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Endogenous Hormones and Coronary Heart Disease in Postmenopausal Women

Yu Chen[1,2], **Anne Zeleniuch-Jacquotte**[1,2], **Alan A. Arslan**[1,3], **Oktawia Wojcik**[1], **Paolo Toniolo**[2], **Roy Shore**[1,4], **Mortimer Levitz**[2], and **Karen Koenig**[1,5]

[1]Division of Epidemiology, Department of Environmental Medicine, New York University School of Medicine

[2]New York University Cancer Institute, New York, New York

[3]Department of Obstetrics and Gynecology, New York University School of Medicine, New York, New York

[4]Radiation Effects Research Foundation, Hiroshima, Japan

Abstract

The association between serum levels of endogenous estrogens in postmenopausal women and the subsequent risk of coronary heart disease (CHD) was examined in a prospective case-control study nested within the New York University Women's Health Study (NYUWHS). The NYUWHS is a prospective cohort study of 14,274 healthy women enrolled between 1985 and 1991. A total of 99 women who were postmenopausal and free of cardiovascular disease at enrollment and who experienced CHD, defined as non-fatal myocardial infarction (MI), fatal CHD, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG), were matched 1:2 by baseline age, blood sampling date, and postmenopausal status to controls who remained free of CHD as of the date of diagnosis of the matching case. Biochemical analyses for total estradiol, estrone, percent free estradiol, percent estradiol bound to sex hormone-binding globulin (SHBG), and SHBG were performed on pre-diagnostic stored serum samples. Participants had not used any hormone medications in the 6 months prior to blood collection. In the model adjusting only for matching factors, the risk of CHD in the top tertile of calculated bioavailable estradiol was elevated compared with the bottom tertile (OR=2.10; 95% CI = 1.13-3.90, p for trend = 0.03), and the risk in the top tertile of SHBG was reduced (OR = 0.50, 95% CI = 0.28-0.92, p for trend < 0.01). However, these associations disappeared after adjusting for baseline hypertension status, body mass index, and serum cholesterol levels. These findings suggest that circulating estradiol and SHBG are not associated with CHD risk in postmenopausal women beyond what can be explained by the variation in hypertension status, BMI, and cholesterol.

Background

The role of endogenous sex-hormones in coronary heart disease (CHD) among postmenopausal women has not been extensively studied. Many studies have indicated that

[5]Requests for reprints: Dr. Karen Koenig, New York University School of Medicine, 650 First Avenue, 5th Floor, New York, NY 10016-3240. Phone: 212-263-6501; Fax: 212-263-8570 karen.koenig@nyumc.org.

among postmenopausal women, sex hormone binding globulin (SHBG) levels are positively associated with a more favorable lipid profile, including lower levels of total cholesterol, LDL-cholesterol, and triglycerides, and higher levels of HDL cholesterol [1-5]. More recent data have suggested that SHBG may influence inflammatory risk factors for CHD such as levels of C-reactive protein (CRP) [5, 6]. On the other hand, the evidence supporting possible relationships of endogenous estradiol and estrone with lipid profile and other CHD risk factors is not consistent [4, 7, 8]. Some studies found that endogenous estradiol was negatively associated with total cholesterol [4, 5], but others suggest no associations [7, 8] or positive associations with risk factors such as CRP levels [9, 10].

Despite research interest in the relationships between endogenous hormone levels and cardiovascular risk factors in women, currently there are only three prospective studies that have evaluated the association between circulating levels of endogenous hormones such as estradiol, estrone, and SHBG with the risk of cardiovascular disease (CVD). In a cohort study of 651 postmenopausal women followed-up for 19 years, there was no association between baseline levels of estrone or estradiol and the risk of CVD (n = 158) or CHD (n = 82) [11]. A nested case-control study of 40 CHD cases and 80 controls observed no association between levels of estradiol, estrone, or SHBG and the risk of CHD [12]. However, all the study participants in the latter study were diabetic, thus limiting the generalizability of the findings. In addition, it was not clear whether participants had used exogenous hormones, which could have affected the levels and reproducibility of the measurements of endogenous hormones. More recently, in a case-control study nested in the Women's Health Study [13], SHBG was inversely associated with the risk of CVD among the 85 cases and 85 controls who were non-users of hormone replacement therapy. However, adjustment for body mass index (BMI) and cholesterol level eliminated the association. A limitation of the study is that stroke and CHD were analyzed together as a combined endpoint. Although CHD and stroke share important risk factors, it is not known whether SHBG is similarly related to both of these diseases.

