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ORIGINAL CONTRIBUTION

Association between plant and animal protein and biological aging: findings from the UK Biobank

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Abstract

Purpose This study aimed to evaluate the relationship between plant protein, animal protein and biological aging through different dimensions of biological aging indices. Then explore the effects of substitution of plant protein, animal protein, and their food sources on biological aging.

Methods The data came from 79,294 participants in the UK Biobank who completed at least two 24-h dietary assessments. Higher Klemera-Doubal Method Biological Age (HKDM-BA), higher PhenoAge (HPA), higher allostatic load (HAL), and longer telomere length (LTL) were estimated to assess biological aging. Logistic regression was used to estimate protein-biological aging associations. Substitution model was performed to assess the effect of dietary protein substitutions.

Results Plant protein intake was inversely associated with HKDM-BA, HPA, HAL, and positively associated with LTL (odds ratios after fully adjusting and comparing the highest to the lowest quartile: 0.83 (0.79–0.88) for HKDM-BA, 0.86 (0.72–0.94) for HPA, 0.90 (0.85–0.95) for HAL, 1.06 (1.01–1.12) for LTL), while animal protein was not correlated with the four indices. Substituting 5% of energy intake from animal protein with plant protein, replacing red meat or poultry with whole grains, and replacing red or processed meat with nuts, were negatively associated with HKDM-BA, HPA, HAL and positively associated with LTL. However, an inverse association was found when legumes were substituted for yogurt. Gamma glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase mediated the relationship between plant protein and HKDM-BA, HPA, HAL, and LTL (mediation proportion 11.5–24.5%; 1.9–6.7%; 2.8–4.5%, respectively).

Conclusion Higher plant protein intake is inversely associated with biological aging. Although there is no association with animal protein, food with animal proteins displayed a varied correlation.

Keywords Plant protein · Animal protein · Dietary protein food sources · Biological aging · Substitution · UK Biobank

Introduction

Aging is a complex process that gradually undermines the integrity of cells, tissues, and organs [1]. Over the years, people have been searching for measures to delay aging, with aging affected by genetic, environmental, and lifestyle factors [2–4]. Among these, diet has been shown to play a crucial role in influencing aging [5]. One key component of a wholesome diet is protein, which can be categorized into plant and animal sources.

Previous studies have suggested that different protein sources have different impacts on mortality, for example, increased intake of plant protein is associated with a reduction in the risk of chronic disease and all-cause mortality, whereas increased intake of animal protein has the opposite or no association [6–8]. A study performed in the elderly also found that increasing plant protein intake reduced the health deficit accumulation index [9]. On this basis, some studies have further found that substituting animal protein with plant protein can reduce the risk of aging-related disease and all-cause mortality [6, 10, 11]. However, there is limited research on the relationship between plant protein, animal protein, and their major food sources and biological aging in large populations. At the same time, the possible

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biological mechanisms by which they affect biological aging remain unclear.

A single biomarker of aging may not systematically reflect true organismal aging [12]. Biological age is a more ideal indicator as it utilizes a variety of biomarkers that accurately reflect the functioning of multiple organ systems and the health status of an individual to describe biological aging [13]. Earlier studies have proposed and validated multiple approaches to calculating biological age, such as the Klemera-Doubal Method Biological Age (KDM-BA) and the PhenoAge (PA) algorithm [14, 15], which can quantify biological age and predict mortality through commonly assessed clinical parameters [16, 17]. Allostatic load (AL) is also a key indicator of biological aging [18], reflecting the accumulated burden of chronic stress [19], and is associated with subsequent functional decline and death [20, 21]. Repetitive DNA sequences known as telomeres, situated at the termini of eukaryotic chromosomes, undergo attrition with each division of a somatic cell [22]. Telomere length (TL) has emerged as a potential biomarker of biological age, as shorter telomeres are associated with a higher biological age [23].

Considering the current research gaps mentioned above, we first studied the relationship between plant protein, animal protein, their twelve food sources and four biological aging indices separately in this study. Then, we conducted substitution analyses of various protein sources to determine if better improvements in biological aging could be achieved. Additionally, we explored whether some biochemical indexes could explain the association between plant or animal protein and biological aging.

Methods

Study population

The UK Biobank (UKB) is a large-scale population-based cohort study of over 500,000 participants aged 40–69 years at recruitment between 2006 and 2010 [24]. The study used data from the UKB and involved non-pregnant adults who took part in the survey. Exclusion criteria included participants with any of the following conditions: missing dietary energy data (n = 291,454) and unrealistic dietary energy intake (< 800 or > 4200 kcal/day for men and < 500 or > 3500 kcal/day for women) (n = 2,529), pregnant (n = 71), data that were not available or had missing values for covariates (n = 34,580), plant protein and animal protein (n = 0), lack of physiological data for calculating the four biological aging indices (n = 45,220), did not complete two or more dietary assessments (n = 49,263). After excluding the above participants, 79,294 individuals were ultimately considered in this study (Supplementary Fig. 1).

Dietary assessment

The Oxford WebQ was developed for large population studies and validated against an interviewer-administered 24-h recall questionnaire [25, 26]. Dietary information was collected at baseline and followed up four times between April 2009 and June 2012 (cycle 1: February 2011 to April 2011; cycle 2: June 2011 to September 2011; cycle 3: October 2011 to December 2011; cycle 4: April 2012 to June 2012) using Oxford WebQ [27]. Total energy and nutrient intake data were automatically estimated by multiplying the number of portions consumed by the set quantity of each food portion size and its nutrient composition according to the UK Nutrient Databank food composition tables (2012–2013 and 2013–2014) [27]. We used the average of the five measurements of the plant protein variable (ID:26,006, g/d), animal protein variable (ID:26,007, g/d), total energy variable (ID:26,002, kj/d) from the UK Biobank (UKB) database to express their average dietary intakes. We converted energy (kj/d) into energy (kcal/d) and calculated the final percentage of plant and animal protein intake to total energy consumption [6].

The Oxford WebQ also collects information on foods and beverages consumed over the previous day. Participants were presented with a list of up to 206 foods and 32 beverages commonly consumed in the UK and selected the number of portions consumed from each food [28]. Participants with at least two assessments were retained for analysis to better reflect usual intakes [29], and their mean dietary intake was calculated. The food items comprising each of the twelve dietary protein sources were described in Supplementary Table 1. A serving size was defined as 50 g/day for red meat, processed meat, poultry, egg and egg dishes, oily fish, non-oily fish, and legumes; 30 g/day for cheese and whole grains; 200 g/day for milk; 70 g/day for yogurt; and 10 g/day for nuts [30].

