was the immediate cause of death in 52.9% of the patients with VaD, in 38.1% of the patients with AD, and in 35.3% of the patients with mixed dementia; there were no significant differences in pneumonia-associated deaths between the dementia groups (p = 0.231)
Attems et al. [13], 2005 (retrospective study)	308 patients >60 years who had died while patients at a single hospital between 1998 and 2004; the patients were long-term residents of geriatric departments or in the end stages of their respective diseases. The clinical diagnosis of dementia was based on neuropathological assessment using established criteria, including CERAD criteria, Braak scores, and NIA-Reagan Institute criteria	There were 176 cases of dementia and 132 cases without evidence of dementia; among the cases of dementia, AD was determined to be definitive in 135 (76.7%), VaD was present in 8 cases (4.5%), mixed dementia in 7 cases (4.0%), and 'other' in 26 cases (14.8%)	The cause of death was established based on autopsy reports (unclear whether immediate or underlying)	Cardiovascular disease was the most common cause of death in cases without dementia (46.2%); bronchopneumonia was the most common cause of death in dementia cases (45.5%); bronchopneumonia was a more common cause of death in cases with dementia and AD than in those with no dementia (45.5 and 49.6% vs. 28.0%, $\chi^2 = 8.996$, p = 0.0027 and $\chi^2 = 12.2$, p = 0.0005)

Table 2 (continued)

Study (type)	Sample and screening/assessment methods to establish dementia	Participants with/without dementia	Length of follow-up and outcomes	Results
Laditka et al. [14], 2005 (retrospective study)	The medical records of 7,021,065 patients >50 years who had been discharged from hospital during 5 years (1995–2000) were reviewed. The identification of patients with AD was based on associated ICD-9-CM codes from the discharge record; patients with any other form of dementia were excluded from both the AD group and the comparator group	It is unclear what the numbers of admissions with AD and of those with no AD were; 1,345,089 patients without AD died during their hospital stay; 85,249 patients with AD died during their hospital stay; 10.5% of the patients with AD were admitted from nursing homes, compared with 0.3% of the patients without AD; the patients with AD were also older (mean difference of +9.2 years)	The in-hospital mortality was reported Pneumonia	327,425 (12.9%) of the patients without AD died of pneumonia, compared with 36,887 (17.9%) of the patients with AD; the odds of death due to pneumonia (adjusted for age, 25 co-morbidities, race, ethnicity, changes in economic or policy environments, insurance status, and admission from a nursing home) were significantly higher for patients with AD (OR = 1.02, 95% CI 1.01–1.07, $p < 0.01$); men with AD were more likely to die of pneumonia than men without AD (adjusted OR = 1.05, 95% CI 1.00–1.10); women with AD were no more likely to die of pneumonia than women without AD (adjusted OR = 1.01, 95% CI 0.97–1.05)
Brunnström and Englund [6], 2009 (retrospective study)	524 patients admitted to a single hospital from 1974 to 2004 with a clinically diagnosed dementia disorder on whom an autopsy had been performed The identification of AD cases was based on Braak criteria; persons from the Swedish National Register who had died during 2002 were used a comparison group (the cause of death was established based on death certificates)	The dementia subtypes included AD including mixed AD and Lewy body pathology (n = 220, 42.0%), VaD (n = 124, 23.7%), combined AD + VaD (n = 113, 21.6%), and other (n = 67, 12.8%); the mean age of the dementia cases was 79 years; the sample size of the general population used was not stated	The cause of death was established based on autopsy results; the underlying cause of death was reported; the immediate cause of death was reported if the underlying cause of death could not be established Bronchopneumonia and aspiration pneumonia/asphyxia were reported	Bronchopneumonia was the most frequent cause of death in the group of patients with dementia and more frequent than in the general population (38.4 vs. 2.8%); aspiration pneumonia was also more common in patients with dementia (6.7 vs. 0.2%); bronchopneumonia was more common in patients with AD than in those with VaD or AD + VaD (47.3 vs. 27.4% and 32.7%, $p < 0.05$)
Magaki et al. [15], 2013 Abstract of follow-up study (Fu et al. [10], 2004)	90 patients who had died following admission to a single hospital from 2001 to 2010, with clinically and neuropathologically diagnosed dementia, based on a complete autopsy The comparison group comprised 124 elderly inpatients without dementia who had died following hospital admission from 2006 to 2010 and on whom an autopsy had been performed	No details of participant characteristics were reported	Cause of death was established based on autopsy results (unclear if immediate or underlying)	Pneumonia was a more common cause of death in persons with dementia (64.4 vs. 28.2%, $\chi^2 = 39.6$, $p < 0.0001$); cardiovascular disease was the most common cause of death in persons without dementia (n = 35, 28.2%); the next most common was pneumonia (n = 26, 21.0%)

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; NIA = National Institute on Aging; VaD = vascular dementia.

