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Exploring the impact of women-specific reproductive factors on phenotypic aging and the role of life's essential 8

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Abstract

Background Aging is an inevitable biological process. Accelerated aging renders adults more susceptible to chronic diseases and increases their mortality rates. Previous studies have reported the relationship between lifestyle factors and phenotypic aging. However, the relationship between intrinsic factors, such as reproductive factors, and phenotypic aging remains unclear.

Methods This study utilized data from the National Health and Nutrition Examination Survey (NHANES), spanning from 1999 to 2010 and 2015–2018, with 14,736 adult women. Random forest imputation was used to handle missing covariate values in the final cohort. Weighted linear regression was utilized to analyze the relationship between women-specific reproductive factors and PhenoAgeAccel. Considering the potential impact of menopausal status on the results, additional analyses were conducted on premenopausal and postmenopausal participants. Additionally, the Life's Essential 8 (LE8) was used to investigate the impact of healthy lifestyle and other factors on the relationship between women-specific reproductive factors and PhenoAgeAccel. Stratified analyses were conducted based on significant interaction p-values.

Results In the fully adjusted models, delayed menarche and gynecological surgery were associated with increased PhenoAgeAccel, whereas pregnancy history were associated with a decrease. Additionally, early or late ages of menopause, first live birth, and last live birth can all negatively impact PhenoAgeAccel. The relationship between women-specific reproductive factors and PhenoAgeAccel differs between premenopausal and postmenopausal women. High LE8 scores positively impacted the relationship between certain reproductive factors (age at menarche, age at menopause, age at first live birth, and age at last live birth) and phenotypic age acceleration. Stratified analysis showed significant interactions for the following variables: BMI with age at menarche, pregnancy history, and

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age at menopause; ethnicity with age at menopause, age at first live birth, and parity; smoking status with use of contraceptive pills and gynecologic surgery; hypertension with use of contraceptive pills, pregnancy history, and age at menopause.

Conclusion Delayed menarche, gynecological surgery, and early or late ages of menopause, first live birth, and last live birth are associated with accelerated phenotypic aging. High LE8 score may alleviate the adverse effects of reproductive factors on phenotypic aging.

Keywords Women-specific reproductive factors, Phenotypic age, Aging, Life's essential 8

Introduction

Aging is an inevitable part of life, wherein the physiological functions of various body systems and organs gradually decline [1]. This process involves molecular, cellular, tissue, and organ-level changes, such as genomic instability, telomere attrition, and stem cell depletion [2]. Accelerated aging increases adults' susceptibility to chronic diseases, thereby increasing their mortality rates [1, 2]. While aging is irreversible, identifying risk factors, and intervening to mitigate and prevent them can reduce the incidence of chronic diseases, improve the quality of life, and slow down the aging process. Previous studies have found that modifiable unhealthy lifestyles (such as smoking, drinking alcohol, high BMI, and lack of physical activity) accelerate phenotypic aging [3, 4], However, the relationship between intrinsic factors (such as reproductive factors) and aging remains unclear. Furthermore, despite prior descriptions of potential gender differences in healthspan [5], the role of gender-specific factors in aging is poorly understood and contentious.

Evidence suggests that women-specific reproductive factors are related to telomere length [6–11]. J. Koss and colleagues discovered that early menarche is associated with shorter telomere length [6]. Kresovich et al. found that a longer reproductive period and increased parity are linked to shorter telomere length, whereas breastfeeding duration correlates positively with telomere length, with no association found for exogenous hormone use [7]. Fan et al., using data from the UK Biobank, identified significant correlations between early menarche (<12 years), early menopause (<45 years), shorter reproductive span (<30 years), multiparity, early age at first live birth (<20 years), and shorter LTL [11]. However, in a 13-year follow-up study, a higher number of surviving children among 75 Maya women was associated with longer telomeres, suggesting childbirth may protect against cellular aging [9]. Nonetheless, no studies to date have reported on the relationship between gender-specific reproductive factors and phenotypic aging.

Telomeres primarily reflect the molecular level of organismal aging; therefore, examining aging only from this perspective is not comprehensive enough. Phenotypic Age (PhenoAge) serves as a standard for measuring the biological age. It assesses an individual's mortality risk score by comparing it with the observed average mortality risk in the National Health and Nutrition Examination Survey (NHANES) reference sample, thereby determining the individual's PhenoAge [12, 13]. PhenoAge Acceleration (PhenoAgeAccel) represents the disparity between PhenoAge and chronological age and quantifies an individual's degree of physiological aging [13]. Participants with positive PhenoAgeAccel values exhibited greater physiological aging, while those with negative values demonstrated a relatively young physiological state [13]. Based on these considerations, we employed PhenoAgeAccel as the dependent variable to elucidate the relationship between women-specific reproductive factors and aging.

Women-specific reproductive factors are significantly influenced by internal factors such as hormonal levels [14–16]. The close association between these factors and phenotypic aging reflects inherent biological characteristics of the body. However, investigating whether adopting healthy lifestyle habits can improve the impact of reproductive factors on phenotypic aging. This question raises the question of the interaction between lifestyle and reproductive factors, prompting the inclusion of the Life's Essential 8 (LE8) [17]. In this context, we hypothesized that a higher LE8 score may exert a positive effect on the relationship between women-specific reproductive factors and PhenoAgeAccel.

