Associations between physical frailty and dementia incidence: a prospective study from UK Biobank

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Summary

Background Dementia is associated with a high burden of dependency and disability. Physical frailty (hereafter referred to as frailty) is a multisystem dysregulation that has been identified as a risk factor for dementia. The aim of this study was to examine the association of frailty and its individual components with all-cause dementia incidence in a cohort of UK adults.

Methods Participants in UK Biobank with data available for dementia incidence and without any form of dementia at baseline were included in this prospective study. Frailty was defined using a modified version of the frailty phenotype based on five individual components (weight loss, tiredness, physical activity, gait speed, and grip strength), with participants classified as pre-frail if they fulfilled one or two criteria or frail if they fulfilled three or more. Associations between frailty and dementia incidence were investigated using Cox proportional hazard models adjusted for sociodemographic factors, lifestyle factors, and morbidity count. The population attributable fraction was also estimated.

Findings Of 502 535 participants in UK Biobank, 143 215 met the inclusion criteria and were included in our analyses. 68 500 (47·8%) of the participants were pre-frail and 5565 (3·9%) were frail. During a median follow-up period of 5·4 years, 726 individuals developed dementia. Compared with non-frail individuals, the risk of dementia incidence was increased for individuals with pre-frailty (hazard ratio 1·21 [95% CI 1·04–1·42]) and frailty (1·98 [1·47–2·67]) in the fully adjusted model. Of the five components used to define frailty, weight loss (1·31 [1·09–1·58]), tiredness (1·48 [1·18–1·86]), low grip strength (1·38 [1·17–1·63]), and slow gait speed (1·55 [1·22–1·96]) were independently associated with incident dementia. Based on population attributable fraction analyses, in the study sample, pre-frailty and frailty accounted for 9·9% and 8·6% of dementia cases, respectively.

Interpretation Individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounding factors. Early detection and interventions for frailty could translate into prevention or delayed onset of dementia.

Funding None.

Introduction

Dementia is characterised by a progressive deterioration of cognition and the ability to perform activities of daily living. It is a heterogeneous syndrome associated with a high burden of dependency and disability and has a large emotional, economic, and psychological impact on families and society.[1,2] More than 850 000 people have dementia in the UK.[3] Globally, approximately 50 million individuals have dementia, and this number is estimated to increase to 152 million by 2050.[1]

Given that currently available pharmacological interventions can neither cure nor reverse dementia and offer little symptom relief, there is an urgent need to identify potential modifiable risk factors that could prevent or slow development of the disease. A 2020 report[2] on dementia prevention, intervention, and care identified that if 12 major risk factors were modified, 40% of dementias could be prevented or delayed. Physical frailty (hereafter referred to as frailty) has also been proposed as a risk factor.[4] Frailty is a state of high vulnerability to adverse health outcomes, including hospitalisations and deaths.[5] Several studies have reported that frailty is associated with cognitive impairments and a higher risk of dementia,[6–9] which might be explained by frailty and dementia sharing many risk factors and clinical features, including age, inflammation, functional impairment, and multimorbidity.[4]

The evidence from prospective cohort studies regarding the association between frailty and dementia has been conflicting. Some studies have suggested that frailty is an independent risk factor for dementia,[6–9] whereas others have reported that the association between these two conditions is weak and could be explained mainly by confounding factors, including pre-existing health conditions.[10] Discrepancies between existing studies could, in part, be attributable to their relatively small sample sizes (<10 000 participants),[7–9] as well as differences in how frailty has been defined and measured in each

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Research in context

Evidence before this study

We searched Web of Science on June 1, 2020, for articles published in English between Jan 1, 1980, and June 1, 2020, using medical subject heading terms for "dementia", "Alzheimer", "neurodegenerative diseases", "pre-frailty", and "frail". Both dementia and frailty have a substantial impact on individuals, families, and society. Several studies have reported that frailty is associated with a higher risk of dementia. However, the evidence from prospective cohort studies regarding this association has been conflicting, in part because of small sample sizes and differences in how frailty has been defined and measured in each study.

Added value of this study

This study provides a better understanding of the association between frailty and dementia incidence in middle-aged and older adults. Individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounder factors, including multimorbidity. We also identified that weight loss, low grip strength, tiredness, and slow gait speed were the main components of the frailty phenotype that were associated with dementia. These findings highlight that public health strategies aiming to improve physical capabilities in middle-aged and older adults could reduce the burden of both frailty and dementia.

Implications of all the available evidence

Given the increased risk of dementia incidence in people with frailty, early assessment and interventions from middle age should be implemented in the general population to prevent frailty, and consequently, reduce the risk of dementia.

study. Moreover, we do not fully understand to what extent the association between frailty and dementia could be explained or moderated by pre-existing and shared risk factors for both conditions, and the components of the frailty phenotype that are most strongly associated with dementia remain to be elucidated. Understanding these features could help to tailor future interventions for dementia prevention. To answer these gaps in the current evidence, we used data from UK Biobank, a prospective cohort study, to investigate the association of the frailty phenotype, along with its individual components, with all-cause dementia incidence.

Methods

Study design and participants

For more on the **UK Biobank protocol** see http://www.ukbiobank.ac.uk

UK Biobank recruited more than 500 000 participants (5·5% response rate), aged 37–73 years, from the general population between 2006 and 2010.[11] Participants attended their closest of 22 assessment centres across England, Wales, and Scotland, where they completed a touchscreen questionnaire, had physical measurements taken, and provided biological samples (blood, urine, and saliva) at a baseline assessment visit. UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (reference 11/NW/0382).

Procedures

See Online for appendix

For more on the **linkage procedure for hospital admissions** see http://content.digital.nhs.uk/services

Record linkage to Health Episode Statistics (England and Wales) and the Scottish Morbidity Records (Scotland) was used to identify the date and cause of hospital admissions. Detailed information regarding the linkage procedure can be found online.

