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Protein intake and transitions between frailty states in middle-aged and older adults: a multi-state transition model in the UK Biobank

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Abstract

Background Dietary protein may prevent or modulate the progression of frailty, by slowing down the decline of muscle mass, strength, and physical function with ageing. We aimed to examine the association between higher protein intake and transitions between frailty states.

Methods The analytic sample included 27,128 participants aged 50 + from the UK Biobank cohort study. Physical frailty at baseline and follow-up was based on slow walking speed, unintentional weight loss, exhaustion, low physical activity, and weakness. Protein intake was assessed with web-based 24 h recalls on up to 5 occasions. The effect of protein intake on forward and backward transitions (and maintenance) between frailty states (non-frailty, pre-frailty, and frailty) and to death over a mean of 5 (max 16) years was examined with multi-state models.

Results There were 5646 transitions from non-frail to pre-frail, 4187 from pre-frail to non-frail, 552 from pre-frail to frail, and 311 from frail to pre-frail. Middle-aged and older participants with higher protein intake (increments of 0.1 g/kg bodyweight/day and protein categories of < 0.8 (ref), 0.8 to < 1.0, 1.0 to < 1.2, ≥ 1.2 g/kg bodyweight/day) were less likely to progress from pre-frailty to frailty, and appeared to be more likely to recover from pre-frailty to non-frailty, with evidence of a dose-dependent relationship. E.g. For participants with protein intake of 0.8 to < 1.0, 1.0 to < 1.2 and ≥ 1.2, hazard ratios (95%CI) for incident frailty were 0.80 (0.71–0.91), 0.72 (0.63–0.81) and 0.68 (0.60–0.78), respectively, compared to < 0.8 g/kg bodyweight/day. Higher protein intake had no effect on recovery from frailty to pre-frailty.

Conclusions Higher protein intake moderately reduced the risk for frailty incidence and may have increased the likelihood of recovery from pre-frailty in a dose-dependent manner in middle-aged and older adults. These findings may optimize strategies to prevent frailty in middle-aged and older adults and inform dietary protein guidelines in this population.

Keywords Frailty, Protein, Ageing, Transitions, Cohort

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Background

Higher life expectancy, lower mortality, and declining fertility rates mean that over one fifth of Europeans are now 65+, and the 80+age group will nearly triple by the end of the century [1]. However, the increase in healthy life years, the number of years an individual can expect to live without an activity limitation, has not kept pace. For example, European men and women spend, on average, 16 and 21 years, respectively, living with a long-term functional limitation and/or disability [2]. Maximising the healthy life years is of special interest; not only to increase quality of life, but also to relieve the immense strain on the European healthcare systems. Frailty is a clinically recognisable dynamic state of reduced reserves and increased vulnerability to stressors, increasing the risk of dependency, hospitalisation and mortality [3]. Pre-frailty is an intermediate prodromal state between non-frailty and frailty that increases the risk to progress to frailty [4]. Physical pre-frailty and frailty are estimated to be present in 42 and 8% of European community-dwelling adults aged 50+, respectively; a prevalence that increases with age and for institutional settings [4]. Besides a multicomponent physical activity programme, better management of chronic diseases and deprescription of unnecessary medication, dietary interventions hold promise in the prevention or even, in some instances, recovery from frailty [5]. Specifically, dietary protein may be a sensible candidate to prevent or modulate the progression of frailty, by slowing down the decline of muscle mass, strength and physical function with ageing [6–8]. We have previously shown that very old adults (85+) with higher protein intake were less likely to progress from pre-frailty to frailty but not for other transitions [9]. The limited number of transitions over 5 years in the Newcastle 85+Study, namely from non-frailty to pre-frailty, may explain the negative findings for other transitions. Therefore, we aimed to provide robust estimates of the impact of protein intake on transitions to and from frailty states (non-frail, pre-frail and frail) and to death in middle-aged and older adults, and address the shortcomings of previous research by using a healthier and larger prospective cohort (UK Biobank) with thousands of transitions over time.

Methods

Population and study design

The UK Biobank is one of the largest and most extensively phenotyped population-based prospective cohort studies globally. It recruited 502,536 participants aged 37 to 73 years between 2006 and 2010, with a response rate of 5.5%. Participants attended one of the 22 assessment centres across England, Wales and Scotland, and data on sociodemographic characteristics, self-reported behaviours and health were collected, as well as its linkage to electronic health records. A subsample of participants was followed in 2012–2013 (follow-up 1), 2014 and onwards (first imaging visit or follow-up 2), and in 2019 and onwards (repeat imaging visit or follow-up 3) (Fig. 1). Data were downloaded on the 7th of December of 2023. Details on UK Biobank protocols and assessments have been published elsewhere [10].

Exclusion criteria and analytic sample

The analytic sample included adults aged 50 or older who had frailty state ascertainment and at least one transition between two frailty states or a transition between one frailty state and a death state, or maintenance in the same frailty state. Participants were included if they had data on protein intake (g/kg bodyweight/day), provided two or more 24-h dietary recalls, and had dietary energy intake between > 500 kcal/day and < 4780 kcal/day for men or < 4302 kcal/day for women (Fig. 1) (energy intakes outside of this interval were considered implausible [11, 12]).

Frailty

There was a median (IQR) of 4.4 (3.6–4.9), 4.7 (2.9–6.3) and 2.3 (2.2–5.0) years between baseline and 1st follow-up, between the 1st and the 2nd follow-up, and between the 2nd and the 3rd follow-up, respectively. Data collection/ observation times were assumed to be non-informative for the frailty process as these followed a predefined schedule. Physical frailty or Fried frailty phenotype was derived for each available timepoint (2006–2010, 2012–2013, 2014+and 2019+) from adaptations of the Cardiovascular Health Study [13] like previous approaches in the UK Biobank [14, 15]. The physical frailty phenotype was based on five criteria: slow walking speed, unintentional weight loss, exhaustion, low physical activity, and weakness. A frailty score was calculated by scoring (1)

(See figure on next page.)

