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Multi-dimensional evidence from the UK Biobank shows the impact of diet and macronutrient intake on aging

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Chen Zhu[1,2,3], Youfa Wang[4], Xiaosong Yang[5], Qiran Zhao[1,2], Wenyan Xu[2], Xiaolu Wang[2,6], Yanjun Liang[7,8], Qihui Chen[3] ✉ & Shenggen Fan[1,2] ✉

Abstract

Background The role of diet in aging is crucial, yet research findings on how specific diets influence human aging remain inconsistent. Understanding the relationship between dietary factors and aging could inform interventions to promote healthier aging outcomes.

Methods We analyzed data from the UK Biobank baseline survey and a 24-hour dietary assessment survey to investigate the association between diet and aging. The study examined 18 individual food intakes, 6 dietary patterns, 3 macronutrient intakes, and 3 dietary quality scores. High-dimensional Fixed Effects (HDFE) models were used to assess associations between dietary factors and aging measures, including telomere length, phenotypic age, and brain grey/white matter volumes. Multivariable Mendelian Randomization (MVMR) was employed to explore causal links between macronutrient consumption and aging outcomes.

Results Our results show that healthier diets are generally associated with improved aging outcomes from HDFE analyses. Plant-based food consumption correlates with increased telomere length and reduced phenotypic age, while animal-based food intake is linked to adverse aging effects. MVMR results confirm the causal benefits of carbohydrate intake, including reductions in phenotypic age ($\beta = -0.0025$; 95% CI = [−0.0047, −0.0003]; $p = 0.0253$) and increases in whole-brain grey matter volume ($\beta = 0.0262$; 95% CI = [0.007, 0.046]; $p = 0.0087$). The latter association remains significant after multiple testing correction.

Conclusions This study underscores the significant role of diet in biological aging and provides robust evidence for the benefits of carbohydrate intake in promoting healthier aging. These findings highlight the potential of dietary interventions to improve aging-related outcomes.

Plain language summary

We investigated the impact of diet on aging using a large amount of data about people living in the UK. We investigated the impact of dietary habits such as food consumed, eating patterns, and nutrient intake on indicators of aging, including biological age, brain health, and changes in the composition of people's cells. We found that healthier diets, particularly those rich in carbohydrates, are linked to slower aging and improved brain health. Plant-based foods showed benefits, while animal-based diets were linked to negative effects. These findings emphasize the importance of diet in aging, offering insights for individuals and policymakers that could promote healthier, longer lives.

Aging is a complex biological process involving molecular changes, cellular senescence, and physiological dysregulation[1]. While chronological aging is inevitable, biological aging varies among individuals due to genetic and environmental factors[2]. Geroscience theory posits that slowing biological aging could prevent diseases, extend healthy lifespan, and reduce healthcare costs[1,3]. Lifestyle factors such as diet, alcohol consumption, smoking, and physical activity significantly influence aging[4,5]. Diet, in particular, directly impacts health outcomes, including chronic diseases, serum biomarkers, and DNA methylation, suggesting its potential role in modulating aging[6–8].

However, research on specific dietary patterns and their effects on aging has yielded inconsistent and inconclusive results[9]. These discrepancies can be attributed to varying methods of measuring biological aging, limited

[1]Academy of Global Food Economics and Policy (AGFEP), China Agricultural University, Beijing, China. [2]College of Economics and Management, China Agricultural University, Beijing, China. [3]Beijing Food Safety Policy and Strategy Research Base, China Agricultural University, Beijing, China. [4]School of Public Health, Xi'an Jiaotong University, Xi'an, China. [5]Beijing Jishuitan Hospital, Beijing, China. [6]Stanford Center on China's Economy and Institutions, Stanford University, Stanford, USA. [7]Nanjing Starhomes Health Management and Consulting Co. Ltd., Nanjing, China. [8]Jiangsu Minsheng Vocational Training School, Nanjing, China. ✉e-mail: chenqihui2002@126.com; S.FAN@cgiar.org

sample sizes, and a lack of controlled trials or robust causal inference approaches. For instance, while some studies suggest that low-carbohydrate diets improve serum factors related to aging, others link these diets to higher mortality rates[10,11]. Similarly, reviews on diet's impact on cognitive aging and telomere length report mixed outcomes[12–14].

Given the imperative to promote healthy aging—a state where individuals maintain functional abilities that enable well-being—the lack of clear guidance from existing studies is a significant gap in knowledge. This study aims to systematically investigate the relationships between dietary factors and multidimensional measures of aging (i.e., telomere length, clinical biomarkers-based phenotypical age, and brain volumetric measurements of grey/white matter volumes), focusing particularly on the causal impacts of macronutrient intakes using cohort study data. Our goal is to clarify the role of diet in biological aging processes and provide robust evidence to support dietary recommendations for healthy aging. In this study, we find that healthier diets, particularly those rich in carbohydrates, are linked to slower aging and improved brain health. In addition, plant-based foods show benefits, while animal-based diets are linked to negative effects on healthy aging.