Incident dementia cases were ascertained from two sources. Hospital admission records were available until February, 2018, for the full UK Biobank cohort, whereas linkage to primary care records was available for 45% of the UK Biobank cohort (approximately 230 000 participants) until May, 2017, for Scotland, September, 2017, for Wales, and August, 2017, for England. The detailed linkage procedures relating to primary care records are available online. The analyses of incident cases were restricted to the 230 000 participants with linkage to both primary care and hospital records, and the outcome was defined as either a primary care or hospital record of dementia, whichever occurred first. Follow-up was censored at the primary-care data end date for the relevant country, or the date of incident dementia or all-cause death, if this occurred earlier. Dementia was defined as International Classification of Diseases (10th revision) code F00 (dementia in Alzheimer disease), F01 (vascular dementia), F02 (dementia in other diseases), or F03 (unspecified dementia).

For more on **linkage procedures relating to primary care records** see http://content.digital.nhs.uk/services

Frailty

The Fried frailty phenotype was used in this study because it is based on physical-related frailty, including the following five criteria: weight loss, exhaustion, physical activity, walking speed, and grip strength.[5] However, some of these items were adapted to fit the data available within UK Biobank.[12] Previous studies have suggested that physical capability markers, including low grip strength and slow walking pace, are related to a higher risk of dementia;[13,14] however, little evidence is available regarding their associations as part of the frailty phenotype in the UK. Weight loss, tiredness or exhaustion, gait speed, and grip strength were derived following a similar approach to that of Hanlon and colleagues (appendix pp 1–4).[12] Physical activity was self-reported and collected using the International Physical Activity Questionnaire short form. Total physical activity was computed as the sum of walking, moderate activity, and vigorous activity, measured as metabolic equivalents (MET-h) per week. To derive a proxy for the Fried frailty phenotype, physical activity was categorised into age-specific and sex-specific quintiles, in which the lowest quintile was classified as meeting the physical inactivity criterion for frailty. Participants were

classified as frail if they fulfilled three or more of the five criteria, pre-frail if they fulfilled one or two criteria, and robust (non-frail) if they did not fulfil any criteria at baseline. The three groups were mutually exclusive.

Covariates

Age was calculated from dates of birth and based on the date of baseline assessment. Area-based socioeconomic status (deprivation) was derived from the postcode of residence using the Townsend score.[15] Ethnicity was self-reported and categorised into white, south Asian, black, Chinese, or mixed ethnic background. Education attainment was self-reported and coded as an ordinal variable. Participants were asked which of the following qualifications they held: CSEs, O-levels, A-levels, college or university degree, NVQ, HND, NHC, or equivalent, other professional qualification, or none of these. Self-reported smoking status was categorised as never, former, or current smoker. Total time spent in discretionary sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer, and watching television during leisure time. Body-mass index (BMI) was calculated as weight divided by the square of height (kg/m²) and WHO criteria were applied to define weight categories.[16] Hours of sleep were self-reported and categorised as normal (7–9 h) and long or short sleep (>9 h or <7 h, respectively). Leisure or social activities, frequency of alcohol intake, and frequency of friend and family visits were self-reported at baseline via touchscreen questionnaire. Red meat, processed meat and fruit and vegetable intake were also collected through the touch-screen questionnaire at baseline. Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count (coded as 1, 2, 3, 4, or ≥5) based on 43 long-term conditions developed initially for a large epidemiological study in Scotland and subsequently adapted for UK Biobank.[17] Total cholesterol and glycated haemoglobin A_{1c} (HbA_{1c}) were analysed from serum and packed red blood cell samples. Systolic and diastolic blood pressure were derived from the mean of two readings recorded in the left arm. Reaction-time tests (timed tests of symbol matching) were completed through a touchscreen tool (Snap). Further details of these measurements can be found in the appendix (pp 3–4). Only participants with complete data available for the five components of frailty and covariates were included in analyses.

Statistical analysis

Descriptive characteristics are presented as means with SDs for quantitative variables that were normally distributed, and as medians with IQRs for those that were non-normally distributed. Categorical variables are presented as frequencies and percentages. STATA 16 statistical software was used for all analyses.

Associations between frailty and dementia incidence were investigated using Cox proportional hazard models.

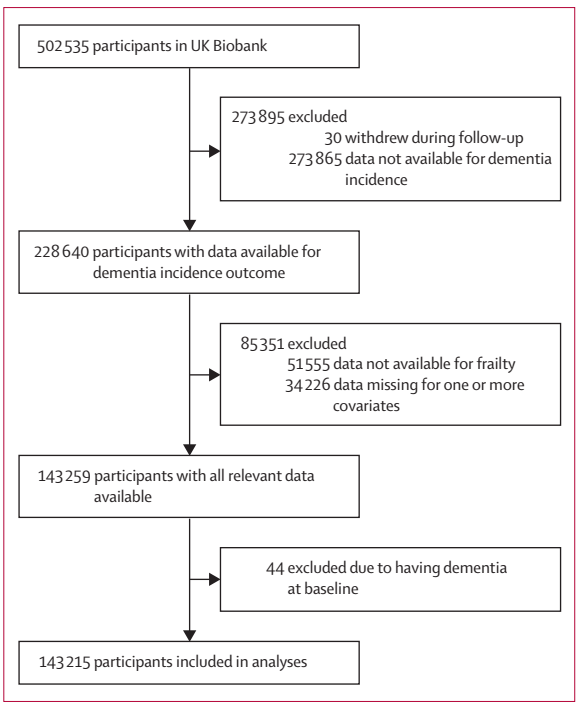

Figure 1: **Participant selection**

Individuals classified as non-frail were used as the reference group. The results are reported as hazard ratios (HRs) with 95% CIs. In addition, a sensitivity analysis was done a posteriori to evaluate associations between frailty and three subtypes of dementia incidence: vascular dementia, non-specific dementia, and Alzheimer's diseases (including early, late, and other non-specified Alzheimer's disease). Associations between the five components of the frailty phenotype and dementia incidence were investigated using the aforementioned analyses. The normal range for each component was used as the reference group. Additionally, non-linear associations between the number of individual components of frailty and the outcome were formally tested using penalised cubic splines fitted in the Cox proportional hazard models.

