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Dietary flavonoid intake is negatively associated with accelerating aging: an American population-based cross-sectional study

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Abstract

Background Flavonoids are believed to have potential anti-aging effects due to their anti-inflammatory and antioxidant properties. However, the effectiveness of dietary flavonoids and their subclasses in delaying aging has yet to be confirmed. Our study intends to examine relationship between them.

Methods Data from three survey cycles (2007–2008, 2009–2010, and 2017–2018) of the National Health and Nutrition Examination Survey (NHANES) was used to investigate the relationship between PhenoAgeAccel and dietary flavonoid intake. Weighted linear regression was conducted to evaluate the relationship between dietary flavonoid intake and PhenoAgeAccel, and the dose-response relationship was investigated by limited cubic spline (RCS) analysis. Mixed effects were explored using weighted quantile sum (WQS) regression. Further, the subgroup analyses were also conducted.

Results A total of 5391 participants were included, after multivariable adjustments, a negative association was found with total dietary flavonoid, flavan-3-ols, flavanone, flavones and flavonols with a β (95% CI) of -0.87 (-1.61, -0.13), -0.83 (-1.95, -0.08), -1.18 (-1.98, -0.39), -1.64 (-2.52, -0.77) and − 1.18 (-1.98, -0.39) for the higher quintile compared to the lowest quintile. The RCS analysis show a non-linear relationship between flavan-3-ols (*P* for nonlinear = 0.024), flavanones (*P* for nonlinear = 0.005), flavones (*P* for nonlinear < 0.001), flavonols (*P* for nonlinear < 0.001) and total flavonoid intake (*P* for nonlinear < 0.001) and PhenoAgeAccel. WQS regression indicated that flavones had the primary effect on the mixture exposures (52.72%). Finally, the subgroup analysis indicated that participants without chronic kidney disease are more likely to benefit from dietary flavanone and flavone intake in mitigating aging, while the benefits of flavanone intake are more significant in participants with a lower body mass index.

Conclusion Our study suggested that dietary flavonoid intake is negatively associated with accelerating aging in adults of American, and the most influential ones are flavones, flavanones, flavan-3-ols and flavonols.

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Keywords Flavonoid, Aging, Flavones, NHANES

Introduction

Aging has emerged as a critical global issue. By 2050, the population aged 60 and over is projected to reach 2 billion, accounting for 22% of the global population [1]. According to the 2017 Global Burden of Disease (GBD) study, 92 diseases have been identified as age-related, accounting for 51.3% of the total disease burden among adults worldwide [2]. This poses substantial challenges to families, healthcare systems, and social security frameworks. Consequently, the identification and deceleration of the aging process are imperative for promoting healthy aging.

Due to the inherent inter-individual variability in the aging process, discernible differences in the aging process among individuals are observed [3, 4]. Therefore, efforts have been initiated to develop measures that capture the concept of biological age (BA), which integrates composite clinical biomarkers with chronological age [5, 6]. These aging biomarkers serve to elucidate the underlying biological heterogeneity in aging and uncover factors that influence the rate of aging, playing a critical role in human research aimed at decelerating the aging process [7, 8]. Phenotypic age is a biological age measurement method developed by Levine et al. based on data from the Third National Health and Nutrition Examination Survey (NHANES) [3]. It integrates composite clinical chemistry biomarkers derived from the parametrization of a Gompertz mortality model and has been shown to effectively differentiate mortality risk among individuals of the same chronological age [4]. Phenotypic age acceleration (PhenoAgeAccel), a biomarker derivative of Phenotypic age, represents the discrepancy between an individual's estimated Phenotypic age and their chronological age. A positive PhenoAgeAccel value indicates accelerated biological aging, while a negative value suggests decelerated aging. In addition to all-cause mortality, PhenoAgeAccel has also been linked to an increased risk of incident cancer and dementia [9, 10], highlighting its potential as a key marker for understanding aging outcomes and guiding interventions for aging-related disease.

Diet and aging are intrinsically linked, with a balanced diet being the safest and most effective method to delay the aging process and extend healthy lifespan [11, 12]. Flavonoids, a group of natural polyphenols, which found in vegetables, fruits, cocoa, oilseeds and tea, consists of six subclasses: isoflavones, anthocyanins, flavan-3-ols, flavanones, flavones and flavonols [13]. Flavonoids exhibit potent anti-inflammatory and antioxidant properties, offering significant potential to attenuate the aging process. Consequently, they have been recognized as promising candidate compounds for retarding aging [14, 15]. As polyphenolic compounds, the hydroxyl groups in the structure of flavonoids are capable of scavenging various types of reactive oxygen species (ROS) [16]. Additionally, flavonoids could maintain and activate SIRT1, and consequently inhibit NF-κB, which could prevent oxidative stress and neuroinflammation to delay brain aging [17]. Research shows that oral treatment with naringenin in young rats could prevent alterations in the brain antioxidant defense system, thereby ameliorating cognitive decline [18], hesperetin could enhance antioxidant cellular defenses through the ERK/Nrf2 signaling pathway [19]. Further, flavonoids have been shown to extend the lifespan of worms, flies, and mice [20]. It is worth noting that fisetin and quercetin, as flavonols, are currently widely studied senolytic agents and are being used in multiple clinical trials [21, 22]. However, the relationship between dietary flavonoid intake and aging process has not been fully studied, especially regarding the mixed effects of different flavonoid subclasses. Therefore, this study intends to use data from the National Health and Nutrition Examination Survey (NHANES) to examine the aging process within the American population by calculating phenotypic age and to explore the association between dietary flavonoid intake and aging.

Materials and methods

Study population

In our study, participants are based on the National Health and Nutrition Examination Survey (NHANES), which aims to assess the health and nutritional status of adults and children in the United States using a complex, multistage probability sampling design [23]. Since the availability of flavonoid databases, we only included data from three survey cycles (2007–2008, 2009–2010, and 2017–2018), and retrieved subject information during these cycles. The flowchart illustrating the selection procedure for all participants involved in the study is exhibited in Fig. 1. Initially, 29,940 participants were included. Considering that the Phenotypic age calculation formula was developed based on participants aged 20 years and above in the Third NHANES, we subsequently excluded participants under the age of 20 (N=12,218), with incomplete information to Phenotypic Age (N=4,673), without flavonoid information and dietary recall status below the minimum criteria (N=2,168) and missing demographic characteristics (N=5,490). Finally, a total of 5391 qualified participants was in the final analysis. The final sample represented a weighted population of 83.3 million non-institutionalized residents in United States. Prior to the survey, all participants provided written informed consent. Furthermore, the National Center for Health

