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Association between lifetime endogenous estrogen exposure and body composition metrics in postmenopausal women: findings from the Tehran Lipid and Glucose Study

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Abstract

Background The role of endogenous estrogen exposure (EEE) in shaping body composition and its implications for cardiometabolic health remain understudied despite its potential significance. This cross-sectional study aimed to investigate the association between EEE and body composition indices among postmenopausal women.

Methods Data were obtained from the Tehran Lipid and Glucose Study (TLGS), including 960 women aged over 40 years. EEE was calculated based on reproductive events, and participants were categorized into tertiles. Anthropometric measurements and body composition were assessed using standardized protocols. Linear regression models were employed to evaluate associations, adjusting for potential confounders.

Results It was revealed significant differences in body composition indices across EEE tertiles, with increasing EEE associated with decreased fat mass, skeletal muscle mass, and fat-free mass. Moreover, women with higher EEE exhibited lower anthropometric and body composition measurements compared to those with lower EEE, even after adjusting for confounding factors. Specifically, for each year of increasing EEE, fat mass decreased by 0.12 kg, skeletal muscle mass by 0.04 kg, fat-free mass by 0.07 kg, and fat mass ratio decreased by 0.003. Comparing tertiles, women with the highest EEE demonstrated significantly lower anthropometric and body composition measurements compared to those with the lowest EEE.

Conclusion These findings suggest a link between EEE and favorable changes in body composition, highlighting the importance of considering reproductive history in health assessment.

Keywords Endogenous estrogen exposure, Body composition, Postmenopausal women, Fat mass, Skeletal muscle mass

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Introduction

The body composition has been proposed as an indicator of cardiometabolic health status in numerous studies [1, 2]. Body composition parameters reflect the difference in fat mass, muscle mass and lean mass, so compared to anthropometric measures, they provide more precise predictors of individuals' health status [2]. In addition to known factors affecting body fat levels such as gender, age, genetics and lifestyle, there is increasing evidence suggesting that estradiol is an important regulator of body composition and bioenergetics. The widespread distribution of estrogen receptors (ERs), their involvement in genomic and non-genomic signaling pathways suggest that the loss of estradiol in menopause likely has prominent effects beyond reproduction. The expression of ERs in brain, adipose tissue, and skeletal muscle highlights the potential role of estradiol in regulating body weight and other metabolic processes [3]. In addition, the presence of mitochondrial ERs suggests the role of estradiol in the regulation of cellular bioenergetics.

There is consistent evidence in basic and preclinical studies that disruption of estradiol signaling through genetic manipulations (such as estrogen receptor deletion) or surgical interventions (such as ovariectomy) leads to accelerated fat accumulation, accompanied by disproportionate increase in abdominal fat [4, 5]. However, the clinical evidence for the regulation of body composition and biological energy by estradiol is contradictory, so that there is evidence both for and against menopause as a mediator of changes in body composition [6]. Moreover, controlled trials evaluating changes in body composition in response to hormone therapy in postmenopausal women or ovarian suppression using GnRH agonists in premenopausal women do not always reveal the same role for estrogens [7, 8]. Furthermore, in studies conducted regarding the relationship between reproductive history and anthropometric measurements as well as body composition, the findings have shown inconsistency [9–11].

Women's reproductive period—menarche to menopause—can be a proxy for premenopausal exposure to endogenous estrogen (estradiol) throughout life, although in addition to the age at menarche and menopause, other reproductive events include the number and duration of pregnancies, breastfeeding duration, and oral contraceptives use, determines the duration and level of exposure to endogenous estrogen [12]. The index of endogenous estrogen exposure (EEE) was first proposed in 2002 in a study by Kleijn et al. [12]. To quantify the premenopausal endogenous estrogen exposure -considering the counteractive effects of progesterone dominant periods, they combined data related to reproductive events including age of menarche, age of menopause, number and duration of pregnancy, duration of breastfeeding, and use oral contraceptives. Later studies have shown that EEE are associated with various aspects of women's health, including the risk of cardiovascular diseases, kidney failure, fractures, and Alzheimer's disease [13–16]. To date, no studies have specifically examined the relationship between EEE and body composition. Research on reproductive factors and their impact on physical health is limited and inconsistent, with most studies focusing on anthropometric measures rather than body composition indices. Therefore, this study aims to investigate the association between EEE and body composition, considering EEE as a comprehensive measure of reproductive events in postmenopausal women, and its implications for cardiometabolic health.

Materials and methods

This study is a cross-sectional analysis conducted as part of the Tehran Lipid and Glucose Study (TLGS), which began in 1998 to assess non-communicable disease risk factors in 15,000 residents aged ≥ 3 years in District 13 of Tehran. Individuals are followed up at three-year interval. So far, 7 phases of TLGS have been done. The data of the present study were extracted from the 7th phase of TLGS (2018–2023). The TLGS details have been previously published on its design, reasoning, data collection methods, and sampling approach [17].

