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The Associations Between Triglyceride-Glucose Related Indices and Biological Ageing Acceleration in American Adults: Evidence from NHANES 1999-2018

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Abstract

Objective: Biological ageing represents a major public health concern. Triglyceride-glucose (TyG)-related indices, which integrate glucose and lipid metabolism and reflect insulin resistance, have been proposed as potential indicators of metabolic dysfunction. The present study investigated whether TyG-related indices were associated with biological ageing acceleration and explored the mediating roles of inflammation and oxidative stress.

Materials and Methods: Twelve thousand five hundred seventy participants whose age ≥18 years were obtained from the National Health and Nutrition Examination Survey cycles spanning 1999 to 2018. Biological age was calculated using the Klemera–Doubal method. Weighted logistic regression and mediation analyses were conducted to evaluate associations between TyG-related indices and inflammation, oxidative stress, and biological ageing acceleration.

Results: Increasing levels of all TyG-related indices were significantly associated with higher odds of biological ageing acceleration. Individuals in the highest quartile had elevated odds of accelerated biological ageing relative to those in the lowest quartile, with odds ratios (95% confidence intervals) of 2.68 (2.39-3.01) for TyG, 3.66 (3.25-4.12) for TyG-waist circumference, 3.69 (3.28-4.16) for TyG-waist-to-height, and 3.40 (3.03-3.81) for TyG-body mass index. Mediation analyses suggested that inflammatory and oxidative stress markers, including white blood cell count and GGT, accounted for approximately 9.4% and 16.2% of the association between TyG and biological ageing acceleration, respectively.

Conclusion: These findings demonstrate significant associations between TyG-related indices and biological ageing acceleration. Because of the cross-sectional design of National Health and Nutrition Examination Survey, causal inferences should be made cautiously, and further longitudinal studies are necessary to confirm these relationships. Nonetheless TyG and its related indices may serve as simple, practical markers for early metabolic risk classification and prevention of age-related health decline by identifying individuals with increased metabolic and inflammatory burden.

Keywords: Triglyceride-glucose index, TyG-related indices, obesity, biological ageing, NHANES

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Introduction

Ageing is a multifactorial biological process characterized by progressive declines in structural integrity and physiological function, ultimately increasing susceptibility to disease and mortality (1). At the molecular level, ageing involves cumulative alterations in genes, metabolism, and cellular homeostasis, resulting in impaired repair capacity and organ dysfunction (2-4). Recent evidence highlights that biological ageing acceleration—the difference between biological and actual age—serves as an important determinant of chronic disease risk, frailty, and premature mortality (1,5-7). Therefore, identifying metabolic and inflammatory pathways that contribute to accelerated biological ageing is a critical step toward developing effective prevention strategies.

As a simple and reliable alternative indicator, the triglyceride-glucose (TyG) index is increasingly used to evaluate insulin resistance and cardiometabolic health. This measure, determined based on levels of fasting triglycerides and glucose, indicates impaired insulin sensitivity and contributes to metabolic abnormalities such as hyperglycemia and dyslipidemia (8,9). Evidence in the literature links the TyG index to the development of type 2 diabetes and cardiovascular disease and to an increased risk of all-cause mortality (10-12). Several composite indices that integrate the TyG index with obesity indicators, including TyG-body mass index (BMI), TyG-waist circumference (WC), and TyG-waist-to-height ratio (WHtR), have emerged to improve predictive validity and exhibit enhanced performance in assessing metabolism-related risks (13,14).

Biological ageing is a multifactorial phenomenon characterized by the progressive loss of functional integrity, largely driven by chronic inflammation, oxidative stress, and metabolic dysregulation (15,16). Persistent low-grade inflammation, often associated with visceral adiposity and insulin resistance, accelerates molecular damage and functional decline (17). Excessive generation of reactive oxygen species and mitochondrial dysfunction contribute to cellular senescence and telomere shortening—one of the molecular hallmarks of ageing (18,19). Emerging evidence also suggests that metabolic stress influences epigenetic ageing, as reflected by DNA methylation clocks, reinforcing the interplay between metabolism, inflammation, and biological ageing (20). Research directly examining the correlation between metabolic indicators and biological ageing remains limited; however, metabolic dysfunction and obesity are closely associated with the ageing process (21-24). These processes suggest that metabolic, inflammatory, and oxidative stress–related pathways may jointly influence the pace of biological ageing. Therefore, TyG-related indices cannot only reflect metabolic disorders but also serve as accessible indicators of accelerated biological ageing.