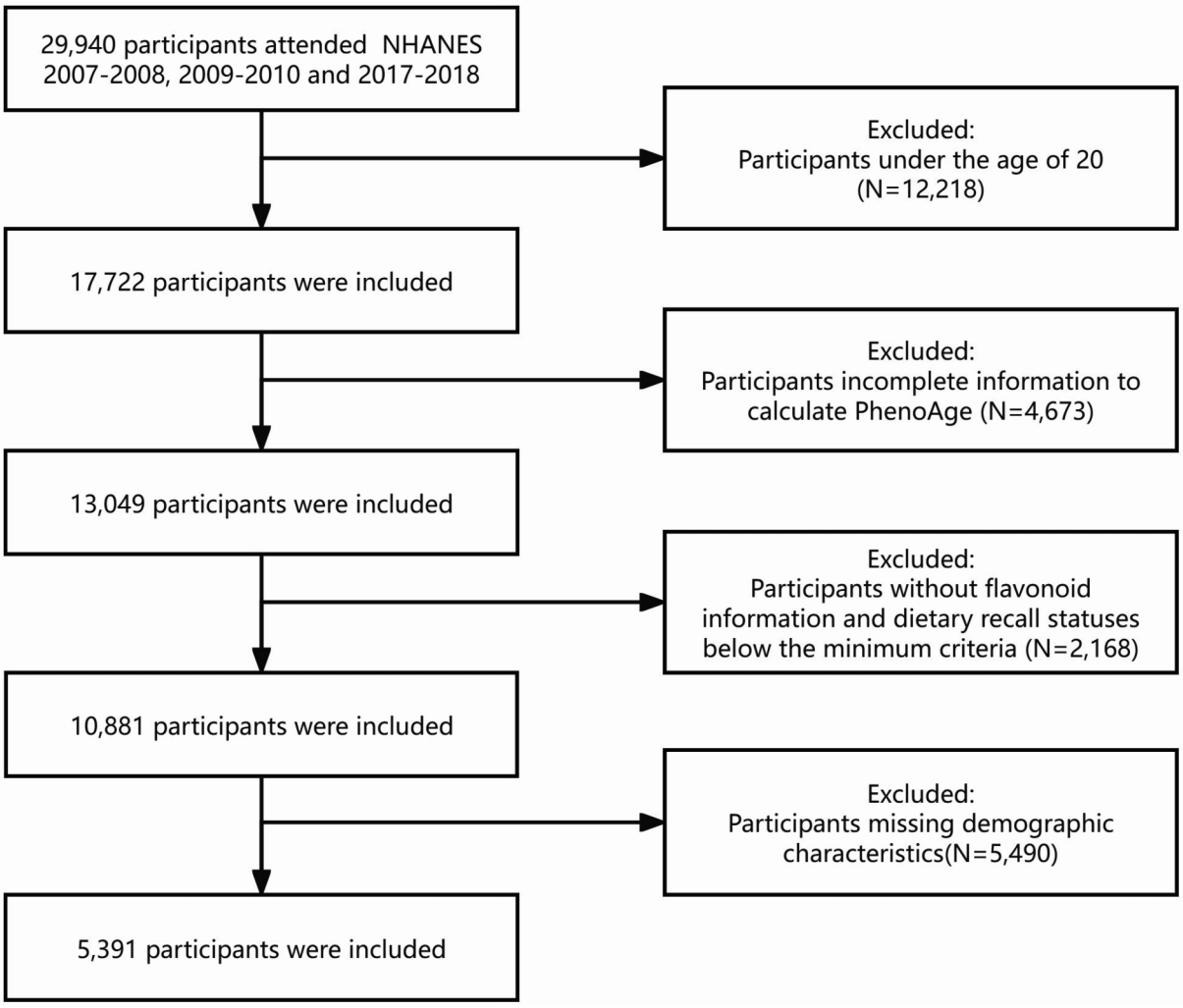

Fig. 1 Flowchart of the participants

Statistics (NCHS) Ethics Review Board granted approval for the NHANES protocol.

Assessment of phenotypic age acceleration

Phenotypic age is calculated by a combination of chronological age and nine biomarkers: albumin, creatinine, glucose, C-reactive protein (log-transformed), lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count. The formula for the determination of phenotypic age is as follows [4]:

$$\text{Phenotypic age} = 141.5 + \frac{ln\left[-0.00553 \times\ ln\left(1 - xb\right)\right]}{0.09165}$$

Where:

$$\begin{aligned} xb = &-19.907 - 0.0336 \times\ albumin + 0.0095 \times\ creatinine \\ &+ 0.0195 \times\ glucose + 0.0954 \times\ \ln\left(CRP\right) \\ &- 0.0120 \times\ lymphocyte\ precent \\ &+ 0.0268 \times\ mean\ cell\ volume \\ &+ 0.3356 \times\ red\ blood\ cell\ distrion\ width \\ &+ 0.00188 \times\ alkaline\ phosphatase \\ &+ 0.0554 \times\ white\ blood\ cell\ count \\ &+ 0.0804 \times\ chronological\ age \end{aligned}$$

PhenoAgeAccel was calculated as the residuals resulting from the regression of phenotypic age on chronological age. A positive PhenoAgeAccel value indicates accelerated biological aging, while a negative value suggests decelerated aging. Participants with a positive PhenoAgeAccel value were regarded as "with PhenoAgeAccel" while those with a negative value were regarded as "without PhenoAgeAccel".

Assessment of dietary flavonoid intake

Data on dietary flavonoid intake were obtained from the USDA Food and Nutrient Database for Dietary Studies (FNDDS), which includes calculated data from two 24-hour dietary recall interviews conducted as part of NHANES [24, 25]. As of now, data on dietary flavonoid intake for the years 2007–2008, 2009–2010, and 2017–2018 have been published. The FNDDS database categorizes dietary flavonoid into six subclasses: isoflavones, anthocyanins, flavan-3-ols, flavanones, flavones and flavonols. Total dietary flavonoid intake is defined as the sum of these six subclasses. The mean value of dietary flavonoid intake from the two 24-hour dietary recalls was defined as the final dietary flavonoid intakes.

Covariates

In our analysis, covariates encompassed three categories. Sociodemographic characteristics included gender, age, race, poverty income ratio (PIR), education level and marital status. Behavioral characteristics encompassed drinking, smoking, body mass index (BMI), physical activity. Health characteristics encompassed the history of diabetes, chronic kidney disease (CKD) and hypertension.

The family poverty income ratio (PIR) was computed by dividing the household income by the poverty threshold corresponding to the household size, PIR values < 1 indicate poverty, while higher values indicate higher socioeconomic status [24]; Drinking was defined as participants who consumed alcohol drink more than 12 times per year; smoking was defined as participants who smoked at least 100 cigarettes in their lifetime; BMI was stratified into three levels: < 25, 25–30, and > 30 kg m^{-2}; physical activity was categorized into four groups: inactive (participants lacking regular physical exercise), insufficient (< 500 MET per week), moderate (500–1000 MET per week), and high (> 1000 MET per week) [26]; participants with diabetes were defined by fasting plasma glucose ≥ 7.0 mmol L^{-1}, HbA1c ≥ 6.5% or self-reported diabetes status; CKD was defined by urinary albumin-to-creatinine ratio over 30 mg g^{-1}, the estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m^2 or self-reported CKD status; Hypertension was defined by the average of three systolic pressure of ≥ 130 mmHg or diastolic pressure of ≥ 80 mmHg or self-reported hypertension status.

Statistical analysis

According to NHANES analytic guidelines, our analyses were incorporated appropriate sample weights to account for the complex sampling design. As dietary flavonoid intakes, participants were divided into five quintiles [Q1 (quintile 1), Q2 (quintile 2), Q3 (quintile 3), Q4 (quintile 4) and Q5 (quintile 5)]. PhenoAgeAccel was described as a categorical variable (participants with PhenoAgeAccel or participants without PhenoAgeAccel) and continuous variable. Since all the variables were categorical, the baseline data were described as frequency with weighted percentages. They were then compared using the Scott-Rao chi-square test. Furthermore, three weighted linear regression models were used to investigate the relationship between six subclasses of flavonoid and PhenoAgeAccel. In Model 1, no adjustments were implemented; Model 2 was adjusted for gender, age, race, PIR, education level and marital status; Model 3 was adjusted for gender, age, race, PIR, education level, marital status, drinking, smoking, BMI, physical activity, diabetes, CKD and hypertension. We used dietary flavonoid intake (quintile-categorical) as a continuous variable in all models to conduct trend tests (*P* for trend). Subsequently, the restricted cubic splines (RCS) analyses were applied to examine the dose-response relationships between four flavonoid subclasses and PhenoAgeAccel with four knots (5th, 35th, 65th and 95th percentiles), the RCS plots have been adjusted for all covariates.

Consequently, the weighted quantile sum (WQS) regression model was used to explore the overall effect of flavonoid subclasses on PhenoAgeAccel and the WQS index calculation was utilized for the determination of advantage type [27]. For further investigate the association between flavonoid subclasses and PhenoAgeAccel in different population, the subgroup analysis and interaction test was conducted.

All statistical analyses were performed using R software (version 4.3.2). $P < 0.05$ indicated statistical significance (two-sided).

Results

Baseline characteristics

A total of 5391 participants were enrolled for the associated analysis of dietary flavonoid intakes and PhenoAgeAccel. Table 1 presents the sociodemographic, behavioral health and dietary flavonoid intake characteristics of participants with or without PhenoAgeAccel. Significant differences were observed in age, race, PIR, education level, marital status, drinking, smoking, BMI, physical activity, diabetes, chronic kidney disease, and hypertension between the two groups. Furthermore, participants with higher intake of isoflavones, anthocyanins, flavan-3-ols, flavanones, flavones, flavonols and total flavonoid, were less likely to experience PhenoAgeAccel.