Main outcomes

We used the best-validated algorithms to construct KDM-BA, PA, and AL based on ten blood chemistry parameters that could be implemented with data available in the UK Biobank (Supplementary Table 2) [31–33]. The R package 'BioAge' provided access to the corresponding algorithms and R code at https://github.com/dayoonkwon/BioAge. Briefly, the KDM-BA was derived from a series of regressions of individual biomarkers on chronological age in a reference population, which allowed us to quantitatively assess the decline in system integrity [34]. PA was computed using an algorithm derived from multivariate analysis of mortality hazards to estimate the risk of

death [15]. AL was a composite measure of biomarkers associated with the neuroendocrine, neurophysiological, and inflammatory systems, and it was determined by evaluating the percentage of biomarkers that indicated an increased risk for an individual [35]. In our study, the risk level was established by assessing individuals in the highest quartile of a biomarker's distribution for nine out of the ten biomarkers, except for albumin, for which risk was defined as residing in the lowest quartile [36]. The final AL, ranging from 0 to 1, was considered as the ratio of biomarkers classified as "at risk" within the ten selected biomarkers [37].

At baseline (recruitment), DNA was extracted from the peripheral blood leukocytes of all UKB participants. Multiple quantitative polymerase chain reaction (qPCR) was used to measure leucocyte TL with T/S ratio, comparing the amount of the telomere amplification product (T) to that of a single-copy gene (S) [38, 39]. In this study, the TL measurement results were first approximated to normal distribution by $\log_e$-transformed, and then further analyzed by Z-standardized value.

Overall, we set KDM-BA, PA, AL, and TL as binary variables for analysis according to the following standards [40]. Participants with KDM-BA and PA beyond their chronological age are thought to have experienced accelerated biological aging [14, 41], which we defined as higher KDM-BA (HKDM-BA) and higher PA (HPA), respectively. Individuals with higher levels of AL were at greater risk of physiological stress. Based on the median AL, participants with AL levels above the median were classified as dysregulated in our study [42], which we defined as higher AL (HAL). Given the correlation between TL shortening and biological aging, individuals with TL above the median in our study were classified as abiotic senescence [43], which we defined as longer TL (LTL) (Supplementary Fig. 2).

Covariates

Referring to existing studies, the variables that influenced the association between plant and animal protein and biological aging were considered covariates to control for potential confounders. These variables included age (years), sex (male/female), ethnicity (White/Mixed/Asian or Asian British/Black or Black British/Chinese/Other ethnic group), Townsend deprivation index (TDI), education level (< high school/high school/ > high school), smoking status (never/previous/current), drinking status (never/previous/current), physical activity (International Physical Activity Questionnaire activity group: low/moderate/high), body mass index (BMI) (kg/m^2), overall health rating (excellent/good/fair/poor), diabetes mellitus type 2 (T2DM) (yes/no), cancer (yes/no), intakes of total energy (quartiles), fruits (quartiles), vegetables (quartiles), saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, and trans-fatty acids (all expressed as a percentage of energy and categorized into quartiles), intake of dietary cholesterol, diet quality score, and multiple vitamin supplement use (yes or no). T2DM was identified through self-reported medical history and use of anti-diabetic medication, hospital inpatient records (ICD-9 codes 250.00, 250.10, 250.20, and 250.90 and ICD-10 code E11), and abnormal glucose levels (random glucose ≥ 199.8 mg/dL or glycated hemoglobin ≥ 6.5%) [44]. Cancer was identified using ICD-10 code C00–C99 [45].

Statistical analysis

General characteristics across quartiles of plant and animal protein intake (energy%) were expressed as the mean value (standard deviation) for continuous variables and number (%) for categorical variables. We used general linear regression models for continuous variables and the Chi-square test for categorical variables to test differences across quartiles.

Logistic regression analyses were conducted to test the association between plant protein, animal protein, and twelve dietary protein sources with HKDM-BA, HPA, HAL, and LTL, with the lowest quartile of plant protein, animal protein, and twelve dietary protein sources as the reference. Generalized linear regression analyses were used when treating biological aging indices as continuous variables. Model 1 was adjusted for demographic and lifestyle factors, including sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, and BMI; Model 2 was further adjusted for overall health rating, T2DM, cancer, intake of total energy; In Model 3 we additionally adjusted for the intake of fruits, vegetables, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and trans-fatty acids, dietary cholesterol, diet quality, multiple vitamin supplement use. In addition to all the above variables, the animal protein was also adjusted for plant protein in Model 3 and vice versa. When analyzing the relationship between plant and animal protein food sources and biological aging indices, Model 1 and Model 2 remain unchanged. Model 3 adjusts eleven protein food sources other than this food but not plant or animal protein (energy%) variable, with the remaining covariates unchanged. Logistic regression was used to examine the linear trends, with the median intake of plant and animal protein per quartile as a continuous variable. Besides, the non-linear relationship was analyzed by restricted cubic splines (RCS).

Then, we constructed a substitution model mentioned in the previous study [6] to estimate the relationship between replacing animal protein with plant protein and HKDM-BA, HPA, HAL, and LTL. To fit the substitution model, we simultaneously included the percentage of energy derived from animal protein and plant protein along with the covariates mentioned in Model 3 above.

We used the original plant protein intake (energy%) and animal protein intake (energy%) data divided by 5 to estimate the association of replacing 5% of energy. We also investigated the association between substituting 1 serving of plant protein source foods (whole grains, nuts, legumes) for 1 serving of animal protein source foods (red meat, processed meat, poultry, egg and egg dishes, oily fish, non-oily fish, cheese, milk, yogurt). For all substitution models, the odds ratios (ORs) of plant protein or plant protein food from the model can be interpreted as the estimated effect of replacing the same proportion of animal protein with a certain proportion of plant protein.

Model-based causal mediation analysis was conducted using the mediation package (http://cran.r-project.org/web/packages/mediation/) and adjusted using covariates in Model 3. The mediating variables we used, including gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were obtained from blood assays in the UKB database.

We did some sensitivity analyses. First, we excluded participants with extreme energy supply ratios (> 99% and/or < 1%) of plant or animal protein to minimize the possibility of bias and confirm the stability of our results. Then, subgroup analyses were conducted based on variables we are interested in: age (≤ 60 and > 60 years), sex, physical activity (low, moderate, high), body mass index (BMI) (≤ 25 and > 25 kg/m2), diagnosed diabetes mellitus type 2 (T2DM) (yes and no), diagnosed cancer (yes and no).