Fig. 1 Recruitment centres and flowchart for the analytic sample. Recruitment centres in the UK Biobank, and flowchart with the exclusion criteria, analytic sample, and follow-up. Population images are proportional to the number of participants recruited on that site (rough UK geographical areas). The analytic sample is the baseline for this study's purposes, as 446 participants did not have a frailty state at UK Biobank's baseline but had it during the first follow-up. Follow-up 2 was the first imaging visit with data collected from 2014 onwards. Follow-up 3 was the repeat imaging visit with data collected in 2019 and onwards. Not all participants who participated in follow-up 2, participated in follow-up 1

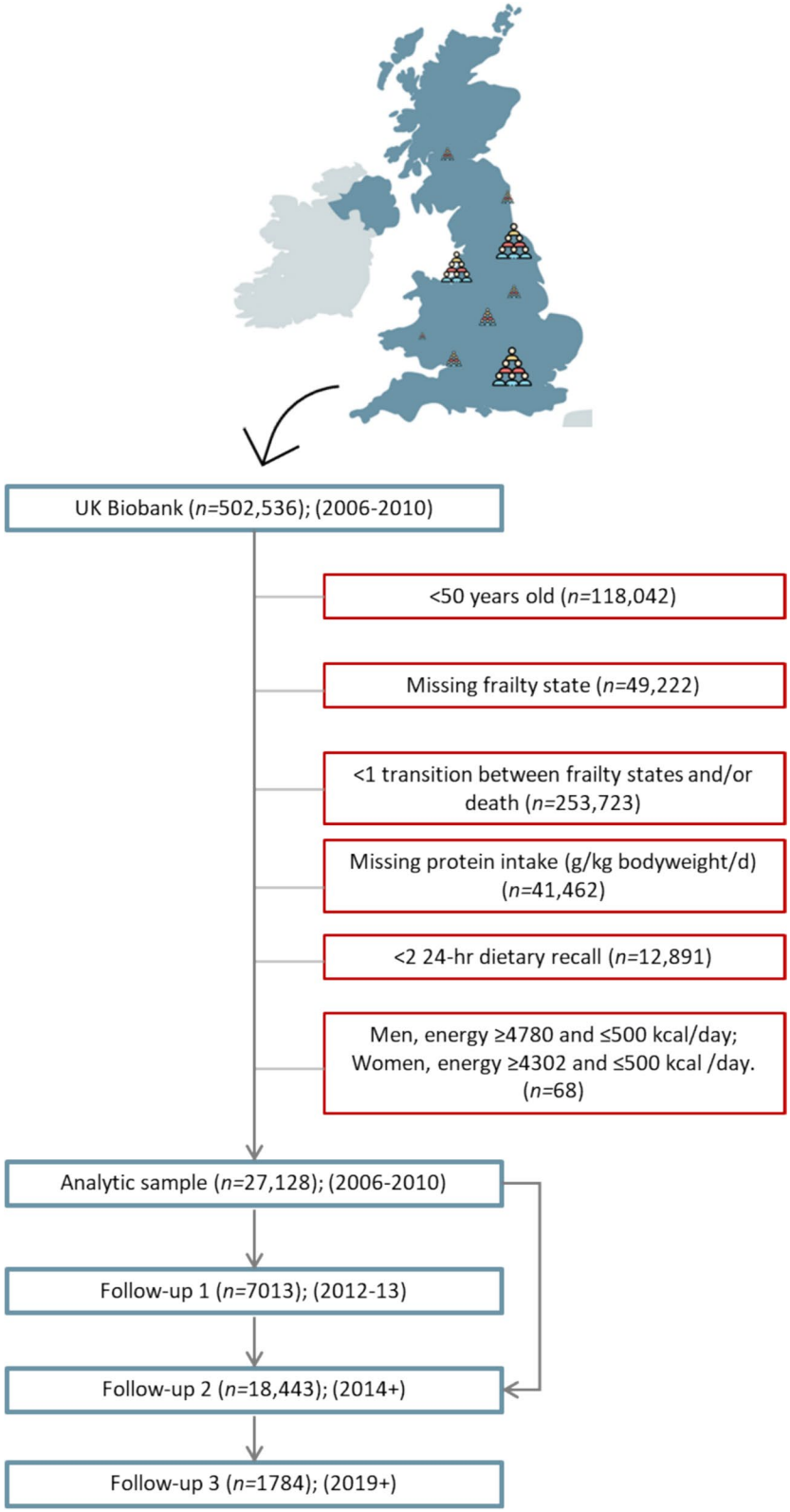

Fig. 1 (See legend on previous page.)

for every criteria that was present and (0) if absent (range 0–5). The number of criteria met indicated the severity of frailty. Participants with a score of zero were defined as non-frail; with 1 to 2 as pre-frail; and with ≥ 3 criteria as frail. Participants with a total score of 1 and only one criteria missing were still defined as pre-frail (possible minimum score of 1 and maximum of 2), and participants with a total score of ≥ 3 but one or two missing criteria were still defined as frail (possible minimum score of 3 and maximum of 5). Briefly, walking speed was categorised as slow or normal (steady average or brisk) based on self-reported walking pace; unintentional weight loss was derived from self-reported weight change in the past year (intentional or unintentional); exhaustion was defined as feeling tired or having little energy in the past two weeks nearly every day or more than half the days; low physical activity was defined from an adapted international physical activity questionnaire covering frequency, duration and intensity of walking, as well as moderate and vigorous activities [16, 17]; and weakness was defined by measured grip strength below sex and body mass index (BMI)-specific cut-offs. Grip strength was measured on both arms by a calibrated Jamar J00105 hydraulic hand dynamometer, and the higher of the two was used. More details are shown in Additional file 1: Table S1.

Frailty state transitions

Participants were categorized into three frailty states, i.e., non-frail, pre-frail, and frail (transient states), and death (absorbing state as there is no recovery from this state), at each data collection timepoint (2006–2010, 2012–2013, 2014 + and 2019 +). If death had not occurred, participant's final observation was censored as they were only known to be alive at that point. The frailty states were unknown between timepoints and were therefore interval censored. From one timepoint to another, participants could either, remain in the same frailty state (maintenance), move forward/progress (non-frail → pre-frail AND pre-frail → frail) or backward/recover (pre-frail → non-frail AND frail → pre-frail) to/from any immediately adjacent state over the follow-up, or move to the absorbing state, death (non-frail → death AND pre-frail → death AND frail → death). Figure 2A shows the allowed transitions (and maintenance) between frailty states and death over time.

One additional assumption is that participants cannot skip a state in the process. It is however possible, e.g. that participants non-frail at the beginning of an interval were directly frail at the end. In these cases, the model implicitly considered that these participants transited through pre-frailty during the interval, even if it had not been recorded.

Mortality

Date of death was of interest as the absorbing state in the frailty transitions. Moreover, failure to account for mortality in an ageing cohort might result in biased estimates. Date of death was provided as part of the available UK Biobank dataset that uses linkage with death certificates held by the National Health Service (NHS) Information Centre for England and Wales, and the NHS Central Register for Scotland. At the time of analysis, mortality data were available up to 19th December 2022. Participants were censored at date of death or this date, whichever came first.