Association between total flavonoid, flavonoid subclasses and PhenoAgeAccel

The results of three weighted linear regression models investigating the association between six flavonoids subclasses and PhenoAgeAccel are presented in Table 2. In model 3, after adjusting all covariates, compared to

Table 1 Baseline characteristics of the study population

Variables	Total ($n=5391$)	Without PhenoAgeAccel ($n=3581$)	With PhenoAgeAccel ($n=1810$)	*P*-value
Sociodemographic characteristics				
Gender, n (%)				0.109
Male	2590 (48.47)	1642 (47.39)	948 (51.04)	
Female	2801 (51.53)	1939 (52.61)	862 (48.96)	
Age, n (%)				**< 0.001**
20–50	2527 (54.42)	1805 (57.70)	722 (46.62)	
50–65	1483 (26.94)	967 (26.42)	516 (28.17)	
> 65	1381 (18.64)	809 (15.88)	572 (25.21)	
Race, n (%)				**< 0.001**
Non-Hispanic White	2609 (69.87)	1792 (72.56)	817 (63.43)	
Mexican American	863 (8.28)	608 (8.06)	255 (8.85)	
Other Hispanic	503 (4.87)	343 (4.59)	160 (5.54)	
Non-Hispanic Black	1008 (10.02)	551 (7.72)	457 (15.51)	
Other Race	408 (6.96)	287 (7.07)	121 (6.68)	
PIR, n (%)				**< 0.001**
< 1	1005 (13.53)	607 (11.90)	398 (17.42)	
1–3	2389 (36.78)	1505 (33.88)	884 (43.73)	
> 3	1997(49.69)	1469 (54.23)	528 (38.86)	
Education level, n (%)				**< 0.001**
Below high school	1286 (15.15)	794 (13.33)	492 (19.51)	
High school graduate or GED	1276 (24.84)	792 (22.55)	484 (30.29)	
Some colleges or above	2829 (60.01)	1995 (64.12)	834 (50.19)	
Marital status, n (%)				**0.012**
Married/cohabiting	3280 (62.74)	2235 (63.79)	1045 (60.24)	
Widowed/divorced/separated	1253 (19.23)	748 (17.34)	505 (23.74)	
Never married	858 (18.03)	598 (18.87)	260 (16.01)	
Behavioral characteristics				
Drink, n (%)				**< 0.001**
No	3272 (60.87)	2327 (65.52)	945 (49.78)	
Yes	2119 (39.13)	1254 (34.48)	865 (50.22)	
Smoke, n (%)				**< 0.001**
No	2929 (54.96)	2095 (58.47)	834 (46.57)	
Yes	2462 (45.04)	1486 (41.53)	976 (53.43)	
BMI, n (%)				**< 0.001**
< 25	1484(29.86)	1179 (35.78)	305 (15.71)	
25–30	1809(32.28)	1330 (35.45)	479 (24.72)	
> 30	2098(37.86)	1072 (28.77)	1026 (59.57)	
Physical activity, n (%)				**< 0.001**
Inactive	2251 (35.68)	1318 (30.68)	933 (47.61)	
Insufficient	889 (16.74)	606 (17.70)	283 (14.45)	
Moderate	701 (14.19)	502 (14.82)	199 (12.69)	
High	1550 (33.39)	1155 (36.79)	395 (25.25)	
Health characteristics				
Diabetes, n (%)				**< 0.001**
No	4523 (88.89)	3309 (94.97)	1214 (74.35)	
Yes	868 (11.11)	272 (5.03)	596 (25.65)	
Chronic Kidney Disease, n (%)				**< 0.001**
No	4730 (91.18)	3316 (94.58)	1414 (83.04)	
Yes	661 (8.82)	265 (5.42)	396 (16.96)	
Hypertension, n (%)				**< 0.001**
No	3358 (67.59)	2454 (72.84)	904 (55.04)	
Yes	2033 (32.41)	1127 (27.16)	906 (44.96)	

Table 1 (continued)

Variables	Total (*n* = 5391)	Without PhenoAgeAccel (*n* = 3581)	With PhenoAgeAccel (*n* = 1810)	*P*-value
Dietary flavonoid intake (mg per day)				
Isoflavones, n (%)				**0.017**
Q1 (0–0)	2039 (36.60)	1292 (34.49)	747 (41.63)	
Q2 (0-0.005)	354 (7.19)	228 (6.97)	126 (7.71)	
Q3 (0.005–0.02)	788 (15.88)	520 (16.20)	268 (15.11)	
Q4 (0.02–0.145)	1106 (17.98)	773 (18.49)	333 (16.74)	
Q5 (0.145–390.6)	1104 (22.36)	768 (23.84)	336 (18.81)	
Anthocyanidins, n (%)				**< 0.001**
Q1 (0-0.020)	1102 (21.84)	651 (19.88)	451 (26.52)	
Q2 (0.02–1.005)	1055 (18.54)	658 (17.33)	397 (21.43)	
Q3 (1.005–4.010)	1079 (18.21)	729 (18.99)	350 (16.35)	
Q4 (4.010-16.815)	1078 (19.78)	758 (20.79)	320 (17.36)	
Q5 (16.815–543.83)	1077 (21.63)	785 (23.01)	292 (18.34)	
Flavan-3-ols, n (%)				**0.007**
Q1 (0-3.560)	1079 (18.50)	620 (16.31)	459 (23.73)	
Q2 (3.560-10.055)	1080 (18.14)	729 (17.96)	351 (18.56)	
Q3 (10.055–24.890)	1076 (19.08)	757 (19.95)	319 (16.98)	
Q4 (24.890-229.820)	1078 (20.97)	735 (21.79)	343 (18.99)	
Q5 (229.820-4939.790)	1078 (23.32)	740 (23.99)	338 (21.74)	
Flavanones, n (%)				**< 0.001**
Q1 (0-0.005)	1108 (21.17)	634 (18.99)	474 (26.37)	
Q2 (0.005–0.250)	1056 (20.96)	682 (20.52)	374 (22.02)	
Q3 (0.250–2.495)	1073 (21.79)	745 (22.66)	328 (19.70)	
Q4 (2.495–25.400)	1076 (20.00)	774 (21.56)	302 (16.28)	
Q5 (25.400-345.685)	1078 (16.08)	746 (16.26)	332 (15.63)	
Flavones, n (%)				**< 0.001**
Q1 (0-0.135)	1094 (19.41)	619 (16.33)	475 (26.76)	
Q2 (0.135–0.365)	1073 (18.64)	668 (17.63)	405 (21.05)	
Q3 (0.365–0.705)	1078 (19.07)	750 (20.11)	328 (16.59)	
Q4 (0.705–1.315)	1072 (20.55)	760 (21.94)	312 (17.23)	
Q5 (1.315–87.245)	1074 (22.33)	784 (23.99)	290 (18.38)	
Flavonols, n (%)				**0.006**
Q1 (0-5.880)	1079 (17.46)	633 (15.68)	446 (21.71)	
Q2 (5.880–10.250)	1080 (18.09)	708 (17.47)	372 (19.57)	
Q3 (10.250–15.900)	1077 (19.97)	730 (20.14)	347 (19.58)	
Q4 (15.900-25.390)	1078 (20.74)	756 (21.91)	322 (17.94)	
Q5 (25.390-262.435)	1077 (23.74)	754 (24.81)	323 (21.20)	
Total flavonoids, n (%)				**0.005**
Q1 (0-19.350)	1079 (19.65)	622 (17.26)	457 (25.35)	
Q2 (19.350-44.555)	1078 (17.64)	728 (18.13)	350 (16.46)	
Q3 (44.555–97.660)	1078 (18.66)	738 (19.05)	340 (17.72)	
Q4 (97.660-283.950)	1078 (20.57)	758 (21.29)	320 (18.85)	
Q5 (283.950-5177.470)	1078 (23.48)	735 (24.26)	343 (21.61)	

Abbreviations BMI, body mass index; PIR, poverty income ratio; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5

the lowest quintile, the second (β: -0.95, 95% CI: -1.61, -0.30), third (β: -1.05, 95% CI: -1.79, -0.31) and highest (β: -0.83, 95% CI: -1.95, -0.08) quintiles of flavan-3-ols (*P* for trend = 0.473); the third (β: -1.14, 95% CI: -1.90, -0.38) and fourth (β: -1.18, 95% CI: -1.98, -0.39) quintiles of flavanone (*P* for trend = 0.016); the third (β: -1.75, 95% CI: -2.56, -0.95), fourth (β: -1.83, 95% CI: -2.83, -0.84) and highest (β: -1.64, 95% CI: -2.52, -0.77) quintiles of flavones (*P* for trend < 0.001); the third (β: -1.14, 95% CI: -1.90, -0.38) and fourth (β: -1.18, 95% CI: -1.98, -0.39) quintiles of flavonols (*P* for trend = 0.032); the third (β: -0.87, 95% CI: -1.61, -0.13) quintile of total dietary flavonoid intake exhibited a significant associated with the decreased of PhenoAgeAccel. However, the result