Pneumonia – or what were regarded as similar terms, including aspiration pneumonia, bronchopneumonia, or bronchitis/pneumonia – as a cause of death was reported significantly more often among patients with dementia than among patients without dementia in the majority of studies [3, 6, 13–19]. In 3 of the 4 large prospective population-based studies, a significantly higher percentage of participants with dementia died as a result of pneumonia, ranging from 12.3 to 14.3%, compared with 5–11.5% of patients in the control (no dementia) groups [3, 17, 18]. In hospital-based studies, the percentages of both patients with and those without dementia who died from pneumonia were much higher (38–64.4% vs. 21.0–34.2%) [6, 12, 13, 15], and significantly more persons with dementia died as a result of the condition. When reported, a small percentage of patients' deaths were attributed to dementia or AD (2.4–4.0%), although it was much higher in 1 study, accounting for 23.5% of deaths among patients in the dementia group [4]. The most common causes of death of patients without dementia were cardiovascular and cerebrovascular diseases (including stroke and myocardial infarction) and cancer.

Data from 12 studies were available for pooled analysis. The odds of pneumonia-associated mortality were significantly increased for persons with any form of dementia compared with those without dementia (OR = 2.22, 95% CI 1.44–3.42, $p < 0.001$) (fig. 2). In the subgroup analysis, using the results from 8 studies that restricted inclusion to persons with AD or in which the results from this group were reported separately, the pooled odds of death resulting from pneumonia were also significantly higher (OR = 1.70, 95% CI 1.12–2.58, $p = 0.013$) (fig. 3). The odds of pneumonia-associated mortality were higher in studies using population-based samples (OR = 2.32, 95% CI 1.15–3.53, $p < 0.001$) than in studies in which data from hospital-based samples were used (OR = 2.12, 95% CI 0.99–4.52, $p = 0.053$).

Discussion

The results of this study indicated that the odds of pneumonia-associated mortality were increased more than 2-fold in patients with dementia. In studies using hospital-based samples, the reasons for admission, the living arrangements prior to admission, the presence of co-morbid conditions, the stage of dementia, swallowing status, and other salient medical information were not reported. Similarly, in studies that had recruited patients from the community and followed them up for years, the locations and circumstances surrounding their deaths were unknown, although it may be assumed that the majority of patients were admitted to the hospital or were institutionalized at the time of death. As a result, it was unclear whether the increased rates of death from pneumonia were disproportionately due to infection that was contracted in the advanced stage of dementia or whether, alternatively, patients who were admitted to the hospital in the milder stage of disease progression for unrelated medical or surgical reasons developed pneumonia as a complication during their hospital stay and died. Evidence suggests that excess mortality rates could have been linked to both causes. It has been reported that patients who develop dementia are hospitalized more frequently than those without dementia [21–23] and are often admitted on an emergent basis [9, 24]. The odds of hospital admission given the presence of pre-existing dementia have been reported to be 1.41 [22] and 3.68 times higher [25] and are known to rise with an increasing number of co-morbid conditions [26]. Following an initial hospitalization, patients with dementia are also more likely to be re-admitted within 3 months of discharge [27]. While it might be expected that increased hospital admission rates occur with increasing frequency in patients with more advanced disease progression, few studies have examined this relationship. Compared with persons without dementia, the odds of hospital admission were reported to be 2.3 times greater in patients with severe AD, but they were not raised signifi-

Fig. 2. Forest plot of pneumonia-associated mortality.

cantly in patients with mild-to-moderate AD, even when accounting for co-morbid medical conditions [28]; however, in a study that included community-dwelling individuals, the majority of whom were in the mild stage of AD with low co-morbidity, 66% were hospitalized at least once during a median follow-up of 2.2 years [26].

