Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project

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Summary

Background Some people with substantial Alzheimer's disease pathology at autopsy had shown few characteristic clinical symptoms or signs of the disease, whereas others with little Alzheimer's disease pathology have been diagnosed with Alzheimer's dementia. We aimed to examine whether frailty, which is associated with both age and dementia, moderates the relationship between Alzheimer's disease pathology and Alzheimer's dementia.

Methods We did a cross-sectional analysis of data from participants of the Rush Memory and Aging Project, a clinical–pathological cohort study of older adults (older than 59 years) without known dementia at baseline, living in Illinois, USA. Participants in the cohort study underwent annual neuropsychological and clinical evaluations. In the present cross-sectional analysis, we included those participants who did not have any form of dementia or who had Alzheimer's dementia at the time of their last clinical assessment and who had died and for whom complete autopsy data were available. Alzheimer's disease pathology was quantified by a summary measure of neurofibrillary tangles and neuritic and diffuse plaques. Clinical diagnosis of Alzheimer's dementia was based on clinician consensus. Frailty was operationalised retrospectively using health variable information obtained at each clincial evaluation using the deficit accumulation approach (41-item frailty index). Logistic regression and moderation modelling were used to assess relationships between Alzheimer's disease pathology, frailty, and Alzheimer's dementia. All analyses were adjusted for age, sex, and education.

Findings Up to data cutoff (Jan 20, 2017), we included 456 participants (mean age at death 89·7 years [SD 6·1]; 316 [69%] women). 242 (53%) had a diagnosis of possible or probable Alzheimer's dementia at their last clinical assessment. Frailty (odds ratio 1·76, 95% CI 1·54–2·02; p<0·0001) and Alzheimer's disease pathology (4·81, 3·31–7·01; p<0·0001) were independently associated with Alzheimer's dementia, after adjusting for age, sex, and education. When frailty was added to the model for the relationship between Alzheimer's disease pathology and Alzheimer's dementia, model fit improved (p<0·0001). There was a significant interaction between frailty and Alzheimer's disease pathology (odds ratio 0·73, 95% CI 0·57–0·94; $p_{interaction}$=0·015). People with an increased frailty score had a weakened direct link between Alzheimer's disease pathology and Alzheimer's dementia; that is, people with a low amount of frailty were better able to tolerate Alzheimer's disease pathology, whereas those with higher amounts of frailty were more likely both to have more Alzheimer's disease pathology and for it to be expressed as dementia.

Interpretation The degree of frailty among people of the same age modifies the association between Alzheimer's disease pathology and Alzheimer's dementia. That frailty is related to both odds of Alzheimer's dementia and disease expression has implications for clinical management, since individuals with even a low level of Alzheimer's disease pathology might be at risk for dementia if they have high amounts of frailty. Further research should assess how frailty and cognition change over time to better elucidate this complex relationship.

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Introduction

The neuropathological features of Alzheimer's disease (amyloid-based plaques and neurofibrillary tangles) do not correlate well with the clinical expression of dementia (cognitive and functional decline).[1] Many people with a high burden of Alzheimer's disease pathology at autopsy had few characteristic clinical symptoms or signs, whereas others with little Alzheimer's disease pathology had Alzheimer's dementia.[2] These discrepancies suggest that some latent factors might affect the relationship between Alzheimer's disease pathology and dementia, determining which people are most vulnerable to pathological abnormalities. Although some people who develop Alzheimer's dementia are young and otherwise

Research in context

Evidence before this study

Using the terms "neuropathology", "frailty", "dementia", and "Alzheimer's disease" and their synonyms, which have been published previously, we searched Google Scholar and PubMed for articles published between Jan 29, 2017, and July 3, 2018, in English or French. We found that no pathophysiological mechanism has yet been able to account for: (1) the weak relationship between Alzheimer's disease pathology and dementia (ie, Alzheimer's disease pathology does not seem to be necessary or sufficient to cause dementia symptoms); (2) the high prevalence of mixed dementia; (3) and the many, diverse genetic and environmental risk factors that have been associated with Alzheimer's disease.

Added value of this study

This study shows that the relationship between Alzheimer's disease pathology and dementia changes over levels of frailty, such that as frailty increases, the pathology–dementia relationship weakens. These findings suggest that frailty plays a key role in the natural history of Alzheimer's disease.