Dietary assessment

Dietary information was collected using the Oxford WebQ, a validated web-based 24 h recall questionnaire used in large population studies to record the consumption of 200 + food and beverages in the previous 24 h [18]. UK Biobank participants were invited to complete the Oxford WebQ on five distinct occasions between 2011–2012. Nutrient intake was estimated using the McCance and Widdowson's Composition of Foods and the mean of all available recalls used [19]. The exposure, protein intake, was expressed as g/kg bodyweight (BW)/day and categorised into < 0.8, 0.8 to < 1.0, 1.0 to < 1.2, and ≥ 1.2 g/kg BW/day. These categories were based on expert recommendations for optimal protein intake [20, 21], on currently used recommended dietary allowances (RDAs) for protein (e.g. ≥ 0.8 is the European Food Safety Authority [22] and the Institute of Medicine's RDA [23], ≥ 1.0 is recommended by the European DACH countries [24] and ≥ 1.2 by the European Nordic countries [25]), and on previously published studies on protein intake in older adults conducted by our group [6, 7, 9, 26–30]. Percentage of energy from protein, carbohydrates and fat was calculated using the general Atwater factors of 17, 17, and 37 kj/g [31]. Energy intake was expressed in kcal/day by diving kj/day by 4.184.

Covariates

The highest education attainment (GCSE/CSE or equivalent, A/AS levels or equivalent, NVQ/HNC or equivalent, Other professional, University/ college degree) was recorded and further transformed into years of full-time education according to the International Standard Classification for Education (ISCED) definition. Self-reported age, sex (men, women), ethnicity (white, non-white), average total household income before tax (< £18,000, £18,000 to 30,999, £31,000 to 51,999, £52,000 to 100,000, > £100,000), smoking status (never, previous, current) and self-rated health (poor, fair, good, excellent)

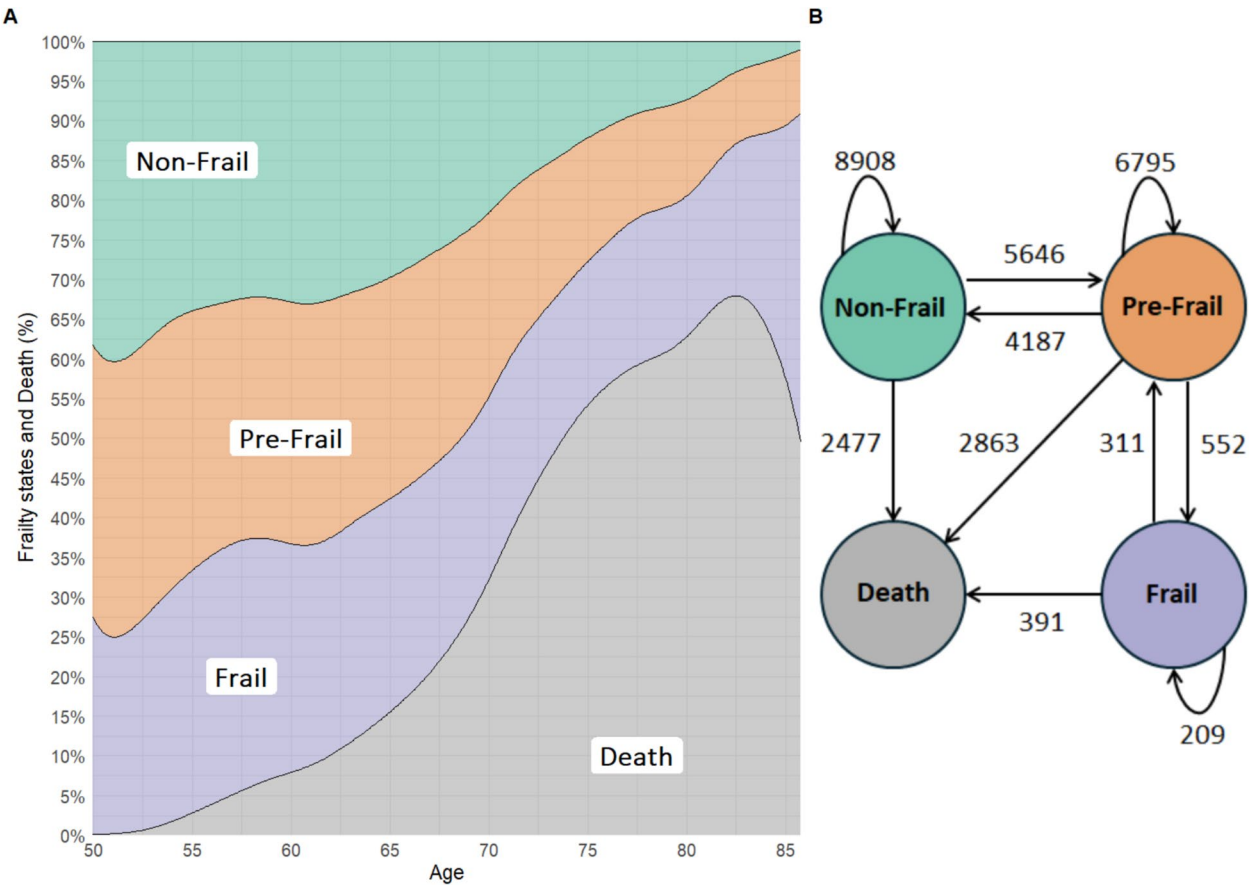

Fig. 2 Prevalence by age, and transitions between frailty states and death over time. **A** Proportional frailty state and death occupancy by age (stacked) excluding censoring over time. These estimates are not derived from the multistate models and are simply descriptive. **B** Allowed transitions between frailty states (non-frail, pre-frail, and frail) and death and the corresponding transitions for the multistate model. There were 8743 transitions from non-frailty, 7634 from pre-frailty and 493 from frailty to censoring (not depicted)

were recorded. Height and weight were collected when participants attended the assessment centre and measured to the nearest 0.1 cm (or 0.5 or 1 cm depending on the study centre) and 0.1 kg, respectively. BMI was calculated as weight/height^2. Waist circumference was measured at the natural indent or umbilicus, hip circumference at the widest point of the hip, and waist-hip ratio was calculated as waist circumference/hip circumference. Self-reported diseases, including a range of diseases such as stroke, hypertension, chronic liver disease, diabetes, chronic bronchitis, asthma and cancer were recorded during the touchscreen questionnaire and confirmed with a trained nurse during the verbal interview [32]. Multimorbidity was defined as having 2 or more self-reported chronic illnesses and polypharmacy as using 5 or more medications [33].