Subjects

The study analyzed data from 3,953 women who participated in the 7th phase of the Tehran Lipid and Glucose Study (TLGS) and had available body composition data. Among these, 2,411 women were over 40 years of age. To clarify, women included in the study were indeed selected based on their age, specifically those over 40 years old. The focus on this age group was intentional to align with the study's aim of investigating endogenous estrogen exposure in relation to body composition in postmenopausal women. To focus specifically on postmenopausal women, only those with documented reproductive event information were considered, resulting in a sample of 1,363 postmenopausal women. It was necessary for the participants to be postmenopausal, as this group was specifically chosen to examine the effects of endogenous estrogen exposure following the cessation of menstrual cycles.

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Exclusion criteria were strictly applied, eliminating individuals with the following conditions: past history of irregular menstruation ($n = 89$), surgical menopause

($n=78$), hormone replacement therapy ($n=62$), corticosteroid use ($n=24$), diuretic use ($n=114$), malignancy ($n=20$), chronic lung disease ($n=1$), heart failure ($n=1$), kidney failure ($n=1$), and a history of bariatric surgery ($n=2$). After applying these criteria, the final study sample consisted of 960 postmenopausal women aged over 40 years (see Fig. 1).

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Research Institute for Endocrine Sciences (RIES) at the

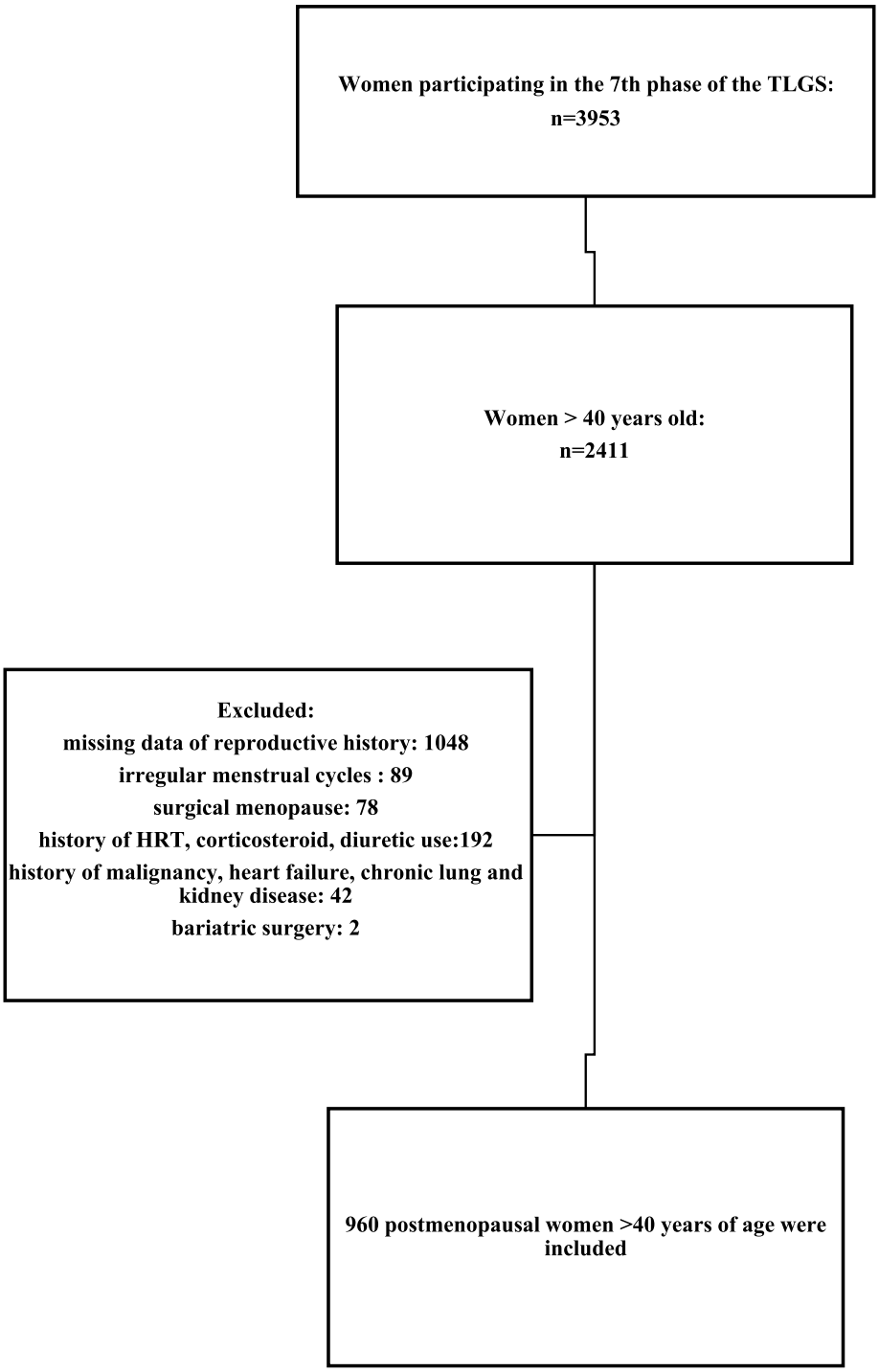

Fig. 1 Flowchart of the study population

Shahid Beheshti University of Medical Sciences (code: IR.SBMU.ENDOCRINE.REC.1402.134). All participants provided written informed consent prior to participating in the study.

Measurements

Basic data was collected by trained interviewers through face-to-face interviews using demographic information questionnaires, disease records questionnaire, Food Frequency Questionnaire (FFQ) [17], and fertility history questionnaires. During the anthropometric measurements, the participants were attired in light clothing and without shoes. Weight and height were assessed using a digital electronic weighing scale (Seca 707; range 0.1–150 kg; Seca, Hanover, MD) with a precision of up to 100 g and a tape meter stadiometer, respectively. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters).

Waist circumference (WC) was measured in centimeters at the level of the umbilicus using an inflexible tape measure (TABIB TECH, Iran).

Body composition was assessed using a portable multi-frequency bioelectrical impedance analyzer (BIA) device (Model: InBody 570, InBody Co., Ltd., Seoul, KOREA) following a standardized protocol [18]. Participants were instructed to fast for at least 8 h before measurement and to refrain from vigorous physical activity for 24 h prior. During the measurement, participants stood barefoot on the BIA platform, with electrodes placed on their hands and feet. The device operates by passing a low-level electrical current through the body and measuring the resistance encountered by the current as it travels through different tissues. This bioelectrical impedance reflects the resistance and reactance of body tissues and is used to estimate total body water, fat mass, and fat-free mass.

