Endogenous Sex Steroid Levels and Cardiovascular Disease in Relation to the Menopause

A Systematic Review

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KEYWORDS

• Coronary heart disease • Coronary artery disease • Endogenous estrogen
• Hormone therapy • Menopause • Estradiol • Sex hormone-binding globulin

KEY POINTS

- Favorable effects of oral estrogen therapy on increases in high-density lipoprotein and decreases in low-density lipoprotein did not translate to demonstrable decreases in coronary heart disease (CHD) events in randomized controlled trials of postmenopausal hormone therapy (HT) for women.
- Nearly all large HT trials with CHD outcomes used pharmacologic doses of oral conjugated equine estrogen.
- Endogenous estrogen levels are more relevant to the true associations between postmenopausal estrogen and CHD risk factors or clinical outcomes.

INTRODUCTION

Heart disease remains a major cause of death among women in the United States.[1] In 2008, 1 in 31 deaths in US women was attributable to breast cancer, whereas 1 in 6.6 deaths was attributable to coronary heart disease (CHD).[2] The remaining lifetime risk for CHD (acute myocardial infarction [MI], angina pectoris, and chronic ischemic heart disease) among US women at age 40 is 1 in 3.[2]

For many years, researchers and clinicians have observed gender differences in the patterns of CHD. Because the incidence of CHD in women lags behind that of men by 10 years,[2] it was hypothesized that changes in the endogenous estrogen milieu during or after the menopause transition explains most of these gender differences in CHD

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prevalence. In support of this hypothesis, the severity of coronary artery disease (CAD) in women referred to coronary angiography is correlated with measures of exposure to endogenous estrogen (time since menopause, age at menopause), independently of age.[3] Also, a cohort study reported that older age at menopause is related to reduced cardiovascular disease (CVD) mortality over 20 years of follow-up.[4] In the Multi-Ethnic Study of Atherosclerosis, early menopause (before age 46 years) was associated with shorter CHD-free survival over 4.8 years of follow-up, even after adjustment for other coronary risk factors.[5] The large Nurses' Health Study did not find this association except in women without ovaries.[6]

The menopause transition is associated with adverse changes in lipoprotein pattern; postmenopausal women have higher total cholesterol, low-density lipoprotein (LDL), and triglycerides, and lower high-density lipoproteins (HDL), than do premenopausal women.[7–9] In the Study of Women's Health Across the Nation, SWAN, a large prospective study of the menopause transition, only total cholesterol, LDL, and apolipoprotein-B showed substantial increases within the 1-year interval before and after the final menstrual period, consistent with menopause-induced changes.[10] Other CHD risk factors were consistent with a linear model, indicating chronologic aging.

Based on adverse menopause-related changes in lipoprotein profiles and gender differences in CHD incidence, one might predict that CHD risk would be decreased by menopausal hormone therapy (HT). Indeed, in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, conjugated equine estrogen (CEE), either alone or in combination with medroxyprogesterone acetate (MPA) or micronized progesterone) increased HDL and decreased LDL.[11] However, the favorable effects of oral estrogen therapy on increases in HDL and decreases in LDL did not translate to demonstrable decreases in CHD events in randomized controlled trials of postmenopausal women (**Table 1**). Instead, primary and secondary prevention trials of CEE 0.625 mg/d plus MPA 2.5 mg/d (CEE + MPA) versus placebo showed adverse effects on CHD events.[12,13] In the Heart and Estrogen/progestin Replacement Study (HERS), a secondary prevention trial, CEE + MPA for a mean of 4.1 years did not reduce the rate of CHD events in postmenopausal women with established CHD and there was a pattern of early increase in risk of CHD events in the CEE + MPA group compared with the group assigned to placebo, despite beneficial effects of CEE + MPA on serum lipoproteins.[12] The Women's Health Initiative (WHI), a primary prevention trial of CEE + MPA versus placebo among women aged 50 to 79 years old at baseline, was terminated early (after a mean follow-up of 5.2 years) due to a 24% increase in the risk of CHD in the CEE + MPA group compared with the placebo group (nominal 95% CI 1.00–1.54).[13] As in the HERS study, the WHI also demonstrated an early increase in the risk of CHD in the CEE + MPA group compared with the placebo group (hazard ratio [HR] at 1 year 1.81, 95% CI 1.09–3.01). Even among women who had initiated CEE + MPA within 10 years of menopause, CEE + MPA was not associated with a significantly decreased risk for CHD.[14,15]