Table 2 Association between total flavonoid, six flavonoid subclasses and PhenoAgeAccel

Variable	Model 1	Model 2	Model 3
	β (95% CI)	β (95% CI)	β (95% CI)
Isoflavones			
Q1	Reference	Reference	Reference
Q2	-0.26 (-1.20, 0.68)	0.32 (-0.59, 1.23)	-0.27 (-1.34, 0.79)
Q3	-1.00 (-1.89, -0.11)	-0.54 (-1.35, 0.26)	-0.49 (-1.19, 0.21)
Q4	-0.87 (-1.84, 0.11)	-0.52 (-1.42, 0.38)	-0.73 (-1.49, 0.03)
Q5	-1.55 (-2.46, -0.63)	-0.9 (-1.80, -0.00)	-0.51 (-1.17, 0.15)
P for trend	**< 0.001**	**0.020**	**0.049**
Anthocyanidins			
Q1	Reference	Reference	Reference
Q2	-0.37 (-1.22, 0.48)	-0.33 (-1.16, 0.51)	-0.27 (-1.34, 0.79)
Q3	-1.42 (-2.44, -0.40)	-1.58 (-2.56, -0.61)	-0.49 (-1.19, 0.21)
Q4	-1.82 (-2.64, -1.01)	-1.74 (-2.42, -1.06)	-0.73 (-1.49, 0.03)
Q5	-2.00 (-3.00, -1.00)	-1.52 (-2.42, -0.61)	-0.51 (-1.17, 0.15)
P for trend	**< 0.001**	**< 0.001**	**0.049**
Flavan-3-ols			
Q1	Reference	Reference	Reference
Q2	**-1.57 (-2.30, -0.83)**	**-1.47 (-2.25, -0.69)**	**-0.95 (-1.61, -0.30)**
Q3	**-2.06 (-2.95, -1.18)**	**-1.90 (-2.73, -1.08)**	**-1.05 (-1.79, -0.31)**
Q4	**-1.62 (-2.57, -0.68)**	**-1.23 (-2.14, -0.32)**	0.08 (-0.78, 0.94)
Q5	**-1.90 (-2.68, -1.12)**	**-1.34 (-2.06, -0.63)**	**-0.83 (-1.59, -0.08)**
P for trend	**< 0.001**	**0.007**	0.473
Flavanones			
Q1	Reference	Reference	Reference
Q2	-0.97 (-1.88, -0.06)	-0.44 (-1.41, 0.52)	-0.05 (-0.85, 0.75)
Q3	**-2.17 (-3.02, -1.31)**	**-1.58 (-2.46, -0.70)**	**-1.14 (-1.90, -0.38)**
Q4	**-2.71 (-3.65, -1.77)**	**-2.32 (-3.29, -1.34)**	**-1.18 (-1.98, -0.39)**
Q5	**-1.55 (-2.59, -0.51)**	**-1.66 (-2.68, -0.63)**	-0.57 (-1.43, 0.28)
P for trend	**< 0.001**	**< 0.001**	**0.016**
Flavones			
Q1	Reference	Reference	Reference
Q2	-0.66 (-1.61, 0.30)	-0.61 (-1.52, 0.31)	-0.73 (-1.56, 0.10)
Q3	**-2.36 (-3.10, -1.62)**	**-2.08 (-2.81, -1.35)**	**-1.75 (-2.56, -0.95)**
Q4	**-2.89 (-3.97, -1.80)**	**-2.5 (-3.59, -1.41)**	**-1.83 (-2.83, -0.84)**
Q5	**-2.69 (-3.63, -1.74)**	**-2.27 (-3.22, -1.31)**	**-1.64 (-2.52, -0.77)**
P for trend	**< 0.001**	**< 0.001**	**< 0.001**
Flavonols			
Q1	Reference	Reference	Reference
Q2	-0.94 (-1.91, 0.03)	-0.87 (-1.81, 0.07)	-0.49 (-1.40, 0.43)
Q3	**-1.65 (-2.63, -0.67)**	**-1.47 (-2.35, -0.59)**	**-0.86 (-1.72, -0.01)**
Q4	**-2.33 (-3.20, -1.47)**	**-2.05 (-2.82, -1.28)**	**-1.20 (-2.01, -0.39)**
Q5	**-1.92 (-2.76, -1.09)**	**-1.46 (-2.25, -0.68)**	-0.90 (-1.84, 0.04)
	β (95% CI)	β (95% CI)	β (95% CI)
P for trend	**< 0.001**	**< 0.001**	**0.032**
Total flavonoids			
Q1	Reference	Reference	Reference
Q2	**-1.61 (-2.49, -0.73)**	**-1.51 (-2.33, -0.68)**	-0.78 (-1.57, 0.01)
Q3	**-1.76 (-2.58, -0.94)**	**-1.89 (-2.68, -1.09)**	**-0.87 (-1.61, -0.13)**
Q4	**-1.68 (-2.66, -0.69)**	**-1.36 (-2.29, -0.42)**	-0.07 (-0.92, 0.77)

Table 2 (continued)

Variable	Model 1	Model 2	Model 3
Q5	**-1.81 (-2.63, -0.99)**	**-1.34 (-2.16, -0.52)**	-0.74 (-1.64, 0.15)
P for trend	**< 0.001**	**0.008**	0.413

Abbreviations CI, confidence interval; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5

Model 1: No adjustments were implemented; Model 2: Adjusted for gender, age, race, poverty income ratio, education level and marital status; Model 3: Adjusted for gender, age, race, poverty income ratio, education level, marital status, drinking, smoking, body mass index, physical activity, diabetes, chronic kidney disease and hypertension