Implications of all the available evidence

The expression of dementia symptoms results from several causes, particularly in people who are most likely to develop dementia: those who are older and who have several comorbidities. These causes are unlikely to be explained by a single mechanism. Our hypothesis follows an emerging concept of dementia, and particularly Alzheimer's disease dementia, as a complex disease of ageing, rather than a single disease entity marked by genetic risk or a particular protein abnormality. In a specialty with so many competing claims about individual risk factors, understanding how they work together to give rise to clinical dementia is likely to offer a new way to advance the epidemiological study of dementia and the development of targeted treatment options.

healthy (typically with familial Alzheimer's disease), most people who develop Alzheimer's dementia are usually older than 65 years with several other health problems. People with several, age-related health deficits are often considered frail.[3] Frailty might help explain the relationship between Alzheimer's disease pathology and the clinical expression of dementia.

People with frailty have a decreased physiological reserve and increased vulnerability to adverse health outcomes (including hospitalisation and death) compared with other people of the same age.[4] Frailty has been most commonly operationalised using a deficit accumulation approach or a phenotypic approach.[5,6] Unfortunately, people who are frail are routinely excluded from clinical trials.[7]

Frailty is related to neuropathological features of Alzheimer's disease, cognitive decline, and dementia.[8–10] Frailty and Alzheimer's dementia share many risk factors and clinical features, including age, inflammation, functional impairment, and atypical illness presentation.[9] The link between frailty and Alzheimer's dementia has been shown both in clinical and epidemiological settings, but less so using neuropathological studies. So far, such studies assessing Alzheimer's disease pathology have been restricted to the phenotypic definition of frailty and none has examined the potential for frailty to moderate the relationship between Alzheimer's disease pathology and dementia.[11,12]

We hypothesised that frailty is a latent factor that moderates clinical dementia expression in relation to Alzheimer's disease pathology. By reducing an individual's physiological reserve, frailty could precipitate dementia disease expression when it might have remained asymptomatic in a non-frail individual. We aimed to examine the effect of frailty on the relationship between Alzheimer's disease pathology and expression of Alzheimer's dementia.

Methods

Study design and data sources

Data are from the Rush Memory and Aging Project (MAP), which has been described elsewhere.[13] The MAP is a clinical–pathological cohort study that, since 1997, has enrolled over 2100 old people without dementia from about 40 residential facilities, senior and subsidised housing, church groups, and social service agencies in northeastern Illinois. The aim of the MAP is to identify factors associated with maintenance of cognitive health despite the accumulation of neuropathological lesions. This cohort has been followed for 21 years with data collected annually via home visits. Participants provide blood samples and undergo detailed clinical evaluation, including cognitive assessments. All participants signed the Uniform Anatomical Gift Act, agreeing to donate their brain, spinal cord, and other biospecimens at death. The MAP was selected for our analysis because it combines comprehensive clinical and cognitive assessments and essential neuropathological characterisation, with sufficient data to allow for operationalisation of a frailty index.

Approval from the Dalhousie and Nova Scotia Health Authority Research Ethics Boards was granted before initiating any of the study procedures. The MAP was approved by the Institutional Review Board of Rush University Medical Center. All participants signed an informed consent and Anatomical Gift Act for organ donation before enrolment.

Procedures

Clinical diagnosis of cognitive status done at each annual assessment is comprised of three-steps: (1) computer scoring of a neuropsychological battery including 19 instruments (eg, word list recall, category fluency, digit ordering, and Stroop word reading);[11,12] (2) clinical judgment by a neuropsychologist masked to participant

demographics; and (3) diagnostic classification by a clinician (neurologist, geriatrician, geriatric nurse practitioner, or neuropsychologist).[14] Clinical diagnoses of Alzheimer's dementia are based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association joint working group.[15] For the analyses presented here, people diagnosed with mild cognitive impairment or other forms of dementia were excluded; our dementia status variable refers to only Alzheimer's dementia or no dementia.