We conducted a prospective case-control study nested in the NYUWHS with 99 cases of CHD and 198 matched controls to evaluate the associations of pre-diagnostic serum levels of estrone, estradiol, and SHBG with CHD risk. All participants in the NYUWHS were non-users of hormone medications at enrollment when blood was collected, providing an opportunity to test the associations.

Methods

New York University Women's Health Study

Detailed information about the NYUWHS has been presented elsewhere [14]. Briefly, the NYUWHS is a prospective cohort study of women enrolled at a mammography screening center in New York City. From March 1985 to June 1991, 14,274 women between the ages of 34 and 65 were enrolled in the study. Participants in the cohort are well educated, with 44% of the women having a college degree; health conscious, with only 19% of the women smoking and 49% taking multivitamins at the time of enrollment; and mainly Caucasian (81%). Because the original focus of the study was endogenous hormones and breast cancer, women who had taken hormone medications in the 6 months preceding baseline enrollment were not eligible for the study.

At the time of enrollment, data on demographics, anthropometric measures, medical history, reproductive and lifestyle variables were collected through self-administered questionnaires after written informed consent was obtained. Hypertension status was ascertained using self-report information on physician-diagnosis of the condition prior to baseline and/or medicine use for hypertension collected at baseline. Outcomes are identified through active follow-up

of the cohort conducted with questionnaires mailed approximately every two to four years, telephone interviews for nonrespondents, as well as record linkage with the National Death Index (NDI). Physical activity was assessed at baseline and in two of the follow-up questionnaires in which participants were requested to report their activity levels during the baseline period. Data were coded to reflect the metabolic equivalent (MET) hours per week for vigorous exercise and walking.

Serum samples were collected at enrollment from all participants and stored at -80° C. Based on previous breast cancer studies in the same cohort [14, 15], Women were classified as postmenopausal if they reported no menstrual cycles in the previous 6 months, a total bilateral oophorectomy or a hysterectomy without total oophorectomy prior to natural menopause and their age was 52 years or older.

Nested case-control study of CHD

Participants who reported having had coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), or myocardial infarction (MI) during the active follow-up were contacted for further information, including authorization to obtain their medical records. Non-fatal MI was considered confirmed if it met the World Health Organization criteria [16], i.e., symptoms, and either diagnostic electrocardiographic changes (EKG) or elevated levels of cardiac enzymes, based on review of medical records. If information on EKG and cardiac enzymes was not available, a definitive diagnosis of MI noted in the medical record was accepted. CABG/PTCA confirmation was based on review of medical records. If medical records were not available, a telephone interview of the participant was conducted. Cases were considered confirmed if participants reported that they underwent the procedure because of angina pectoris. Fatal CHD was confirmed if the underlying cause of death from the NDI was CHD (codes 410-414 in ICD9 or codes I20-I25 in ICD10) and there was evidence from questionnaires or medical records that the participant had pre-existing CHD (including angina or silent MI). To reduce the possibility of misclassification, sudden deaths and CHD deaths with no pre-existing CHD were not considered cases in the study. Complete information, including medical records when indicated, was obtained for 86.4% of these potentially incident conditions.

Cases of CHD were defined as women who had non-fatal MI, PTCA, CABG, or death from CHD. The present study included the 99 incident CHD cases, consisting of 43 non-fatal/fatal MI and 56 CABG or PTCA, diagnosed prior to 1995 among participants who were postmenopausal and free of CVD at enrollment. For each of the cases, two controls were selected at random from the relevant risk set. The risk set for a given CHD case included all subjects postmenopausal at enrollment who were alive and free of CVD as of the date of the coronary event of the case, and who matched the case on the date (± 6 months) and age (± 6 months) at the blood donation. The Ethical Review Boards of New York University School of Medicine reviewed and approved the present study.