Statistical analyses

Normality was assessed by Q-Q plots. Non-Gaussian distributed variables are presented as medians (50th percentile) and interquartile ranges (25th-75th percentile), and categorical data as percentages (with corresponding frequency). To partly assess selection bias, baseline characteristics between the included (analytic sample) and excluded participants were compared (Additional file 1: Table S2). To determine the number of transitions (and maintenance) between adjacent frailty states and to death the *state.msm* function of the *msm* package in R v4.1.2 was used [34]. Maintenance was modelled alongside forward and backward frailty state transitions and transitions to death.

To determine the contribution of protein intake (increments of 0.1 or categories of <0.8, 0.8 to <1.0, 1.0 to <1.2, and ≥ 1.2 g/kg of bodyweight/day) to transitions (and maintenance) between frailty states and to death over time, we fitted three multistate Markov models with increasing complexity: Model l only included protein intake (continuous or categorical) and age (time-varying), Model II was further adjusted for sex, years of education, smoking status, and alcohol and energy intake, and

Model III was further adjusted for multimorbidity. Apart from the exposure (protein intake), all continuous variables were centred prior to fitting to aid convergence and improve interpretation of the intercept. These covariates were selected based on their theoretical, clinical and statistical relevance, their position in a directed acyclic graph (Additional file 1: Fig. S1), and previous literature [3, 9, 35–41]. The main resulting output from a multistate model are transition intensities with hazard ratios for transitions between frailty states and death for protein intake and other covariates in the model. The Markov assumption of multistate models is that the next state is only influenced by the current state, i.e. the model has no memory of past state transitions before the current transitions [42, 43]. Age was used as time-varying covariate to partially mitigate possible effects of the assumption. Our multistate model is based on a continuous-time Markov process, which accommodates interval-censored and irregularly spaced observations by allowing transitions to occur at any time between two data collections. Another assumption was that due to the continuous and progressive nature of the frailty syndrome, and the limited number of transitions between non-adjacent frailty states, models were constrained to only allow transitions between adjacent states (and death).

Multistate models were fitted with the *msm* package in R v4.1.2 [34]. The BFGS algorithm (quasi-newton optimization) was used to maximise the likelihood with results presented as hazard ratios and 95% confidence intervals. Mean sojourn times (95%CI delta method) spent in each frailty state before transitioning out to another state (conditional on being in that state at any point in time) were also extracted from the fully adjusted model (Model III). Mean sojourn times were estimated for non-smoking, 60 year-old men or women with protein intake < 0.8 or 0.8 to < 1.0 or 1.0 to < 1.2 or ≥ 1.2 g/kg bodyweight/day. Other covariates from Model III were held at their mean.

Sensitivity analyses

The fully adjusted model (Model III) was re-run further excluding participants with < 1.1 or > 2.5 × the basal metabolic rate, calculated with the Henry equations [44], or excluding participants that considered that none of the 24 h recalls were reflective of a typical diet. Model III was further adjusted for physical activity or BMI or a piecewise constant transition rate from baseline to 2 years and from 2 years onwards to try to account for some of the potential selection bias introduced by the attrition between baseline and the 1st follow-up.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The analytic sample included 27,128 middle-aged and older adults at baseline (Fig. 1) with a mean age of 60.3 (min–max: 50–79) years and very high educational attainment (almost 50% had a university/college degree) (Table 1). Participants in the analytic sample were, on average, 1 year younger than those who were excluded, there were more men, had higher educational attainment, greater household income, less frailty, multimorbidity and polypharmacy, and reported better self-rated health. There were no differences in other characteristics, including dietary intake and body weight (Additional file 1: Table S2).

Participant health and sociodemographic characteristics by protein intake

Among participants with higher protein intake at baseline (< 0.8, 0.8 to < 1.0, 1.0 to < 1.2, ≥ 1.2 g/kg BW/day) there were fewer men, weighted less, had lower BMI, there were fewer frailty and pre-frailty states, and used fewer medications, and more had never smoked and reported better self-rated health. Those with higher protein intake also had higher energy intake, and higher absolute intake of carbohydrates and fat, while the percentage of energy from macronutrients was similar except for protein. The rest of the covariates were similar between protein categories at baseline (Table 1).

Transitions between frailty states and to death over time

The number of forward (non-frail → pre-frail AND pre-frail → frail) and backward transitions (pre-frail → non-frail AND frail → pre-frail), as well as transitions to death (non-frail → death AND pre-frail → death AND frail à death) over a maximum of 16.3 years (mean 4.8 [5.1]) are shown in Fig. 2. Briefly, out of 32,339 allowed transitions there were 19% forward transitions to pre-frailty and frailty, 14% backward transitions from frailty or pre-frailty, and 18% to death from any state ($n = 5731$). Most participants remained in the same frailty state (49%).

Effect of protein intake on transitions

Forward transitions/progression (non-frail → pre-frail AND pre-frail → frail)

An increment of 0.1 g/kg BW/d of protein intake (equivalent to an increment of 7 g of protein for a 70 kg person) slightly decreased the probability of a middle-aged and older adult to transition from non-frail to pre-frail (HR:0.96, 95%CI:0.94–0.98) and from pre-frail to frail

Table 1 Baseline health and sociodemographic characteristics by protein intake (g/kg bodyweight/day)

