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Dose-response relationship between leisure-time physical activity patterns and phenotypic age acceleration in American adults: A cross-sectional analysis

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ABSTRACT

Background/Objectives: With the accelerating global population aging, delaying aging and promoting healthy aging have become focal points in public health and clinical medicine. Phenotypic age acceleration (PhenoAgeAccel) is an important indicator of biological aging speed. This study aims to explore the relationship between different leisure-time physical activity (LTPA) patterns and PhenoAgeAccel, analyzing the association and dose-response relationship.

Methods: This study utilized data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018, including 14,868 adults. Multivariable linear regression models and restricted cubic spline methods were used to assess the relationship between LTPA and PhenoAgeAccel, with segmented likelihood ratio tests to detect non-linear thresholds. Stratified regression and interaction tests explored potential modifications by sex, age, race, and socioeconomic status.

Results: Compared to individuals with no LTPA, those with inactive and regular LTPA patterns had significantly lower PhenoAgeAccel scores ($P < 0.05$), while the weekend warrior pattern showed no significant effect ($P > 0.05$). A non-linear threshold effect was found; below 560 min of weekly LTPA, a significant negative correlation existed ($\beta = -0.001$, 95 % CI: 0.001 to −0.0003, $P < 0.001$). Above this threshold, LTPA was positively correlated with PhenoAgeAccel, indicating a risk for accelerated aging ($\beta = 0.0003$, 95 % CI: 0.00002 to 0.001, $P = 0.03$). Similar non-linear threshold effects were found for both males and females.

Conclusion: Regular LTPA significantly reduces phenotypic age acceleration, with a non-linear threshold effect indicating moderate physical activity is most beneficial. The weekend warrior pattern was less effective. These findings highlight the necessity of personalized physical activity recommendations and provide evidence for public health strategies to promote healthy aging.

1. Introduction

With the accelerating global population aging, delaying aging and promoting healthy aging have become focal issues in public health and clinical medicine. Aging not only severely impacts individual health and quality of life but also poses significant challenges to socio-economic development. The scientific community has gradually realized that merely extending lifespan cannot address the problems brought about by aging; improving the health expectancy of the elderly population is crucial.[1]

Leisure-Time Physical Activity (LTPA) has been widely recognized for its crucial role in promoting health and preventing disease. Numerous studies have demonstrated a significant dose-response relationship between LTPA and both all-cause mortality and chronic

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diseases. For instance, Martinez-Gomez et al.[2] found a non-linear inverse association between long-term LTPA and both all-cause and cardiovascular disease mortality in a large cohort study, highlighting that increasing LTPA is associated with a substantial reduction in mortality risk, even at levels below the recommended LTPA guidelines. This finding is consistent with that of Samitz et al.,[3] which confirmed that higher levels of physical activity are associated with a 26 % risk reduction in all-cause mortality. Similarly, Arem et al.[4] demonstrated that achieving the minimum recommended level of moderate to vigorous physical activity was associated with nearly maximum longevity benefits, with a benefit threshold of around 3–5 times the recommended minimum for LTPA, and no excess harm observed at levels 10 times the minimum. Zhao et al.[5] further validated these conclusions, showing that even very low levels of LTPA significantly lowered all-cause mortality risk, with additional benefits observed at higher intensities of LTPA. Additionally, Ekelund et al.[6,7] confirmed a clear non-linear dose-response relationship between physical activity intensity and mortality risk using accelerometer data. Although existing research has clarified the dose-response relationship between LTPA and both all-cause mortality and health outcomes, the dose-response relationship between LTPA and biological aging remains unclear.

In recent years, the "weekend warrior" model—characterized by high-intensity physical activity performed less frequently—has emerged as a popular form of LTPA. Research indicates that this pattern is associated with similar reductions in all-cause mortality and specific disease risks (such as cardiovascular disease and cancer) compared to regular LTPA.[8–10] However, despite the significant health benefits associated with the weekend warrior model, its specific impact on biological aging remains unclear.

Phenotypic Age Acceleration (PhenoAgeAccel) integrates multiple key biomarkers to accurately assess an individual's biological age and mortality risk.[11] Using data from NHANES III, researchers employed a Cox proportional hazards model combined with Lasso regression to select the nine most relevant biomarkers from an initial set of 42 clinical indicators associated with aging and all-cause mortality risk. These biomarkers include albumin, creatinine, glucose, total white blood cell count, lymphocyte percentage, red cell distribution width (RDW), mean corpuscular volume (MCV), alkaline phosphatase (ALP), and C-reactive protein (CRP). Low albumin levels have been identified as independent predictors of all-cause mortality in elderly individuals and patients with chronic kidney disease.[12] Creatinine concentration reflects renal function, with higher levels indicating increased mortality risk as kidney function declines.[13] Chronic hyperglycemia is closely linked to accelerated aging and metabolic disorders, significantly raising the incidence of cardiovascular disease.[14] Changes in immune function, such as elevated total white blood cell count and decreased lymphocyte percentage, are associated with enhanced inflammatory responses and aging, with the former also correlating with higher all-cause mortality.[15] Elevated RDW is considered a marker of disrupted erythropoiesis and is linked to various diseases and increased mortality risk.[16] Abnormal MCV often indicates anemia and other hematological disorders, particularly in the elderly, and is strongly associated with increased mortality.[17] Elevated ALP levels suggest declining bone and liver function, both of which are closely related to increased all-cause mortality.[18] As a marker of chronic inflammation, CRP, especially when combined with albumin in the CRP-to-albumin ratio (CAR), has demonstrated significant prognostic value in predicting cardiovascular and all-cause mortality.[19] PhenoAgeAccel not only predicts the risk of diseases and mortality but also provides important guidance for personalized health interventions.[20,21] Previous studies have demonstrated that PhenoAgeAccel is a crucial tool for assessing healthy aging, with high sensitivity and specificity, making it widely applicable in clinical and public health fields.[22,23]

Against this background, this study aims to systematically explore the relationship between different LTPA patterns and PhenoAgeAccel, with a particular focus on analyzing the association and dose-response relationship between LTPA patterns and the total amount of LTPA with PhenoAgeAccel. We hypothesize that different patterns and the total amount of LTPA can significantly influence PhenoAgeAccel, thus mediating the biological aging process. This study utilizes data from the National Health and Nutrition Examination Survey (NHANES) and employs multivariable linear regression models and restricted cubic spline (RCS) analysis to comprehensively evaluate the linear and nonlinear relationships between LTPA and PhenoAgeAccel. This research not only provides new scientific evidence for the formulation of physical activity intervention strategies but also offers theoretical support and practical guidance for delaying aging and promoting healthy aging.

2. Methods

2.1. Study population

This study utilized data collected from the NHANES for the period 1999–2018 (*Data accessed from the National Center for Health Statistics, CDC. Available at:* https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). This survey, overseen by the Centers for Disease Control and Prevention (CDC), aims to assess the health and nutritional status of the non-institutionalized civilian population in the United States. Implemented by the CDC's National Center for Health Statistics, the survey employs a stratified multistage probability sampling strategy to assess approximately 10,000 Americans biennially. The data collection process includes in-depth interviews conducted within households and comprehensive physical assessments. The interview process gathers detailed demographic, socioeconomic, dietary, and health-related information. Physical assessments encompass medical, dental, and a broad range of physiological and biochemical markers.

For this survey, a stringent selection protocol was used, ultimately including 14,868 adults for analysis. This protocol primarily excluded participants who did not meet the age requirements or were unable to complete the necessary survey and physical assessments. Data analysis was performed using a complete case analysis strategy. The complex details of the selection process are illustrated in Fig. 1. The NHANES survey data used in this study have received appropriate ethical approval and comply with the ethical standards set by the Declaration of Helsinki.

