TITLE: Frailty trajectories preceding dementia in the United States and United Kingdom

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STRUCTURED ABSTRACT (337/350 words)

Importance: An accessible marker of both biological age and dementia risk is crucial to advancing dementia prevention and treatment strategies. Although frailty is a candidate for that role, the nature of the relationship between frailty and dementia is not well understood.

Objective: We aimed to clarify the temporal relationship between frailty and incident dementia by investigating frailty trajectories in the years preceding dementia onset.

Design: Participant data came from four prospective cohort studies: English Longitudinal Study of Ageing; Health and Retirement Study; Rush Memory and Aging Project; and National Alzheimer's Coordinating Center. Data were collected between 1997–2024 and were analysed from July 2023 to August 2024.

Setting: The settings were retirement communities, national-level surveys, and a multi clinic-based cohort.

Participants: Individuals were aged 60 years or over and without cognitive impairment at baseline. They also had data on age, sex, education level and ethnicity, and a frailty index score calculated at baseline. The number before exclusion was 87,737.

Exposure: Frailty was the main exposure, with participants' degrees of frailty quantified using retrospectively calculated frailty index scores.

Main Outcome: Incident all-cause dementia ascertained through physician-derived diagnoses, self- and informant-report, and estimated classifications based on combinations of cognitive tests.

Results: Data from 29,849 participants were analysed (62% female, 257,963 person-years of follow-up; 3,154 cases of incident dementia). Bayesian generalised linear mixed regression models revealed accelerations in frailty trajectories 4–9 years before incident

dementia. Overall, frailty was positively associated with dementia risk (adjusted hazard ratios, aHRs ranged from 1.18 [95% confidence interval, CI = 1.13–1.24] to 1.73 [CI = 1.57–1.92]). This association held among participants whose time between frailty measurement and incident dementia exceeded the identified acceleration period (aHRs ranged from 1.18 [CI = 1.12–1.23] to 1.43 [CI = 1.14–1.80]).

Conclusions and Relevance: These findings indicate that frailty measurements can be used to identify high-risk population groups for preferential enrolment into clinical trials for dementia prevention and treatment. Frailty itself may represent a useful upstream target for behavioural and societal approaches to dementia prevention.

KEY POINTS (86/100 words)

Question: When does the degree of frailty accelerate before dementia, and how is it associated with dementia risk?

Findings: In this analysis of 29,849 participants of four cohort studies in the United States and United Kingdom, frailty trajectories accelerated 4–9 years before the onset of dementia. Even among participants whose baseline frailty measurement occurred before that acceleration period, frailty was positively associated with dementia risk.

Meaning: Frailty may have value in identifying at-risk populations for clinical trials and as a target for dementia prevention strategies.

INTRODUCTION

Dementia most commonly arises in older people due to mixed age-related neuropathologies [1,2], suggesting that the ageing process influences disease susceptibility [3,4]. A deeper understanding of the relationship between ageing and late-life dementia could inform drug discovery and effective behavioural and societal strategies to dementia prevention. To optimise these approaches, it is important to have a readily measurable target that reflects biological ageing and associates with dementia risk. Accumulating evidence indicates that frailty may be a viable candidate for that role [5–7].

Frailty can be understood as a gradable health state of increased vulnerability due to the accumulation of multiple age-related health deficits and reduced physiological reserve [8]. At any age, frailty is positively associated with all-cause mortality, and to a greater degree than are common lab-based estimates of biological age [6,9], indicating that higher frailty reflects older biological age [5,8]. As observational data consistently show dementia occurring more frequently among individuals who have a higher degree of frailty [7,10–13], frailty may represent a target for interventions aimed at reducing dementia risk.

Accumulating evidence suggests that frailty is modifiable. For example, physical activity, which has been associated with lower dementia risk and better cognition in both observational studies and randomised controlled trials [14,15], is a strong determinant of frailty [16]. A systematic review of 21 randomised controlled trials found that interventions involving both exercise delivered in group sessions and nutrition supplementation were the most effective in reducing frailty [17]. Addressing the determinants of frailty, including physical activity and its other social, physical and health-related modifiable factors [18], may therefore represent a strategy to reduce risk of developing clinical dementia symptoms. However, considering the long preclinical phase of Alzheimer's disease (up to 15–20 years) [19,20] and the strong likelihood of reverse causality in the association of frailty with dementia risk, further investigation is required.

