

# Serum oestradiol levels are inversely associated with C-reactive protein levels in premenopausal women, but not postmenopausal women

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## Abstract

**Objective:** Epidemiological studies on the association of serum oestradiol levels and inflammatory markers have reported inconsistent and conflicting results. Therefore, we investigated the association between serum oestradiol and high-sensitivity C-reactive protein (CRP) levels in women on the basis of their menopausal status.

**Methods:** This cross-sectional study examined the association between serum oestradiol and CRP levels on the basis of menopausal status in 151 premenopausal women aged  $42.7 \pm 6.7$  years and 394 postmenopausal women aged  $58.1 \pm 6.7$  years who participated in a health examination program. Multiple linear regression analysis was conducted using CRP levels as the dependent variable.

**Results:** Multiple linear regression analysis showed that serum oestradiol levels were inversely associated with CRP levels in premenopausal women ( $\beta$  coefficient =  $-0.298$ ) after adjusting for age, body mass index, smoking, mean arterial pressure, and levels of fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, aspartate aminotransferase, and alanine aminotransferase. However, this association was not found in postmenopausal women after adjusting for the same confounding factors.

**Conclusions:** Serum oestradiol levels are inversely associated with CRP levels in premenopausal women, but not in postmenopausal women. Lower oestrogenic activity may at least partly contribute to the pathogenesis of chronic inflammation, particularly in premenopausal women.

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## Keywords

Menopause, oestradiol, C-reactive protein, chronic inflammation, cardiovascular disease, sex hormone

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## Introduction

Cardiovascular disease (CVD) is caused by multifactorial interrelated mechanisms, among which chronic low-grade inflammation plays a major role.<sup>1</sup> In women, menopause is an important contributing factor to CVD in addition to traditional risk factors, including obesity, hypertension, type 2 diabetes, and dyslipidaemia.<sup>2</sup> Postmenopausal women are more susceptible to weight gain and visceral fat accumulation accompanied by a marked decrease in oestrogen levels.<sup>3</sup> These changes influence lipid metabolism and the vascular endothelium,<sup>4</sup> increasing the risk of atherosclerotic CVD in postmenopausal women.<sup>5</sup>

Current evidence supports the existence of sex-specific relationships between sex hormones and inflammatory markers. There is a consistent inverse relationship between serum testosterone levels and inflammatory markers in men.<sup>6,7</sup> However, epidemiological studies that investigated the association between serum oestradiol levels and inflammatory markers in women, particularly when categorized by menopausal status, have shown inconsistent and even conflicting results. Some observational studies found a positive association of serum oestradiol levels and inflammatory markers in postmenopausal women<sup>8,9</sup> and an inverse association in premenopausal women,<sup>10,11</sup> whereas others did not show significant relationships between these variables.<sup>12</sup> Although the reasons for this discrepancy among studies are not clear, the effects of endogenous oestrogen 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.<sup>13</sup> We hypothesized that serum oestrogen levels play differing roles in inflammation according to menopausal status. Therefore, this study aimed to investigate the association between serum oestradiol and CRP levels in women while taking into account their menopausal status.

## Methods

### *Study participants*

We reviewed the medical records of 689 women who voluntarily visited the Health Promotion Center of Gangnam Severance Hospital, for a routine health check-up, between November 2013 and July 2015. Natural menopause was defined as the absence of menstrual periods for 12 consecutive months. The exclusion criteria were as follows: current intake of oral contraceptives; exogenous oestrogen replacement; history of tamoxifen therapy; induced menopause, including bilateral oophorectomy-, radiation-, or drug-induced menopause; history of ischaemic heart disease or cerebrovascular, thyroid, respiratory, renal, liver, or rheumatological disease; missing data; and no fasting for 12 hours before testing (n=81). Of the remaining participants, those with a CRP level  $\geq 10$  mg/L were excluded to rule out the possibility of infection or an inflammatory disorder

(n=9). We also excluded women who reported irregular menstruation over the previous year to rule out the possibility of polycystic ovarian syndrome or perimenopause (n=54). Written 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 Yonsei University Gangnam Severance Hospital (institutional review board number: 3-2019-0267).