All analyses were performed in SPSS 26.0 and R 4.2.1. A P value of < 0.05 (two-sided) was considered statistically significant. The Bonferroni correction was used to explain the multiple testing.

Results

Participants' characteristics

The characteristics of participants across quartiles of plant protein and animal protein are shown in Table 1. The total mean age of the participants was 56.0 (SD = 7.8) years and 46.6% were male. Participants with higher plant protein intake were more likely to have lower BMI, higher education level, physical activity level, better overall health level, and use vitamin supplements; be less likely to be current smokers and current drinkers. They also consumed more vegetables, fruits, and polyunsaturated fatty acids; less cholesterol, saturated fatty acids, monounsaturated fatty acids, and trans fatty acids. The trends observed for these characteristics were roughly reversed among participants with a higher intake of animal protein.

Associations of plant and animal protein with biological aging

The associations between plant protein with four biological aging indices are shown in Table 2. After the adjustment of Model 1, we found that a higher intake of plant protein was inversely related to HKDM-BA, HPA, and HAL and positively related to LTL. After further adjustment for more covariates (Model 2), these associations were maintained. In the fully adjusted model (Model 3), compared to the lowest quartile of plant protein, the highest quartile was still inversely associated with HKDM-BA (OR: 0.83, 95%CI 0.79–0.88), HPA (OR: 0.86, 95%CI 0.79–0.94), HAL (OR: 0.90, 95%CI 0.85–0.95) and positively associated with LTL (OR: 1.06, 95%CI 1.01–1.12). Additionally, the RCS model did not indicate any non-linear dose–response relationships between plant protein and HKDM-BA (P for overall < 0.0001, P for nonlinear = 0.8497), HPA (P for overall < 0.0001, P for nonlinear = 0.6747), HAL (P for overall < 0.0001, P for nonlinear = 0.5629), LTL (P for overall < 0.0001, P for nonlinear = 0.6561) (Fig. 1).

In terms of animal protein, after adjusting for all covariates in Model 3, we found no consistent association between animal protein and four indices (Table 3). An inverted "U" curve was observed between animal protein and HKDM-BA (P for overall < 0.0001, P for nonlinear = 0.0032) and HAL (P for overall < 0.0001, P for nonlinear = 0.0037), but no nonlinear relationship was found with HPA (P for overall < 0.0001, P for nonlinear = 0.1963) and LTL (P for overall < 0.0001, P for nonlinear = 0.4465) (Fig. 1).

When KDM-BA, PA, AL, and TL were treated as continuous variables, the above results did not change. Higher plant protein was still negatively associated with biological aging (Supplementary Table 3), and while we found that higher animal protein was positively associated with higher PA (beta: 0.15, 95%CI 0.07–0.22 when Q4 vs Q1 in Model 3), there was no consistent association with the other three biological aging indices (Supplementary Table 4).

Associations of dietary plant and animal protein food sources intake with biological aging

Associations between the intake of twelve plant and animal protein dietary sources and four biological aging indices are shown in Supplementary Tables 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16. In the fully adjusted model, compared with the lowest tertile, the highest tertile of whole grains intake was negatively associated with HKDM-BA (OR: 0.90, 95%CI 0.86–0.93), HPA (OR: 0.85, 95%CI 0.79–0.90), HAL (OR: 0.89, 95%CI 0.86–0.93), and higher odds of LTL (OR: 1.05, 95%CI 1.01–1.09) (Supplementary Table 5). Participants in the highest tertile of nuts intake had a negative association with biological aging than those in the lowest tertile (OR:

Table 1 General characteristics of participants stratified by quartiles of plant and animal protein intake [a]