Understanding the dynamics of frailty trajectories in the years before dementia can inform use of its measurement in dementia prevention programs and in the targeted recruitment of high-risk populations into clinical trials for dementia. We aimed to clarify the temporal relationship between frailty and incident dementia, examining how the timing of frailty measurement relative to dementia onset influences its association with dementia risk. We pursued two objectives: (1) determine when an acceleration in the accumulation of frailty due to impending dementia is first observable and (2) measure the association of frailty and dementia risk after controlling for any impact of that pre-dementia frailty acceleration period.

METHODS

Datasets

We analysed participant data from four large prospective cohort studies: the English Longitudinal Study of Ageing (ELSA), Health and Retirement Study (HRS), Rush Memory and Aging Project (MAP), and National Alzheimer's Coordinating Center (NACC). Study procedures were reviewed and approved by local institutional review boards and written informed consent was obtained from study participants. Details of study methodology, ethics approval, and data access are included in eMethods in the Supplement. Participants were included if they were aged 60 years or over at baseline, were without cognitive impairment, and had at least one follow-up assessment. To remove the influence of early-onset dementia cases that often occur exclusively due to genetic causes [21], participants were excluded if they developed dementia before age 65 years. At baseline, participants were required to have data available on age, sex, education level and ethnicity, and sufficient data to calculate a frailty index score (eFigure 1 in the Supplement). Frailty index scores were only calculated where participants had information available on at least 30 deficits used in that study's frailty index [22]. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Incident dementia

Given that mixed dementia is what occurs chiefly in late life [1,2], the study outcome was all-cause dementia. The method of determining this outcome differed between studies. In ELSA, classifications were derived through either a self-report of physician diagnosis of dementia or a mean score of ≥ 3.4 on the 16-item Informant Questionnaire on Cognitive Decline in Elderly (IQCODE) completed by family members/caregivers, which represents a decline in the ability of daily function compared to two years prior of a magnitude indicating dementia [23]. In HRS, classifications of dementia were obtained using the Langa-Weir Classification of Cognitive Function method, which applies validated cut-points to summary scores obtained from a range of cognitive tests (scores ranged from 0–27; scores of 0–6 indicated the presence of dementia) [24]. In MAP, presumptive diagnoses of dementia and Alzheimer's disease were calculated via an algorithmic decision tree using accepted clinical criteria and confirmed by a clinician [25]. In NACC, either a consensus team or a single physician used standard diagnostic criteria to classify participants as having all-cause dementia [25,26].

Frailty measurement

Frailty was the main exposure in this study, with each participant's degree of frailty quantified using retrospectively calculated frailty index scores. The frailty index is a measure of health state, combining information from multiple physiological systems and closely reflecting an individual's risk for adverse health events and mortality independently of chronological age [8]. The variables included in a frailty index are routinely collected clinical data such as symptoms, signs, disabilities and diseases that meet standard criteria [22]. Frailty index scores had been developed and validated previously in each cohort [12,27–30]. Each frailty index was adapted for our investigation by ensuring that deficits closely reflecting cognition were removed from their composition (Table 1). As frailty index scores represent the proportion of total health deficits of an individual, higher scores indicate the accumulation of more age-

related health deficits and worse health. For more information on the frailty index approach, see eMethods in the Supplement.

Covariates

Participant age, sex, education level and ethnicity were included as covariates due to possibly confounding the relationship between frailty and incident dementia. In all datasets, age was measured in years at baseline; sex was a self-reported binary variable (male/female); education was reported at baseline and for consistency between studies was recoded into a three-category variable (lower, intermediate and higher education; eMethods in the Supplement); race and ethnicity were collected via self-report. For information regarding mortality data, which were used in censoring, see eMethods in the Supplement.