Laboratory analyses

Samples from a case and her matched controls were analyzed in the same batch to assure measurement comparability, and laboratory personnel were blinded to the disease status of the samples. Biochemical analyses for total estradiol, estrone, percent free estradiol, percent estradiol bound to SHBG, and SHBG were performed on pre-diagnostic stored serum samples collected at the enrollment visit. Percent estradiol bound to SHBG was determined by a Concanavalin A-agarose binding assay and percent free estradiol by an ultrafiltration method, as described previously [17]. A chemiluminescent immunometric assay using immunolite technology was used to quantify SHBG (Diagnostic Products Corp, Los Angeles, CA). The assays for total estradiol and estrone were performed by the Clinical

Studies Center of Quest Diagnostics, Inc (Nichols Institute, San Juan Capistrano, CA). For these assays, serum samples were subjected to organic extraction and celite chromatography and the appropriate fractions were analyzed by radioimmunoassay [18, 19]. Previous analyses of endogenous hormones in the NYUWHS have shown that the intra-batch coefficients of variation (CVs) were all below 10% except for percent free estradiol, with an intra-batch CV of 16% [20]. All CVs were therefore in a range considered acceptable for epidemiologic studies [21].

Measurements of serum cholesterol were conducted by Pacific Biometrics, Inc., a participant in the CDC-NHLBI Lipid Standardization Program. Total cholesterol was measured using an enzymatic assay with a Trinder end-point reaction. HDL-cholesterol was measured using precipitation [22] followed by an enzymatic method similar to that the CDC Cholesterol Reference Method [23]. LDL was measured by a direct assay which does not require fasting status.

Statistical analyses

We first conducted descriptive analyses to compare distributions of conventional risk factors and endogenous hormone levels between cases and controls. In addition, Pearson correlations between serum hormones of interest and established risk factors were estimated among controls.

To evaluate the association between prediagnostic levels of endogenous hormones and the risk of CHD, we used conditional logistic regression models (conditioned on the matching case-control sets) to estimate the odds ratios (ORs) for CHD in relation to tertiles of hormone variables including estrone, total estradiol, percent free estradiol, percent of estradiol bound to SHBG, SHBG, and bioavailable estradiol computed as [total estradiol times (1 minus the percent of estradiol bound to SHBG)]. Hormone concentrations were also log2 transformed to estimate the OR associated with a doubling in hormone level. Effect estimates in relation to percent of estradiol bound to SHBG were nearly identical to those for SHBG and therefore are not shown. In addition to controlling for the matching factors through the use of conditional logistic regression, we calculated ORs associated with each of the endogenous hormones adjusting for potential confounders identified in the data, i.e., factors related to both hormone levels and CHD risk. These factors include baseline hypertension, BMI, and serum cholesterol levels. We first evaluated the influence of each of these potential confounder separately and then included all three of them in the same models. We controlled for serum total and HDL cholesterol; similar results were obtained when LDL cholesterol was instead adjusted for in the analyses (data not shown). A separate model was constructed to additionally adjust for other potential confounders based on the literature such as family history of MI, baseline cigarette smoking status, alcohol consumption, and physical activity. Additional adjustment for HRT use between baseline and index date (date of diagnosis of the case), surgical menopause, and baseline aspirin use was conducted. All analyses were conducted using SAS 8.0 (SAS Institute, Inc., Cary, North Carolina).

Results

Compared with their age-matched controls, incident cases of CHD were more likely at baseline (time of entry to the study and blood draw) to have higher BMI, lower levels of physical activity, higher levels of total and LDL-cholesterol, lower levels of HDL-cholesterol, and a family history of MI (Table 1). Cases also had a higher level of bioavailable estradiol and a lower level of serum SHBG and percent of estradiol bound to SHBG at baseline in comparison to controls. The median time from blood collection to diagnosis among the cases was 5 years (range, 1-10 years).