However, evidence directly linking TyG-related indices to biological ageing remains limited. Despite these insights, few population-based studies have simultaneously explored the correlation between TyG-related indices and biological ageing acceleration and evaluated the underlying mediating roles of inflammation and oxidative stress. The novelty of this study is that it investigates these associations in a large, nationally representative U.S. sample using National Health and Nutrition Examination Survey (NHANES) data and quantifies the indirect pathways linking metabolic dysregulation to accelerated biological ageing. Given their simplicity and availability from routine laboratory tests, TyG-related indices may provide a clinically viable and cost-effective tool for identifying individuals at high risk of accelerated ageing, thereby guiding the development of prevention strategies in clinical and public health settings. We hypothesized that elevated TyG-related indices would be positively associated with accelerated biological ageing, and that this relationship would be partially mediated by inflammation and oxidative stress.

Materials and Methods

Population and Inclusion Criteria

We analyzed combined data from ten NHANES cycles spanning 1999 to 2018. A total of 101316 participants participated in the survey during the specified timeframe. Figure 1 shows that the final study population comprised 12,570 participants aged 18 years or older. Exclusion criteria were as follows: (1) age below 18 years or pregnancy; (2) missing data on TyG and obesity

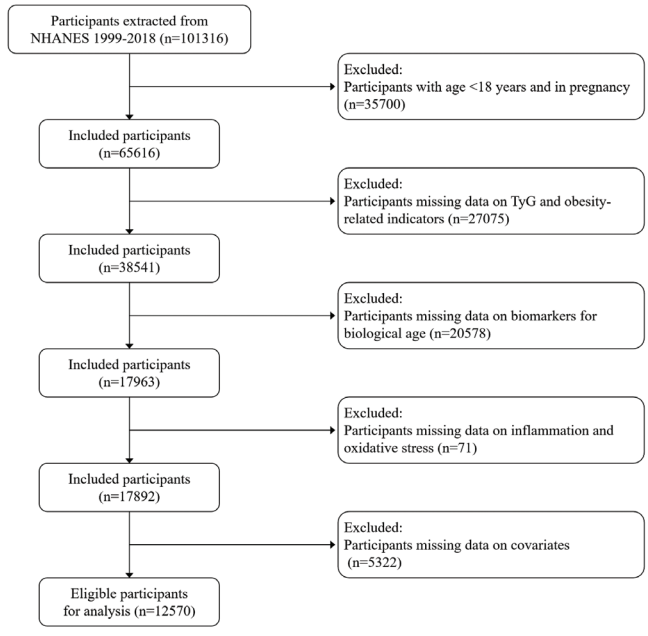

Figure 1. Diagram depicting the participant recruitment process.

TyG: Triglyceride-glucose.

markers; (3) missing data on biomarkers of biological age; (4) missing data on inflammation and oxidative stress; (5) missing covariate data. Of the 101,316 individuals initially enrolled in NHANES 1999–2018, 35,700 were excluded for being under 18 or pregnant; 27,075 were excluded for missing TyG or obesity-related indicators; 20,578 were excluded for missing biological ageing biomarkers; 71 were excluded for missing inflammation or oxidative stress markers; and 5,322 were excluded for missing covariates, leaving a final sample of 12,570 participants.

Assessment of TyG-Related Indices

The TyG index integrates triglyceride and fasting glucose levels measured in participants' blood samples. During physical assessments at the mobile health screening center, participants' waist circumference, height, and body weight were measured. Assessment of indicators of inflammation and oxidative stress is presented in Supplementary Method S1. The formulas for calculating TyG and its combined obesity indices are presented in Supplementary Method S2.

Assessment of Biological Age and Ageing Acceleration

Biological age was expressed as Klemera-Doubal Method Biological Age (KDM-BA), following the method proposed by Klemera and Doubal (25), and was determined using systolic blood pressure in conjunction with seven blood-based biochemical indicators illustrated in Table 1. The R package "BioAge" was employed to assess participants' biological age. Within this package, the reference dataset is derived from non-pregnant individuals aged 30–75 years in NHANES III. The algorithm's settings are tailored for male and female participants to ensure accuracy. The KDM-BA of participants aligns with the age at which their physiology is approximately typical. The KDM-BA is the result of multiple regression analyses of each biomarker on actual age in the reference population. The equation used for the calculation is illustrated in Supplementary Method S3. As the KDM-BA algorithm relies on regression parameters derived from non-pregnant adults aged 30–75 years in NHANES III, potential cultural and ethnic biases may exist when extrapolating these parameters to broader populations.