To avoid a possible reverse causality (ie, a causal relationship operating in the opposite way to that which truly occurs),[18] all analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up. Participants with all-cause dementia at baseline were also excluded from the follow-up analyses. The proportional hazard assumptions were checked using Schoenfeld residuals.

We ran three models for each outcome, including an increasing number of covariates: model 1 (minimally adjusted) included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol

	Whole population	Non-frail	Pre-frail	Frail
Total	143 215 (100·0%)	69 150 (48·3%)	68 500 (47·8%)	5565 (3·9%)
Sociodemographic factors				
Age at baseline, years	58·0 (50·0–63·0)	57·0 (50·0–63·0)	58·0 (51·0–63·0)	59·0 (53·0–64·0)
Sex				
Female	77 320 (54·0%)	35 216 (50·9%)	38 564 (56·3%)	3540 (63·6%)
Male	65 895 (46·0%)	33 934 (49·1%)	29 936 (43·7%)	2025 (36·4%)
Deprivation				
Lower	49 250 (34·4%)	25 564 (37·0%)	22 478 (32·8%)	1208 (21·7%)
Middle	49 781 (34·8%)	24 627 (35·6%)	23 494 (34·3%)	1660 (29·8%)
Higher	44 184 (30·9%)	18 959 (27·4%)	22 528 (32·9%)	2697 (48·5%)
Ethnicity				
White	137 759 (96·2%)	67 341 (97·4%)	65 425 (95·5%)	4993 (89·7%)
Mixed	1595 (1·1%)	593 (0·9%)	858 (1·3%)	144 (2·6%)
South Asian	2378 (1·7%)	614 (0·9%)	1442 (2·1%)	322 (5·8%)
Black	1167 (0·8%)	472 (0·7%)	607 (0·9%)	88 (1·6%)
Chinese	316 (0·2%)	130 (0·2%)	168 (0·2%)	18 (0·3%)
Education				
CSEs	7617 (5·3%)	3682 (5·3%)	3638 (5·3%)	297 (5·3%)
O-levels	31 238 (21·8%)	15 074 (21·8%)	15 012 (21·9%)	1152 (20·7%)
A-levels	15 970 (11·2%)	7746 (11·2%)	7690 (11·2%)	534 (9·6%)
College or university degree	47 936 (33·5%)	24 865 (36·0%)	21 837 (31·9%)	1234 (22·2%)
NVQ, HND, HNC, or equivalent	9800 (6·8%)	4728 (6·8%)	4666 (6·8%)	406 (7·3%)
Other professional qualification	7612 (5·3%)	3611 (5·2%)	3740 (5·5%)	261 (4·7%)
None of the above	23 042 (16·1%)	9444 (13·7%)	11 917 (17·4%)	1681 (30·2%)
Obesity-related markers				
Bodyweight, kg	77·6 (15·4)	76·3 (14·7)	78·4 (15·8)	82·7 (18·0)
Height, m	1·69 (0·09)	1·70 (0·09)	1·68 (0·09)	1·65 (0·09)
BMI, kg/m²	27·2 (4·5)	26·4 (4·01)	27·8 (4·7)	30·4 (6·0)
BMI category, kg/m²				
<18·5 (underweight)	700 (0·5%)	323 (0·5%)	342 (0·5%)	35 (0·6%)
18·5–24·9 (normal weight)	47 959 (33·5%)	27 197 (39·3%)	19 777 (28·9%)	985 (17·7%)
25·0–29·9 (overweight)	61 985 (43·3%)	30 454 (44·0%)	29 704 (43·4%)	1827 (32·8%)
≥30·0 (obese)	32 571 (22·7%)	11 176 (16·2%)	18 677 (27·3%)	2718 (48·8%)
Fitness and lifestyle				
Total physical activity, MET-h per week	1866·0 (855·0–3750·0)	2493·0 (1422·0–4 506·0)	1222·5 (495·0–2 986·0)	540·0 (346·5–990·0)
Sedentary behaviour, h per day	5·0 (4·0–6·0)	5·0 (3·0–6·0)	5·0 (4·0–6·0)	5·0 (4·0–7·0)
Alcohol intake frequency				
Daily or almost daily	29 872 (20·9%)	15 986 (23·1%)	13 173 (19·2%)	713 (12·8%)
3–4 times a week	34 635 (24·2%)	18 418 (26·6%)	15 519 (22·7%)	698 (12·5%)
Once or twice a week	37 702 (26·3%)	18 269 (26·4%)	18 143 (26·5%)	1290 (23·2%)
1–3 times a month	15 645 (10·9%)	6956 (10·1%)	7957 (11·6%)	732 (13·2%)
Special occasions only	15 076 (10·5%)	5816 (8·4%)	8139 (11·9%)	1121 (20·1%)
Never	10 285 (7·2%)	3705 (5·4%)	5569 (8·1%)	1011 (18·2%)
Red meat intake, portions per week	1·5 (1·5–2·5)	2·0 (1·5–2·5)	2·0 (1·5–2·5)	1·5 (1·5–2·5)
Processed meat intake, portions per week	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–3·0)
Fruit and vegetable intake, g per day	337·5 (193·5)	341·2 (189·5)	334·6 (195·8)	327·7 (213·7)
Smoking status				
Never	78 961 (55·1%)	38 956 (56·3%)	37 251 (54·4%)	2754 (49·5%)
Previous	50 323 (35·1%)	24 108 (34·9%)	24 275 (35·4%)	1940 (34·9%)
Current	13 931 (9·7%)	6086 (8·8%)	6974 (10·2%)	871 (15·7%)