The frailty index is a health state measure designed to integrate several types of health information. The frailty index reflects vulnerability to adverse outcomes and proximity to death.[4] It reliably predicts adverse outcomes in large health databases from many countries.[4] A frailty index can be created using routinely collected clinical information such as symptoms, signs, disabilities, and diseases that meet standard criteria.[16] The frailty index is calculated as the number of health deficits present divided by the number of health variables measured. For example, a person with ten of 40 potential deficits measured has a frailty index score of 0·25 (10/40). The frailty index takes advantage of the high redundancy of the human body (ie, several systems or mechanisms are in place to complete the same task), making it replicable across different databases, even when different items, and numbers of items, are used.[4]

We created a frailty index from health variables obtained at each clinical evaluation. Candidate variables included symptoms, signs, comorbidities, and function. Variables were screened for inclusion based on standard procedures;[16] variables strongly related to dementia status (cognitive variables) were excluded. Our 41-item frailty index can be found in the appendix. Higher values on the frailty index suggest poorer health. For the purpose of interpretation, the frailty index value was multiplied by ten so that odds ratios would represent the proportion of change for an increment of 0·1 of the frailty index (an additional three to four deficits).

The MAP includes data from post-mortem neuropathological evaluation. Global Alzheimer's disease pathology burden was quantified into tertiles (T1=0·000–0·327, T2=0·0328–1·002, and T3=1·003–3·212), as described elsewhere.[10,12,13] Briefly, Global Alzheimer's disease pathology burden is a quantitative summary of three Alzheimer's disease pathologies (neuritic plaques, diffuse plaques, and neurofibrillary tangles), as measured by microscopic examination of Bielschowsky silver-stained slides from five brain regions (midfrontal, midtemporal, inferior parietal, and entorhinal cortices, and the hippocampus) resulting in 15 separate counts. A summary score for each of the three pathological findings is obtained by dividing the count for each index in each region by the corresponding SD and then averaging the five scaled regional measures to obtain a scaled mean. The three scaled means are then averaged and the square root is calculated to obtain the measure of Alzheimer's disease pathology.[17] Additional information can be found in the appendix. Higher values on the Alzheimer's disease pathology measure suggest greater burden of pathological abnormalities. For sensitivity analyses, counts of the three individual pathological measures were also used, as were mean percent volume of amyloid calculated over eight regions (hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal cortex, angular gyrus, calcarine cortex, anterior cingulate cortex, and superior frontal cortex) and Braak staging (a score between 1 and 6 of tangle pathology burden and spread), for which higher scores suggest worse pathology.[18] Age was calculated from birth to date of the final cognitive assessment. Sex and education were self-reported. *APOE* status (presence of at least one ε*4* allele) was obtained via genotyping of brain tissue using high-throughput sequencing of codons 112 (position 3937) and 158 (4075) of exon 4 on the *APOE* gene on chromosome 19.[19]

See Online for appendix

	All (n=456)	Frailty index <0·41 (n=233)	Frailty index ≥0·41 (n=223)	p value*
Age at baseline, years	83·1 (5·9)	82·1 (5·8)	84·2 (5·8)	<0·0001
Age at death, years	89·7 (6·1)	88·3 (6·2)	91·2 (5·6)	<0·0001
Sex				
Male	140 (31%)	83 (36%)	57 (26%)	0·020
Female	316 (69%)	150 (64%)	166 (74%)	..
Years of education	14·4 (2·9)	14·5 (3·0)	14·3 (2·9)	0·45
Frailty index at last assessment before death	0·42 (0·18)	0·28 (0·09)	0·58 (0·10)	<0·0001
Alzheimer's disease dementia diagnosed before death	242 (53%)	79 (34%)	163 (73%)	<0·0001
MMSE at last assessment before death	19·8 (9·8)	23·4 (8·2)	16·1 (10·0)	<0·0001
Braak stage	3·7 (1·2)	3·4 (1·2)	3·9 (1·1)	<0·0001
APOE genotype (≥1 ε*4* alleles)	106 (23%)	48 (21%)	58 (26%)	0·35
10-item CES-D	2·0 (2·2)	1·4 (1·8)	2·6 (2·5)	<0·0001
Number of medications	1·9 (1·1)	1·7 (1·1)	2·0 (1·2)	0·002

Data are mean (SD) or number (%).CES-D=Center for Epidemiologic Studies Depression Scale. MMSE=Mini-Mental State Examination. *For the difference between frailty groups.

Table 1: **Descriptive characteristics of the study cohort**

Statistical analysis

We investigated participants' characteristics and validated the frailty index using a standard approach including descriptive statistics and appropriate statistical tests. For the purpose of describing our sample, we categorised participants into two frailty groups using the median as the cut-point.

