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Frailty and neuropathology in relation to dementia status: the Cambridge City over-75s Cohort study

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ABSTRACT

Objective: To examine the relative contributions of frailty and neuropathology to dementia expression in a population-based cohort study.
Design: Cross-sectional analysis of observational data.

Setting: Population-representative clinicopathological cohort study.

Participants: Adults aged 75 + recruited from general practice registries in Cambridge, UK, in 1985.

Measurements: A 39-item frailty index and 15-item neuropathological index were used to operationalize frailty and neuropathology, respectively. Dementia status was ascertained by clinical consensus at time of death. Relationships were evaluated using logistic regression models in participants with autopsy records ($n = 183$). Model fit was assessed using change in deviance. Population attributable fraction for frailty was evaluated in relation to dementia incidence in a representative sample of the survey participants ($n = 542$).

Results: Participants with autopsy were 92.3 ± 4.6 years at time of death, and mostly women (70%). Average frailty index value at last survey before death was 0.34 ± 0.16. People with dementia (63% of the sample) were frailer, had lower MMSE scores, and a higher burden of neuropathology. Frailty and neuropathological burden were significantly and independently associated with dementia status, without interaction; frailty explained an additional 3% of the variance in the model. Assuming a causal relationship and based on population-attributable fraction analyses, preventing severe frailty (Frailty Index ≥ 0.40) could have avoided 14.2% of dementia cases in this population-based cohort.

Conclusions: In the very old, frailty contributes to the risk for dementia beyond its relationship with the burden of traditional dementia neuropathologies. Reducing frailty could have important implications for controlling the burden of dementia. Future research on frailty interventions should include dementia risk as a key outcome, public health interventions and policy decisions should consider frailty as a key risk factor for dementia, and biomedical research should focus on elucidating shared mechanisms of frailty and dementia development.

Key words: aging, dementia, frailty, neuropathology, Alzheimer's disease
Abbreviations: CC75C, Cambridge City over-75s Cohort study; SD, Standard Deviation; CAMDEX, Cambridge Mental Disorders of the Elderly Examination; DSM-IV, Diagnostic and Statistical Manual 4th Edition; MMSE, Multiple Mini State Examination; LATE-NC, Limbic-predominant Age-related TDP-43 Encephalopathy-Neuropathologic Changes; AD, Alzheimer's disease; PAF, Population Attributable Fraction

Background

As treatments for clinically diagnosed Alzheimer's disease continue to fail in clinical trials, evidence is accumulating to suggest that diverse risk factors and mechanistic pathways are important, especially in late-life dementia (Canevelli *et al.*, 2017). Many studies have now shown that single-protein abnormalities (e.g. plaques and tangles) are not highly correlated with the clinical expression of dementia, especially in the oldest old (Boyle *et al.*, 2013; Brayne *et al.*, 2009; Jansen *et al.*, 2018; MRC CFAS, 2001; Wallace *et al.*, 2019). The research paradigm for tackling dementia has assumed that Alzheimer's disease pathology is responsible for the majority of clinical expression of dementia (Jack *et al.*, 2018),

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though increasingly evidence suggests that the majority of late-life dementia is associated with mixed pathology, including vascular abnormalities, and hippocampal sclerosis among others (Boyle *et al.*, 2018; Wilson *et al.*, 2010). In the general population, age remains the number one risk factor for dementia (Livingston *et al.*, 2017), and understanding the context and contributions of aging in the development of dementia may provide insight into its complex etiology (Canevelli *et al.*, 2015; Searle and Rockwood, 2015). Age-related diseases, such as heart disease and osteoarthritis, not only accumulate with age but also appear to be the result of small-scale (i.e. molecular) deficits which scale up to affect whole bodily systems in the form of frailty (Castell *et al.*, 2015; Rockwood *et al.*, 2015; Wallace *et al.*, 2014). Internal or external insults are usually repaired easily by redundant repair mechanisms before becoming deficits, but as the body ages, the repair mechanisms fail and lead to the accumulation of deficits (Mitnitski *et al.*, 2013; Mitnitski and Rockwood, 2015; Mitnitski *et al.*, 2001).

