Original research

Frailty and accelerated dementia onset in genetic, sociodemographic and neuropathologic subgroups

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Received 16 January 2026
Accepted 31 May 2026
Published Online First 21 July 2026

To cite: Strating TR, Haapanen MJ, Ma D, *et al*. *J Neurol Neurosurg Psychiatry* 2026;**97**:883–889.

ABSTRACT

Background Quantifying how risk factors shape the timing of dementia onset can inform care and prevention strategies. We aimed to establish the degree to which and in whom frailty accelerates time to a diagnosis of dementia.

Methods Longitudinal data came from community-dwelling participants of the Rush Memory and Aging Project in Northeastern Illinois. At baseline, participants had data on age, education, sex, *APOE* ε4 status and sufficient health/functional variables to calculate a frailty index score. In a subset of participants who underwent autopsy, neuropathologic burden was quantified using a 10-item index of markers of Alzheimer's disease and mixed brain pathology. Accelerated failure time models estimated associations of frailty and age at dementia diagnosis.

Results In 1614 participants (mean age 79.6 years, 75% female) over 23.9 years of follow-up, frailty (frailty index scores ≥0.25) was associated with 3.6% younger age at dementia diagnosis (time ratio, TR 0.96 (95% CI 0.95, 0.98)), equating to 2–3 years earlier. That association was stronger in males than females, but present across each sex, education and *APOE* ε4 subgroup. In the autopsy subset (n=906), frailty was associated with 9.8% younger dementia diagnosis among those who died with low neuropathologic burden (TR 0.90 (95% CI 0.85, 0.96)) but had no association in those with intermediate or high burden.

Conclusions Frailty appears to independently accelerate dementia onset, particularly for individuals whose neurodegenerative lesions might be insufficient to explain their dementia diagnosis. Its routine measurement in clinical practice could hold benefit for risk stratification and care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Frailty is a multidimensional, potentially modifiable health state associated with increased dementia risk, and its assessment is increasingly recommended in memory and neurology clinics. However, the extent to which frailty influences when dementia manifests, and whether this differs across genetic, sociodemographic or neuropathological contexts is unclear.

WHAT THIS STUDY ADDS

⇒ Using accelerated failure time models, this study shows that frailty is associated with dementia being diagnosed 2–3 years earlier overall and up to 5–6 years earlier among individuals with low neuropathological burden. The findings demonstrate that frailty helps explain clinical–biological mismatch in dementia, acting as an independent driver of earlier phenotypic expression when neuropathology is low.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Routine frailty measurement may aid prognostication, risk stratification and interpretation of cognitive symptoms in neurology and memory clinics. Addressing frailty could represent a modifiable target to potentially delay dementia onset and inform care, particularly among patients with limited underlying neuropathological disease.

INTRODUCTION

Frailty, a multidimensional health state reflecting diminished physiological reserve and increased vulnerability to stressors,[1] is increasingly recognised as playing a key role in the development and progression of neurological diseases.[2–4] It is associated with disability, hospitalisation and mortality,[5 6] and accelerates in the years preceding dementia diagnosis.[7] This positions frailty as a clinically relevant marker and potential target for intervention.[2] Guidelines now recommend frailty assessment in memory clinics[8] to guide care planning in neurological practice[9] and to inform the management of Alzheimer's disease.[10] Yet, its prognostic significance for dementia remains poorly defined.

A key unanswered question relates to the temporal impact of frailty on dementia onset—we do not know how many years earlier dementia manifests in people living with frailty compared with those without. Critically, frailty is modifiable[11 12]—interventions could extend the period of preserved cognition, offering a lever for prevention and care optimisation. Equally unclear is whether this relationship is consistent across other key determinants of dementia risk. Sex differences,[13] educational inequalities,[14] *APOE* ε4 status[15 16] and varying neuropathological burden[17 18] can each alter the extent to which frailty accelerates the clinical expression of dementia. For example, one study reported that frailty was most strongly associated with phenotypic Alzheimer's dementia among individuals with low Alzheimer's neuropathological burden.[18]