### *Data collection*

Each participant completed a self-reported questionnaire on lifestyle habits and menstrual and medical history. Cigarette smoking, alcohol consumption, and physical activity were determined on the basis of responses. Cigarette smoking was defined as a current habit of smoking. Alcohol drinking was defined as alcohol consumption on 2 or more days per week. Regular exercise was defined as engaging in purposeful physical activity three or more times per week. Menstrual history was determined by the response to the following question: "Has there been menstruation for 1 or more years?" with three response options. These response options were as follows: "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, and participants wore 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 ( $\text{kg}/\text{m}^2$ ). 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 following equation:  $\text{SBP} + 2 \times \text{DBP} / 3$ .

All blood samples were obtained from the antecubital vein after fasting for 12 hours. Fasting plasma glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were measured via enzymatic methods using the AU5800 automated chemistry analyser (Beckman Coulter, Fullerton, CA, USA). Serum oestradiol levels were measured by electrochemiluminescence immunoassay using the Cobas e601 immunoanalyser (Roche Diagnostics, Basel, Switzerland). In the present study, serum oestradiol levels were measured because there is strong agreement between serum and plasma oestrogen levels.<sup>14</sup> High-sensitivity CRP levels were measured using the Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN, USA) with a latex-enhanced immunoturbidimetric method with a lower limit of detection of 0.02 mg/L.

### *Statistical analysis*

Normal distribution of data was evaluated with determination of skewness using the Kolmogorov–Smirnov test. Triglyceride, AST, ALT, oestradiol, and CRP levels had a skewed distribution. The clinical characteristics of the cohort were compared by menopausal status using the independent two-sample test or the Wilcoxon rank-sum test for continuous variables taking into account normality of distribution, and the chi-squared test was used for categorical variables. Continuous data are presented as the mean  $\pm$  standard deviation or median (interquartile range), whereas categorical data are presented as frequency. Pearson's correlation was used to examine bivariate correlations between

log-transformed CRP levels and clinical variables. Multiple linear regression analysis was conducted with the log-transformed CRP level as the dependent variable to examine the independent association between oestrogen and CRP levels. In this analysis, model 1 was adjusted for age and BMI. Model 2 was adjusted for age, BMI, cigarette smoking, mean arterial pressure, and levels of fasting plasma glucose, log-transformed triglyceride, and high-density lipoprotein-cholesterol. Model 3 was adjusted for age, BMI, cigarette smoking, mean arterial pressure, and levels of fasting plasma glucose, log-transformed triglycerides, high-density lipoprotein cholesterol, log-transformed AST, and log-transformed ALT. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). All

statistical tests were two-sided and a  $P$  value  $< 0.05$  was considered statistically significant.

## Results

Table 1 shows the clinical and biochemical characteristics of 545 participants who were included in the final analysis, including 151 premenopausal women and 394 postmenopausal women, by menopausal status. The mean  $\pm$  standard deviation age of the premenopausal women was  $42.7 \pm 6.7$  years (range: 21–52 years), whereas that of the postmenopausal women was  $58.1 \pm 6.7$  years (range: 46–75 years). The mean age, BMI, blood pressure, and fasting plasma glucose levels, and the median triglyceride, AST, ALT, and CRP levels were significantly higher in postmenopausal women