Frailty is conceptualized as multisystem impairment giving rise to physiologic vulnerability to adverse health outcomes (Clegg *et al.*, 2013) and is most commonly operationalized as a health state characterized by the accumulation of health deficits (Mitnitski *et al.*, 2001), or as a phenotypic syndrome (Fried *et al.*, 2001). Frailty is recognized as contributing to the dementia syndrome (Song *et al.*, 2014; Sterniczuk *et al.*, 2015), brain atrophy (Gallucci *et al.*, 2018), mild cognitive impairment (Trebbastoni *et al.*, 2017), cognitive decline (Thibeau *et al.*, 2019) and predicts dementia incidence (Rogers *et al.*, 2017). This evidence suggests that it is possible that the expression of dementia, even in the face of neuropathology, may be modified by frailty as measured by deficit accumulation (Anstey *et al.*, 2014). Therefore, the objective of the current study was to examine the relative contributions of frailty and neuropathology to dementia expression in a population-based representative cohort study and to build on earlier work where frailty and neuropathology contributed independently to dementia risk in a sample of older adults in retirement homes (Wallace *et al.*, 2020; 2019).

Methods

Sample/participants

The Cambridge City over-75s Cohort study was initiated in 1985 as a population representative sample (95% response rate) of people aged 75 or above on general practice registers in Cambridge, UK, including those living in care (Fleming *et al.*, 2007). It aimed to study cognition and function in older adults and enrolled 2610 participants of whom 2166 (all excluding one practice) were followed-up until their death (10 surveys over 28 years; see Additional Supplementary File 1 for study design). Each survey included questions on demographics, activities of daily living, and health problems. In cases where participants were unable to respond, proxy informants were sought. Early surveys were supplemented with additional CAMDEX (Cambridge Mental Disorders of the Elderly Examination) psychiatric assessments which included mental state examination, psychiatric history, performance-based cognitive testing, and a proxy informant interview. A brain donation program was initiated in survey 2 (year 2), and donation was agreed to and fulfilled by 242 participants, with known representation from the base population.

For the purpose of this cross-sectional study, we used the survey 3 (7 years after the initial survey) as our baseline as surveys from this wave on had the largest number of relevant variables to create a frailty index which could be used consistently across the remaining surveys.

At survey 3, 714 participants were interviewed, of whom 175 became brain donors; of these, 170 had complete neuropathological and frailty data, as well as known dementia status were included in the cross-sectional analysis. Some participants ($n = 68$) missed survey 3 but were followed-up in subsequent surveys and donated their brains, of these, 13 had complete neuropathological and frailty data, and known dementia status, providing a total sample of 183 for cross-sectional analysis (Additional Supplementary File 2).

For the population-attributable risk analyses, we extended our inclusion criteria to participants who were not brain donors (as we were not assessing neuropathology, but rather the attributable risk of frailty to dementia). Here, we sampled the original 714 participants at survey 3, excluded those with prevalent dementia ($n = 153$) or missing prevalence data at survey 3 ($n = 2$), and incomplete frailty data ($n = 17$) leaving us with a sample of 542 (Additional Supplementary File 2).

Measures

Dementia status

All clinical study records for brain donors were reviewed post-mortem and dementia status was ascertained by consensus by at least two clinicians using the Diagnostic and Statistical Manual 4th Edition (DSM-IV) criteria and blinded to neuropathological data (Brayne *et al.*, 2009; Fleming *et al.*, 2007).