Clinical–biological mismatch in dementia is common, underscoring the contribution of non-Alzheimer disease processes and the need to identify modifiers of resilience in the clinical expression of dementia.[19] In this context, frailty may represent an integrative vulnerability factor that explains variability in the timing of dementia onset among individuals whose neuropathologic lesions may otherwise be insufficient to cause dementia. To inform prognosis, refine diagnostic interpretation and highlight the potential role of frailty as a modifiable target in clinical practice, we sought to test the hypothesis that frailty accelerates the onset of clinical symptoms, leading to earlier dementia onset. Our objectives were to: (1) quantify the extent to which frailty is associated with a younger age of dementia diagnosis; (2) evaluate whether the strength of that relationship differs by sex, educational attainment or *APOE* ε4 status; and (3) determine whether that relationship is most pronounced among those with low neuropathological burden.

METHODS

Participants

This study was a secondary analysis of data from the Rush Memory and Aging Project (MAP)—a longitudinal, ongoing clinicopathological cohort study focusing on ageing and dementia.[20] We used data from 1997 until 2024, comprising 2305 participants. From that sample, participants were excluded if they: were assessed as having clinically diagnosed dementia at baseline (n=121); developed dementia before the age of 65 (n=1); had only one recorded study visit (n=192); did not have data available on age, sex, *APOE* ε4 status and education level (n=376); or did not have a valid frailty index score at baseline assessment (n=1). The final analysed sample included 1614 participants (table 1).

Table 1 Characteristics of analytical samples

Characteristic	Total sample	Autopsy subsample
N	1614	906
Age, mean (SD), years	79.6 (7.4)	82.1 (6.0)
Sex, N (%)		
Male	400 (25)	243 (27)
Female	1214 (75)	663 (73)
Frailty index scores		
Mean (SD)	0.19 (0.09)	0.21 (0.09)
Not frail, <0.25, N (%)	1230 (76)	650 (72)
Frail, ≥0.25, N (%)	384 (24)	256 (28)
Educational attainment, N (%)		
Low	62 (4)	17 (2)
Intermediate	397 (25)	244 (27)
High	1155 (72)	645 (71)
APOE ε4 status, N (%)		
Non-carrier	1241 (77)	708 (78)
Carrier	373 (23)	198 (22)
Race and ethnic group, N (%)		
Black	89 (6)	18 (2)
White	1508 (93)	887 (98)
Other/unknown	17 (1)	1 (0)
Incident dementia		
Cases, No. (absolute risk %)	531 (33)	368 (41)
Rate per 100 person-years (total person-years of follow-up)	4.3 (12,369.6)	5.9 (6,212.9)

Note: Other ethnic group includes American Indian or Alaska native, Asian, Native Hawaiian or Pacific Islander, and multiethnic group.

All participants enrolled without known dementia and agreed to detailed clinical evaluation and brain donation at death. MAP was approved by an Institutional Review Board of Rush University Medical Centre (IRB number L86121802). Each participant signed informed and repository consents, and all MAP participants signed an Anatomic Gift Act. Full details of the MAP study are available elsewhere.[20] Data are reported in adherence to the STROBE Checklist for observational studies.

Incident dementia

The primary outcome was age at all-cause dementia diagnosis, owing to later-life dementia being predominantly of mixed causes.[21 22] Cognitive status was determined through a three-stage process at each annual assessment, including cognitive tests, neuropsychological review and a final clinical diagnosis.[20]

Frailty measurement

Frailty was the primary exposure of interest and quantified retrospectively at participants' baseline study visits using frailty index scores. The frailty index estimates an individual's overall frailty status by assessing the accumulation of health deficits across multiple physiological systems, serving as an indicator of an individual's vulnerability to adverse health outcomes and mortality independently of chronological age.[23] The frailty index had been constructed previously in MAP from 41 routinely collected clinical data including symptoms, diseases, disabilities and functional impairments, with variables closely related to cognition excluded to avoid overlap with the outcome (table 2).[18] Frailty index scores were calculated as the proportion of present deficits out of the total possible, with higher scores indicating greater frailty. For example, 10 deficits present out of 40 assessed equals a frailty index score of 0.25. We used frailty index scores primarily as a continuous variable, although multiplied by 10, so that associations are interpreted meaningfully as the change in mean age at dementia diagnosis associated with each 0.1 increase in score. We also categorised frailty index scores into two frailty