The endogenous hormones of interest were moderately or highly correlated with one another (Table 2). Among the controls, serum levels of estrone were strongly positively correlated with the levels of total estradiol and bioavailable estradiol ($r \geq 0.75$), and total and bioavailable estradiol were highly correlated with each other ($r = 0.98$). The percent of estradiol bound to SHBG was highly correlated with SHBG ($r = 0.91$), and the percent free estradiol was inversely related to the level of SHBG ($r = -0.76$). BMI was positively correlated with serum levels of estrone, total estradiol, bioavailable estradiol, and percent free estradiol ($r \geq 0.27$, $p < 0.01$) (Table 2). BMI was also inversely related to SHBG level ($r = -0.30$, $p < 0.01$) and percent of estradiol bound to SHBG ($r = -0.33$, $p < 0.01$). Serum levels of HDL-cholesterol were positively related to SHBG and percent of estradiol bound to SHBG ($r \geq 0.38$). The correlations between HDL-cholesterol and total and bioavailable estradiol were weak ($r = -0.01$ and -0.10, respectively). The associations between other risk factors for CHD and the serum hormones of interest were mostly weak, except that participants with hypertension had higher levels of estrone, total estradiol, and bioavailable estradiol, and lower levels of percent of estradiol bound to SHBG.

In Table 3, three conditional logistic regression models are presented to examine the associations of CHD and serum levels of the hormones of interest. In **Model 1** (adjusted only for the matching factors), women in the highest tertile of total estradiol were 1.8 times more likely to have a CHD event (OR = 1.84, 95% CI, 1.00-3.38), compared with their counterparts in the lowest tertile of total estradiol. Model 1 estimates also showed a negative association between SHBG and CHD risk, with an OR of 0.50 (95% CI, 0.28-0.92) comparing the highest to the lowest level. Similarly, there was a positive association between bioavailable estradiol, the composite variable of total estradiol and SHBG, and CHD risk. Postmenopausal women in the top tertile of bioavailable estradiol were 2.10 times more likely to develop CHD (95% CI, 1.13-3.90) during the follow-up, compared with women in the bottom tertile (p for trend = 0.03).

In Model 2 in Table 3, which controlled for baseline hypertension status, serum total and HDL-cholesterol and BMI in addition to the matching factors, the associations of serum SHBG, bioavailable estradiol, and total estradiol with CHD risk disappeared. When we evaluated the influence of each of these potential confounders separately, we found that controlling for either BMI, hypertension status, or serum cholesterol alone led to a substantial change in effect estimates for each of the hormones (> 10% on log scale, data not shown). In fully adjusted models, the association between hormone levels and CHD risk was weak in all individual hormone categories and there was no trend in the estimates. Additional adjustments for cigarette smoking, alcohol consumption, physical activity, and family history of MI, shown in Model 3, did not change the odds ratio estimates appreciably. Nor were the odds ratio estimates changed appreciably with additional adjustment for HRT use between baseline and index date, surgical menopause, and baseline aspirin use (data not shown).

Discussion

Among postmenopausal women, we found a positive association between bioavailable estradiol and risk of CHD and an inverse association between SHBG levels and CHD risk. However, the associations disappeared after adjustment for hypertension status, BMI and serum cholesterol profile.

In the model adjusted only for matching variables, although levels of bioavailable estradiol and SHBG were both associated with CHD risk, the associations of total estradiol and estrone with CHD risk were not as strong (p for trend = 0.09 and 0.48, respectively) (Table 3). Since bioavailable estradiol is determined by both estradiol and SHBG, the findings

suggest that SHBG may be primarily responsible for the association between bioavailable estradiol and the risk of CHD. Our finding that the association between SHBG levels and CHD risk can be explained by variation in hypertension status, BMI and lipid profile is consistent with a previous nested case-control study with a similar study design using the combined endpoint of CHD and stroke [13]. BMI is a major determinant of SHBG concentrations in women [26, 27]. Several prior cross-sectional studies have found an association of SHBG with hypertension and lipoprotein levels in postmenopausal women [1-5]. The liver produces plasma SHBG, which transports sex steroids and regulates their access to tissues. Taken together, these data do not support that there is an association between SHBG and the risk of CHD independent of the influence of BMI, blood pressure and cholesterol levels.