We used logistic regression to examine the relationship between neuropathological markers (exposure, continuous variable), frailty index (exposure, continuous variable), and dementia status (outcome, binary variable). We then assessed whether the frailty index improved model fit when added to an adjusted model including Alzheimer's disease pathology, using Akaike information

	Low burden		Intermediate burden		High burden		p value*
	Number of participants	Mean (SD)	Number of participants	Mean (SD)	Number of participants	Mean (SD)	
No Alzheimer's disease	102	0·33 (0·14)	77	0·36 (0·15)	35	0·35 (0·15)	0·37
Alzheimer's disease	50	0·55 (0·15)	75	0·50 (0·18)	117	0·46 (0·18)	0·012
p value†	..	<0·0001	..	<0·0001	..	0·001	..

Data are mean (SD). *For the difference across burden groups. †For the difference between no Alzheimer's disease and Alzheimer's disease groups.

Table 2: **Frailty index values by neuropathological burden and dementia status**

		Frailty index							
		Low		Medium		High		Total	
		Number of participants	Number (%) with dementia	Number of participants	Number (%) with dementia	Number of participants	Number (%) with dementia	Number of participants	Number (%) with dementia
Neuropathological burden	Low	56	3 (5%)	54	18 (33%)	42	29 (69%)	**152**	**50 (33%)**
	Medium	54	16 (30%)	48	22 (46%)	50	37 (74%)	**152**	**75 (49%)**
	High	45	30 (67%)	53	39 (74%)	54	48 (89%)	**152**	**117 (77%)**
	Total	155	49 (32%)	155	79 (51%)	146	114 (78%)	**456**	**242 (53%)**

Data are n/N (%)

Figure 1: **Proportion of people with Alzheimer's disease according to frailty index values by neuropathological burdern**

criterion, Bayesian information criterion, and deviance (–2 log likelihood).

We built moderated logistic regression models (Process syntax[20]) using 5000 bootstrapped samples and bias-corrected 95% CIs. We used these models to report the relationship between Alzheimer's disease pathology and Alzheimer's dementia at three different levels of frailty: the mean frailty index value (intermediate frailty), 1 SD above the mean (high frailty), and 1 SD below the mean (low frailty).

All analyses were adjusted for age, sex, and education; *APOE* status was evaluated and found not to significantly affect the results and so it was excluded from the final models. Age, sex, education, and *APOE* status were evaluated as confounders with respect to the outcome. Age and education were measured in years and analysed as continuous variables, whereas sex was analysed as a binary variable. *APOE* status was coded as binary (presence or absence of ≥1 ε*4* allele). Sensitivity analyses examining measures including a modified frailty phenotype, Braak stage, amyloid burden (calculated as percent volume), depression (as measured by the Centre for Epidemiologic Studies ten-item depression scale), and polypharmacy (as measured by the sum of prescription medications) were done. Details on these measures can be found elsewhere.[12] All analyses were done using SPSS version 24.

Role of the funding source

There was no funding source for this study. LMKW and KR had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Since its inception 21 years ago, 3869 people have expressed interest in inclusion in the MAP, of whom 2112 (55%) were enrolled; 193 (9%) participants have discontinued study participation, reflecting an average loss to follow-up of 1% based on person-years in the study. The dataset was locked for the present study on Jan 20, 2017, and included 1843 enrolled participants, of whom 831 had died and 675 had complete autopsy data. Of those with autopsy records, 456 had either no dementia or Alzheimer's dementia at their last cognitive assessment and had enough information to create a frailty index and were therefore included in this analysis (appendix). The mean time from last assessment to death was 0·89 years (SD 1·13; median 0·61), mean age at death was 89·7 years (SD 6·1), and 316 (69%) were women (table 1). 242 (53%) had a diagnosis of possible or probable Alzheimer's dementia at their last clinical assessment. The mean frailty index for the whole sample was 0·42 (SD 0·18), with a median of 0·41 (range 0·04–0·91); this median cut-point is similar to that typically used to distinguish between moderately and severely frail people.[21] The 95th percentile was 0·71 and the 99th was 0·81. The frailty index had a characteristic skewed distribution with a long right tail. People who had high frailty index scores (≥0·41; n=223) were older, had lower Mini-Mental State Examination scores, were more likely to have a dementia diagnosis, and had a higher Braak stage than those with a frailty index score less than 0·41 (table 1).