Table 2 Composition of frailty index

No.	Item	No.	Item
1	Congestive heart failure	22	Walk half a mile
2	Diabetes	23	Walk up and down stairs
3	Depression	24	Managing medications
4	Cancer	25	Light housekeeping
5	Osteoporosis	26	Heavy housekeeping
6	Falls	27	Eating
7	Joint pain	28	Dressing
8	Diastolic blood pressure	29	Bathing
9	Hypertension	30	Toileting
10	Grip strength	31	Walking
11	Walking speed	32	Getting from bed to chair
12	Fatigue (everything I did was an effort)	33	Stroke
13	Travelling in the community	34	Heart problems
14	Meal prep	35	Claudication
15	Managing finances	36	Finger tap
16	Using telephone	37	Leg stand
17	Shopping	38	Pegboard
18	Physical activity	39	Pinch strength
19	Head injury	40	Fatigue (I could not get going)
20	Polypharmacy	41	Body mass index
21	Taking care of home		

groups (not frail: <0.25, frail ≥0.25) to aid in producing clinically accessible estimates of associations.[24]

Neuropathology

For participants who died, underwent autopsy and had neuropathological data available, we calculated a 10-item neuropathologic index using the same approach as for the frailty index, which has been calculated previously in MAP.[25] In brief, the neuropathologic index comprised the following: (1) overall level of β-amyloid (Aβ); (2) typical hippocampal sclerosis; (3) Lewy body pathology as determined by the distribution of α-synuclein; (4) cortical tangle density; (5) TDP-43 pathology; (6) arteriolosclerosis; (7) cerebral amyloid angiopathy; (8) cerebral large vessel atherosclerosis; (9) acute gross cerebral infarcts and (10) chronic micro cerebral infarcts. The overall level of beta-amyloid was quantified as the percent area of the cortex occupied by beta-amyloid, stained using immunohistochemistry. This was measured over eight regions: hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal, angular gyrus, calcarine cortex, anterior cingulate cortex and superior frontal cortex. Cerebral amyloid angiopathy was quantified as a summary score of amyloid deposition in meningeal and parenchymal vessels in four neocortical regions: midfrontal, midtemporal, parietal and calcarine cortices. We categorised neuropathologic index scores into three levels (tertiles) to form a stratifying factor reflecting underlying disease severity at death (low <0.27; intermediate ≥0.27 and <0.42; high ≥0.42). This allowed us to test whether any association of frailty index scores with age at dementia diagnosis differed between neuropathologic burden groups.

Covariates

Age at baseline was calculated from date of birth. Sex (male or female) was self-reported. Educational attainment was determined by the number of years of formal school reported and categorised as low (<10 years), intermediate (10–12 years) or high (>12 years). *APOE* ε4 status was determined by carriage or non-carriage of the *APOE* ε4 allele. For descriptive purposes, we also derived racial groups as White, Black and other/unknown.

Statistical analysis

Baseline characteristics of eligible participants were first summarised using descriptive statistics for the total analytical sample and the autopsy subsample.

We used parametric accelerated failure time (AFT) models to investigate the relationship between frailty index scores and age at all-cause dementia diagnosis as they can directly predict the expected age at dementia diagnosis and offer a straightforward interpretation of parameters (a time ratio less than 1 suggests an acceleration or earlier expected time to event, while a time ratio greater than 1 suggests a deceleration or later time to event). Others have recently applied AFT models to MAP data to evaluate if scam susceptibility is associated with earlier Alzheimer's dementia.[26]

Follow-up began at participants' baseline assessments and continued to either the occurrence of all-cause dementia or censoring. To quantify the extent to which frailty is associated with accelerated dementia diagnosis (objective 1), we first used an AFT model to assess the association of frailty index scores (continuous) with mean age at dementia diagnosis. Next, to gauge the degree to which that association varied by sex, educational attainment or *APOE* ε4 status (objective 2), we added interaction terms between frailty and each covariate, in separate models. Finally, to evaluate whether the association differed by neuropathologic burden at autopsy (objective 3), in the autopsy subsample, we constructed a further AFT model that included an interaction term between frailty and neuropathologic tertile group. From each fitted model, while holding other covariates constant, we also calculated expected mean ages at dementia diagnosis for not frail (frailty index scores<0.25) and frail (frailty index scores ≥0.25) participants. Those expected values were estimated using restricted mean survival time calculated up to a truncation age of 100 years, representing the average expected age at dementia diagnosis within that age range.

