



## Observational Study

# Association between serum estradiol level and appendicular lean mass index in middle-aged postmenopausal women

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## Abstract

### BACKGROUND

Previous studies investigating the association between loss of estrogen at menopause and skeletal muscle mass came to contradictory conclusions.

### AIM

To evaluate the association between serum estradiol level and appendicular lean mass index in middle-aged postmenopausal women using population-based data.

### METHODS

This study included 673 postmenopausal women, aged 40-59 years, from the National Health and Nutrition Examination Survey between 2013 and 2016. Weighted multivariable linear regression models were used to evaluate the association between serum E2 Level and appendicular lean mass index (ALMI). When non-linear associations were found by using weighted generalized additive model and smooth curve fitting, two-piecewise linear regression models were further applied to examine the threshold effects.

### RESULTS

There was a positive association between serum E2 level and ALMI. Compared to individuals in quartile 1 group, those in other quartiles had higher ALMI levels. An inverted U-shaped curve relationship between serum E2 Level and ALMI was found on performing weighted generalized additive model and smooth curve fitting, and the inflection point was identified as a serum E2 level of 85 pg/mL.

### CONCLUSION

Our results demonstrated an inverted U-shaped curve relationship between serum E2 levels and ALMI in middle-aged postmenopausal women, suggesting that low serum E2 levels play an important role in the loss of muscle mass in middle-aged postmenopausal women.

**Key Words:** Estradiol; Skeletal muscle; Menopause; Health; The National Health and Nutrition Examination Survey

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**Core Tip:** This paper evaluated the association between serum E2 level and appendicular lean mass index in middle-aged postmenopausal women from the National Health and Nutrition Examination Survey between 2013 and 2016, and found an inverted U-shaped curve relationship between them, with the point of inflection at a serum E2 level of 85 pg/mL.

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## INTRODUCTION

Most women experience menopausal transition in middle age, when aging-related hormonal changes accelerate[1]. The onset of sarcopenia, a multifactorial condition related to the loss of muscle mass and quality, has been intimately linked to menopause[2,3].

Compared with the anabolic effects of androgens on the skeletal muscle mass in men[4,5], the effects of estrogens on the skeletal muscle mass in women are less clearly understood[6]. Moreover, previous studies on the association between the loss of estrogen at menopause and skeletal muscle mass or function came to contradictory conclusions[7]. As the most potent estrogen hormone, estradiol (E2) is responsible for the maintenance of sexual characteristics and muscle health[8]. Thus, we aimed to evaluate the association between serum E2 level and appendicular lean mass index (ALMI) in middle-aged postmenopausal women using population-based data.

## MATERIALS AND METHODS

### Data source and study population

The National Health and Nutrition Examination Survey (NHANES) is a large, ongoing cross-sectional survey conducted annually in a nationally representative sample of the non-institutionalized United States population. Data for this study were pooled from the NHANES between 2013 and 2016. The study population was restricted to postmenopausal women aged 40-59 years. Individuals with a regular period in the past 12 mo ( $n = 840$ ), or with an unrecorded menopausal status ( $n = 287$ ), as well as those with missing serum E2 Levels ( $n = 69$ ) or ALMI data ( $n = 171$ ) were excluded. Finally, 673 women were included in the analysis.

Written informed consent was obtained from all participants and the Institutional Review Board of the National Center for Health Statistics (NCHS) approved the survey protocols (Protocol #2011-17).

### Study variables

The exposure variable was the serum E2 level, which was measured based on the reference method of the National Institute for Standards and Technology, using isotope dilution liquid chromatography tandem mass spectrometry. The outcome variable was ALMI, which was measured by dual-energy X-ray absorptiometry whole-body scans and calculated as the appendicular lean mass (kg) divided by height squared ( $m^2$ ). The covariates included in this study were age, race, educational level, body mass index (BMI), ratio of family income to poverty, moderate activities, total protein, blood urea nitrogen, and serum uric acid and calcium levels. Detailed information on these variables can be found on the NHANES website (<https://www.cdc.gov/nchs/nhanes/>).