(Table 1 continues on next page)

	Whole population	Non-frail	Pre-frail	Frail
(Continued from previous page)				
Sleep time				
Normal	106 894 (74·6%)	53 859 (77·9%)	49 708 (72·6%)	3327 (59·8%)
Long or short	35 947 (25·1%)	15 184 (21·9%)	18 565 (27·1%)	2198 (39·5%)
Do not know or prefer not to answer	374 (0·3%)	107 (0·2%)	227 (0·3%)	40 (0·7%)
Social activities				
Sports club or gym	34 635 (24·2%)	27 109 (39·2%)	19 421 (28·4%)	873 (15·7%)
Pub or social club	37 702 (26·3%)	12 235 (17·7%)	13 263 (19·4%)	1116 (20·1%)
Religious group	15 645 (10·9%)	5022 (7·3%)	6721 (9·8%)	777 (14·0%)
Adult education class	15 076 (10·5%)	1839 (2·7%)	2094 (3·1%)	178 (3·2%)
Another group activity	10 285 (7·2%)	5831 (8·4%)	6461 (9·4%)	473 (8·5%)
None of the above	29 872 (20·9%)	17 114 (24·7%)	20 540 (30·0%)	2148 (38·6%)
Frequency of friend or family visits				
Almost daily	17 384 (12·1%)	7942 (11·5%)	8577 (12·5%)	865 (15·5%)
2–4 times a week	45 111 (31·5%)	22 229 (32·1%)	21 210 (31·0%)	1672 (30·0%)
About once a week	50 862 (35·5%)	25 048 (36·2%)	24 025 (35·1%)	1789 (32·1%)
About once a month	18 387 (12·8%)	8853 (12·8%)	8905 (13·0%)	629 (11·3%)
Once every few months	8929 (6·2%)	4119 (6·0%)	4411 (6·4%)	399 (7·2%)
Never or almost never	1869 (1·3%)	724 (1·0%)	998 (1·5%)	147 (2·6%)
No friends or family outside household	259 (0·2%)	73 (0·1%)	154 (0·2%)	32 (0·6%)
Do not know or prefer not to answer	414 (0·3%)	162 (0·2%)	220 (0·3%)	32 (0·6%)
Health status				
Multimorbidity				
None	50 278 (35·1%)	28 473 (41·2%)	21 117 (30·8%)	688 (12·4%)
One or more conditions	92 937 (64·9%)	40 677 (58·8%)	47 383 (69·2%)	4877 (87·6%)
Reaction time, ms	721·6 (119·6)	714·1 (112·0)	726·9 (123·5)	750·4 (151·7)
Total cholesterol, mmol/L	5·7 (1·1)	5·8 (1·1)	5·7 (1·2)	5·4 (1·2)
HbA_{1c}, mmol/L	35·9 (6·5)	35·3 (5·3)	36·3 (7·0)	39·3 (10·7)
Systolic blood pressure, mm Hg	138·0 (18·6)	138·3 (18·7)	137·8 (18·5)	136·7 (18·6)
Diastolic blood pressure, mm Hg	82·3 (10·1)	82·4 (10·1)	82·2 (10·1)	81·6 (10·3)

Data are n (%), median (IQR), or mean (SD). Percentages might not add to 100% due to rounding. BMI=body-mass index. MET-h=metabolic equivalents. HbA_{1c}=glycated haemoglobin A_{1c}.

Table 1: **Baseline characteristics by frailty category**

intake, and consumption of red meat, processed meat, and fruit and vegetables) and BMI; and model 3 additionally included morbidity count (based on 43 diseases and coded as 1, 2, 3, 4, or ≥5; appendix pp 3–4), vascular factors (blood pressure, total cholesterol, and HbA_{1c}), and reaction time (log-transformed to avoid the effect of outliers) at baseline. Model 4 was run only for the analyses of the five individual components of frailty and included mutual adjustment for the other four components of frailty. Percentage risk difference across models was estimated using the formula: $(HR_{model\ 2} - HR_{model\ 1})/(HR_{model\ 1} - 1) \times 100\%$.

The cumulative crude hazard rate of incident dementia and the frailty phenotype by age was estimated using the Nelson-Aalen estimator. The rate advancement period was also estimated, defined as the number of additional chronologic years that would be required to yield the equivalent risk rate for dementia incidence among the frailty phenotype and its individual components. For its estimation, the logarithm HR for incidence of the frailty phenotype and its individual components was divided by the corresponding incidence associated with each yearly increase in age—eg, $\log(HR_{frail})$ divided by $\log(HR_{age})$.[19] Additionally, the population attributable fraction was estimated to calculate the proportion of dementia incident cases that were attributable to both the frailty phenotype (pre-frail and frail) and its individual components, assuming causality. This population attributable fraction was estimated on the basis of the adjusted HR derived from model 3 and prevalence in the sample.

Finally, to investigate whether the associations between frailty and incident dementia differed by subgroups, the models were run stratified by sex, age category (<60 and ≥60 years), deprivation index (below and above median), level of adiposity (normal and overweight or obese), sleep pattern (normal and long or short sleep duration), morbidity count (none and one or more) and smoking status (never and previous or current). A further sensitivity analysis was done in which age was stratified with 65 years as the cutoff.