In preliminary models, we evaluated five commonly used AFT error distributions and found that the generalised gamma distribution provided best model fit in all cases (lowest Akaike Information Criterion). We also evaluated nonlinearity in associations by fitting frailty index scores using natural cubic splines (up to six df), but these did not improve model fit and were discarded in favour of linearity. We conducted two sensitivity analyses to assess the robustness of the neuropathologic findings. First, to assess the impact of accounting for inter-correlations between individual neuropathologic markers in the calculation of global neuropathology, we recalculated the composite score through weighted summation of the first five components of a principal components analysis. Second, to ensure that neuropathologic findings were not driven by the interval between initial dementia diagnosis or last cognitive evaluation (for those who remained dementia-free) and autopsy, we restricted the sample to participants who died within 1 year of dementia diagnosis or their last cognitive assessment (n=465) and additionally adjusted for this interval as a covariate in the model. All models were left-truncated and included covariates of sex, educational attainment and *APOE* ε4 status; they did not include age as a covariate as it was used as the timescale of the outcome. We used R V. 4.4.1 (R Foundation for Statistical Computing) and the *flexsurv* package to fit AFT models.[27] All statistical tests were two-tailed using alpha level of 0.05.

RESULTS

Sample characteristics

In the total sample, participants were nearly 80 years old at baseline, on average, and most were female, highly educated and did not carry an *APOE* ε4 allele (table 1). Almost all self-reported as White race/ethnicity, with 7% reporting either Black or other/unknown. Frailty was present in 24% of participants, with frailty index scores slightly higher among females (0.20) than males (0.17), equating to approximately seven to eight accumulated deficits. Over 23.9 years of follow-up (median observation time 7 years), 531 cases of incident dementia were detected, equating to an incidence rate of 4.3 per 100 person-years. The mean age at dementia diagnosis was 88.9 years old (SD 6.3). The median time between last cognitive evaluation (time of first dementia diagnosis or time of last evaluation as dementia-free before death) and death was 1.0 year (IQR=2.3 years) overall, 0.8 years (IQR=0.8 years) among participants who died without dementia and 2.7 years (IQR=4.2 years) among those who died with dementia.

Frailty and age at dementia diagnosis

Before statistical adjustment, we observed little difference in the mean age at dementia diagnosis between participants classified as not frail (frailty index scores<0.25; 88.8 years) and those classified as frail (scores ≥0.25; 89.2 years). After adjusting for sex, educational attainment and *APOE* ε4 status, each 0.1 increase in frailty index scores was associated with a 1.8% younger age