**Table 1.** Characteristics of the study population.

Variables	Premenopausal women (n = 151)	Postmenopausal women (n = 394)	P value
Age (years)	42.7 $\pm$ 6.7	58.1 $\pm$ 6.7	<0.001
BMI (kg/m <sup>2</sup> )	21.5 $\pm$ 3.1	23.1 $\pm$ 3.0	<0.001
SBP (mmHg)	114.6 $\pm$ 17.8	124.8 $\pm$ 19.1	<0.001
DBP (mmHg)	70.5 $\pm$ 11.1	76.0 $\pm$ 11.0	<0.001
MAP (mmHg)	85.2 $\pm$ 12.9	92.3 $\pm$ 13.2	<0.001
FPG (mmol/L)	4.83 $\pm$ 0.63	5.30 $\pm$ 1.01	<0.001
Triglycerides (mmol/L)	0.76 (0.58–1.09)	0.90 (0.74–1.38)	<0.001
HDL cholesterol (mmol/L)	1.53 $\pm$ 0.32	1.41 $\pm$ 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
Oestradiol (pmol/L)	442.4 (205.6–742.6)	29.4 (18.4–45.2)	<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

Data are expressed as mean  $\pm$  standard deviation, median (interquartile range), or %.

$P$  values were calculated using the independent two sample t-test or the Wilcoxon rank-sum test for continuous variables on the basis of normality of distribution, or the chi-squared test for categorical variables.

Alcohol drinking refers to consuming alcohol on 2 or more days per week. Regular exercise refers to activity three or more times per week.

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 aminotransferase; ALT, alanine aminotransferase.

than in premenopausal women (all  $P < 0.001$ ). However, mean HDL cholesterol and median oestradiol levels were significantly lower in postmenopausal women than in premenopausal women (both  $P < 0.001$ ).

Table 2 shows the results of Pearson's correlation analysis between log-transformed CRP levels and clinical variables. Log-transformed CRP levels were significantly correlated with BMI, SBP, log-transformed triglyceride levels, log-transformed AST levels, and log-transformed oestradiol levels in premenopausal women (all  $P < 0.05$ ). In postmenopausal women, log-transformed CRP levels were significantly correlated with age, BMI, SBP, DBP, mean arterial pressure, and levels of fasting plasma glucose, log-transformed triglycerides, HDL cholesterol, log-transformed AST, and log-transformed ALT (all  $P < 0.001$ ). However, log-transformed CRP levels were not correlated with log-transformed oestradiol levels.

Table 3 shows the results of multiple linear regression analysis of the independent relationship between oestradiol and

CRP levels. Log-transformed oestradiol levels were inversely associated with log-transformed CRP levels only in premenopausal women ( $P < 0.01$  for all three models). However, log-transformed oestradiol levels were not associated with log-transformed CRP levels in postmenopausal women after adjusting for age, BMI, cigarette smoking, mean arterial pressure, and levels of fasting plasma glucose, log-transformed triglycerides, HDL cholesterol, log-transformed AST, and log-transformed ALT.

## Discussion

We found that serum oestradiol levels were inversely and independently associated with CRP levels in premenopausal women after adjusting for potential confounding variables. However, there was no such inverse relationship in postmenopausal women. Our findings are consistent with the results of previous studies, which showed that oestradiol levels were inversely associated with

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

	Premenopausal women		Postmenopausal women	
	r	P value	r	P value
Age (years)	0.075	0.372	0.186	<0.001
BMI (kg/m <sup>2</sup> )	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
Triglycerides (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
Oestradiol (pmol/L)*	-0.303	<0.001	-0.008	0.872

P values were calculated using Pearson's correlation analysis.

\*Indicates log-transformed values.

CRP, C-reactive protein; 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 aminotransferase; ALT, alanine aminotransferase.

**Table 3.** Multiple linear regression analysis of the independent relationship between log-transformed oestradiol levels and log-transformed C-reactive protein levels.

	$\beta$ 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

$\beta$  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, and levels of fasting plasma glucose, log-transformed triglycerides, and high-density lipoprotein cholesterol.

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

inflammatory markers in premenopausal women.<sup>10,11</sup>

Previous studies on the association between oestradiol levels and inflammatory markers in women were inconclusive. Using the BioCycle Study dataset, Gaskins et al.<sup>10</sup> reported an inverse association between oestradiol and CRP levels in 259 reproductive-aged women in the United States, which is consistent with the findings of our study. In contrast, serum oestradiol levels were positively associated with CRP levels in 513 Italian postmenopausal women who were investigated in the Invecchiare in Chianti study.<sup>9</sup> Therefore, additional longitudinal studies are warranted to establish the relationship between serum oestradiol and CRP levels on the basis of menopausal status.