	Pre-frail (n=68 500)			Frail (n=5565)		
	HR (95% CI)	p value	Risk difference from model 1, %	HR (95% CI)	p value	Risk difference from model 1, %
Model 1	1·20 (1·03–1·40)	0·019	..	2·08 (1·57–2·76)	<0·0001	..
Model 2	1·24 (1·06–1·45)	0·0060	20·0%	2·20 (1·64–2·94)	<0·0001	11·1%
Model 3	1·21 (1·04–1·42)	0·016	5·0%	1·98 (1·47–2·67)	<0·0001	−9·3%

Total number of participants was 143 103; 726 events (incident dementia) occurred. Dementia incidence was estimated using primary care data. Non-frail people were used as the reference group. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline.

Table 2: **Associations between frailty and dementia incidence**

	HR (95% CI)	p value
Weight loss		
Model 1	1·36 (1·13–1·64)	0·0010
Model 2	1·34 (1·11–1·61)	0·0020
Model 3	1·31 (1·09–1·58)	0·0040
Model 4	1·31 (1·09–1·58)	0·0050
Tiredness or lack of energy		
Model 1	1·61 (1·30–2·01)	<0·0001
Model 2	1·60 (1·28–1·99)	<0·0001
Model 3	1·48 (1·18–1·86)	0·0010
Model 4	1·39 (1·10–1·74)	0·0050
Low physical activity levels		
Model 1	0·95 (0·79–1·14)	0·56
Model 2	0·98 (0·82–1·18)	0·84
Model 3	0·97 (0·80–1·16)	0·73
Model 4	0·93 (0·78–1·12)	0·48
Low grip strength		
Model 1	1·39 (1·18–1·63)	<0·0001
Model 2	1·44 (1·22–1·69)	<0·0001
Model 3	1·38 (1·17–1·63)	<0·0001
Model 4	1·34 (1·13–1·58)	0·0010
Slow gait speed		
Model 1	1·62 (1·30–2·03)	<0·0001
Model 2	1·72 (1·36–2·16)	<0·0001
Model 3	1·55 (1·22–1·96)	<0·0001
Model 4	1·41 (1·10–1·79)	0·0060

Total number of participants was 143 103; 726 events (incident dementia) occurred. Participants with a normal range for each component was used as the reference group. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline; model 4 additionally included the five individual components when these were not the exposure (sensitivity analysis).

Table 3: **Individual components of frailty and their association with all-cause dementia incidence**

Role of the funding source

There was no funding source for this study. FP-R, FKH, JPP, and CC-M had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 502 535 participants in UK Biobank, 228 640 had data available for dementia incidence, of whom 143 259 had data available for the frailty components and covariates. 44 of these participants had dementia at baseline and were excluded. Therefore, this prospective study included 143 215 participants (figure 1). After excluding the 2-year landmark period, the median follow-up period was 5·4 years (IQR 4·8–6·3) for dementia incidence. Over the follow-up period, 726 (0·5%) of the participants developed dementia.

Cohort characteristics by overall frailty phenotype are presented in table 1; characteristics by individual frailty component are presented in the appendix (pp 5–7). 69 150 (48·3%) of 143 215 participants were in the normal range for all five components; 51 047 (35·6%) had at least one frailty component, and 102 (0·1%) had all components. Of those who had one or more components, 68 500 (47·8%) were classified as pre-frail and 5565 (3·9%) as frail. Compared with non-frail people, those with frailty were more likely to be older, more deprived, more likely to be south Asian, female, obese, and a current smoker, and to report that they never drank alcohol. They were less likely to have a formal education, to take part in social activities, and to have visits from friends or family outside the household. They also had lower levels of physical activity and slower reaction times than non-frail individuals. Lastly, individuals with pre-frailty and frailty were more likely to have long or short sleep, higher levels of HbA_{1c}, and one or more morbidities than non-frail individuals (table 1).

Associations between the frailty phenotype and dementia incidence are shown in table 2. In the minimally adjusted model, individuals with pre-frailty (HR 1·20 [95% CI 1·03–1·40]) and frailty (2·08 [1·57–2·76]) had an increased risk of incident dementia compared with non-frail individuals. The magnitude of these associations was slightly higher if the model was further adjusted for lifestyle factors and BMI (model 2; 20·0% higher risk for pre-frailty and 11·1% higher risk for frailty). However, the associations were attenuated after adjusting for morbidity count and health-related factors (model 3; 1·21 [1·04–1·42] for pre-frailty and 1·98 [1·47–2·67] for frailty). Individuals with frailty had a steeper crude cumulative incidence of dementia compared with non-frail individuals (appendix p 9). When the analyses were stratified by the subtypes of dementia (vascular dementia, non-specific dementia, and Alzheimer's disease), pre-frailty and frailty were

associated with vascular dementia (model 3; 1·70 [1·10–2·62] for pre-frailty, 3·00 [1·54–5·82] for frailty) but not non-specific dementia or Alzheimer's disease (appendix p 10).

Of the five components used to define frailty, weight loss (HR 1·31 [95% CI 1·09–1·58]), tiredness (1·48 [1·18–1·86]), low grip strength (1·38 [1·17–1·63]), and slow gait speed (1·55 [1·22–1·96]) were independently associated with the risk of dementia incidence (model 3; table 3). When the analyses were mutually adjusted by components of frailty (model 4), the associations were attenuated but remained significant. Although we found no evidence of a non-linear association between the number of frailty components and logarithm risk of dementia incidence, the risk for dementia incidence increased markedly for individuals who had two to five components of the frailty phenotype. The hazard for dementia incidence was two-times higher for individuals with five components of the frailty criteria compared with those with none (figure 2, lower panel).

