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RESEARCH ARTICLE

The L-shaped link between total antioxidant capacity and phenotypic age acceleration: evidence from NHANES 2003–2010

Yukun Wu · Mengxiang Xiang · Yangcheng Zhao · Yu Zhang · Wenxiang Cheng · Jiangbei Deng

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Abstract This study aimed to investigate the relationship between total antioxidant capacity (TAC) and phenotypic age acceleration (PhenoAgeAccel), a measure of accelerated biological aging, using data from the National Health and Nutrition Examination Survey (NHANES). Data from the 2003–2010 NHANES surveys, encompassing 16,395 participants, were analyzed. Principal component analysis (PCA) was used to reduce data dimensionality. Multivariate logistic regression models were employed to evaluate the association between TAC and antioxidant vitamins (α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein-zeaxanthin, vitamin A, vitamin C, vitamin E) with PhenoAgeAccel, adjusting for demographic, lifestyle, and clinical factors. Smoothed curve fitting and threshold effects analysis were conducted to explore the nonlinear relationship between log-transformed TAC and PhenoAgeAccel. Subgroup analyses were performed to assess potential effect modifiers based on age, gender, race, education, smoking, alcohol use, diabetes, hypertension, and hyperlipidemia. The weak correlations between the original variables prevent PCA from effectively capturing the primary variability within the data. Higher TAC was significantly inversely associated with PhenoAgeAccel in both unadjusted and adjusted models. Participants in the second tertile (T2) of TAC exhibited 11% lower odds of PhenoAgeAccel compared to those in the first tertile (T1) (OR = 0.89, 95% CI: 0.81–0.98, $P = 0.0176$). Intake of several antioxidant vitamins, including α-carotene, β-carotene, lutein-zeaxanthin, vitamin A, vitamin C, and vitamin E, was also inversely associated with the odds of PhenoAgeAccel. A nonlinear relationship between log-transformed TAC and PhenoAgeAccel was observed, with a significant protective effect within a specific range of TAC. Subgroup analyses revealed no significant effect modification by most factors, except for gender, smoking, and alcohol consumption. TAC is closely associated with PhenoAgeAccel. A nonlinear relationship was observed, with higher TAC exhibiting significant protective effects within a specific range, particularly among males, smokers, and alcohol consumer. These findings underscore the potential value of TAC in mitigating the aging process.

Keywords Total antioxidant capacity · Phenotypic age acceleration · Oxidative stress · NHANES · Cross-sectional study

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Y. Wu · M. Xiang · Y. Zhao · Y. Zhang · W. Cheng · J. Deng (✉)
The Affiliated Changsha Central Hospital, Department of Peripheral Vascular Intervention, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, China
e-mail: dengjiangbei1988@hotmail.com

Introduction

The global ageing of the population has emerged as a critical public health challenge, primarily driven by rising life expectancy and declining fertility rates. By 2050, it is projected that the global elderly population will constitute one-sixth of the total population (Giacomello and Toniolo 2021). The risk of numerous chronic diseases associated with aging escalates markedly with advancing age (Kennedy 2014; Niccoli and Partridge 2012), thereby placing a substantial economic burden on society (Sierra 2021). Research has demonstrated that a delay of 2.2 years in the population aging process could result in savings of approximately 7 trillion dollars in economic costs over the next 50 years (Fitzgerald 2021). Consequently, the formulation and implementation of effective prevention strategies and interventions for healthy aging are crucial to mitigating this global challenge.

Aging is a progressive biological process during which individuals gradually experience a decline in physiological functions and adaptive capacity at the cellular, tissue, and organ levels (Kennedy, et al. 2014). Although aging is a universal phenomenon, substantial individual variations in aging manifestations exist even among individuals of the same age group (Chen Y. 2024). This variation has driven researchers to investigate biomarkers that more accurately reflect individual aging processes. In recent years, phenotypic age (PhenoAge), based on clinical biomarkers, has garnered growing attention (Mak 2023). In comparison to single molecular markers, PhenoAge offers a more comprehensive health assessment, provides superior predictions of health outcomes, and aids in identifying individuals at higher risk for age-related diseases (Levine 2018).

Despite significant advances in biogerontology, critical knowledge gaps remain in our understanding of the fundamental mechanisms driving aging. Recently, Rattan identified seven key knowledge gaps in modern biogerontology, organized into three categories: (1) evolutionary aspects of longevity, (2) biological survival and death mechanisms, and (3) heterogeneity in the progression and phenotype of aging (Rattan 2024). Given these knowledge gaps, future research must focus on deepening our understanding of the aging process and on devising effective interventions to fill these gaps. One of the central mechanisms implicated in aging is the imbalance between free radicals and antioxidants within the body. This imbalance leads to oxidative stress (OS) and accelerated cellular damage, which in turn drives the aging process (Monti 2019). Diet plays a pivotal role in regulating OS, and studies have demonstrated that antioxidant-rich diets not only effectively reduce OS but may also lower the risk of age-related diseases (Bondonno 2020;Ivey 2017;Lindsay 1999;Martemucci 2022). Antioxidants serve a protective role in mitigating aging and disease by scavenging free radicals and alleviating their toxic effects on biological systems (Conti 2016).

Total antioxidant capacity (TAC) quantifies the combined effect of dietary antioxidants and reflects the synergistic interactions between various antioxidant molecules in food (Serafini 1994; Sies 2007). It is primarily determined by the combination of eight antioxidant vitamins (vitamin A, vitamin C, vitamin E, α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein-zeaxanthin), offering a comprehensive assessment of the body's capacity to counteract OS (Floegel 2010; Serafini and Del Rio 2004). Previous studies have demonstrated that dietary antioxidant intake inhibits the production of reactive oxygen species (ROS) and may mitigate oxidative DNA damage (Beydoun 2014). TAC levels are closely associated with the degree of OS and the health status of an individual. Higher TAC is typically associated with reduced oxidative damage and a lower risk of age-related diseases. However, the precise relationship between TAC and phenotypic age acceleration (PhenoAgeAccel) remains unclear. This study aimed to investigate the relationship between TAC and PhenoAgeAccel using data from the National Health and Nutrition Examination Survey (NHANES) and to evaluate the potential role of TAC in the aging process.