Biological ageing acceleration was defined as the excess of biological age over chronological age. It was quantified as the residual obtained from a linear regression of chronological age on biological age, with positive residuals indicating accelerated ageing.

Ethical approval was obtained from the NCHS Ethics Review Board (ERB) (protocols number: #98-12, #2005-06, #2011-17, and #2018-01, date: 18.12.2024). All individuals volunteered to participate in the study and provided written informed consent for participation and follow-up.

Table 1. Participants' characteristics (n = 12,570).

Characteristic	Median (IQR) or n (%)
Age, years	50.00 (36.00, 65.00)
<45	4948 (39.4)
45-59	3124 (24.9)
60-74	3131 (24.9)
≥75	1367 (10.9)
Gender, n (%)	
Male	6297 (50.1)
Female	6273 (49.9)
Race and ethnicity, n (%)	
Hispanic	3192 (25.4)
Non-hispanic	8617 (68.6)
Other	761 (6.1)
Educational level, n (%)	
<9 years	1398 (11.1)
9-11 years	1810 (14.4)
12 years	2987 (23.8)
>12 years	6375 (50.7)
Marital status, n (%)	
Married or living with partner	7896 (62.8)
Widowed, divorced or separated	2750 (21.9)
Never married	1924 (15.3)
Family PIR	2.35 (1.24, 4.29)
<1.3	3375 (26.8)
1.3-3.5	5027 (40.0)
>3.5	4168 (33.2)
Energy intake (kcal)	1924.00 (1466.00, 2506.00)
Smoking, n (%)	6012 (47.8)
Drinking, n (%)	9242 (73.5)
BMI (kg/m^2)	27.92 (24.40, 32.20)
Waist circumference (cm)	97.80 (88.00, 108.40)
Height (cm)	167.60 (160.40, 175.30)
Weight (kg)	78.90 (67.30, 92.80)
Triglyceride (mg/dL)	110.00 (76.00, 161.00)
Plasma glucose (mg/dL)	100.00 (92.80, 110.00)
TyG	8.60 (8.20, 9.10)
TyG-WC	852.95 (738.10, 972.00)
TyG-WHtR	5.10 (4.40, 5.80)
TyG-BMI	243.60 (206.10, 287.50)
Biological ages	
KDM-BA	43.18 (30.74, 57.70)
KDM-BA acceleration	-1.82 (-9.41, 6.54)

Table 1. Continued.	
Characteristic	**Median (IQR) or n (%)**
Components of biological ages	
SBP (mmHg)	122.00 (111.00, 135.00)
Albumin (g/dL)	4.20 (4.00, 4.40)
Alkaline phosphatase (U/L)	69.00 (56.00, 84.00)
Blood urea nitrogen (mg/dL)	13.00 (10.00, 16.00)
Total cholesterol (mg/dL)	193.00 (167.00, 221.00)
Creatinine (mg/dL)	0.84 (0.70, 1.00)
C-reactive protein (mg/dL)	0.21 (0.08, 0.47)
Glycated hemoglobin (%)	5.50 (5.20, 5.80)
Indicators of inflammation and oxidative stress	
White blood cell count (1000/μL)	6.50 (5.40, 7.80)
SII	476.80 (340.33, 672.18)
GGT (IU/L)	21.00 (15.00, 32.00)
Total bilirubin (mg/dL)	0.70 (0.50, 0.80)
Uric acid (mg/dL)	5.40 (4.50, 6.40)
Major diseases	
Hypertension, n (%)	4488 (35.7)
Diabetes, n (%)	1486 (11.8)
Stroke, n (%)	466 (3.7)
CVD history, n (%)	1099 (8.7)
Liver condition, n (%)	478 (3.8)
Cancer or malignancy, n (%)	1208 (9.6)

Continuous variables are presented as medians and interquartile ranges, while categorical variables are described using raw frequencies and percentages.
IQR: Interquartile range, BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio, KDM-BA: Klemera-Doubal method for biological age, PIR: Poverty income ratio.

Statistics

We selected the two-day dietary sample weights and followed NHANES' prescribed approach to generate individual sample weights that appropriately reflect the U.S. population. To examine the differences between participants with and without biological ageing acceleration, categorical and continuous variables were examined using the chi-square and rank-sum tests, respectively. Binary logistic regression was used to estimate odds ratios (ORs) for the association between TyG-related indices and biological ageing acceleration. For each TyG-related index, subjects were grouped into four quartiles with approximately equal sample sizes; the lowest quartile (Q1) served as the reference group. Trend tests were conducted by assigning to each quartile the median of the corresponding index and entering these medians as continuous variables into logistic regression models. Dose-response curves (linear or non-linear) for associations with biological ageing acceleration were assessed using restricted cubic spline (RCS) regression after adjusting for all potential confounders. Detailed definitions and measurements of all covariates are described in Supplementary Method S4.