In the WHI Estrogen-Alone Trial (comparing CEE without MPA with placebo) in women without a uterus, the risk of CHD events after a mean of 6.8 years of follow-up was similar among women assigned to CEE and women assigned to placebo.[16] In a post hoc analysis, women assigned to CEE who were aged 50 to 59 years at baseline had lower CHD risk than women assigned to placebo in this age group (HR 0.55, nominal 95% CI 0.35–0.86).[16] A subset of participants of that trial were assessed by cardiac CT.[17] Among participants 50 to 59 years old at enrollment, very few had a clinically significant coronary artery calcified plaque burden in the coronary arteries after trial completion; the difference was slightly but significantly lower among these younger women who were assigned to estrogen than in those assigned to placebo.[17]

Table 1
Major clinical trials testing the effects of estrogen (with or without progestogen) on CHD risk

Trial	Number of Participants	Intervention	Duration of Intervention	Main Intention-to-Treat Result	Reference
Heart and Estrogen/progestin Replacement Study (HERS)	2763 postmenopausal women with CAD, aged <80 y	Daily CEE 0.625 mg + MPA 2.5 mg vs placebo	Mean 4.1 y	No significant difference in 1° outcome (nonfatal MI or CHD death)	12
Women's Health Initiative (WHI) Estrogen Plus Progestin Trial	16,608 postmenopausal women aged 50–70 y	Daily CEE 0.625 mg + MPA 2.5 mg vs placebo	Mean 5.2 y	HT increased risk of 1° outcome (nonfatal MI or CHD death), HR 1.24 (1.00–1.54)	13
Women's Health Initiative (WHI) Estrogen-Alone Trial	10,739 postmenopausal women aged 50–70 y with prior hysterectomy	Daily CEE 0.625 mg/d vs placebo	Mean 6.8 y	No significant difference in 1° outcome (nonfatal MI or CHD death)	16
Danish Osteoporosis Prevention Study[a]	1006 health perimenopausal or postmenopausal women aged 45–58 y	Triphasic E_2 + norethisterone acetate (or E_2 alone for women with hysterectomy) vs no treatment	Mean 10.1 y	HT associated with decreased risk of 1° outcome (death, admission to hospital for heart failure, or MI) HR was 0.48 (0.26–0.87)	18
Kronos Early Estrogen Prevention study (KEEPS)[b]	727 women aged 42–58 y, within 3 y of final menstrual period	Cyclical micronized progesterone with one of the following: CEE 0.45 mg/d, transdermal 0.05 mg/d, or placebo	4 y	No significant difference among groups in risk of MI, but number of events in all 3 groups was very small	19

[a] This trial did not include a placebo group.
[b] Results of this study are not yet published.

The possibility that younger early postmenopausal women may derive benefit from HT is also suggested by a recent Danish report[18]: 1006 participants, who were, on average, 50 years-old at baseline, were randomly assigned to receive HT (a triphasic regimen of estradiol [E_2] plus norethisterone acetate, or E_2 2 mg/d if they had undergone previous hysterectomy) or no treatment. The primary endpoint was a combined outcome of all-cause mortality, heart failure, or MI. After 10 years of follow-up, participants who were assigned to HT and were aged less than 50 years at baseline had a 65% lower risk of the primary endpoint (HR 0.35, 95% CI 0.13–0.89), whereas women aged 50 years or more at baseline who were assigned to HT did not have a significant reduction in the primary outcome.[18] Unfortunately, there was no placebo and the trial was not blinded.

Recently, initial results of the Kronos Early Estrogen Prevention Study (KEEPS), a 4-year clinical trial of estrogen (either daily CEE 0.45 mg/d or E_2 patch 50 μg/d, combined with micronized progesterone 300 mg/d for 12 days monthly) or placebo reported no difference in rates of MI or subclinical disease (coronary artery calcium or carotid artery intima-media thickness) among the three treatment groups.[19,20] Participants were healthy women aged 42 to 58 years within 3 years of their last menstrual period.[19,20] Because no older women were included in this study, this study does not provide information about HT in younger versus older women.

These pharmacologic intervention trials, almost entirely without CVD benefit despite favorable changes in lipoproteins, may reflect the large estrogen (pharmacologic) doses, the oral route of administration (with first pass liver effects explaining the lipoprotein changes), or the diversity of postmenopausal women, although nearly all trials were conducted in women of European ancestry. Despite effects of HT on serum inflammatory marker, homocysteine, and lipoprotein (a) levels, evidence is lacking to show that changes in these marker levels alter CVD risk.[21,22] It is not clear that effects vary according to whether estrogen is given with progestogen or according to age. Some experts believe that HT may have beneficial effects on CVD risk if it is initiated in early menopause, but not if it is initiated in late menopause, the "timing hypothesis."[16,23] Of note, interaction testing among prespecified subgroup analyses in the WHI Estrogen Plus Progestin trial and the Estrogen-Alone trial found no significant differences in effects of HT on CVD risk according to age or years since menopause.[24] Observed differences in CVD risk among women taking estrogen alone (given to women who have undergone hysterectomy) and women taking estrogen plus progestogen (given to women who have not undergone hysterectomy) may reflect the underlying differences in CVD risk related to undergoing hysterectomy and/or oophorectomy.