Skeletal muscle mass (SMM) was calculated using proprietary equations provided by the manufacturer, which take into account impedance values along with participant-specific variables, including age, sex, height, and weight. The standard equation used for estimating SMM is based on the following formula:

$$\mathrm{SSM} = \alpha + \mathrm{b} \times \mathrm{height} + \mathrm{c} \times \mathrm{weight} + \mathrm{d} \times \mathrm{resistance}$$

where a, b, c, and d are constants determined from population studies.

The fat mass ratio was calculated by determining the total fat mass, which is derived by subtracting fat-free mass from total body weight. The fat mass ratio is then computed as follows:

$$\text{Fat Mass Ratio} = \left(\frac{\text{Total Fat Mass}}{\text{Total Body Weight}}\right) \times 100$$

Here, the total fat mass represents the amount of fat tissue in the body, while total body weight encompasses all body components, including fat, muscle, bone, and water.

To ensure accuracy, the precision and reproducibility of these measurements within the TLGS were evaluated through intraclass correlation coefficient (ICC) analysis [18]. The ICC values for percent body fat (PBF) and fat-free mass (FFM) were found to be 0.996 (95% CI: 0.991–0.998) and 0.998 (95% CI: 0.997), respectively, with an average difference of 0.04 between two measurements. These high ICC values indicate strong reliability and reproducibility of the BIA results, affirming the robustness of the body composition assessments in this study.

Endogenous estrogen exposure

Endogenous estrogen exposure duration was initially defined as the time interval between age at menarche and age at menopause. Cumulative duration of progesterone dominant (luteal) phases of menstrual cycles (2 weeks for each menstrual cycle), pregnancy (40 weeks for each birth or 20 weeks for each miscarriage), breastfeeding (ie, number of months per child) and use of contraceptives were subtracted from the primary EEE variable to include only E2-dominant (follicular) phases of the menstrual cycle.

Data analysis

The statistical analysis involved descriptive statistics to summarize participant characteristics, including mean and standard deviation for continuous variables and frequencies for categorical variables. One-way ANOVA and the Kruskal–Wallis test were used to compare tertiles of EEE for normally and skewed distributed continuous variables, respectively, with post hoc tests for significant differences. The Pearson correlation coefficient was calculated to evaluate the correlation between the body composition indices and EEE duration. Linear regression models, including an unadjusted model and two adjusted models for age and confounding factors, explored the association between EEE duration and body composition. Statistical significance was set at $P < 0.05$ for all analyses. Data analysis was performed using SPSS software (version 22.0, released in 2013, IBM Corp., Armonk, NY, USA).