	Total (*n* = 27,128)	**< 0.8 (*n* = 4351)**	**0.8 to < 1.0 (*n* = 6758)**	**1.0 to < 1.2 (*n* = 7084)**	**≥ 1.2 (*n* = 8935)**	**Missing, % (*n*)**
Age (yrs), median (25th-75th)	60.3 (55.7–64.2)	60.3 (55.5–64.2)	60.5 (56.0–64.2)	60.4 (55.9–64.2)	60.1 (55.5–64.0)	0 (0)
Men, % (*n*)	53.0 (14,379)	64.9 (2823)	60.5 (4088)	52.6 (3724)	41.9 (3744)	0 (0)
Education						0.2 (53)
Years, median (25th-75th)	19.0 (15.0–20.0)	19.0 (13.0–20.0)	19.0 (15.0–20.0)	20.0 (15.0–20.0)	20.0 (15.0–20.0)	
Qualifications, % (*n*)						
None mentioned	6.5 (1763)	8.3 (358)	6.7 (450)	5.9 (421)	6.0 (534)	
GCSE/CSE or equivalent	11.4 (3096)	11.7 (509)	11.5 (778)	11.4 (806)	11.2 (1003)	
A/AS levels or equivalent	5.7 (1539)	5.8 (253)	6.2 (416)	5.1 (363)	5.7 (507)	
NVQ/HNC or equivalent	13.1 (3559)	13.5 (585)	12.3 (833)	12.9 (910)	13.8 (1231)	
Other professional	13.3 (3610)	15.6 (675)	13.9 (940)	13.4 (948)	11.7 (1047)	
University/ college degree	49.9 (13,508)	45.1 (1954)	49.3 (3329)	51.3 (3630)	51.5 (4595)	
Ethnicity, % (*n*)						0 (1)
White	97.7 (26,505)	97.3 (4232)	98.0 (6621)	98.3 (6962)	97.3 (8690)	
Non-white	2.3 (622)	2.7 (119)	2.0 (136)	1.7 (122)	2.7 (245)	
Household income, % (*n*)						7.5 (2016)
Less than £18,000	14.4 (3610)	16.1 (652)	13.9 (881)	14.3 (935)	14.0 (1142)	
£18,000 to 30,999	25.6 (6434)	24.2 (978)	25.5 (1617)	25.0 (1638)	26.9 (2201)	
£31,000 to 51,999	29.1 (7297)	28.5 (1153)	29.0 (1836)	29.2 (1919)	29.3 (2389)	
£52,000 to 100,000	23.9 (5993)	24.1 (976)	24.2 (1532)	24.1 (1579)	23.3 (1906)	
Greater than £100,000	7.1 (1778)	7.1 (286)	7.5 (473)	7.5 (490)	6.5 (529)	
Nutritional intake, median (25th-75th)						0 (0)
Energy, kcal/d	2081 (1778–2432)	1720 (1464–1989)	1972 (1712–2250)	2114 (1843–2425)	2346 (2030–2726)	
Total carbohydrates, g/d	249 (207–297)	211 (174–251)	237 (199–277)	253 (214–296)	278 (233–330)	
Energy carbohydrates, %/d	49.0 (44.1–53.7)	50.2 (44.6–56.0)	49.3 (44.3–53.9)	48.9 (44.2–53.4)	48.5 (43.6–53.0)	
Total fat, g/d	75.9 (60.6–93.8)	60.3 (47.3–74.3)	71.1 (57.7–86.0)	77.4 (63.3–93.5)	87.4 (71.0–106.7)	
Energy fat, %/d	32.4 (28.6–36.1)	31.2 (27.0–35.5)	32.1 (28.3–36.0)	32.5 (28.7–36.1)	32.9 (29.3–36.6)	
Total protein, g/d	81.2 (69.3–94.5)	60.2 (51.8–68.8)	74.2 (66.0–82.5)	82.8 (74.1–92.3)	96.7 (86.0–109.7)	
Energy protein, %/d	15.8 (14.0–17.7)	14.2 (12.5–16.1)	15.2 (13.6–17.1)	15.9 (14.3–17.7)	16.7 (15.0–18.6)	
Total protein, g/kg BW/d	1.1 (0.9–1.3)	0.7 (0.6–0.8)	0.9 (0.9–1.0)	1.1 (1.0–1.1)	1.4 (1.3–1.5)	
Alcohol, g/d	12.0 (0.9–26.4)	11.2 (0.0–27.9)	13.0 (1.9–28.0)	12.6 (1.9–26.6)	11.2 (0.9–24.1)	
Smoking status, % (*n*)						0.2 (45)
Never	55.2 (14,955)	48.5 (2104)	51.5 (3473)	56.5 (3994)	60.3 (5384)	
Previous	38.7 (10,483)	44.0 (1910)	42.3 (2852)	38.0 (2689)	34.0 (3032)	
Current	6.1 (1645)	7.5 (327)	6.2 (420)	5.5 (388)	5.7 (510)	
Anthropometry, median (25th-75th)						
Weight (kg)	76.6 (66.9–87.0)	88.8 (78.8–99.7)	81.9 (73.3–91.0)	75.8 (67.7–84.1)	68.2 (60.7, 76.8)	0 (0)
BMI (kg/m^2)	26.2 (23.8–29.1)	29.4 (26.6–32.8)	27.5 (25.2–30.1)	26.0 (24.0–28.3)	24.3 (22.4–26.5)	0 (4)
Waist-hip ratio	0.9 (0.8–0.9)	0.9 (0.9–1.0)	0.9 (0.8–1.0)	0.9 (0.8–0.9)	0.8 (0.8–0.9)	0 (5)
Frailty, % (*n*)						0 (0)
Non-frail	54.1 (14,682)	45.3 (1970)	51.6 (3484)	56.0 (3966)	58.9 (5262)	
Pre-frail	43.1 (11,694)	49.5 (2154)	45.5 (3072)	41.8 (2961)	39.3 (3507)	
Frail	2.8 (752)	5.2 (227)	3.0 (202)	2.2 (157)	1.9 (166)	
Multimorbidity, % (*n*)	51.2 (13,891)	58.3 (2536)	53.5 (3615)	50.4 (3567)	46.7 (4173)	0 (1)
Polypharmacy, % (*n*)	16.7 (4530)	22.2 (967)	18.3 (1239)	15.0 (1064)	14.1 (1260)	0 (1)
Self-rated health, % (*n*)						0.2 (46)
Poor	2.7 (742)	5.3 (232)	2.7 (181)	2.3 (165)	1.8 (164)	
Fair	14.9 (4035)	21.4 (929)	17.1 (1155)	13.0 (917)	11.6 (1034)	

Table 1 (continued)

	Total ($n=27,128$)	<0.8 ($n=4351$)	0.8 to<1.0 ($n=6758$)	1.0 to<1.2 ($n=7084$)	≥1.2 ($n=8935$)	Missing, % (n)
Good	59.2 (16,043)	56.5 (2454)	59.4 (4010)	60.9 (4307)	59.1 (5272)	
Excellent	23.1 (6262)	16.7 (726)	20.8 (1402)	23.8 (1686)	27.5 (2448)	

Data are presented as percentages (%) and counts (n) for categorical variables and median (25th – 75th percentile) for continuous variables. Energy carbohydrates, fat and protein refers to the percentage of energy out of the total energy intake provided by that macronutrient. Multimorbidity was defined as the presence of 2 or more chronic illnesses. Polypharmacy was defined as the use of 5 or more drugs at the same time. £18,000≈€20,797 and ≈$24,321 in July 2025. *BMI* body mass index, *BW* bodyweight, *CSE* certificate of secondary education, *GCSE* general certificate of secondary education, *HNC* higher national certificate, *NVQ* national vocational qualification, *yrs* years