Methods

Study population

Since C-reactive protein, one of the key biomarkers required to calculate PhenoAgeAccel, is only fully available in the 2003–2010 NHANES survey cycles, we chose this period to explore the relationship between TAC and PhenoAgeAccel. Exclusion criteria

included those under 20 years of age (n = 18,983) and participants lacking essential data: PhenoAge (n = 2418), dietary information or anti-oxidative vitamin intake (n = 840), education level (n = 19), marital status (n = 7), poverty income ratio (PIR) (n = 1314), alcohol consumption (n = 929), smoking status (n = 5), hypertension (n = 57), diabetes (n = 8), body mass index (BMI) (n = 177), and high-density lipoprotein levels (n = 4). Following these exclusions, the final analysis cohort comprised 16,395 participants (Fig. 1). The study was conducted in accordance with the ethical standards of the National Health Statistics Center Institutions and all participants provided written informed consent before data collection. All procedures involving human participants in this study were conducted in accordance with the ethical standards set by the relevant institutional and national research committees. This is in compliance with the 1964 Helsinki Declaration and its subsequent revisions, or other equivalent ethical guidelines. The analyses employed data from the NHANES, which was approved by the Ethics Review Board of the National Center for Health Statistics. Further details regarding the ethical approval and informed consent process for this study can be found on the NHANES website. Prior to their inclusion in the NHANES database, written informed consent was obtained from all participants.

PhenoAgeAccel

PhenoAge was calculated using the method proposed by Morgan E. Levine et al. (Levine, et al. 2018). The method combines chronological age and nine biomarkers (Mekary 2009), including creatinine, albumin, log-transformed C-reactive protein, glucose, alkaline phosphatase, lymphocyte percentage, red blood cell distribution width, mean cell volume, and white blood cell count. Due to the limited length of the manuscript, we have not included the full experimental methods. For more detailed information, the complete laboratory methods for each parameter can be accessed on the NHANES website: https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2009/DataFiles/BIOPRO_F.htm#Descr

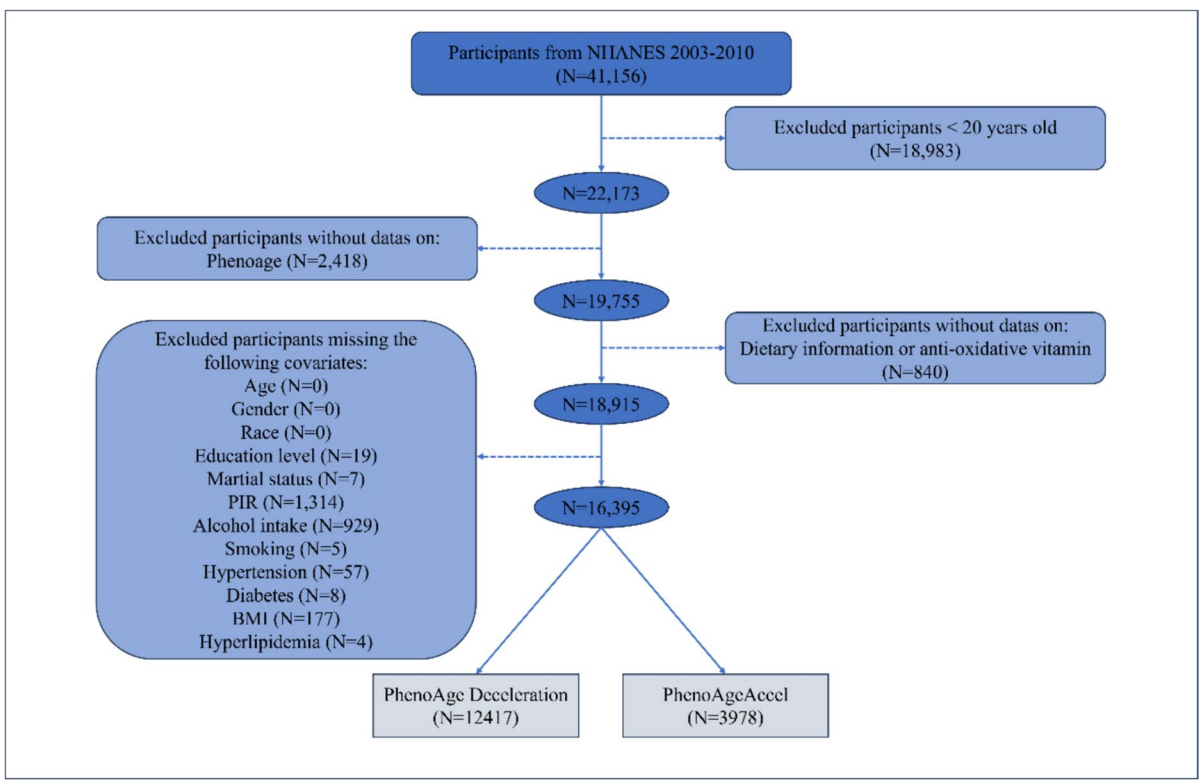

Fig. 1 Flowchart of study participants selection

iption_of_Laboratory_Methodology. The PhenoAgeAccel reflects the degree of phenotypic aging adjusted for chronological age. When PhenoAgeAccel ≤ 0, it indicates that an individual's PhenoAge is lower than the expected age corresponding to their CA; if PhenoAgeAccel > 0, it indicates that the PhenoAge is higher than expected (He K. 2024b).

PhenoAge calculation formula (Zhu 2024):

$$PhenoAge = 141.50 + \frac{\ln\left\{-0.00553 \times \frac{-1.51714 \times exp(xb)}{0.0076927}\right\}}{0.09165}$$

$$xb = -18.511 - 0.2502 \times Albumin + 0.0063 \times Creatinine + 0.1741 \times Glucose + 0.1393 \times LnCRP - 0.0126 \times LymphocytePercentage + 0.0292 \times MeanCellVolume + 0.2318 \times ErythrocyteDistributionWidth + 0.0021 \times AlkalinePhesphatase + 0.0547 \times LeukocyteCount + 0.0777 \times chronologicalage$$

Estimationof TAC from diet

Dietary information was obtained via two 24-h dietary recall interviews. The initial interview was conducted at a mobile examination center, while the subsequent interview was conducted via telephone. The interviews encompassed sections on dietary recall, supplement usage, and antacid consumption. As documented in the Food and Nutrient Database for Dietary Studies (2013–2014), the intake of food and beverages was converted to 64 nutrients, including eight antioxidant vitamins: vitamin A, vitamin C, vitamin E, α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein-zeaxanthin. The data obtained from the initial interview were utilized to calculate the TAC, which served to assess the dietary antioxidant potential. The method of calculating TAC has been validated by Floegel et al. (Floegel, et al. 2010), who used a process of multiplication and summation, where antioxidant intake is multiplied by its corresponding antioxidant capacity to determine the TAC for each individual. The Vitamin C Equivalent (VCE) is used to measure the antioxidant capacity of other substances, representing the degree of their antioxidant activity relative to that of vitamin C. Due to the skewed distribution of TAC data, a log transformation was applied.