### Statistical analyses

All estimates were applied with weights, in accordance with the guidelines edited by the NCHS[9], to account for the NHANES sampling method. All analyses were performed using EmpowerStats software (<http://www.empowerstats.com>) and R software (version 3.4.3). The statistical significance was set at  $P < 0.05$ . Weighted multivariable linear regression models were used to evaluate the association between serum E2 level and ALMI. Following the Strengthening the Reporting of Observational Studies in Epidemiology statement[10], we constructed three models: Model 1, no covariates were adjusted; Model 2, age and race were adjusted; and Model 3, all covariates presented in Table 1 were adjusted. When non-linear associations were found by using weighted generalized additive model and smooth curve fitting, two-piecewise linear regression models were further applied to examine the threshold effects.

**Table 1** Weighted characteristics of study population based on serum estradiol level quartiles

Serum estradiol level (pg/mL)	Q1 ( $\leq 3.80$ )	Q2 (3.88-7.42)	Q3 (7.45-17.50)	Q4 ( $\geq 17.60$ )	P value
Age (yr)	54.4 $\pm$ 4.1	53.6 $\pm$ 4.0	52.9 $\pm$ 4.8	49.6 $\pm$ 4.9	< 0.001
Race/Ethnicity (%)					0.584
Non-Hispanic White	70.9	68.3	70.1	73.6	
Non-Hispanic Black	7.8	14.1	10.9	10.4	
Mexican American	6.1	8.3	8.3	6.3	
Other race/ethnicity	15.2	9.3	10.7	9.7	
Education level (%)					0.520
Less than high school	13.3	14.1	12.7	10.1	
High school	24.5	19.2	24.9	19.0	
More than high school	62.2	66.6	62.3	71.0	
Body mass index (kg/m <sup>2</sup> )	25.6 $\pm$ 4.7	28.8 $\pm$ 4.8	32.2 $\pm$ 5.9	32.0 $\pm$ 8.3	< 0.001
Income to poverty ratio	3.0 $\pm$ 1.8	3.3 $\pm$ 1.7	3.1 $\pm$ 1.5	3.4 $\pm$ 1.6	0.143
Moderate activities (%)					0.965
Yes	49.1	47.2	49.7	49.8	
No	50.9	52.8	50.3	50.2	
Total protein (g/L)	69.9 $\pm$ 4.6	70.5 $\pm$ 4.1	71.1 $\pm$ 4.0	70.0 $\pm$ 3.4	0.022
Blood urea nitrogen (mg/dL)	5.0 $\pm$ 1.6	4.8 $\pm$ 1.6	4.8 $\pm$ 1.8	4.6 $\pm$ 1.2	0.076
Serum uric acid (umol/L)	263.8 $\pm$ 57.0	287.1 $\pm$ 69.7	302.9 $\pm$ 68.2	286.6 $\pm$ 67.6	< 0.001
Serum calcium (mg/dL)	2.4 $\pm$ 0.1	2.4 $\pm$ 0.1	2.4 $\pm$ 0.1	2.3 $\pm$ 0.1	0.092
Appendicular lean mass index (kg/m <sup>2</sup> )	6.1 $\pm$ 1.0	6.8 $\pm$ 1.0	7.3 $\pm$ 1.1	7.5 $\pm$ 1.4	< 0.001

mean  $\pm$  SD for continuous variables; P value was calculated by weighted linear regression model. “%” for categorical variables; P value was calculated by weighted chi-square test.

## RESULTS

Demographic characteristics of the participants subclassified based on the serum E2 level quartiles (Q1:  $\leq 3.80$  pg/mL; Q2: 3.88-7.42 pg/mL; Q3: 7.45-17.50 pg/mL; and Q4:  $\geq 17.60$  pg/mL) are shown in Table 1. Compared with the Q1 group, individuals in other groups were younger, and had lower levels of blood urea nitrogen, and higher levels of income to poverty ratio, BMI, total protein, serum uric acid, and ALMI.