2.2. Definitions of leisure time physical activity

In this study, LTPA was assessed using the Global Physical Activity Questionnaire (GPAQ).[24] Participants were asked about the frequency (sessions per week) and duration (minutes per session) of their engagement in vigorous and moderate sports, fitness, and recreational activities that lasted for at least 10 consecutive minutes in a typical week. Vigorous-intensity activities were defined as activities with a MET value of 8.0, which lead to substantial increases in breathing or heart rate, while moderate-intensity activities were defined as activities with a MET value of 4.0, which cause relatively smaller increases in breathing or heart rate. To quantify moderate-to-vigorous physical activity (MVPA), we used the following formula to calculate the total MVPA duration: LTPA-MVPA = 2 × Vigorous PA + Moderate PA.[25] This approach aligns with physical activity guidelines, which equate 1 min of vigorous activity to 2 min of moderate activity. The total frequency of MVPA was determined by summing the number of sessions of both moderate and vigorous activities. Based on the weekly total MVPA duration (threshold of 150 min) and total frequency (threshold of 2 sessions per week), we categorized PA patterns into four groups: No-LTPA, meaning no engagement in vigorous or moderate PA; Insufficiently active-LTPA, with less than 150 min of total MVPA per week; Weekend Warrior, achieving at least 150 min of total MVPA per week in only 1 or 2 sessions; and Regular-LTPA, achieving at least 150 min of total MVPA per week spread over 3 or more sessions.[26–29]

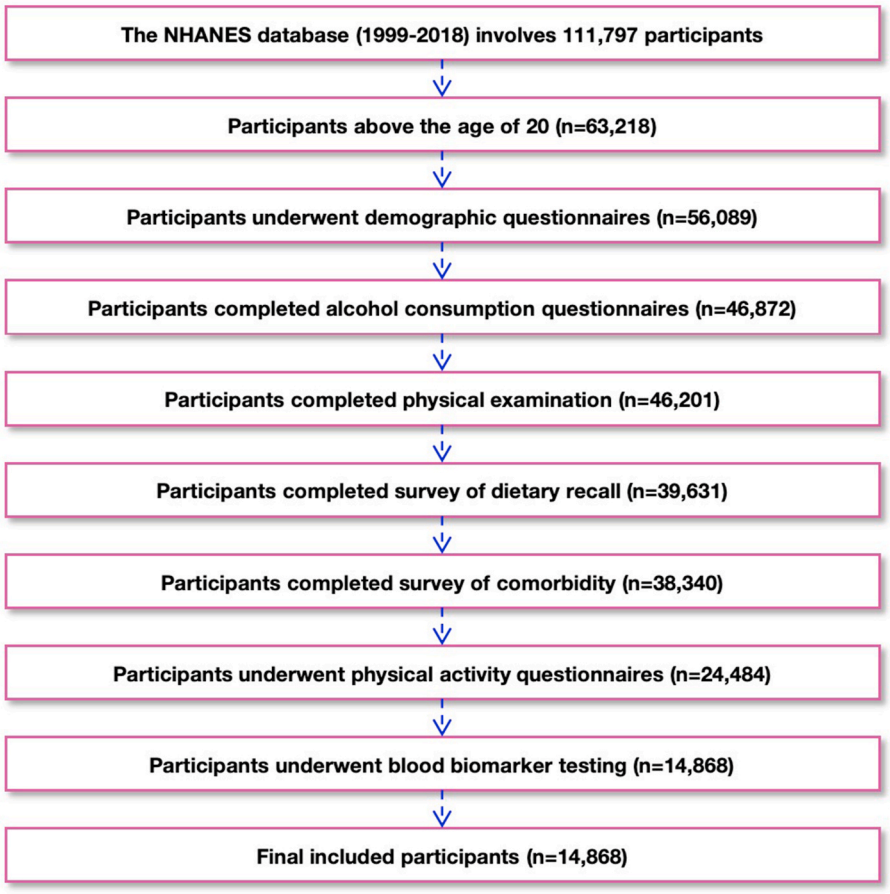

Fig. 1. Flow chart.

2.3. Definitions of phenotypic age acceleration

This study builds upon prior significant research on phenotypic age, employing an integrative approach to compute an individual's phenotypic age.[11] The algorithm utilizes clinical laboratory blood chemistry parameters, incorporating multiple biomarkers such as albumin, creatinine, glucose, total white blood cell count, percentage of lymphocytes, red cell distribution width, mean corpuscular volume, and alkaline phosphatase. These biomarkers were modeled using elastic-net regression within NHANES III. Due to the absence of CRP data from 2011 to 2018, CRP was not included as a clinical biomarker in our study, following precedents from previous research.[30] Notably, earlier studies comparing phenotypic ages calculated with and without CRP biomarker sets found a high correlation between the two (correlation coefficient of 0.99),[31,32] indicating that the absence of CRP has a limited impact on the calculation of phenotypic age.

Particular attention was given to PhenoAgeAccel, a metric derived from the residuals of linear regression analysis between phenotypic age and chronological age.[33,34] For instance, if two individuals are of the same age but one exhibits a younger state due to better physiological health and vitality, while the other appears older due to health issues or poor lifestyle choices, their PhenoAgeAccel values will differ. Serving as a de-merit indicator, lower values of PhenoAgeAccel represent a slower biological aging process, providing a crucial perspective on the discrepancy between an individual's physiological state and their actual age.

The specific formula is as follows:

$$\text{PhenoAge} = 143.5671 + \frac{\ln[-0.0059383581 \times \ln[1 - \text{mortality risk}]]}{0.08548908}$$

$$\text{mortality risk} = 1 - e^{-e^{xb}\left[\exp(120x\gamma)-1\right]/\gamma}$$

$$\gamma = 0.007354285$$

$$\begin{aligned} xb = {} & -18.311623487 - 0.029197296 \times \text{albumin} + 0.002285539 \times \text{alkaline phosphatase} + 0.006379140 \times \text{creatinine} + 0.177752648 \\ & \times \text{glycated hemoglobin} + 0.055248172 \times \text{white blood cell count} - 0.013502137 \times \text{lymphocyte percentage} + 0.029331315 \\ & \times \text{mean corpuscular volume} + 0.234452108 \times \text{red cell distribution width} + 0.077245523 \times \text{chronological age} \end{aligned}$$

2.4. Covariate

This study incorporated multiple covariates for a comprehensive analysis, including basic demographic information, lifestyle factors, and

health status indicators. The basic demographic information encompassed age, sex (male, female), ethnic backgrounds were categorized as Mexican American, Non-Hispanic Black, Non-Hispanic White, among others (including multi-racial and other Hispanic), and levels of education were delineated as below high school, at high school level, and above high school education. Economic classification was gauged through the Poverty Income Ratio (PIR), a scale juxtaposing the income of a household or individual against the annual poverty benchmarks (categorized as low income for a PIR of 1.3 or less, moderate income for a PIR greater than 1.3 but less than 3.5, and high income for a PIR of 3.5 or above).

Lifestyle factors included marital status (married/cohabiting, widowed/divorced/separated), Body Mass Index (BMI) categories (<25, 25–29.9, ≥30 kg/m^2), smoking status (never, former, current), and alcohol status (never, former, mild, moderate, heavy).