We hypothesized that there were both direct (average direct effect) and indirect (average causal mediation effect) effects between TyG-related indices of obesity and biological ageing acceleration. The indicators of oxidative stress and inflammation served as mediators in mediation models. The proportion mediated (PM) was computed using the formula: PM = indirect effect/total effect. We sampled each mediation model 5000 times to minimize bias due to sampling error. Interpretation of mediation effects assumes temporal precedence of exposure, mediator, and outcome, and no unmeasured confounding among them. As the present analysis is based on cross-sectional data, these results should be interpreted cautiously.

To ensure robustness, we performed stratified analyses comparing the highest (Q4) and lowest (Q1) quartiles of TyG and its combined obesity indices, and examined the interaction between stratification variables and exposure factors using likelihood ratio tests. Furthermore, to test the robustness of the findings, a series of sensitivity analyses were conducted. First, we repeated the analyses among participants with available data on frailty, sarcopenia, and physical activity, respectively, additionally adjusting for these variables alongside the covariates included in the main models. Secondly, because information on tumor malignancy was not available, we repeated the primary analyses after excluding participants with a self-reported tumor history. All sensitivity analyses were conducted using the same modeling approach as in the primary analyses. All analyses were based on complete cases. Data analyses were carried out in R (version 4.4.1). Statistical significance was defined as two-sided $p < 0.05$.

Results

Participants' Baseline Characteristics and Biological Ages

Table 1 summarizes participants' baseline characteristics. Overall, the median age was 50.0 years (interquartile range, 36.0–65.0 years); 68.6% were non-hispanic, and 50.1% were male. 50.7% had received education beyond 12 years. As indicated in Supplementary Table S1, 43.6% of individuals exhibited KDM-BA acceleration. Significant group differences were observed for age, gender, marital status, education, family poverty income ratio, dietary energy intake, alcohol use, smoking, and chronic diseases ($p < 0.05$), whereas no significant difference was observed for race/ethnicity ($p > 0.05$). Furthermore, Supplementary Tables S2 and S3 show substantial differences in TyG-related indices and indicators of inflammation and oxidative stress between groups ($p < 0.05$). For details on biological ages and KDM-BA acceleration by quartiles of TyG-related indices at baseline, see Supplementary Table S4.

Table 2. Binary logistic regression analysis of TyG-related indices in relation to biological ageing acceleration.

	Crude model		Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
TyG								
Q1	1.00		1.00		1.00		1.00	
Q2	1.26 (1.14–1.39)	<0.001	1.38 (1.25–1.54)	<0.001	1.41 (1.27–1.56)	<0.001	1.37 (1.23–1.52)	<0.001
Q3	1.55 (1.41–1.72)	<0.001	1.81 (1.63–2.01)	<0.001	1.84 (1.66–2.04)	<0.001	1.71 (1.54–1.90)	<0.001
Q4	2.66 (2.40–2.95)	<0.001	3.19 (2.85–3.57)	<0.001	3.27 (2.92–3.66)	<0.001	2.68 (2.39–3.01)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-WC								
Q1	1.00		1.00		1.00		1.00	
Q2	1.40 (1.26–1.56)	<0.001	1.67 (1.49–1.86)	<0.001	1.67 (1.49–1.86)	<0.001	1.58 (1.42–1.77)	<0.001
Q3	1.95 (1.76–2.16)	<0.001	2.45 (2.20–2.74)	<0.001	2.45 (2.20–2.74)	<0.001	2.18 (1.95–2.44)	<0.001
Q4	3.61 (3.26–4.01)	<0.001	4.67 (4.17–5.23)	<0.001	4.71 (4.21–5.29)	<0.001	3.66 (3.25–4.12)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-WHtR								
Q1	1.00		1.00		1.00		1.00	
Q2	1.43 (1.29–1.59)	<0.001	1.71 (1.53–1.90)	<0.001	1.70 (1.52–1.89)	<0.001	1.62 (1.45–1.81)	<0.001
Q3	2.11 (1.91–2.34)	<0.001	2.61 (2.34–2.92)	<0.001	2.60 (2.33–2.91)	<0.001	2.32 (2.07–2.59)	<0.001
Q4	3.85 (3.46–4.28)	<0.001	4.78 (4.26–5.36)	<0.001	4.78 (4.26–5.36)	<0.001	3.69 (3.28–4.16)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001
TyG-BMI								
Q1	1.00		1.00		1.00		1.00	
Q2	1.40 (1.26–1.55)	<0.001	1.55 (1.39–1.72)	<0.001	1.54 (1.38–1.71)	<0.001	1.46 (1.30–1.62)	<0.001
Q3	1.97 (1.77–2.18)	<0.001	2.21 (1.99–2.47)	<0.001	2.20 (1.97–2.45)	<0.001	1.94 (1.74–2.16)	<0.001
Q4	3.89 (3.50–4.32)	<0.001	4.32 (3.87–4.82)	<0.001	4.32 (3.87–4.82)	<0.001	3.40 (3.03–3.81)	<0.001
p for trend	/	<0.001	/	<0.001	/	<0.001	/	<0.001