The association between serum E2 level and ALMI was positive in each model, with a significant P for trend among the different serum E2 level quartile groups (Table 2). In the subgroup analysis stratified by BMI and race, this positive association was significant in the group with BMI < 25 kg/m<sup>2</sup> (Table 3).

An inverted U-shaped curve relationship between serum E2 level and ALMI was found, as shown in Figure 1, and the inflection point was identified at a serum E2 level of 85 pg/mL (Table 4).

## DISCUSSION

This study evaluated the association between serum E2 level and ALMI in middle-aged postmenopausal women, and found an inverted U-shaped curve relationship between them, with the point of inflection at a serum E2 level of 85 pg/mL.

Estrogens, especially E2, are known to play an important role in the preservation of muscle health. Several studies have investigated the effects of hormone replacement therapy (HRT) and found that it has a positive and measurable impact on muscle function[11,12]. Conversely, other studies found that HRT does not protect against muscle loss[13,14]. Moreover, it was reported that menopausal HRT was associated with an increased risk of adverse events, such as dementia[15], stroke[16], and breast cancer[17]. Therefore, it is important to balance the potential benefits against risks. Our results revealed an inverted U-shaped curve relationship between serum E2 level and ALMI, suggesting that adequate E2 supplementation may be a useful adjunct therapy for individuals with a low serum E2 level.

**Table 2 Association between serum estradiol level (pg/mL) and appendicular lean mass index (kg/m<sup>2</sup>)**

	Model 1 $\beta$ (95%CI)	Model 2 $\beta$ (95%CI)	Model 3 $\beta$ (95%CI)
Serum estradiol level	0.004 (0.002, 0.007) <sup>a</sup>	0.003 (0.001, 0.005) <sup>a</sup>	0.001 (0.000, 0.002) <sup>b</sup>
Serum estradiol level categories			
Q1	Reference	Reference	Reference
Q2	0.665 (0.406, 0.924)	0.607 (0.356, 0.859)	0.090 (-0.036, 0.216)
Q3	1.222 (0.969, 1.475)	1.199 (0.953, 1.445)	0.128 (-0.002, 0.258)
Q4	1.369 (1.126, 1.612)	1.385 (1.133, 1.637)	0.268 (0.133, 0.402)
P value	< 0.001	< 0.001	< 0.001

<sup>a</sup>*P* < 0.001.<sup>b</sup>*P* < 0.01.

Model 1: No covariates were adjusted. Model 2: Age and race were adjusted. Model 3: Age, race, educational level, body mass index, ratio of family income to poverty, moderate activities, total protein, blood urea nitrogen, serum uric acid, and serum calcium were adjusted.

**Table 3 Association between serum estradiol level (pg/mL) and appendicular lean mass index (kg/m<sup>2</sup>), stratified by body mass index and race**

	Model 1 $\beta$ (95%CI)	Model 2 $\beta$ (95%CI)	Model 3 $\beta$ (95%CI)
Stratified by BMI			
BMI (< 25 kg/m <sup>2</sup> )	0.002 (-0.000, 0.004)	0.001 (-0.001, 0.004)	0.002 (0.000, 0.003) <sup>a</sup>
BMI (25-29.9 kg/m <sup>2</sup> )	0.003 (0.001, 0.005) <sup>b</sup>	0.002 (0.000, 0.004) <sup>a</sup>	0.001 (-0.001, 0.003)
BMI ( $\geq$ 30 kg/m <sup>2</sup> )	0.006 (0.004, 0.009) <sup>c</sup>	0.005 (0.002, 0.008) <sup>a</sup>	0.001 (-0.001, 0.003)
Stratified by race			
Non-Hispanic White	0.003 (-0.000, 0.007)	0.002 (-0.002, 0.006)	0.002 (-0.000, 0.004)
Non-Hispanic Black	0.004 (0.000, 0.007) <sup>a</sup>	0.004 (-0.000, 0.007)	0.001 (-0.000, 0.003)
Mexican American	0.003 (-0.002, 0.008)	0.003 (-0.002, 0.008)	-0.003 (-0.005, 0.000)
Other race	0.015 (0.009, 0.022) <sup>c</sup>	0.013 (0.007, 0.020) <sup>c</sup>	0.002 (-0.001, 0.006)