Sedentary time was quantified using the GPAQ, which assessed the amount of time participants spent sitting at school, at home, traveling to and from places, or with friends, including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer, excluding time spent sleeping. Participants reported

Table 1
Baseline characteristics of the participants.

Characteristic	Overall	No-LTPA	Insufficiently Active-LTPA	Regular-LTPA	Weekend Warrior	*P*-value
N	14868	7753	2144	4351	620	
PhenoAgeAccel	−2.95 (0.09)	−2.26 (0.09)	−3.24 (0.17)	−3.80 (0.11)	−2.33 (0.22)	<0.0001
LTPA (min/wk)	219.05 (6.08)	0.00 (0.00)	82.84 (1.04)	555.03 (9.75)	336.95 (9.93)	<0.0001
Age,years	47.70 (0.31)	50.43 (0.38)	48.29 (0.48)	44.46 (0.39)	43.52 (0.78)	<0.0001
Sex,n (weighted %)						<0.0001
Female	7461 (51)	4085 (53.3)	1163 (55.2)	2066 (50)	147 (22.8)	
Male	7407 (49)	3668 (46.7)	981(44.8)	2285(50)	473(77.2)	
Race,n (weighted %)						<0.0001
Non-Hispanic White	6740(70.3)	3309(66.1)	1075(75.6)	2074(72.9)	282(72.1)	
Mexican American	2449(8)	1458(9.9)	272(5.4)	620(6.6)	99(8.3)	
Non-Hispanic Black	2771(9.7)	1497(11.2)	399(8.4)	753(8.5)	122(8.9)	
Other race (including multi-racial and other Hispanic)	2908(12)	1489(12.7)	398(10.6)	904(12)	117(10.7)	
BMI, kg/m^2,n (weighted %)						<0.0001
<25	3985(28.6)	1807(23.3)	585(28.9)	1424(35.6)	169(27)	
25–29.9	4878(32)	2440(30.2)	681(31.4)	1510(33.7)	247(39.6)	
≥30	6005(39.4)	3506(46.5)	878(39.7)	1417(30.8)	204(33.4)	
Marital status,n (weighted %)						<0.0001
Married/living with partner	9204(66)	4787(65.2)	1346(67.3)	2681(66.4)	390(65.9)	
Never married	2364(16.1)	1001(13.4)	309(15)	923(19.8)	131(19.4)	
Widowed/Divorced/Separated	3300(17.9)	1965(21.4)	489(17.7)	747(13.8)	99(14.7)	
Education,n (weighted %)						<0.0001
Below	3529(14.3)	2533(22.6)	347(9.1)	542(6.6)	107(10.2)	
High school	3448(23.6)	2014(29)	478(22.5)	798(16.9)	158(24.6)	
Above	7891(62.1)	3206(48.4)	1319(68.4)	3011(76.5)	355(65.2)	
PIR,n (weighted %)						<0.0001
<1.3	4326(18.6)	2785(25.3)	486(13.6)	898(12.8)	157(16.3)	
1.3–3.49	5811(35.2)	3175(39.9)	841(34.4)	1557(29.8)	238(33.4)	
≥3.5	4731(46.2)	1793(34.9)	817(52.1)	1896(57.5)	225(50.3)	
Smoke status,n (weighted %)						<0.0001
Former smoker	3736(25.5)	1971(25.6)	545(26.3)	1090(25.5)	130(21.4)	
Nonsmoker	8078(55.2)	3920(50)	1215(57.5)	2619(61.3)	324(53.1)	
Current smoker	3054(19.3)	1862(24.4)	384(16.2)	642(13.2)	166(25.6)	
Alcohol status,n (weighted %)						<0.0001
Former	2208(11.9)	1436(16.1)	281(10)	422(7.7)	69(8.5)	
Never	1960(9.7)	1219(12)	254(9.2)	425(7.5)	62(7)	
Mild	5192(38.5)	2365(34.1)	852(42.3)	1761(42.3)	214(39.7)	
Moderate	2391(18.3)	1128(16.7)	344(17.8)	814(20.8)	105(16.6)	
Heavy	3117(21.6)	1605(21.3)	413(20.7)	929(21.7)	170(28.1)	
Healthy eating index,n (weighted %)						<0.0001
Q1,[0,43.95]	4956(34)	2915(40.5)	663(31.9)	1140(25.9)	238(38)	
Q2,(43.95,56.27]	4956(33.1)	2681(34.7)	730(34)	1333(30.1)	212(37)	
Q3,(56.27,95.89]	4956(32.9)	2157(24.8)	751(34.1)	1878(44.1)	170(25)	
Sedentary behavior,n (hour/day, weighted %)						<0.001
<4	4630(26.3)	2546(28.3)	607(24.2)	1297(24.7)	180(25.8)	
4-6	5436(36.5)	2793(36.3)	774(34.6)	1618(36.9)	251(41.4)	
>6	4802(37.2)	2414(35.3)	763(41.2)	1436(38.4)	189(32.8)	
Diabetes,n (weighted %)						<0.0001
No	10734(77.1)	5156(70.8)	1580(77.6)	3493(83.8)	505(85.4)	
Yes	4134(22.9)	2597(29.2)	564(22.4)	858(16.2)	115(14.6)	
Hypertension,n (weighted %)						<0.0001
No	8509(62.6)	3970(55.1)	1216(63)	2892(70.9)	431(71.6)	
Yes	6359(37.4)	3783(44.9)	928(37.1)	1459(29.1)	189(28.4)	
Hyperlipidemia,n (weighted %)						<0.0001
No	4067(29.1)	1836(24.5)	583(27.7)	1447(35.4)	201(31.4)	
Yes	10801(70.9)	5917(75.5)	1561(72.3)	2904(64.7)	419(68.6)	
Cancer,n (weighted %)						0.04
No	13391(89.8)	6920(89.2)	1935(90.5)	3950(89.6)	586(94.3)	
Yes	1477(10.2)	833(10.8)	209(9.5)	401(10.5)	34(5.7)	

Continuous variables are summarized as mean values with standard errors, and categorical variables are presented as counts with their weighted percentages. One-way ANOVA was utilized for continuous data, while the Chi-square test was employed for categorical data.
Abbreviations used: Quantile 1: Q1—first quartile; Quantile 2: Q2—second quartile; Quantile 3: Q3—third quartile.

the amount of time they usually spent sitting on a typical day, which was then quantified in hours. Subsequently, sedentary time was categorized into three groups: <4 h, 4–6 h, and ≥6 h.

Dietary quality was assessed by the Healthy Eating Index 2015 (HEI-2015), which evaluates the consistency of an individual's or group's diet with the Dietary Guidelines for Americans published by the United States Department of Agriculture.[35] This index comprises several components, each representing a critical aspect of the diet, such as fruits, vegetables, whole grains, dairy, proteins, the ratio of unsaturated to saturated fats, sodium, and added sugars intake. The HEI-2015 scoring system is quantitative, with a total score of 100, where higher scores indicate better diet quality and greater adherence to the Dietary Guidelines for Americans.[36]

Health status indicators included criteria for diagnosing hypertension, hyperlipidemia, and diabetes. Hypertension was determined based on physician diagnosis, use of antihypertensive medication, and blood pressure measurements (systolic ≥140 mmHg or diastolic ≥90 mmHg). The diagnosis of hyperlipidemia was based on lipid levels (triglycerides, total cholesterol, LDL, and HDL levels) and the use of lipid-lowering medications. Diabetes criteria were based on physician diagnosis, glycated hemoglobin levels, fasting glucose levels, and the use of antidiabetic medications. Cancer prevalence was determined by diagnosis from a physician or health professional.