Therefore, this article focuses on physiologic endogenous estrogen levels with a systematic review of literature related to endogenous sex steroid levels and CAD among postmenopausal women with natural or surgical menopause.

METHODS

In October 2012, the authors performed a systematic PubMed review using the following keywords (limiting to female humans and English language): serum estradiol AND cardiovascular disease AND menopause (218 references), endogenous estrogen AND cardiovascular disease (310 references), and androgen AND cardiovascular disease (309 references). We retained for inclusion in this article the publications that assessed endogenous serum levels of estrogens, androgens, and/or sex hormone binding-globulins (SHBGs) in relation to CAD (n = 20 articles, **Table 2**) or traditional clinical CAD risk factors among postmenopausal women not taking

exogenous HT (n = 18 articles, **Table 3**). Four publications met criteria for inclusion in both **Tables 2** and **3**.[25–28]

RESULTS

The study design, numbers of participants, and findings of the studies are presented in **Table 2** (CHD outcome) and **Table 3** (CHD risk factors). Wherever possible, 95% CIs are displayed; *P* values are substituted if corresponding 95% CIs were not described in an article.

Associations Between Serum Sex Steroid and SHBG Levels and CVD Among Postmenopausal Women

Study outcomes

Study outcomes varied considerably according to how CAD was assessed and the study design (see **Table 2**). Of the 20 studies, 14 were cross-sectional[25,28–40] and 6 were longitudinal.[26,27,41–44] Information presented in publications was sometimes inadequate for us to determine how CAD was reported or verified (eg, self-report, medical record review).

Of the 20 articles, 3 articles used CAD assessed by coronary angiography as their key outcomes,[29,30,38] 4 articles reported joint outcomes of angioplasty, nonfatal and fatal MI, and coronary artery bypass grafting,[31,34,36,43] 4 articles reported coronary artery calcium assessed by CT,[32,33,35,41] 2 articles used self-reported CVD as outcomes without giving further detail,[25,39] 2 articles reported joint outcomes of coronary revascularization, MI, stroke death, or coronary death,[28,37] 1 article reported MI as an outcome without further details of MI ascertainment,[40] 2 articles reported ischemic heart disease death based on death certificates as an outcome,[26,27] 1 article reported medical record-based MI as an outcome,[42] and 1 article reported primary care physician-assessed CAD as the outcome without providing further criteria for diagnosis.[44]

Associations of circulating estrogens with CAD

In cross-sectional studies outcomes and potential predictors varied across the studies and circulating estrogen levels were not consistently associated with CAD (see **Table 2**). Cross-sectional studies reported no association between estrone (E_1) level and angiographic CAD,[30] positive associations of bioavailable E_2 (bioE_2) level with medical record-confirmed CHD events that disappeared after adjustment for other CAD risk factors,[31] inverse associations between E_2 level and coronary calcium score,[32] lack of association between E_2 level and coronary calcium plaques after adjustment for other risk factors,[33,35] no association of free estrogen index (FEI) with medical record-confirmed CVD,[28,37] no association of free E_2 with angiographic CAD,[38] and inverse association between high serum E_2 levels ($\geq$55 pmol/L) and self-reported CVD.[39] A study with unclear methods for ascertainment of MI reported no association between E_2 level and MI.[40]

In the only longitudinal study that confirmed CAD by angiography, death certificate, and/or medical records, bioE_2, E_2, and/or E_1 levels were not associated with ischemic heart disease death.[26]

Associations of circulating androgens with CAD

In cross-sectional studies outcomes and predictors varied across the studies and circulating androgen levels were not consistently associated with CAD (see **Table 2**). The following associations were suggested regarding testosterone (T) and CAD: positive associations of total T and/or free T and/or free androgen index (FAI)

Table 2
Characteristics of studies examining associations of serum sex steroid and SHBG levels with CVD in postmenopausal women