From a clinical perspective, the findings suggest that the knowledge of the level of SHBG in postmenopausal women may not add additional information about their risk of CHD beyond what is known from hypertension status, BMI and cholesterol profile. However, levels of SHBG and testosterone have been shown to be predictive of type 2 diabetes risk in several studies [28-31]. A recent meta-analysis also indicates that the protective effect of SHBG on type 2 diabetes risk is stronger in women than in men and is independent of BMI [32]. Additional studies are needed to evaluate to what extent SHBG is predictive of diabetes risk among individuals with common risk factors for diabetes and CHD.

Strengths of the present study include the prospective study design, the detailed information on lifestyle factors in the NYUWHS, and the inclusion in the case definition of not only CHD deaths but also women who had other non-fatal forms of CHD. Limitations in the present study should also be considered when interpreting our results. The available prospective studies, including our study, all had < 200 cases of CHD and/or stroke, and therefore are limited in detecting small effects. However, a recent cross-sectional analysis from the multi-ethnic study of atherosclerosis with > 800 subjects also found that an inverse association between SHBG and abdominal aortic calcification quantified by computed tomography was no longer apparent after adjustment for total and HDL-cholesterol [33]. Due to the limited sample size, we are not able to evaluate the joint effect of different sex hormones or the interaction of sex hormones and other lifestyle factors on CHD risk. Whether sex hormones are predictive of CHD risk in subgroups of women awaits future investigation.

In conclusion, our findings showed that among postmenopausal women, there was a positive association between pre-diagnostic serum levels of SHBG and CHD risk which was largely explained by variation in serum cholesterol, hypertension status, and BMI.

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Table 1

Distribution of Demographic, Lifestyle Factors, and Endogenous Estrogens in Cases of Coronary Heart Disease and Controls (Postmenopausal Women, NYUWHS, 1985-1994)

Characteristics	Cases (Total n = 99)	Controls (Total n = 198)	p-value*
Baseline characteristics			
Age in years, mean (SD)	60.2 (4.1)	60.1 (4.2)	Matched
Age at menopause in years, mean (SD)	50.0 (4.9)	50.3 (4.3)	0.69
BMI in kg/m^2			
> 25, n (%)	64 (65.3)	73 (38.6)	<0.01
Mean (SD)	27.1 (4.3)	25.1 (4.3)	<0.01
Family history of MI, n (%)	52 (55.3)	72 (38.4)	<0.01
History of high blood pressure, n (%)	32 (32.3)	27 (13.6)	<0.01
Smoking status, n (%)			
Never	33 (35.1)	72 (39.6)	0.26
Past	35 (37.2)	74 (40.7)	
Current	26 (27.7)	36 (19.8)	
Alcohol consumption in glass/day)			
≥ 1, n (%)	31 (31.6)	63 (33.3)	0.77
Mean (SD)	1.5 (3.3)	2.5 (6.0)	0.09
Use of aspirin within two weeks of baseline, n (%)	31 (31.3)	58 (29.3)	0.72
Surgical menopause, n (%)	8 (8.1)	15 (7.6)	0.87
Physical activity in met-hours/week, mean (SD)			
Vigorous activity	9.9 (18.2)	11.4 (22.1)	0.27
Walking	5.1 (6.0)	6.7 (7.9)	0.16
Use of HRT before onset date of the case, n (%)	14 (14.9)	31 (16.0)	0.61
Biochemical measurements in baseline serum samples			
Total cholesterol in mg/dl, mean (SD)	273.1 (56.1)	251.1 (43.7)	<0.01
LDL-cholesterol in mg/dl, mean (SD)	169.9 (52.7)	150.7 (41.7)	<0.01
HDL-cholesterol in mg/dl, mean (SD)	50.7 (15.8)	58.5 (16.5)	<0.01
Estrone in pg/mL, mean (SD)	25.3 (13.2)	24.6 (15.0)	0.48
Total estradiol in pg/mL, mean (SD)	9.1 (9.7)	7.5 (6.4)	0.09
SHBG in nmol/L, mean (SD)	51.4 (28.3)	60.6 (29.4)	<0.01