Crude model: unadjusted. Model 1 controlled for demographic and socioeconomic factors. Model 2: additionally adjusted for dietary energy intake, alcohol consumption and smoking. Model 3: further adjusted for major chronic conditions (hypertension, diabetes, stroke, cardiovascular disease, liver disease, and cancer/malignancy).
IQR: Interquartile range, BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio, KDM-BA: Klemera-Doubal method for biological age, PIR: Poverty income ratio.

Relationships Among TyG-Related Indices and Biological Ageing Acceleration

Table 2 shows the relationships between TyG-related indices and biological ageing acceleration. Significant positive correlations were observed between all TyG-related indices and biological ageing acceleration after adjustment for covariates. In the fully adjusted model (Model 3), comparison of the highest (Q4) with the lowest (Q1) quartile of TyG-related indices showed a significant increase in odds: ORs [95% confidence intervals (CIs)] were 2.68 (2.39–3.01) for TyG, 3.66 (3.25–4.12) for TyG-WC, 3.69 (3.28–4.16) for TyG-WHtR, and 3.40 (3.03–3.81) for TyG-BMI.

Curvilinear Relation Analysis

As shown in Figure 2, RCS models were employed to flexibly model the dose–response relationships between TyG-related indices and biological ageing acceleration. Three obesity-related TyG indices, including TyG-WC, TyG-WHtR, and TyG-BMI, exhibited roughly linear associations with accelerated ageing after adjustment for multiple variables (p for non-linearity >0.05), whereas the TyG index exhibited a pronounced non-linear association (p for non-linearity = 0.002). Specifically, the risk of accelerated biological ageing increased gradually with higher TyG values and rose steeply beyond the upper range of TyG values, indicating a potential threshold effect.

Relationships Among TyG-Related Indices and Inflammation and Oxidative Stress

We observed that all TyG-related indices exhibited positive associations with white blood cell levels, systemic immune-

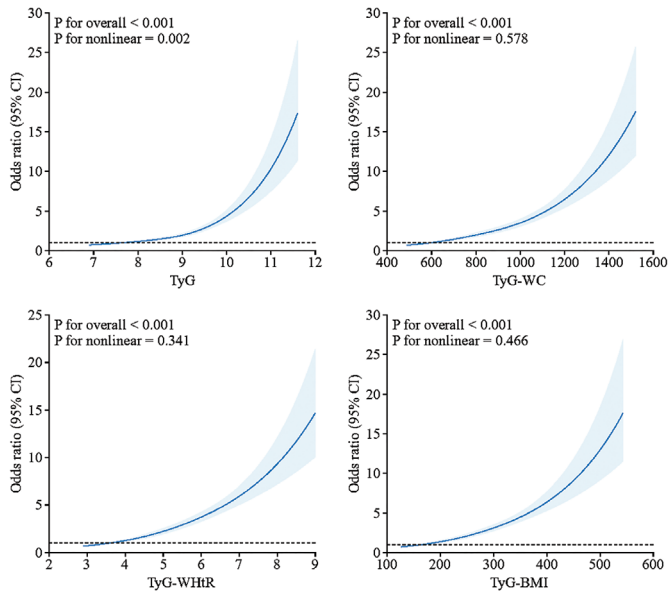

Figure 2. After adjustment for all covariates, restricted cubic spline analysis was used to visualize associations; the central estimate and the 95% confidence interval are shown as a solid blue line and a shaded area, respectively.