<sup>a</sup>*P* < 0.05.<sup>b</sup>*P* < 0.01.<sup>c</sup>*P* < 0.001.

Model 1: No covariates were adjusted. Model 2: Age, and race were adjusted. Model 3: Age, race, educational level, body mass index, ratio of family income to poverty, moderate activities, total protein, blood urea nitrogen, serum uric acid, and serum calcium were adjusted. BMI: Body mass index.

The exact mechanism underlying the effects of E2 on skeletal muscle remains unclear. A possible explanation for the potentially beneficial effect is that E2 can stimulate the proliferative activity of the muscle satellite cells (stem cells) that are responsible for muscle tissue maintenance[18,19]. Another possible explanation is that estrogen deficiency results in the loss of muscle mass through apoptotic mechanisms[20,21]. Despite these possibilities, the molecular mechanism of the impact of E2 on muscle function needs to be further explored.

Data from the NHANES surveys were acquired following standard protocols, which ensured that the data were accurate and consistent. However, the limitations of this study should also be noted. First, a causal relationship between serum E2 level and ALMI in middle-aged postmenopausal women could not be determined due to the cross-sectional design of the NHANES surveys. Second, biases caused by unmeasured confounding factors cannot be excluded. Third, the conclusion cannot be generalized to older women because the population of this study was restricted to middle-aged postmenopausal women.

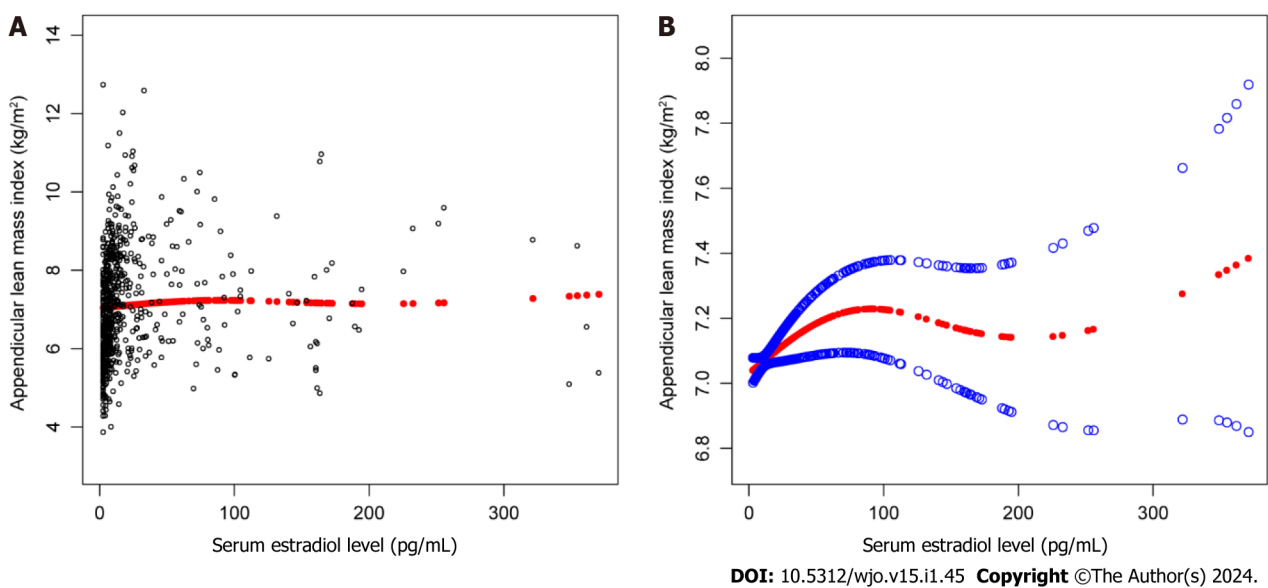
## CONCLUSION

Overall, this study showed an inverted U-shaped curve relationship between serum E2 levels and ALMI in middle-aged postmenopausal women, suggesting that low serum E2 levels play a crucial role in the loss of muscle mass in middle-aged postmenopausal women.