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Frailty Index

The frailty index is a health state measure that reflects vulnerability to adverse health outcomes (Clegg *et al.*, 2013). The *frailty index = (number of health deficits present)/(number of health deficits measured)*. For example, a person with 5 of 30 potential deficits measured has a frailty index score of 5/30 = 0.17. Candidate variables from respondent interviews were indicative of poor health and included symptoms, signs, functional impairments, and comorbidities. These variables were screened against four criteria: (1) Relationship with age; (2) Prevalence of at least 1%; (3) Less than 5% missing data across participants at any survey; (4) No more than 80% prevalence (saturation). A total of 39 items met all criteria and were included in the index. The index demonstrated properties consistent with frailty indices from similar samples (i.e. normal distribution with right skewed tail, higher frailty index in women than men, increase with age). As the goal of the regression analyses was to examine the cross-sectional relationship between frailty, neuropathology, and dementia, but neuropathology could only be obtained post-mortem via autopsy, we used a frailty index and dementia measurements obtained from participants' last survey prior to death. Baseline frailty index (survey 3) was used to predict population-attributable risk. Refer to Additional Supplementary File 3 for list of variables included in the frailty index. The frailty index was categorized into tertiles for the descriptive analyses, using cut-points of 0.27, 0.43, and a cut-point of 0.40 (corresponding to severely frail; Guaraldi *et al.*, 2019) was used for the population-attributable risk analyses.

Neuropathological Index

Neuropathological data were obtained at autopsy by semi-quantitative scoring by trained neuropathologists according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (Mirra, 1997; Mirra *et al.*, 1991). Fifteen neuropathological variables were included in the index including: (1) atrophy, (2) pallor of substantia nigra and/or locus coerulus, (3) significant obstruction of large cerebral vessels, (4) gross parenchymal vascular lesions, (5) small vessel disease, (6) microinfarcts, (7) white matter pallor, (8) neuritic plaques, (9) amyloid deposits, (10) neurofibrillary tangles, (11) vascular amyloid, (12) granulovacuolar degeneration, (13) severe neuronal loss, (14) severe gliosis, (15) Lewy bodies. Other neuropathologies available in this cohort relating to Pick's disease, leukoencephalopathy, lobar atrophy, Creutzfeldt–Jakob disease, spongiform encephalopathy, neoplasms/tumors, Hirano bodies, ubiquitin, and Huntington's disease were not included in the index because they were absent in all cases. TDP-43 was excluded as there were too many missing cases. Full information on regional inclusions and coding are detailed in Additional Supplementary File 4. Included neuropathological variables were summed and divided by the number of valid variables (according to the deficit accumulation approach detailed above). The neuropathological index was then categorized into tertiles for the descriptive analyses, using cut-points of 0.30, 0.42. Details of autopsy and neuropathological assessment can be found at cc75c.group.cam.ac.uk and Brayne *et al.* (2009).

Other measures

Age, sex, education, post-mortem interval, and time from frailty evaluation to death were evaluated as confounders. Education (in years) was the only covariate found to be a significant independent predictor of the outcome, but age, sex, and education were conserved in final model for conceptual reasons.

Statistical analysis

Descriptive analysis techniques (including analysis of variance and χ^2 tests) were used to describe the characteristics of the sample and assess distributions of frailty, neuropathology, and dementia in the sample.

Logistic regression models were used to explore the effect of frailty (frailty index) and neuropathology (neuropathological index) on dementia status independently and in the same model. Their interaction was also evaluated. Model fit was evaluated by change in deviance (χ^2 of -2LogLikelihood values). Model assumptions including binary outcome, independent observations, no collinearity among independent variables, linearity of independent variables with log odds (according to Box Tidwell test), and large enough sample size based on least frequent outcome (Stoltzfus, 2011) were tested. Nagelkerke Pseudo R^2 was reported to show goodness of fit.

Complete-case analysis was employed, though 56 participants were excluded as they were missing more than 20% of the variables needed to calculate a frailty index. We undertook two sensitivity analyses to attempt to evaluate the effect of the missing data on our findings. First, we used an extreme case sensitivity analysis where missing frailty index values were allocated the highest level of frailty. Further, we attempted multiple imputations (chained equations algorithm) for frailty index values.

