Serum Estradiol Levels Are Inversely Associated With C-Reactive Protein in Premenopausal Women but Not Postmenopausal Women: a cross–sectional study

Jae-Min Park
Yonsei University Health System
Yong-Jae Lee (ukyjhome@yuhs.ac)
Gangnam Severance Hospital

Research article

Keywords: menopause, estradiol, C-reactive protein, cardiovascular diseases, chronic inflammation

Posted Date: September 24th, 2019

DOI: https://doi.org/10.21203/rs.2.14903/v1

Abstract

Background Epidemiological studies investigating the link between serum estradiol levels and inflammatory markers have produced inconsistent or conflicting results. We hypothesized that serum estrogen plays differing roles in inflammation according to menopausal status. Thus, we aimed to investigate the association between serum estradiol and C-reactive protein (CRP) levels in women according to their menopausal status.

Methods We examined the association between serum estradiol and high-sensitivity CRP levels based on the menopausal status of 151 premenopausal women aged 21–52 years and in 394 postmenopausal women aged 46–75 years who participated in a health examination program. A multiple linear regression analysis was conducted using CRP level as the dependent variable.

Results Multiple linear regression analysis showed that serum estradiol levels were inversely associated with CRP levels in premenopausal women (β coefficient = -0.298, P = 0.001). However, this was not the case in postmenopausal women after adjusting for age, body mass index, cigarette smoking, mean arterial pressure, fasting plasma glucose, triglyceride, high-density lipoprotein-cholesterol, aspartate aminotransaminase, and alanine aminotransaminase levels. Serum estradiol levels were inversely associated with CRP in premenopausal women but not in postmenopausal women.

Conclusion Our findings suggest that lower estrogenic activity may at least partly contribute to the pathogenesis of chronic inflammation, particularly in premenopausal women.

Background

The development of cardiovascular diseases (CVD) is caused by multifactorial interrelated mechanisms, among which chronic low-grade inflammation plays a key role [1]. In women, menopause is another important factor that contributes to CVD, in addition to traditional risk factors such as obesity, hypertension, type 2 diabetes, and dyslipidemia [2]. Postmenopausal women are more susceptible to increased weight gain and visceral fat accumulation accompanied by marked decreases in estrogen levels [3,4]. These changes influence lipid metabolism and the vascular endothelium [5,6], thereby increasing the risk of atherosclerotic CVD in postmenopausal women [7].

Current evidence supports the existence of sex-specific relationships between sex hormones and inflammatory markers. In contrast to the consistent inverse relationship between serum testosterone levels and inflammatory markers in men [8,9], epidemiological studies that investigated the association between serum estradiol levels and inflammatory markers in women, particularly when categorized by menopausal status, have shown inconsistent and even conflicting results. Some observational studies found positive associations in postmenopausal women [10,11] and inverse associations in premenopausal women [12,13], whereas others did not reveal significant relationships [14]. Although the reasons for these discrepancies between serum estradiol levels and inflammatory markers among

women are not clear, the effects of endogenous estrogen on chronic low-grade inflammation may differ by menopausal status.

C-reactive protein (CRP) has traditionally been considered a non-specific marker of inflammation, but recent epidemiological evidence has highlighted the significance of high CRP levels in patients with CVD through cross-sectional and longitudinal studies [15,16]. We hypothesized that serum estrogen plays differing roles in inflammation according to menopausal status. Thus, we performed this study to investigate the association between serum estradiol and CRP levels in women according to their menopausal status.