Cross-Sectional Analyses

Reference	Study Population	CAD Assessment	Results
Braunstein et al,[29] 2008	Women's Ischemia Syndrome Evaluation Study (WISE) study 284 postmenopausal women with chest pain or suspected MI, not taking HT	CAD by coronary angiography	Significant association of total T (OR 1.03, 95% CI 1.00–1.04) and free T (OR 1.12, 95% CI 1.01–1.23) with presence of CAD after adjustment for free E_2 level, but no mention of analysis of E_2 level itself with CAD
Cauley et al,[30] 1994	87 postmenopausal women aged 50–81 y admitted for diagnostic cardiac catheterization, not taking HT (62 cases with $\geq$1 coronary artery $\geq$50% occluded, 25 controls)	Cardiac catheterization (diagnostic)	No significant difference in estrone concentrations between case and control groups in unadjusted and adjusted models
Chen et al,[31] 2011	Nested case-control study 99 postmenopausal healthy women who later had CHD event and 198 controls without CHD, not taking HT	CHD events (percutaneous transluminal coronary angioplasty, nonfatal MI, fatal MI, coronary artery bypass grafting)	Association of top tertile of bioE_2 level with increased CHD event risk (OR 2.10, 95% CI 1.13–3.90), and association of top tertile of SHBG level with decreased CHD event risk (OR 0.50, 95% CI 0.28–0.92) Associations disappeared after adjustment for BMI, cholesterol, HTN
Jeon et al,[32] 2010	436 postmenopausal women not using HT	Coronary artery calcium by CT	Women with higher serum E_2 ($\geq$20 pg/mL) had lower chance of having high coronary artery calcium score ($\geq$100) (crude OR 0.28, 95% CI 0.08–0.95), even after adjusting for age, years since menopause, cholesterol, BMI, blood pressure, HTN, DM, and glucose (adjusted OR 0.25, 95% CI 0.07–0.86)

Khatibi et al,[25] 2007	6440 women aged 50–59 y the Women's Health in the Lund Area Study, half of whom were using HT	Self-reported CVD (details not given)	Among women not using HT, median values of androstenedione, T index, T, and SHBG were similar among cases (prevalent CVD) and controls
Munir et al,[33] 2012	126 asymptomatic perimenopausal women (mean age 50 y), assessment of the Transition of Hormonal Evaluation with Noninvasive Imaging of Atherosclerosis, a substudy of the Prospective Army Coronary Calcium project, HT use not described	Calcified and noncalcified coronary artery plaques by contrast-enhanced multidetector CT angiography	Increased free T levels were significantly associated with increased number of calcified (correlation 0.21) and noncalcified (0.24) coronary artery plaque SHBG level was inversely correlated with total number of coronary artery plaques (−0.14) (associations were not independent of cardiovascular risk factors) E_2 levels were unrelated to plaque presence and extent
Naessen et al,[34] 2010	72 women 70 y old in the Vasculature in Uppsala Seniors, not taking HT	CHD (MI, angina pectoris, coronary bypass, or balloon angioplasty)	Odds of CVD were associated with levels of pregnenolone (OR 0.31, 95% CI 0.11–0.90), 17-hydroxypregnenolone (0.18, 95% CI 0.06–0.61), DHEA (OR 0.33, 95% CI 0.15–0.71), but was not associated with E_2/T or E_2/E1 ratios All associations lost statistical significance after adjustment for statin use, smoking, and BMI

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Table 2
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Cross-Sectional Analyses			
Reference	**Study Population**	**CAD Assessment**	**Results**
Ouyong et al,[35] 2009	1947 postmenopausal women in the Multiethnic Study of Atherosclerosis, not taking HT	Coronary calcium by CT	Serum E_2, T, bioT, and SHBG levels were not associated with coronary calcium, after adjustment for age, race/ethnicity, and BMI Among women with measurable coronary calcium, higher SHBG and lower bioT were associated with greater coronary calcium score, but E_2 levels were not associated with coronary calcium score β-coefficient for ln bioT −1.82 (95% CI −0.35 to −0.02); β-coefficient for ln SHBG level 0.30 (95% CI 0.02–0.57) After additional simultaneous adjustment for levels of all sex steroids, a 2.72-fold (1 log-unit) greater SHBG was associated with a 1.30-fold geometric mean coronary calcium score
Page-Wilson et al,[28] 2009	200 nondiabetic postmenopausal women ≥45 y old not using HT in the Women's Health Study of female health professionals, (98 with incident CVD over 2.9 y follow-up, remainder matched controls without CVD)	Composite endpoint of CVD (1st occurrence of nonfatal MI, coronary revascularization, nonfatal stroke, coronary disease, or stroke death) confirmed by medical records	Higher FAI among CVD cases (geometric mean 0.01 nmol/L) than among controls (geometric mean 0.02 nmol/L) No difference in mean FEI between case and control groups
Patel et al,[36] 2009	344 women aged 65–98 y in the Cardiovascular Health Study (included HT users but adjusted statistical models for HT use)	CHD defined as angina, MI, coronary angioplasty, or coronary artery bypass graft surgery based on medical record review	After adjustment, women with T levels in the top quartile had a 3-fold greater odds of CHD than those in the second quartile (OR 2.95, 95% CI 1.2–7.3), but free T was not significantly associated with CHD risk