Methods

Study participants

This study utilized data from the NHANES, a large-scale national survey conducted by the National Center for Health Statistics (NCHS) in the United States [18]. NHANES covers diverse populations across various regions, age groups, and ethnicities throughout the United States [18]. To ensure adequate representative and statistical significance sampling, we selected NHANES data spanning survey cycles from 1999 to 2010 and 2015–2018. To ensure the reliability of the study, a detailed process of participant inclusion and exclusion was conducted. Initially, 18,551 adult women with complete phenotypic age data from the NHANES database were included. Subsequently, we excluded two women who had not experienced menarche and 2,918 participants

with missing data on age at menarche or menopause. Additionally, 858 pregnant and lactating participants were excluded due to physiological influences during these stages, which could affect women's phenotypic age; hence, potential confounding factors were reduced. Following these steps, 14,773 participants were included in the study. Furthermore, we excluded participants with age at menopause above 70 or under 18 years, age at menarche below 8 years, age at first live birth below 14 or above 49 years, and pregnancy occurrences above 20 births. These criteria were set to minimize potential heterogeneity effects on the research outcomes. Ultimately, we included 14,736 participants in the final analysis and employed the random forest imputation method to interpolate covariates with missing values (Fig. 1).

Calculation of phenotypic age

PhenoAge is a reliable tool to estimate biological age. PhenoAge was calculated using chronological age and nine biological markers: albumin, logarithm of C-reactive protein, erythrocyte distribution width, lymphocyte percentage, mean cell volume, creatinine, white blood cell count, glucose, and alkaline phosphatase [12, 19]. These biomarkers were selected using the Cox proportional hazards elastic net model. The final formula for calculating PhenoAge is as follows: PhenoAge = 141.50 + ln[-0.00553*ln(1-xb)]/0.09165 [12, 19]. This calculation provides a more precise estimate of an individual's age. To calculate PhenoAge accurately, we employed the BioAge R package [13].

Women-specific reproductive factors

Women-specific reproductive factors in this study included age at menarche, use of contraceptive pills, pregnancy history, gynecologic surgery, age at menopause among postmenopausal women, age at first live birth among parous women, age at last live birth among parous women, and number of live births among parous women. The specific method of determination is detailed in the Supplementary Methods. Supplementary Fig. 1 shows the distribution of certain women-specific reproductive factors.

Life's essential 8

The LE8 score is calculated based on previous research, encompassing four health behaviors and four health factors [13, 20]. Health behaviors include diet, physical activity, nicotine exposure, and sleep health, while health factors comprise body mass index (BMI), lipid levels, blood glucose, and blood pressure. Each participant receives scores on these eight indicators, ranging from 0 to 100 for each. The LE8 total score is the average of these indicator scores. Additionally, total scores for health behaviors and health factors are computed. Supplementary Fig. 1 shows the distribution of LE8.

Total nutrient intake is derived from participants' first 24-hour dietary recalls, documenting the types and quantities of foods and beverages consumed in the 24 h preceding the interview. Diet quality is assessed using the Healthy Eating Index-2015 (HEI-2015), calculated based on consumption amounts of various food components in the recall (see Reedy et al., 2018). Data on physical activity, nicotine exposure, sleep health, diabetes history, and medication use are collected during home interviews

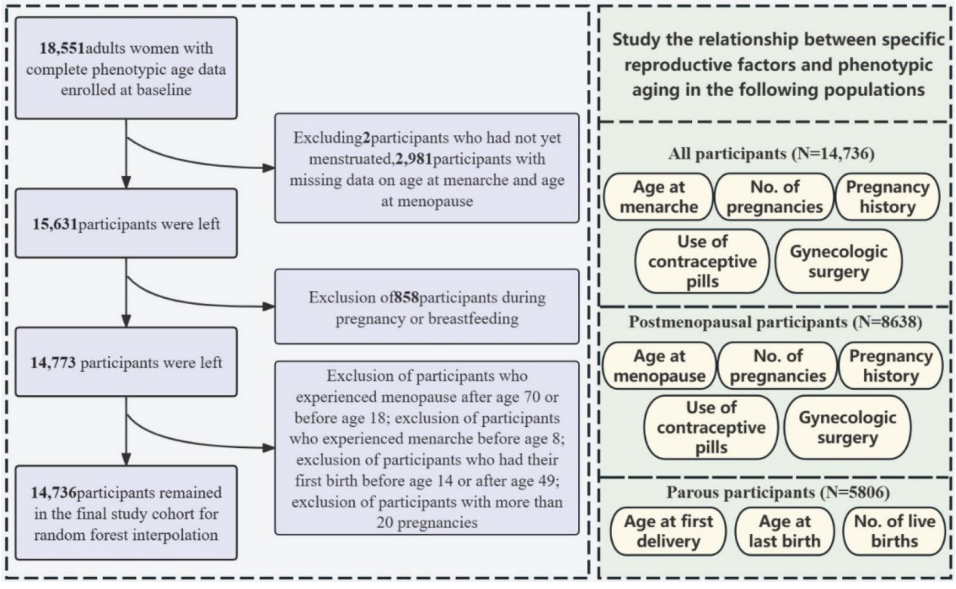

Fig. 1 Flow chart

using standardized questionnaires. Height, weight, and blood pressure data are measured at Mobile Examination Centers (MEC). Body mass index (BMI) is calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure values represent the average of three measurements. Blood samples are collected and sent to central laboratories for analysis of lipids, plasma glucose, and glycated hemoglobin A1c.