Characteristic	Total (n = 79,294)	Quartiles of plant protein intake (% energy)				*P* value [b]	Quartiles of animal protein intake (% energy)				*P* value
		≤4.64 (n = 19,823)	4.65–5.36 (n = 19,824)	5.37–6.21 (n = 19,823)	≥6.22 (n = 19,824)		≤8.29 (n = 19,823)	8.30–10.19 (n = 19,824)	10.20–12.19 (n = 19,823)	≥12.20 (n = 19,824)	
Age (years)	56.0 (7.8)	55.6 (8.0)	56.3 (7.8)	56.4 (7.8)	55.8 (7.8)	0.222	55.5 (7.9)	56.5 (7.8)	56.4 (7.8)	55.7 (7.9)	0.125
Male (%)	36,946 (46.6)	9,816 (12.4)	9,353 (11.8)	9,278 (11.7)	8,499 (10.7)	< 0.001	9,978 (12.6)	10,151 (12.8)	9,141 (11.5)	7,676 (9.7)	< 0.001
White race (%)	76,979 (97.1)	19,332 (24.4)	19,370 (24.4)	19,336 (24.4)	18,941 (23.9)	< 0.001	19,113 (24.1)	19,402 (24.5)	19,366 (24.4)	19,098 (24.1)	< 0.001
BMI (kg/m^2)	26.6 (4.5)	27.2 (4.6)	26.8 (4.4)	26.5 (4.4)	26.0 (4.5)	< 0.001	25.9 (4.3)	26.5 (4.3)	26.8 (4.4)	27.5 (4.7)	< 0.001
TDI	−1.7 (2.8)	−1.6 (2.9)	−1.8 (2.7)	−1.8 (2.8)	−1.5 (2.9)	< 0.001	−1.3 (3.0)	−1.8 (2.7)	−1.8 (2.7)	−1.7 (2.8)	< 0.001
High School Graduated (%)	59,092 (74.5)	14,359 (18.1)	14,685 (18.5)	14,810 (18.7)	15,238 (19.2)	< 0.001	15,352 (19.4)	14,958 (18.9)	14,634 (18.5)	14,148 (17.8)	< 0.001
Current smokers (%)	5,597 (7.1)	2,042 (2.6)	1,330 (1.7)	1,189 (1.5)	1,036 (1.3)	< 0.001	1,527 (1.9)	1,301 (1.6)	1,345 (1.7)	1,424 (1.8)	< 0.001
Current drinkers (%)	74,975 (94.6)	18,967 (23.9)	18,969 (23.9)	18,809 (23.7)	18,230 (23.0)	< 0.001	18,589 (23.4)	18,853 (23.8)	18,853 (23.8)	18,680 (23.6)	< 0.001
Physical activity -high (%)	30,387 (38.3)	6,975 (8.8)	7,317 (9.2)	7,708 (9.7)	8,387 (10.6)	< 0.001	8,132 (10.3)	7,710 (9.7)	7,295 (9.2)	7,250 (9.1)	< 0.001
Overall health level-excellent (%)	17,829 (22.5)	4,049 (5.1)	4,478 (5.6)	4,636 (5.8)	4,666 (5.9)	< 0.001	4,799 (6.1)	4,531 (5.7)	4,388 (5.5)	4,111 (5.2)	< 0.001
Diagnosed T2DM (%)	4,646 (5.9)	1,076 (1.4)	1,086 (1.4)	1,159 (1.5)	1,325 (1.7)	< 0.001	987 (1.2)	1,113 (1.4)	1,183 (1.5)	1,363 (1.7)	< 0.001
Diagnosed cancer (%)	17,306 (21.8)	4,370 (5.5)	4,463 (5.6)	4,376 (5.5)	4,097 (5.2)	< 0.001	4,193 (5.3)	4,539 (5.7)	4,442 (5.6)	4,132 (5.2)	< 0.001
Multiple vitamin supplement use (%)	43,479 (54.8)	10,035 (12.7)	10,608 (13.4)	11,000 (13.9)	11,836 (14.9)	< 0.001	11,020 (13.9)	10,784 (13.6)	10,778 (13.6)	10,897 (13.7)	0.047
Healthy dietary quality (%)	16,227 (20.5)	3,109 (3.9)	3,514 (4.4)	4,210 (5.3)	5,394 (6.8)	< 0.001	3,776 (4.8)	3,845 (4.8)	3,979 (5.0)	4,627 (5.8)	< 0.001
Energy intake (kcal/d)	2,066.6 (498.3)	2,142.8 (529.7)	2,112.6 (485.6)	2,051.1 (474.4)	1960.0 (481.9)	< 0.001	2,165.7 (526.5)	2,171.3 (481.2)	2,064.3 (456.8)	1,865.2 (462.9)	< 0.001
Vegetable intake (g/d)	207.9 (139.7)	156.3 (108.1)	189.3 (117.0)	215.4 (129.5)	270.6 (170.2)	< 0.001	221.0 (156.4)	202.5 (132.6)	201.6 (129.5)	206.5 (138.0)	< 0.001
Fruit intake (g/d)	215.6 (154.9)	162 4 (133.5)	205.1 (142.5)	230.6 (153.1)	264.5 (169.7)	< 0.001	236.4 (166.4)	219.6 (153.0)	209.1 (147.1)	197.5 (149.6)	< 0.001
Cholesterol (mg/d)	246.9 (133.5)	301.1 (153.1)	260.4 (124.6)	233.5 (115.0)	192.6 (113.6)	< 0.001	182.8 (106.4)	236.6 (113.2)	264.3 (125.7)	303.8 (153.8)	< 0.001
Saturated fatty acids (% energy)	11.7 (2.9)	13.1 (3.0)	12.2 (2.7)	11.4 (2.6)	10.1 (2.6)	< 0.001	11.4 (3.0)	11.8 (2.8)	11.8 (2.9)	11.7 (3.0)	< 0.001

Table 1 (continued)

Characteristic	Total (n = 79,294)	Quartiles of plant protein intake (% energy)				*P* value [b]	Quartiles of animal protein intake (% energy)				*P* value
		≤4.64 (n = 19,823)	4.65–5.36 (n = 19,824)	5.37–6.21 (n = 19,823)	≥6.22 (n = 19,824)		≤8.29 (n = 19,823)	8.30–10.19 (n = 19,824)	10.20–12.19 (n = 19,823)	≥12.20 (n = 19,824)	
Monounsaturated fatty acids (% energy)	11.5 (2.4)	12.0 (2.4)	11.6 (2.2)	11.3 (2.3)	11.1 (2.7)	< 0.001	11.5 (2.5)	11.5 (2.3)	11.4 (2.3)	11.5 (2.6)	< 0.001
Polyunsaturated fatty acids (% energy)	5.6 (1.6)	5.3 (1.4)	5.4 (1.4)	5.6 (1.4)	6.3 (1.8)	< 0.001	5.9 (1.7)	5.6 (1.5)	5.5 (1.4)	5.5 (1.5)	< 0.001
Trans fatty acids (% energy)	0.5 (0.2)	0.6 (0.2)	0.5 (0.2)	0.5 (0.2)	0.4 (0.2)	< 0.001	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.6 (0.2)	< 0.001
Whole grains (g/d)	66.5 (69.1)	39.8 (52.7)	59.1 (60.6)	73.4 (67.4)	93.6 (80.9)	< 0.001	72.6 (73.0)	67.4 (68.0)	64.7 (66.7)	61.3 (67.9)	< 0.001
Nuts (g/d)	7.2 (13.2)	3.2 (7.1)	5.4 (10.0)	7.7 (12.7)	12.4 (18.5)	< 0.001	10.3 (16.7)	7.7 (13.4)	6.0 (11.2)	4.7 (10.0)	< 0.001
Legumes (g/d)	13.4 (24.5)	7.0 (17.1)	10.7 (20.7)	13.7 (24.0)	22.1 (31.4)	< 0.001	17.9 (28.6)	13.0 (23.8)	11.8 (22.6)	10.8 (22.0)	< 0.001
Red meat (g/d)	37.4 (41.4)	50.1 (47.2)	41.5 (40.9)	35.1 (38.1)	22.9 (33.2)	< 0.001	15.4 (25.7)	34.2 (34.9)	44.0 (39.4)	56.1 (50.2)	< 0.001
Processed meat (g/d)	18.4 (24.9)	24.4 (29.5)	20.2 (25.1)	17.5 (22.8)	11.4 (19.0)	< 0.001	12.7 (19.7)	18.6 (23.5)	20.2 (25.3)	22.1 (29.0)	< 0.001
Poultry (g/d)	30.7 (39.6)	34.4 (43.1)	32.6 (39.6)	30.8 (38.1)	24.8 (36.5)	< 0.001	11.3 (22.1)	25.6 (32.0)	35.0 (37.6)	50.8 (50.1)	< 0.001
Egg and egg dishes (g/d)	21.3 (32.9)	27.3 (39.3)	21.5 (32.2)	19.1 (29.7)	17.5 (28.6)	< 0.001	16.1 (26.8)	19.0 (29.7)	22.4 (33.1)	27.8 (39.7)	< 0.001
Oily fish (g/d)	11.8 (22.7)	11.5 (22.8)	11.5 (21.8)	12.2 (22.6)	12.2 (23.5)	0.450	7.8 (17.5)	11.0 (21.0)	12.9 (23.2)	15.6 (27.3)	< 0.001
Non-oily fish (g/d)	17.7 (29.5)	18.6 (31.9)	18.2 (29.5)	17.8 (28.9)	16.3 (27.7)	< 0.001	12.2 (23.9)	17.7 (28.4)	19.0 (30.0)	22.1 (34.1)	< 0.001
Cheese (g/d)	17.6 (18.0)	18.8 (19.4)	18.1 (17.7)	17.1 (17.3)	16.5 (17.6)	< 0.001	18.1 (17.9)	18.0 (17.7)	17.7 (17.9)	16.7 (18.6)	< 0.001
Yogurt (g/d)	43.4 (53.0)	39.3 (52.5)	43.3 (51.7)	44.4 (52.3)	46.5 (55.0)	< 0.001	37.0 (48.2)	41.0 (50.1)	44.6 (52.4)	50.9 (59.5)	< 0.001
Milk (g/d)	198.6 (122.2)	208.4 (129.7)	210.8 (115.9)	205.7 (115.6)	169.4 (122.6)	< 0.001	167.0 (116.7)	203.1 (115.7)	211.9 (119.0)	212.3 (131.2)	< 0.001
Serum GGT (U/L)	34.1 (33.9)	38.4 (50.0)	34.6 (32.6)	33.0 (30.1)	30.5 (30.1)	< 0.001	32.6 (32.7)	34.3 (32.9)	35.3 (37.4)	34.3 (32.2)	< 0.001
Serum ALT (U/L)	22.8 (13.0)	23.8 (14.6)	23.0 (13.0)	22.5 (12.2)	21.8 (12.0)	< 0.001	21.9 (12.7)	22.8 (12.3)	23.1 (13.0)	23.2 (13.9)	< 0.001
Serum AST (U/L)	25.9 (9.4)	26.2 (10.8)	25.8 (8.6)	25.8 (9.6)	25.7 (8.3)	< 0.001	26.0 (9.2)	26.0 (8.7)	25.9 (10.1)	25.6 (9.3)	0.001