Methods

Study sample and data

Our analysis draws dietary, biomarker, and socio-demographic data from the UK Biobank baseline survey. UK Biobank is the database for a population-based study involving 502,409 UK residents approved by the NHS National Research Ethics Service (ref. 11./NW/0382). Between March 2006 and July 2010, individuals residing within 25 miles of one of the 22 study assessment centers in England, Scotland, and Wales were recruited to provide data on a wide range of socio-demographic, clinical, and lifestyle outcomes. Blood, urine, and saliva samples, as well as physical measurements, were collected from all participants with their written informed consent during the interviews. For this study, permission to access and analyse the UK Biobank data was approved under the application numbered 89068.

At the baseline (2006), a food frequency touchscreen questionnaire was used to collect data on all participants' dietary habits[14], including single food intakes (e.g., cooked vegetables consumed), food types (e.g., types of cereal primarily consumed), and intake frequencies (e.g., frequency of oily fish consumption). Observations (7848 participants) with unrealistic answers were dropped. In early 2009, the main UK Biobank study protocol further included the Oxford WebQ, a web-based dietary assessment tool that asks about the consumption of up to 206 types of foods and 32 types of drinks during the previous 24 h[15,16]. In total, 210,977 participants had completed at least one assessment.

Serum biomarker data used to construct phenotypic age were obtained from the UK Biobank blood samples collected from all participants at the baseline and analyzed within 24 h of the blood draw with Beckman Coulter LH750 instruments at the UK Biobank central laboratory[17].

Participants' genotypes were analyzed with the Affymetrix (Santa Clara, CA, USA) UK Biobank Axiom Array and the UK BiLEVE Axiom Array. Information regarding principal components analysis and genetic principal components is provided elsewhere[18]. Telomere length data measuring biological age were also derived from the DNA samples[19].

High-quality MRI (magnetic resonance imaging) brain imaging data were available for a subset of participants ($N = 42{,}942$) upon additional agreement. These data were acquired using a Siemens Skyra 3 T scanner (Siemens Healthcare, Erlangen, Germany) with a standard 32-channel head coil. Structural imaging and diffusion data were processed by UK Biobank technicians and made available to approved researchers as imaging-derived phenotypes (IDPs)[20,21].

Measurements of dietary factors

Individual food intake. The consumption of seven common food groups (vegetables, fruits, grains, fish, meat, dairy products, and beverages) and intakes of 18 specific food categories were investigated: cooked vegetables (tablespoons/day), salad/raw vegetables (tablespoons/day), fresh fruits (pieces/day), dried fruits (pieces/day), bread (pieces/day), cereal (bowls/week), oily fish (times/week), non-oily fish (times/week), processed meat (times/week), poultry (times/week), beef (times/week), lamb/mutton (times/week), pork (times/week); cheese (times/week), milk (full cream/semi-skimmed/skimmed=1; never/rarely consumed/soya=0), hot drinks (very hot/hot=1; warm/never hot drinks=0), coffee (cups/day), and tea (cups/day). Detailed UK Biobank data field codes were provided in Supplementary Table 1.

Dietary patterns. This study considers six dietary patterns: low-carb, high-carb, high-protein, low-fat, high fat, and ketogenic diets, which are defined based on the absolute intake of a macronutrient as a function of body weight or a proportion to total energy intake—Supplementary Table 2 provides more details.

Macronutrient intake. Daily macronutrient intakes of carbohydrates, protein, and fat (all in grams) were calculated by UK Biobank experts based on responses from the computerized 24-hour dietary recall follow-up questionnaire (described above)[15,16]. Data were available for 210,977 participants in this study.

Diet quality scores. Following detailed protocols provided by FAO (Food and Agriculture Organization) and USDA (US Department of Agriculture) guidelines, we calculated three diet-quality scores using the 24-hour dietary recall data: Individual Diet Diversity Score (IDDS)[22,23], Healthy Eating index (HEI-2015)[24], and Dietary Approaches to Stop Hypertension (DASH) index[25].

Measurements of aging

Telomere length. Leucocyte telomere length (LTL) was measured using an established multiplex qPCR assay on DNA samples from UK Biobank participants. After extensive quality checks and adjustments for technical factors, 473,994 participants in our sample had valid LTL measurements. The LTL was then log-transformed to yield an approximately normal distribution and z-standardized using the distribution of all individuals with valid LTL measurements[19].

Clinical biomarkers-based phenotypic age. *Clinical biomarkers-based phenotypic age w*as determined using chronological age and nine clinical biomarkers as proposed by Yang et al.[4]: albumin, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean corpuscular volume, red cell distribution width, alkaline phosphatase, and white blood cell count[4]. Employing a parametric proportional hazards model based on the Gompertz distribution, this approach calculates a "phenotypic age" by modeling 10-year mortality risk, offering a robust quantifiable measure of biological aging. Biomarker data were obtained from UK Biobank samples collected at enrollment, typically analyzed within 24 h at the central laboratory using Beckman Coulter LH750 instruments.

Grey/white matter volume. Participants' whole-brain grey and white matter volume data (normalized for head size) were obtained from the UK Biobank brain imaging datasets.