BMI: Body mass index, TyG: Triglyceride-glucose, WC: Waist circumference, WHtR: Waist-to-height ratio.

inflammation index (SII), gamma-glutamyl transferase (GGT), and uric acid in ordinal multivariable logistic regression analyses (Supplementary Table S5). For example, participants with TyG in Q4 exhibited significantly elevated white blood cell counts, SII, GGT, and uric acid compared with those in Q1, and the ORs (95% CI) were 2.94 (2.75–3.13), 1.45 (1.36–1.55), 4.38 (4.10–4.68) and 3.35 (3.13–3.58), respectively. Similar relationships were also observed in TyG-WC, TyG-WHtR, and TyG-BMI. Conversely, all TyG-related indices were inversely related to total bilirubin levels.

Relationships Between Inflammation and Oxidative Stress and Biological Ageing Acceleration

As illustrated in Supplementary Table S6, white blood cell count, SII, GGT, and uric acid were significantly and positively associated with biological ageing acceleration ($p < 0.05$). Compared with the reference (Q1), the ORs (95% CI) in Q4 were 1.82 (1.63–2.03), 1.33 (1.20–1.47), 2.22 (1.99–2.48) and 2.65 (2.35–2.98), respectively. In contrast, total bilirubin (Q4: OR: 0.53, 95% CI: 0.48–0.59) was inversely associated with biological ageing acceleration ($p < 0.05$).

Mediation Analyses

Figure 3 illustrates the mediating effects of inflammation and oxidative stress on the associations between TyG-related indices and biological ageing acceleration. Specifically, white blood cell count significantly mediated the relationships with TyG (PM = 9.4%), TyG-WC (PM = 6.5%), TyG-WHtR (PM = 6.4%), and TyG-BMI (PM = 6.1%) ($p < 0.05$). Additionally, GGT and uric acid exhibited strong mediating effects on the relationships between TyG-related indices and biological ageing acceleration ($p < 0.05$). In contrast, the SII and total bilirubin exhibited relatively weak mediation effects, as shown in Supplementary Figure S1.

Stratified Analyses and Interaction Analyses

The correlations of TyG-related indices with biological ageing acceleration across different subgroups are illustrated in Supplementary Figure S2. Upon stratification of participants, the positive association between TyG-related indices and biological ageing acceleration remained consistent across all subgroups. In addition, interaction analyses demonstrated significant effect modification of TyG-related indices by age, hypertension, history of CVD, and diabetes. Notably, the strength of the correlations between TyG-related indices and biological age acceleration gradually decreased with increasing participant age. In particular, participants without hypertension had higher odds of accelerated biological ageing. Similar associations were observed in participants with and without a history of CVD or diabetes.

Sensitivity Analysis

In Supplementary Table S7, the results remained robust after additionally adjusting for frailty and sarcopenia. Taking the extreme quartiles of the TyG index as an example, the adjusted ORs were 2.14 (1.80–2.54) and 3.41 (2.38–4.92), corresponding to Model 1 (with frailty adjustment) and Model 2 (with additional sarcopenia adjustment), respectively (both $p < 0.001$). After excluding the individuals with tumors, the associations between the TyG-related indices and biological ageing acceleration remained robust (Supplementary Table S8). Similarly, the other three indices revealed progressively elevated ORs across quartiles in all models (all $p < 0.05$). In addition, the results remained robust after further adjustment for physical activity (Supplementary Table S9).

Discussion

This large-scale cross-sectional analysis provides new evidence of a correlation between TyG-related indices and accelerated biological ageing. To our knowledge, this is one of the first studies to systematically evaluate TyG and its obesity-related indices in relation to biological ageing acceleration and to explore the mediating effect of oxidative stress and inflammation.

Although previous studies have extensively investigated associations of TyG and its related indices with metabolic diseases, cardiovascular outcomes, and mortality (11,26,27), evidence regarding their relationship with biological ageing remains limited. Our findings extend prior research by demonstrating that TyG-related indices—simple, routinely