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Population-attributable fraction estimates the proportion of cases that hypothetically could be avoided if the exposure were eliminated or reduced. Here, we used this to determine the fraction of dementia cases (ascertained at time of death) that could be avoided if severe frailty (frailty index ≥ 0.40) was "eliminated" or avoided at baseline. Population-attributable fraction was calculated using the following formula (Lin and Chen, 2019):

$$\text{Population attributable fraction} = [\text{proportion exposed in whole sample} \times (\text{RR} - 1)] / [\text{proportion exposed in whole sample} \times (\text{RR} - 1) + 1]$$

where RR = relative risk. As the exposure was rare, the hazard ratio approximates the relative risk and was used in order to control for time from baseline. By using a Cox proportional hazards model, we were able to control for time from baseline to death, as well as control for the contributions of baseline age, sex, and education. For this analysis, we extended our sample to include participants who did not have autopsy to achieve a larger and population-representative sample. Statistical analyses were performed in SPSS version 25.0 and R version 3.5.2.

Results

Autopsy sample participants ($n = 183$) were aged 92.3 (SD 4.6; normally distributed) years on average at time of death, and mostly women (69.4%). Average frailty index at last survey before death was 0.34 (SD 0.16; normally distributed). People with dementia were frailer, had lower Mini-Mental State Examination scores, and a higher burden of neuropathology (Table 1).

Very few participants demonstrated little to no neuropathology at death ($n = 7$; 4%). Among people with no dementia, 7.1% had a high burden of neuropathology. Among people with dementia, 16.3% demonstrated a low burden of neuropathology. Within each level of neuropathological burden, those with dementia generally had higher frailty (Figure 1), though dose-response was not consistent (likely due to small sample size).

The proportion of people with dementia was highest among people with a high frailty index and high burden of neuropathology, low among those with low frailty index and low burden of neuropathology, and in between for intermediate or either high frailty index or high neuropathology, suggesting these risk factors may be additive (Figure 1).

Logistic regression models satisfied assumptions and demonstrated that both frailty (at last survey before death) and neuropathological burden (at death) were significantly and independently associated with dementia status at last survey (Table 2), although they did not interact ($p = 0.81$). Addition of the frailty index to the model with the neuropathological index significantly improved model fit $X^2(1)$ 5.44, $p < 0.01$). Pseudo R^2 increased from 0.085 to 0.123 suggesting that the addition of frailty to the model increased the explained variance by 3.8%. Sensitivity analysis using extreme case imputation did not significantly change the results (Additional Supplementary File 5). Multiple Imputation by Chained Equations (MICE) was not used in this analysis as the only significant predictors of missing frailty index data were related to pathological measures that would be used in an interaction with the frailty index and would produce nonsensical results.

Based on a hazard ratio of 2.15 (95% CI 1.01–4.60, $p = 0.048$) and proportion of exposed (0.142) among 542 participants with no dementia at baseline (survey three), the PAF = 0.142, indicating that preventing severe frailty (frailty index ≥ 0.40) on average 5.6 years before death would avoid 14.2% of dementia cases in this cohort.

Table 1. Descriptive characteristics of sample

	Whole sample ($n = 183$)	No dementia ($n = 67$)	Dementia ($n = 116$)
Age at baseline (median; mean ± SD)	85.2; 86.1 ± 3.9	85.4; 86.3 ± 4.3	85.0; 85.9 ± 3.6
Age at death (median; mean ± SD)	92.1; 92.3 ± 4.6[a]	92.0; 92.3 ± 4.8	92.1; 92.4 ± 4.4[a]
Sex (*n*, % female)	127 (69.4%)	44 (65.7%)	84 (71.8%)
Years of education (median; mean ± SD)	14.0; 15.3 ± 2.4	15.0; 15.8 ± 2.6	14.0; 15.0 ± 2.2*
Years from last survey to death (median; mean ± SD)	1.8; 2.2 ± 1.8	1.8; 1.9 ± 1.2	2.0; 2.4 ± 2.0
MMSE at last survey before death (median; mean ± SD)	24.0; 21.4 ± 6.6	26.0; 25.7 ± 3.1	19.0; 18.7 ± 6.8*
Frailty index (mean ± SD)	0.34 ± 0.16[a]	0.30 ± 0.13[a]	0.36 ± 0.17*,[a]
Neuropathological index (mean ± SD)	0.37 ± 0.13[a]	0.34 ± 0.14[a]	0.39 ± 0.13*,[a]

[a]Normally distributed.
*$p < 0.05$.