Covariates

To control for potential confounding factors, we included a series of socio-demographic, physiological, and genetic characteristics in the statistical analysis: gender, chronological age, education (whether with a college/university degree), body mass index (BMI), top ten genetic principal components (PCs), and the Townsend Deprivation Index (TDI)—a measure of local material deprivation: positive (negative) numbers indicate lower (higher) socioeconomic status.

Statistics and Reproducibility

Statistical models. We used four measures of aging (telomere length, clinical biomarkers-based phenotypic age, whole-brain grey matter

volume, and whole-brain white matter volume) as the primary outcomes and four sets of dietary factors (dietary habits/food intake, dietary patterns, macronutrient intakes, and diet quality scores) as main explanatory variables.

First, high-dimensional fixed effects (HDFE) models[26] were fitted to examine the associations of dietary factors with aging while controlling for a large number of occupational, ethnicity, regional, and ethnicity-by-region fixed effects (FEs) to mitigate unobserved confounding. HDFE is essential for accurately identifying the influence of confounding variables across varied ethnic, regional, and occupational groups. It has particular advantages over traditional multivariate linear regression when handling large numbers of fixed effects or multi-dimensionally clustered standard errors. In those cases, HDFE can adjust degrees of freedom more efficiently, providing more precise estimates (i.e., with smaller standard errors) under complex fixed-effect structures when standard errors are clustered in multiple dimensions. Additionally, HDFE offers superior computational efficiency, which is especially important when dealing with very large datasets and numerous covariates. The HDFE models take the following form:

$$Aging = \boldsymbol{\lambda}\boldsymbol{\Psi} + \boldsymbol{\beta}\boldsymbol{X} + \theta_1 Occupation + \theta_2 Ethinicity + \theta_3 Region + \theta_4 Ethnicity\,Region + \varepsilon \quad (1)$$

where *Aging* is one of the four aging measures of interest; $\boldsymbol{\Psi}$ represents a particular set of dietary factors (e.g., dietary patterns or macronutrient intakes); $\boldsymbol{\lambda}$ is the parameter vector of primary interest; $\boldsymbol{X}$ is the set of covariates discussed above; also included are a total of 477 FEs: 336 occupational FEs, 18 race/ethnicity FEs, 10 regional FEs, and 113 race/ethnicity-by-region FEs; ε is a disturbance term. A detailed list of the 477 fixed effects used in HDFE were provided in Supplementary Data 1.

Second, we address the potential endogeneity and interrelatedness of macronutrient intakes using a Multivariate Mendelian Randomization (MVMR) framework. This approach leverages multiple genetic variants as instrumental variables (IVs) to *simultaneously* assess the effects of multiple related endogenous dietary exposures on outcomes[27]. The strength of Mendelian randomization stems from the random allocation of genes at meiosis, resembling random treatment assignments in randomized controlled trials that may be infeasible or unethical in our setting[28]. MVMR improves upon traditional univariate MR by incorporating multiple genetic instruments and accounting for the interrelations among different macronutrient intakes, thereby deriving more robust causal inferences. The combination of the HDFE approach and MVMR analysis forms a triangulation design, which can strengthen findings when different statistical methods, based on distinct assumptions, reach the same conclusion[28,29]. The STROBE-MR checklist is available elsewhere[30].

Based on recent genome-wide association studies (GWAS) that identified genetic variants that are closely related to diet compositions and macronutrient intakes[31], we used nine independent single nucleotide polymorphisms (SNPs)—rs10510554, rs8097672, rs10206338, rs10962121, rs2472297, rs33988101, rs57193069, rs1461729, and rs445551—as genetic IVs in our MVMR design[32]. To rule out potential mediating effects of genetic variants on aging outcomes via other traits that could violate the statistical assumptions of MR designs[33], these SNPs were selected based on functional annotation results from SNPnexus and GWAS Catalog online tools[34,35]. Detailed information on these SNPs, including chromosome, position, effect allele, alternative allele, effect allele frequency, beta values, *p*-values, and nearest gene were provided in Supplementary Table 3. It is worth noting that we selected only a subset of dietary markers (namely, dietary intakes of carbohydrates, proteins, and fats) for MVMR, given data on these macronutrients robustly available from previous genome-wide association studies, to ensure the reliability of MR results[31]. Formally, we estimate the following two-stage least-squares (2SLS) specifications:

First stage:

$$carbohydrate = \delta^{carb}\boldsymbol{G} + \mu^{carb}\boldsymbol{X} + \pi_1^{carb} Ethinicity + \pi_2^{carb} Region + \xi^{carb} \quad (2a)$$

$$protein = \delta^{protein}\boldsymbol{G} + \mu^{protein}\boldsymbol{X} + \pi_1^{protein} Ethinicity + \pi_2^{protein} Region + \xi^{protein} \quad (2b)$$

$$fat = \delta^{fat}\boldsymbol{G} + \mu^{fat}\boldsymbol{X} + \pi_1^{fat} Ethinicity + \pi_2^{fat} Region + \xi^{fat} \quad (2c)$$

Second stage:

$$Aging = \gamma^{carb}\overline{carbohydrate} + \gamma^{protein}\overline{protein} + \gamma^{fat}\overline{fat} + \mu\boldsymbol{X} + \rho_1 Ethinicity + \rho_2 Region + \epsilon \quad (3)$$

Mechanically, in the first stage (Equations 2a–2c), each of the macronutrient intakes is regressed on a set of nine genetic IVs ($\boldsymbol{G}$), the set of covariates ($\boldsymbol{X}$), ethnicity fixed effects, and regional fixed effects. In the second stage (Equation 3), each aging outcome is regressed on the fitted values of all three macronutrient intakes simultaneously, along with all control variables used in the first stage. In practice, all regressions involved in the 2SLS framework were performed at once using STATA 15. A detailed list of the 28 fixed effects used in MVMR were provided in Supplementary Table 4.