Phillips et al,[38] 1997	60 postmenopausal undergoing coronary angiography	CAD by coronary angiography, expressed as % maximal luminal diameter	In models containing free T, E_2, age, BMI, systolic blood pressure, total cholesterol, smoking, and insulin, free T level, but not E_2 level, was significantly associated with extent of CAD (β-coefficient 0.38, $P<.008$) The association was almost identical after additional adjustment for SHBG and DHEA-S levels (β-coefficient 0.41, $P = .03$) SHBG and DHEA-S levels were not significantly associated with extent of CAD in fully adjusted models (containing all sex steroid levels together)
Rexrode et al,[37] 2003	200 postmenopausal women ≥45 y old not using HT in the Women's Health Study of female health professionals, (nested case-control study of 98 women with incident CVD over 2.9 y follow-up, remainder matched controls without CVD)	Composite end point of CVD, (1st occurrence of nonfatal MI, coronary revascularization, nonfatal stroke, coronary disease, or stroke death) confirmed by medical records	Among HT nonusers, E_2 and FEI were not associated with CVD risk but the lowest quartile of SHBG was associated with odds of CVD (OR 2.25, 95% CI 1.03–4.91), and the odds of CVD increased with increasing quartiles of FAI (p_{trend} 0.03) (associations were only statistically significant before adjustment for BMI, HTN, DM, and elevated cholesterol)
Shakir et al,[39] 2007	104 postmenopausal women with CVD (MI or stroke) and 208 controls, stratified by HT use	Self-reported CVD	In postmenopausal women who were not taking HT, E_2 levels ≥55 pmol/L were less frequent among cases than among controls ($P = .04$, exact frequencies not presented) Median T, E_2, androstenedione, and SHBG levels were not different in cases than controls

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Table 2
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Cross-Sectional Analyses

Reference	Study Population	CAD Assessment	Results
Skalba et al,[40] 2003	35 postmenopausal women (18 women with CVD, 17 women without CVD) aged 65–75 y not using HT	Myocardial infarction or coronary insufficiency in the past 5 y, details not further described	No difference in total T, free T, androstenedione, DHEA, DHEA-S, SHBG, or E_2 levels between the groups with CVD and without CVD

Longitudinal Studies

Reference	Study Population	Cardiovascular Disease Assessed	Results
Barrett-Connor et al,[26] 1995	Rancho Bernardo study, 651 Caucasian postmenopausal women not using HT, 19-y follow-up	Ischemic heart disease death confirmed by death certificates	Age-adjusted bioT, bioE_2, estrone, E_2, and T levels did not predict age-adjusted ischemic heart disease death
Calderon-Margalit et al,[41] 2010	1629 women aged 18–30 at baseline in the Coronary Artery Risk Development in Young Adults (CARDIA) study, population-based cohort study, 20-y follow-up, statistical models adjusted for oral contraceptive use	Coronary artery calcified plaques by chest CT assessed at year 20	SHBG level (mean of years 2, 10, and 16) was inversely associated with the presence of coronary artery calcium (SHBG > median vs $\leq$ median adjusted OR 0.59, 95% CI 0.40–0.87) No association of total or free T with coronary artery calcified plaques E_2 levels not examined
Goodman-Gruen et al,[27] 1996	624 women followed for 19 y for incident ischemic heart disease death, not using HT	Ischemic heart disease death by death certificate	SHBG levels were not significantly associated with ischemic heart disease mortality either before or after adjustment for covariates
Lapidus et al,[42] 1986	253 postmenopausal women who were 54 or 60 y old at baseline, not taking HT, 12-y follow-up	Nonfatal or fatal MI, angina, or stroke confirmed by medical record review	Plot of the 12-y incidence of MI vs SHBG concentration was U-shaped Statistical analysis of the U-shaped association was not performed due to small number of participants

Laughlin et al,[43] 2010	Rancho Bernardo study, prospective population-based study, 639 white postmenopausal women 50–91 y old not using HT, median follow-up 12.3 y	Incident CHD (nonfatal MI, fatal MI, coronary revascularization)	Women in lowest quintile of T had 1.62-fold increased risk of incident CHD (95% CI 1.10–2.39), after adjustment for lifestyle, adiposity, E2, and CHD risk factors There was a U-shaped curve for association of bioT with CHD after adjustment for lifestyle, adiposity, E_2, and CHD risk factors Compared with the other quintiles, women with highest bioT quintiles had 1.79-fold higher CHD risk (95% CI 1.03–3.16) Women with lowest bioT quintiles had 1.96-fold higher CHD risk (95% CI 1.13–3.41) Associations between E_2 level and CHD events were not described
Sievers et al,[44] 2010	Prospective cohort study with 4.5-y follow-up of 2914 female patients between 18 and 75 y from representative sample of Germany primary care practices, 1394 of the 2914 women were postmenopausal analyses among women not taking HT were performed	CAD as ascertained by patient's primary care physician	Patients with total T in the lowest quintile had higher risk of cardiovascular events during follow-up compared with the higher quintiles (quintiles 2–5 vs quintile 1 crude HR 0.54, 95% CI 0.38–0.77; adjusted HR 0.68, 95% CI 0.48–0.97) E2 levels were not examined

Abbreviations: bioE_2, bioavailable E_2; bioT, bioavailable testosterone; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; FAI, free androgen index; FEI, free estrogen index; OR, odds ratio; P_{trend}, P values for test of trend; T, testosterone.