Statistical analysis

Full details of the statistical analyses are included in eMethods in the Supplement. In brief, to determine when an acceleration in the accumulation of frailty associated with impending dementia is first observable (objective 1), we modelled trajectories in frailty index scores (the dependent variable) using a backwards timescale with Bayesian generalised linear mixed regression models [31]. In each model, population-level effects of time were fitted using natural cubic splines, which allow for non-linear trajectories in frailty index scores (e.g. rate of increase in frailty may hasten with advancing age [32]), and included both a random intercept and slope (linear fit) for participants. We estimated the start of the pre-dementia frailty acceleration period as the year after which the size of differences in frailty index scores between the incident dementia group and the censored group were observed to be statistically significant and increase consistently. We next measured the association of frailty and incident dementia after controlling for any impact of the pre-dementia frailty acceleration period (objective 2). To do this, we first used Cox proportional hazards models to examine the relationships between frailty index scores and dementia risk. This model was then

estimated separately within two subgroups. The first subgroup included participants whose time between baseline frailty measurement and event (incident dementia, censor) was less than or equal to the pre-dementia frailty acceleration period (as estimated in objective 1). The second subgroup included participants whose time between baseline frailty measurement and event was greater than the pre-dementia frailty acceleration period. All statistical models included covariates of age, sex, education and ethnicity. Multiple sensitivity analyses were conducted to assess the robustness of associations of frailty index scores and incident dementia.

RESULTS

Sample characteristics

Data from 29,849 participants (62% female) were included in this analysis (Table 2). Most participants were contributed by NACC (42%) and least by MAP (5%). In total, 257,963 person-years of follow-up and 3,154 cases of incident dementia were analysed. Among the cohorts, participants in MAP were oldest and had the highest degrees of frailty, on average, corresponding to the highest observed rates of incident dementia.

Frailty trajectories prior to dementia

To determine when an acceleration in the accumulation of frailty associated with impending dementia might be first observable (objective 1), we modelled frailty index scores using backwards timescales and adjusted for potential confounders. In the years before incident dementia or censor, frailty index scores tended to increase (Figure 1). Among the censored groups, gradual increases in frailty index scores were observed in all datasets, although these were smallest in NACC. Among the incident dementia groups, we observed accelerations in the rates of increase in frailty index scores in the years proximal to dementia. These accelerations began 4–9 years before dementia, varied by dataset, and were particularly pronounced in ELSA and NACC and less so in MAP and HRS, although

still present in those datasets. That divergence in frailty trajectories associated with incident dementia was supported by the model results, whereby, for all datasets but HRS, the inclusion of an event group (incident dementia or censored) by time interaction term resulted in improved model fit (eTable 1 in the Supplement). The population-level effects from the interaction model (i.e. that which included the event group by time interaction term) are presented in eTable 2 in the Supplement. Among participants who developed dementia, covariate-adjusted expected frailty index scores were, on average, higher in females than in males by 18.5% in ELSA (95% CI = 7.3%–32.3%), 20.9% in HRS (95% CI = 12.7%–28.4%) and 16.2% in MAP (95% CI = 5.1%–28.4%), but not different in NACC (1.5% [95% CI = −3.9%–7.2%]) (Figure 2).

Expected frailty index scores, calculated from the interaction model while holding the covariates of age, sex, education and ethnicity constant, were then compared between the incident dementia and censored groups at each year (Figure 1). Compared with the censored groups, these frailty scores were consistently higher in the incident dementia groups, 20, 13, 12, and 8 years before dementia in HRS, MAP, ELSA and NACC, respectively. At the point of dementia detection, frailty index scores were most elevated in ELSA (0.21 points higher than censored participants), elevated to a similar degree in both MAP and NACC (0.13 and 0.12 points higher, respectively), and to a lesser extent in HRS (0.04 points higher). The start of the pre-dementia frailty acceleration period, i.e. the year after which the size of differences in frailty index scores between the incident dementia group and the censored group were observed to be statistically significant and increase consistently, was estimated at 9, 6, 4 and 4 years before dementia for NACC, MAP, ELSA and HRS, which was similar in both males and females (eFigures 2-5 in the Supplement). Mean differences in expected frailty index scores and *P* values are presented in eTable 3 in the Supplement.