2.5. Statistical analysis

In the investigation, rigorous adherence to the detailed sampling methodologies prescribed by the NHANES was maintained, with the computation of complex sampling weights conforming to NHANES analytical standards. To reflect the U.S. population accurately, weighted data underpinned all statistical evaluations. Continuous measures were expressed as means with their respective standard errors (Mean ± SE), and categorical data were depicted through frequency counts and their corresponding weighted proportions.

To discern group variances, the analysis applied one-way Analysis of Variance (ANOVA) for continuous measures and Chi-square testing for categorical data. Additionally, this research incorporated weighted generalized linear regression models to probe the association between LTPA and PhenoAgeAccel, with further subgroup analyses by sex to examine potential sex-based effects on this linkage. Both the continuous values of LTPA and the LTPA patterns were analyzed using regression models to explore their respective impacts on PhenoAgeAccel.

Moreover, based on the outcomes of the linear regression model, this research employed restricted cubic splines to examine the non-linear trends between variables. For associations exhibiting non-linear trends, the study further elucidated the threshold effects of LTPA on PhenoAgeAccel through piecewise regression combined with likelihood ratio tests. Lastly, to validate the impact of control variables on the relationship between LTPA and PhenoAgeAccel, these variables were incorporated into the interaction effect test model.

All statistical analyses were conducted with a two-tailed *P*-value of less than 0.05 as the threshold for statistical significance, using R Studio (version 4.2.1, USA) for data processing and analysis.

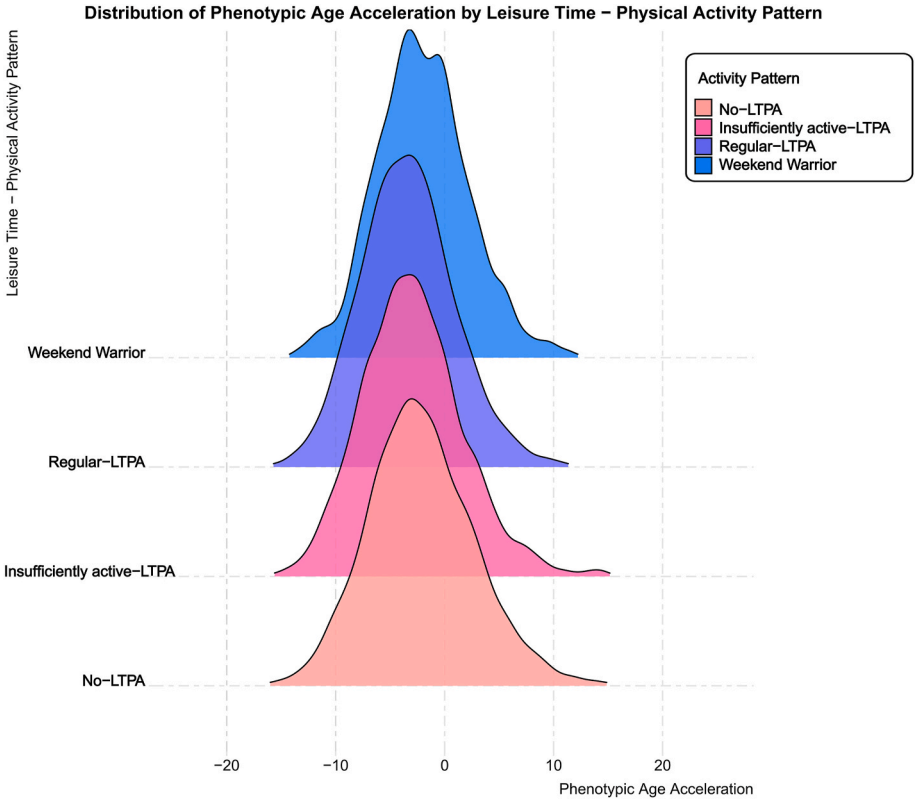

Fig. 2. Distribution of PhenoAgeAccel by LTPA Patterns in American Adults (Including Both Males and Females) Legend: This figure illustrates the distribution of PhenoAgeAccel across different LTPA patterns in American adults. The LTPA patterns are categorized as follows:
1. No-LTPA: Participants who reported no engagement in vigorous or moderate PA.
2. Insufficiently active-LTPA: Participants who engaged in less than 150 min of total MVPA per week.
3. Regular-LTPA: Participants who achieved at least 150 min of total MVPA per week, distributed over 3 or more sessions.
4. Weekend Warrior: Participants who achieved at least 150 min of total MVPA per week, but concentrated primarily in only 1 or 2 sessions.

3. Results

3.1. Baseline characteristics of the participants

This study included baseline characteristics of 14,868 adults, categorized based on their LTPA patterns (Table 1).

Participants with no LTPA had significantly higher PhenoAgeAccel scores and lower LTPA levels compared to those in other groups. Significant differences were also observed across demographic indicators (age, sex, race, and BMI), lifestyle factors (marital status, education, PIR, smoking status, alcohol consumption, HEI scores), and health status indicators (diabetes, hypertension, hyperlipidemia, and cancer) among different LTPA groups ($P < 0.05$).

Participants in the No-LTPA group tended to be older and had a higher proportion of females. Non-Hispanic Whites constituted the largest proportion in the No-LTPA group, while other races were more prevalent in the Regular-LTPA and Weekend Warrior groups. Participants in the No-LTPA group generally had lower education levels, poorer economic status, and a higher prevalence of comorbidities. The No-LTPA group also had a higher proportion of individuals with lower HEI scores and higher sedentary behavior.

The distribution of PhenoAgeAccel by LTPA patterns is illustrated in Fig. 2. The density plot shows that individuals with no activity or insufficiently active-LTPA patterns have higher PhenoAgeAccel scores, indicating accelerated phenotypic aging, compared to those with regular activity or weekend warrior patterns. Specifically, the No-LTPA group shows a broader and more right-skewed distribution, suggesting a higher degree of age acceleration. In contrast, the Regular-LTPA and Weekend Warrior groups exhibit a more concentrated and left-skewed distribution, indicating lower PhenoAgeAccel. This visualization underscores the potential protective effects of regular and even intermittent physical activity against accelerated aging.

3.2. Association analysis between LTPA and PhenoAgeAccel in American adults

This study utilized multivariate linear regression models to analyze the association between LTPA and PhenoAgeAccel in American adults. The results are presented in Figs. 3–5.

Overall, the analysis revealed a significant inverse association between both LTPA levels and LTPA patterns with PhenoAgeAccel. Higher LTPA levels were associated with significantly lower PhenoAgeAccel scores. In the fully adjusted model, compared to individuals with no LTPA, those with insufficiently active-LTPA, regular-LTPA, and Weekend Warrior patterns exhibited significantly lower PhenoAgeAccel scores (insufficiently active-LTPA: $\beta = -0.28$, 95 % CI: 0.53 to −0.04, $P = 0.02$; regular-LTPA: $\beta = -0.48$, 95 % CI: 0.69 to −0.26, $P < 0.0001$; Weekend Warrior: $\beta = -0.18$, 95 % CI: 0.51 to 0.15, $P = 0.28$) (Fig. 3). The RCS analysis indicated a nonlinear threshold effect at 560 min per week (P for Nonlinear <0.0001).