TAC calculation formula (Floegel, et al. 2010):

$$TAC = \sum \left[Antioxidant\ content\left(\frac{mg}{100g}\right) \times Antioxidant\ capacity\left(\frac{mgVCE}{100g}\right)\right]$$

Covariables

To enhance the accuracy of this study, we included a variety of sociodemographic and behavioral factors, along with some diseases that may be associated with aging, as potential confounding variables. The included covariates were: age (years), gender (male/female), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other), education level (less than high school, high school, more than high school), PIR, BMI, marital status (married or living with partner, divorced, separated, or widowed, and never married), smoking (indicating if the participant has smoked at least 100 cigarettes in their life: Yes/No), alcohol intake (drank at least 12 alcoholic drinks in the past year: Yes/No), diabetes (Yes/No), hypertension (Yes/No) and hyperlipidemia (Yes/No).

Statistical analysis

The statistical analysis followed established survey methodologies and NHANES analytical guidelines. Continuous variables are presented as means ± standard deviations (Mean ± SD), while categorical variables are expressed as percentages. Given the large number of independent variables and the need to reduce data dimensionality, principal component analysis (PCA) was employed to evaluate the relationships between the intake of eight vitamins (Vitamin A, Vitamin C, Vitamin E, Alpha-carotene, Beta-carotene, Beta-cryptoxanthin, Lycopene, and

Lutein + zeaxanthin) and TAC levels with PhenoAgeAccel. PCA and result visualization were performed using GraphPad Prism 9.5.0. TAC values were categorized into tertiles: first tertile (T1) (0 < TAC < 3751 mg VCE/d), second tertile (T2) (3753 ≤ TAC ≤ 10,287 mg VCE/d), and third tertile (T3) (TAC ≥ 10,287 mg VCE/d). A multivariate logistic regression model was employed to investigate the relationship between tertiles, log-transformed TAC, 8 antioxidant vitamins, and PhenoAgeAccel. The model consisted of two components: an unadjusted model and an adjusted model. Smoothed curve fitting was applied to characterize the nonlinear relationship between log-transformed TAC and PhenoAgeAccel. Furthermore, a threshold effects analysis model was utilized to assess the association and identify inflection points between log-transformed TAC and PhenoAgeAccel. Finally, subgroup analysis was performed to assess effect modification across various groups, including age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. Interaction tests were conducted to evaluate the consistency of these associations across the subgroups. Statistical analyses mentioned above were carried out using R software (version 4.2) and EmpowerStats (v.2.0, http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA), with a two-sided p-value of less than 0.05 considered statistically significant.

Results

Participant characteristics

Table 1 presents the demographic and clinical characteristics of participants classified into two groups based on PhenoAge deceleration/stasis (n = 12,417) and PhenoAgeAccel (n = 3978). There were differences between the PhenoAgeAccel and deceleration/stasis groups in several demographic and clinical characteristics. Age, gender, race/ethnicity, education level, and BMI all showed significant differences between the two groups. Lifestyle factors such as smoking, alcohol intake, and the prevalence of diabetes, hypertension, and hyperlipidemia also differed between the groups.

Regarding TAC, the PhenoAgeAccel group had a slightly lower TAC (9,053.47 ± 10,609.83 mg VCE/d) compared to the deceleration/stasis group (9,630.26 ± 10,187.29 mg VCE/d) ($P = 0.002$). Intake of several antioxidant vitamins was also significantly different between the groups. The PhenoAgeAccel had lower intake of α-carotene (327.74 ± 907.04 mcg/d) and β-carotene (1,762.06 ± 3,259.62 mcg/d) compared to the deceleration/stasis group (382.57 ± 1,016.64 mcg/d and 2,023.32 ± 3,570.10 mcg/d, respectively) (both $P < 0.01$). The PhenoAgeAccel group also had significantly lower intake of lycopene (4,905.94 ± 9,267.88 mcg/d), lutein-zeaxanthin (1,272.70 ± 2,886.46 mcg/d), vitamin A (986.90 ± 1,443.04 mcg/d), vitamin C (84,545.50 ± 104,318.51 mcg/d), and vitamin E (6,876.99 ± 6,436.67 mcg/d) (all $P < 0.05$), except for β-cryptoxanthin, where no significant difference was observed (P = 0.313) (Table 2). These findings suggest that individuals with PhenoAgeAccel tend to have lower levels of dietary antioxidants and a higher prevalence of adverse health conditions compared to those with PhenoAge deceleration/stasis.

Principal component analysis

The PCA revealed that the variance explained by principal component 1 (PC1) was 32.72%, while the variance explained by principal component 2 (PC2) accounted for 18.59%. The cumulative variance explained by both PC1 and PC2 was 51.31% (Fig. S1). Table S1 presents the contribution of each variable to PC1 and PC2, whereas **Fig. S2** illustrates the PhenoAge Acceleration scores for both groups in relation to PC1 and PC2. The PCA results indicated that the cumulative variance explained by PC1 and PC2 was 51.31%, which is substantially lower than the 70%−85% threshold typically expected for effective dimensionality reduction. This discrepancy is likely attributed to weak correlations between the original variables, which hinder the principal components from effectively capturing the primary variability within the data. The score scatter plot revealed significant overlap between the PhenoAge Acceleration and PhenoAge Deceleration groups, suggesting that the two groups could not be effectively distinguished based on PC1 and PC2. In summary, PC1 and PC2 failed to capture the majority of the information. To ensure the inclusion of all relevant data, we subsequently analyzed the relationships between the independent variables and PhenoAgeAccel individually.