(HR:0.98, 95%CI:0.96–0.99) in models adjusted for age, sex, years of education, smoking status, alcohol and energy intake, and number of chronic diseases. Participants who had protein intakes ≥1.0 g/kg BW/day may have had a reduction of 15–18% of the probability of incident pre-frailty (HR:0.85, 95%CI:0.71–1.02 and HR:0.82, 95%CI:0.68–1.00). Higher protein intake also reduced, in a dose-dependent manner, the probability of transitioning from pre-frailty to frailty. For example, the hazard ratio for incident frailty for participants with protein intake 0.8 to <1.0, 1.0 to <1.2 and ≥1.2 was 0.80 (95%CI:0.71–0.91), 0.72 (95%CI: 0.63–0.81) and 0.68 (95%CI: 0.60–0.78), respectively, as compared to the reference of <0.8 g/kg BW/day (Table 2 and Fig. 3). There was no statistical or clinical interaction between protein and sex. Excluding possible misreporters, or excluding those that did not consider the dietary intake to reflect their typical diet, or further adjusting for physical activity, or adding a piecewise constant from baseline to 2 years and from 2 years onwards, did not considerably change the direction. However, further adjusting for BMI reduced the possible effect of protein intake on incident pre-frailty but not on incident frailty (Additional file 1: Table S3).

Backward transitions/recovery (pre-frail → non-frail AND frail → pre-frail)

An increment of 0.1 g/kg BW/d of protein intake also slightly increased the probability of recovering from pre-frailty to non-frailty (HR:1.03, 95%CI:1.01–1.06) and from frailty to pre-frailty (HR:1.06, 95%CI:1.01–1.11) in fully adjusted models (Model III). Using protein categories as the exposure, there was an increase

Table 2 Hazard ratios of frailty transitions over time by protein intake

	Protein Intake (g/kg bodyweight/day)								
	+0.1		<0.8	0.8 to<1.0		1.0 to<1.2		≥1.2	
	HR	95% CI	HR	HR	95% CI	HR	95% CI	HR	95% CI
Non-Frail → Pre-Frail ($n=5646$ transitions)									
Model I	0.95	0.94–0.97	1	0.93	0.80–1.09	0.84	0.71–0.98	0.80	0.69–0.93
Model II	0.97	0.95–0.99	1	0.95	0.81–1.10	0.87	0.70–1.00	0.84	0.70–1.00
Model III	0.96	0.94–0.98	1	0.92	0.77–1.10	0.85	0.71–1.02	0.82	0.68–1.00
Pre-Frail → Non-Frail ($n=4187$ transitions)									
Model I	1.02	1.00–1.04	1	1.07	0.89–1.28	1.22	1.01–1.46	1.34	1.12–1.59
Model II	1.04	1.02–1.07	1	1.16	0.96–1.40	1.38	1.14–1.67	1.65	1.34–2.02
Model III	1.03	1.01–1.06	1	1.09	0.88–1.33	1.28	1.04–1.57	1.49	1.20–1.86
Pre-Frail → Frail ($n=552$ transitions)									
Model I	0.95	0.94–0.97	1	0.81	0.72–0.91	0.71	0.63–0.79	0.69	0.62–0.77
Model II	0.97	0.95–0.98	1	0.77	0.69–0.87	0.68	0.60–0.76	0.63	0.56–0.72
Model III	0.98	0.96–0.99	1	0.80	0.71–0.91	0.72	0.63–0.81	0.68	0.60–0.78
Frail → Pre-Frail ($n=311$ transitions)									
Model I	1.01	0.98–1.05	1	1.26	0.91–1.74	1.04	0.73–1.46	0.99	0.71–1.40
Model II	1.05	1.01–1.10	1	1.32	0.94–1.84	1.11	0.76–1.61	1.15	0.76–1.75
Model III	1.06	1.01–1.11	1	1.28	0.90–1.81	1.09	0.74–1.60	1.24	0.80–1.94

Hazard ratios (HR) and 95% confidence intervals (CI) of forward (non-frail to pre-frail, pre-frail to frail) and backward frailty (pre-frail to non-frail, frail to pre-frail) transitions over time by protein intake (by increments of 0.1 or by protein intake categories). Protein intake <0.8 g/kg bodyweight/day was the reference category when protein categories were the exposure. *N* are the number of transitions. Apart from the exposure (protein intake), all continuous variables were centred prior to fitting. Model I only included protein intake (continuous or categorical) and age (time-varying) (255,690 person-years); Model II was further adjusted for sex, years of education, smoking status, and alcohol and energy intake and (254,860 person-years); and Model III was further adjusted for disease count (254,848 person-years)