In each model, we excluded those with missing data on particular dietary factors, aging outcomes, or genotyping information, resulting in 24,875 to 493,478 participants in different regression models. All regressions were followed by Sidak-Holm *post hoc* analyses to correct for multiple comparisons[36,37].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Summary statistics

Among all 493,478 participants, 45.7% are male; 54.3% are female (Table 1). Over 90% of the participants are White; 32.2% had a college/university degree. The average participant was 56.5 years old, with a BMI of 27.2 kg/m^2 and a Townsend Deprivation Index of −1.3, consuming 255 grams of carbohydrates, 78 grams of fat, 82 grams of protein, and a total of 2121 calories daily. Detailed pairwise Pearson's correlation coefficients between aging outcomes and dietary exposures are displayed in Fig. 1, panel a and panel b, respectively.

Associations of dietary factors with aging

In our HDFE analyses, we found 45 significant associations out of 120 between individual food intakes, dietary patterns, daily intakes of macronutrients, diet quality scores, and four measures of aging, after applying the Sidak-Holm *post hoc* correction for multiple comparisons. Figure 2 presents a heatmap summarizing estimated effects of all dietary exposures (in rows) on different aging outcomes (in columns), where red dots indicate potential risky effects, green dots indicate protective effects, and white dots indicate null (i.e., insignificant after the Sidak-Holm correction for multiple testing) effects on specific measures of aging. Detailed information on effect sizes (i.e., beta), original *p* values, and *p* values after the Sidak-Holm correction of all estimated parameters are included in Supplementary Data 2.

Individual food intakes and aging. For individual food intakes, as illustrated in panel a of Fig. 2, we observed that animal-based foods generally have adverse effects on aging. For instance, processed meat intake is significantly correlated with both shorter telomere length and increased biomarkers-based phenotypical age. Similarly, intakes of beef, lamb/mutton, pork, and milk are associated with elevated biomarkers-

Table 1 | Summary statistics of the analytical sample (*N* = 493,478)

		Pooled		Male		Female	
		N = 493478 (100%)		*N* = 225676 (45.7%)		*N* = 267802 (54.3%)	
Variable		% or Mean	S.D.	% or Mean	S.D.	% or Mean	S.D.
Age		56.5	8.1	56.8	8.2	56.4	8.0
College degree		32.2%	-	33.6%	-	31.1%	-
BMI		27.2	4.4	27.7	4.0	26.8	4.7
Townsend deprivation index[a]		−1.3	3.1	−1.3	3.1	−1.4	3.0
Daily intake of calories		2120.9	642.7	2300.1	675.3	1974.1	574.5
Daily intake of carbohydrates (grams)		254.9	89.5	273.1	93.3	240.0	83.4
Daily intake of fat (grams)		77.9	30.6	83.8	32.7	73.0	27.9
Daily intake of protein (grams)		82.4	26.0	87.3	27.8	78.3	23.6
Ethnicity	*White*	91.4%	-	91.7%	-	91.2%	-
	African	1.4%	-	1.3%	-	1.5%	-
	East Asian	0.4%	-	0.3%	-	0.4%	-
	South Asian	1.7%	-	2.0%	-	1.4%	-
	Other[b]	5.1%	-	4.7%	-	5.5%	-
Region	*East Midlands*	8.0%	-	8.0%	-	8.0%	-
	East of England	0.3%	-	0.3%	-	0.3%	-
	London	12.4%	-	12.0%	-	12.7%	-
	North East	11.1%	-	11.2%	-	11.1%	-
	North West	16.3%	-	16.7%	-	16.0%	-
	Scotland	7.3%	-	7.1%	-	7.4%	-
	South East	9.8%	-	9.6%	-	10.0%	-
	South West	8.4%	-	8.1%	-	8.7%	-
	Wales	4.3%	-	4.3%	-	4.3%	-
	West Midlands	8.2%	-	8.8%	-	7.7%	-
	Yorkshire and The Humber	14.0%	-	14.0%	-	14.0%	-

[a]The Townsend Deprivation Index is a measure of local material deprivation in UK Biobank data, in which positive numbers indicate lower socioeconomic status, and negative numbers indicate higher socioeconomic status. [b]Other includes any races or ethnicities not otherwise specified.

based phenotypical ages. Conversely, plant-based foods show potential anti-aging benefits; for example, consumption of cooked/raw vegetables and fresh/dried fruits is linked to longer telomeres and/or reduced phenotypic age. Cereal intake is positively associated with longer telomere length, a younger phenotypical age, and greater grey matter volume, though bread intake shows an adverse association with phenotypical age. Among beverages, while tea intake shows negative associations with aging markers, hot drinks are linked with a younger phenotypical age.