Results

The mean (SD) age of the participants was 63.3 (7.8) years. The mean (SD) duration of EEE was 14.4 (3.1) years in T1, 25.3 (3.07) years in T2, and 35.17 (4.5) years

Table 1 Baseline characteristics and reproductive history in different tertiles of endogenous estrogen exposure.[**]

Variables	T1 *N* = 320	T2 *N* = 322	T3 *N* = 318	Total *N* = 960	*P* value[¥]
EEE, years	14.4 (3.1)[ǂ]	25.3 (3.07)•	35.1 (5.4)*	24.9 (9.3)	< 0.001
Age, years	65.6 (8.2)[ǂ]	60.8 (6.7) •	64.6 (7.7)	63.7 (7.8)	< 0.001
Educational level (≥ 12 years), n (%)	21 (6.6%)	27 (8.6%)•	52 (15.8%)*	100(10.1%)	< 0.001
Calorie intake, kcal	1820 (649)	1903 (608)	1849 (562)	1858 (607)	0.312
Physical activity (Low), n (%)	163 (50%)	191(59.7%)	177(57.1%)	531(56%)	0.183
Smoking (yes), n (%)	7 (2.2%)	10 (3.1)	9 (2.6%)	26 (2.6%)	0.788
Menarcheal age, years	12.8 (1.6)	12.9 (1.5) •	12.6 (1.5)	12.8 (1.5)	0.049
Menopausal age, years	48.1 (6.1)	47.9 (4.3) •	51.3 (3.8)*	49.1 (5.1)	< 0.001
Duration of pregnancies, weeks	162 (67) [ǂ]	141 (58)	144 (63)*	149 (63)	< 0.001
Duration of breastfeeding, weeks	26 (16–54)	32 (16–58) •	16 (4–24)*	20 (12–48)	< 0.001
Duration of hormonal contraceptive use, weeks	0 (0–24)	0 (0–12) •	0 (0–1)*	0 (0–6)	< 0.001
Duration after menopause, years	17 (11–22) [ǂ]	12 (7–17)	11 (7–18)*	13 (8–20)	< 0.001

[**] The continous variables with normal distribution are reported as mean (SD), continous variables with non-normal distribution are reported as median (IQR) and qualitative variables are reported as number (percentage)

[¥] *P* value is reported based on one-way ANOVA for continuous variables with normal distribution, Kruskal–Wallis for continuous variables with non-normal distribution, and Chi-square for categorical variables

[ǂ] Indicates a significant difference between T1 and T2, based on Bonferroni adjustment

[*] Indicates a significant difference between T1 and T3, based on Bonferroni adjustment

• Indicates a significant difference between T2 and T3, based on Bonferroni adjustment

Abbreviations: EEE Endogenous estrogen exposure, *N* Number

in T3. There was a statistically significant difference between the age groups of T2 compared to T1 and T3 ($p < 0.001$). Education level was significantly higher in T3 compared to other tertiles ($P < 0.001$). No significant differences were observed in calorie intake, physical activity, and smoking across groups. The mean (SD) age of menarche and menopause were 12.8 (1.5) and 49.1 (5.1), respectively. The mean (SD) gestational weeks was 149 (63) weeks, with a median (IQR) of 20 (12–48) weeks for breastfeeding duration. Participants in different groups had significant differences in terms of fertility events, also use of hormonal contraceptive in the T3 was notably shorter than in T1 and T2 ($p < 0.001$). Time after menopause was significantly longer in T3 compared to T2 and T3 ($p < 0.001$) (Table 1).

The mean (SD) weight and BMI in the study population were 71.3 (12) (kg) and 29.7 (4.8) (kg/m^2), respectively. In general, the mean (SD) of FM, SMM, FFM and FMR were 31.5 (9.05) kg, 21.6 (2.8) kg, 40.2 (4.8) kg and 1.45 (0.36). There were significant differences in all anthropometric and body composition indices among the different tertiles of endogenous estrogen exposure. According to the results of the ANOVA test and post hoc test, there was a significant difference between T1 and T3 in all anthropometric and body composition indices, and it was always lower in T3 (Table 2) (Figs. 2 and 3).