Covariates

In terms of covariates, we considered multiple important factors to adjust for potential confounding variables that may have affected the study results. These factors include age (continuous variable), ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race - Including Multi-Racial), education level (Less than 9th grade, 9-11th grade, High school graduate/GED or equivalent, Some college or AA degree, College graduate or above), marital status (Married, Widowed, Divorced, Separated, Never married, Living with a partner), poverty income ratio (continuous variable), body mass index (BMI) (<18.5 kg/m2, 18.5–25 kg/m2, 25–30 kg/m2, ≥30 kg/m2), smoking status (never, former and now), alcohol consumption (never, former, mild, moderate and heavy), chronic kidney disease (yes, no), stroke (yes, no), cancer (yes, no), chronic obstructive pulmonary disease (yes, no), hypertension (yes, no), and diabetes (no, diabetes mellitus, impaired fasting glycemia, impaired glucose tolerance). Specific definitions of the covariates are shown in Supplementary Methods.

Statistical analysis

We first compared the baseline characteristics of the participants to explore the differences between those with positive and negative PhenoAgeAccel. Continuous variables were assessed using either the t-test or Mann-Whitney U test, based on the normality of the data distribution, while categorical variables were analyzed using the chi-square test. Subsequently, we investigated the relationship between women-specific reproductive factors and PhenoAgeAccel using a weighted linear regression analysis. In Model 1, we adjusted the results for age, education, ethnicity, marital status, and poverty-income ratio. Model 2 included additional adjustments for BMI, smoking status, alcohol consumption, chronic kidney disease, stroke, tumors, chronic obstructive pulmonary disease, hypertension, and diabetes. In addition, considering the impact of menopausal status on the outcomes, this study conducted additional analyses on the relationship between age at menarche, contraceptive use, pregnancy history, gynecological surgery, and PhenoAgeAccel among premenopausal and postmenopausal women. To investigate the influence of lifestyle and other factors on the relationship between women-specific reproductive factors and PhenoAgeAccel, this study explored the relationships between women-specific reproductive factors and PhenoAgeAccel within the high and low LE8 score subgroups. Finally, this study calculated the interaction P-values between women-specific reproductive factors and other variables (BMI, smoking, alcohol consumption, ethnicity, marital status, education, hypertension, diabetes). Subgroup analyses were performed for variables with significant interaction P-values. Statistical significance was set at $P<0.05$. All statistical analyses were conducted using R 4.2.0 (R Core Team (2022). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Results

Baseline characteristics

The results indicated that participants with a positive PhenoAgeAccel tended to be older, had higher BMI, and an increased prevalence of comorbidities. Regarding marital status, divorced, unmarried, and widowed individuals were more prevalent in the positive PhenoAgeAccel group than in the negative one. Concerning education level, participants with a positive PhenoAgeAccel typically had lower educational attainment. In terms of lifestyle habits, the PhenoAgeAccel group exhibited a relatively higher proportion of current smokers and had lower LE8 scores. Regarding the impact of women-specific reproductive factors, participants with a positive PhenoAgeAccel had an earlier age at menarche and a higher incidence of gynecologic surgeries, including hysterectomy or bilateral oophorectomy. Among postmenopausal participants, the positive PhenoAgeAccel group experienced an earlier onset of menopause. Among parous women, those with a positive PhenoAgeAccel exhibited a younger age at the first and last live births. Table 1 presents the study results.

The relationship between women-specific reproductive factors and phenoageaccel

In the fully adjusted model, all women-specific reproductive factors, excluding the use of exogenous estrogen and number of live births, exhibited a significant relationship with PhenoAgeAccel. After adjusting for confounding factors, participants with menarche at ≥15 years showed an increase in PhenoAgeAccel by 0.31 (95% CI: 0.10, 0.51; $P=0.003$) compared to those at age 12. Also, participants with a history of pregnancy experienced a decrease in PhenoAgeAccel by 0.54 (95% CI: -0.75, -0.34; $P<0.001$) compared to those who had never been pregnant. Individuals who underwent gynecological surgery showed an increase in PhenoAgeAccel by 0.42 (95% CI: 0.25, 0.58; $P<0.001$). Among postmenopausal participants, compared to participants with menopause at the