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *GGT* gamma glutamyltransferase, *TDI* Townsend deprivation index, *T2DM* Type 2 diabetes mellitus

[a]Mean value (standard deviation) for continuous variables and number (%) for categorical variables

[b]General linear regression models for continuous variables and chi-squared test for categorical variables

Table 2 Odds ratios (95% confidence interval) for biological aging indices by quartiles of plant protein (energy%) among 79,294 participants [a]

	Quartiles of plant protein (energy%)				*P* for trend[b]
	Q1	Q2	Q3	Q4	
Higher Klemera-Doubal Method Biological Age					
Case/N	6,771/19,823	6,360/19,824	6,072/19,823	5,569/19,824	
Model 1[d]	Ref	**0.94 (0.90–0.98)**[c]	**0.91 (0.87–0.95)**	**0.83 (0.80–0.87)**	< 0.001
Model 2[e]	Ref	**0.94 (0.90–0.98)**	**0.91 (0.87–0.95)**	**0.83 (0.79–0.86)**	< 0.001
Model 3[f]	Ref	**0.94 (0.90–0.98)**	**0.91 (0.87–0.96)**	**0.83 (0.79–0.88)**	< 0.001
Higher PhenoAge					
Case/N	2,396/19,823	2,021/19,824	1,936/19,823	1,642/19,824	
Model 1	Ref	**0.90 (0.84–0.96)**	**0.90 (0.84–0.97)**	**0.85 (0.79–0.91)**	< 0.001
Model 2	Ref	**0.89 (0.83–0.95)**	**0.88 (0.82–0.94)**	**0.79 (0.73–0.85)**	< 0.001
Model 3	Ref	**0.91 (0.85–0.98)**	0.93 (0.86–1.00)	**0.86 (0.79–0.94)**	0.003
Higher Allostatic Load					
Case/N	8,599/19,823	8,053/19,824	7,631/19,823	6,867/19,824	
Model 1	Ref	**0.92 (0.88–0.96)**	**0.87 (0.83–0.91)**	**0.81 (0.78–0.85)**	< 0.001
Model 2	Ref	**0.92 (0.88–0.96)**	**0.87 (0.83–0.91)**	**0.79 (0.76–0.83)**	< 0.001
Model 3	Ref	0.96 (0.92–1.00)	**0.93 (0.89–0.98)**	**0.90 (0.85–0.95)**	< 0.001
Longer Telomere Length					
Case/N	9,815/19,823	9,731/19,824	9,807/19,823	10,294/19,824	
Model 1	Ref	0.99 (0.95–1.03)	1.01 (0.97–1.05)	**1.06 (1.02–1.11)**	0.002
Model 2	Ref	0.99 (0.95–1.03)	1.01 (0.97–1.05)	**1.07 (1.02–1.11)**	0.001
Model 3	Ref	0.99 (0.95–1.03)	1.01 (0.96–1.05)	**1.06 (1.01–1.12)**	0.009

BMI body mass index, *Ref* reference, *TDI* Townsend deprivation index, *T2DM* Type 2 diabetes mellitus

[a]Data were listed as odds ratios (95% confidence interval) calculated using binomial logistic regression

[b]Tests for trends based on the variables containing the median values for each group

[c]Bold values denote statistical significance (significance criterion 0.05/3 = 0.017 for each quartile) after the Bonferroni correction

[d]Model 1: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI

[e]Model 2: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI, overall health rating, T2DM, cancer, intake of total energy

[f]Model 3: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI, overall health rating, T2DM, cancer, intakes of total energy, dietary animal protein, fruits, vegetables, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and trans-fatty acids, intake of dietary cholesterol, diet quality, multiple vitamin supplement use

0.84, 95%CI 0.79–0.90, OR: 0.94, 95%CI 0.90–0.98, OR: 1.07, 95%CI 1.03–1.11 for HPA, HAL, and LTL, respectively) (Supplementary Table 6). Yogurt intake was inversely related to HKDM-BA (OR: 0.90, 95%CI 0.86–0.94), HPA (OR: 0.89, 95%CI 0.83–0.95) and HAL (OR: 0.90, 95%CI 0.86–0.94) (Supplementary Table 15). Red meat and processed meat intake were associated with HKDM-BA (OR: 1.15, 95%CI 1.09–1.22; OR: 1.12, 95%CI 1.07–1.17, respectively), HPA (OR: 1.15, 95%CI 1.05–1.26; OR: 1.10, 95%CI 1.03–1.18, respectively) and HAL (OR: 1.08, 95%CI 1.02–1.14; OR: 1.05, 95%CI 1.01–1.10, respectively) (Supplementary Table 8,9). The intake of egg and egg dishes was not correlated with any of the four indices (Supplementary Table 11). The intake of other food categories did not show a relatively stable relationship with the four biological aging indices (Supplementary Table 7,10,12, 13, 14,16).