Table 3
Characteristics of studies examining associations of serum sex steroid and sex hormone-binding globulin levels with cardiovascular risk factors in postmenopausal women

Cross-Sectional Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Barrett-Connor et al,[26] 1995	Rancho Bernardo study, 651 white postmenopausal women not using HT, 19-y follow-up	SBP, DBP, fasting glucose, BMI, smoking	After adjustment for age, and BMI, mean levels of the hormones (androstenedione, T, E_1, E_2, bioE, and bioT) did not vary significantly by category of risk factors (SBP, DBP, cholesterol, fasting glucose, BMI, history of smoking)
Goodman-Gruen et al,[45] 2000	Rancho Bernardo study, 633 white postmenopausal women $\geq$55 y old not using HT	IGT, type 2 DM, fasting glucose, BMI, physical activity, smoking	After adjustment for age and BMI, women with IGT had significantly higher bioT (0.18 nmol/L vs 0.15 nmol/L), total E_2 (23.3 pol/L vs 20.6 pmol/L) and bioE_2 (11.4 pmol/L vs 10.3 pmol/L) levels than women with normal glucose tolerance After adjustment for age and BMI, women with type 2 DM had significantly higher bioT (0.18 nmol/L vs 0.15 nmol/L), total E2 (25.4 pmol/L vs 20.6 pmol/L) and bioE_2 (15.0 pmol/L vs 10.3 pmol/L) levels than women with normal glucose tolerance After adjustment for age, median values of total E_2 were higher above vs below median BMI (27.6 vs 21.2 pmol/L), higher above vs below median waist-to-hip ratio (24.2 vs 22.5 pmol/L), and higher with physical activity less than 3 times weekly (22.6 vs 21.4 pmol/L) After adjustment for age, median values of bioE_2 were higher above vs below median BMI (16.3 vs 11.1 pmol/L), higher above vs below median waist-to-hip ratio (13.6 vs 12.1 pmol/L), and higher with physical activity less than 3 times weekly (14.6 vs 11.9 pmol/L) Median values of total T and bioT did not differ according to categories of waist-to-hip ratio, smoking, or physical activity Median bioT level was higher above vs below the median BMI (0.19 vs 0.16 nmol/L) Median values of total T did not differ according to BMI above vs below median

Haffner et al,[46] 1995	263 postmenopausal women not using HT in a population-based Beaver Dam Eye Study	HDL, HDL/total cholesterol ratio, BMI, glycosylated hemoglobin, SBP, DBP	Before adjustment for other factors, E_1 was significantly (inversely) correlated with HDL/total cholesterol, but was not significantly correlated with BMI, total cholesterol, HDL, glycosylated hemoglobin, SBP, or DBP Before adjustment for other factors, DHEA-S was not correlated with BMI, total cholesterol, HDL, HDL/total cholesterol, glycosylated hemoglobin, SBP, or DBP Before adjustment for other factors, SHBG was inversely correlated with BMI ($r = -0.53$, $P<.001$), glycosylated hemoglobin ($r = -0.34$, $P<.001$), and DBP ($r = -0.25$, $P<.01$), and positively correlated with HDL and HDL/total cholesterol (r for each = .31, $P<.001$), but was not correlated with total cholesterol or SBP In models containing all hormonal predictors, age, BMI, glycosylated hemoglobin, presence of diabetes, alcohol, smoking, and physical activity, total T remained associated with total cholesterol, HDL/total cholesterol, and DBP; SHBG remained associated with total cholesterol (inversely), HDL, HDL/total cholesterol, glycosylated hemoglobin (inversely), and DBP (inversely); free T remained associated with HDL; E_1 remained associated with HDL (inversely), HDL/total cholesterol (inversely), and SBP
Kalish et al,[47] 2003	Postmenopausal Estrogen/ Progestin Interventions Trial, 845 postmenopausal women 45–64 y old not using HT	HOMA-IR, BMI	Correlations of BMI with bioT, E_2, bioE_2, and SHBG, but not T, were statistically significant Correlations of HOMA-IR with bioT, E_2, bioE_2, and SHBG (inversely), but not T, were statistically significant After adjustment for BMI and waist-to-hip ratio, bioE_2 and SHBG were significantly associated with being in the highest quartile of HOMA-IR: OR for 4th quartile vs 1st quartile of bioE_2 2.7, p_{trend} 0.01; OR for 4th quartile vs 1st quartile of SHBG 0.2, p_{trend} <0.001 After adjustment for BMI and waist-to-hip ratio, bioT, total T, and total E_2 were not associated with odds of being in highest quartile of HOMA-IR