Table 1 Baseline characteristics

Characteristics	PhenoAgeAccel		
	< 0	> 0	*P*
N	11,829	2907	
Age (median [IQR])	45.00 [33.00, 62.00]	51.00 [35.00, 67.00]	**< 0.001**
BMI (mean (SD))	27.747(6.443)	33.677 (8.703)	**< 0.001**
Smoking status (%)			**< 0.001**
former	2324 (21.12)	610 (21.14)	
never	7626 (60.97)	1557 (50.88)	
now	1879 (17.91)	740 (27.98)	
Alcohol consumption (%)			**< 0.001**
former	1812 (13.10)	599 (19.33)	
heavy	1841 (17.24)	513 (20.08)	
mild	3484 (31.96)	734 (26.55)	
moderate	2222 (22.21)	434 (16.82)	
never	2470 (15.49)	627 (17.22)	
CKD (%)			**< 0.001**
no	10,187 (87.97)	1827 (66.87)	
yes	1642 (12.03)	1080 (33.13)	
CVD (%)			**< 0.001**
no	10,927 (93.60)	2379 (84.00)	
yes	902 (6.40)	528 (16.00)	
Cancer (%)			**0.019**
no	10,682 (89.13)	2548 (87.36)	
yes	1147 (10.87)	359 (12.64)	
COPD (%)			**< 0.001**
no	11,455 (96.56)	2750 (94.31)	
yes	374 (3.44)	157 (5.69)	
Hypertension (%)			**< 0.001**
no	7338 (66.92)	991 (39.51)	
yes	4491 (33.08)	1916 (60.49)	
DM (%)			**< 0.001**
DM	1283 (7.73)	1064 (31.06)	
IFG	415 (3.42)	144 (5.18)	
IGT	333 (2.49)	54 (2.00)	
no	9798 (86.36)	1645 (61.76)	
Ethnicity (%)			**< 0.001**
Mexican American	2336 (7.22)	453 (6.11)	
Non-Hispanic Black	2068 (9.67)	755 (15.51)	
Non-Hispanic White	5519 (70.96)	1362 (69.20)	
Other Hispanic	1050 (5.73)	201 (4.76)	
Other Race	856 (6.42)	136 (4.42)	
Marital status (%)			**< 0.001**
Divorced	1381 (11.18)	365 (12.47)	
Living with partner	788 (6.82)	184 (6.92)	
Married	5851 (54.52)	1175 (42.96)	
Never married	1898 (15.53)	499 (18.78)	
Separated	411 (2.51)	143 (4.03)	
Widowed	1500 (9.44)	541 (14.85)	
PIR (median [IQR])	2.92 [1.60, 4.80]	2.180 [1.20, 3.78]	**< 0.001**
Education (%)			**< 0.001**
Less than 9th grade	1416 (5.35)	344 (6.81)	
9-11th grade	1581 (10.05)	556 (15.70)	
High School Grad/GED or Equivalent	2737 (24.14)	729 (28.28)	
Some college or AA degree	3540 (32.14)	921 (33.53)	

Table 1 (continued)

Characteristics	PhenoAgeAccel		
	< 0	**> 0**	***P***
College graduate or above	2555 (28.33)	357 (15.68)	
PhenoAgeAccel (median [IQR])	-5.21 [-7.61, -3.04]	2.24 [0.93, 4.19]	**< 0.001**
Age at menarche (mean (SD))	12.72 (1.66)	12.56 (1.74)	**0.004**
Use of contraceptive pills (%)			**0.003**
No	4241 (28.12)	1111 (31.49)	
Unknown	18 (0.12)	5 (0.09)	
Yes	7570 (71.76)	1791 (68.42)	
Gynecologic surgery (%)			**< 0.001**
No	4917 (40.71)	1033 (36.35)	
Unknown	3923 (35.03)	944 (32.42)	
Yes	2989 (24.26)	930 (31.23)	
Pregnancy history (%)			0.714
No	1458 (14.54)	307 (13.62)	
Unknown	375 (3.89)	74 (3.66)	
Yes	9996 (81.58)	2526 (82.73)	
Age at menopause among postmenopausal women (mean (SD))	44.95 (8.72)	43.85 (9.44)	**0.001**
Age at first delivery among parous women (mean (SD))	23.166 (5.226)	21.237 (4.303)	**< 0.001**
No. of live births among parous women (median [IQR])	2.00 [2.00, 3.00]	2.000 [2.00, 3.00]	**0.005**
Age at last birth among parous women (mean (SD))	28.61 (5.828)	27.42 (5.88)	**< 0.001**
LE8 (mean (SD))	70.48 (13.91)	57.25 (14.17)	**< 0.001**

Notes Continuous variables are presented as means (SD) or medians [IQR], and categorical variables are presented as numbers (percentages)

Abbreviations PhenoAgeAccel: phenotypic age acceleration; BMI, body mass index; CKD: completely knock down; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; PIR, poverty to income ratio; LE8, Life's Essential 8; SD: standard deviation; IQR: inter-quartile range

age of 50–54, those with menopause at <45, 45–49, and ≥55 years showed an increase in PhenoAgeAccel (P for trend=0.001). Among parous women, compared to those with first live births at the age of ≥31 years, those with earlier first live births exhibited an increase in PhenoAgeAccel by 0.72 (95% CI: 0.33, 1.10; $P<0.001$). Furthermore, compared to those with last live births at the age of 21–25, those at ≤20 and ≥31 years showed an increase in PhenoAgeAccel by 0.70 (95% CI: 0.31, 1.08; $P<0.001$) and 0.48 (95% CI: 0.22, 0.74; $P<0.001$), respectively. Table 2 presents the results.