Sex-specific analyses showed consistent findings. For males, higher LTPA levels were significantly associated with lower PhenoAgeAccel scores. Compared to males with no LTPA, those with insufficiently active-LTPA, regular-LTPA, and Weekend Warrior patterns showed significant reductions in PhenoAgeAccel (insufficiently active-LTPA: $\beta = -0.66$, 95 % CI: 1.02 to −0.3, $P < 0.001$; regular-LTPA: $\beta = -0.62$, 95 % CI: 0.9 to −0.34, $P < 0.0001$; Weekend Warrior: $\beta = -0.22$, 95 % CI: 0.61 to 0.17, $P = 0.27$) (Fig. 4). The RCS analysis for males indicated a nonlinear threshold effect at 637 min per week (P for Nonlinear = 0.001).

Similarly, for females, the inverse association between LTPA levels and PhenoAgeAccel was significant. Compared to females with no LTPA, those with insufficiently active-LTPA and regular-LTPA patterns exhibited significant reductions in PhenoAgeAccel (insufficiently active-LTPA: $\beta = -0.002$, 95 % CI: 0.37 to 0.37, $P = 0.99$; regular-LTPA: $\beta = -0.36$, 95 % CI: 0.66 to −0.05, $P = 0.02$; Weekend Warrior: $\beta = -0.31$, 95 % CI: 1.14 to 0.52, $P = 0.45$) (Fig. 5). The RCS analysis for females revealed a nonlinear threshold effect at 482 min per week (P for Nonlinear = 0.01).

3.3. Threshold effect analysis of the relationship between LTPA and PhenoAgeAccel

In this study, the adjusted Model 2 indicates a nonlinear relationship between LTPA levels and PhenoAgeAccel (Table 2). Specifically, at LTPA levels below 560 min per week, the association with PhenoAgeAccel is significant ($\beta = -0.001$, 95 % CI: 0.001 to −0.0003, $P < 0.001$), while levels above 560 min per week show a different associatio n ($\beta = 0.0003$, 95 % CI: 0.00002 to 0.001, $P = 0.03$). The likelihood ratio test strongly supports the statistical significance of the two-piecewise linear regression model ($P < 0.001$).

In the sex subgroup analysis, for males with LTPA levels below 637 min per week, the association with PhenoAgeAccel is significant ($\beta = -0.001$, 95 % CI: 0.001 to −0.0002, $P = 0.01$), whereas levels above

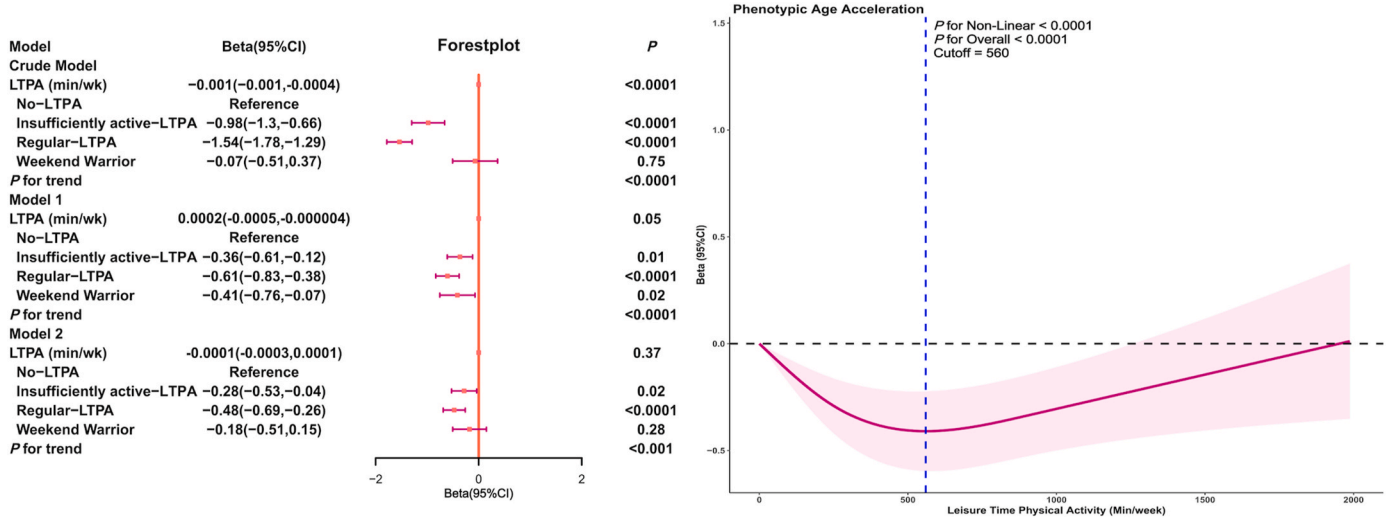

Fig. 3. Association analysis between LTPA and PhenoAgeAccel in American adults Legend: Crude Model is the unadjusted model. Model 1 adjusted for age, sex, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior. Model 2 adjusted for age, sex, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior, diabetes, hypertension, hyperlipidemia and cancer.

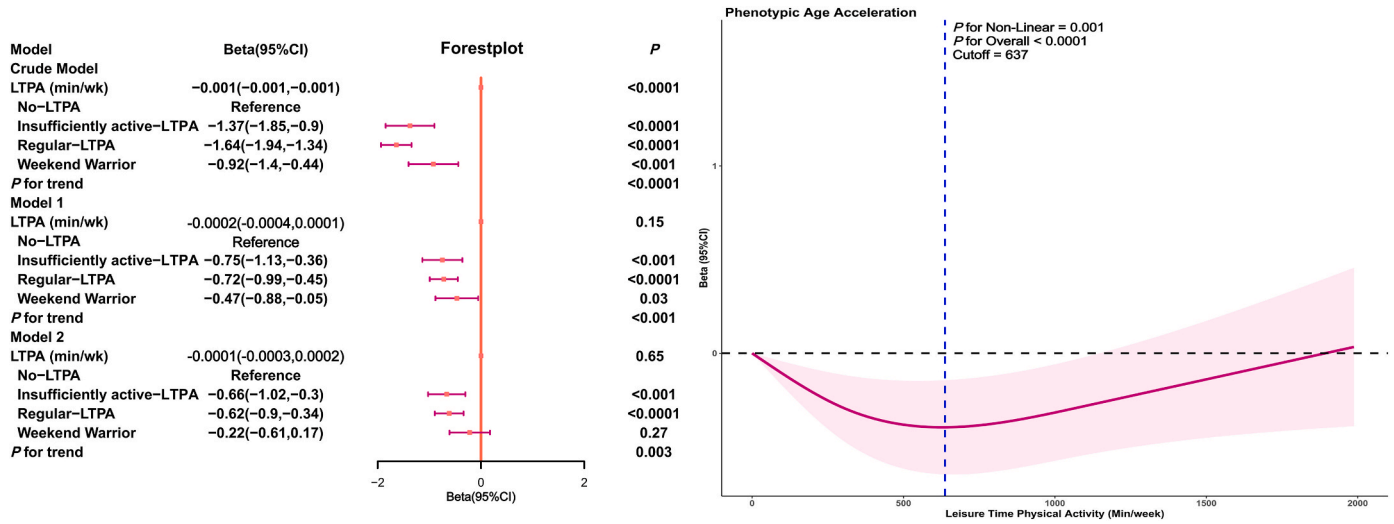

Fig. 4. Association analysis between LTPA and PhenoAgeAccel in American adults (Male). Legend: Crude Model is the unadjusted model 1 adjusted for age, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior. Model 2 adjusted for age, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior, diabetes, hypertension, hyperlipidemia and cancer.