Methods

Study participants

We reviewed the medical records of 689 women who underwent medical examinations at the Health Promotion Center of the Gangnam Severance Hospital in Seoul, Korea, between November 2013 and July 2015. The participants voluntarily visited the health promotion center for regular health assessments. Natural menopause was defined as 12 consecutive months with no menstrual periods. We excluded participants who met at least one of the following criteria: currently taking oral contraceptive medication; undergoing exogenous estrogen replacement; a history of tamoxifen therapy, induced menopause such as bilateral oophorectomy, radiation or drug-induced menopause; history of ischemic heart disease, cerebrovascular disease, thyroid, respiratory, renal, liver, or rheumatologic disease; CRP ≥10 mg/L; missing data; or not having fasted for 12 h prior to testing. We also excluded women who reported intermittent menstruation over the previous year to rule out the possibility of polycystic ovarian syndrome or perimenopause. After these exclusions, 545 participants (151 premenopausal women aged 21–52 years and 394 postmenopausal women aged 46–75 years) were included in the final analysis. Informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University College of Medicine, Seoul, Korea.

Data collection

Each participant completed a questionnaire that inquired about lifestyle habits, menstrual and medical history; cigarette smoking, alcohol consumption, and physical activity were determined based on the responses. Cigarette smoking was defined as an individual who currently smokes. Alcohol drinking was defined as alcohol consumption on two days or more per week. Regular exercise was defined as engaging in purposeful physical activity three or more times per week. Menstrual history was determined via responses to the following question: “Has there been no menstruation for one year or more?” with three response options: “Yes,” “No, but there has been intermittent menstruation over the last year,” and “No, there has been no menstruation.” Medical examinations were performed by trained medical staff using a standardized procedure. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm,

respectively, with participants in light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the patient's right arm with a standard mercury sphygmomanometer (Baumanometer, W. A. Baum Co Inc., Copiague, NY, USA). Mean arterial pressure was calculated using the equation (SBP + [2×DBP])/3. All blood samples were obtained from the antecubital vein after fasting for 12 h overnight. Fasting plasma glucose, triglyceride, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were measured via enzymatic methods using the AU5800 automated chemistry analyzer (Beckman Coulter, CA, USA). Serum estradiol concentration was measured via an electrochemiluminescence immunoassay (ECLIA) using the Cobas e601 immunoanalyzer (Roche Diagnostics, Basel, Switzerland). High-sensitivity CRP concentrations were measured using the Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN, USA), a latex-enhanced immunoturbidimetric method with a lower limit of detection of 0.02 mg/L.

Statistical analysis

Normal distribution was evaluated with determination of skewness using a Kolmogorov-Smirnov test; the triglyceride, AST, ALT, estradiol, and CRP levels had skewed distributions. The clinical characteristics of the cohort were compared according to menopausal status using independent two-sample tests or Wilcoxon's rank-sum tests for continuous variables, according to distribution normality, and the chi-squared test for categorical variables. Continuous data are presented as the mean ± standard deviation or median (interquartile range), whereas categorical data are presented as frequencies. A Pearson correlation analysis was conducted to examine bivariate correlations between log-transformed CRP and clinical variables. A multiple linear regression analysis was conducted with the log-transformed CRP level as the dependent variable to examine the independent association between estrogen and CRP levels. All analyses were conducted using the SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the clinical and biochemical characteristics of the participants, including 151 premenopausal women and 394 postmenopausal women, by menopausal status. The mean age of the premenopausal women was 42.7 ± 6.7 years, whereas that of the postmenopausal women was 58.1 ± 6.7 years. The mean values of age, BMI, blood pressure, and fasting plasma glucose, as well as the median values of triglycerides, AST, ALT, and CRP, were significantly higher in postmenopausal women than those in premenopausal women, while the mean HDL cholesterol and median estradiol levels were significantly lower in postmenopausal women than those in premenopausal women.

Table 2 presents the results of the Pearson's correlation analysis between log-transformed CRP levels and clinical variables. Log-transformed CRP levels significantly correlated with BMI, SBP, log-transformed

triglycerides, log-transformed AST, and log-transformed estradiol levels in premenopausal women. Among postmenopausal women, log-transformed CRP levels were significantly correlated with age, BMI, SBP, DBP, MAP, fasting plasma glucose, log-transformed triglycerides, HDL cholesterol, log-transformed AST, and log-transformed ALT levels but were not correlated with log-transformed estradiol levels.