The relationship between women-specific reproductive factors and phenoageaccel in different menopausal status

Among both premenopausal and postmenopausal participants, a later age at menarche and gynecological surgery were associated with increased PhenoAgeAccel (Table 3). In premenopausal participants, a later age at menarche (≥15 years) was associated with an increase in PhenoAgeAccel by 0.40 (95% CI: 0.09, 0.71; $P=0.011$), and in postmenopausal participants, it was associated with an increase in PhenoAgeAccel by 0.29 (95% CI: 0.07, 0.47; $P=0.031$). Gynecological surgery was associated with an increase in PhenoAgeAccel by 0.35 (95% CI: 0.16, 0.53; $P<0.001$) in premenopausal participants and by 0.63 (95% CI: 0.41, 0.86; $P<0.001$) in postmenopausal participants. Notably, a history of pregnancy did not show a significant protective effect in premenopausal women, but in postmenopausal women, it was associated with a decrease in PhenoAgeAccel by 0.57 (95% CI: -0.93, -0.22; $P=0.001$). Additionally, contraceptive use was associated with an increase in PhenoAgeAccel in premenopausal women, while it was associated with a decrease in PhenoAgeAccel in postmenopausal women.

The effect of LE8 on the relationship of women-specific reproductive factors with PhenoAgeAccel

Firstly, this study examined the relationship between LE8 and PhenoAgeAccel (Supplementary Table 1). The results showed that as LE8 scores increased, the degree of decrease in PhenoAgeAccel also increased (P for trend<0.001). The highest quartile of LE8 was associated with a reduction in PhenoAgeAccel by 2.09 (95% CI: -2.42, -1.77; $P<0.001$). The LE8 scores were divided into high and low groups based on the median. In the high LE8 score group, a delayed age at menarche was no longer associated with PhenoAgeAccel ($P=0.091$). An age at menopause of <45 years was realated with an increase in PhenoAgeAccel by 0.17 (95% CI: 0.10, 0.89; $P=0.016$); however, a delayed age at menopause (≥55 years) was no longer realated with an increased risk of PhenoAgeAccel. Additionally, the risk of increased PhenoAgeAccel related to early or late age at first and last live births was reduced (Table 4). Interestingly, in the low LE8 score group, the increased risk of PhenoAgeAccel related to the

Table 2 The relationship between women-specific reproductive factors and phenoageaccel

reproductive factors	participants	model 1 (β)	p_value	model 2 (β)	p_value
Age at menarche					
≤ 11	3121	**0.29 (0.09, 0.50)**	**0.005**	-0.08 (-0.26, 0.09)	0.352
12	3778	ref	ref	ref	ref
13	3643	**-0.29 (-0.48, -0.09)**	**0.004**	-0.08 (-0.25, 0.09)	0.340
14	2046	**-0.45 (-0.68, -0.21)**	**< 0.001**	-0.13 (-0.34, 0.07)	0.200
≥ 15	2148	-0.19 (-0.43, 0.04)	0.112	**0.31 (0.10, 0.51)**	**0.003**
P for trend			**< 0.001**		**0.020**
Use of contraceptive pills					
Never	5352	ref	ref	ref	ref
Ever	9361	0.14 (-0.02, 0.31)	0.093	-0.09 (-0.24, 0.06)	0.233
Unknown	23	-2.19 (-4.29, -0.09)	**0.041**	-0.92 (-2.84, 1.01)	0.351
Pregnancy history					
Never	1765	ref	ref	ref	ref
Ever	12,522	**-0.40 (-0.64, -0.17)**	**0.001**	**-0.54 (-0.75, -0.34)**	**< 0.001**
Unknown	449	0.17 (-0.23, 0.57)	0.396	0.24 (-0.11, 0.59)	0.182
Gynecologic surgery					
Never	5950	ref	ref	ref	ref
Ever	3919	**0.62 (0.43, 0.81)**	**< 0.001**	**0.42 (0.25, 0.58)**	**< 0.001**
Unknown	4867	**0.25 (0.09, 0.41)**	**0.003**	**0.45 (0.31, 0.60)**	**< 0.001**
Age at menopause among postmenopausal women					
< 45	3349	**0.85 (0.61, 1.10)**	**< 0.001**	**0.54 (0.33, 0.76)**	**< 0.001**
45–49	1953	**0.56 (0.28, 0.84)**	**< 0.001**	**0.60 (0.36, 0.84)**	**< 0.001**
50–54	2065	ref	ref	ref	ref
≥ 55	1271	**0.65 (0.39, 0.91)**	**0.001**	**0.68 (0.46, 0.91)**	**< 0.001**
P for trend			**< 0.001**		**0.001**
Age at first delivery among parous women					
≤ 20	541	**0.53 (0.26, 0.81)**	**< 0.001**	**0.25 (0.12, 0.49)**	**0.032**
21–25	1599	ref	ref	ref	ref
26–30	1941	**0.22 (0.08, 0.35)**	**0.027**	0.03 (-0.28, 0.33)	0.868
≥ 31	1388	**0.85 (0.41, 1.29)**	**< 0.001**	**0.72 (0.33, 1.10)**	**< 0.001**
P for trend			**< 0.001**		**< 0.001**
Age at last birth among parous women					
≤ 20	541	**0.83 (0.39, 1.27)**	**< 0.001**	**0.70 (0.31, 1.08)**	**< 0.001**
21–25	1599	ref	ref	ref	ref
26–30	1941	-0.13 (-0.42, 0.16)	0.383	-0.10 (-0.35, 0.16)	0.462
≥ 31	1388	**0.62 (0.32, 0.91)**	**< 0.001**	**0.48 (0.22, 0.74)**	**< 0.001**
P for trend			**< 0.001**		**< 0.001**
No. of live births					
1–2	3849	ref	ref	ref	ref
3–4	2852	0.24 (-0.06, 0.54)	0.124	0.03 (-0.18, 0.31)	0.857
≥ 5	956	0.19 (-0.18, 0.55)	0.317	0.07 (-0.28, 0.35)	0.757