**Table 4 Threshold effect analysis of serum estradiol level on appendicular lean mass index using two-piecewise linear regression model**

Appendicular lean mass index	Adjusted $\beta$ (95%CI), <i>P</i> value
Serum estradiol level	
Fitting by standard linear model	0.001 (0.000, 0.002), 0.006
Fitting by two-piecewise linear model	
Inflection point	85 (pg/mL)
Serum estradiol level < 85 (pg/mL)	0.004 (0.002, 0.007), < 0.001
Serum estradiol level > 85 (pg/mL)	-0.001 (-0.003, 0.001), 0.280
Log likelihood ratio	0.003

Age, race, educational level, body mass index, ratio of family income to poverty, moderate activities, total protein, blood urea nitrogen, serum uric acid, and serum calcium were adjusted.



**Figure 1** The association between serum estradiol level and appendicular lean mass index. A: Each black point represents a sample; B: Solid red line represents the smooth curve fit between variables.

## ARTICLE HIGHLIGHTS

### Research background

The onset of sarcopenia, a multifactorial condition related to the loss of muscle mass and quality, has been intimately linked to menopause.

### Research motivation

Compared with the anabolic effects of androgens on the skeletal muscle mass in men, the effects of estrogens on the skeletal muscle mass in women are less clearly understood. Moreover, previous studies on the association between the loss of estrogen at menopause and skeletal muscle mass or function came to contradictory conclusions.

### Research objectives

We aimed to evaluate the association between serum E2 level and appendicular lean mass index (ALMI) in middle-aged postmenopausal women using population-based data.

### Research methods

This study included 673 postmenopausal women, aged 40-59 years, from the National Health and Nutrition Examination Survey between 2013 and 2016. Weighted multivariable linear regression models were used and when non-linear associations were found by using weighted generalized additive model and smooth curve fitting, two-piecewise linear regression models were further applied to examine the threshold effects.

## Research results

There was a positive association between serum E2 level and ALMI. Compared to individuals in quartile 1 group, those in other quartiles had higher ALMI levels. An inverted U-shaped curve relationship between serum E2 level and ALMI was found on performing weighted generalized additive model and smooth curve fitting, and the inflection point was identified as a serum E2 Level of 85 pg/mL.

## Research conclusions

Our results demonstrated an inverted U-shaped curve relationship between serum E2 levels and ALMI in middle-aged postmenopausal women, suggesting that low serum E2 Levels play an important in the loss of muscle mass in middle-aged postmenopausal women.

## Research perspectives

The molecular mechanism of the impact of E2 on muscle function needs to be further explored.

## FOOTNOTES

**Author contributions:** Jin F, Wang YF, and Zhu ZX contributed to data collection, analysis and writing of the manuscript; Zhu ZX contributed to study design and editing of the manuscript.

**Institutional review board statement:** The Institutional Review Board of the National Center for Health Statistics (NCHS) approved the survey protocols (Protocol #2011-17).

**Informed consent statement:** The datasets analysed during the current study are available at NHANES website. In accordance with ethical guidelines and research standards, informed consent was not required for this database-based study.

**Conflict-of-interest statement:** All the authors declare that they have no competing interests.

**Data sharing statement:** The datasets analysed during the current study are available at NHANES website (<https://www.cdc.gov/nchs/nhanes/index.htm>).

**STROBE statement:** The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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