There was a significant negative correlation between anthropometric and body composition indices (except

Table 2 Anthropometric and body composition indices in different tertiles of endogenous estrogen exposure.[**]

Variables	T1	T2	T3	Total	*P*value
Weight, kg	73.1 (11.7)	72.1 (11.6)•	68.7 (12)*	71.3 (12)	< 0.001
BMI, kg/m^2	30.5 (4.6) [ǂ]	29.5 (4.7)	29.04 (5)*	29.7 (4.8)	< 0.001
WC,cm	101.3 (10.2) [ǂ]	99.06 (9.5)	97.9 (11.06)*	99.4 (10.4)	< 0.001
FM, kg	32.9 (9)	31.4 (8.9)	30.09 (9.4)*	31.5 (9.05)	0.001
SMM, kg	21.7 (2.9)	22.1 (2.8)•	20.9 (2.7)*	21.6 (2.8)	< 0.001
FFM,kg	40.6 (4.9)	41 (4.8)•	39.02 (4.5)*	40.2 (4.8)	< 0.001
FMR	1.51 (0.36) [ǂ]	1.41 (0.35)	1.43 (0.37)*	1.45 (0.36)	0.002

[**] The continous variables with normal distribution are reported as mean (SD) and continous variables with non-normal distribution are reported as median (IQR)

[¥] *P* value is reported based on one-way ANOVA for continuous variables with normal distribution, and Kruskal–Wallis for continuous variables with non-normal distribution

[ǂ] Indicates a significant difference between T1 and T2, based on Bonferroni adjustment

[*] Indicates a significant difference between T1 and T3, based on Bonferroni adjustment

[·] Indicates a significant difference between T2 and T3, based on Bonferroni adjustment

Abbreviations: *T* Tertile, *BMI* Body-mass index, *WC* Waist circumference, *FM* Fat mass, *SMM* Skeletal muscle mass, *FFM* Fat free mass, *FMR* Fat mass ratio

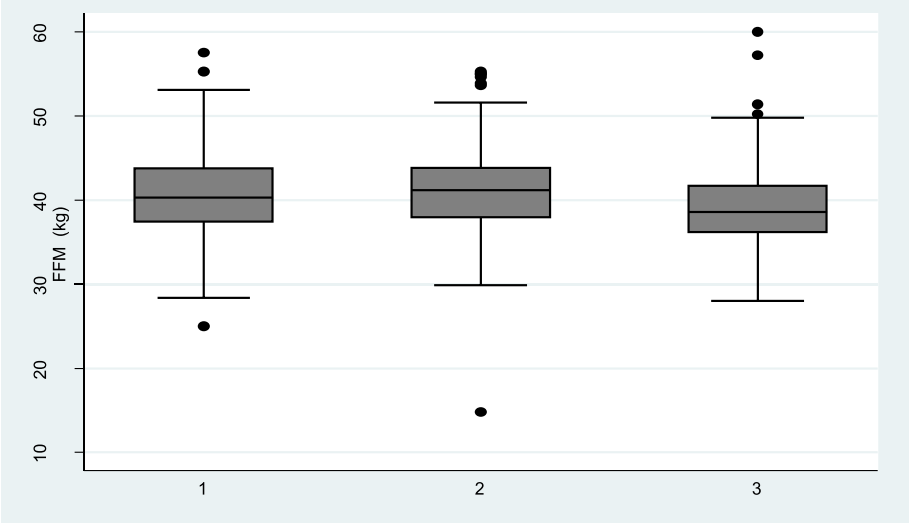

Fig. 2 Box plot of Fat Mass (kg) in different tertiles of endogenous estrogen exposure (EEE)

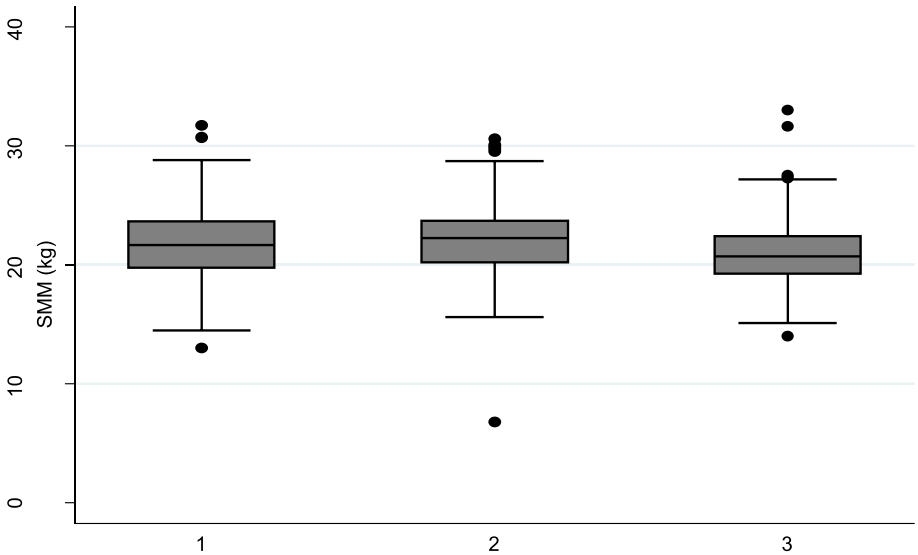

Fig. 3 Box plot of Skeletal Muscle Mass (kg) in different tertiles of endogenous estrogen exposure (EEE)

for the fat mass-to-muscle mass ratio) and endogenous estrogen exposure duration (Table 3).