Data in bold type indicate the *P* values below 0.05

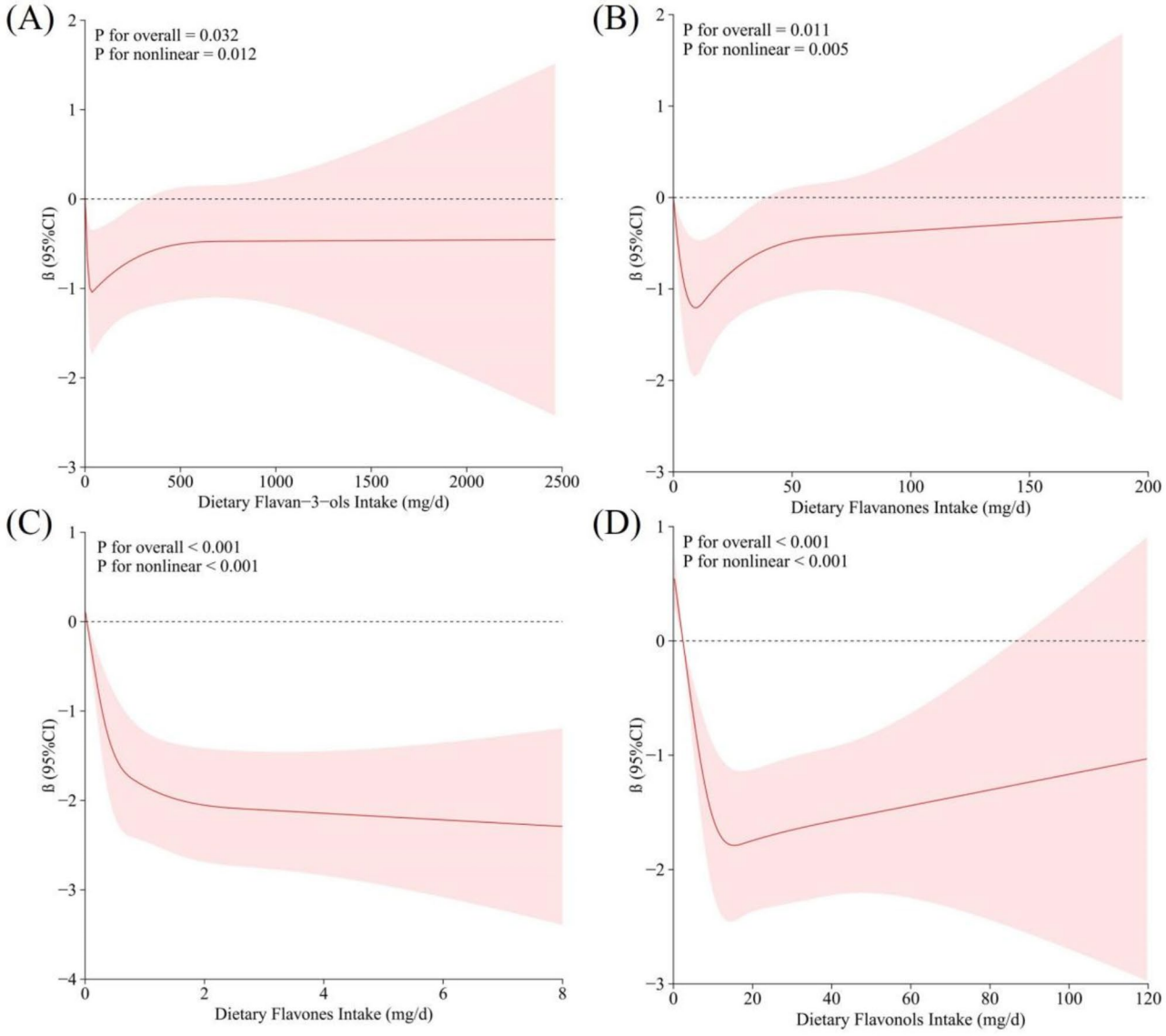

Fig. 2 Dose-response relationship between four flavonoid subclasses, total flavonoid intake and PhenoAgeAccel: (**A**) flavan-3-ols (**B**) flavanones (**C**) flavones (**D**) flavonols. Covariates included gender, age, race, poverty income ratio, education level, marital status, drinking, smoking, BMI, physical activity, diabetes, chronic kidney disease and hypertension

indicated no significant association between isoflavones, anthocyanidins and PhenoAgeAccel. Consequently, they were excluded from subsequent analyses.

Restricted cubic splines (RCS) analyses were employed to assess the dose-response relationship between four flavonoids, total flavonoid intake and PhenoAgeAccel, the result is presented in Figs. 2 and 3. After adjusting for all covariates, we found there is a U-shaped association between flavan-3-ols (*P* for nonlinear = 0.024), flavanones (*P* for nonlinear = 0.005), flavonols (*P* for

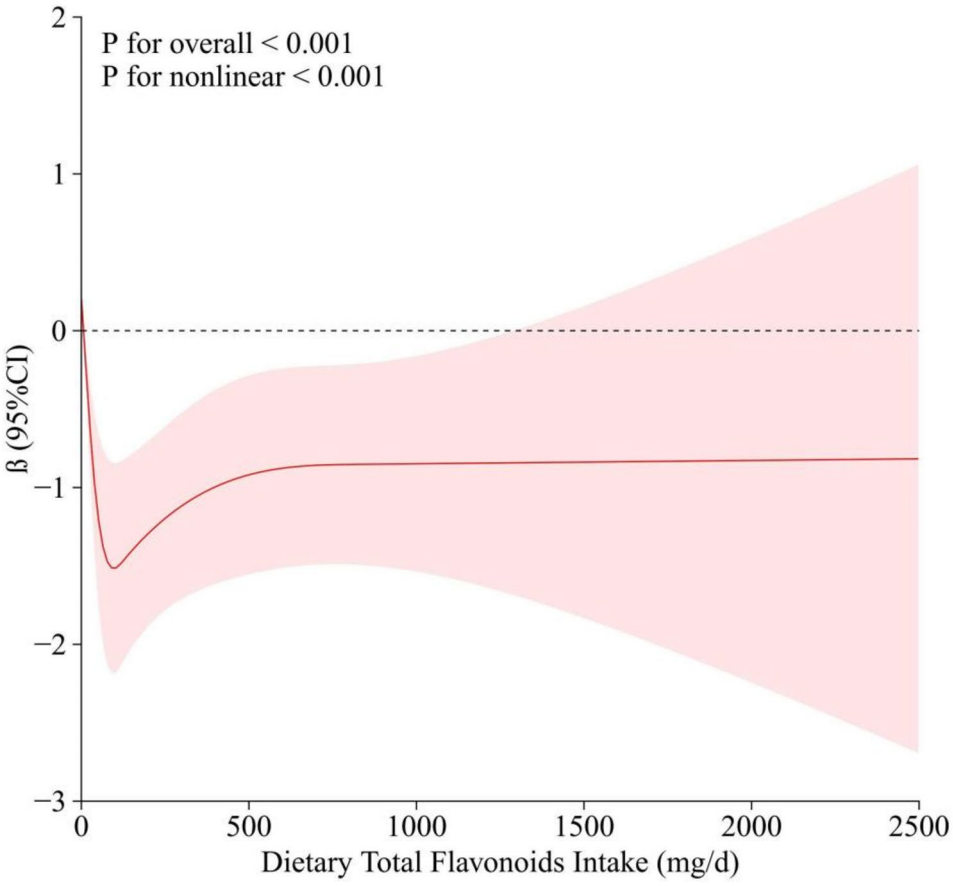

Fig. 3 Dose-response relationship between total flavonoid intake and PhenoAgeAccel Covariates included gender, age, race, poverty income ratio, education level, marital status, drinking, smoking, BMI, physical activity, diabetes, chronic kidney disease and hypertension

nonlinear < 0.001), and total flavonoid intake (*P* for nonlinear < 0.001) suggesting that intermediate intakes of these subclasses of flavonoids and total flavonoid intake may contribute to the reduction of PhenoAgeAccel. Meanwhile, an L-shaped association was observed between flavones and PhenoAgeAccel (*P* for nonlinear < 0.001), suggesting that higher intake of flavones could potentially delay senescence.

To analyze the mixed effects of four flavonoid subclasses on PhenoAgeAccel, weighted quantile sum (WQS) regression was conducted. The result indicates that the WQS index had statistically significant effect in reducing PhenoAgeAccel (OR = 0.9, 95% CI: 0.83, 0.98). The estimated weights of the WQS index are exhibited in Fig. 4. The largest weight in the reduction of PhenoAgeAccel is attributed to flavones (52.72%), and the following by flavanones (22.44%), flavan-3-ols (19.43%), with flavonols (5.4%) having the smallest weight.

Subgroup analysis

For the purpose of investigating the association between total flavonoid, flavonoid subclasses intake and PhenoAgeAccel, subgroup analysis was conducted. We stratified by behavioral (drinking, smoking, BMI, physical activity) and health characteristics (participants with diabetes, chronic kidney disease and hypertension). The results are presented in supplementary Tables 1–5. The Fig. 5A and B indicates a negative association between flavanones (*P* for interaction = 0.047), flavones (*P* for interaction = 0.012) intake and PhenoAgeAccel in participants without chronic kidney disease. In Fig. 6, the interaction was also observed in the participants with a BMI of 25–30 (*P* for interaction = 0.044). However, no statistically significant results were found in the other flavonoid subclasses and subgroups.

Discussion

In this cross-sectional American population-based study, we investigated the association between dietary flavonoid intake and aging process. The results indicated that the total dietary flavonoid intake has a negative association with PhenoAgeAccel, and the similar association were observed in the four flavonoid subclasses (flavan-3-ols, flavanones, flavones and flavonols). Moreover, a nonlinear dose-response relationship was identified between flavonoid intake and PhenoAgeAccel. The mixed effect