Frailty and incident dementia

We next measured the association of frailty index scores and incident dementia after controlling for the pre-dementia frailty acceleration period (objective 2). This we did by using Cox proportional-hazards models to determine the associations of frailty with incident dementia for participants whose time between baseline frailty measurement and event (incident dementia or censored) was greater than the cohort-specific pre-dementia frailty acceleration period (as estimated under objective 1). The size of analysed samples, the pre-dementia frailty acceleration periods, and the number of deficits included in frailty indices varied in the main and sensitivity analyses (eTable 4 in the Supplement).

In the main analyses, in each dataset, each 0.1 increase in frailty index scores (equivalent to 4–5 additional health deficits) was associated with higher dementia risk (Figure 3). This association was strongest in NACC, weakest in HRS, and similar in ELSA and MAP, with hazard ratios ranging from 1.18 (95% CI = 1.13–1.24) to 1.73 (95% CI = 1.57–1.92). When the time between frailty measurement and incident dementia or censor was considered, in most datasets, associations remained similar in both groups (i.e. in participants whose time between frailty measurement and incident dementia or censor was less than or equal to the pre-dementia frailty acceleration period, and in participants whose time between measurement and outcome exceeded that period). Here, event timing x frailty index score interaction terms were not statistically significant in ELSA ($P = 0.51$), MAP ($P = 0.48$) or NACC ($P = 0.57$) but were in HRS ($P < .001$). Across datasets and in participants whose baseline frailty measurement was conducted before the pre-dementia acceleration period had begun, the associations of frailty index scores with dementia risk were consistently positive and statistically significant. There, each 0.1 increase in frailty index scores was associated with hazard ratios ranging from 1.18 (95% CI = 1.12–1.23) to 1.43 (95% CI = 1.14–1.80), and in the absence of meaningful differences in this association between males and females (eFigures 2-5 in the Supplement). The results from both sensitivity analyses demonstrated a robustness in these findings, whereby frailty index scores calculated before the pre-dementia frailty acceleration period remained associated with incident dementia at a

statistically significant level even when that period was extended by two years (sensitivity analysis 1). Likewise, our results were robust to removing health deficits that were independently associated with incident dementia from the calculation of frailty index scores (sensitivity analysis 2).

DISCUSSION

With the purpose of clarifying the temporal relationship between frailty and dementia, we modelled frailty trajectories in the years preceding dementia and assessed how the timing of frailty measurement relative to dementia onset influences its association with dementia risk. From this analysis of almost 30,000 individuals participating in four cohort studies in the United Kingdom and United States, we report four main findings: 1) an elevated degree of frailty was observed 8–20 years before dementia onset; 2) the rate of decline in health and function in prodromal dementia, as reflected in a higher degree of frailty, accelerated from 4–9 years before dementia onset; 3) frailty was higher in females compared to males among those who developed dementia, with the greatest differences observed further from dementia onset; 4) frailty was a robust risk factor for incident dementia even when its measurement occurred before the pre-dementia frailty acceleration period. These results offer insight into the natural course of declining health in the subclinical stages of neurodegenerative diseases, position frailty index scores as a measure effective in identifying high-risk individuals for inclusion into treatment and prevention trials for dementia, and support the notion that frailty may serve as an upstream dementia risk factor.

Previous reports have suggested a preclinical phase of Alzheimer's disease up to 15–20 years in length [19,20], with changes in health and function first detectable at a population level from 10 years before dementia onset. Examples of these include higher health care usage and lower social engagement (2 years prior to diagnosis) [33,34], accelerated cognitive decline (6–10 years prior) [20,35], and more depressive symptoms (10 years prior) [36]. Even though we observed a degree of heterogeneity in frailty trajectories between the datasets, in each case

the pre-dementia frailty acceleration period was estimated to lie within that 10-year prodromal period, supporting those earlier studies. Consequently, one explanation for elevated frailty in the years proximal to dementia relates to the adverse impacts of neurodegenerative changes.