Table 1 Basic characteristics of participants by PhenoAgeAccel status

Characteristics	PhenoAge Deceleration/Stasis (n = 12,417)	PhenoAgeAccel (n = 3978)	*P*-value
Age(years)	48.54 ± 17.91	52.79 ± 18.92	< 0.001
Gender, (%)			0.001
Male	6012 (48.42%)	2044 (51.38%)	
Female	6405 (51.58%)	1934 (48.62%)	
Race/ethnicity, (%)			< 0.001
Mexican American	2352 (18.94%)	673 (16.92%)	
Other Hispanic	860 (6.93%)	223 (5.61%)	
Non-Hispanic White	6575 (52.95%)	1957 (49.20%)	
Non-Hispanic Black	2107 (16.97%)	992 (24.94%)	
Other race/multiracial	523 (4.21%)	133 (3.34%)	
Education level, (%)			< 0.001
Less than high school	3180 (25.61%)	1322 (33.23%)	
High school	2889 (23.27%)	1042 (26.19%)	
More than high school	6348 (51.12%)	1614 (40.57%)	
BMI (kg/m^2)	28.09 ± 5.80	31.57 ± 8.17	< 0.001
Smoking, (%)			< 0.001
Yes	5650 (45.50%)	2257 (56.74%)	
No	6767 (54.50%)	1721 (43.26%)	
Alcohol intake, (%)			< 0.001
Yes	8930 (71.92%)	2713 (68.20%)	
No	3487 (28.08%)	1265 (31.80%)	
Diabetes, (%)			< 0.001
Yes	850 (6.85%)	937 (23.55%)	
No	11,567 (93.15%)	3041 (76.45%)	
Hypertension, (%)			< 0.001
Yes	3781 (30.45%)	1877 (47.18%)	
No	8636 (69.55%)	2101 (52.82%)	
Hyperlipidemia, (%)			< 0.001
Yes	2663 (21.45%)	1087 (27.33%)	
No	9754 (78.55%)	2891 (72.67%)	

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages. Abbreviation: *PhenoAgeAccel* Phenotypic age acceleration; *BMI*, Body mass index

Table 2 TAC and antioxidant vitamin intake

Characteristics	PhenoAge Deceleration/Stasis (n = 12,417)	PhenoAgeAccel (n = 3978)	*P*-value
TAC (mg VCE/d)	9630.26 ± 10,187.29	9053.47 ± 10,609.83	0.002
Intake of anti-oxidative vitamins (mcg/d)			
α-carotene	382.57 ± 1016.64	327.74 ± 907.04	0.002
β-carotene	2023.32 ± 3570.10	1762.06 ± 3259.62	< 0.001
β-cryptoxanthin	113.15 ± 272.18	108.36 ± 219.73	0.313
lycopene	5680.75 ± 10,255.06	4905.94 ± 9267.88	< 0.001
lutein-zeaxanthin	1405.67 ± 3006.32	1272.70 ± 2886.46	0.014
Vitamin A	1034.45 ± 1203.00	986.90 ± 1443.04	0.039
Vitamin C	89,480.86 ± 99,719.47	84,545.50 ± 104,318.51	0.007
Vitamin E	7819.43 ± 6960.08	6876.99 ± 6436.67	< 0.001

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages. Abbreviation: *PhenoAgeAccel* Phenotypic age acceleration; *TAC* Total antioxidant capacity; *VCE* Vitamin C equivalent

Table 3 Association of TAC and 8 anti-oxidative vitamins with PhenoAgeAccel among participants by logistic regression

	Unadjusted		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Tertiles of TAC (mg VCE/d)				
T1	Ref	Ref	Ref	Ref
T2	0.82 (0.76, 0.90)	< 0.0001	0.89 (0.81, 0.98)	0.0176
T3	0.81 (0.74, 0.88)	< 0.0001	0.93 (0.85, 1.02)	0.1402
logTAC	0.80 (0.74, 0.85)	< 0.0001	0.90 (0.84, 0.97)	0.0055
8 antioxidative vitamins (Log-transformed)				
α-carotene (mcg/d)	0.92 (0.88, 0.96)	< 0.0001	0.94 (0.90, 0.99)	0.0206
β-carotene (mcg/d)	0.79 (0.75, 0.84)	< 0.0001	0.86 (0.81, 0.91)	< 0.0001
β-cryptoxanthin (mcg/d)	0.98 (0.93, 1.02)	0.3207	1.02 (0.96, 1.07)	0.5630
Lycopene (mcg/d)	0.93 (0.89, 0.98)	0.0044	0.97 (0.92, 1.02)	0.2751
lutein-zeaxanthin (mcg/d)	0.79 (0.74, 0.84)	< 0.0001	0.84 (0.78, 0.90)	< 0.0001
Vitamin A (mcg/d)	0.76 (0.70, 0.83)	< 0.0001	0.86 (0.78, 0.94)	0.0011
Vitamin C (mcg/d)	0.83 (0.78, 0.89)	< 0.0001	0.92 (0.86, 0.99)	0.0224
Vitamin E (mcg/d)	0.54 (0.48, 0.61)	< 0.0001	0.66 (0.58, 0.74)	< 0.0001

Adjusted for age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. Abbreviations: *TAC* Total antioxidant capacity; *PhenoAgeAccel* Phenotypic age acceleration; *VCE* Vitamin C equivalent; *T1* First tertile; *T2* Second tertile; *T3* Third tertile; *PIR* Poverty income ratio; *BMI* Body mass index; *OR* Odds ratio; *CI* Confidence interval; *Ref* Reference

Associations between TAC and PhenoAgeAccel

Table 3 presents the results of multivariate logistic regression analysis examining the association of TAC and eight antioxidative vitamins with PhenoAgeAccel. In both unadjusted and adjusted models, higher TAC was inversely associated with the odds of PhenoAgeAccel. In the adjusted model, participants in the second tertile of TAC had 11% lower odds of PhenoAgeAccel compared to the first tertile (OR = 0.89, 95% CI: 0.81–0.98, $P = 0.0176$), while the association for the third tertile was not statistically significant (OR = 0.93, 95% CI: 0.85–1.02, $P = 0.1402$). Log-transformed TAC also showed a significant negative association with PhenoAgeAccel in the adjusted model (OR = 0.90, 95% CI: 0.84–0.97, $P = 0.0055$).