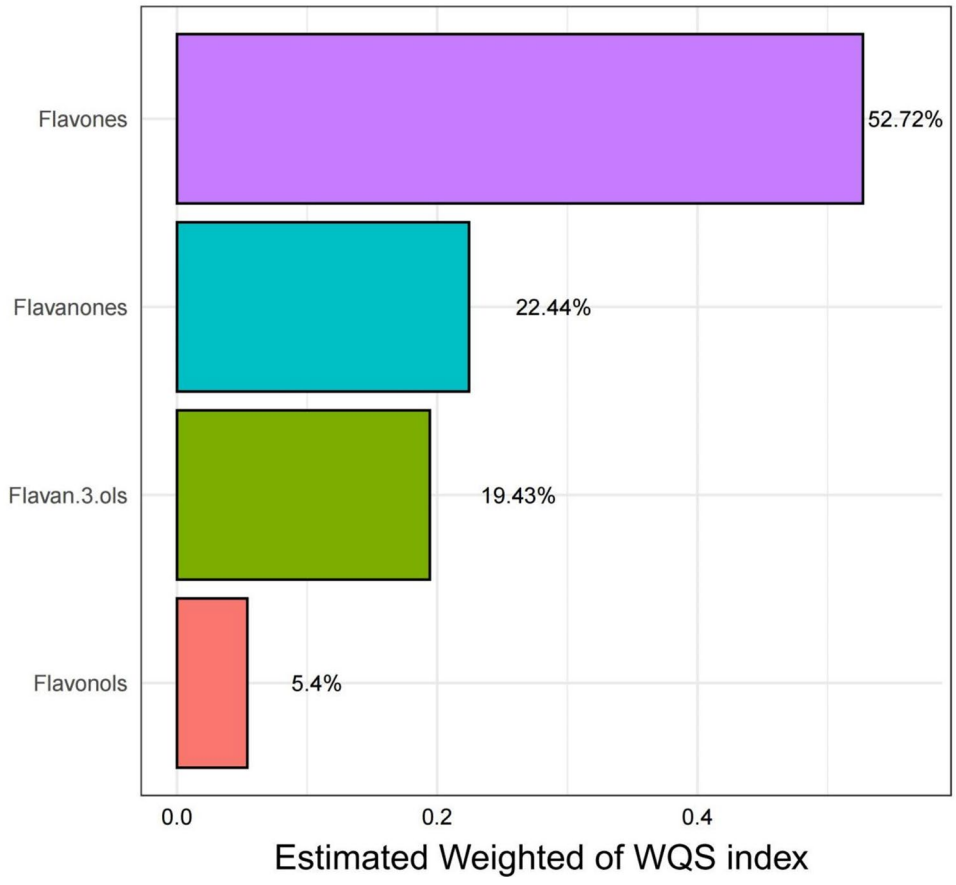

Fig. 4 WQS model regression index weights for dietary flavonoid intake and PhenoAgeAccel. The model was adjusted for gender, age, race, poverty income ratio, education level, marital status, drinking, smoking, body mass index physical activity, diabetes, chronic kidney disease and hypertension

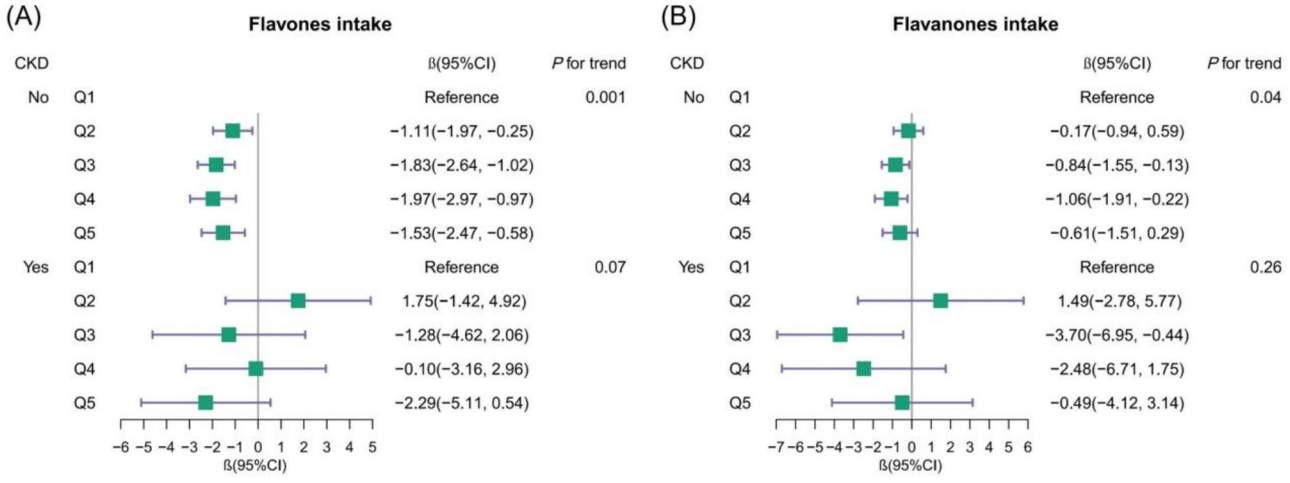

Fig. 5 Subgroup analysis for the association between flavanones, flavones intake and PhenoAgeAccel. (**A**) Association between flavones intake and PhenoAgeAccel in different CKD status. (**B**) Association between flavanones intake and PhenoAgeAccel in different CKD status. Abbreviations: CI, confidence interval; CKD, chronic kidney disease

analyses indicated that flavones were the primary contributors to the deceleration of the aging process.

Previous studies have indicated a beneficial association between flavonoid intake and delayed aging, which is consistent with our findings. A study from TwinsUK cohort suggests that increasing the intake of foods rich in flavonoids may potentially attenuate cognitive aging [28]. Meanwhile, another cohort study indicates that

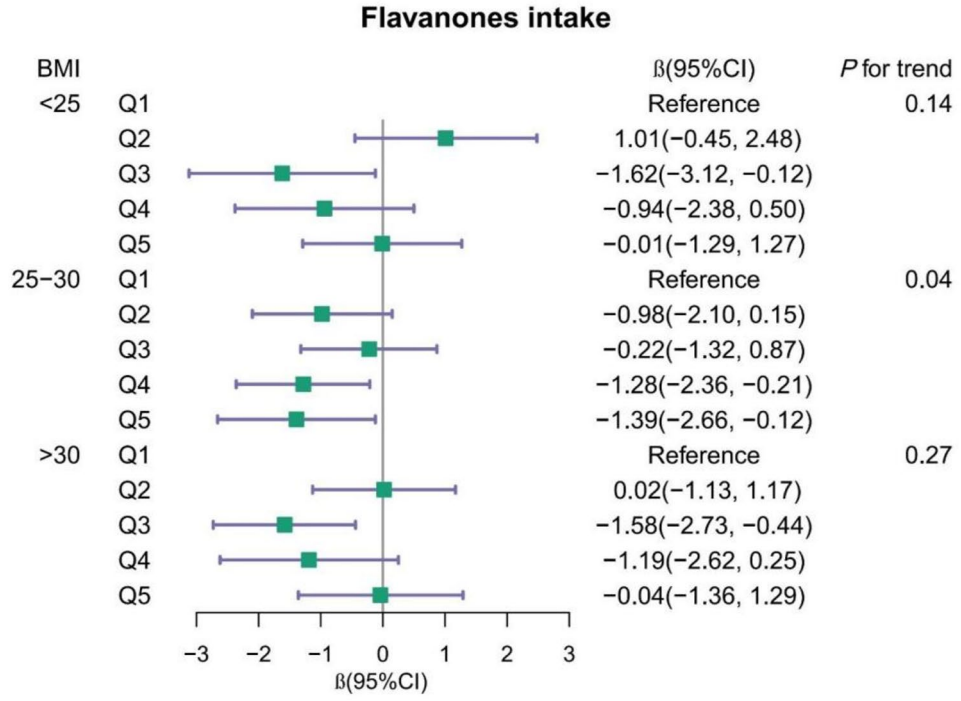

Fig. 6 Subgroup analysis for the association between flavanones intake and PhenoAgeAccel in different BMI groups. Abbreviations: CI, confidence interval; BMI, body mass index

women who have a higher intake of flavonoids during their middle age are more likely to experience better health and well-being in their later years [29]. Similarly, a study conducted among American adults found that flavonoid intake positively contributes to delaying the biological aging process [30]. Furthermore, additional research indicates that higher consumption of flavonoid-rich foods and beverages is associated with a lower all-cause mortality rate [31, 32]. In our study, we found that moderate dietary total flavonoid intake was associated with a younger phenotypic age. To date, the specific mechanisms by which flavonoids influence aging remain unclear, but they may involve the following mechanisms: Firstly, flavonoids could inhibit the formation of the senescence-associated secretory phenotype (SASP) and selectively eliminate senescent cells, thereby mitigating the aging process [33–35]. Secondly, due to the structural basis of flavonoids, they possess direct antioxidant activity which could directly scavenge ROS and upregulate antioxidant responses through the transcription factor NRF2 (Nuclear factor erythroid 2-related factor 2), which enhances proteasome activity and maintaining proteostasis to delay the aging process [36, 37]. Thirdly, flavonoids could inhibit the release of pro-inflammatory cytokines and reduce inflammation by modulating the MAPK and NF-κB signaling pathways [38, 39]. Fourthly, flavonoids could further induce autophagy by modulating autophagy-related signaling pathways, including PI3K/Akt/mTOR and AMPK/mTOR. This regulation promotes the clearance of abnormal protein aggregates within cells, maintains cellular homeostasis, and prevents the deterioration of cellular function [40–42].