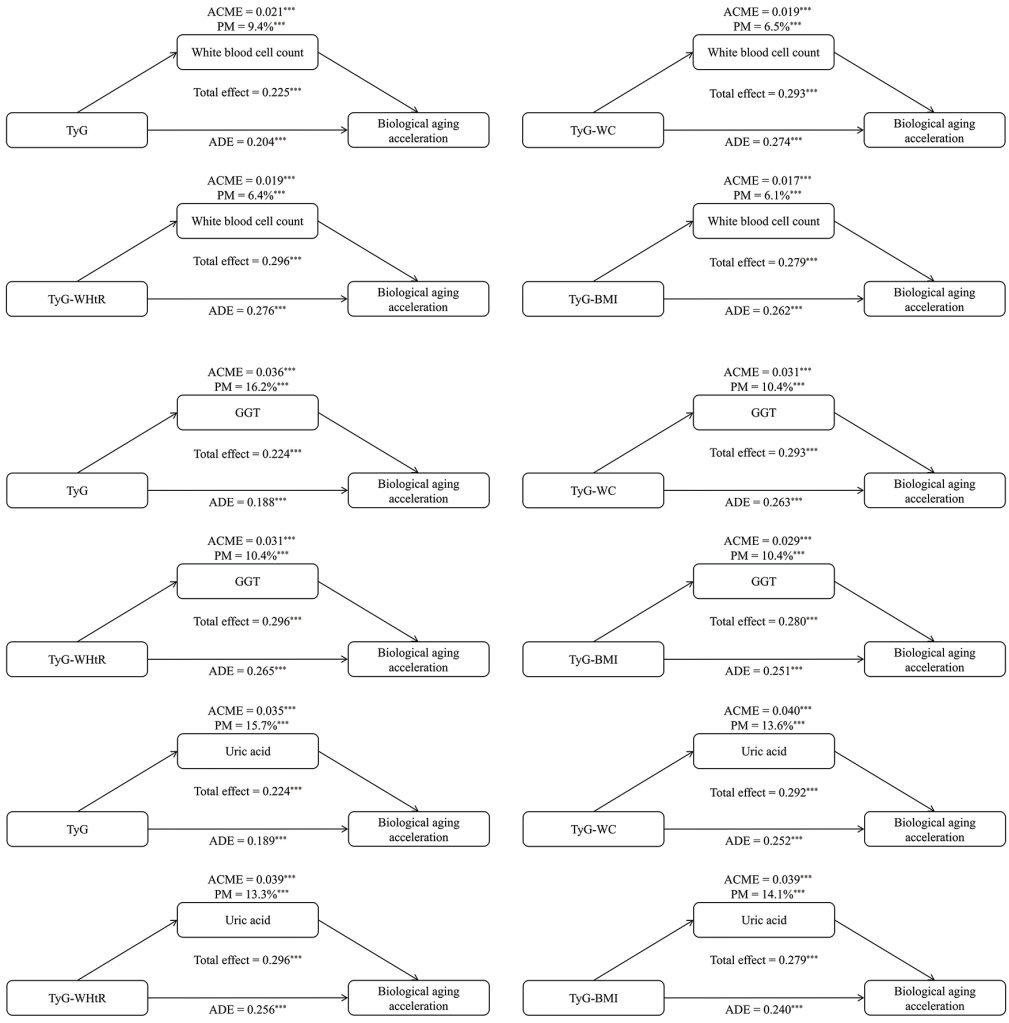

Figure 3. Proportions of mediation by inflammation and oxidative stress markers in the relationships between TyG-related indices and biological ageing acceleration adjusting for all covariables.

ACME: Average causal mediation effect, ADE: Average direct effect, BMI: Body mass index, GGT: Gamma-glutamyl transferase, PM: Proportion mediated, TyG: Triglyceride-glucose index, WC: Waist circumference, WHtR: Waist-to-height ratio.

obtainable indicators of insulin resistance (28)—are also strongly correlated with accelerated biological ageing. This result is consistent with growing evidence that metabolic impairment plays a central role in the ageing process. For instance, insulin resistance and visceral adiposity are known to induce oxidative stress and chronic low-grade inflammation, which accelerate cellular senescence and epigenetic ageing through increased production of reactive oxygen species and mitochondrial dysfunction (29,30). Furthermore, metabolic stress may disrupt DNA methylation homeostasis, thereby promoting epigenetic drift and advancement of biological age (20,31). One study reported that higher TyG index levels were linked to α-Klotho (32), which is known to function as an anti-ageing protein. α-Klotho has been demonstrated to slow the ageing process through multiple mechanisms, including inhibition of insulin and IGF-1 signaling and mitigation of oxidative stress and inflammation (33,34), which supports the biological plausibility of our results. We also found consistent positive associations between obesity-related TyG indices and acceleration of biological ageing, aligning with previous studies showing that central obesity and metabolic dysfunction are associated with epigenetic ageing and telomere shortening (35,36). Our results corroborate these mechanistic insights, suggesting that TyG-related indices may capture broader aspects of metabolic and inflammatory burden relevant to biological ageing.