Aside from neurodegenerative processes hastening frailty accumulation, another explanation for our findings is that accelerated biological ageing is a dementia cause rather than consequence. In support, strong links have been established between changes in the hallmarks of ageing and the development of neurodegenerative diseases [3,4], and chronological age itself has long been understood as a key risk factor. Rapidly increasing frailty index scores, observed here up to 9 years before dementia onset, may therefore signal an exhaustion of systemic reserves leaving affected individuals vulnerable to diseases that might otherwise have remained subclinical [8]. This loss of reserve associated with higher frailty has been demonstrated previously in dementia, where frailty was associated with weaker relationships between dementia and neuropathological burden and polygenic risk despite persistently high dementia rates [7,37,38]. Another mechanism through which frailty may precipitate dementia is by accelerating the accumulation of age-related brain changes. In support, cross-sectional analyses of cognitively intact individuals have linked frailty with smaller brain volumes and more vascular neuropathology [39,40]. This interpretation of our findings highlights the potential of frailty as a target of modifiable risk for dementia [16,18].

Regardless of the nature of the relationship between the pre-dementia frailty acceleration period and subsequent dementia, the findings from our analyses align with the position that frailty could be a strong dementia risk factor. In individuals whose measurement of frailty occurred before the pre-dementia frailty acceleration period had begun, and in both males and females, we observed positive associations between frailty index scores and incident dementia. Our findings join previous reports of a robust association between frailty and incident dementia, even when adjusting for a polygenic dementia risk score and a marker of

area-level deprivation [7], adjusting for the competing risk of death [11], including only non-traditional risk factors in the composition of the frailty index [13], or when conceptualising frailty as a phenotype [10].

Strengths and limitations

A considerable strength of our investigation was the use of four different cohort studies across two continents, which varied in participant characteristics and in study methodologies (e.g. settings, methods of dementia detection, time between repeat assessments). These differences contributed to variability in our statistical findings, both in terms of the frailty trajectories and in the strength of associations between frailty index scores and incident dementia. In datasets with annual monitoring of functioning and physician-derived dementia classifications (NACC, MAP), the onset of the pre-dementia frailty acceleration period was detected earlier compared to in those with biennial assessments involving self-reported or estimated dementia classifications (ELSA, HRS), likely due to higher accuracy and timeliness in diagnoses. Despite these differences, by applying a consistent analytical approach to each dataset and reviewing results independently, we observed an encouraging consistency in findings supportive of strong external validity.

Our results should be interpreted with respect to limitations. 1) A degree of reverse causality remains likely in the absence of a randomised design, particularly considering the up-to 20-year preclinical phase of dementia [19,20]. 2) To enhance consistency and comparability in analyses between cohorts, we did not include potentially relevant covariates in statistical models unless they were universally available. Although we included education level, which is an important marker of socioeconomic status, we did not include other markers of social deprivation that may be causally associated with dementia [41]. Similarly, genetic risk for dementia, often approximated using *APOE* ε4 status, was not adjusted for. Nonetheless, previous reports of strong associations between frailty and incident dementia even after

adjusting for social deprivation [7], and within both *APOE* ε4 carriers and non-carriers [12], lead us to maintain confidence in our findings.

Conclusion

This study offers novel insights into the temporal relationship between frailty and dementia and provides robust observational evidence that frailty serves as a risk factor for dementia even when measured distally to dementia onset. These findings suggest that frailty measurements can be used to identify high-risk population groups for preferential enrolment into clinical trials for dementia prevention and treatment, and that frailty itself may represent a useful upstream target for behavioural and societal approaches to dementia prevention.

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DW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Role of Funder/Sponsor

Funders/sponsors had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement

The data that support the findings of this study are available from the English Longitudinal Study of Ageing (https://ukdataservice.ac.uk/), Health and Retirement Study (https://hrs.isr.umich.edu/), Rush Memory and Aging Project (https://www.radc.rush.edu/), and National Alzheimer's Coordinating Center (https://www.naccdata.org/). Some restrictions may apply to the availability of these data.

Author Contributions

DW, JF, TL, IF, MC, LW, DL, JR and ES were involved in the conception of the study. JR conceived and organised the workshop from which this paper originated. DW, JF and ES designed and undertook the analyses. DW wrote the first draft of the paper. All authors revised the manuscript for important intellectual content. All authors contributed to the interpretation of findings. All authors read and approved the final manuscript.