Furthermore, we investigated the association between flavonoid subclasses and PhenoAgeAccel by examining both single and mixed effects. In the single effect analysis, we found that moderate intake of flavanones and flavonols, as well as moderate to high intake of flavan-3-ols and flavones, is associated with a younger phenotypic age. Meanwhile, all of these subclasses exhibit a non-linear association with PhenoAgeAccel. Several studies supported our results, derivatives of flavan-3-ols, such as catechins, have been demonstrated to enhance the overall health and survival rate of aged mice fed a standard diet [43]. Additionally, epicatechin has been shown to ameliorate age-related degenerative changes in the neuromuscular system of mice [44]. Naringenin, a flavanone, has been shown to extend lifespan and slow down aging through the IIS and MAPK pathways in Caenorhabditis elegans [45]. Apigenin is a kind of flavones with great anti-aging capability, a vivo research shows that apigenin could prevents signs of skin aging [46]. Moreover, recent studies have demonstrated that apigenin could reduce the SASP in a human fibroblast strain induced to senescence by bleomycin [47]. As for flavonols, their subclass quercetin, which is abundant in many fruits, vegetables, leafy greens, seeds, and grains, has been widely applied as a senolytics, demonstrating potent efficacy in the treatment of various age-related diseases and in anti-aging

[48–50]. In the mix effect analysis, the results of WQS regression model indicated that flavones had the primary effect on the mixture exposures, followed by flavanones, flavan-3-ols and flavonols, which consistent with the results of the single effect analysis. Interestingly, flavonols were the least significant contributors to the mixture exposures, although quercetin having demonstrated a potent effect in delaying senescence. This may be related to the low bioavailability and actual dietary intake concentration [51].

The subgroup analysis indicated that participants without CKD are more likely to benefit from dietary flavanones and flavones intake in mitigating aging. This may be attributed to the fact that individuals without CKD generally exhibit better health, allowing their bodies to utilize the health benefits of flavonoids more efficiently. In contrast, the protective effects of flavonoids in individuals with CKD may be diminished due to the impact of disease [52, 53]. Meanwhile, the benefits of flavanone intake are more significant in participants with a lower BMI. Research shows that the metabolic status of high BMI population is different, which may affect the absorption and metabolic efficiency of flavonoids [54].

There are several significant strengths exhibited in our study. To the best of our knowledge, this research is the first to examine the association between PhenoAgeAccel and dietary flavonoid intake. Further, our study included a substantial sample size of 5,391 participants and employed complex weight sampling, ensuring the representativeness of our findings for the overall adult population in the United States. Finally, we employed linear regression, RCS analyses, WQS regression and subgroup analysis to improve the reliability and robustness of our results. However, there are several limitations in our study. Firstly, a causal relationship between dietary flavonoid intake and aging cannot be determined because of the cross-sectional design. Secondly, dietary flavonoid intake data was collected by a two-day 24-hour dietary recall survey, which may lead to recall bias and might not reflect the long-term dietary intake habits of participants accurately. Thirdly, phenotypic age is calculated using multiple biomarkers. Although it has been shown to predict age-related diseases in different populations, it may differ from actual aging. Fourth, this study only includes the NHANES cycles of 2007–2008, 2009–2010, and 2017–2018. During this period, owing to the influence of secular trends, an increasing number of Americans have succumbed to drug overdoses, suicides, and organ system diseases, resulting in a downward trend in life expectancy in the United States [55]. This may potentially affect the indicators of aging and thus affect the associations observed in our study. Therefore, in the future, we should consider the impact of such as health care opportunities, medical practices, and socioeconomic status on outcomes. Finally, our study population was derived from the NHANES database, so the generalizability of our findings to populations in other regions may be limited.

Conclusions

To summarize, our study suggests that dietary total flavonoid intake and the four flavonoid subclasses (including flavan-3-ols, flavanones, flavones and flavonols) is associated with a younger phenotypic age. Mixed effects analyses indicated that the anti-aging effects may primarily stem from flavones. Furthermore, participants without CKD are more likely to benefit from dietary flavanone and flavone intake in mitigating aging, while the benefits of flavanone intake are more significant in participants with a lower BMI. Our findings suggested that flavonoid-rich diets may be beneficial for delaying aging. However, due to the limitations of our study, further prospective studies are needed to validate the causal relationship of dietary flavonoid intake and aging.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-01052-x.

Supplementary Material 1

Author contributions

Conceptualization: Jintao Zhong, Yixuan Wang; Data Curation: Biyu Wan, Mengya Wang; Formal analysis: Jiamin Fang, Pinli Lin; Writing – original draft: Jintao Zhong; Writing – review and editing: Jintao Zhong, Xiaona Tang. Funding acquisition: Xiaona Tang, Lili Deng; Supervision: Xiaona Tang. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The NHANES was approved by National center for Health Statistics Research Ethics Review Board, all participants provided informed consent.

Competing interests

The authors declare no competing interests.