It is notable that some foods and beverages show mixed effects on aging outcomes. For example, oily fish intake is beneficial for phenotypic age but negatively impacts grey matter volume. Cheese consumption is associated with both increased telomere length and a younger phenotypical age, yet it also correlates with reduced brain grey/white matter volumes. Surprisingly, coffee, despite its adverse association with telomere length and grey matter volume, is beneficially linked with reduced phenotypic age.

Dietary patterns and aging. Figure 2, panel b, reports estimated associations of six dietary patterns with aging. Two common dietary patterns display consistently adverse effects: (1) a low-carbohydrate diet is negatively associated with three of the four aging outcomes (column 1, 3, and 4); and (2) a high-fat diet is linked to reduced brain grey and white matter volumes. Conversely, a high-protein diet appears to benefit white matter volume of brain. A low-fat diet shows mixed effects; while it is linked to reduced grey matter volume, it is also associated with a decrease in biomarkers-based phenotypic age.

Macronutrients and aging. Figure 2, panel c, highlights the associations between macronutrient intake and aging outcomes. Specifically, carbohydrate intake is beneficially linked to both a younger biomarkers-based phenotypic age and a larger grey matter volume. Conversely, fat intake is associated with an increase in phenotypic age. No significant associations between protein intake and aging outcomes were found after the correction for multiple testing.

Diet quality and aging. Figure 2, panel d, illustrates positive associations between three common diet quality scores and aging outcomes. The three diet quality scores—HEI-2015, DASH, and Food Diversity Index—are all beneficially linked to reduced blood-based phenotypic ages. Additionally, higher HEI-2015 and Food Diversity Index scores are associated with longer telomere lengths.

However, these diet quality scores do not show significant associations with grey/white matter volumes, suggesting that while these metrics effectively capture benefits on telomere length and blood-based phenotypic age, they may not adequately reflect aging-related changes in brain health. This highlights the need for an improved dietary assessment toolbox to comprehensively evaluate the impact of diet across various aspects of aging closely related to individual well-being.

Calorie restriction and aging. Calorie restriction (CR) has been recently associated with increased longevity and improved health in both model organisms and humans[38,39]. To further explore the role of caloric intake, we conducted additional HDFE regressions on various aging measures