Table 3 presents the results of multiple linear regression analysis that shows the independent relationship between estradiol and CRP levels. Log-transformed estradiol was inversely associated with log-transformed CRP only in premenopausal women (β coefficient = −0.298, $P = 0.001$) but not in postmenopausal women after adjusting for age, BMI, cigarette smoking, mean arterial pressure, fasting plasma glucose, log-transformed triglycerides, HDL-cholesterol, log-transformed AST, and log-transformed ALT levels.

Discussion

In this cross-sectional study, we found that serum estradiol levels were inversely and independently associated with CRP in premenopausal women after adjusting for potential confounding variables. Conversely, there was no such inverse relationship among postmenopausal women. Our findings are consistent with results of previous studies demonstrating that estradiol levels are inversely associated with inflammatory markers in premenopausal women [12,13].

The results from previous studies on the association between estradiol levels and inflammatory markers in women were inconclusive. Using the BioCycle Study dataset, Gaskins *et al.* reported an inverse association between estradiol and CRP levels in 259 reproductive-aged women in the United States, which is consistent with the findings of our study [12]. In contrast to our findings, serum estradiol was positively associated with CRP levels in 513 Italian postmenopausal women investigated in the Invecchiare in Chianti (InCHIANTI) study [11]. Therefore, additional longitudinal studies have been warranted to establish the relationship between serum estradiol levels and CRP on the basis of menopausal status.

The mechanisms underlying the menopause-specific relationship between serum estradiol and CRP level remain unclear, but some hypotheses have been suggested. Estrogen has an inhibitory effect on inflammatory cytokine production and inflammatory cell migration in non-reproductive tissues [17,18], and estrogen receptors are highly expressed in vascular smooth muscle and endothelial cells throughout the human body [18,19]. Estrogen's anti-inflammatory effects are in part mediated by nitric oxide (NO) production and cytokine suppression [17], particularly as NO is a key vasodilator [20,21]. NO also has an anti-inflammatory role in the endothelium owing to its role as a scavenger of reactive oxygen species (ROS) and an inhibitor of leukocyte recruitment [22–24]. Moreover, estrogen has been found to decrease the levels of tumor necrosis factor-α, a major pro-inflammatory cytokine [25]. These cascades potentially inhibit the synthesis and release of platelet-activating factors and chemokines such as interleukin–6 and may also down-regulate leukocyte-recruiting adhesion molecules such as intercellular adhesion molecule–1, vascular cell adhesion molecule–1, and E-selectin [26–28]. Estrogen could also decrease the

production of ROS in mitochondria, which reduces chronic low-grade inflammation [29,30]. However, these effects of estradiol may differ according to menopausal status. The lack of an inverse relationship between estradiol and CRP in postmenopausal women may be explained by the observation that 80% of circulating estradiol in such individuals originates from the aromatization from testosterone, especially in adipose tissue; aromatase, which is the enzyme that converts testosterone into estradiol, is stimulated by inflammatory cytokines and CRP [11,31].

There are several limitations that should be considered when interpreting our findings. First, this study had a cross-sectional design; therefore, the results should be interpreted while taking into account causal and temporal considerations. Additional longitudinal studies are required to establish causality between serum estradiol levels and CRP based on menopausal status. Second, because the study participants were confined to women who underwent routine health promotion screenings at a single hospital and may therefore have comprised a relatively healthier proportion of the community, our cohort may not be representative of the general population. Third, the estradiol concentration was measured by ECLIA and not by liquid chromatography-mass spectrometry, even though the latter method is considered the gold standard for measuring serum estradiol. However, the ECLIA method has several advantages such as a rapid turnaround time, high-throughput, and full automation. Fourth, serum estradiol levels and CRP levels may fluctuate during the menstrual cycle [32], and we did not measure serum estradiol levels and CRP levels at a common point during the cycle in our pre-menopausal participants. Lastly, although CRP is currently considered a reliable biomarker of chronic inflammation [16], caution should be taken when assuming anti- or pro-inflammatory activity based only on this biomarker, especially as we did not directly quantify other serum inflammatory markers such as tumor necrosis factor -α, serum interleukin–6, and other cytokines to support our findings.