Associations between substituting different protein sources and biological aging

Substituting 5% energy from plant protein for 5% of energy from animal protein was associated with 19–28% lower odds of HKDM-BA (OR: 0.72, 95%CI 0.67–0.78), HPA (OR: 0.81, 95%CI 0.72–0.90), HAL (OR: 0.80, 95%CI 0.74–0.85) and 12% higher odds of LTL (OR: 1.12, 95%CI 1.07–1.17) (Table 4).

Specifically, when exploring the impact of plant protein food as a substitute for animal protein food on biological aging, we found that substituting whole grains for red meat or poultry, and substituting nuts for red or processed meat were negatively related to biological aging as defined by four biological aging indices (Table 4). It is worth mentioning that not all plant protein foods were inversely associated

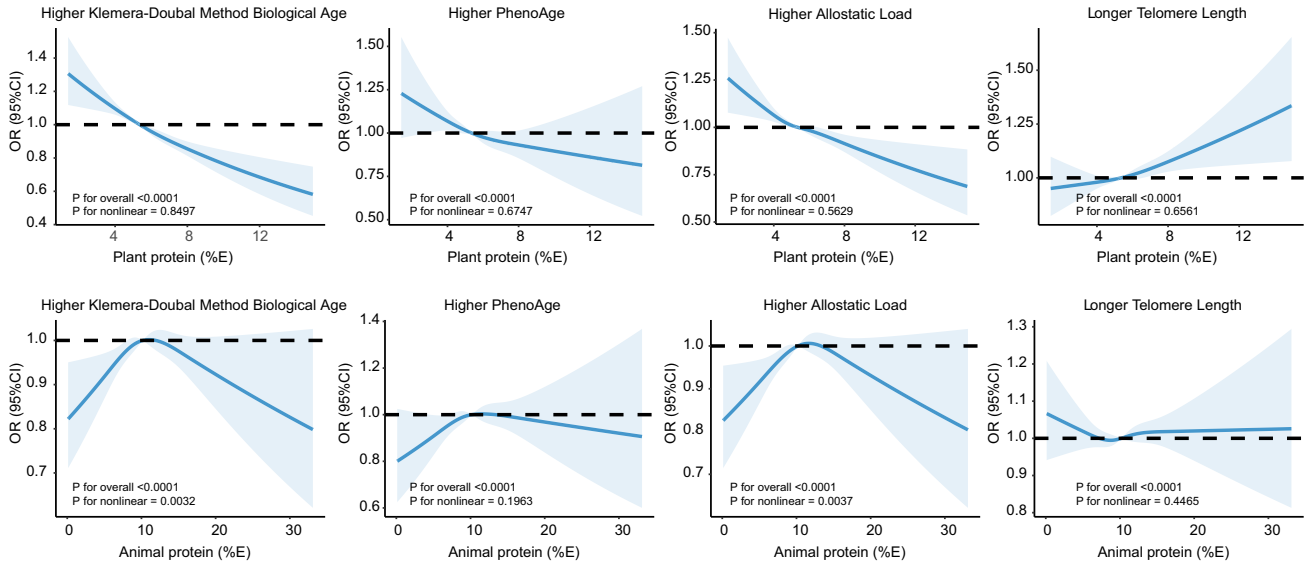

Fig. 1 The RCS curve of the association between plant and animal protein and biological aging indices. After adjusting for sex, age, ethnicity, Townsend deprivation index, education level, smoking status, drinking status, physical activity, body mass index, overall health rating, type 2 diabetes mellitus, cancer, intakes of total energy, fruits, vegetables, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and trans-fatty acids, intake of dietary cholesterol, diet quality, multiple vitamin supplement use. The mutual adjustment was conducted for plant protein and animal protein analysis

with biological aging when they substituted animal protein foods. The ORs (95%CI) of HKDM-BA, HPA, HAL and LTL for replacing 1 serving/day yogurt with legumes were 1.04 (1.01–1.07), 1.10 (1.06–1.15), 1.07 (1.04–1.09), 0.97 (0.95–0.99), respectively (Table 4).

The inconsistently stable results of substituting whole grains, nuts, or legumes for the remaining animal protein source foods are shown in Supplementary Table 17. Substituting 1 serving/day whole grains for 1 serving/day processed meat or non-oily fish; replacing 1 serving/day of poultry or non-oily fish with 1 serving/day of nuts was inversely associated with biological aging (indicated by three of the four biological aging indices). Also, substituting 1 serving/day of whole grains for yogurt; substituting 1 serving/day legumes for cheese was positively associated with biological aging (indicated by three of the four biological aging indices) (Supplementary Table 17).

Mediation analysis

Through mediation analysis, we found that serum, GGT, ALT, and AST mediated the indirect effect of plant protein on the HKDM-BA, HPA, HAL, and LTL (all $P < 0.001$). Specifically, GGT, ALT, and AST were estimated to explain 19.1, 4.4 and 2.8% of the association between plant protein and HKDM-BA, respectively; 24.5, 6.7 and 4.4% of the association between plant protein and HPA, respectively; 21.2, 6.0 and 4.5% of the association between plant protein and HAL, respectively; 11.5, 1.9 and 4.1% of the association between plant protein and LTL, respectively (Fig. 2).

Sensitivity analysis

We reran the logistic regression analyses for the 76,544 participants remaining after excluding those with extreme values for the percentage of energy from plant and animal protein. The above-mentioned association between plant and animal protein and four biological aging indices remains consistent (Supplementary Tables 18,19). Notably, stratified analyses showed no association between plant protein and any of the four biological aging indices in participants with T2DM (all P for trend > 0.05) (Supplementary Table S20). The remaining results are generally consistent with the conclusions obtained from the main analysis (Supplementary Tables S20, S21).