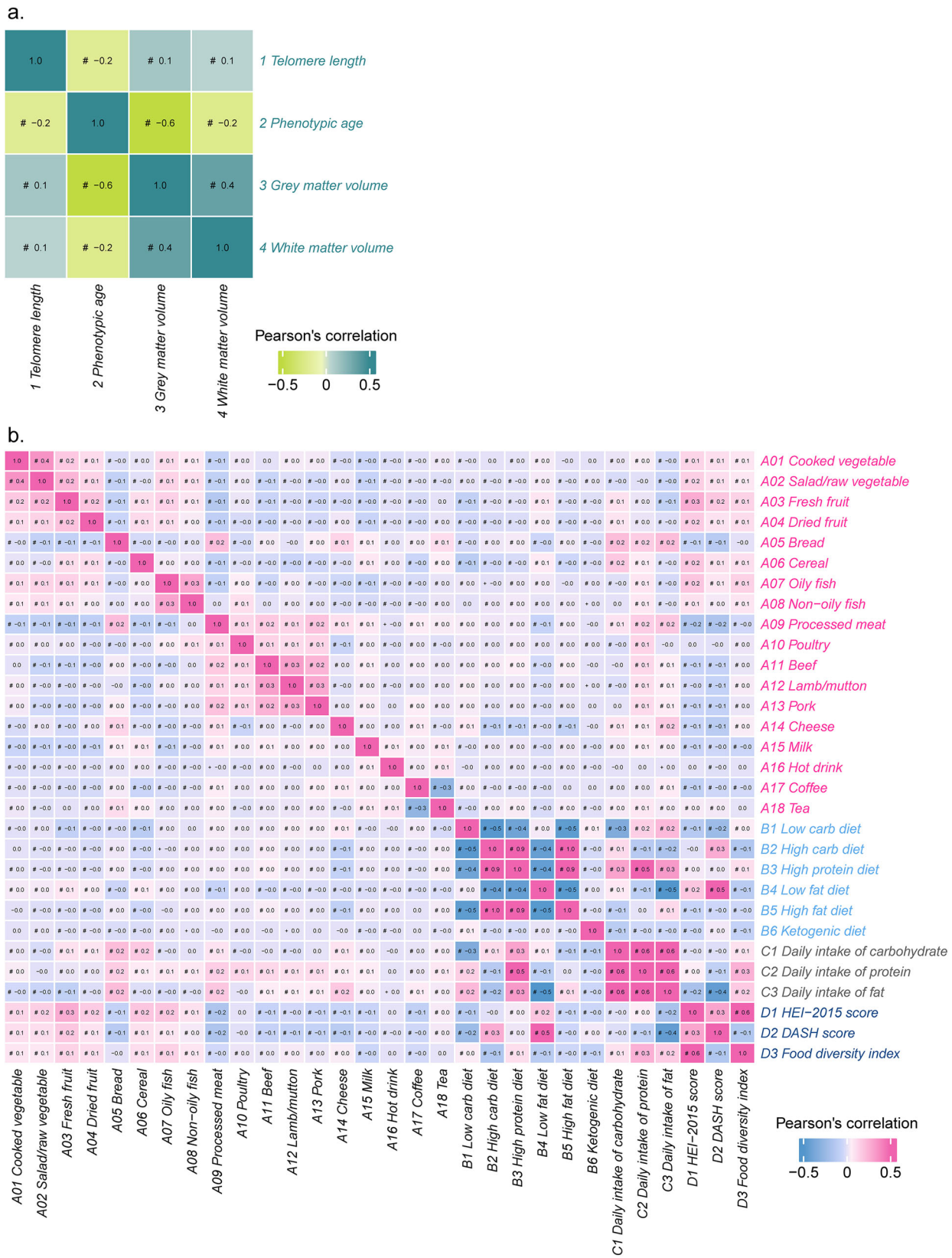

Fig. 1 | Pairwise Pearson's correlation coefficients of aging outcomes and dietary exposures. a Correlation coefficients of aging outcomes. **b** Correlation coefficients of dietary exposures. # and * represent statistical significance at $p < 0.01$ and $p < 0.05$, respectively.

based on daily total caloric intake (in 1000 calories). Initially, the models only included a set of previously described fixed effects; subsequently, we added controls for gender, age, education, BMI, and TDI. Our findings, as detailed in Supplementary Table 5, indicate that the associations of caloric intake with aging outcomes were *not* robust once adjusted for individual factors. This suggests that the nutritional composition of diets plays a more critical role in aging than mere calorie restriction. In essence, *not* all dietary calories are equivalent in their impact on the aging process,