According to the results of the linear regression model in model 1 (unadjusted model) and in model 2 (adjusted for age), there were a significant relationship between all anthropometric and body composition indices (except for FMR) and duration of EEE, and the increase in EEE was associated with a decrease in anthropometric indices and body composition (except for FMR). After adjusting for all possible confounding factors (model 3) including age, education, calorie intake, physical activity, smoking, and duration after menopause, a significant relationship was observed

Table 3 Correlation between endogenous estrogen exposure duration with anthropometric and body composition indices

Variable	R	*P*-value[¥]
Weight, kg	-0.15	< 0.001
BMI, kg/m^2	-0.01	< 0.01
WC,cm	-0.01	< 0.01
FM, kg	-0.11	< 0.01
SMM, kg	-0.15	< 0.001
FFM,kg	-0.15	< 0.001
FMR	-0.05	0.13

[¥] P value is reported based on Pearson correlation

Abbreviations: *BMI* Body-mass index, *WC* Waist circumference, *FM* Fat mass, *SMM* Skeletal muscle mass, *FFM* Fat free mass, *FMR* Fat mass ratio

Table 4 Association between endogenous estrogen exposure duration with anthropometric and body composition indices

Variables	Model 1 Coefficient (95% CI)	Model 2 Coefficient (95% CI)	Model 3 Coefficient (95% CI)
Weight, kg	-0.19 (-.27 to -0.11)*	-0.17 (-0.25 to -0.10)*	-0.19 (-0.28 to -0.09)*
BMI, kg/m^2	-0.05 (-0.09 to -0.02)●	-0.05 (-0.09 to -0.02)●	-0.07 (-0.11 to -0.03)●
WC,cm	-0.11 (-0.19 to -0.05)●	-0.12 (-0.19 to -0.05)●	-0.14 (-0.23 to -0.05)●
FM, kg	-0.11 (-0.17 to -0.05)●	-0.10 (-0.16 to -0.04)●	-0.12 (-0.20 to -0.05)●
SMM, kg	-0.05 (-0.06 to -0.03)*	-0.04 (-0.05 to -0.02)*	-0.04 (-0.06 to -0.02)*
FFM,kg	-0.02 (-0.11 to -0.05)*	-0.07 (-0.10 to -0.04)*	-0.07 (-0.10 to -0.03)*
FMR	-0.002 (-.004 to 0.001)	-0.002 (-0.005 to 0.000)	-0.003 (-0.006 to 0.000)●

Model 1: Unadjusted

Model 2: Adjusted for age

Model 3: Adjusted for age, education, caloric intake, physical activity, smoking, and duration after menopause

Abbreviations: *BMI* Body mass index, *WC* Waist circumference, *FM* Fat mass, *SMM* Skeletal muscle mass, *FFM* Fat free mass, *FMR* Fat mass ratio, *CI* Confidence interval

* *P* value < 0.001. • *P* value < 0.05

Table 5 Association between different tertiles of endogenous estrogen exposure duration with anthropometric and body composition indices

Variables	Model 1 Coefficient (95% CI)			Model 2 Coefficient (95% CI)			Model 3 Coefficient (95% CI)		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Weight, kg	**ref**	-0.95 (-2.79 to 0.89)	-4.36 (-6.21 to -2.51) *	ref	-2.10 (-3.99 to -0.23) •	-4.53 (-6.39 to -2.71)*	ref	-1.95 (-4.14 to .22)	-5.04 (-7.29 to -2.88)*
BMI, kg/m^2	**ref**	-1.00 (-1.74 to -0.25)•	-1.49 (-2.24 to -0.74) *	ref	-1.07 (-1.84 to -0.31) •	-1.50 (-2.24 to -0.76) *	ref	-1.08 (-1.97 to -0 .18) •	-1.90 (-2.85 to -0.97)*
WC, cm	**ref**	-2.25 (-3.84 to -0.65) •	-3.44 (-5.04 to -1.83) *	ref	-1.78 (-3.49 to -0.14) •	-3.37 (-4.97 to -1.76) *	ref	-1.93 (-3.31 to 0.01)	-4.15 (-6.11 to -2.15)*
FM, kg	**ref**	-1.46 (-2.85 to -0.07) •	-2.76(-4.15 to -1.37) *	ref	-1.84 (-3.27 to -0.41) •	-2.85 (-4.24 to -1.45) *	ref	-1.65 (-3.29 to -0 .02) •	-3.45 (-5.17 to -1.76)*
SMM, kg	**ref**	0.36 (-0.07 to 0.79)	-0.89 (-1.32 to -0.45) *	ref	-0.18 (-0.61 to .24)	-0.99 (-1.40 to -0.57) *	ref	-0.25 (-0.78 to 0.22)	-1.00 (-1.50 to -0.51) *
FFM, kg	**ref**	0.49 (-0.30 to 1.18)	-1.60 (-2.34 to -0.86) *	ref	-0.35 (-1.07 to 0.38)	-1.74 (-2.40 to -1.03) *	ref	-0.40 (-1.26 to 0.37)	-1.76 (-2.62 to -0.91)*
FMR	**ref**	-0.09 (-0.15 to -0.04) •	-0.08 (-0.14 to -0.02) •	ref	-0.08 (-0.13 to -0.02) •	-0.07 (-0.13 to-0.01) •	ref	-0.06 (-0.13 to 0.00)	-0.11 (-0.17 to -0.03) •