Characteristics	Cases (Total n = 99)	Controls (Total n = 198)	p-value*
Percent free estradiol, mean (SD)	1.2 (0.2)	1.1 (0.2)	0.14
Percent of estradiol bound to SHBG, mean (SD)	34.3 (11.3)	37.6 (9.0)	<0.01
Bioavailable estradiol in pg/mL, mean (SD)	6.0 (6.0)	4.8 (4.2)	0.03

*P-values were based on conditional logistic regression; smoking status was entered as a ordered variable with 0, 1, and 2, indicating never, past, and current smokers, respectively. Data were missing on body mass index for 1 case and 1 control; on family history of MI for, respectively, 5 and 13 subjects; on smoking for 5 and 16 subjects; on alcohol consumption for 1 and 9 subjects; on use of HRT before index date for 5 and 4 subjects; on walking for 2 and 6 subjects; and on estrone for 1 and 1 subjects.

Table 2

Correlations with Endogenous Hormone Variables in Controls (n = 198), NYUWHS, 1985-1994

	Estrone, pg/mL	Total estradiol, pg/mL	SHBG, nmol/L	Percent free estradiol	Percent of estradiol bound to SHBG	Bioavailable estradiol [4], pg/mL
Correlations between serum hormones [1]						
Estrone, pg/mL	1.00					
Total estradiol, pg/mL	0.76**	1.00				
SHBG, nmol/L	−0.19**	−0.22**	1.00			
Percent free estradiol	0.18*	0.13	−0.76**	1.00		
Percent of estradiol bound to SHBG	−0.23**	−0.23**	0.91**	−0.70**	1.00	
Bioavailable estradiol, pg/mL	0.75**	0.98**	−0.41**	0.29**	−0.43**	1.00
Correlations with baseline risk factors [1]						
BMI, kg/m^2	0.27*	0.41 **	−0.30**	0.29**	−0.33**	0.46**
Total cholesterol, mg/dl	−0.16	−0.11	−0.20	−0.04	−0.24	−0.05
HDL-cholesterol, mg/dl	−0.10	−0.01	0.40**	−0.42**	0.38**	−0.10
LDL-cholesterol, mg/dl	−0.18	−0.17	−0.26*	0.05	−0.27*	−0.10
Alcohol consumption, glasses/day	−0.17*	−0.11	0.04	−0.16	0.05	−0.12
Physical activity, met-hours/week (Vigorous activity + walking)	−0.06	−0.14	0.02	0.06	0.09	−0.14
Category-specific median hormone values [2]						
Hypertension status						
No (n = 170)	22.58	6.89	61.40	1.12	38.10	4.33
Yes (n = 27)	37.59	11.59	55.66	1.18	34.23	7.66
P value [3]	<0.01	<0.01	0.10	0.16	0.03	<0.01
Current smokers						
No (n = 146)	23.70	7.17	59.71	1.13	37.49	4.56
Yes (n = 36)	27.20	8.52	57.31	1.15	36.54	5.54
P value [3]	0.09	0.27	0.25	0.19	0.21	0.25
Family history of MI						
No (n = 114)	23.76	7.12	61.09	1.12	38.07	4.49

	Estrone, pg/mL	Total estradiol, pg/mL	SHBG, nmol/L	Percent free estradiol	Percent of estradiol bound to SHBG	Bioavailable estradiol [4], pg/mL
Yes (n = 71)	26.73	8.31	59.08	1.16	36.69	5.33
P value [3]	0.24	0.18	0.43	0.10	0.25	0.15

[1]Pearson correlation coefficients based on log-transformed values. One control with unknown BMI was excluded from the analyses. * $0.01 \leq p < 0.05$, ** $p < 0.01$

[2]Median values of endogenous hormone variables by categorical risk factors of CHD.