A higher proportion of patients with dementia are known to be hospitalized with potentially preventable conditions including pneumonia, urinary tract infections, and dehydration [22]. A portion of the increased risk of hospitalization among persons with dementia has been directly attributed to an increase in the number of cases of pneumonia [28]. The odds of admission due to pneumonia were reported to be 1.50 [21] and 1.88 [22] times greater in patients with dementia than in a control group. Pneumonia has also been reported as an in-hospital complication more frequently for patients with dementia. The risk of developing pneumonia was significantly elevated in patients with dementia admitted for medical and surgical reasons – by 37% and 66%, respectively [29]. In a large sample restricted to surgical admissions, the presence of dementia was associated with a significant increase in the development of a number of post-operative complications, including pneumonia (OR = 2.44, 95% CI 2.31–2.58) [30]. In addition to a greater frequency of hospitalizations related to dementia, the age- and sex-adjusted odds of in-hospital mortality from all causes have been reported to be 1.77 [31] and 2.1 [5] times higher for patients with dementia. The odds of death are further increased if patients experience at least 1 adverse clinical event during hospitalization [5].

There are several mechanisms through which patients with dementia may be especially vulnerable to the development of pneumonia. Pneumonia can be precipitated by an episode of aspiration associated with dysphagia [32, 33], a common sequela of dementia [34–36]. While dysphagia is most commonly reported in patients with advanced dementia [32, 33], it has also been observed in patients in the earlier, milder stages of disease progression [37].

Fig. 3. Forest plot of pneumonia-associated mortality (AD).

Gastro-oesophageal reflux may also contribute to the development of pneumonia, particularly when enteral feeding tubes are used in the management of dysphagia [38]. While these devices are intended as a lower-risk means of feeding persons with severe dysphagia, their use has been associated with an increased incidence of aspiration pneumonia in advanced dementia [39].

Although the potential contribution of swallowing problems and gastro-oesophageal reflux could not be investigated in the present review, one author noted that death due to bronchopneumonia and aspiration pneumonia was common, and that the presence of dysphagia was often noted in the clinical record [6]. The presence of a swallowing disorder has previously been correlated with death from pneumonia in persons with advanced dementia [40], and aspiration has been cited as a major cause of death in individuals fed with percutaneous endoscopic gastrostomy tubes [38]. To help reduce the risk of potentially avoidable cases of pneumonia associated with dysphagia and gastro-oesophageal reflux, several measures can be taken. Closer attention to oral care and hygiene, diet modifications to facilitate swallowing in the presence of dysphagia, and education for caregivers who may assist with oral feeding may help to reduce the risk of pneumonia associated with dysphagia-related aspiration. In the more advanced stages of the disease, when pneumonia may be an indicator of approaching death [41], aggressive measures such as the use of tube feeding, intended to help reduce the dangers of aspiration, may not be appropriate [42].

It has also been suggested that the diagnosis and treatment of pneumonia may be delayed in patients whose ability to communicate is impaired, especially in the early stages when patients may be afebrile [30]. A bidirectional relationship between cognitive function and pneumonia has recently been demonstrated, whereby declines in cognitive status increased patients' risk of the development of pneumonia and the rate of cognitive decline accelerated following an episode of pneumonia [43]. Impairment of the inflammatory response system, resulting in higher levels of circulating cytokines and pro-inflammatory markers, in turn leading to neuroinflammation, was suggested as a possible mechanism. Side effects caused by

some types of medications such as neuroleptics may also contribute to pharyngeal dysphagia [44]. Additional, non-specific factors that may have contributed to the excess rates of death from pneumonia in persons with dementia, and which are common in frail seniors, include a reduced ability to clear secretions, impaired immune function [10], increased co-morbidity, and reduced mobility [45].

Potential sources of heterogeneity between studies that may have affected the overall effect size estimate included the cause of death that was reported (underlying vs. immediate), the method used to establish the cause of death (autopsy vs. death certificate), the dementia type and severity, and the study sample (hospital vs. population-based cases and controls). Due to a lack of reporting details, not all sources of variability could be explored. Type of dementia has been suggested as a potential effect modifier, with an increased risk of pneumonia-associated mortality noted among patients with AD [13, 46]. In the present study, when the analysis was restricted to 8 studies that included patients with AD only, the pooled estimate was 33% lower than the overall result (OR = 1.670 vs. 2.22). The difference in estimates may be accounted for, in part, by the higher risk of pneumonia-related death associated with vascular dementia (data not shown). Although only 2 studies were included in this subgroup, the effect size was very large in one of them [17]. Suh et al. [47] reported that sensory dysfunction was seen more frequently in patients with AD, while patients with vascular dementia had more difficulties with bolus formation and mastication of semi-solid food. The incidence of both aspiration and silent aspiration was significantly higher among patients with vascular dementia (47 vs. 13.3%, $p = 0.024$ and 32 vs. 0%, $p = 0.011$, respectively), which potentially may have placed them at a higher risk of pneumonia. Although studies examining other types of dementia were not identified, dysphagia has been documented in Lewy body dementia, Parkinson's disease dementia, and frontotemporal dementia, and all are associated with aberrant eating behaviour as well as motor and sensory disturbances, potentially increasing the risk of aspiration leading to pneumonia [48–52].