To further explore the biological mechanisms that likely involve the interplay among insulin resistance, inflammation, and oxidative stress, we conducted mediation analyses and found that inflammation and oxidative stress partially mediated the relationships between TyG-related indices and biological ageing acceleration. These findings align with well-established biological mechanisms whereby insulin resistance and

adiposity promote oxidative stress and inflammation, which in turn accelerate molecular ageing processes. Previous studies have demonstrated positive correlations between TyG and inflammatory biomarkers such as C-reactive protein and SII (37-39), supporting our mediation results. The observed associations may reflect chronic low-grade inflammation induced by TyG-related metabolic dysregulation and adiposity (40). Similarly, oxidative stress markers significantly mediated the relationships between TyG-related indices and biological ageing acceleration. Elevated oxidative stress damages DNA and cellular structures, leading to telomere attrition and increased vulnerability to age-related disorders (41,42). Obesity-related excess reactive oxygen species and inflammatory adipokine release further amplify these effects (43).

In addition, we identified significant effect modification of TyG-related indices by age, hypertension, a history of CVD, and diabetes. Compared with older adults, younger individuals with elevated TyG-related indices had a higher risk of accelerated biological ageing. This may be because most older adults suffer from various chronic diseases related to biological ageing and are already in an adverse metabolic state characterized by high TyG-related indices, which may accelerate biological ageing. In stratified analyses, the positive association between TyG and biological age acceleration was more evident among participants without hypertension or a history of CVD. Several mechanisms may explain this pattern. Individuals with these conditions often receive treatments such as angiotensin-converting enzyme inhibitors, ARBs, β-blockers, or statins, which have metabolic and anti-inflammatory benefits (44,45), and may mitigate the detrimental effects of TyG. In addition, pre-existing vascular and metabolic damage in diseased individuals may lead to a “ceiling effect” whereby further metabolic disturbances exert limited additional influence on aging biomarkers. In contrast, among those without hypertension or CVD history, elevated TyG levels more directly reflect early-stage insulin resistance, lipid toxicity, and mitochondrial dysfunction, promoting oxidative stress and inflammation that accelerate biological ageing. Similarly, the positive association between TyG-WC and acceleration of biological ageing was more evident in participants without diabetes. This may reflect differences in medical management and disease stage. Individuals with diabetes often receive glucose- and lipid-lowering therapies and adopt healthier lifestyles, thereby mitigating insulin resistance and inflammation (46).

These results underscore the potential clinical and public health value of TyG-related indices as accessible, low-cost markers for the early recognition of populations at risk of accelerated biological ageing. Given their availability in routine health examinations, adding TyG-related indices to metabolic health assessment frameworks could facilitate early risk stratification and preventive interventions. Nevertheless, certain limitations of this work must be acknowledged. Despite extensive covariate adjustments, causal inference remains constrained by cross-sectional designs and cannot fully rule out residual confounding. Secondly, KDM-BA, while widely used as a biomarker of biological ageing, represents only one of several available ageing metrics and may not fully capture the multidimensional nature of the ageing process. Thirdly, because the data were derived from an American population, generalizability to other ethnic or regional groups may be limited. In addition, certain covariates were self-reported, which might introduce measurement bias. The associations observed merit further investigation through prospective and interventional research to elucidate causality, mechanisms, and the cross-population applicability of TyG-related indices serving as aging biomarkers.

Conclusion

Significant associations were found between TyG-related indices and accelerated biological ageing in this cross-sectional study. Increasing levels of TyG-related indices were positively correlated with acceleration of biological ageing, and these correlations were partly mediated by inflammation and oxidative stress. Based on these findings, TyG-related indices could be considered early markers for identifying individuals susceptible to accelerated biological ageing. This large-scale study is one of the earliest studies to examine the relationships between TyG-related indices and biological age acceleration in a nationally representative U.S. population and also to incorporate inflammation and oxidative stress as potential mediating pathways. Prospective and interventional studies are necessary to verify these observations and to elucidate the causal pathways connecting metabolic dysfunction, inflammation, oxidative stress, and biological ageing.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the NCHS Ethics Review Board (ERB) (protocols number: #98-12, #2005-06, #2011-17, and #2018-01, date: 18.12.2024).

Informed Consent: All individuals volunteered to participate in the study and provided written informed consent for participation and follow-up.

Footnotes

Authorship Contributions

Concept: H.Z., F.J., Y.G., Z.X., Design: H.Z., F.J., L.L., T.G., Data Collection or Processing: X.X., Analysis or Interpretation: H.Z., X.X., Literature Search: Y.G., L.L., T.G., Writing: H.Z., Z.X.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Methods: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/d5a2a03d-3f81-4245-8d1b-bda74bb1b7de.pdf

Supplementary Figures: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/b57eecc9-a7e7-40f7-a61b-05c6a55b4a64.pdf

Supplementary Tables: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/a57fd6e6-9d78-4428-92f5-058f9f036e08.pdf

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