[3]p value for T-test based on log-transformed hormone values.

[4]Bioavailable estradiol [computed as total estradiol times (1 minus the percent of estradiol bound to SHBG)].

Table 3

Odds Ratios of Coronary Heart Disease for Tertiles of Serum Levels of Total, Bioavailable, and Percent Free Estradiol, SHBG, and Estrone in Postmenopausal Women (NYUWHS, 1985-1994)

	n		OR for CHD (95% CI)		
	Control	Case	Model 1 [1]	Model 2 [2]	Model 3 [3]
Estrone, pg/mL					
5-17	67	35	1.00	1.00	1.00
18-27	73	21	0.51 (0.26-1.02)	0.41 (0.19-0.88)	0.32 (0.14-0.73)
28-86	57	42	1.34 (0.74-2.43)	0.86 (0.43-1.71)	0.76 (0.37-1.55)
P for trend			0.48	0.40	0.22
Continuous scale (log_2)			1.11 (0.83-1.48)	0.87 (0.62-1.21)	0.80 (0.56-1.14)
Total estradiol, pg/mL					
1-4	67	27	1.00	1.00	1.00
5-7	69	24	1.28 (0.67-2.44)	0.78 (0.39-1.58)	0.73 (0.35-1.52)
8-74	62	48	1.84 (1.00-3.38)	1.20 (0.58-2.49)	1.20 (0.57-2.55)
P for trend			0.09	0.81	0.70
Continuous scale (log_2)			1.27 (0.96-1.69)	0.96 (0.69-1.34)	0.93 (0.66-1.32)
SHBG, nmol/L					
7.9-43.0	60	39	1.00	1.00	1.00
43.1-63.4	61	36	0.88 (0.49-1.56)	1.44 (0.72-2.88)	1.40 (0.68-2.91)
63.5-178.0	77	24	0.50 (0.28-0.92)	1.13 (0.51-2.50)	1.08 (0.48-2.44)
P for trend			<0.01	0.55	0.46
Continuous scale (log_2)			0.59 (0.42-0.83)	0.88 (0.57-1.35)	0.85 (0.54-1.32)
Percent free estradiol					
0.70-1.07	77	30	1.00	1.00	1.00
1.08-1.21	60	31	1.32 (0.73-2.40)	0.82 (0.42-1.62)	0.82 (0.40-1.68)
1.22-1.81	61	38	1.58 (0.89-2.82)	0.87 (0.42-1.81)	0.85 (0.40-1.83)
P for trend			0.13	0.41	0.35
Continuous scale (log_2)			2.20 (0.78-6.21)	0.55 (0.13-2.29)	0.48 (0.10-2.24)
Bioavailable estradiol (pg/mL)					
0.53-2.88	71	28	1.00	1.00	1.00

	n		OR for CHD (95% CI)		
	Control	Case	Model 1 [1]	Model 2 [2]	Model 3 [3]
2.89-4.84	72	26	0.99 (0.53-1.88)	0.68 (0.33-1.37)	0.62 (0.30-1.30)
4.85-41.63	55	45	2.10 (1.13-3.90)	1.09 (0.51-2.30)	1.03 (0.47-2.24)
P for trend			0.03	0.79	0.71
Continuous scale (log_2)			1.32 (1.02-1.72)	0.96 (0.69-1.33)	0.94 (0.67-1.32)

[1] ORs adjusted for matching factors.

[2] ORs additionally adjusted for baseline hypertension status, BMI, and serum total and HDL cholesterol.

[3] ORs adjusted for variables in models 1 and 2 and for smoking status (current vs. past or never), family history of MI, physical activity, and alcohol consumption.