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Table 2. Logistic regression models for dementia status ($n = 183$; all models adjusted for age, sex, education) demonstrating that the frailty index and neuropathological index are independently associated with dementia status, even when included in the same model. Model fit is significantly improved when both frailty index and neuropathological index are included in a model for dementia status

Model 1	Frailty Index (per 0.1)	OR = 1.33 (95% CI 1.06–1.68), $p = 0.015$	Deviance = 229.10 Nagelkerke $R^2 = 0.082$
Model 2	Neuropathological index (per 0.1)	OR = 1.39 (95% CI 1.06–1.81), $p = 0.016$	Deviance = 227.75 Nagelkerke $R^2 = 0.085$
Model 3	Frailty Index (per 0.1)	OR = 1.31 (95% CI 1.04–1.66), $p = 0.023$	Deviance = 222.31 Nagelkerke $R^2 = 0.123$
	Neuropathological index (per 0.1)	OR = 1.38 (95% CI 1.05–1.81) $p = 0.021$	

OR, Odds Ratio.

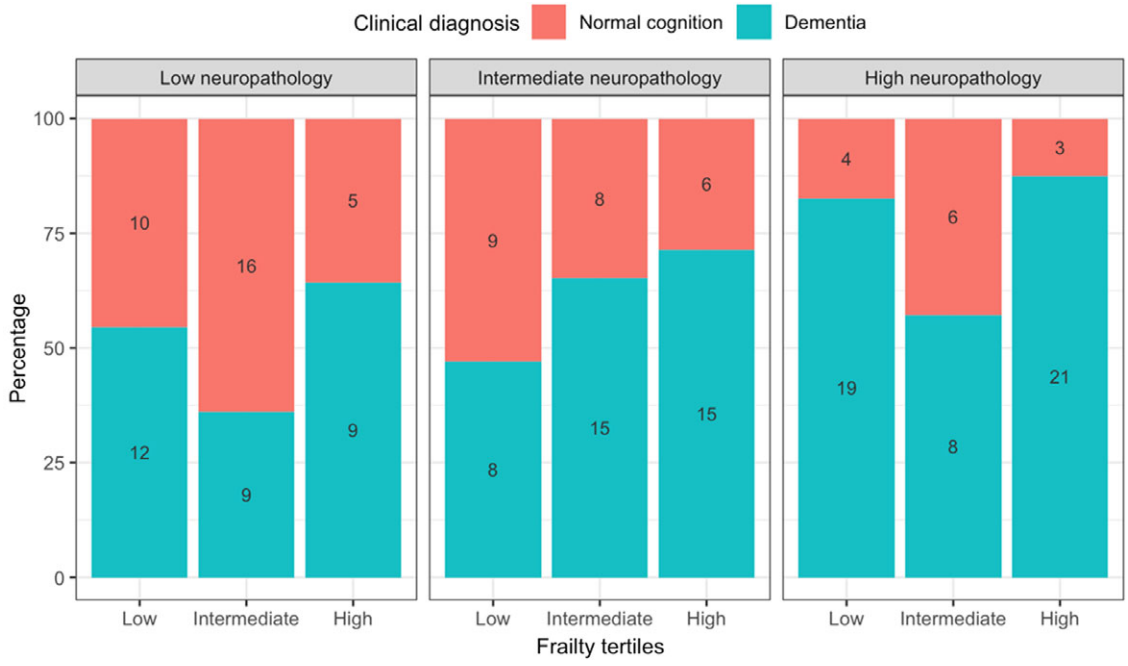

Figure 1. Proportion of participants with dementia according to tertiles of neuropathological index and frailty tertiles. *Note:* Frailty and dementia status were assessed at last survey before death (median 1.9 years pre-mortem), neuropathological burden was assessed at time of death. Numbers within the bars represent sample size.