Notes model 1: Adjusted for age, ethnicity, marital status, PIR and education; model 2: BMI, smoking status, alcohol consumption, CKD, cancer, COPD, hypertension and DM were additionally adjusted

Abbreviations PhenoAgeAccel, phenotypic age acceleration

aforementioned female reproductive factors remained significant (Supplementary Table 2).

The relationship between women-specific reproductive factors and PhenoAgeAccel across different subgroups

This study first calculated the interaction P-values between various variables and women-specific reproductive factors, with the results shown in Supplementary Table 3. The results indicated that the following variables had statistically significant interaction P-values: BMI with age at menarche, pregnancy history, and age at menopause; ethnicity with age at menopause, age at first live birth, and parity; smoking status with use of contraceptive pills and gynecologic surgery; and hypertension with use of contraceptive pills, pregnancy history, and age at menopause. In the BMI subgroup, the results showed

Table 3 The relationship between women-specific reproductive factors and PhenoAgeAccel in different menopause status

	Premenopause			Postmenopause		
	Participants	**β**	**P_value**	**Participants**	**β**	**P_value**
Age at menarche						
≤11	1612	-0.03 (-0.29, 0.23)	0.815	1692	-0.13 (-0.38, 0.11)	0.284
12	1429	ref	ref	2166	ref	ref
13	1506	-0.10 (-0.34, 0.15)	0.450	2137	-0.03 (-0.25, 0.20)	0.825
14	790	0.04 (-0.27, 0.34)	0.819	1256	-0.26 (-0.53, 0.01)	0.058
≥15	761	**0.40 (0.09, 0.71)**	**0.011**	1387	**0.29 (0.07, 0.47)**	**0.031**
P for trend			**<0.001**			**0.034**
Use of contraceptive pills						
Never	1686	ref	ref	3666	ref	ref
Ever	4410	**0.45 (0.22, 0.69)**	**<0.001**	4951	**-0.31 (-0.51, -0.12)**	**0.002**
Unknown	2	-3.51 (-8.84, 1.83)	0.197	21	-0.78 (-2.84, 1.27)	0.454
Pregnancy history						
Never	1253	ref	ref	512	ref	ref
Ever	4550	-0.16 (-0.42, 0.11)	0.242	7972	**-0.57 (-0.93, -0.22)**	**0.001**
Unknown	295	0.33 (-0.07, 0.73)	0.106	154	0.11 (-0.57, 0.80)	0.742
Gynecologic surgery						
Never	3176	ref	ref	2774	ref	ref
Ever	25	-0.24 (-1.72, 1.24)	0.750	3894	**0.58 (0.39, 0.77)**	**<0.001**
Unknown	2897	**0.35 (0.16, 0.53)**	**<0.001**	1970	**0.63 (0.41, 0.86)**	**<0.001**

Notes Adjusted for age, ethnicity, marital status, PIR, education, BMI, smoking status, alcohol consumption, CKD, cancer, COPD, hypertension and DM were additionally adjusted

Abbreviations PhenoAgeAccel: phenotypic age acceleration

that the relationship between later age at menarche and increased PhenoAgeAccel was primarily present in participants with a BMI of 18.5–25, while the relationships between pregnancy history and reduced PhenoAgeAccel, and early age at menopause and increased PhenoAgeAccel, were primarily present in participants with a BMI of ≥18.5 (Supplementary Table 4). Additionally, the results showed that the association of early or late age at menopause with PhenoAgeAccel was primarily present in Non-Hispanic Whites (Supplementary Table 5). The subgroup analysis results for smoking status and hypertension are shown in Supplementary Tables 6 and 7, respectively.

Discussion

This study investigated the relationship between women-specific reproductive factors and phenotypic aging. Specifically, age at menarche, pregnancy history, gynecological surgery, age at menopause, age at first live birth and age at last live birth were related with the PhenoAgeAccel, indicating the role of reproductive history in shaping the physiological aging trajectory. Notably, High LE8 score may be a potential approach to alleviate the adverse effects of these reproductive factors on phenotypic aging, offering a positive lifestyle intervention.