Discussion

Using the large-scale data, we found that a higher plant protein intake was negatively associated with biological aging, while animal protein intake did not show a consistent association with biological aging. Replacing animal protein with plant protein is inversely associated with biological aging, but this does not necessarily apply to all of their major food sources, and we present some suitable food alternatives. The association between plant protein and biological aging is partially mediated through serum GGT, ALT, and AST.

Table 3 Odds ratios (95% confidence interval) for biological aging indices by quartiles of animal protein (energy%) among 79,294 participants[a]

	Quartiles of animal protein (energy%)				*P* for trend[b]
	Q1	Q2	Q3	Q4	
Higher Klemera-Doubal method Biological Age					
Case/N	5,461/19,823	5,991/19,824	6,433/19,823	6,887/19,824	
Model 1[d]	Ref	**1.06 (1.01–1.11)**[c]	**1.10 (1.05–1.15)**	**1.07 (1.02–1.12)**	0.003
Model 2[e]	Ref	**1.06 (1.01–1.11)**	**1.11 (1.06–1.16)**	**1.08 (1.03–1.13)**	< 0.001
Model 3[f]	Ref	1.03 (0.99–1.08)	**1.07 (1.02–1.12)**	1.03 (0.98–1.09)	0.196
Higher PhenoAge					
Case/N	1,829/19,823	2,029/19,824	2,077/19,823	2,060/19,824	
Model 1	Ref	1.03 (0.96–1.10)	1.07 (1.00–1.15)	1.07 (0.99–1.14)	0.050
Model 2	Ref	1.03 (0.96–1.10)	1.07 (0.99–1.15)	1.05 (0.97–1.13)	0.142
Model 3	Ref	1.00 (0.93–1.08)	1.04 (0.96–1.12)	1.02 (0.94–1.11)	0.509
Higher Allostatic Load					
Case/N	7,001/19,823	7,861/19,824	8,038/19,823	8,250/19,824	
Model 1	Ref	**1.08 (1.03–1.12)**	**1.11 (1.06–1.16)**	**1.12 (1.07–1.17)**	< 0.001
Model 2	Ref	**1.08 (1.03–1.13)**	**1.11 (1.06–1.16)**	**1.12 (1.07–1.18)**	< 0.001
Model 3	Ref	1.04 (0.99–1.09)	1.06 (1.01–1.11)	1.05 (1.00–1.11)	0.054
Longer Telomere Length					
Case/N	10,041/19,823	9,775/19,824	9,900/19,823	9,931/19,824	
Model 1	Ref	1.00 (0.96–1.04)	1.01 (0.97–1.05)	0.97 (0.93–1.01)	0.181
Model 2	Ref	1.00 (0.96–1.04)	1.01 (0.97–1.05)	0.97 (0.93–1.01)	0.155
Model 3	Ref	1.01 (0.97–1.06)	1.03 (0.99–1.08)	1.00 (0.95–1.05)	0.997

BMI body mass index, *Ref* reference, *TDI* Townsend deprivation index, *T2DM* Type 2 diabetes mellitus

[a]Data were listed as odds ratios (95% confidence interval) calculated using binomial logistic regression

[b]Tests for trends based on the variables containing the median values for each group

[c]Bold values denote statistical significance (significance criterion 0.05/3 = 0.017 for each quartile) after the Bonferroni correction

[d]Model 1: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI

[e]Model 2: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI, overall health rating, T2DM, cancer, intake of total energy

[f]Model 3: Adjusted for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI, overall health rating, T2DM, cancer, intakes of total energy, dietary plant protein, fruits, vegetables, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and trans-fatty acids, intake of dietary cholesterol, diet quality, multiple vitamin supplement use

Increasing the intake of plant protein has the opposite relationship with biological aging. Previous studies support our results, as they found that plant protein intake was inversely associated with diabetic nephropathy, cardiovascular and all-cause mortality [46, 47]. Aging is often accompanied by an increased risk of mortality, but mortality does not reflect age-related changes in physiological integrity. A recent study among female nurses found that a higher intake of plant protein in middle age was associated with higher odds of healthy aging [48]. Our results further demonstrate that plant protein was inversely associated with biological aging in a larger population by using four specific biological aging indices in multiple dimensions.

We did not find that animal proteins showed a consistent relationship with biological aging. Previous studies have also found a variety of roles for animal protein. For example, increasing the intake of animal protein may positively or not associated with all-cause mortality [49, 50], whereas a cross-sectional study conducted on elderly Japanese women suggested that increased animal protein consumption will reduce frailty prevalence [51]. The reason for this complex result may be related to the wide range of dietary sources of animal protein. In our daily lives, we often provide dietary recommendations based on the increase or decrease in the intake of the primary dietary sources of nutrients. Therefore, it is important to explore the influence of dietary sources of protein on biological aging.

Whole grains and nuts rich in plant protein had a stronger inverse association with biological aging, while legumes had inconsistent relationships with the four indices. Previous studies have suggested that higher whole grains and nuts intake can increase life expectancy [52],

Table 4 Associations of substitution of different protein and food sources with participants in the UKB

Equivalent amount of substituted protein[a]	Substituted protein	Biological aging indices	OR (95% CI)
Plant protein	5% of energy from animal protein	Higher Klemera-Doubal method Biological Age	0.72 (0.67–0.78)
		Higher PhenoAge	0.81 (0.72–0.90)
		Higher Allostatic Load	0.80 (0.74–0.85)
		Longer Telomere Length	1.12 (1.07–1.17)
1 serving/day whole grains	1 serving/day red meat	Higher Klemera-Doubal method Biological Age	0.92 (0.90–0.94)
		Higher PhenoAge	0.92 (0.90–0.95)
		Higher Allostatic Load	0.95 (0.93–0.96)
		Longer Telomere Length	1.03 (1.01–1.04)
	1 serving/day poultry	Higher Klemera-Doubal method Biological Age	0.94 (0.92–0.96)
		Higher PhenoAge	0.95 (0.92–0.98)
		Higher Allostatic Load	0.97 (0.95–0.99)
		Longer Telomere Length	1.02 (1.01–1.04)
1 serving/day nuts	1 serving/day red meat	Higher Klemera-Doubal method Biological Age	0.92 (0.90–0.95)
		Higher PhenoAge	0.92 (0.88–0.95)
		Higher Allostatic Load	0.96 (0.93–0.98)
		Longer Telomere Length	1.03 (1.01–1.05)
	1 serving/day processed meat	Higher Klemera-Doubal method Biological Age	0.90 (0.88–0.93)
		Higher PhenoAge	0.90 (0.86–0.93)
		Higher Allostatic Load	0.95 (0.93–0.98)
		Longer Telomere Length	1.03 (1.01–1.05)
1 serving/day legumes	1 serving/day yogurt	Higher Klemera-Doubal method Biological Age	1.04 (1.01–1.07)
		Higher PhenoAge	1.10 (1.06–1.15)
		Higher Allostatic Load	1.07 (1.04–1.09)
		Longer Telomere Length	0.97 (0.95–0.99)