Discussion

Almost a quarter of the sample (23.4%) demonstrated a mismatch between neuropathological burden and clinical dementia (i.e. either dementia with low neuropathology or no dementia with high neuropathology), similar to previous reports (Brayne *et al.*, 2009; Savva *et al.*, 2009). Frailty explained additional variance and significantly predicted dementia status, even after controlling for the neuropathological index, but did not interact with the neuropathological index. Taken together, these results suggest that frailty and neuropathology may be additive risk factors that independently are neither necessary nor sufficient but are largely responsible for creating the conditions in which the clinical syndrome of dementia is experienced. Given the independent risk conferred by frailty, we investigated what the scale of reduction of incidence of dementia would be, assuming a causal relationship. If this is the case, preventing severe frailty could reduce dementia risk by 14.2%. This indicates that frailty treatment and management is a worthwhile area to focus on, not only in its own right but also for its consequences as part of societal attempts to reduce the impact of dementia in populations.

Although the sample was drawn from a population-representative cohort, those who participated in the autopsy subset (i.e. brain donors) were more likely to be diagnosed with dementia than those who did not have autopsy, as they were more likely to be followed-up and undergo clinical testing (see Additional Supplementary File 6 for comparisons). Nevertheless, the autopsy subset

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has shown to have cognitive score distributions that closely match those of the full cohort (Brayne *et al.*, 2009; EClipSE Collaboration, 2009). The expected impact on our results here is minor, and likely reflects that frailty management would be slightly more important to control dementia in this group due to their other intersecting risks.

Another limitation was the sample size. While the sample size for the overall cohort study is quite large, by Survey 3 there had been significant attrition from this "older old" cohort due primarily to mortality, and missingness is to be expected as individuals become frail (Brayne *et al.*, 1999; Chatfield *et al.*, 2005; Matthews *et al.*, 2006; 2004). In an effort to determine the impact of the missing data on our results, we used an extreme sensitivity analysis in which imputed cases missing frailty index data were allocated the highest level of frailty. This sensitivity analysis did not change our results. Further, when we attempted multiple imputation (chained equations algorithm) for frailty index values we found the only predictors of missing frailty index data were related to pathological measures, suggesting that frailty is highly associated with informative dropout in this sample. Our future work will aim to investigate this relationship.

The goal of the cross-sectional regression analyses was to examine the relationship between pathology, frailty, and dementia as close to death as possible, therefore data on frailty and dementia were obtained from the last survey prior to death. This was done to minimize the effect of the autopsy results reflecting worse pathology than was present at the time of the survey from which frailty and dementia measurements were obtained. Even so, the median time from last survey to autopsy was about 2 years and it is likely we were not able to capture terminal decline that would influence frailty. Future investigations should address the issues of terminal decline.

Assessment of neuropathology was not stereological, being based on only one tissue section from each brain area for each staining method. This may lead to under- or over-estimates of pathology in a few cases. However, given the sample size, we assume that the effects of any discrepancies will be minor and cancel out.

Our results are consistent with other reports which show that the vast majority community-dwelling people are not free of neuropathology at time of death (Boyle *et al.*, 2018; Brayne *et al.*, 2009), and neuropathologies typically occur together. In other words, not only are pathological substrates of dementia rarely singular or "pure" in nature but also a "clean" or "unburdened" brain from a pathological perspective is almost unseen in the oldest old (MRC CFAS and CC75C *et al.*, 2012). A few groups have also examined the combined effect of pathology on disease and demonstrated generally, that the more pathology is considered, the better the prediction of dementia (Boyle *et al.*, 2018). While this may not be surprising it is a fact that has been ignored by those seeking a specific treatment for a specific pathology. It is important to consider the combined small effects of all such pathologies as an indicator of the overall health of the system, rather than focus on which one is the most predictive as has been done with the amyloid hypothesis, and now Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathologic Changes (LATE-NC) (Nelson *et al.*, 2019).