An increasing severity of dementia has been associated with an increased risk of death from all causes, including pneumonia. Dementia severity was found to be an independent predictor of pneumonia-associated mortality within the first week of diagnosis and at 3 months [53]. The relationship between baseline dementia severity and risk of death from pneumonia was explored in only 1 of the prospective studies included in the present review [18]. Compared with patients in a mild dementia group, severe dementia was associated with a non-significant increased odds of death (OR = 1.99, 95% CI 0.88–4.50). In the same study, there was no association between the severity of dementia at the time of death and pneumonia-related mortality, using the proxy measures of baseline severity and duration of disease. In contrast, Kukull et al. [20] reported that deaths from pneumonia as an underlying cause were more frequent in patients with severe dementia than in those with mild dementia (22.2 vs. 9.1%). Neoplasms, stroke, and other vascular diseases were the most commonly reported causes of death for patients with mild dementia, while pneumonia and death from dementia itself were the most common underlying causes of death in patients with severe impairment. Since the severity (or stage) of dementia was not reported at the time of death in any of the other studies, its effect as a potential source of variability could not be examined further.

Speculating as to the variability in effect size associated with using autopsy versus death certificates to determine the cause of death is challenging. Poor agreement between causes of death based on death certificates and those based on autopsy reports has previously been noted, and information on death certificates is known to be less accurate. Pneumonia as a cause of death has been under-reported when autopsy results have been compared with death certificates in persons with dementia [7, 8]. Pneumonia was identified as the primary cause of death in 47% of cases based on death certificates and in 57% of cases based on

autopsy results and was missed on 11 of 53 death certificates [8]. We included 9 studies that relied on death certificate or registry data to establish a cause of death. While the number of true cases in which pneumonia had been the cause of death was unknown in these studies, it is possible that they were under-estimated, although a bias favouring one group (dementia or control) is unlikely. Pneumonia-associated mortality may have been under-reported in studies that only reported the underlying cause of death, given that pneumonia is more likely to be reported as an immediate cause. In 1 of the included studies, the first-listed causes of death on parts 1a, b, and c of the death certificates were all reported [16]. Pneumonia was identified as an immediate cause of death in both cases and controls 6 times more frequently than as an underlying cause.

Limitations

In some of the included studies, an estimation of the effect size was calculated using crude (unadjusted) data, likely resulting in an over-estimation of the effect size. This fact may help to explain why, contrary to expectation, the odds of pneumonia-related death were 9% higher in studies including population-based samples, even though patients in hospital-based studies were perceived to be at higher risk. In only 1 of the hospital-based studies was the analysis adjusted for potentially confounding variables [14], while adjustments were made in 3 of the population-based studies [3, 16, 18]. In the remaining studies, when reported, a greater proportion of patients at higher risk, including females and those of more advanced age, were represented in the dementia group. It is possible that, despite our best effort, potentially relevant articles were missed in the literature search.

In summary, the results from 13 studies suggest that the odds of pneumonia-associated mortality were significantly increased for persons with any form of dementia compared with those without dementia. The causes of the increased risk may include aspiration – associated with dysphagia – as well as non-specific factors, which are common in frail seniors and further increased in the terminal stages of dementia. Although it was not possible to determine at what stage of the disease process pneumonia developed, it is likely that a portion of the excess mortality rates in dementia could be prevented by appropriate early diagnosis and management.