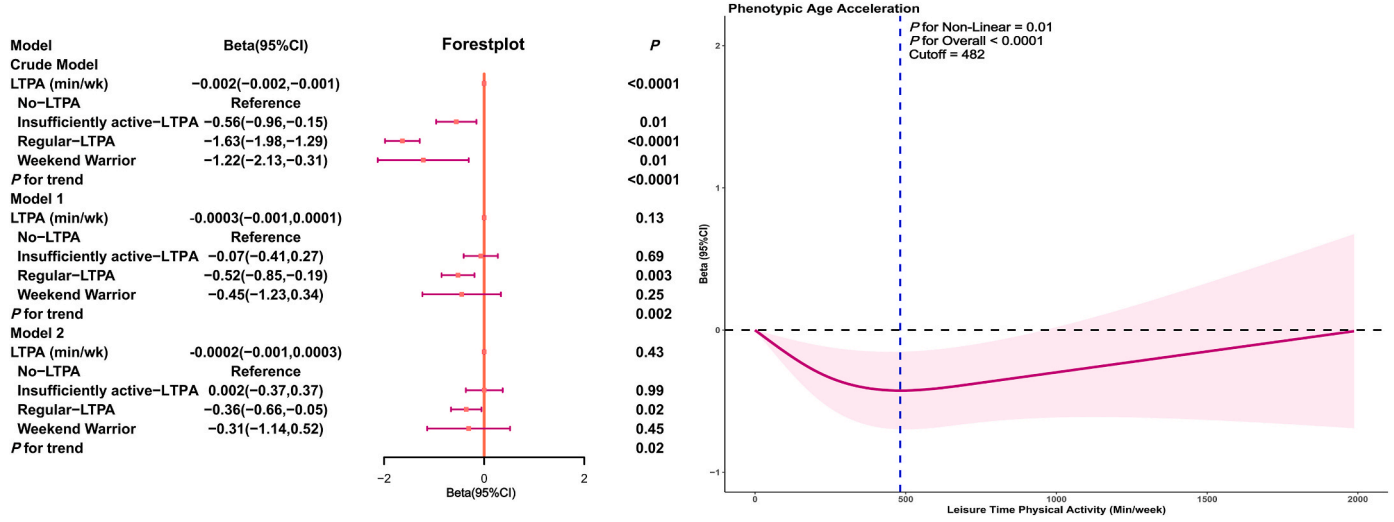

Fig. 5. Association analysis between LTPA and PhenoAgeAccel in American adults (Female) Legend:
Crude Model is the unadjusted model. Model 1 adjusted for age, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior. Model 2 adjusted for age, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior, diabetes, hypertension, hyperlipidemia and cancer.

637 min per week show a different association (β = 0.0003, 95 % CI: 0.00001 to 0.001, $P = 0.06$). The likelihood ratio test confirms the nonlinear relationship for males ($P = 0.004$).

For females, the association at LTPA levels below 482 min per week is significant (β = −0.001, 95 % CI: 0.002 to −0.0003, $P = 0.02$), and levels above 482 min per week show a different association (β = 0.0003, 95 % CI: 0.0002 to 0.001, $P = 0.27$). The likelihood ratio test indicates the superiority of the nonlinear model for females ($P = 0.02$).

These results highlight the importance of considering the nonlinear threshold effects of LTPA levels in predicting PhenoAgeAccel, suggesting that both males and females benefit from LTPA up to specific thresholds, beyond which additional LTPA does not provide further significant reductions in PhenoAgeAccel.

3.4. Interaction effect test of the relationship between LTPA and PhenoAgeAccel

This study analyzed the relationship between LTPA and PhenoAgeAccel, examining the interaction effects of sex, age, race, marital status, educational level, PIR, BMI, smoking status, alcohol consumption, sedentary behavior, HEI, diabetes, hyperlipidemia, hypertension, and cancer (Table 3). The analysis indicated that none of these characteristics demonstrated a statistically significant interaction with LTPA and PhenoAgeAccel (P for interaction >0.05). This suggests that the relationship between LTPA and PhenoAgeAccel is stable across different subgroups, including variations in sex, race, BMI, and lifestyle factors. While trends varied slightly among these factors, the lack of significant interaction effects underscores the consistent benefit of LTPA in reducing PhenoAgeAccel across diverse populations. These findings highlight the robustness of LTPA's positive impact on healthy aging.

4. Discussion

This study systematically explored the relationship between various LTPA patterns and PhenoAgeAccel, revealing several pivotal findings. Firstly, the comprehensive analysis demonstrated significant differences

Table 2
Threshold effect analysis of the relationship between LTPA and PhenoAgeAccel.

Outcome	Beta	95%CI	*P*-value
LTPA			
One-line linear regression model	−0.0001	−0.0003,0.0001	0.37
Two-piecewise linear regression model			
Inflection point	560		
LTPA <560	−0.001	−0.001,-0.0003	<0.001
LTPA ≥560	0.0003	0.00002,0.001	0.03
P for Log-likelihood ratio test			<0.001
LTPA (Male)			
One-line linear regression model	−0.0001	−0.0003,0.0002	0.65
Two-piecewise linear regression model			
Inflection point	637		
LTPA <637	−0.001	−0.001,-0.0002	0.01
LTPA ≥637	0.0003	−0.00001,0.001	0.06
P for Log-likelihood ratio test			0.004
LTPA (Female)			
One-line linear regression model	−0.0002	−0.001,0.0003	0.43
Two-piecewise linear regression model			
Inflection point	482		
LTPA <482	−0.001	−0.002,-0.0003	0.02
LTPA ≥482	0.0003	−0.0002,0.001	0.27
P for Log-likelihood ratio test			0.02

Adjusted for age, sex, race, PIR, education, BMI, marital status, smoke, alcohol, HEI, sedentary behavior, diabetes, hypertension, hyperlipidemia and cancer.

in PhenoAgeAccel across distinct LTPA patterns. Specifically, compared to no-LTPA, both insufficiently active-LTPA and regular-LTPA patterns significantly reduced PhenoAgeAccel.

The weekend warrior pattern demonstrated a potential anti-aging effect when compared to the no-LTPA group, as observed in both the crude model and Model 1. However, this effect did not achieve statistical significance in the fully adjusted model, indicating that while there is suggestive evidence for the benefits of the weekend warrior pattern, these findings are not conclusive and warrant further exploration in subsequent studies. Moreover, RCS analysis elucidated a nonlinear threshold effect between LTPA and PhenoAgeAccel. Within the range of less than 560 min of LTPA per week, there was a significant negative association between LTPA and PhenoAgeAccel; however, beyond this threshold, the association became non-significant. This indicates that while increasing physical activity is beneficial in delaying aging, excessive physical activity does not confer additional benefits.

Sex-subgroup analysis revealed analogous nonlinear relationships for both men and women. For men, LTPA below 637 min per week significantly reduced PhenoAgeAccel, but beyond this threshold, the association was no longer significant. For women, the threshold effect was observed at 482 min per week; similarly, LTPA was significantly negatively associated with PhenoAgeAccel below this threshold, but the association became non-significant beyond it. These results underscore the universal effect of moderate and consistent physical activity in delaying biological aging, while excessive physical activity does not yield further health benefits.