35 participants (8%) had a high burden of Alzheimer's disease pathology without having been diagnosed with dementia, and 50 (11%) had Alzheimer's dementia but had

a low burden of Alzheimer's disease pathology (table 2). Therefore, for about one person in six, the relationship between Alzheimer's disease pathology and dementia was weak. The mean frailty index was significantly higher for people with Alzheimer's dementia compared with those without (table 2); however, the mean frailty index was highest among people with Alzheimer's dementia with a low burden of Alzheimer's disease pathology (table 2). Among people with a low burden of Alzheimer's disease pathology, the prevalence of Alzheimer's dementia was higher in those who had high frailty than those with low frailty (69% *vs* 5%; figure 1).

Frailty index scores (odds ratio [OR] 1·76, 95% CI 1·54–2·02; p<0·0001) and Alzheimer's disease pathology (4·81, 3·31–7·01; p<0·0001) were independently associated with dementia status, after adjusting for age, sex, and education. When the frailty index was added to a model with Alzheimer's disease pathology, the model fit improved significantly according to the reduction in Akaike information criterion (from 533·48 to 449·41), Bayesian information criterion (from 554·10 to 474·15), and deviance (from 523·48 to 437·41; p<0·0001). Furthermore, there was a significant interaction between frailty index and Alzheimer's disease pathology (OR 0·73, 95% CI 0·57–0·94; $p_{interaction}$=0·015). Moderation analyses showed that the relationship between Alzheimer's disease pathology and dementia status differed according to level of frailty, with a weaker relationship with increased frailty (figure 2).

Sensitivity analyses were done to establish whether the interaction was being driven by the type of Alzheimer's disease pathology. Only neuritic plaques showed a significant interaction between frailty index and dementia status (OR 0·80, 95% CI 0·66–0·96; $p_{interaction}$=0·019). Moderation analyses suggested that, with increasing frailty, the relationship between neuritic plaques and dementia status weakened, which is consistent with our original results. We also explored the effects of amyloid calculated as percent volume occupied (rather than plaque counts) and found that the relationship was consistent (ie, significant interaction between amyloid and frailty index: OR 0·96, 95% CI 0·93–1·00; $p_{interaction}$=0·027). Braak staging was also associated with the frailty index (OR 0·80, 95% CI 0·68–0·93; p=0·004) in relation to dementia status, and moderation analyses suggested that, with increasing frailty, the relationship between Braak stage and dementia status weakened, which is consistent with our original results. We investigated whether including people with mild cognitive impairment in the reference group (ie, no dementia) would alter the results and found that, although the frailty index and Alzheimer's disease pathology remained independent predictors of Alzheimer's dementia, their interaction was not significant. To be sure that the results were not being driven by variables in activities of daily living, we recreated the frailty index excluding these variables (n=14; appendix), and found similar results. We also controlled for the effects of possible risk factors, including self-reported history of stroke, hypertension, diabetes, congestive heart failure, and depression (as measured by the Center for Epidemiologic Studies Depression Scale) and found that, although stroke and congestive heart failure were significantly associated with dementia status, the frailty×pathology interaction remained significant (appendix). When the frailty phenotype (Z score; as detailed elsewhere[10]) was used in place of the frailty index, it significantly predicted the outcome (OR 2·46, 95% CI 1·76–3·45; p<0·0001), but with no significant interaction with Alzheimer's disease pathology (0·57, 95% CI 0·29–1·14; $p_{interaction}$=0·11).

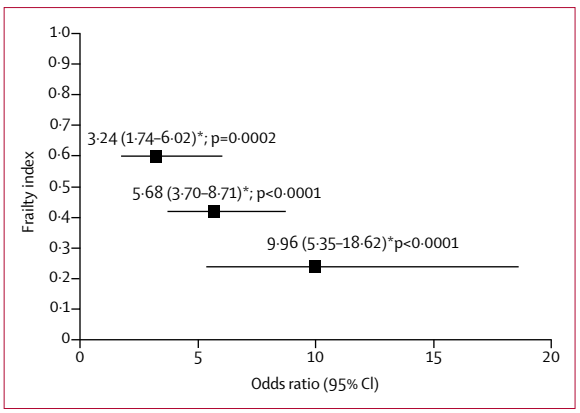

Figure 2: **Conditional effect of Alzheimer's disease pathology on Alzheimer's dementia status at values of the moderator (frailty), adjusted for age, sex, and education**