Despite these limitations, there were also several strengths to this study. We assessed the association between serum estradiol and CRP in premenopausal and postmenopausal women separately, which may provide valuable insight into the association between serum estradiol and CRP on the basis of menopausal status. Moreover, a wide range of confounding factors closely related to chronic inflammation, including BMI, smoking status, blood pressure, fasting plasma glucose, triglycerides, HDL-cholesterol, and hepatic enzymes, were considered when performing multiple linear regression analyses. Additionally, to determine the true nature of the relationship between estradiol and CRP in pre- and postmenopausal women, our study excluded participants with induced or secondary menopause as well as women who used oral contraceptives or who were undergoing estrogen replacement therapy. Induced menopause causes a sudden onset of obesity and metabolic disturbances followed by an abrupt decline in ovarian hormones, which could cause chronic inflammation [33,34].

Conclusions

Our data show that serum estradiol levels are inversely associated with CRP levels in premenopausal women but not in postmenopausal women. Our findings suggest that lower estrogenic activity may at

least partly contribute to the pathogenesis of chronic inflammation, particularly in premenopausal women.

Abbreviations

CRP: C-reactive protein; CVD: Cardiovascular disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; HDL: high-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ECLIA: electrochemiluminescence immunoassay

Declarations

Acknowledgments

Not applicable.

Authors' contributions

YJL: Conception and design, data collection, data analysis. JMP: drafting the article, revising it for intellectual content.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University College of Medicine, Seoul, Korea.

Consent for publication

All participants provided written consent for their anonymized data to be used in publications.

Competing Interests

The authors declare that they have no competing interests.

Author detail

[1]Department of Health Promotion, Severance Hospital, Seoul, Korea

[2]Department of Medicine, Graduate School of Medicine, Yonsei University

[3]Department of Family Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea

References

1.Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep. 2014;16:435.

2.Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric. 2007;10:19–24.

3.Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, et al. Understanding weight gain at menopause. Climacteric. 2012;15:419–29.

4.Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes. (Lond) 2008;32:949–58.

5.Izumi S, Muano T, Mori A, Kika G, Okuwaki S. Common carotid artery stiffness, cardiovascular function and lipid metabolism after menopause. Life Sci. 2006;78:1696–701.

6. Rendell M, Hulthén UL, Törnquist C, Groop L, Mattiasson I. Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. J Clin Endocrinol Metab. 2001;86:744–49.

7.Newson L. Menopause and cardiovascular disease. Post Reprod Health. 2018;24:44–9.

8.Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Bárány P, Heimbürger O. Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol. 2009;20:613–20.

9.Bobjer J, Katrinaki M, Tsatsanis C, Giwercman YL, Giwercman A. Negative association between testosterone concentration and inflammatory markers in young men: a nested cross-sectional study.

PLoS One. 2012;8:e61466.

10.Störk S, Bots ML, Grobbee DE, Van Der Schouw YT. Endogenous sex hormones and C-reactive protein in healthy postmenopausal women. J Intern Med. 2008;264:245–53.

11.Maggio M, Ceda GP, Lauretani F, Bandinelli S, Corsi AM, Giallauria F, et al. SHBG, sex hormones, and inflammatory markers in older women. J Clin Endocrinol Metab. 2001;96:1053–9.

12.Gaskins AJ, Wilchesky M, Mumford SL, Whitcomb BW, Browne RW, Wactawski-Wende J, et al. Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. Am J Epidemiol. 2012;175:423–31.

13.Blum CA, Müller B, Huber P, Kraenzlin M, Schindler C, De Geyter C, et al. Low-grade inflammation and estimates of insulin resistance during the menstrual cycle in lean and overweight women. J Clin Endocrinol Metab. 2005;90:3230–5.

14.Wunder DM, Yared M, Bersinger NA, Widmer D, Kretschmer R, Birkhauser MH, et al. Serum leptin and C-reactive protein levels in the physiological spontaneous menstrual cycle in reproductive age women. Eur J Endocrinol. 2006;155:137–42.