Over the years, numerous studies have extensively explored the dose-response relationship between LTPA and all-cause mortality, providing a robust scientific foundation for the development of global physical activity guidelines. The large cohort studies of Arem et al.[4] and Zhao et al.[5] concluded that 150–300 min of moderate to vigorous intensity LTPA per week significantly reduced all-cause mortality risk. However, as the duration of LTPA increases beyond this range, the reduction in mortality tends to plateau or even cease. This finding is consistent with the physical activity guidelines recommended by countries such as the United States, Australia, and the United Kingdom, and further reinforces the scientific basis for these recommendations. The study by Sun et al.[37] further refined this relationship, revealing that LTPA exceeding 1500 min per week significantly lowered the risk of cardiovascular disease-specific mortality. Garcia et al.[38] and Ekelund et al.[7,6] reported similar results, indicating that the health benefits of physical activity are most pronounced within the recommended range, with diminishing returns beyond this threshold. Moreover, Jeong et al.[39] emphasized that incremental increases in physical activity are particularly crucial for patients with pre-existing cardiovascular disease, where an additional 500 MET minutes per week significantly reduces mortality risk. These studies, conducted across various populations and methodologies, further validate the nonlinear dose-response relationship between LTPA and all-cause mortality, providing multifaceted support for the recommended levels of physical activity in current guidelines.

By introducing PhenoAgeAccel as a biological aging indicator, this study systematically explored the dose-response relationship between LTPA and biological aging, revealing a nonlinear threshold effect. These findings not only further enrich the understanding of the impact of LTPA on health outcomes from traditional research but also identify the optimal dose range of LTPA for mitigating biological aging. Specifically, the study found that moderate LTPA (less than 637 min per week for male and less than 482 min per week for female) significantly delays biological aging, while exceeding this threshold does not confer additional benefits. Compared to previous studies that primarily focused on the impact of LTPA on all-cause mortality, this research offers a new perspective by emphasizing the need to consider sex-specific effects and their unique influence on biological aging when recommending physical activity levels. This finding serves as an important supplement to existing guidelines, suggesting that personalized physical activity recommendations may be a potential strategy for optimizing healthy aging.

Furthermore, the pattern of LTPA also shows differential impacts on aging. The weekend warrior pattern has limited health benefits, with regular physical activity more effective in combating aging. Hamer et al.'s survey[40] of British adults found that regular physical activity is significantly associated with lower psychological distress risk, whereas the weekend warrior pattern is less effective in this regard. Additionally, O'Donovan et al.'s study[8,9] demonstrated that while the weekend warrior pattern provides some health benefits, its effects are not as significant as regular physical activity. Further research also shows that long-term regular physical activity not only helps reduce mortality risk but also effectively slows the aging process. Roberts et al.'s study[41] indicated that the intermittent high-intensity activity of the weekend warrior pattern may increase the risk of major trauma, particularly musculoskeletal injuries, further emphasizing the importance of regular physical activity. Synthesizing the above literature, this study, through nonlinear threshold analysis and comparison of different physical activity patterns, further confirms the crucial role of regular physical activity in mitigating PhenoAgeAccel.

This study, although providing new scientific evidence on the dose-response relationship between LTPA and PhenoAgeAccel, has several limitations that need to be addressed in future research. Firstly, the study is cross-sectional in design, which, although revealing associations between LTPA and PhenoAgeAccel, cannot establish causality. Longitudinal study designs would better capture the long-term effects of LTPA on biological age acceleration and should be considered in future research. Secondly, the data used in this study were sourced from NHANES. While NHANES data are widely representative, reliance on self-reported physical activity data may introduce recall bias and social desirability bias. These biases can affect the accurate measurement of physical activity, thereby impacting the reliability of the results. Future studies could consider using objective measurement tools, such as accelerometers or other wearable devices, to improve data accuracy. Additionally, although the analysis models in this study adjusted for various confounding factors, including demographic information, lifestyle factors, and health status indicators, there may still be unmeasured confounding factors. For instance, hereditary factors, psychological stress, and social support might influence the relationship between LTPA and PhenoAgeAccel. Future research should aim to include more potential confounders to minimize bias. Finally, the study sample

Table 3
Interaction effect test.

Characteristic	Q1	Q2	*P*	Q3	*P*	Q4	*P*	*P* for trend	*P* for interaction
Sex									0.73
Female	ref	−2.9(-29.9, 24.1)	0.83	6.7(-24.7, 38.2)	0.67	−1.1(-32.3, 30)	0.94	0.87	
Male	ref	9.1(-37, 55.2)	0.69	18.3(-25.2, 61.8)	0.40	−4.5(-49, 39.9)	0.84	0.78	
Race									0.14
Non-Hispanic White	ref	2.3(-26.4, 31.1)	0.87	15.6(-17.7, 48.8)	0.35	−15.2(-51.1, 20.8)	0.40	0.65	
Mexican American	ref	24.9(−40.6, 90.3)	0.44	4.6(−47.2, 56.3)	0.86	39(−19.6, 97.6)	0.18	0.3	
Non-Hispanic Black	ref	−6.4(−59.7, 46.9)	0.81	10.8(−49.6, 71.1)	0.72	1.2(−58.3, 60.8)	0.97	0.82	
Other Race	ref	−13.5(−67.5, 40.4)	0.61	−3.7(−56.3, 49)	0.89	0.5(−63.5, 64.5)	0.99	0.94	
Education									0.4
Below	ref	19.1(-30.5, 68.7)	0.44	−7.2(-49.7, 35.3)	0.73	−6.8(-43.8, 30.1)	0.71	0.44	
High School	ref	14.9(−40.1, 69.91)	0.58	0.2(−51.8, 52.1)	0.99	−15.5(-75.7, 44.7)	0.6	0.43	
Above	ref	−6.3(−34.1, 21.5)	0.65	21.6(−12.7, 55.8)	0.21	−2.3(−43.7, 39.2)	0.91	0.65	
PIR									0.2
<1.3	ref	2.9(−53.4, 59.2)	0.92	−1.8(−52.7, 49.1)	0.94	4.7(−47.3, 56.7)	0.86	0.91	
1.3–3.49	ref	−4.9(-34.2, 24.5)	0.74	36.6(−1.8, 74.9)	0.06	−3.3(-44.5, 37.8)	0.87	0.56	
≥3.5	ref	1.7(−32.7, 36.1)	0.92	−4.6(−43.8, 34.7)	0.81	−17.6(-67.9, 32.8)	0.48	0.49	
BMI									0.67
<25	ref	18.8(−23.4, 61)	0.37	3.2(−40.3, 46.8)	0.88	34.3(−21.8, 90.5)	0.22	0.33	
25–29.9	ref	−17.7(−59.1, 23.8)	0.39	12.5(−35.4, 60.3)	0.60	−15.4(-78, 47.1)	0.62	0.98	
≥30	ref	1.9(-29.5, 33.4)	0.90	17.2(-12.5, 47)	0.25	−16.5(-44.8, 11.9)	0.25	0.24	
Marital status									0.33
Widowed/Divorced/Separated	ref	2.1(-27.3, 31.4)	0.89	−1(-29.1, 27.1)	0.94	−27(-54.7, 0.7)	0.06	0.1	
Never married	ref	31.4(−47.5110.3)	0.42	63.6(−1.1128.3)	0.05	66.73(-10.3143.8)	0.09	0.04	
Married/living with partner	ref	−38(−74.8, −1.3)	0.04	6.1(−42.8, 55)	0.80	−10.6(-77.2, 56.1)	0.75	0.89	
Smoke status									0.64
Former smoker	ref	0.7(−33, 34.4)	0.97	4.9(−29.3, 39)	0.77	−8.2(−42.6, 26.3)	0.63	0.79	
Nonsmoker	ref	16.7(−26.5, 59.8)	0.44	16.3(−23.6, 56.2)	0.41	−6.3(−62.9, 50.3)	0.82	0.84	
Current smoker	ref	−29.8(-79, 19.4)	0.23	14.2(-33.9, 62.3)	0.55	−12.4(-67.8, 42.9)	0.65	0.83	
Alcohol status									0.42
Former	ref	−5.1(−86.7, 76.4)	0.90	−2.6(−66, 60.8)	0.93	−36.2(-108.6, 36.2)	0.31	0.28	
Never	ref	−5.5(−58.1, 47)	0.83	5.8(−57.4, 69)	0.85	−14.9(-86.2, 56.4)	0.67	0.79	
Mild	ref	3.8(-32.4, 40)	0.83	3.4(-35.3, 42)	0.86	−19.7(-63.5, 24.2)	0.37	0.46	
Moderate	ref	−44.5(−83.7, −5.2)	0.03	−31.6(-79.6, 16.5)	0.19	−38.7(-94.4, 16.9)	0.17	0.19	
Heavy	ref	56.2(−14.5126.8)	0.12	81.7(22.3141)	0.01	71.5(5.4137.5)	0.03	0.04	
Sedentary behavior									0.36
<4	ref	21.5(−26.1, 69.2)	0.37	7.4(−36.9, 51.7)	0.74	14.2(−48.1, 76.5)	0.65	0.76	
4-6	ref	−14.4(-51, 22.1)	0.43	6(-30.3, 42.2)	0.74	1.3(-41.4, 44)	0.95	0.69	
>6	ref	−0.6(-33.3, 32.2)	0.97	18.4(-15.9, 52.6)	0.28	−35.4(-70.9, 0.1)	0.05	0.17	
Healthy eating index									0.22
Q1	ref	1.7(−34.2, 37.6)	0.92	4.2(−37.5, 45.9)	0.84	0.4(−41, 41.8)	0.98	0.97	
Q2	ref	11(−25.5, 47.5)	0.54	34.4(5.9, 63)	0.02	−1.7(−52.5, 49)	0.94	0.77	
Q3	ref	−8.5(−49.4, 32.3)	0.67	1.7(−39.1, 42.6)	0.93	−23.8(-67.2, 19.7)	0.28	0.47	
Diabetes									0.06
Yes	ref	−31.4(-71.7, 8.8)	0.12	−17.8(-53.4,17.9)	0.32	−59.7(-92.7,-26.6)	<0.001	<0.001	
No	ref	6.7(-21.5, 34.8)	0.63	16.8(-14, 47.7)	0.27	12.1(-24.8, 49.1)	0.51	0.38	
Hyperlipidemia									0.44
Yes	ref	−3.5(-33.5, 26.6)	0.82	5.9(-22.5, 34.2)	0.68	−25.4(-50.9, 0.2)	0.05	0.11	
No	ref	12.3(−30.1, 54.7)	0.56	26.2(−24.9, 77.4)	0.30	48.3(−18.8115.5)	0.15	0.14	
Hypertension									0.11
Yes	ref	3.2(-40.1, 46.5)	0.88	−7(-47.6, 33.7)	0.73	−43.2(-80.1, −6.2)	0.02	0.002	
No	ref	−4.1(−33.3, 25.1)	0.78	19.6(−15.3, 54.5)	0.26	23.2(−18.6, 65)	0.27	0.17	
Cancer									0.42
Yes	ref	−20.1(−75.1, 34.9)	0.46	−25.8(-88.9, 37.3)	0.41	−43.9(-107.4,19.6)	0.17	0.2	
No	ref	3(-23.6, 29.6)	0.82	16.6(-10, 43.2)	0.21	−1.1(-32.3, 30.1)	0.94	0.77	