Appendix

Literature Search Strategy

PubMed (n = 179)

((('Dementia'[MeSH]) OR ('Alzheimer Disease'[MeSH])) AND (('Pneumonia'[MeSH]) OR ('Pneumonia, Aspiration'[MeSH]))

Limits: English language, adults (≥19 years)

EMBASE (n = 276)

(Dementia/ or Alzheimer disease/) AND (bacterial pneumonia/ or community acquired pneumonia/ or aspiration pneumonia/ or pneumonia/ or hospital acquired pneumonia/) AND (cause of death'/ or mortality)

Limits: English language, human

Scopus (n = 403)

KEY(dementia OR 'Disease, Alzheimer' OR 'Alzheimer's Disease' OR 'Disease, Alzheimer's' OR 'Alzheimer Type Dementia' OR 'Senile Dementia, Alzheimer Type' OR 'Dementia, Primary Senile Degenerative' OR 'Dementia, Senile' OR 'Dementias, Senile' OR 'Senile Dementia' OR 'Senile Dementias' OR 'Primary Senile Degenerative Dementia' OR 'Alzheimer Type Senile Dementia' OR 'Dementia, Presenile' OR 'Dementias, Presenile' OR 'Presenile Dementia' OR 'Presenile Dementias' OR 'Alzheimer Disease, Late Onset' OR 'Late Onset Alzheimer Disease' OR 'Alzheimer's Disease, Focal Onset' OR 'Focal Onset Alzheimer's Disease' OR

'Acute Confusional Senile Dementia' OR 'Senile Dementia, Acute Confusional' OR 'Alzheimer Disease, Early Onset' OR 'Presenile Alzheimer Dementia' OR 'Alzheimer Dementia, Presenile' OR 'Dementia, Presenile Alzheimer' OR 'Early Onset Alzheimer Disease' OR 'Dementias, Vascular' OR 'Vascular Dementias' OR 'Vascular Dementia' OR 'Vascular Dementia, Acute Onset' OR 'Acute Onset Vascular Dementia' OR 'Subcortical Vascular Dementia' OR 'Dementia, Subcortical Vascular' OR 'Dementias, Subcortical Vascular' OR 'Subcortical Vascular Dementias' OR 'Vascular Dementia, Subcortical' OR 'Vascular Dementias, Subcortical' OR 'Dementia, Multi Infarct' OR 'Dementias, Multi-Infarct' OR 'Multi-Infarct Dementias' OR 'Multi-Infarct Dementia' OR 'Multi Infarct Dementia' OR 'Dementia, Multiinfarct' OR 'Dementias, Multiinfarct' OR 'Multiinfarct Dementia' OR 'Multiinfarct Dementias' OR 'Dementia Multi-Infarct' OR 'Dementia Multi Infarct' OR 'Dementia Multi-Infarcts' OR 'Multi-Infarct, Dementia' OR 'Multi-Infarcts, Dementia' OR 'Dementias, Frontotemporal' OR 'Frontotemporal Dementias' OR 'Frontotemporal Lobe Dementia' OR 'Dementia, Frontotemporal Lobe' OR 'Dementias, Frontotemporal Lobe' OR 'Frontotemporal Lobe Dementias' OR 'Lewy Body Dementia' OR 'Lewy Body Disease, Cortical' OR 'Dementia, Lewy Body' OR 'Lewy Body Type Senile Dementia' OR 'Cortical Lewy Body Disease' OR 'Diffuse Lewy Body Disease' OR 'Lewy Body Disease, Diffuse') AND KEY(Pneumoni* OR 'Pulmonary Inflammation' OR 'Inflammation, Pulmonary' OR 'Inflammations, Pulmonary' OR 'Pulmonary Inflammations' OR 'Lung Inflammation' OR 'Inflammations, Lung' OR 'Lung Inflammations' OR 'Lobar Pneumonia' OR 'Pneumonia, Lobar' OR 'Aspiration Pneumonias' OR 'Pneumonias, Aspiration' OR 'Aspiration Pneumonia' OR 'Acid Aspiration Syndrome' OR 'Acid Aspiration Syndromes' OR Bronchopneumonia* OR 'Bronchial Pneumonia' OR 'Bronchial Pneumonias' OR 'Pneumonia, Bronchial' OR 'Pneumonias, Bronchial') AND KEY(Mortality OR 'Mortality, In-Hospital' OR 'In-Hospital Mortalities' OR 'Mortalities, In-Hospital' OR 'In-Hospital Mortality' OR 'Mortality, Hospital' OR 'Mortalities, Hospital' OR 'Mortalities, In-house' OR 'In-house Mortalities' OR 'In-house Mortality' OR 'Mortalities, In house' OR 'Mortality, In-house' OR 'Mortality, Inhospital' OR 'Hospital Mortalities' OR 'In Hospital Mortalities' OR 'Inhospital Mortalities' OR 'Mortalities, Inhospital' OR 'In Hospital Mortality' OR 'Hospital Mortalities, In' OR 'Hospital Mortality, In' OR 'Mortalities, In Hospital' OR 'Mortality, In Hospital' OR 'Inhospital Mortality' OR 'Cause of Death')