The mechanism underlying the menopause-specific relationship between

serum oestradiol and CRP levels remains unclear. Oestrogen has an inhibitory effect on inflammatory cytokine production and inflammatory cell migration in non-reproductive tissues,<sup>15,16</sup> and oestrogen receptors are highly expressed in vascular smooth muscle and endothelial cells throughout the human body.<sup>16,17</sup> Oestrogen's anti-inflammatory effects are, in part, mediated by nitric oxide production and cytokine suppression<sup>15</sup> because nitric oxide is a key vasodilator.<sup>18,19</sup> Nitric oxide also plays an anti-inflammatory role in the endothelium owing to its role as a reactive oxygen species scavenger and an inhibitor of leukocyte recruitment.<sup>20-22</sup> Moreover, oestrogen decreases levels of tumour necrosis factor- $\alpha$ , which is a major pro-inflammatory cytokine.<sup>23</sup> These cascades potentially inhibit the synthesis and release of platelet-activating factors and chemokines, including interleukin-6, and may also down-regulate leukocyte-recruiting adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin.<sup>24-26</sup> Oestrogen could also decrease production of reactive oxygen species in mitochondria, and this reduces chronic low-grade inflammation.<sup>27,28</sup> However, these effects of oestradiol may differ with the menopausal status. The lack of an inverse relationship between oestradiol and CRP levels in postmenopausal women may be explained by the observation that 80% of circulating oestradiol in such individuals originates from aromatization of testosterone, especially in adipose tissue.<sup>9,29</sup> Aromatase, which is an enzyme that converts testosterone into oestradiol, is stimulated by inflammatory cytokines and CRP.

There are several limitations of this study. 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 oestradiol and CRP levels based on menopausal status. Second, the study participants included only women who underwent routine health screening at a single hospital. Therefore, these women may have comprised a relatively healthier proportion of the community and our cohort may not be representative of the general population. Third, oestradiol levels were measured by electrochemiluminescence immunoassay and not by liquid chromatography-mass spectrometry, even though the latter is considered the best method for measuring serum oestradiol levels. However, the electrochemiluminescence immunoassay method has several advantages, including a rapid turnaround time, high-throughput, and full automation. Fourth, serum oestradiol and CRP levels may fluctuate during the menstrual cycle.<sup>30</sup> We did not measure serum oestradiol levels and CRP levels at a common point during the cycle in our premenopausal participants. Fifth, other sex hormones, such as testosterone, were not measured in the present study. Further studies are required to determine the relationship between other sex hormones and inflammatory markers while taking into account menopausal status. Finally, although CRP is currently considered a reliable biomarker of chronic inflammation,<sup>13</sup> caution is required when assuming anti- or pro-inflammatory activity based only on this biomarker because we did not directly quantify other serum inflammatory markers, such as tumour necrosis factor- $\alpha$  and interleukin-6, to support our findings.

Despite these limitations, this study has several strengths. We assessed the association between serum oestradiol and CRP levels in premenopausal and postmenopausal women separately. This may provide useful insight into the association between serum oestradiol and CRP levels 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 levels, triglyceride levels, HDL-cholesterol levels, and hepatic enzymes, were considered when performing multiple linear regression analyses. Additionally, to determine the true nature of the relationship between oestradiol and CRP levels 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 oestrogen replacement therapy. Induced menopause causes a sudden onset of obesity and metabolic disturbance followed by an abrupt decline in ovarian hormones, which could cause chronic inflammation.<sup>31</sup>

In conclusion, our data show that serum oestradiol levels are inversely associated with CRP levels in premenopausal women, but not in postmenopausal women. Our findings suggest that lower oestrogenic activity may at least partly contribute to the pathogenesis of chronic inflammation, particularly in premenopausal women.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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