Model 1: Unadjusted

Model 2: Adjusted for age

Model 3: Adjusted for age, education, caloric intake, physical activity, smoking, and duration after menopause

* *P* value < 0.001

• *P* value < 0.05

Abbreviations: *BMI* Body mass index, *WC* Waist circumference, *FM* Fat mass, *SMM* Skeletal muscle mass, *FFM* Fat free mass, *FMR* Fat mass ratio, *CI* Confidence interval

in all indices, and as shown in model 3, for each year of increasing exposure to endogenous estrogen, FM decreases by 0.12 kg, SMM by 0.04 kg, FFM by 0.07 kg, and FMR decreased by 0.003, indicating a continued reduction in fat mass without evidence of muscle mass preservation with increasing EEE (Table 4).

To compare the relationship between EEE and anthropometric and body composition indices between different tertiles, T1, which had the lowest EEE, was used as the reference group. Accordingly, all anthropometric and body composition indices in women in T3, who had the highest EEE (35.1 ± 5.4 years), compared to T1 (14.4 ± 3.1) year) was significantly less. After adjusting for confounding factors, it remained significant (Table 5).

Discussion

The findings of this cross-sectional study in 960 postmenopausal women revealed that- following adjustments for confounding factors- for each year of increasing exposure to endogenous estrogen, fat mass decrease by 0.12 kg, skeletal muscle mass by 0.04 kg, fat free mass by 0.07 kg and the ratio of fat mass to muscle mass by 0.003. Moreover, the research showed that women in T3 with the highest EEE (35.1 ± 5.4 years) demonstrated a decrease in all anthropometric and body composition measurements, such as weight, waist circumference, BMI, FM, SMM, FMM, and FMR, compared to those in T1 with the lowest exposure (14.4 ± 3.1 years).

Several previous studies have shown conflicting results regarding the relationship between the age of menarche and menopause, number and duration of pregnancy and breastfeeding on anthropometric indices and body composition. What stands out in these studies is that the collective influence of all fertility events has not been examined as a single variable. Instead, each reproductive event has been individually assessed in relation to anthropometric indicators and body composition. This approach may partially explain the contradictory findings in previous research. However, this study utilizes the variable of EEE, encompassing all reproductive events [9–11, 19–21].

According to prior research, there is compelling evidence indicating that estrogen plays a significant role in the regulation of adipogenesis. Animal studies have shown that complete removal of the Estrogen Receptor α (Erα) or the aromatase enzyme—essential in estrogen production—via genetic manipulation results in a substantial increase (50–180%) in the number of fat cells [22, 23]. In clinical observations, mutations in CYP19A1 (gene encoding aromatase enzyme) and ESR1 (gene encoding ERα) have been linked to increased fat tissue [24, 25]. Estrogen mainly inhibits the recruitment of Peroxisome Proliferator-Activated Receptor gamma (PPARɣ) activators including Steroid Receptor Coactivator-1 (SRC-1) and CREB-Binding Protein (CBP), thereby impacting adipocyte proliferation [26]. It may also activate Cyclin-Dependent Kinase Inhibitors (CDKIs) p21 and p27 to influence fat mass. Additionally, estrogen impacts appetite, food intake, and fat distribution [27, 28].

Postmenopausal bleeding (PMB) is a significant clinical symptom that may be associated with various uterine pathologies. Nguyen and Nguyen (2022) assessed the clinical features of intrauterine pathologies in women presenting with peri- and postmenopausal bleeding and highlighted that common symptoms include abnormal vaginal bleeding, pelvic pain, and changes in menstrual patterns. Their study suggested that abnormal bleeding in postmenopausal women is often linked to conditions such as endometrial hyperplasia, fibroids, and, in some cases, endometrial carcinoma [29]. These symptoms should be considered in the management and diagnostic evaluation of postmenopausal women.