Regarding antioxidative vitamins, significant associations were found for several vitamins in both unadjusted and adjusted models. The intake of α-carotene, β-carotene, lutein-zeaxanthin, vitamin A, vitamin C, and vitamin E were inversely associated with the odds of PhenoAgeAccel. Specifically, higher intake of α-carotene (OR = 0.94, 95% CI: 0.90–0.99, $P = 0.0206$), β-carotene (OR = 0.86, 95% CI: 0.81–0.91, $P < 0.0001$), lutein-zeaxanthin (OR = 0.84, 95% CI: 0.78–0.90, $P < 0.0001$), vitamin A (OR = 0.86, 95% CI: 0.78–0.94, $P = 0.0011$), vitamin C (OR = 0.92, 95% CI: 0.86–0.99, $P = 0.0224$), and vitamin E (OR = 0.66, 95% CI: 0.58–0.74, $P < 0.0001$) were significantly associated with a lower likelihood of PhenoAgeAccel after adjusting for potential confounders. However, no significant associations were observed for β-cryptoxanthin or lycopene in adjusted models ($P = 0.5630$ and $P = 0.2751$, respectively).

Smoothed curve fitting and threshold effects analysis

The smoothed curve fitting shows a non-linear relationship between log-transformed TAC and PhenoAgeAccel (P for non-linearity = 0.0023) (Fig. 2). Table 4 presents the threshold effects analysis of log-transformed TAC on PhenoAgeAccel using both a standard linear model and a two-piecewise linear regression model. In the standard linear model, log-transformed TAC was significantly inversely associated with the odds of PhenoAgeAccel, with an OR of 0.80 (95% CI: 0.74–0.85, $P < 0.0001$) in

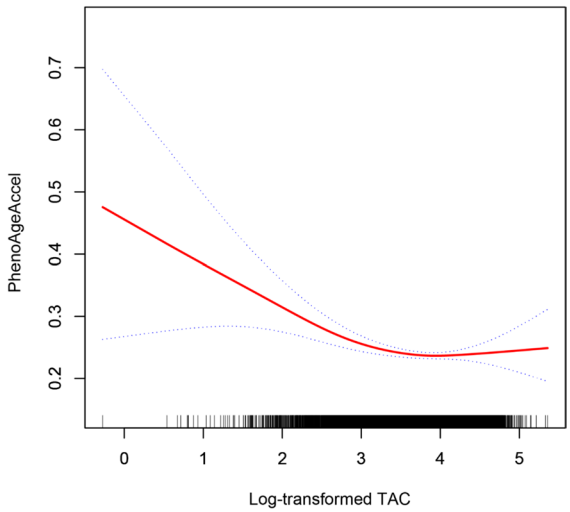

Fig. 2 Correlation between log-transformed TAC and PhenoAgeAccel

the unadjusted model, and 0.90 (95% CI: 0.84–0.97, $P = 0.0055$) in the adjusted model. When fitting the data using the two-piecewise linear regression model, an inflection point (K) of 3.69 in the unadjusted model and 3.73 in the adjusted model was identified. Below the inflection point, log-transformed TAC was strongly associated with reduced odds of PhenoAgeAccel, with an OR of 0.70 (95% CI: 0.62–0.78, $P < 0.0001$) in the unadjusted model, and 0.78 (95% CI: 0.69–0.88, $P < 0.0001$) in the adjusted model. However, above the inflection point, there was no significant association between log-transformed TAC and PhenoAgeAccel.

The natural spline curve shows a non-linear relationship between log-transformed TAC and PhenoAgeAccel (P for non-linearity = 0.0023). The solid red line represents the estimated value and the blue dashed areas indicate their corresponding 95% confidence interval. Age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia were adjusted. Abbreviations: TAC, total antioxidant capacity; PhenoAgeAccel, phenotypic age acceleration; PIR, poverty income ratio; BMI, body mass index.

Subgroup analysis

As shown in Fig. 3 and Table 5, our study assessed the association between log-transformed TAC and PhenoAgeAccel across various subgroups based on age, gender, race, education level, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. The analyses were adjusted for multiple covariates, including age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. Subgroup analyses revealed that the relationship between log-transformed TAC and PhenoAgeAccel was consistent across the subgroups defined by age, race, education level, diabetes, hypertension, and hyperlipidemia, with no significant interaction observed (P for interaction > 0.05). However, significant interaction effects were observed for gender, smoking, and alcohol intake (P for interaction < 0.05).

Table 4 Threshold effect analysis of Log-transformed TAC on PhenoAgeAccel using the two-piecewise linear regression model

	Unadjusted		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Fitting by the standard liner model	0.80(0.74,0.85)	< 0.0001	0.90(0.84,0.97)	0.0055
Fitting by Two-piecewise Linear Model				
Inflection point(K)	3.69		3.73	
Log-transformed TAC < K	0.70(0.62,0.78)	< 0.0001	0.78(0.69,0.88)	< 0.0001
Log-transformed TAC > K	0.96(0.83,1.12)	0.6340	1.13(0.96,1.34)	0.1504
Log likelihood ratio	0.005		0.003	

Adjusted for age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. Abbreviations: *TAC* Total antioxidant capacity; *PhenoAgeAccel* Phenotypic age acceleration; *PIR* Poverty income ratio; *BMI* Body mass index; *OR* Odds ratio; *CI* Confidence interval