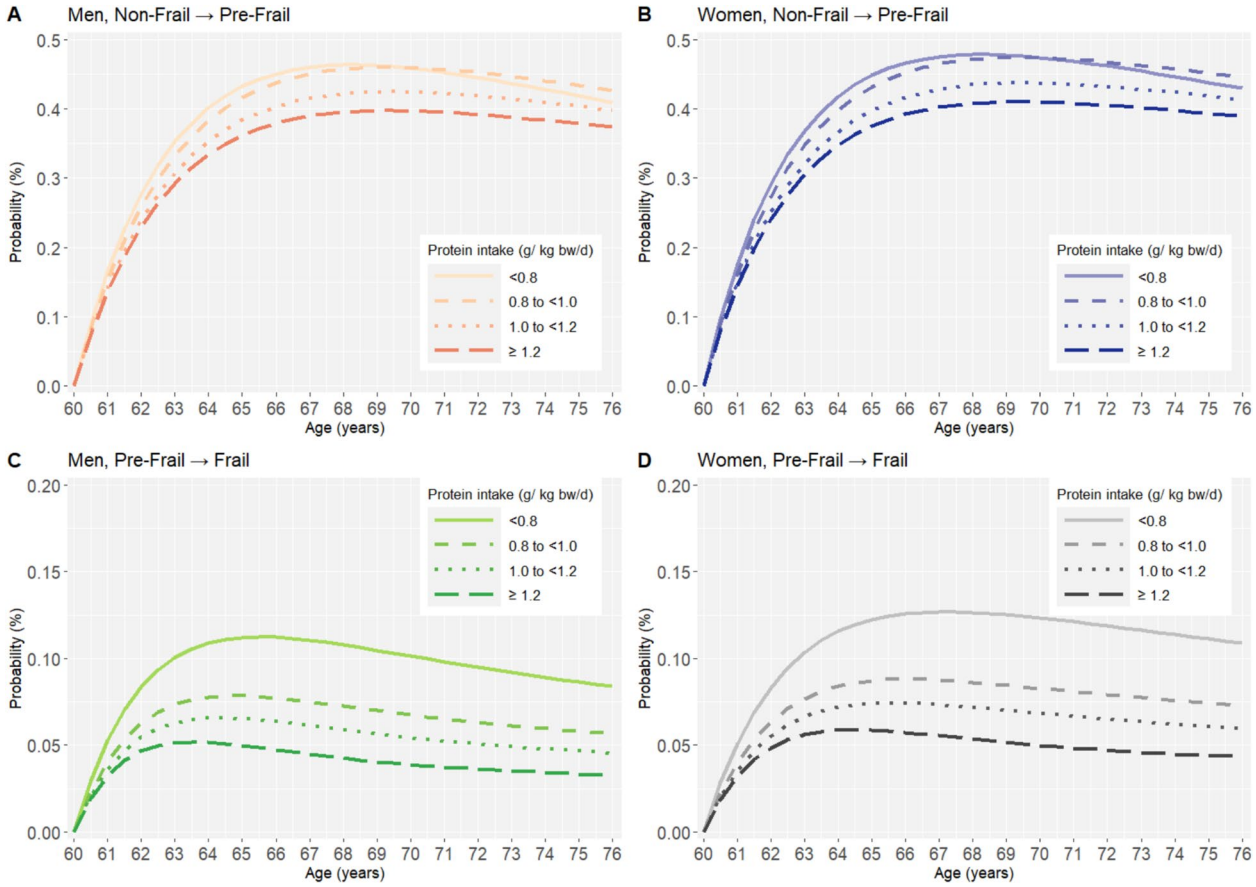

Fig. 3 Probability of forward frailty transitions for a non-smoking 60-year-old man or woman by protein intake. Conditional probability (%) of a non-smoking 60-year-old man (**A**) or woman (**B**) to transition from non-frail to pre-frail, and a non-smoking 60-year-old man (**C**) or woman (**D**) to transition from pre-frail to frail per protein intake categories (< 0.8, 0.8 to < 1.0, 1.0 to < 1.2 and ≥ 1.2 g/kg bodyweight/d). Apart from protein intake, sex and smoking, covariates from Model III were held at their mean

in the probability of recovering from pre-frailty in those who had protein intakes ≥ 1.0 g/kg BW/day. However, higher protein intake did not increase the probability of recovering from frailty (Table 2 and Additional file 1: Fig. S2). There was no statistical or clinical interaction between protein and sex. Excluding those that did not consider the dietary intake to reflect their typical diet, or adding a piecewise constant did not change conclusions from the main model (Model III) but excluding possible misreporters, further adjusting for physical activity and BMI attenuated the observed associations (Additional file 1: Table S3).

Frailty state-specific sojourn times

On average, participants with higher protein intake spent fewer years in a pre-frailty and frailty state and more years as non-frail than those with lower protein intake. For example, a non-smoking 60 year-old woman (all other covariates held at their mean) with protein intake ≥ 1.2 g/kg BW/day was expected to spend 2.6 (95%CI:2.3–3.1) years in a frailty state whereas a woman with protein intake < 0.8 g/kg BW/day was expected to spend 4.0 years (95%CI:3.4–4.8) years in a frailty state (Additional file 1: Table S4).

Discussion

Main findings

Our study indicated that middle-aged and older participants with higher protein intake (increments of 0.1 g/kg BW/day and protein categories of < 0.8 (ref.), 0.8 to < 1.0, 1.0 to < 1.2, ≥ 1.2 g/kg BW/day) were less likely to progress from pre-frailty to frailty, and appeared to be more likely to recover from pre-frailty to non-frailty, with some evidence for dose-dependency. Higher protein intake seemed to have no important effect on the recovery from frailty to pre-frailty.

Interpretation and comparison with other studies

The presence of slow walking speed, unintentional weight loss, exhaustion, low physical activity, and weakness are frequently used to operationalize physical

frailty. Nutrition, specifically protein intake, plays a key role in all these criteria. Higher protein intake has been associated with a slower decline in grip strength (weakness) [6] and walking speed [29], reduced weight-loss [45] and fatigue (exhaustion), and loss of muscle mass [46]. We found that middle-aged and older adults with higher protein intake (using continuous protein intake or categories) were at reduced risk to transition from pre-frailty to frailty. For example, an increment of 7 g/d of protein for a 70 kg individual (the amount of protein in 1 cup of semi-skimmed milk or in 1 large egg; Additional file 1: Table S5 for the protein content of common foods) resulted in a small reduction of 2% of the risk of incident frailty in fully adjusted multi-state models, whereas an intake ≥ 1.2 g/kg BW/d (or ≥ 84 g/d for a 70 kg individual) resulted in a reduction in 32% of the risk compared to those who had an intake < 0.8 g/kg BW/d (or < 56 g/d for a 70 kg individual). However, the potential for higher protein intake to meaningfully reduce the probability of transitioning between non-frailty and pre-frailty is less clear. Although there were a large number of transitions between non-frailty and pre-frailty states ($n = 5646$) the effect of protein intake at such an early stage of the frailty process may be too small and could not be fully captured. The protective effect of protein on frailty incidence and recovery from pre-frailty seemed to be dose responsive. In fact, previous results from a pooled analysis of four longitudinal aging cohorts showed that, in a dose-dependent way, older adults with higher protein intake had slower decline in walking speed and reduced incident difficulty walking > 200 m, criteria used to operationalise physical frailty [29].

We also found that participants who had higher protein intake might have been more likely to recover from pre-frailty to non-frailty, but we failed to see an association for recovery from frailty. It is very possible that the effect of protein, at least, at the range of protein intakes observed (0.1–3.1 g/kg BW/d), was not large enough to warrant a recovery from such an advanced stage in the frailty process. Recovery from a frail state may require more comprehensive interventions, as protein intake alone may be insufficient.