Limits: English language

ISI Web of Science (n = 188)

TS = (Pneumoni* OR 'Pulmonary Inflammation' OR 'Inflammation, Pulmonary' OR 'Inflammations, Pulmonary' OR 'Pulmonary Inflammations' OR 'Lung Inflammation' OR 'Inflammations, Lung' OR 'Lung Inflammations' OR 'Lobar Pneumonia' OR 'Pneumonia, Lobar' OR 'Aspiration Pneumonias' OR 'Pneumonias, Aspiration' OR 'Aspiration Pneumonia' OR 'Acid Aspiration Syndrome' OR 'Acid Aspiration Syndromes' OR Bronchopneumonia* OR 'Bronchial Pneumonia' OR 'Bronchial Pneumonias' OR 'Pneumonia, Bronchial' OR 'Pneumonias, Bronchial') AND TS = (dementia OR 'Disease, Alzheimer' OR 'Alzheimer's Disease' OR 'Disease, Alzheimer's' OR 'Alzheimer Type Dementia' OR 'Senile Dementia, Alzheimer Type' OR 'Dementia, Primary Senile Degenerative' OR 'Dementia, Senile' OR 'Dementias, Senile' OR 'Senile Dementia' OR 'Senile Dementias' OR 'Primary Senile Degenerative Dementia' OR 'Alzheimer Type Senile Dementia' OR 'Dementia, Presenile' OR 'Dementias, Presenile' OR 'Presenile Dementia' OR 'Presenile Dementias' OR 'Alzheimer Disease, Late Onset' OR 'Late Onset Alzheimer Disease' OR 'Alzheimer's Disease, Focal Onset' OR 'Focal Onset Alzheimer's Disease' OR 'Acute Confusional Senile Dementia' OR 'Senile Dementia, Acute Confusional' OR 'Alzheimer Disease, Early Onset' OR 'Presenile Alzheimer Dementia' OR 'Alzheimer Dementia, Presenile' OR 'Dementia, Presenile Alzheimer' OR 'Early Onset Alzheimer Disease' OR 'Dementias, Vascular' OR 'Vascular Dementias' OR 'Vascular Dementia' OR 'Vascular Dementia, Acute Onset' OR 'Acute Onset Vascular Dementia' OR 'Subcortical Vascular Dementia' OR 'Dementia, Subcortical Vascular' OR 'Dementias, Subcortical Vascular' OR 'Subcortical Vascular Dementias' OR 'Vascular Dementia, Subcortical' OR 'Vascular Dementias, Subcortical' OR 'Dementia, Multi Infarct' OR 'Dementias, Multi-Infarct' OR 'Multi-Infarct Dementias' OR 'Multi-Infarct Dementia' OR 'Multi Infarct Dementia' OR 'Dementia, Multiinfarct' OR 'Dementias, Multiinfarct' OR 'Multiinfarct Dementia' OR 'Multiinfarct Dementias' OR 'Dementia Multi-Infarct' OR 'Dementia Multi Infarct' OR 'Dementia Multi-Infarcts' OR 'Multi-Infarct, Dementia' OR 'Multi-Infarcts, Dementia' OR 'Dementias, Frontotemporal' OR 'Frontotemporal Dementias' OR 'Frontotemporal Lobe Dementia' OR 'Dementia, Frontotemporal Lobe' OR 'Dementias, Frontotemporal Lobe' OR 'Frontotemporal Lobe Dementias' OR 'Lewy Body Dementia' OR 'Lewy Body Disease, Cortical' OR 'Dementia, Lewy Body' OR 'Lewy Body Type Senile Dementia' OR 'Cortical Lewy Body Disease' OR 'Diffuse Lewy Body Disease' OR 'Lewy Body Disease, Diffuse') AND TS = ('cause of death' OR mortality)

Limits: English language

Total unique hits: n = 568

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Disclosure Statement

The authors have no conflicts of interest to declare.

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