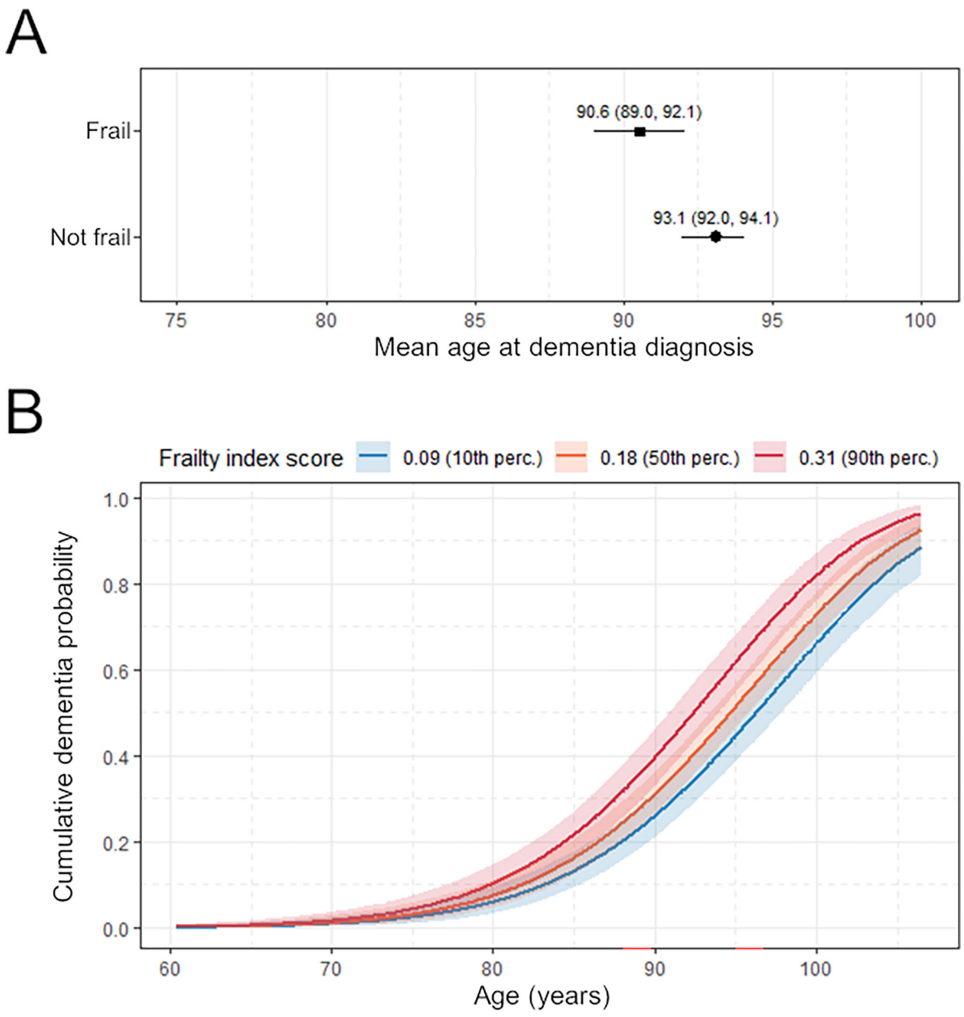

Figure 1 Association of frailty with age at dementia diagnosis. (A) Expected mean age at dementia diagnosis and 95% CIs calculated for frail (n=384) and not frail (n=1230) participants. Values were derived from an accelerated failure time model adjusted for sex, educational attainment and *APOE* ε4 status. (B) Predicted cumulative probability of dementia diagnosis by age at three degrees of frailty (10th, 50th and 90th percentile values) derived from an accelerated failure time model adjusted for sex, educational attainment and *APOE* ε4 status and using continuous frailty index scores (n=1614).

at dementia diagnosis (time ratio, TR=0.98 (95% CI=0.97, 0.99)). Compared with individuals who were classified as not frail, frail individuals had a 3.6% younger age at dementia diagnosis (TR 0.96 (95% CI=0.95, 0.98)). Individuals with higher frailty had a greater cumulative probability of dementia at any given age (figure 1); when expected ages at dementia diagnosis were calculated for frailty groups while holding other covariates constant, those differences equated to dementia onset 2.5 years earlier for frail individuals.

Associations across genetic and sociodemographic factors

We then tested whether those relationships differed by sex, educational attainment or *APOE* ε4 status. For sex, each 0.1 increase in frailty index scores was associated with a larger reduction in dementia age among males compared with females (interaction TR=0.97 (95% CI=0.95, 0.99)). Compared with females classified as not frail, females living with frailty had a 2.6% younger age at dementia diagnosis (TR 0.97 (95% CI=0.96, 0.99)). In contrast, compared with males classified as not frail, those living with frailty had an 8.0% younger age at dementia diagnosis (TR 0.92 (95% CI=0.88, 0.96)). Statistically significant differences in associations were not observed by the other characteristics: interaction TRs for lower education and intermediate education (relative to the association of frailty index scores and dementia age in participants with higher education) and *APOE* ε4 status were 0.98 (95% CI=0.96, 1.02), 1.01 (95% CI=0.99, 1.03) and 1.00 (95% CI=0.99, 1.02), respectively). Calculated expected ages at dementia diagnosis while holding other covariates constant, within each subgroup, are presented in figure 2.