Conflict of Interest and Financial Disclosures

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FIGURE LEGENDS AND TABLES

Figure 1. Frailty trajectories before dementia or censor. Plots used expected frailty index scores calculated from Bayesian generalised linear mixed regression models that included fixed effects of time, event group, time x event group, age, sex, education and ethnicity, as well as random participant intercepts and slopes. For the trajectory plots, the lines are mean trajectories surrounded by 95% credible intervals. For the forest plots, mean differences (95% confidence intervals) are between the censored group (reference line) and the incident dementia group, and the dashed line represents the estimated start of the pre-dementia frailty acceleration period. ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; MAP, Rush Memory and Aging Project; NACC, National Alzheimer's Coordinating Center.

Figure 2. Sex differences in frailty before dementia. Plots used expected frailty index scores calculated from Bayesian generalised linear mixed regression models that included fixed effects of time, sex, time x sex, age, education and ethnicity, as well as random participant intercepts and slopes. The lines are mean trajectories surrounded by 95% credible intervals. ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; MAP, Rush Memory and Aging Project; NACC, National Alzheimer's Coordinating Center.

Figure 3. Associations of frailty and incident dementia. Hazard ratios were calculated from Cox proportional-hazards models that included covariates of age, sex, education and ethnicity. Sensitivity analysis 1, the pre-dementia frailty acceleration period was increased by two years; sensitivity analysis 2, deficits found to be independently associated with incident dementia were removed from the calculation of frailty index scores. Details regarding sizes of samples and subgroups included in these analyses are presented in eTable 4 in the Supplement. ELSA, English Longitudinal Study of Ageing, HRS, Health and

Retirement Study; MAP, Rush Memory and Aging Project; NACC, National Alzheimer's Coordinating Center.

Table 1. Composition of frailty indices

No.	ELSA	HRS	MAP	NACC
1	Walking 100 metres	Dressing	Congestive heart failure	Diagnosis of depression
2	Sitting for 2 hours	Walking in house	Diabetes	Delusions
3	Getting up from chair	Bathing/showering	Depression	Hallucinations
4	Climbing several flights of stairs	Eating	Cancer	Agitation or aggression
5	Climbing one flight of stairs	Getting in and out of bed	Osteoporosis	Anxiety
6	Stooping, kneeling or crouching	Use toilet	Falls	Apathy or indifference
7	Reaching or extending arms above shoulder level	Shop groceries	Joint pain	Disinhibition
8	Pulling or pushing large objects	Use telephone	Diastolic blood pressure	Irritability or lability
9	Lifting over 10 pounds	Manage money	Hypertension	Night-time behaviours
10	Picking up a coin from a table	Preparing a hot meal	Grip strength	Psychiatric disorder
11	Dressing	Taking medications	Walking speed	History of seizures
12	Walking across a room	Walking one block	Fatigue (everything I did was an effort)	Not satisfied with life
13	Bathing or showering	Walking several blocks	Travelling in the community	Lacking energy
14	Eating	Climbing one flight of stairs	Meal prep	Appetite and eating problems
15	Getting in and out of bed	Lifting 5 kg	Managing finances	Hypertension
16	Using the toilet	Getting up from chair	Using telephone	Heart attack
17	Using a map	Stooping	Shopping	Atrial fibrillation
18	Preparing a hot meal	Reaching	Physical activity	Heart failure
19	Shopping for groceries	Picking up a coin	Head injury	Other cardiovascular disease
20	Making telephone calls	Heart problems	Polypharmacy	Diagnosis of stroke
21	Taking medications	High blood pressure	Taking care of home	Low body massive index
22	Doing work around the house or garden	Stroke	Walk half a mile	Focal neurological symptoms
23	Managing money	Diabetes	Walk up and down stairs	Focal neurological signs
24	High blood pressure	Chronic lung disease	Managing medications	Abnormal vision
25	Angina	Arthritis	Light housekeeping	Abnormal hearing
26	Heart attack	Cancer	Heavy housekeeping	Diabetes
27	Congestive heart failure	Incontinence	Eating	Hypercholesterolemia
28	Abnormal heart rhythm	Self-rated health	Dressing	Vitamin B12 deficiency
29	Diabetes or high blood sugar	Underweight	Bathing	Thyroid disease
30	Stroke	Hearing impairment	Toileting	Incontinence (urinary)
31	Lung disease	Visual impairment (close)	Walking	Incontinence (bowel)

Table 1. Composition of frailty indices (continued)