15.Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005;294:326–33.

16.Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499–511.

17.Chakrabarti S, Lekontseva O and Davidge ST. Estrogen is a modulator of vascular inflammation. IUBMB Life 2008;60:376–82.

18.Gilliver SC. Sex steroids as inflammatory regulators. J Steroid Biochem Mol Biol. 2010;120:105–15.

19.Gray GA, Sharif I, Webb DJ, Seckl JR et al. Oestrogen and the cardiovascular system: the good, the bad and the puzzling. Trends Pharmacol Sci. 2001;22:152–6.

20.MacRitchie AN, Jun SS, Chen Z, German Z, Yuhanna IS, Sherman TS, et al. Estrogen upregulates endothelial nitric oxide synthase gene expression in fetal pulmonary artery endothelium. Circ Res. 1997;81:355–62.

21.Haynes MP, Li L, Sinha D, Russell KS, Hisamoto K, Baron R, et al. Src kinase mediates phosphatidylinositol 3-kinase/Akt-dependent rapid endothelial nitric-oxide synthase activation by estrogen. J Biol Chem. 2003;278:2118–23.

22.Kubes P, Kurose I and Granger DN. NO donors prevent integrin-induced leukocyte adhesion but not P-selectin-dependent rolling in postischemic venules. Am J Physiol. 1994;267:H931–37.

23.Wink DA, Hanbauer I, Krishna MC, DeGraff W, Gamson J, Mitchell JB, et al. Nitric oxide protects against cellular damage and cytotoxicity from reactive oxygen species. Proc Natl Acad Sci. USA 1993;90:9813–7.

24.Niu XF, Smith CW and Kubes P. Intracellular oxidative stress induced by nitric oxide synthesis inhibition increases endothelial cell adhesion to neutrophils. Circ Res. 1994;74:1133–40.

25.Srivastava S, Weitzmann MN, Cenci S, Ross FP, Adler S, Pacifici R. et al. Estrogen decreases TNF gene expression by blocking JNK activity and the resulting production of c-Jun and JunD. J Clin Invest. 1999;104:503–13.

26.Korpelainen EI, Gamble JR, Smith WB, Goodall GJ, Qiyu S, Woodcock JM, et al. The receptor for interleukin 3 is selectively induced in human endothelial cells by tumor necrosis factor alpha and potentiates interleukin 8 secretion and neutrophil transmigration. Proc Natl Acad Sci. USA 1993;90:11137–41.

27.Camussi G, Albano E, Tetta C, Bussolino F. The molecular action of tumor necrosis factor-alpha. Eur J Biochem. 1991;202:3–14.

28.Kim I, Moon SO, Kim SH, Kim HJ, Koh YS, Koh GY, et al. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM–1), vascular cell adhesion molecule 1 (VCAM–1), and E-selectin through nuclear factor-κB activation in endothelial cells. J Biol Chem. 2001;276:7614–20.

29.Stirone C, Duckles SP, Krause DN, Procaccio V. Estrogen increases mitochondrial efficiency and reduces oxidative stress in cerebral blood vessels. Mol Pharmacol. 2005;68:959–65.

30.Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med. 2010;49:c1603–1616.

31.Zhao Y, Nichols JE, Valdez R, Mendelson CR, Simpson ER. Tumor necrosis factor-alpha stimulates aromatase gene expression in human adipose stromal cells through use of an activating protein–1 binding site upstream of promoter 1.4. Mol Endocrinol. 1996;10:1350–7.

32.Wander K, Brindle E and O'Connor KA. C-reactive protein across the menstrual cycle. Am J Phys Anthropol. 2008;136:138–46.

33.Gohlke-Barwolf C. Coronary artery disease—is menopause a risk factor? Basic Res Cardiol. 2000;95:177–83.

34.Romero-Aleshire MJ, Diamond-Stanic MK, Hasty AH, endelson CR, Simpson ER. Loss of ovarian function in the VCD mouse-model of menopause leads to insulin resistance and a rapid progression into

the metabolic syndrome. Am J Physiol Regul Integr Comp Physiol. 2009;297:R587–92.