Frailty, neuropathologic burden and dementia age

Finally, after adjusting for sex, educational attainment, *APOE* ε4 status and the time interval between death and autopsy, we examined the relationship between frailty index scores and age at dementia diagnosis in individuals classified with low, intermediate or high neuropathologic burden at death (n=906). Among participants who died with a low (n=302, 46 cases of dementia), intermediate (n=302, 124 cases of dementia) or high (n=302, 198 cases of dementia) neuropathologic burden, each 0.1 increase in frailty index scores was associated with a 5.1% (TR 0.95 (95% CI=0.92, 0.98)), 0.6% (TR 0.99 (95% CI=0.96, 1.03)) and 0.7% (TR 0.99 (95% CI=0.95, 1.03)) younger age at dementia diagnosis, respectively. The differences in the association of frailty index scores and age at dementia diagnosis between neuropathologic burden groups were statistically significant, with interaction TRs of 1.05 [95% CI 1.01,

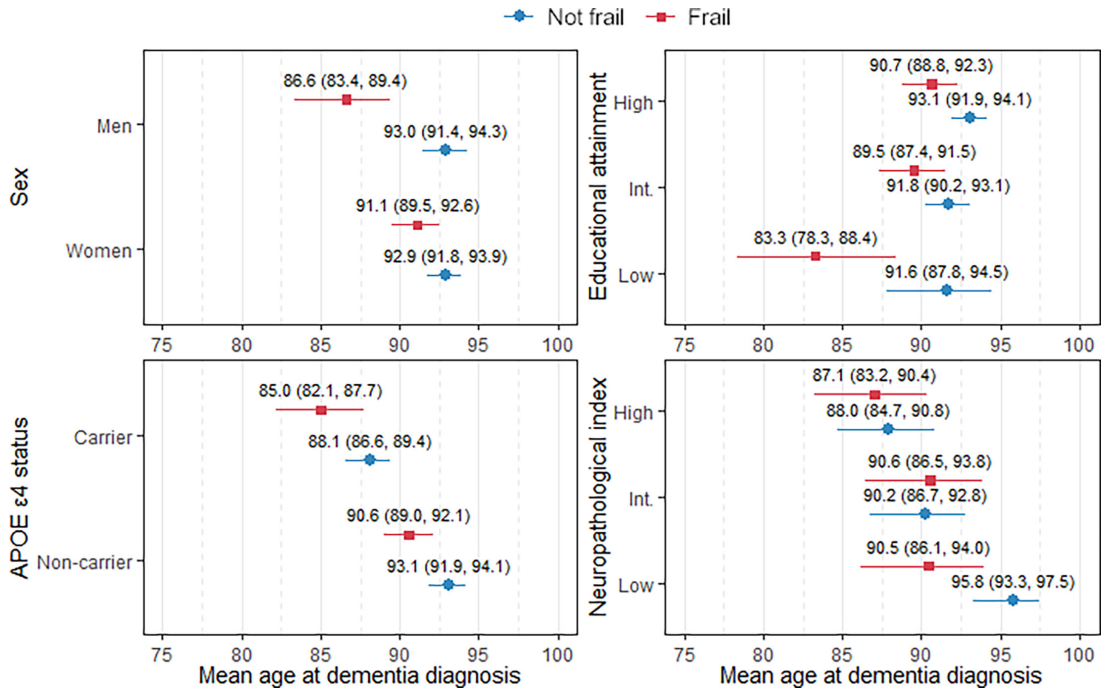

Figure 2 Age at dementia diagnosis by frailty across participant characteristics. Expected mean age at dementia diagnosis and 95% CIs calculated for frail and not frail participants across levels of demographic, genetic and neuropathologic characteristics. Values were derived from accelerated failure time models adjusted for sex, educational attainment and *APOE* ε4 status. Analysis of autopsy data was additionally adjusted for the time interval between death and autopsy. Subgroup analyses included the following counts of participants: male (n=400), female (n=1214); high educational attainment (n=1155), intermediate educational attainment (n=397), low educational attainment (n=62); *APOE* ε4 carrier (n=373), *APOE* ε4 non-carrier (n=1241); high neuropathological index (n=302), intermediate neuropathological index (n=302), low neuropathological index (n=302).

1.09] in both cases (i.e. low vs intermediate and low vs high). Among participants who died with low neuropathologic burden, and compared with those classified as not frail, frail participants had a 9.8% younger age at dementia diagnosis (TR 0.90 (95% CI=0.85, 0.96)). Calculated expected ages at dementia diagnosis while holding other covariates constant, within each subgroup, are presented in figure 2.