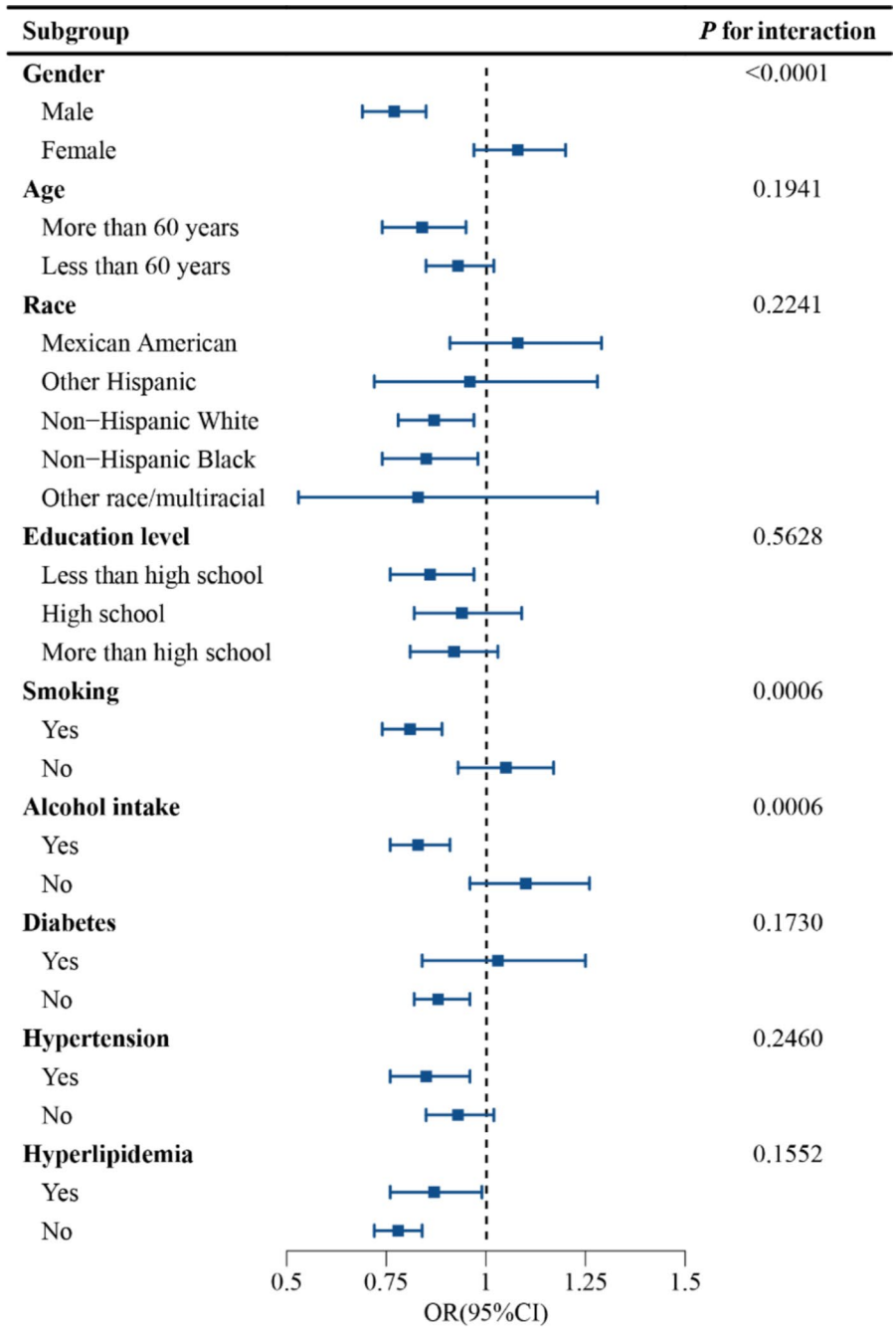

Fig. 3 Subgroup analysis of TAC(Log-transformed) and PhenoAgeAccel

Adjusted for age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia. Abbreviations: *TAC* Total antioxidant capacity; *PhenoAgeAccel* Phenotypic age acceleration; *PIR* Poverty income ratio; *BMI* Body mass index; *OR* Odds ratio; *CI* Confidence interval.

Discussion

This study reveals a significant inverse association between TAC and PhenoAgeAccel, indicating that higher TAC may serve a protective role in delaying biological aging. Additionally, the intake of several antioxidant vitamins, such as α-carotene, β-carotene,

Table 5 Subgroup analysis of TAC(Log-transformed) and PhenoAgeAccel

Subgroup	Count	Percent(%)	OR (95%CI)	*P*-value	*P* for interaction
Gender					< 0.0001
Male	8056	49.14%	0.77(0.69, 0.85)	< 0.0001	
Female	8339	50.86%	1.08(0.97, 1.20)	0.1633	
Age					0.1941
More than 60 years	5556	33.89%	0.84(0.74, 0.95)	0.0061	
Less than 60 years	10,839	66.11%	0.93(0.85, 1.02)	0.1089	
Race					0.2241
Mexican American	3025	18.45%	1.08(0.91, 1.29)	0.3837	
Other Hispanic	1083	6.61%	0.96(0.72, 1.28)	0.8015	
Non-Hispanic White	8532	52.04%	0.87(0.78, 0.97)	0.0098	
Non-Hispanic Black	3099	18.90%	0.85(0.74, 0.98)	0.0215	
Other race/multiracial	656	4.00%	0.83(0.53, 1.28)	0.3876	
Education level					0.5628
Less than high school	4502	27.46%	0.86(0.76, 0.97)	0.0126	
High school	3931	23.98%	0.94(0.82, 1.09)	0.4288	
More than high school	7962	48.56%	0.92(0.81, 1.03)	0.1468	
Smoking					0.0006
Yes	7907	48.23%	0.81(0.74, 0.89)	< 0.0001	
No	8488	51.77%	1.05(0.93, 1.17)	0.43	
Alcohol intake					0.0006
Yes	11,643	71.02%	0.83(0.76, 0.91)	< 0.0001	
No	4752	28.98%	1.10(0.96, 1.26)	0.1709	
Diabetes					0.173
Yes	1787	10.90%	1.03(0.84, 1.25)	0.8014	
No	14,608	89.10%	0.88(0.82, 0.96)	0.002	
Hypertension					0.246
Yes	5658	34.51%	0.85(0.76, 0.96)	0.0085	
No	10,737	65.49%	0.93(0.85, 1.02)	0.1351	
Hyperlipidemia					0.1552
Yes	3750	77.13%	0.87(0.76, 0.99)	0.0366	
No	12,645	22.87%	0.78(0.72, 0.84)	< 0.0001	

Adjusted for age, gender, race, education level, PIR, BMI, marital status, smoking, alcohol intake, diabetes, hypertension, and hyperlipidemia.
Abbreviations: TAC, total antioxidant capacity; PhenoAgeAccel, phenotypic age acceleration; PIR, poverty income ratio; BMI, body mass index; OR, odds ratio; CI, confidence interval

lutein-zeaxanthin, vitamin A, vitamin C, and vitamin E, was linked to a reduced risk of PhenoAgeAccel, further substantiating the potential protective effects of antioxidants in aging. Moreover, smoothed curve fitting analysis demonstrated a nonlinear relationship between TAC and PhenoAgeAccel, with a significant protective effect observed within a specific range of TAC. Stratified analyses further revealed that this association was consistent across most subgroups. These findings collectively support the hypothesis that higher dietary antioxidant intake, as reflected by increased TAC, may contribute to slowing biological aging, particularly in individuals with lower antioxidant levels.