Discussion

Three main conclusions can be drawn from our results. First, people with Alzheimer's dementia but a low burden of Alzheimer's disease pathology had the highest frailty scores, suggesting that frailty is implicated in dementia expression in this group. Frailty might reduce the threshold of Alzheimer's disease pathology needed to cause clinical disease, or it could be a marker of impaired repair processes that might otherwise allow for Alzheimer's disease pathology to be better tolerated.[3] Furthermore, frailty levels were no higher than average in people without Alzheimer's dementia but with a high burden of Alzheimer's disease pathology. Together, these results suggest that the frailer an individual is, the less likely they are to be able to tolerate a given burden of Alzheimer's disease pathology. Second, frailty improved the fit of our model of the association between Alzheimer's disease pathology and dementia status, probably because frailty might be able to account for several pathways in old adults in whom dementia has several causes.[3,22–24] Third, frailty is a substantial moderator in the relationship between Alzheimer's disease pathology and dementia status; increasing frailty weakens the relationship between Alzheimer's disease pathology and dementia.

Together, these findings support the idea that frailty influences the clinical expression of dementia. Although frailty is likely to reduce the threshold for Alzheimer's disease pathology to cause cognitive decline, it probably also contributes to other mechanisms in the body that give rise to dementia (eg, inflammation, immunosenescence), weakening the direct link between Alzheimer's disease pathology and dementia. This hypothesis suggests that frailty should be used for risk stratification and to guide the management and treatment of older adults and supports the notion that many factors contribute to the development of late-life dementia.

Our results are consistent with findings from previous work. Dementia is associated with ageing,[25] but people age at varying rates. This is reflected in the heterogeneity in the occurrence of age-related signs, symptoms, and diseases. Failing mechanisms manifested by age-related signs, symptoms, and diseases can inform risk for adverse health outcomes, and the frailty index is able to package this information into a single value that represents health status. Studies are beginning to suggest that so-called age-related diseases are actually frailty related.[26]

Frailty has also been linked with both cognition and dementia status, cross-sectionally and longitudinally, whether measured by frailty index or phenotype.[8,27] The construct of cognitive frailty remains debated; some researchers view it as a clinical entity, with comorbid presence of both physical frailty and cognitive impairment, with the potential for targeted intervention in early or preclinical dementia.[28] A previous analysis[13] of the dataset used in the present study revealed that higher baseline frailty (as measured by a modified frailty phenotype) and increase in frailty over time led to a higher incidence of Alzheimer's dementia after 3 years of follow-up. Higher baseline frailty was also associated with lower baseline cognition and faster cognitive decline.[13] Change in frailty has also been associated with changes in cognition in other studies.[12,29]

Our findings build on work relating frailty to Alzheimer's disease pathology in two ways. First, we show that this relationship still holds with a broadly construed approach to frailty captured by deficit accumulation. Second, we show that the degree of frailty helps explain the circumstances under which Alzheimer's disease pathological markers and dementia are less well associated; people with a low amount of frailty were better able to tolerate Alzheimer's disease pathology, whereas those with higher amounts of frailty were more likely both to have more Alzheimer's disease pathology and for it to be expressed as dementia. These findings were robust; they held when controlled for vascular factors and when functional deficits were excluded from the frailty index.

In a recent scoping review,[24] we synthesised evidence from existing studies that measured both Alzheimer's disease biomarkers (such as in-vivo protein deposition, MRI abnormalities, or post-mortem plaque and tangle pathology) and frailty. Ten studies were identified, of which eight reported direct relationships between biomarkers and frailty. All of these eight studies showed a positive relationship between biomarkers and frailty, regardless of measurement, suggesting that frailty and Alzheimer's disease pathology are somehow intrinsically related. Here, we confirm this relationship and suggest a shared cause, and that these two factors interact to produce dementia.

The dementia literature raises several issues for which no pathophysiological mechanism has yet been able to account, including (1) the weak relationship between Alzheimer's disease pathology and Alzheimer's dementia (ie, Alzheimer's disease pathology does not seem to be sufficient); (2) the high prevalence of mixed dementia; and (3) the many, diverse risk factors. Our model contributes to the emerging conceptualisation of dementia as a heterogeneous disease with many possible causes, which provides the opportunity for the development of novel interventions.