Neuropathologic findings were comparable in both sensitivity analyses. We first recalculated a measure of global burden through a principal components analysis of the neuropathologic markers, which was positively correlated with neuropathologic index scores (r=0.78). When it was substituted into the main statistical model, each 0.1 increase in frailty index scores was associated with a 3.4% (TR 0.97 (95% CI=0.94, 0.99)) younger age at dementia diagnosis among participants who died with low neuropathologic burden, an association that was marginally weaker among participants who died with intermediate burden (interaction TR 1.02 (95% CI=0.98, 1.05)) and significantly weaker among those who died with high burden (interaction TR 1.04 (95% CI=1.00, 1.07)). Next, we restricted the sample to participants who died within 1 year of initial dementia diagnosis or last cognitive evaluation (for those who remained dementia-free) (n=465) and additionally adjusted for this interval in the model. Each 0.1 increase in frailty index scores was associated with a 4.1% (TR 0.96 (95% CI=0.93, 0.99)) younger age at dementia diagnosis among participants who died with low neuropathologic burden, an association that was significantly weaker among participants who died with intermediate or high burden (interaction TRs 1.05 (95% CI=1.00,1.09) and 1.04 (95% CI=1.00, 1.08), respectively).

DISCUSSION

Previous work has established a robust association between frailty and incident dementia that persists across populations, study designs and methods of frailty assessment.[3 4 7] Here, through this analysis of community-dwelling older adults initially free from dementia, we build on that evidence by estimating the number of years earlier dementia is diagnosed in those living with frailty compared with those without. We report two main findings: (1) frailty was associated with accelerations in dementia onset across sex, educational attainment and *APOE* ε4 status—by 2–3 years of difference in the predicted mean age; (2) the association of higher frailty and younger dementia onset was strong among participants who died with fewer neuropathologic brain changes and absent among those dying with more. These results emphasise frailty as a potentially modifiable state[11 12] that could accelerate dementia onset by several years, strengthening the rationale for frailty assessment to be considered when evaluating cognitive status and risk.[9 10 28]

Optimal care requires understanding which patients might experience faster functional decline, and which slower. Here, we have demonstrated how frailty measurements can meaningfully—and in a graded manner—explain heterogeneity in the age at dementia onset. This association was consistent across educational strata and among both *APOE* ε4 carriers and non-carriers. Notably, we found variation in the association by sex: frailty was associated with earlier dementia by almost 6.5 years in predicted mean age for males but by just under 2 years in females. Previous studies have shown that frailty is typically higher in females than males overall[13 29] and in the years before incident dementia,[7] but sex differences in dementia risk attributable to frailty are inconclusive.[3 4 15] Regardless, preventing frailty onset or slowing

its progression through proven multicomponent interventions—typically involving exercise and dietary improvements[11 12]—represents a tangible strategy for clinicians to recommend to patients, even among those with more worrisome risk profiles (eg, *APOE* ε4 carriers with fewer years of education).

Our findings are timely in the face of increasing availability and use of electronic medical records in healthcare. A frailty index can be derived automatically from routinely collected information on health and function—given data requirements are met[30]—typically at no extra burden to clinicians. For example, in the United Kingdom the electronic frailty index is embedded at scale where it is used to automatically identify frailty in primary care patients,[31] and it has undergone varying degrees of feasibility testing and piloting in other countries, including the United States, Spain and Australia.[32–34] An automated frailty index has several implications. First, it helps identify cognitively unimpaired individuals at risk of accelerated dementia onset, enabling targeted risk-reduction interventions. Second, it demonstrably aids in predicting progression to dementia following the onset of mild cognitive impairment.[35] Finally, it can inform prescribing practices, as frail individuals are more susceptible to adverse effects such as those from anticholinergic medications,[36] the use of which is associated with higher dementia risk.[37]

We also found that the relationship between frailty and age at dementia diagnosis depended on lower neuropathologic burden at death. Among individuals with a low neuropathologic burden (categorised as roughly three or fewer of the 10 pathologies contributing to the neuropathologic index), frailty was associated with an accelerated dementia onset corresponding to a predicted 5–6 years earlier. Strikingly, although those who died with low neuropathology and without frailty had the latest dementia onset, individuals with low neuropathology but with frailty developed dementia at an age more comparable to those with intermediate or high neuropathology. This suggests that in the absence of severe neuropathology, frailty itself can become a primary driver of phenotypic dementia. By contrast, among individuals with intermediate or high burden, frailty did not meaningfully differentiate dementia age. These findings support previous work showing an interaction between frailty and neuropathology in the context of dementia[17 18] and suggest that treatments aimed at reducing neuropathologic burden may have limited effectiveness if frailty is not addressed in parallel.