In a cohort study with a 10-year follow-up of the UK Biobank in 2021, it has been shown that FM has a strong linear relationship with cardiovascular disease (CVD) in men and women. Specifically, for every standard deviation increase in fat mass in women (8.29 kg), there is 25% higher risk of CVD (HR = 1.25, 95% CI: 1.23–1.27). Similarly, for each standard deviation increase in FM in men (6.75 kg), there is a 20% higher risk of CVD (risk ratio = 1.20, 95% CI: 1.19–1.22) [30]. According to the study by Farahmand et al. in the frame of the TLGS cohort, it was discovered that a shorter EEE is linked to increased CVD incidence (HR = 2.2, 95% CI: 2.6–6.1) [15]. In our study, increasing the duration of EEE is associated with a decrease in FM. Considering the findings of these studies together, it can be suggested that the direction of our study is consistent with the Biobank study [30] and Farahmand's study [15], and one possible explanation for the impact of EEE on CVD could be its influence on fat mass levels.

Estrogen's impact on skeletal muscle mass remains incompletely understood, with conflicting study findings [31]. In vitro research indicates estrogen can influence myoblast cell growth and reduce inflammation post muscle injury [32]. In some in vivo studies, estrogen has been associated with an increase in muscle size in female mice and a decrease in inflammation following muscle damage [33, 34]. However, in other studies following ovariectomy in adult female rats, an increase in skeletal muscle mass due to elevated collagen and/or non-protein content has been observed [35, 36]. Moreover, although daily estradiol treatment is generally associated with an increase in muscle weight, some studies have reported variable results, indicating that the response to estradiol may differ among individuals or under specific conditions [36, 37].

In humans, the effects of estrogen on muscle are also poorly understood. For example, while some studies have shown that hormone replacement therapy with estrogen may reduce or even reverse the age-related loss of lean muscle mass and size in postmenopausal women [38, 39], other studies have not shown an effect of estradiol on muscle mass, size or cross-sectional area following hormone replacement therapy in postmenopausal women [40, 41]. It seems that understanding the effects of estrogen and its mechanisms on skeletal muscle mass compared to fat mass is more complex and more research is needed in this field.

Strengths of this study include its novelty in exploring the association between lifetime EEE and body composition metrics in postmenopausal women, employing a

comprehensive index of EEE encompassing various reproductive events, a large sample size of 960 postmenopausal women, standardized protocols for anthropometric measurements and body composition assessment, and adjustment for potential confounders. However, limitations include the cross-sectional design, which precludes establishing causality or temporal relationships, retrospective data collection methods that may introduce recall bias, the possibility of residual confounding from unmeasured variables or unaccounted lifestyle factors influencing the observed associations, such as complete data on nutrition intake, including macronutrient composition especially protein intake, which could impact body composition outcomes. Additionally, we did not collect data on the types of contraceptives used by the participants, which may limit our understanding of their potential impact on body composition outcomes, as different hormonal combinations and dosages could significantly influence these results. Bioelectrical impedance analysis is not the gold standard for determining body composition, but it has been shown in various studies that it is closely related to DEXA—the gold standard for determining body composition—and since it is cheap and available, its use is practical. To estimate the follicular phase, the same duration was used for all participants, which may be considered as a limitation of the present study.

Conclusion

In conclusion, our study reveals a significant association between lifetime endogenous estrogen exposure (EEE) and body composition metrics in postmenopausal women. Increasing EEE was linked to favorable changes in body composition, particularly a reduction in fat mass. While the results indicated a decrease in both fat mass and fat-free mass (including skeletal muscle mass) with higher EEE, the data did not clearly support a strong preservation of skeletal muscle mass as initially hypothesized. However, the observed reduction in the fat mass-to-muscle mass ratio (FMR) suggests that the overall balance between fat and muscle mass may still be influenced by estrogen exposure.

Through comprehensive analysis of reproductive events and confounding factors, this study provides valuable insights into the role of EEE in shaping body composition, particularly with respect to fat mass. These findings highlight the importance of considering reproductive history in understanding body composition and cardiometabolic health in postmenopausal women. Further research is warranted to explore the mechanisms underlying these associations and their long-term health implications.

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Authors' contributions
E.R., F.H., and F.RT. conceived and designed the study. M.M., E.R., M.N., B.A., and M.F. contributed to the interpretation of the results and wrote the first draft of the manuscript. M.V., F.H., F.A., and F.RT. critically revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available on request from the corresponding author, FH.

Declarations

Ethics approval and consent to participate
This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Research Institute for Endocrine Sciences (RIES) at Shahid Beheshti University of Medical Sciences (code IR.SBMU.ENDOCRINE.REC.1402.134). All participants provided written informed consent.

Consent for publication
All authors have given consent for the paper to be published by the corresponding author.

Competing interests
The authors declare no competing interests.

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