When the analyses were stratified by subgroup, no significant interactions were identified for pre-frailty and dementia incidence (figure 3). However, a significant interaction between frailty and age was observed (p=0·0050); individuals with frailty aged younger than 60 years had an increased risk of dementia incidence compared with those aged 60 years and older (figure 3). When the analyses were performed using a cutoff of 65 years, the associations were attenuated, but a similar pattern of association was observed (appendix p 11).

Based on population attributable fraction analyses, pre-frailty accounted for 9·90% (95% CI 1·61–17·5) of dementia cases and frailty accounted for 8·55% (3·83–13·00; table 4). Among the five individual components, low grip strength had the highest population attributable fraction compared with the other individual components, accounting for 8·84% (3·99–13·40) of incident dementia cases. Based on rate advancement period analyses, individuals with frailty are likely to experience dementia 3·58 years (95% CI 2·33–4·74) earlier than non-frail individuals. Among the frailty components, individuals with slow gait speed have the largest rate advancement (2·3 years [1·20–3·25] before those with normal gait speed).

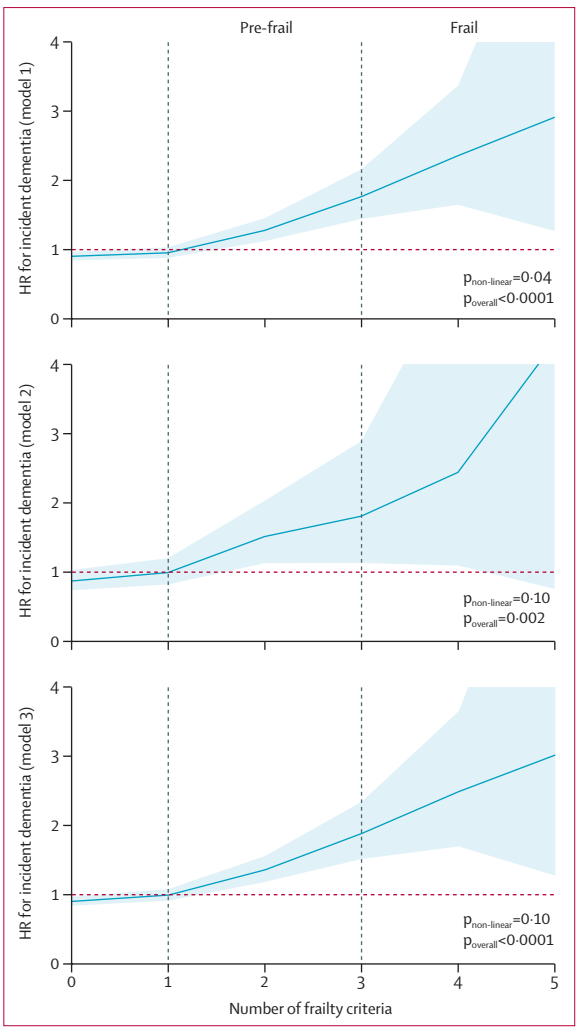

***Figure 2*: Non-linear associations between number of individual components of the frailty phenotype and dementia incidence**
Data are presented as adjusted HR with the 95% CI shown as shading. Non-frail people were used as the reference group. Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline. HR=hazard ratio.

Discussion

In this study, using data from 143 215 participants from UK Biobank, we identified that individuals with pre-frailty and frailty were at a higher risk of dementia incidence compared with non-frail individuals, even after adjusting for a wide range of confounding factors, including sociodemographic factors, lifestyle factors, adiposity, morbidity count, and health-related markers. Furthermore, pre-frailty and frailty accounted for 9·9% and 8·6% of dementia cases in the study sample, respectively. Pre-frailty accounts for a greater proportion of dementia cases than frailty because of the higher prevalence of pre-frailty compared with frailty in UK Biobank. Participants with pre-frailty could also be at a milder stage of dementia,[20] which warrants further investigation. Considering that frailty might be a reversible syndrome and that dementia is not part of the natural ageing process, the burden of dementia-related morbidity attributable to frailty might be modifiable by delaying its onset. Therefore, public strategies aiming to improve physical capabilities, especially those related to muscle strength in middle-aged and older adults, might contribute to reducing the burden of frailty and, as a consequence, reduce the dementia risk attributable to frailty.