Previous work by our groups has shown not only that frailty is associated with biomarkers of Alzheimer's disease (Wallace *et al.*, 2018) but also that the relationship between Alzheimer's-specific neuropathology and dementia changes over levels of frailty and age (Savva *et al.*, 2009; Wallace *et al.*, 2019). While our results were similar in that we see a significant mismatch in neuropathology and dementia status, we did not find an interaction between neuropathology and frailty in relation to dementia status. There are a few differences to take into account when considering the implications of such findings. Perhaps the most influential is the type of pathology measured. The original analysis (Wallace *et al.*, 2019) included very specific "hallmark" features of AD (i.e. plaques and tangles) and examined AD-specific dementia as the outcome, whereas the analyses presented here combine several forms of neuropathology in an index with respect to all-cause dementia as an outcome. The mixed neuropathological index may represent a brain-specific frailty index, and may act as an indicator of overall deficit accumulation in the brain, and thus would not interact with the original frailty index (indicating bodily health) because it would be a reflection of it (with some expected variation).

As our population ages, a growing number of people will live long enough to accumulate several neuropathologies, but many of these people will reach older ages without necessarily experiencing dementia before their deaths. The implications of the current strategies for early detection of specific pathologies is that to "prevent" dementia may actually create more harm than good, in that younger and fitter people will be screened and "disease" will be detected in people who would not have necessarily gone on to develop symptoms. In this way, our work can inform a more public health oriented, preventative approach, by targeting frailty as a means of effective behavioral intervention for dementia risk. We hope this work will inform

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research and clinical approaches in considering dementia as a multi-determined disease that occurs in the aging body, which in essence suggests that the interaction of many mechanisms leading to many diverse pathways that give rise to dementia are likely. Single-mechanism treatments are therefore unlikely to be widely successful, and broad pharmaceutical and non-pharmaceutical therapies such as anti-aging compounds (Keller *et al.*, 2019) and exercise (Ahlskog *et al.*, 2011) should be explored more deeply for use in this population.

Conclusions

The analyses presented here suggest that frailty in its own right contributes to risk for dementia in the oldest old and reduction of frailty can contribute meaningfully to dementia risk. This suggests that future research on frailty interventions should include dementia risk as a key outcome, public health interventions and policy decisions should consider frailty as a key risk factor for dementia (Norton *et al.*, 2014), and biomedical research should focus on elucidating shared mechanisms of frailty and dementia development.

Ethics approval and consent to participate

Each phase of the CC75C study has been approved by Cambridge Research Ethics Committee. Secondary analyses of these data have been approved by the Dalhousie University/Nova Scotia Health Authority Research Ethics Board.

Availability of data and materials

The data analysed here are available to be requested from www.cc75c.group.cam.ac.uk.

Conflict of interest

KR is President and Chief Science Officer of DGI Clinical, which in the last 5 years has contracts with pharma and device manufacturers (Baxter, Baxalta, Biogen, Shire, Hollister, Nutricia, Roche, Otsuka) on individualized outcome measurement. In 2017 he attended an advisory board meeting with Lundbeck. Otherwise any personal fees are for invited guest lectures, rounds and academic symposia, received directly from event organizers, for presentations on frailty. He is Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research (CAN-137,794), with additional funding from the Alzheimer Society of Canada and several other charities, as well as from Pfizer Canada and Sanofi Canada (in Phase 1, 2014-2019). The remaining authors have no conflicts of interest to declare.

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Description of authors' roles

LW and KR conceived idea with input from CB. SH prepared and advised on the neuropathological data and analyses and contributed to final draft. LW conceived of design, undertook analyses, interpreted the data, wrote first draft and revised all subsequent drafts. JF advised on methodological design and analysis. OT aided in interpretation and analysis, and revised all drafts. CB is the custodian of the data, and contributed to design, analyses, interpretation, and revised all drafts.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610220003932

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