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Table 3
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Cross-Sectional Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Khatibi et al,[25] 2007	6440 women aged 50–59 y the Women's Health in the Lund Area Study, half of whom were using HT	Total cholesterol, TG, LDL, HDL	Among HT nonusers, after adjustment for age, smoking, and BMI, T was significantly associated with total cholesterol (β-coefficient 0.029, $P<.05$), TG (β-coefficient −0.152, $P<.001$), LDL (β-coefficient 0.031, $P<.05$), and HDL (β-coefficient 0.41, $P<.001$) After adjustment for age, smoking, and BMI, SHBG was significantly associated with HDL (β-coefficient, $P<.01$), but was not associated with total cholesterol, TG, or LDL After adjustment for age, smoking, and BMI, E_2 was significantly associated with total cholesterol (β-coefficient −0.001, $P<.001$) and LDL (β-coefficient −0.001, $P<.001$), but was not significantly associated with TG or HDL Androstenedione was not significantly associated with cholesterol, TG, LDL, or HDL
Lambrinoudaki et al,[48] 2006	598 postmenopausal women not taking HT	HOMA-IR, HDL, LDL, TG	Mean levels of TG were significantly higher in women with highest quartile of T and FAI, and significantly lower in women with highest quartile of SHBG, compared with lower quartiles, but did not differ by quartile of E_2, androstenedione, DHEA-S, or FEI Mean TC levels were higher in women with T or FAI values in the highest quartile compared with other quartiles, but did not differ by quartile of E_2, androstenedione, DHEA-S, SHBG, or FEI Mean LDL was higher in higher quartiles of E_2, T and FAI compared with lower quartiles, but did not differ by quartile of androstenedione, DHEA-S, SHBG, or FEI Mean HDL was higher in higher quartiles of SHBG and in lower quartiles of E_2, T, FEI, and FAI compared with lower quartiles, but did not differ by quartile of androstenedione or DHEA-S

			Mean HOMA-IR was higher in lower quartiles of SHBG and in higher quartiles of E_2, T, FEI, and FAI compared with lower quartiles, but did not differ by quartile of androstenedione or DHEA-S After adjustment for age, BMI, smoking, alcohol, and physical activity, only certain associations persisted: FAI and T with total cholesterol; T, SHBG (inversely), and FAI with TG; T, androstenedione, and FAI with LDL; E_2 (inversely), T (inversely), SHBG, FAI (inversely), and FEI (inversely) with HDL; T, SHBG (inversely), FAI, and FEI with HOMA-IR
Masi et al,[49] 2009	52 women postmenopausal women aged 55–69 y in Illinois, not using HT	SBP	Out of 14 estrogen metabolites measured by mass spectrometry, after adjustment for age, BMI, race or ethnicity, and vasoactive medications, 2 of them were independently (inversely) associated with SBP: ln 16α-hydroxyestrone (β-coefficient -5.3, $P<.05$) and ln 16-ketoestradiol (β-coefficient -4.7, $P<.05$ No significant association between serum E_2 and SBP
Mesch et al,[50] 2008	124 women, of whom 31 were postmenopausal, none using HT	HOMA, TG, HDL, LDL, waist circumference	SHBG was inversely correlated with waist circumference ($r = -0.34$, $P = .006$), HOMA-IR ($r = -0.41$, $P = .0002$), LDL ($r = -0.28$, $P = .02$), TG ($r = -0.40$, $P = .0005$), and positively correlated with HDL ($r = 0.36$, $P = .003$) FAI was correlated with waist circumference ($r = 0.40$, $P = .001$), HOMA-IR ($r = 0.33$, $P = .003$), and TG ($r = 0.31$, $P = .01$) and inversely correlated with HDL ($r = -0.25$, $P = .04$), but not significantly associated with LDL After adjustment for waist circumference, inverse correlation persisted between SHBG and HOMA-IR, but correlations between SHBG and lipoproteins, and correlations of FAI with HOMA-IR, TG and HDL were lost