Dietary habits play a crucial role in the aging process. Research has demonstrated that diet significantly influences the rate of aging and the development of age-related diseases. High-quality carbohydrates contribute to reducing cardiovascular risk, weight, and the risk of diabetes, thereby lowering overall mortality; however, excessive intake may have detrimental effects (He K., et al. 2024b). Diets rich in animal protein, particularly red meat, have been associated with an increased risk of age-related diseases (Kitada 2019). In contrast, plant-based diets rich in antioxidants and plant proteins, such as those found in nuts and soy, have been shown to slow telomere shortening and

extend lifespan (Aubert and Lansdorp 2008;Freitas-Simoes 2016;Rafie 2017;Tucker 2021;Wang S. 2023). Replacing animal protein with plant protein has been shown to reduce the risk of mortality from various causes, including cardiovascular disease (Zheng 2022). High-fat diets, particularly those rich in saturated fats, have been shown to impair cellular stress recovery and accelerate aging (Balasubramanian 2024).

The relationship between dietary inflammatory potential and aging has garnered increasing attention in recent years. A study conducted in the United States found that pro-inflammatory diets, characterized by a higher dietary inflammatory index (DII), were associated with higher PhenoAgeAccel, with this association being particularly pronounced in the elderly population (Sun 2023). These findings further underscore the significant role of dietary inflammation in aging, suggesting that mitigating dietary inflammation may help delay the aging process. In recent years, antioxidant supplements have been widely used to mitigate the risks of aging and disease associated with OS. However, several studies have shown that antioxidant supplements are not as effective as expected. For instance, a systematic review by Simsek et al. (Simsek 2021) analyzed 87 studies and found that vitamin supplements had limited protective effects on the cardiovascular system. In addition, Atayik et al. (Atayik and Cakatay 2023) also noted that although multivitamin supplements are widely used for anti-aging, they may not be effective and may even exacerbate OS in some cases. While the effectiveness of antioxidant supplements is controversial, TAC is different from simple antioxidant supplements. TAC includes not only vitamin-based antioxidants, but also encompasses a wide range of phytochemicals and synergistic effects of other antioxidant components (Floegel, et al. 2010; Serafini and Del Rio 2004). This comprehensive assessment may more accurately reflect the overall effect of antioxidant components of the diet. In addition, the protective effects of TAC may rely more on the natural antioxidants in the diet than on a single supplement form. An increasing body of research has identified TAC as a key factor in reducing the risk of age-related diseases and promoting healthy aging. For instance, studies conducted in Singapore have shown that higher levels of dietary TAC are associated with a reduced risk of cognitive impairment in Chinese individuals, particularly among diabetic patients, and that TAC may exert a protective effect by mitigating oxidative damage (Sheng 2022). Fateh, Han, et al. (Fateh 2022;Han D. 2022) have also found that TAC is associated with a reduced risk of diseases such as hypertension and cancer, suggesting that it plays a broader role in disease prevention. Peng et al. (Peng 2023) found that higher TAC levels were associated with a reduced risk of cognitive dysfunction, particularly in diabetic patients. Furthermore, the intake of an antioxidant-rich diet has been shown to significantly reduce cardiovascular mortality (Wang W. 2022). These findings are consistent with our results, which show that higher TAC levels are associated with a lower risk of PhenoAgeAccel, and that a higher intake of various antioxidant vitamins (e.g., α-carotene, β-carotene, lutein-zeaxanthin, vitamins A, C, and E) correlates with a reduced risk of PhenoAgeAccel. Collectively, these studies suggest that antioxidant-rich diets, as indicated by higher TAC levels, may have a significant protective effect against cognitive decline, depression, common age-related diseases such as hypertension and cancer, and delayed aging (He H. 2024a). A study conducted in 2022 explored the relationship between the Composite Dietary Antioxidant Index (CDAI) and biological aging. The results indicated that CDAI was significantly negatively correlated with PhenoAgeAccel, suggesting that higher CDAI levels are associated with delayed biological aging. Both TAC and CDAI assess the antioxidant capacity of the diet. TAC measures the combined effect of all antioxidants in the diet, whereas the CDAI reflects antioxidant potential by evaluating the intake of antioxidant-rich foods. Consistent with the CDAI study, our research found that dietary antioxidant intake was significantly negatively correlated with PhenoAgeAccel, suggesting that higher antioxidant levels, as reflected by higher TAC, contribute to delayed biological aging. Both studies utilized PhenoAgeAccel as a biological age marker, which enhances the comparability of the findings. However, our study also identified a nonlinear relationship between TAC and PhenoAgeAccel, suggesting that the protective effect of antioxidants may peak within a specific range, which was not addressed in the CDAI study. While CDAI emphasizes the synergistic effects between dietary components and antioxidant molecules, TAC offers a broad measure of dietary antioxidant potential. Thus, our findings

provide a more nuanced understanding of the dietary antioxidant-aging relationship, further validating the potential role of antioxidant-rich diets in delaying aging.