Interestingly, our findings suggest that pregnancy has a positive effect in the postmenopausal participants. Physiologically, a normal pregnancy is associated with increased inflammation, abnormal lipid metabolism, insulin resistance, and enhanced oxidative stress, which may lead to cellular damage and accelerated aging. However, elevated estrogen levels during pregnancy can directly increase telomerase activity through different pathways, thereby preventing telomere shortening and epigenetic aging [20]. Recent research views biological age as a marker of stress, showing that biological age rapidly increases in response to various forms of stress and reverses upon recovery (Poganik et al., 2023). This indicates that reproductive stressors, such as pregnancy, can significantly influence biological age. We found that although physiological and hormonal changes during pregnancy might increase stress, their long-term effects, especially in postmenopausal women, may alleviate the increase in biological age by enhancing telomerase activity and reducing telomere shortening [21].

Moreover, our study highlights the differential impact of reproductive factors on phenotypic aging between premenopausal and postmenopausal women. The significant association between later age at menarche and increased PhenoAgeAccel in both groups indicates that early-life reproductive events have lasting implications on aging. However, the protective effect of pregnancy observed only in postmenopausal women suggests that reproductive factors might interact with menopausal status to influence aging trajectories. This interaction may be mediated by hormonal shifts that occur during menopause, which can amplify or mitigate the effects of earlier reproductive events on aging [22, 23].

Table 4 The relationship between women-specific reproductive factors and PhenoAgeAccel in high LE8 score

Reproductive factors	participants	Model 1 (β)	P_value	Model 2 (β)	P_value
Age at menarche					
≤ 11	927	-0.03 (-0.39, 0.33)	0.873	-0.24 (-0.58, 0.09)	0.156
12	714	ref	ref	ref	ref
13	978	**-0.51 (-0.83, -0.18)**	**0.002**	**-0.36 (-0.66, -0.05)**	**0.021**
14	565	**-0.72 (-1.10, -0.34)**	**< 0.001**	**-0.45 (-0.81, -0.1)**	**0.013**
≥ 15	531	0.03 (-0.37, 0.42)	0.900	-0.02 (-0.21, 0.36)	0.091
P for trend			0.062		0.108
Use of contraceptive pills					
Never	1159	ref	ref	ref	ref
Ever	2553	0.20 (-0.10, 0.49)	0.189	0.06 (-0.22, 0.34)	0.685
Unknown	3	-4.35 (-9.91, 1.20)	0.125	-3.36 (-8.54, 1.81)	0.202
Pregnancy history					
Never	866	ref	ref	ref	ref
Ever	2846	**-0.52 (-0.86, -0.18)**	**0.002**	**-0.53 (-0.84, -0.21)**	**0.001**
Unknown	3	-0.12 (-4.79, 4.55)	0.960	0.33 (-4.01, 4.67)	0.882
Gynecologic surgery					
Never	2566	ref	ref	ref	ref
Ever	657	**0.84 (0.49, 1.20)**	**< 0.001**	**0.66 (0.32, 0.99)**	**< 0.001**
Unknown	492	**0.45 (0.11, 0.79)**	**0.009**	**0.62 (0.30, 0.94)**	**< 0.001**
Age at menopause among postmenopausal women					
< 45	392	**0.36 (0.13, 0.97)**	**< 0.001**	**0.17 (0.10, 0.89)**	**0.016**
45–49	468	**0.21 (0.10, 0.86)**	**0.007**	0.06 (-0.29, 0.77)	0.086
50–54	589	ref	ref	ref	ref
≥ 55	234	0.04 (-0.56, 0.64)	0.895	-0.04 (-0.59, 0.50)	0.874
P for trend			**< 0.001**		**0.004**
Age at first delivery among parous women					
≤ 20	687	**0.63 (0.19, 1.08)**	**0.005**	**0.42 (0.00,0.83)**	**0.048**
21–25	738	ref	ref	ref	ref
26–30	335	-0.03 (-0.50, 0.44)	0.910	0.15 (-0.29, 0.59)	0.500
≥ 31	185	**0.24 (0.60, 0.57)**	**0.026**	**0.16 (0.11, 0.45)**	**0.046**
P for trend			0.223		0.236
Age at last birth among parous women					
≤ 20	545	0.02 (-0.72, 0.75)	0.959	-0.05 (-0.73, 0.63)	0.889
21–25	158	ref	ref	ref	ref
26–30	687	-0.03 (-0.46, 0.40)	0.884	0.06 (-0.34, 0.46)	0.772
≥ 31	809	**-0.25 (-0.98, -0.12)**	**0.013**	-0.34 (-0.74, 0.07)	0.102
P for trend			**0.011**		0.111
No. of live births					
1–2	1580	ref	ref	ref	ref
3–4	251	0.08 (-0.49, 0.66)	0.783	0.12 (-0.42, 0.66)	0.657
≥ 5	193	-0.38 (-1.08, 0.32)	0.289	-0.36 (-1.02, 0.30)	0.288