comprised American adults, which may limit the external validity of the results and their generalizability to other countries or regions. Different cultural, and socio-economic backgrounds, and lifestyles might affect the relationship between LTPA and PhenoAgeAccel. Therefore, future studies should be conducted in diverse populations to validate and extend the findings of this research.

5. Conclusion

This study demonstrates that regular-LTPA is significantly effective in reducing PhenoAgeAccel in American adults. Importantly, we identified a nonlinear relationship with a threshold effect between LTPA and PhenoAgeAccel, indicating that moderate levels of activity are most beneficial for slowing biological aging. Additionally, our findings reveal sex-specific differences in these effects, underscoring the need for tailored physical activity recommendations. These insights provide valuable evidence for public health strategies aimed at promoting healthy aging.

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Ethics approval and consent to participate

The ethical standards of the institutional and/or national research committee [National Health and Nutrition Examination Survey, NCHS IRB/ERB protocol numbers: NHANES 1999–2004 (protocol #98–12); NHANES 2005–2006 (protocol #2005–06); NHANES 2007–2008

(continuation of protocol #2005–06); NHANES 2009–2010 (continuation of protocol #2005–06); NHANES 2011–2012 (protocol #2011–17); NHANES 2013–2014 (continuation of protocol #2011–17); NHANES 2015–2016 (continuation of protocol #2011–17); NHANES 2017–2018 (continuation of protocol #2011–17)] was followed for all procedures involving human beings. As the data did not include personal identifiers, no additional consent was required for this study. Data from the National Health and Nutrition Examination Survey (NHANES), which is publicly available, was utilized with the written consent of its participants, adhering to the ethical approval by the Research Ethics Review Board of the National Center for Health Statistics (NCHS ERB).

Author contributions statement

● **Dongzhe Wu**: Dongzhe Wu was the primary investigator responsible for the overall study design and data analysis. He developed the research framework, conducted data cleaning and analysis, and applied complex statistical techniques across various analytical models. Additionally, he was responsible for drafting the manuscript and contributed significantly to subsequent revisions and edits.

● **Peng Huang**: Peng Huang participated in the study design and methodology development, particularly in the area of the relationship between physical activity patterns and phenotypic age acceleration. He assisted with data collection and partial analysis and provided technical support for manuscript writing.

● **Xue Geng**: Xue Geng was primarily responsible for data collection and organization, including liaising with the NHANES database and data extraction. She also participated in preliminary data analysis and provided expert advice on the methodology section.

● **Chaoyi Qu**: Chaoyi Qu provided key statistical analysis support throughout the study, particularly in the application of stratified regression models and interaction effect testing. He also contributed to data visualization and assisted in the interpretation of research findings.

● **Zhijian Rao**: Zhijian Rao was mainly responsible for project management, including coordinating the research team, managing the research timeline, and ensuring that the study adhered to ethical standards. He also provided constructive feedback during manuscript review and editing.

● **Jianhong Zhang**: Jianhong Zhang provided methodological guidance during the initial design phase, particularly contributing her expertise in dose-response relationship research between physical activity and health outcomes. She also participated in partial data analysis and provided academic support for manuscript writing.

● **Yulin Shen**: Yulin Shen was involved in data analysis and the interpretation of results, helping to design the statistical models used in the study. She also assisted in the completion of multiple manuscript revisions, ensuring the accuracy of the data results and the overall coherence of the article.

● **Qiangman Wei**: Qiangman Wei was primarily responsible for the literature review and reference management. She also contributed to the discussion section, helping to interpret the broader implications of the research findings.

● **Shijie Liu**: Shijie Liu provided technical support in data processing and the selection and application of analytical tools. He also assisted in the writing and review process of the manuscript.

● **Jiexiu Zhao**: As the corresponding author, Jiexiu Zhao oversaw the entire research process, including the initial conception, design, data analysis, and manuscript writing. He was also responsible for securing funding for the project and managing its progress, ensuring the study's successful completion. He provided critical guidance and revision at every stage of the manuscript and gave final approval for submission.

Conflict of interest statement

The authors declare no conflicts of interest related to this study.

Data availability statement

The dataset(s) supporting the conclusions of this article is(are) available in the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/).

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