No.	ELSA	HRS	MAP	NACC
32	Asthma	Visual impairment (distant)	Getting from bed to chair	Difficulty with paying bills
33	Arthritis	Sleep problems	Stroke	Difficulty with shopping
34	Osteoporosis	Pain	Heart problems	Difficulty with meal preparation
35	Cancer	Depressed	Claudication	Difficulty with transportation
36	Psychiatric condition	Sad	Finger tap	Difficulty with community affairs
37	Depressed	Felt everything was effort	Leg stand	Traumatic brain injury
38	Everything was an effort	Lonely	Pegboard	Motor function (falls)
39	Restless sleep	Could not get going	Pinch strength	Motor function (slowness)
40	Happy (rev.)	Enjoyed life (rev.)	Fatigue (I could not get going)	Difficulty arising from a chair
41	Lonely	-	Body mass index	Difficulty with postural stability
42	Enjoyed life (rev.)	-	-	Abnormal posture
43	Sad	-	-	Abnormal gait
44	Could not get going	-	-	Somatic complaints
45	Self-reported general health	-	-	-
46	Self-reported eyesight	-	-	-
47	Self-reported hearing	-	-	-
48	Fallen since last interview	-	-	-
49	Hip fracture	-	-	-
50	Joint replacement	-	-	-
51	Had pain whilst walking	-	-	-

Note: Health and functional deficits highlighted in grey were excluded from the second frailty index used in sensitivity analyses due to being independently associated ($P < 0.05$) with incident dementia in multivariable Cox proportional hazards models adjusted for age, sex, education, ethnicity and all other deficits. ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; MAP, Rush Memory and Aging Project; NACC, National Alzheimer's Coordinating Center; rev., reverse coded.

Table 2. Characteristics of analytical samples

Characteristic	ELSA	HRS	MAP	NACC
N	6,771	9,045	1,451	12,582
Age at baseline, years				
Mean (SD)	69.8 (7.2)	69.9 (7.2)	79.0 (7.0)	72.9 (7.7)
Range	60–99	60–96	60–100	60–104
Sex, No. (%)				
Male	3,046 (45)	3,707 (41)	343 (24)	4,384 (35)
Female	3,725 (55)	5,338 (59)	1,108 (76)	8,198 (65)
Education, No. (%)				
Higher	1,416 (21)	2,067 (23)	1,091 (75)	10,464 (83)
Intermediate	2,239 (33)	5,076 (56)	312 (22)	1,848 (15)
Lower	3,116 (46)	1,902 (21)	48 (3)	270 (2)
Ethnic group, No. (%)				
Black	-	835 (9)	59 (4)	1,751 (14)
White	6,688 (99)	8,002 (89)	1,372 (95)	9,226 (73)
Other/unknown	83 (1)	208 (2)	20 (1)	1,605 (13)
Frailty index score at baseline				
Mean (SD)	0.15 (0.13)	0.17 (0.13)	0.19 (0.09)	0.09 (0.06)
Range	0.00–0.74	0.00–0.84	0.00–0.56	0.00–0.50
Follow-up time, years				
Median (IQR)	10.0 (4.8–14.4)	12.9 (7.3–17.9)	6.9 (4.0–10.8)	5.0 (2.6–8.2)
Range	1.3–17.2	1.1–19.6	0.5–23.9	0.4–17.9
Number of frailty measurements per participant				
Mean (SD)	4.8 (2.3)	6.7 (2.8)	7.8 (4.6)	5.8 (3.5)
Range	1–8	1–10	1–23	1–18
Incident dementia				
Number of cases (% absolute risk)	507 (8)	1,213 (13)	332 (23)	1,102 (9)
Dementia incidence rate per 100 person-years (person-years of follow-up)	0.8 (64,084)	1.1 (108,992)	3.0 (11,029)	1.5 (73,858)

Note: Proportions may not sum to 100% due to rounding. ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; MAP, Rush Memory and Aging Project; NACC, National Alzheimer's Coordinating Center. SD, standard deviation. IQR, interquartile range. 'Other' ethnic group includes American Indian or Alaska native, Asian, Native Hawaiian or Pacific Islander, and mixed ethnic group; for ELSA 'Other' also includes Black.