To our knowledge, this is the first study to use accelerated failure time models to directly quantify the number of years by which frailty can accelerate dementia onset. A key limitation is that neuropathology was only measurable post-mortem—a median of 1 year following last cognitive evaluation—so it cannot be interpreted as a baseline risk factor. Consequently, we could not observe neuropathological burden when frailty was measured or at the point of dementia diagnosis. While cerebrospinal fluid or blood biomarkers can provide complementary in vivo indicators of pathology, we used neuropathology as a marker of disease severity at death to examine whether the association between frailty and age at dementia diagnosis varied by pathological burden. Although we adjusted for key determinants of dementia risk, including sex, educational attainment and *APOE* ε4 status, the inclusion of only basic covariates means residual confounding, for instance from other social risk factors,[38] cannot be excluded. However, this parsimonious modelling strategy ensures our findings rely on only routinely available clinical data while avoiding potential overadjustment from variables that may conceptually overlap with frailty or lie on its causal pathway. Furthermore, we solely used *APOE* ε4 carriage as a single determinant of genetic risk for dementia. Additional information on genetic susceptibility to dementia may be gleaned through analyses incorporating *APOE* ε2 status as well as *APOE* ε4 homozygosity, which we avoided due to concerns about small subgroup counts and modelling stability. Similarly, polygenic dementia risk scores could capture additional susceptibility above and beyond *APOE* ε4, which were not used here. Finally, the low ethnic diversity in our sample limits the generalisability of our findings to other populations.

CONCLUSIONS

Our study demonstrates that frailty is associated with earlier dementia onset by 2–3 years independently of major genetic and sociodemographic risk factors. These findings underscore the potential benefit of routine frailty measurement in memory clinics and neurological practice.

Acknowledgements MAP is supported by grant R01AG17917 from the National Institute on Aging. KR's work on frailty and cognition was supported by CIHR PJT-156114. MJH was supported by the Sigrid Jusélius Foundation, the Biomedicum Helsinki Foundation, the Osk. Huttunen Foundation, Finska Läkaresällskapet r.f., the Research Council of Finland (decision no. 373806), and the Research Council of Finland PROFI 8 funding (decision no. 365202).

Contributors TRS and DDW were involved in the conception of the study. TRS, MJH and DDW designed and undertook the analyses. TRS, MJH and DDW wrote the first draft of the paper. All authors revised significant portions of the manuscript for important intellectual content. All authors contributed to the interpretation of findings. All authors read and approved the final manuscript. AI was not used in the preparation of this manuscript. DDW agrees to be guarantor for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests TRS, MJH, DM, EHG, REH and DDW have nothing to report. KR reports holding copyright over the Clinical Frailty Scale and Pictorial Fit-Frail Scale, which are made freely available for noncommercial education and research, as well as nonprofit health care with completion of a permission agreement stipulating that users will not change or charge for or commercialise the scales; in addition, for-profit entities (including pharma) pay a licensing fee, 15% of which is retained by the Dalhousie University Office of Commercialisation and Innovation Engagement, and all remaining licence fees are donated to the Dalhousie Faculty of Medicine Advancement Fund. In the past 3 years, licences have been negotiated with Rebibus Therapeutics Inc, Cook Research Incorporated, W.L. Gore Associates Inc, Pfizer Inc, Cellcolabs AB, AstraZeneca UK Limited, Qu Biologics Inc, Biotest AG, BioAge Labs Inc, Congenica, Icosavax Inc outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by MAP was approved by an Institutional Review Board of Rush University Medical Center (IRB number L86121802). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified MAP participant data are available for research purposes upon reasonable request at https://www.radc.rush.edu and www.synapse.org.

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