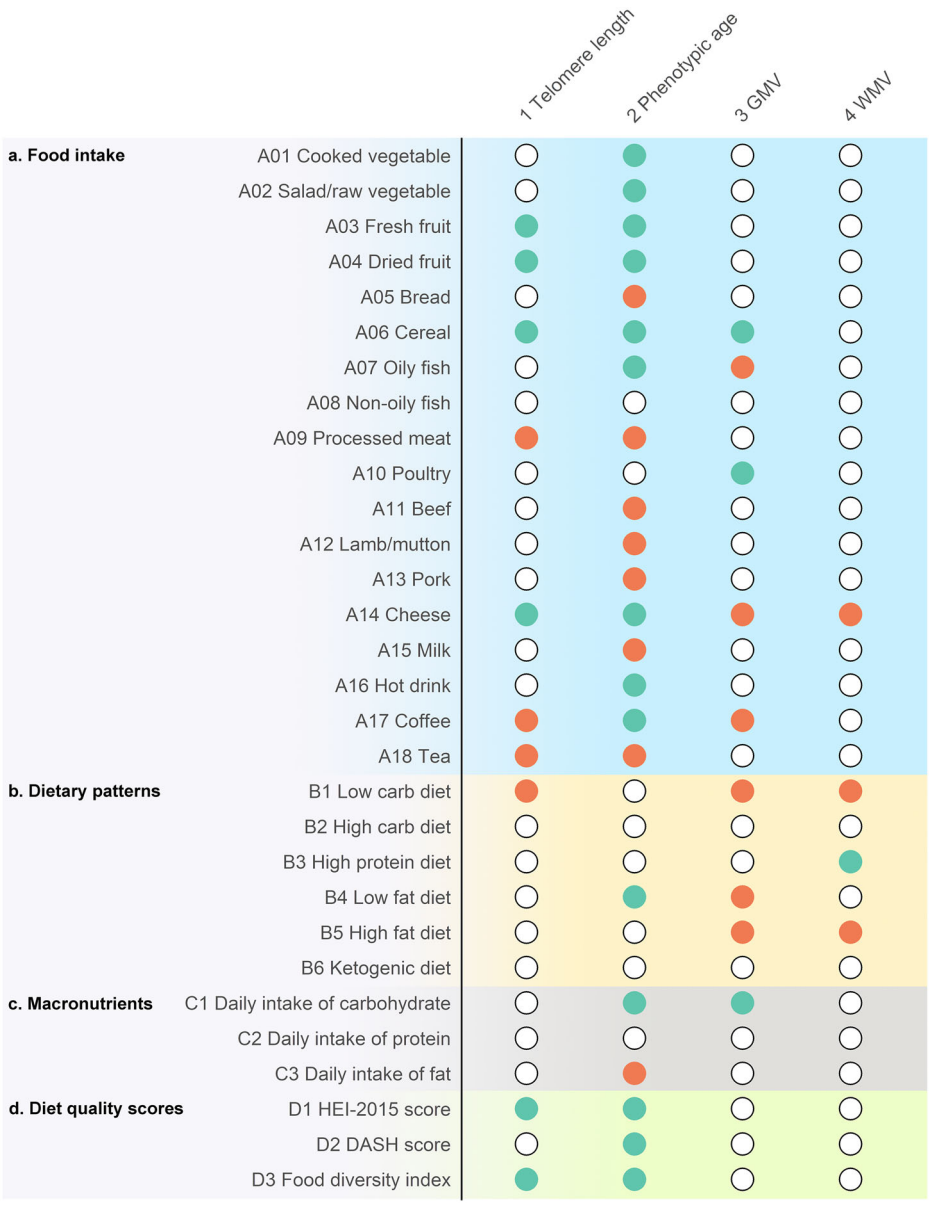

Fig. 2 | Associations between dietary factors and various aging outcomes from high-dimensional fixed effects (HDFE) estimation. a Individual food intakes. **b** Dietary patterns. **c** Macronutrients. **d** Diet quality scores. Colored dots represent statistically significant HDFE estimates of each dietary factor (in rows) on four aging outcomes (in columns) after the Sidak-Holm correction for multiple testing. In specific, red dots indicate risky effects, green dots indicate protective effects, and white dots indicate null effects. Detailed estimation results on effect sizes (i.e., beta), original *p* values, and *p* values after the Sidak-Holm correction are included in Supplementary Data 2.

underscoring the unique effects of different food groups and diet compositions examined in this study.

Overall, the HDFE estimates presented here provide initial evidence that numerous dietary factors are associated with different dimensions of aging. The findings reveal a generally protective role of plant-based foods and carbohydrates, while certain animal-based foods and fats exhibit adverse effects, suggesting that reasonable dietary modifications can promote healthy aging. The varied effects of specific foods and dietary patterns indicate a complex relationship between diet and aging, emphasizing the need for further research to elucidate the causality and underlying mechanisms to refine dietary guidelines. To further enhance the robustness of our findings, we also performed conventional ordinary least squares regressions (OLS). As reported in Supplementary Data 3, the estimated coefficients from HDFE and OLS are nearly identical to the fourth decimal place. However, the raw p-values from OLS are generally larger than those from HDFE, reflecting reduced estimation efficiency in OLS. This comparison underscores the advantage of HDFE in terms of computational efficiency and statistical precision.

Causal relationships between macronutrient intakes and aging

To address unobserved confounding that may contaminate the estimated food-intake and dietary-habit effects on aging, we employ the MVMR method to identify the causal effects of three macronutrient intakes simultaneously[27,32,40]. As noted above, MVMR uses genetic variants associated with diet compositions of carbohydrates, protein, and fat as IVs for their intakes. Nine independent SNPs were selected as genetic IVs based on recent GWAS findings[31]. The validity of jointly using these SNPs as genetic IVs has been established[32]. The Sidak-Holm *post hoc* correction for multiple comparisons were applied to all MVMR models.

As reported in Table 2, the First-stage F-statistics from all MVMR models exceeded the conventional cut-off of 10 for weak-IV tests, suggesting that the nine SNPs are jointly strong IVs in our MVMR design. Supplementary Table 6 reports detailed first-stage regression results. Meanwhile, overidentification (Sargan) tests revealed no evidence of directional pleiotropy, suggesting that our genetic IVs are not likely to be correlated with unobserved confounders.

The raw MVMR estimates reveal a potential protective effect of carbohydrate intake against aging, evidenced by a reduction in phenotypic age

Table 2 | Causal associations of macronutrients with aging from Multivariable Mendelian Randomization (MVMR) estimation

	MVMR Model 1			MVMR Model 2			MVMR Model 3			MVMR Model 4		
	Outcome Variable: Telomere Length			Outcome Variable: Phenotypic Age			Outcome Variable: Grey Matter Volume			Outcome Variable: White Matter Volume		
Exposure	*Beta*	*p-value*	*Sidak-Holm corrected p-value*	*Beta*	*p-value*	*Sidak-Holm corrected p-value*	*Beta*	*p-value*	*Sidak-Holm corrected p-value*	*Beta*	*p-svalue*	*Sidak-Holm corrected p-value*
Daily intake of carbohydrate	0.0012	0.5659	0.9971	−0.0025	0.0253	0.2455	0.0262**	0.0087	0.0399	−0.0440	0.6553	0.9971
Daily intake of protein	0.0033	0.7234	0.9971	0.0087	0.8894	0.9971	0.4464	0.6165	0.9971	−0.7419	0.3940	0.9890
Daily intake of fat	−0.0060	0.5891	0.9971	−0.0814	0.2376	0.9337	−0.3733	0.5811	0.9971	0.4606	0.4864	0.9952
Observations	180,142			157,020			24,875			24,875		
First-stage F score	21.4568			21.6651			21.0362			21.0362		
p-value	0.0000			0.0000			0.0000			0.0000		
Sargan score	4.7265			10.0312			6.3179			4.9119		
p-value	0.5793			0.1233			0.3885			0.5552		

Asterisks represent statistical significance after the Sidak-Holm correction for multiple testing at ***$p < 0.01$, **$p < 0.05$, and *$p < 0.1$ levels, respectively. All MVMR regressions used nine independent SNPs associated with intakes of carbohydrate/fat/protein as instruments: rs10510554, rs8097672, rs10206338, rs10962121, rs2472297, rs33988101, rs57193069, rs1461729, and rs445551 (Meddens et al.[31]; Yao et al.[32]).