Notes model 1: Adjusted for age, ethnicity, marital status, PIR and education; model 2: BMI, smoking status, alcohol consumption, CKD, cancer, COPD, hypertension and DM were additionally adjusted

Abbreviations PhenoAgeAccel, phenotypic age acceleration; LE8, Life's Essential 8

Our study also highlights the potential modifying effect of lifestyle factors on the relationship between reproductive history and phenotypic aging. The LE8 score encompasses four health behaviors (diet, physical activity, nicotine exposure, and sleep health) and four health factors (body mass index, lipid levels, blood glucose, and blood pressure), serving as a comprehensive measure of cardiovascular health and overall well-being [24, 25]. A balanced diet, measured by the Healthy Eating Index-2015, plays a crucial role in maintaining metabolic health and preventing age-related diseases [25, 26]. Diets rich in fruits, vegetables, whole grains, and lean proteins provide essential nutrients and antioxidants that help reduce oxidative stress and inflammation, key contributors to cellular aging. Regular physical activity enhances cardiovascular health, improves metabolic function, and

promotes muscle and bone strength, all vital for healthy aging [27]. Optimizing lipid levels and blood glucose control can reduce the risk of metabolic syndrome and its sequelae, further emphasizing the role of cardiovascular health in aging [28]. Blood pressure management is crucial for preventing hypertension-related damage to the cardiovascular system, a major contributor to age-related morbidity and mortality [25]. In summary, promoting healthy behaviors and managing key health factors are essential for reducing the burden of phenotypic aging and improving the overall quality of life for women.

To the best of our knowledge, there is limited literature on the relationship between women-specific reproductive factors and phenotypic aging. Previous studies have primarily focused on investigating the relationship between women-specific reproductive factors and telomere length [11]. Fan et al. examined women aged 40–69 and found relationships between early menarche, early menopause, shorter reproductive lifespan, early age at first childbirth, multiple pregnancies, use of oral contraceptives (OC) and hormone replacement therapy (HRT), and shorter leukocyte telomere length [6, 11]. Another study investigated the relationship between age at menarche and TL and reported a relationship between early menarche and a shorter TL [6]. A multicenter longitudinal cohort study of 486 women reported that for every 1 kb decrease in TL, the average age at menopause advanced by 10.2 months [29]. In a study of 799 women using the NHANES database, a positive relationship was observed between menopausal age and LTL in Caucasian women; however, a negative relationship was observed in Mexican American women [10]. The negative relationship among Mexican-American women may be attributed to selection bias and relatively small sample size [10]. Women with earlier menopause and shorter reproductive lifespans often have fewer reproductive cycles, resulting in lower cumulative exposure to endogenous estrogen and weakened maintenance of telomerase activity [30]. Ross et al. conducted a follow-up study on pregnant women during pregnancy and at 1 year postpartum, measuring epigenetic age biomarkers such as PEAA, GrimAge, DNAm, PAI-1, and immune cell group epigenetic age indices. They found that the epigenetic clocks became younger during the follow-up period [31].

This study has several strengths. Firstly, we utilized the NHANES database to ensure representativeness and diversity. Second, the study incorporated potential confounding factors, including chronological age, BMI, and marital status, which effectively reduced potential interference with the study results. However, this study has some limitations. Firstly, the use of retrospective survey data may introduce recall bias, affecting the accuracy of the reproductive history data. Additionally, data imputation for confounding factors may lead to differences in the actual values, affecting our accurate understanding of these confounding factors. Secondly, despite adjusting for various confounding factors, eliminating the potential impact of unmeasured factors on the study results remains challenging. Genetic factors and environmental exposure may influence the relationship between reproductive factors and phenotypic aging; however, these factors were not fully considered. Finally, this study was based on the U.S. population, and further validation is needed to generalize the results to other regions. Regional differences could affect the universality of the conclusions of this study. In conclusion, although this study provides an understanding of the relationship between women-specific reproductive factors and phenotypic aging, careful interpretation of the results is necessary, especially considering the aforementioned limitations.

Conclusion

In conclusion, our study provides novel insights into the relationships between women-specific reproductive factors and phenotypic aging. The findings highlight the significant influence of reproductive history on aging and the potential for healthy lifestyle habits, as measured by LE8, to mitigate adverse effects.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-00999-1.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Xin Zheng, Yue Chen, and Shi-Qi Lin were responsible for analyzing. Xin Zheng, Chen-Ning Liu, Tong Liu, Chen-An Liu and Zi-Wen Wang wrote the main manuscript text. Xiao-Yue Liu, Jin-Yu Shi, Zhao-Ting Bu, Hai-Lun Xie were responsible for review and editing. He-Yang Zhang, Hong Zhao, Shu-Qun Li, Xiang-Rui Li were responsible for investigation and methodology. Li-Deng and Han-Ping Shi were responsible for supervision. All authors have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Data availability

The original data can be obtained from NHANES (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethical approval
The protocol was approved by the NCHS Research Ethics Review Board (Protocol #98–12, Protocol #2005–06, and Protocol #2011–17). All participants provide informed consent.

Consent for publication
All authors have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Competing interests
The authors declare no competing interests.

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