The relationship between TAC and the aging process may be regulated through various mechanisms. Firstly, OS is a critical biological process involved in aging, with the generation of ROS being a byproduct of metabolic activity. Elevated ROS levels can lead to oxidative damage and impair cellular functions, particularly mitochondrial function (Han F. 2019; Kulinsky 2007). As individuals age, the efficiency of the endogenous antioxidant system declines, resulting in increased OS, which is closely associated with accelerated aging (Guemouri 1991). TAC serves as an indicator of antioxidant capacity, offering enhanced protection against OS, which may, in turn, decelerate the aging process (Liu Z. 2018). Beyond their direct antioxidant properties, many compounds contributing to TAC may also function as hormetins, inducing mild OS that activates adaptive cellular responses. This phenomenon, known as hormesis, involves a biphasic dose–response relationship where low doses of a stressor (e.g., ROS) stimulate protective mechanisms, while high doses cause damage (Calabrese and Agathokleous 2022;Calabrese and Baldwin 2003;Calabrese 2015;Ng 2019;Radak and Rattan 2024). Halliwell et al. (Gruber 2007) discusses the concept of hormesis mimetic effects, where antioxidants like resveratrol exert life-span–extending effects not through direct antioxidant activity but by mimicking calorie restriction and inducing hormetic stress responses. In addition, Franceschi et al. (Franceschi 2000) demonstrated that a gradual increase in the pro-inflammatory state is a key feature of the aging process, a phenomenon known as "Inflammaging", which is induced by sustained antigenic load and stress. During inflammatory aging, the accumulation of pro-inflammatory factors leads to chronic low-grade inflammation, which in turn triggers OS, which is one of the key mechanisms of aging and several aging-related diseases (Franceschi and Campisi 2014;Li 2023). TAC, an indicator of antioxidant capacity, has the potential to mitigate the process of inflammatory senescence by suppressing OS, thereby delaying aging and reducing the risk of aging-related diseases. Moreover, TAC is associated with body composition, with studies indicating that higher TAC levels are significantly correlated with lower BMI and reduced fat content (Liao and Li 2024). Obesity and elevated BMI are well-known risk factors for accelerated aging, often accompanied by chronic inflammation and OS (Cao 2023;Chen C. 2019;Fohr 2024;Hayes 2017;Liu M. 2021). Therefore, increasing TAC levels may not only slow the aging process but also improve body composition and reduce fat accumulation, further mitigating aging and lowering age-related health risks. In summary, TAC may delay aging through multiple mechanisms, including reducing OS, inhibiting chronic inflammation, and enhancing body composition. These findings support the potential protective role of antioxidants in the aging process.

Subgroup analyses revealed that the protective effect of TAC against aging varied significantly across different populations. Specifically, males, smokers, and alcohol drinkers derived greater benefits from TAC intake, while females, non-smokers, and non-drinkers did not show a significant protective effect. Available evidence suggests that alcohol consumption may contribute to oxidative damage by elevating OS levels and reducing antioxidant enzyme activity (Saribal 2020). Smoking has been shown to exacerbate oxidative damage and impair the function of the antioxidant defense system (Ahmadkhaniha 2021). Therefore, a higher intake of antioxidants (e.g., TAC) may have a more pronounced effect in slowing the aging process. This finding is consistent with previous studies, such as those by Yang et al., who found that higher TAC levels significantly prevented stroke in smokers and alcohol drinkers (Yang 2022). Studies have indicated that men experience higher levels of OS (Brandes and Mugge 1997). Specifically, testosterone may enhance OS, whereas estrogen exerts an inhibitory effect on systemic OS (Coylewright 2008;Sullivan 2007;Xing 2009). Therefore, men may rely more on exogenous antioxidants (e.g., TAC) for protection against aging, which is consistent with our subgroup analysis results. Furthermore, the two-piecewise linear regression model identified an inflection point (K) of 3.73 for log-transformed TAC in the adjusted model. Below this threshold, TAC was inversely associated with PhenoAgeAccel, suggesting a protective effect. However, above this threshold, no further association was observed, suggesting threshold effects where TAC provides maximal protection against biological aging.

Overall, the findings suggest that higher TAC is associated with delayed biological aging. Beyond this key conclusion, our study addresses three critical knowledge gaps in modern biogerontology (Rattan 2024). Firstly, the association between higher TAC and slower biological aging suggests that elevated TAC represents a beneficial age-related change. Secondly, subgroup analyses revealed that the effect of TAC on PhenoAgeAccel varies across different subgroups, reflecting the complexity and individual variability of the aging process. This highlights the importance of accounting for the heterogeneity of aging phenotypes when developing targeted interventions. Finally, we observed a nonlinear relationship between TAC and PhenoAgeAccel, suggesting the existence of an optimal TAC range that provides the greatest protection against accelerated aging. This finding implies that biological systems may have a certain tolerance and adaptive capacity to OS, which could potentially be modulated through dietary antioxidants.

However, several limitations exist. Firstly, due to the cross-sectional design, causal relationships cannot be inferred. Longitudinal studies are required to examine temporal changes. Secondly, dichotomizing age-adjusted biological age may diminish statistical power and introduce residual confounding. Future studies should consider using continuous measures of biological age for more accurate analysis. Thirdly, the calculation of TAC was based on 64 food items and eight antioxidant vitamins using the USDA National Nutrient Database. While this method has been validated (Floegel, et al. 2010), it is important to note that the vitamin C content of foods may vary across regions and populations. For example, the vitamin C content of vegetables and fruits in China or other regions may differ from the USDA database values, potentially affecting the generalizability of our findings. Future studies should incorporate region-specific nutrient databases to improve the accuracy of TAC estimation. Fourthly, the intake of antioxidant vitamins might not always reflect plasma TAC levels due to factors such as age-related malabsorption, drug interactions, and individual metabolic differences. These factors could lead to discrepancies between dietary intake and actual antioxidant availability in the body, potentially influencing the observed associations between TAC and PhenoAgeAccel. Future research should include direct measurements of plasma antioxidant levels to complement dietary assessments. Moreover, one important limitation of our study is the potential drug-nutrient interactions that were not considered, particularly regarding the use of acetylsalicylic acid and warfarin, as well as the presence of comorbidities in the studied population. in the studied population. These medications are known to interact with various antioxidant vitamins, potentially affecting their absorption and bioavailability (Renaud 2024), which may influence the relationships between antioxidant intake and PhenoAgeAccel. Although we accounted for multiple confounders, residual confounding from unmeasured factors may persist. Finally, our study is closely related to aging; however, the relatively low proportion of participants aged over 60 years (33.89%) may limit the generalizability of the findings to older populations. Future research should aim to address these limitations to further elucidate the role of TAC in aging.

Conclusions

In summary, our study demonstrates that TAC, as an indicator of dietary total antioxidant capacity, is closely associated with PhenoAgeAccel. A nonlinear relationship was observed, with higher TAC exhibiting significant protective effects within a specific range, particularly among males, smokers, and alcohol consumer. These findings underscore the potential value of TAC in mitigating the aging process. To further strengthen the persuasiveness and credibility of our conclusions, future high-quality prospective studies are warranted to explore the role of TAC in aging interventions.

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Data availability The data that support the findings of this study are openly available at https://www.cdc.gov/nchs/nhanes/.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethical approval The NHANES study was reviewed and authorized by the NCHS Research Ethics Review Board, and informed consent was obtained in writing from all participants.

Consent for publication Not applicable.

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