(*beta* = -0.0025, $p = 0.0253$) and an increase in grey matter volume (*beta* = 0.0262, $p = 0.0087$). The beneficial effect of carbohydrate intake on grey matter volume remains significant even after correcting for multiple comparisons (*beta* = 0.0262, Sidak-Holm corrected $p = 0.0399$). In contrast, no significant causal associations were observed between protein or fat intakes and aging outcomes after correction for multiple testing.

Lemaitre et al.[41] estimated that the annual grey matter volume (GMV) reduction is 1.89 cm^3 due to aging[41]. Notably, our MVMR results show that an increase of 100 grams in daily carbohydrate intake is significantly associated with an increase in grey matter volume (GMV) by 2.62 cm^3, which potentially offsets brain aging by approximately 1.4 years. Furthermore, our findings suggest that the benefits from this dietary adjustment could be comparable to those achieved through physical activity, as reported in Koblinsky et al.[42], where physical activity increased total GMV by 2.17 cm^3[42].

To further enhance the robustness of our findings, we also employed a Simultaneous Equation Model (SEM) framework. As reported in Supplementary Data 4, the SEM estimates also indicate a potential protective effect of carbohydrate intake against aging, as evidenced by a reduction in phenotypic age and an increase in grey matter volume, aligning with the MVMR findings.

Discussion

This study identified several dietary factors significantly linked to the acceleration or deceleration of aging. Notably, a low-carb diet was associated with accelerated aging, indicated by shorter telomere length and reduced grey/white matter volumes, and triangulated evidence from HDFE and MVMR designs highlights a significant protective effect of carbohydrate intake against aging. These findings underscore the critical role diet plays in influencing biological aging. Our study also shows that existing diet quality scores, such as DASH and HEI-2015, may not fully capture diet's impact on brain health, indicating a need for more comprehensive dietary assessment tools.

While previous studies have reported that carbohydrate-rich diets were associated with accelerated aging in model organisms, such as yeast and roundworms (*Caenorhabditis elegans*), direct evidence regarding whether different levels of carbohydrate intake influence aging in humans remains lacking[43,44]. The current study adds to the literature by underscoring that in humans, carbohydrates may actually play a beneficial role, particularly in reducing phenotypic age and enhancing brain health.

Several potential explanations may account for the beneficial effects of carbohydrate intake on various aspects of aging. For instance, Seidelmann et al.[45] found that a low-carbohydrate diet posed the greatest mortality risk, closely related to epigenetic biomarkers of aging[45,46]. Furthermore, Jensen et al.[47] reported that diets rich in fruits and vegetables and low in meat are linked to increased brain volume and connectivity. The *CPLX3* gene, a key marker of subplate neurons in the brain involved in cortical development and plasticity, is also associated with cereal intake[47,48]. In our sample, higher daily carbohydrate intake correlated with higher intakes of cereal, bread, and fresh/dried fruits. Additionally, Yao et al.[32] reported a causal relationship between higher carbohydrate intake and lower depression risk, with depression and cognitive dysfunction sharing a common neuropathological platform in cortical and sub-cortical brain areas[32,49].

Our study has several potential limitations that should be considered when interpreting the results. First, the participants were predominantly white, relatively healthy, and well-educated, which may limit the generalizability of our findings to other populations. Second, MVMR estimates from unrelated individuals can be biased due to population structure, assortative mating, and genetic nurture. Future research could address these biases by employing a within-family design. Finally, our study does not verify the biological mechanisms underlying the beneficial effects of carbohydrate intake on aging, which may require randomized diet interventions for verification.

Notwithstanding these limitations, our study highlights the fundamental benefits of certain dietary factors, particularly carbohydrate intake, in combating multifaceted aspects of aging. Given that brain volumetric

measurements are strong predictors of longitudinal cognitive change[42], our findings imply that a carbohydrate-rich diet may help maintain cognitive health. With 35.4% of the global population unable to afford a healthy diet[50], these insights can inform the design of more cost-effective dietary interventions aimed at promoting healthy aging and enhancing individual well-being.

Data availability

Eligible researchers may access UK Biobank data on www.ukbiobank.ac.uk, upon registration. For this study, permission to access and analyse the UK Biobank data was approved under the application numbered 89068. Other data are available from the corresponding author on reasonable request.

Code availability

All codes used to perform the analysis can be found at: https://github.com/maxwell2732/diet_and_aging/.

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Author contributions

C.Z., Q.C., and S.F. conceptualized the study and drafted the manuscript. C.Z. conducted all analyses with statistical support from X.Y., W.X., X.W., Y.L., and Q.C.; Y.W., Q.Z., and Y.L. provided feedback on design and analysis. All authors reviewed and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Qihui Chen or Shenggen Fan.

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