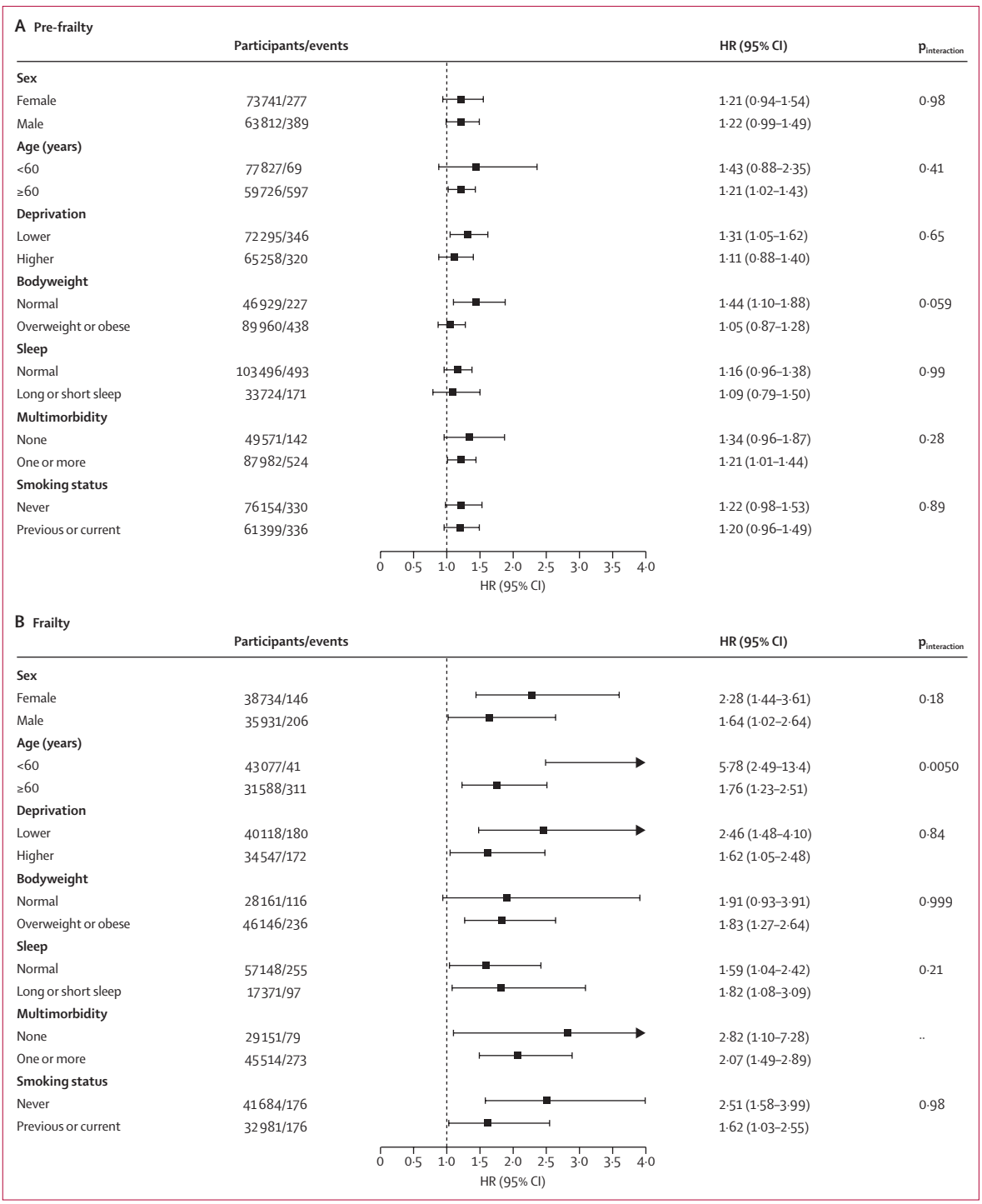

Figure 3: **Associations between all-cause dementia incidence and pre-frailty (A) and frailty (B) by subgroup**
Non-frail people were used as the reference group for each subgroup. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Analyses were adjusted by age, sex, deprivation, ethnicity, education, morbidity count, blood pressure, total cholesterol, glycated haemoglobin A_{1c}, reaction time, body-mass index, leisure or social activities, frequency of friend or family visits, smoking, total discretionary sedentary time, sleep duration, and consumption of alcohol, red meat, processed meat, and fruit and vegetables, when these were not the subgroups used. No $p_{interaction}$ is given for multimorbity because there was not enough power to test for this interaction. HR=hazard ratio.

The associations between dementia and frailty have been previously reported using both multidimensional models (eg, the frailty index),[9] and, as in our study, using the frailty phenotype. However, most studies have used smaller sample sizes and had older populations, in which the risk of dementia could be higher due to the age of the population rather than the frailty status. For instance, Gray and colleagues,[8] who studied 2619 adults older than 65 years, showed that frailty, but not pre-frailty, was associated with a 1·78-times increased risk of incident dementia and a 4·46-times risk of non-Alzheimer dementia, compared with non-frail individuals. These associations were attenuated when the analyses were further adjusted for BMI and health status, and remained significant only for non-Alzheimer's dementia in the maximally adjusted model.[8] Similarly, a study of 2581 Italian adults aged 65–84 years identified that, using the frailty phenotype, individuals with frailty were associated with a 1·85-times risk of overall incident dementia and 2·68-times risk of vascular dementia.[7] In the UK, a dose-response relationship between a frailty index (multidimensional model) and dementia was identified in 8722 older adults from the English Longitudinal Study of Ageing (ELSA).[9] Findings from ELSA were similar to those in our study; individuals who were pre-frail had a 1·60-times increased risk of dementia and individuals who were frail had a 1·60-times increased risk, compared with non-frail individuals. However, in ELSA, dementia cases were self-reported and not clinically diagnosed.[9]

Frailty and dementia are strongly related and share similar common risk factors, such as sociodemographic factors (eg, age and deprivation), morbidities, and lifestyle factors.[21] Of note, in our study, individuals with pre-frailty and frailty with lower levels of deprivation had a higher risk of dementia compared with their counterparts with greater deprivation. This result is discordant with the findings of ELSA, in which individuals who were more deprived (in the lowest quintile) had a 1·68-times increased risk of dementia compared with the least deprived (highest quintile).[22] Individuals with pre-frailty and frailty who are more deprived might have higher resilience than those who are less deprived, allowing for better adaptation or managing of stress situations, trauma, or inequalities.[23] More studies are needed to evaluate the role of deprivation in frailty and dementia. Previous studies have identified that a dysregulation through multiple biological systems is a potential cause for both frailty and dementia.[24] This dysregulation might be caused by the presence of comorbidities, which contribute to both frailty and dementia. However, in our study, an association between frailty and dementia outcomes remained after adjusting for morbidity count, suggesting that the association is not merely the result of confounders.