BMI body mass index, *CI* confidence interval, *OR* odds ratio, *TDI* Townsend deprivation index, *T2DM* Type 2 diabetes mellitus

[a]The substitution analyses included adjustment for sex, age, ethnicity, TDI, education level, smoking status, drinking status, physical activity, BMI, overall health rating, T2DM, cancer, intakes of total energy, fruits, vegetables, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and trans-fatty acids, intake of dietary cholesterol, diet quality, multiple vitamin supplement use. In the substitution analysis of different protein food sources, the intake of other dietary protein sources was also adjusted

reduce the risk of frailty, and improve metabolic health by regulating blood glucose and lipids [53]. Legumes do have many health benefits, such as anti-inflammatory, antioxidant, and improving mitochondria function [54], but they are also positively correlated with the occurrence of hyperuricemia because they may be higher in purines [55]. Since biological aging is a complex process that is influenced by a combination of factors, we believe that it is not yet possible to determine whether legumes are related to biological aging. From the perspective of the overall intake of legumes, the current effect on biological aging is complex and not as obvious as that brought by whole grains, so we subsequently did substitution analysis, not simply from the intake of legumes, but from how to replace dietary protein sources to seek more conducive to improving biological aging measures.

Dietary sources of animal protein do have various effects on biological aging. We found that red and processed meat had a more pronounced positive association with biological aging. This may be related to the fact that red and processed meat tend to contain more sodium and nitrites/nitrates [56], increasing intake of these substances is associated with an increased risk of cancer [57], T2DM, and cardiovascular disease [58]. These effects are likely to be related to the combination of high animal protein content plus nitrites/nitrates. The intake of cheese and yogurt was also negatively associated with biological aging, and the association between yogurt and biological aging was stronger. Increasing dairy intake can improve cognitive function in older adults [59]. Yogurt contains bacterial cultures with proteolytic activity, making it a great source of high-biological-value essential amino acids [60], which has been shown to have a positive effect on improving both bone health in aging and immune aging [61]. This strong healthy effect partly explains our findings that replacing yogurt with plant-based protein sources may not have negative relationships with biological aging. Taken together, these results indicate that after conducting nutritional substitution analysis, it is necessary

Fig. 2 Mediating effects of biochemical indexes on the relationship between plant protein and biological aging indices. **a** Mediation analysis for the indirect effect of gamma glutamyltransferase **b** Mediation analysis for the indirect effect of alanine aminotransferase **c** Mediation analysis for the indirect effect of aspartate aminotransferase. *** means $P < 0.001$. *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *HAL* Higher allostatic load, *HKDM-BA* Higher Klemera-Doubal Method Biological Age, *HPA* Higher PhenoAge, *LTL* Longer telomere length

to conduct further substitution analysis on primary dietary sources, thereby providing some specific reference suggestions for adjusting dietary structure to reduce biological aging risk.

We further explored the potential mechanisms of the association between plant protein and biological aging. GGT, ALT, and AST are enzymes used to detect liver disease, and their levels in serum increase with age [62]. A cohort study reported that plant protein appears to improve metabolic liver diseases related to these three enzymes [63]. These studies provide further support for our finding that plant protein may negatively regulate GGT, ALT, and AST, thereby improving biological aging.

In the stratified analysis, we discovered that the association between plant protein and four biological aging indices disappeared in the T2DM participants. According to the mediating factors we discovered, as well as the levels of GGT, ALT, and AST in T2DM patients are prone to abnormalities due to liver disease complications [64–66] We suppose that compared with non-diabetic individuals, T2DM patients are in a state of metabolic disorder [67]. Therefore, plant protein often needs to adjust a greater degree of GGT, ALT, and AST levels to improve biological aging. This may cause the association between plant protein and biological aging to weaken to the point of disappearance.

Our study has several strengths. First, the study had a large study sample of > 70,000 individuals, with detailed information on various demographics, lifestyles, health status, and diet, which augmented the statistical power and provided a more dependable result. Second, we used four indices to systematically reflect aging from different aspects, which adds confidence to the relationship we found. Third, to facilitate recommendations in practical applications, we specified the main dietary sources of plant and animal protein and evaluated the effects of food substitution from different dietary protein sources. Moreover, we performed mediation analyses to explore potential mechanisms of plant protein's influence on biological aging indices, which could help develop mechanism-based dietary intervention strategies to prevent and mitigate aging in the future. Finally, the results of the stratified analysis remind us of the applicability of increasing plant protein intake in T2DM patients.

Still, some limitations should be mentioned. First, our analysis was performed using cross-sectional data, so we are unable to deduce the causal relationship between dietary protein and biological aging indices. Second, the 24-h dietary recall interview, as a self-reported assessment, may introduce biases in recalling and reporting when assessing dietary intake, which in turn does not fully reflect an individual's daily intake. Nevertheless, we used the average of at least two 24-h dietary recalls as a measure of dietary intake, which may have partially reduced some of the bias. Third, our population consisted predominantly of individuals of a white race, which will limit generalizability. Fourth, our study focuses on results associated with all four biological aging indices, but some foods associated with one or two of the four indices may also have a potential association with biological aging and should be given some attention in future research.

Conclusion

In a word, our study found that higher plant protein intake was negatively associated with biological aging. Although animal proteins showed no correlation, food sources of animal protein displayed different correlations. Our study provides some alternative measures of protein food sources that can help people cope with biological aging. Future research should investigate the causal mechanisms through longitudinal study designs.

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Author contributions XX and YL conceived and designed the study. XX, XP were involved in the data collection. XX, XP, and HX performed the statistical analysis. XX, JH, XY wrote the manuscript. XW, JZ, SP, and WW critically reviewed this draft. 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 '103,547'. The data that support the findings of this study are available from http://www.ukbiobank.ac.uk/.

Declarations

Conflict of interest None declared.

Ethical approval The ethical clearance for the UK Biobank was granted by the North West Multi Center Research Ethics Committee (REC reference: 11/NW/0,3820). Written informed consent was obtained from each participant before participation in this study.

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