Other longitudinal studies have confirmed our findings that higher protein intake (+1 g/kg BW/d, a 20–25% increase in intake, using quartiles or categories) moderately reduced the risk of incident pre-frailty or frailty in middle-aged and older adults [9, 35, 36, 38, 41] while others did not [37, 39, 40, 47]. The conflicting evidence stems from the limited number of incident pre-frailty and frailty cases, different dietary (protein) assessment methods and differences in how protein intake was expressed (g/kg BW/d, g/d or as percentage of energy intake). However, to our knowledge, the only other study to assess other transitions between frailty states (including recovery) was our previous work that found that an increment of 1 g/kg adjusted BW/d and an intake ≥ 0.8 or ≥ 1.0 g/ kg adjusted BW/d decreased the likelihood (HR: 0.44, 95%CI: 0.25–0.77; HR: 0.60, 95%CI: 0.43–0.84; HR: 0.63, 95%CI: 0.44–0.90, respectively) of progressing from pre-frailty to frailty in 85 + year olds over 5 years but not for other transitions. Evidence from experimental studies is arguably less encouraging with systematic reviews of randomised controlled trials failing to find an effect of protein supplementation alone on frailty [48] but favouring a multicomponent intervention with protein supplementation and exercise to reduce several frailty criteria among pre-frail and frail older adults [49].

Clinical and public health implications

Higher protein intake, especially above ≥ 1.0 g/kg BW/day and in a dose-dependent manner, reduced the risk of progressing from pre-frailty to frailty and increased the likelihood of recovering from pre-frailty to non-frailty. These findings align with the broader literature emphasizing the importance of adequate protein intake in preserving muscle strength, walking speed, and overall physical function—key components of physical frailty.

Our findings support the inclusion of protein-focused nutritional strategies as part of a comprehensive approach to frailty prevention, particularly when combined with physical activity interventions. These insights could guide healthcare professionals and policymakers in designing and promoting targeted interventions to delay or reverse frailty, thereby improving quality of life and reducing healthcare costs associated with frailty-related outcomes. Furthermore, the results highlight the need to revisit most protein intake guidelines for healthy older populations and incorporate higher protein intake cut-offs with an emphasis on personalized approaches that consider body weight and individual needs.

Limitations and strengths

Selection bias, namely volunteer vias, evidenced by a 5.5% response rate of participants, is a well-known issue in the UK Biobank. Specifically, in this study, it meant that those participating, and to some extent, those that returned for the follow-up waves, were less frail than what would be expected for the general UK middle-aged and older population. This selection bias persists during follow-up, possibly aggravating it. Another limitation is that the 24 h recalls, although having been measured in five distinct occasions between 2011–2012, and therefore being better suited to capture habitual intake, were assumed to reflect energy and protein intake over the follow-up period, i.e., that intakes were stable or changed

proportionally over the time. Additionally, assessment of dietary intake (and protein intake) may have suffered from non-differential misclassification which, in this case, would make the estimate tend towards the null. However, protein-rich foods are less commonly misreported (unlike snacks and sweets) which may reduce the importance of protein misclassification in this study [50]. Unmeasured confounding cannot be entirely ruled out. However, owing to the extensive set of covariates available in the UK Biobank, encompassing a broad range of sociodemographic, behavioural, and health covariates, and the inclusion of multiple sensitivity analyses, we do not consider unmeasured confounding to be the principal source of bias in our study. Nonetheless, its presence remains a possibility and should be considered when interpreting the findings.

The Markov assumption, used for the multistate models, is that past frailty states (and time spent in a given state) do not affect future frailty state transitions, which may not be true for our study. Semi-Markov models were considered but these were not feasible for physical frailty in the UK Biobank as observation times were interval censored and not closely spaced or exact (2.2–6.3 years). Furthermore, frailty states were assigned at every data collection point (mean of 4.3, 5.1 and 3.2 between baseline and 1st follow-up, between the 1st and the 2nd follow-up, and between the 2nd and the 3rd follow-up, respectively) and it is likely that unobserved incidence and recovery from frailty states occurred between waves.

Generalizability should be taken with some caution as UK Biobank participants were older, more likely to be white, had higher socioeconomic status, and were slightly healthier than the respondents of the Census 2011 for England and Wales [51]. Albeit younger (median age 60.3 yrs) participants of the UK Biobank also had higher energy intakes (2081 vs 1633 kcal/d) and total protein intakes (81.2 vs 67.3 g/d) but similar percentage of energy from protein (15.8 vs 16.4%/d) compared to intakes of older adults (65+) from the National Diet and Nutrition Survey (2008/2009–2011/2012).

Conclusions

Higher protein intake moderately reduces the risk for frailty incidence and increases the likelihood of recovery from pre-frailty in a dose-dependent manner. These findings may optimize strategies to prevent frailty in middle-aged and older adults and inform dietary protein guidelines in this population.

Abbreviations

BMI	Body Mass Index
BW	Bodyweight
CI	Confidence Interval
CSE	Certificate of Secondary Education
D	Day
DACH	Germany, Austria, and Switzerland
GCSE	General Certificate of Secondary Education
HR	Hazard Ratio
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
ISCED	International Standard Classification for Education
Kg	Kilogram
Kj	Kilojoule
m	Meters
MET	Metabolic Equivalents
NHS	National Health Service
NVQ	National Vocational Qualification
RDA	Recommended Dietary Allowance
UK	United Kingdom
Yrs	Years

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04397-0.

Additional file 1. Table S1: Operationalization of the physical frailty phenotype in the UK Biobank [13]. Table S2: Baseline differences between participants included (analytic sample) and excluded from analysis. Table S3: Sensitivity analysis - Hazard ratios of frailty transitions over time by protein intake. Table S4: Mean sojourn times spent in each frailty state for a non-smoking 60-year-old man or woman by protein intake. Table S5: Protein content (g) per 100g of some commonly eaten foods [19]. Fig S1: Directed acyclic graph of the total effects of protein intake on frailty. Fig S2: Probability of backward frailty transitions for a non-smoking 60-year-old man or woman by protein intake.

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Authors' contributions

NM and AR conceptualised the study and secured funding. NM conducted the study, analysed the data, performed statistical analyses, and wrote the paper. NM had primary responsibility for the final content. ARM, ARH, HC, CCM and AR contributed to the interpretation of the findings, read, critically reviewed the paper and commented on the manuscript. All authors read and approved the final manuscript.

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Data availability

This research has been conducted using the UK Biobank Resource under application number 103200. Data are available via the UK Biobank on application and with permission of the UK Biobank Ethics and Governance Council.

Declarations

Ethics approval and consent to participate

The UK Biobank study was conducted according to the Declaration of Helsinki and ethical approval was granted by the North West Multi-Centre Research Ethics Committee (REC: 21/NW/0157). All participants gave informed consent before enrolment in the UK Biobank.

Consent for publication

There are no individual nor traceable data in this manuscript.

Competing interests
The authors declare no competing interests.

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