Consistent with our results, low grip strength and slow gait speed or balance and gait impairment have been attributed to a worse cognitive condition among people with frailty.[21] Previous studies have shown that both gait speed and grip strength could be independent early markers of dementia,[13] and that these two components of frailty are the most strongly associated with cognitive impairment related to frailty.[14] Some of the potential mechanisms implicated are neurodegeneration (which contributes to both dementia and the decrease of physical capability markers); inflammation, described as an increment of pro-inflammatory markers; vascular mechanisms, related to microdamage mainly in the frontal-subcortical region; or a shared brain region (ie, gait speed and cognition could rely on a similar region).[13] Of note, in our study, the strongest association was between frailty and vascular dementia, which highlights that stroke, cerebrovascular disease, or both, could be one of the mechanisms.[25] Additionally, frailty is associated with a reduction in the leisure and social activities that contribute to the wellbeing and life satisfaction of individuals.[26] This lower social interaction could increase the risk of dementia, as has been previously shown.[27]

The assessment and surveillance of frailty could help to decrease its associated adverse health outcomes, including dementia. Of note, according to our rate advancement period analyses, individuals with frailty could experience dementia approximately 3 years earlier than non-frail individuals. However, frailty is not routinely assessed in clinical practice. A multicentre study of 388 clinicians (mainly medical doctors) from 44 countries showed that only 52·8% routinely assessed frailty in daily practice.[28] The assessment rate was higher among geriatricians than other medical specialties,[28] consistent with frailty being normally associated with ageing. However, its development begins earlier in life, and an association between frailty and cognition has been recognised independent of age.[29] Although in our study, only older individuals with pre-frailty had a higher risk of dementia compared with non-frail individuals, individuals with frailty younger than 60 years had

	Population attributable fraction, % (95% CI)	Rate advancement period, years (95% CI)
Weight loss	4·54% (1·08 to 7·88)	1·42 (0·50 to 2·21)
Tiredness	4·27% (1·50 to 6·96)	2·06 (0·95 to 3·00)
Low physical activity	–0·65% (–4·36 to 2·93)	–0·16 (–1·28 to 0·72)
Low grip strength	8·84% (3·99 to 13·40)	1·77 (0·95 to 2·46)
Slow gait speed	4·48% (1·67 to 7·21)	2·30 (1·20 to 3·25)
Pre-frailty	9·90% (1·61 to 17·50)	1·00 (0·24 to 1·69)
Frailty	8·55% (3·83 to 13·00)	3·58 (2·33 to 4·74)

All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Analyses were adjusted by age, sex, deprivation, ethnicity, education, morbidity count, blood pressure, total cholesterol, glycated haemoglobin A_{1c}, reaction time, body-mass index, leisure or social activities, frequency of friend or family visits, smoking, total discretionary sedentary time, sleep duration, and consumption of alcohol, red meat, processed meat, and fruit and vegetables (model 3).

Table 4: **Population attributable fraction and rate advancement periods of incident dementia attributable to frailty and its components**

a 5·78-times increased risk of incident dementia compared with a 1·76-times increased risk among those aged 60 years and older. This finding highlights the association between frailty and dementia as modified by age, and also shows that the onset of frailty could start much earlier in life. Therefore, our study provides novel evidence regarding the association between frailty and dementia incidence, not only in older adults as has been previously shown, but also in middle-aged adults. These findings are supported by a study by Gil-Salcedo and colleagues,[30] which showed that a healthier lifestyle (eg, not smoking, moderate alcohol consumption, 2·5 hours per week of physical activity) during the middle age (at 50 years) of participants from the UK Whitehall II cohort was associated with a lower risk of frailty during 20 years of follow-up. In this context, considering that previous studies have shown that frailty might be reversed with exercise interventions in some older adults,[31] early assessment and interventions from middle age should be implemented among the general population to prevent frailty, and consequently, reduce the risk of dementia. However, further studies in the field are still needed.

For more on **applying for access to UK Biobank data** see http://www.ukbiobank.ac.uk

UK Biobank is a large, prospective, general population cohort with data available on a wide range of potential confounders and health outcomes. As a result, our analyses could be adjusted for multiple confounders and stratified by different subgroups. However, UK Biobank participants are not representative of the UK population because they are more likely to have healthier behaviours than the general UK population;[32] therefore, the summary statistics should not be generalised even though the effect sizes estimated from UK Biobank were generally consistent with those from population-representative cohorts. In addition, the frailty phenotype was created using similar but not identical variables to those suggested by Fried and colleagues,[5] and four of the five variables were self-reported. Furthermore, the frailty phenotype was derived from baseline UK Biobank data, and these data could have changed over time. Our analysis might have underestimated the associations because frailty might not develop until older age for some people. Although we were able to adjust our model for one cognitive test, UK Biobank does not have other cognitive measurements, such as the Mini-Mental State Examination or the Instrumental Activities of Daily Living. Therefore, residual confounding might have occurred due to baseline cognitive ability, which could overestimate the association. Similarly, our study did not adjust for apolipoprotein E polymorphism, a major risk factor for dementia. However, a previous study found no association between apolipoprotein E polymorphism and frailty.[33] Additionally, we note that our sample might not have sufficient power for dementia subtype analysis. Finally, although we performed a 2-year landmark analysis excluding participants who experienced events in the first 2 years after recruitment, reverse causality is possible in any observational study.

In conclusion, frailty (both the pre-frail and frail status) was associated with a higher risk of dementia incidence. Furthermore, among the five components used to define frailty in this study, slow gait speed and low grip strength made the largest contributions to dementia incidence. Considering that frailty is a modifiable syndrome in middle age, its early detection and treatment might represent a target for prevention or delayed onset of neurodegenerative diseases, including dementia.

Contributors

FP-R, FKH, JPP, and CC-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. FP-R did the literature search. FP-R did the analyses with support from FKH, JPP, and CC-M. All authors critically reviewed previous drafts. All authors approved the final draft for submission. CC-M is the guarantor.

Declaration of interests

We declare no competing interests.

Data sharing

Applications for access to UK Biobank data can be made online.

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