Tables

Table 1. Characteristics of the study population

Variables	Premenopausal women	Postmenopausal women	P-value
n	151	394	
Age (year)	42.7 ± 6.7	58.1 ± 6.7	<0.001
BMI (kg/m^2)	21.5 ± 3.1	23.1 ± 3.0	<0.001
SBP (mmHg)	114.6 ± 17.8	124.8 ± 19.1	<0.001
DBP (mmHg)	70.5 ± 11.1	76.0 ± 11.0	<0.001
MAP (mmHg)	85.2 ± 12.9	92.3 ± 13.2	<0.001
FPG (mmol/L)	4.83 ± 0.63	5.30 ± 1.01	<0.001
Triglyceride (mmol/L)	0.76 (0.58-1.09)	0.90 (0.74-1.38)	<0.001
HDL cholesterol (mmol/L)	1.53 ± 0.32	1.41 ± 0.35	<0.001
AST (U/L)	17 (15-20)	21 (18-25)	<0.001
ALT (U/L)	14 (11-18)	19 (15-26)	<0.001
C-reactive protein (mg/L)	0.49 (0.30–1.00)	0.70 (0.32–1.50)	<0.001
Estradiol (nmol/L)	120.5 (56.0–202.3)	8.0 (5.0–12.3)	<0.001
Current smoking (%)	6.9	2.7	0.061
Alcohol drinking (%)	20.4	12.3	0.017
Regular exercise (%)	30.4	40.0	0.044

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase.

Data are expressed as mean ± standard deviation, median (interquartile range) or percentage (%). P-values were calculated using an independent two sample t-test, Wilcoxon rank-sum test, or chi-squared test.

Alcohol drinking refers to consuming on two or more days per week. Regular exercise refers to activity three or more times per week.

Table 2. Correlation between log-transformed CRP levels and clinical variables

	Premenopausal women		Postmenopausal women	
	r	P-value	r	P-value
Age (year)	0.075	0.372	0.186	<0.001
BMI (kg/m^2)	0.294	<0.001	0.388	<0.001
SBP (mmHg)	0.167	0.045	0.187	<0.001
DBP (mmHg)	0.115	0.189	0.178	<0.001
MAP (mmHg)	0.140	0.094	0.188	<0.001
FPG (mmol/L)	0.058	0.490	0.169	<0.001
Triglyceride (mmol/L)*	0.313	<0.001	0.168	<0.001
HDL cholesterol (mmol/L)	-0.144	0.085	-0.234	<0.001
AST (U/L)*	0.107	0.020	0.190	<0.001
ALT (U/L)*	0.149	0.074	0.198	<0.001
Estradiol (nmol/L)*	-0.303	<0.001	-0.008	0.872

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein; AST, aspartate amin otransaminase; ALT, alanine aminotransaminase. P-values were calculated using Pearson's correlation a nalysis. *indicates log-transformed values

Table 3. Multiple linear regression analysis showing the independent relationship between log-transformed estradiol levels and log-transformed C-reactive protein levels

	β coefficient	Standard error	P-value
Premenopausal women			
Model 1	-0.301	0.088	<0.001
Model 2	-0.295	0.087	<0.001
Model 3	-0.298	0.084	0.001
Postmenopausal women			
Model 1	0.004	0.066	0.949
Model 2	-0.016	0.070	0.818
Model 3	-0.018	0.070	0.799

β refers to the standardized beta coefficient.

Model 1: adjusted for age and body mass index.

Model 2: adjusted for age, body mass index, cigarette smoking, mean arterial pressure, fasting plasma glucose, log-transformed triglyceride, and high-density lipoprotein-cholesterol levels.

Model 3: adjusted for age, body mass index, cigarette smoking, mean arterial pressure, fasting plasma glucose, log-transformed triglyceride, high-density lipoprotein-cholesterol, log-transformed aspartate aminotransaminase, and log-transformed alanine aminotransaminase levels.