Our data must be interpreted with caution. A limitation of secondary analyses is that they do not always measure all variables of interest. In this study, however, the relevant measures (cognition and dementia status, Alzheimer's disease pathology, and items to construct a frailty index) were generally available. Furthermore, in this cross-sectional analysis, Alzheimer's disease pathology was measured post mortem. To overcome this limitation, we used frailty measurement and dementia status from the last clinical interview before death. Since Alzheimer's disease pathology begins to accumulate decades before clinical manifestations of the disease,[30] and pathological abnormalities at death are related to the rate of cognitive decline over many years earlier,[2] we are relatively confident that this limitation would not substantially bias our results. Nevertheless, our results confirm associations between frailty, Alzheimer's dementia, and Alzheimer's disease pathology. Future studies should examine longitudinal relationships between frailty, cognition, and biomarkers of Alzheimer's dementia to establish causation, and should include more diverse pathological lesions to facilitate understanding of the interplay between pathology and the dementia syndrome.

Since frailty measurements were taken close to death, the recorded frailty state might be reflective of terminal decline. If this were the case, the relationship between Alzheimer's disease pathology and dementia status among people with high frailty might be over-represented, although this would not explain cases in which frailty was low and Alzheimer's disease pathology was high in people with dementia.

Competing risks are also a potential limitation of this study; if participants died of causes other than those related to dementia before developing dementia, the results might be confounded. We did not have access to cause of death and could not control for this factor.

Analyses were limited to Bielschowsky silver stain, which might be less robust than immunohistochemistry with specific antibodies.[31] Future studies will need to repeat these analyses using more specific markers of β-amyloid and paired helical filament tau tangles. We attempted to account for vascular risk factors by controlling for them in regression sensitivity analyses, although this cannot fully account for the effects of microinfarcts, hypertensive arteriopathology, and other micro-pathologies that have been associated with dementia. We did not control for the contribution of non-Alzheimer's disease pathologies because we aimed to establish links between hallmark diagnostic pathological measures and clinical presentation. Future work will need to address age-related pathologies that contribute to dementia.

Our participants were largely recruited from retirement homes in Illinois. Although this sampling method might introduce bias, the utility of the data to represent varying cognitive and neuropathological profiles was over-riding. Furthermore, a high proportion of participants in the MAP were followed up and had autopsies, thus reducing bias and increasing internal validity, and clinical evaluations in the MAP are identical to those in the population-based Chicago Health and Aging Project.[32] All risk factor associations that have been examined in both cohorts have been cross-replicated. Nevertheless, future research should address our hypothesis using a population-based sample.

Our results suggest that dementia expression has several causes, and a single mechanism is unlikely to explain the diverse expressions that occur in the people who most often develop dementia: those who are older and have several comorbidities. Individuals with even a low level of Alzheimer's disease pathology might be at risk for dementia if they have high amounts of frailty. This factor contributes to an emerging conceptualisation of dementia, and particularly Alzheimer's disease, as a complex disease of ageing rather than as a single disease entity marked by genetic risk or the deposition of a particular protein. This conceptualisation has the potential to improve our understanding of disease expression, explain failures in pharmacological treatment, and aid in the development of more appropriate therapeutic targets, approaches, and measurements of success. These results might therefore contribute to the effective prevention and management of Alzheimer's dementia. This work is a novel contribution to the existing literature because it bridges epidemiological methods and clinical neuropathology in relation to deficit accumulation in Alzheimer's dementia and proposes a unique model of development of Alzheimer's dementia.

Contributors

LMKW and KR conceived the research hypothesis. LMKW did the analyses, wrote the first draft, and revised all drafts. OT and KR contributed to the design and interpretation and reviewed all drafts. JG consulted on the statistical analysis and interpretation and reviewed final drafts. MKA and DAB contributed to the interpretation of the results and reviewed final drafts.

Declaration of interests

LMKW reports personal fees from DGI Clinical. MKA reports grants from GSK, Pfizer, and Sanofi. DAB reports grants from the National Institutes of Health (NIH). KR reports personal fees from Lundbeck. KR is President and Chief Science Officer of DGI Clinical, which has contracts with pharmaceutical companies on individualised outcome measurement. In 2017, KR attended an advisory board meeting with Lundbeck. Otherwise all personal fees are for invited guest lectures and academic symposia. KR is Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, with additional funding from the Alzheimer Society of Canada and several other charities, as well as from Pfizer Canada and Sanofi Canada. KR receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support from the Nova Scotia Health Research Foundation, the Capital Health Research Fund and the Fountain Family Innovation Fund of the Nova Scotia Health Authority Foundation. OT and JG declare no competing interests.

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