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References

1. Bellantuono I. Find drugs that delay many diseases of old age. Nature. 2018;554(7692):293–5.
2. Chang AY, Skirbekk VF, Tyrovolas S, Kassebaum NJ, Dieleman JL. Measuring population ageing: an analysis of the global burden of Disease Study 2017. Lancet Public Health. 2019;4(3):e159–67.
3. Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, Hou L, Baccarelli AA, Stewart JD, Li Y et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging* 2018, 10(4):573–591.
4. Liu Z, Kuo P, Horvath S, Crimmins E, Ferrucci L, Levine M. A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: a cohort study. PLOS MED. 2018;15(12):e1002718.
5. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto RI, Pessin JE, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709–13.
6. Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, Salimi S, Sierra F, de Cabo R. Measuring biological aging in humans: a quest. Aging Cell. 2020;19(2):e13080.
7. Kuo C, Pilling LC, Liu Z, Atkins JL, Levine ME. Genetic associations for two biological age measures point to distinct aging phenotypes. Aging Cell. 2021;20(6):e13376.
8. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol A. 2013;68(6):667–74.
9. Bian L, Ma Z, Fu X, Ji C, Wang T, Yan C, et al. Associations of combined phenotypic aging and genetic risk with incident cancer: a prospective cohort study. ELIFE. 2024;13:RP91101.
10. Ye Z, Lang H, Xie Z, Duan S, Peng B, Chen X, Fang Y, Xin J. Associations of combined accelerated biological aging and genetic susceptibility with incident dementia: a prospective study in the UK Biobank. BMC MED. 2024;22(1):425.
11. Longo VD, Anderson RM. Nutrition, longevity and disease: from molecular mechanisms to interventions. Cell. 2022;185(9):1455–70.
12. Zhang W, Huang Q, Kang Y, Li H, Tan G. Which factors influence healthy aging? A lesson from the Longevity Village of Bama in China. AGING DIS. 2023;14(3):825–39.
13. Liu F, Nie J, Deng M, Yang H, Feng Q, Yang Y, Li X, Li X, Yang X, Li W, et al. Dietary flavonoid intake is associated with a lower risk of diabetic nephropathy in US adults: data from NHANES 2007–2008, 2009–2010, and 2017–2018. FOOD FUNCT. 2023;14(9):4183–90.
14. Kirkland JL, Tchkonia T, Zhu Y, Niedernhofer LJ, Robbins PD. The clinical potential of senolytic drugs. J AM GERIATR SOC. 2017;65(10):2297–301.
15. Joma N, Bielawski P, Saini A, Kakkar A, Maysinger D. Nanocarriers for natural polyphenol senotherapeutics. Aging Cell. 2024;23(5):e14178.
16. Davinelli S, Medoro A, Ali S, Passarella D, Intrieri M, Scapagnini G. Dietary flavonoids and adult neurogenesis: potential implications for Brain Aging. CURR NEUROPHARMACOL. 2023;21(3):651–68.
17. Sarubbo F, Moranta D, Pani G. Dietary polyphenols and neurogenesis: molecular interactions and implication for brain ageing and cognition. NEUROSCI BIOBEHAV R. 2018;90:456–70.
18. Liaquat L, Batool Z, Sadir S, Rafiq S, Shahzad S, Perveen T, Haider S. Naringenin-induced enhanced antioxidant defence system meliorates cholinergic neurotransmission and consolidates memory in male rats. LIFE SCI. 2018;194:213–23.
19. Parhiz H, Roohbakhsh A, Soltani F, Rezaee R, Iranshahi M. Antioxidant and anti-inflammatory properties of the Citrus flavonoids Hesperidin and Hesperetin: an updated review of their molecular mechanisms and experimental models. PHYTOTHER RES. 2015;29(3):323–31.
20. Pallauf K, Duckstein N, Rimbach G. A literature review of flavonoids and lifespan in model organisms. Proc Nutr Soc. 2017;76(2):145–62.
21. García-Fleitas J, García-Fernández A, Martí-Centelles V, Sancenón F, Bernardos A, Martínez-Máñez R. Chemical strategies for the detection and elimination of senescent cells. Acc CHEM RES. 2024;57(9):1238–53.
22. Lagoumtzi SM, Chondrogianni N. Senolytics and senomorphics: natural and synthetic therapeutics in the treatment of aging and chronic diseases. Free Radic Biol Med. 2021;171:169–90.
23. Zhao S, Tang Y, Li Y, Shen H, Liu A. Associations between Life's essential 8 and depression among US adults. PSYCHIAT RES. 2024;338:115986.
24. Zheng Y, Wang J, Xu K, Chen X. Intake of dietary flavonoids in relation to bone loss among U.S. adults: a promising strategy for improving bone health. FOOD FUNCT. 2024;15(2):766–78.
25. Deng M, Liu F, Wang K, Zhang M, Feng Q, Liu J. Association between dietary flavonoid intake and depressive symptoms: a cross-sectional research. GEN HOSP PSYCHIAT. 2024;86:75–84.
26. Hibler EA, Zhu X, Shrubsole MJ, Hou L, Dai Q. Physical activity, dietary calcium to magnesium intake and mortality in the National Health and Examination Survey 1999–2006 cohort. INT J CANCER. 2020;146(11):2979–86.
27. Wei M, Cui Y, Zhou H, Song W, Di D, Zhang R, Huang Q, Liu J, Wang Q. Associations of multiple metals with bone mineral density: a population-based study in US adults. Chemosphere. 2021;282:131150.
28. Jennings A, Steves CJ, Macgregor A, Spector T, Cassidy A. Increased habitual flavonoid intake predicts attenuation of cognitive ageing in twins. BMC MED. 2021;19(1):185.
29. Samieri C, Sun Q, Townsend MK, Rimm EB, Grodstein F. Dietary flavonoid intake at midlife and healthy aging in women. Am J Clin Nutr. 2014;100(6):1489–97.
30. Xing W, Gao W, Zhao Z, Xu X, Bu H, Su H, Mao G, Chen J. Dietary flavonoids intake contributes to delay biological aging process: analysis from NHANES dataset. J TRANSL MED. 2023;21(1):492.
31. Bondonno NP, Lewis JR, Blekkenhorst LC, Bondonno CP, Shin JH, Croft KD, Woodman RJ, Wong G, Lim WH, Gopinath B, et al. Association of flavonoids and flavonoid-rich foods with all-cause mortality: the Blue mountains Eye Study. Clin Nutr. 2020;39(1):141–50.
32. Bondonno NP, Liu YL, Zheng Y, Ivey K, Willett WC, Stampfer MJ, Rimm EB, Cassidy A. Change in habitual intakes of flavonoid-rich foods and mortality in US males and females. BMC MED. 2023;21(1):181.
33. Lim H, Park H, Kim HP. Effects of flavonoids on senescence-associated secretory phenotype formation from bleomycin-induced senescence in BJ fibroblasts. BIOCHEM PHARMACOL. 2015;96(4):337–48.
34. Xu Q, Fu Q, Li Z, Liu H, Wang Y, Lin X, He R, Zhang X, Ju Z, Campisi J, et al. The flavonoid procyanidin C1 has senotherapeutic activity and increases lifespan in mice. NAT METAB. 2021;3(12):1706–26.
35. Lim H, Kwon YS, Kim D, Lee J, Kim HP. Flavonoids from Scutellaria baicalensis inhibit senescence-associated secretory phenotype production by interrupting IκBζ/C/EBPβ pathway: inhibition of age-related inflammation. Phytomedicine: Int J Phytotherapy Phytopharmacology. 2020;76:153255.
36. Rolt A, Cox LS. Structural basis of the anti-ageing effects of polyphenolics: mitigation of oxidative stress. BMC CHEM. 2020;14(1):50.
37. Burda S, Oleszek W. Antioxidant and antiradical activities of flavonoids. J AGR FOOD CHEM. 2001;49(6):2774–9.
38. Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. CURR OPIN FOOD SCI. 2016;8:33–42.
39. Wu M, Luo Q, Nie R, Yang X, Tang Z, Chen H. Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiota. CRIT REV FOOD SCI. 2021;61(13):2175–93.
40. Pazoki-Toroudi H, Amani H, Ajami M, Nabavi SF, Braidy N, Kasi PD, Nabavi SM. Targeting mTOR signaling by polyphenols: a new therapeutic target for ageing. AGEING RES REV. 2016;31:55–66.
41. Che J, Liang B, Zhang Y, Wang Y, Tang J, Shi G. Kaempferol alleviates ox-LDL-induced apoptosis by up-regulation of autophagy via inhibiting PI3K/Akt/mTOR pathway in human endothelial cells. Cardiovasc Pathology: Official J Soc Cardiovasc Pathol. 2017;31:57–62.
42. Bientinesi E, Ristori S, Lulli M, Monti D. Quercetin induces Senolysis of Doxorubicin-Induced senescent fibroblasts by reducing Autophagy, preventing their pro-tumour effect on Osteosarcoma cells. MECH AGEING DEV. 2024;220:111957111957.
43. Gras S, Blasco A, Mòdol-Caballero G, Tarabal O, Casanovas A, Piedrafita L, Barranco A, Das T, Rueda R, Pereira SL, et al. Beneficial effects of dietary supplementation with green tea catechins and cocoa flavanols on aging-related regressive changes in the mouse neuromuscular system. Aging. 2021;13(14):18051–93.
44. Si H, Lai C, Liu D. Dietary epicatechin, a novel anti-aging Bioactive Small Molecule. CURR MED CHEM. 2021;28(1):3–18.

45. Ge Y, Chen H, Wang J, Liu G, Cui SW, Kang J, Jiang Y, Wang H. Naringenin prolongs lifespan and delays aging mediated by IIS and MAPK in Caenorhabditis elegans. FOOD FUNCT. 2021;12(23):12127–41.
46. Choi S, Youn J, Kim K, Joo DH, Shin S, Lee J, Lee HK, An I, Kwon S, Youn HJ, et al. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. INT J MOL MED. 2016;38(2):627–34.
47. Perrott KM, Wiley CD, Desprez P, Campisi J. Apigenin suppresses the senescence-associated secretory phenotype and paracrine effects on breast cancer cells. GEROSCIENCE. 2017;39(2):161–73.
48. Yamaura K, Nelson AL, Nishimura H, Rutledge JC, Ravuri SK, Bahney C, Philippon MJ, Huard J. Therapeutic potential of senolytic agent quercetin in osteoarthritis: a systematic review and meta-analysis of preclinical studies. AGEING RES REV. 2023;90:101989.
49. Sohn E, Kim JM, Kang S, Kwon J, An HJ, Sung J, Cho KA, Jang I, Choi J. Restoring effects of Natural Anti-oxidant Quercetin on Cellular Senescent Human dermal fibroblasts. Am J Chin Med. 2018;46(4):853–73.
50. Cui Z, Zhao X, Amevor FK, Du X, Wang Y, Li D, Shu G, Tian Y, Zhao X. Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism. FRONT IMMUNOL. 2022;13:943321.
51. Kim T, Cho AY, Lee S, Lee HJ. Controlled quercetin release by fluorescent Mesoporous Nanocarriers for Effective Anti-adipogenesis. INT J NANOMED. 2024;19:5441–58.
52. Lin Y, Fang J, Zhang Z, Farag MA, Li Z, Shao P. Plant flavonoids bioavailability in vivo and mechanisms of benefits on chronic kidney disease: a comprehensive review. PHYTOCHEM REV. 2023;22:1541–1565.
53. Cao Y, Lin J, Hammes H, Zhang C. Flavonoids in treatment of chronic kidney disease. Molecules 2022, 27(7).
54. Baky MH, Elshahed M, Wessjohann L, Farag MA. Interactions between dietary flavonoids and the gut microbiome: a comprehensive review. Br J Nutr. 2022;128(4):577–91.
55. Woolf SH, Schoomaker H. Life Expectancy and Mortality Rates in the United States, 1959–2017. JAMA-J AM MED ASSOC. 2019;322(20):1996–2016.

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