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Table 3
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Cross-Sectional Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Mudali et al,[51] 2005	172 postmenopausal women without carotid atherosclerosis, not taking HT	Total cholesterol, TG, HDL, LDL	After adjustment for age, race, smoking, alcohol intake, physical activity, SBP, fasting glucose, and presence of diabetes, SHBG was positively associated with HDL level (β-coefficient 3.11 per SD in SHBG, $P = .004$) and inversely associated with total cholesterol (β-coefficient −9.28 per SD in SHBG, $P = .007$), TG (β-coefficient −20.5 per SD in SHBG, $P<.0001$), and LDL level (β-coefficient −7.87 per SD in SHBG, $P = .01$) No significant associations of E1, total T, or FAI with total cholesterol, TG, HDL, or LDL after adjustment
Phillips et al,[52] 1997	24 hypertensive and 19 healthy postmenopausal women not taking HT	Systolic blood pressure	Mean values of free T were higher in the hypertensive than control group (1.23 vs 0.83 pg/mL, $P = .01$), but mean levels of T, E_2, androstenedione, SHBG and DHEA-S were not statistically different between hypertensive and control groups
Shelley et al,[53] 1998	363 Australian nondiabetic women 45–56 y old not taking HT	HDL, LDL, TG, DBP	HDL was higher with increasing quartiles of E_2 (p_{trend} 0.03), and lower with increasing quartiles of FAI (p_{trend} 0.0007) LDL was higher with increasing quartile of FAI (p_{trend} 0.002) was not significantly related to quartile of E_2 TG levels were lower with increasing quartile of E_2 (p_{trend} 0.02) and higher with increasing quartiles of FAI (p_{trend} 0.0003) After adjustment for age, BMI, smoking, alcohol intake, and physical activity, the only association that remained was a positive association between log FAI and LDL (β-coefficient 1.74, standard error 0.49) Neither FAI nor E_2 level was significantly associated with DBP

Tufano et al,[54] 2004	24 normal-weight premenopausal women, 24 normal-weight postmenopausal women, 24 obese premenopausal women, 20 obese postmenopausal women, all free of HTN and DM	Waist-to-hip ratio, BMI, cholesterol, HDL, LDL, TG, HOMA, SBP, DBP	Significant inverse correlations of waist-to-hip ratio with T ($r = -0.40$, $P<.01$) and SHBG ($r = -0.33$, $P<.03$), but no correlation with FAI Significant inverse correlation of TG with SHBG ($r = -0.31$, $P<.01$) and positive correlation of TG with FAI ($r = 0.47$ ($P<.003$), but no correlation with T Significant inverse correlation of HOMA with SHBG ($r = -0.38$, $P<.01$) and positive correlation of HOMA with FAI ($r = 0.77$, $P<.0001$), but no correlation with T level No significant correlations of T, FAI, or SHBG with the following: BMI, cholesterol, HDL, LDL, SBP, or DBP

Longitudinal Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Ding et al,[56] 2007	Postmenopausal women health professionals in the Women's Health Study, mean age 60 y, not taking HT, free of baseline CVD and DM, average follow-up 10 y	Incident DM confirmed by medical records	E_2, free E_2, free T, T, and DHEA-S were each strongly, positively associated with risk of type 2 DM, even after adjustment for BMI, smoking, alcohol use, exercise, blood pressure, past HT use, remainder of hormonal predictors, and other covariates RR for developing type 2 DM in the highest vs lowest quintiles were: E_2 RR 12.6 (95% CI 2.83–56.3); free E_2 RR 13.1 (95% CI 4.18–40.8), T RR 4.15 (95% CI 1.21–14.2), free T RR 14.8 (95% CI 4.44–49.2) DHEA-S was not significantly associated with risk of incident type 2 DM when adjusted for age and race

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Table 3
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Longitudinal Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Goodman-Gruen et al,[27] 1996	624 women aged 50–82 in the Rancho Bernardo Study, not using HT, 19-y follow-up	Fasting glucose, HFL, BMI, SBP, DBP, cholesterol, TG	After adjustment for age, SHBG level inversely associated with BMI ($r = -0.16$, $P<.005$) After adjustment for age and BMI, SHBG correlated negatively with fasting glucose ($r = -.08$, $P<.05$) Inverse correlation between SHBG and TG ($r = -0.09$, $P<.05$) and positive correlation between SHBG and HDL ($r = 0.18$, $P<.005$) after adjustment for age, but not after additional adjustment for BMI No significant correlations between SHBG and SBP, DBP, TG, or cholesterol levels after adjustment for age or for both age and BMI E_2 not examined
Janssen et al,[57] 2008	949 participants in the Study of Women's Health Across the Nation who had never taken HT, 9-y follow-up	Metabolic syndrome by National Cholesterol Education Program Adult Treatment Panel III criteria	After adjustment for age, ethnicity, BMI, smoking, and other covariates, change in bioT level was positively associated (OR 1.10, 95% CI 1.01–1.20), and change in SHBG was inversely associated (OR 0.87, 95% CI 0.81–0.93), with odds of developing metabolic syndrome Change in E_2 level or T level were not significantly associated with odds of developing metabolic syndrome Change in E_2 level was positively associated with change in HDL, and inversely associated with change in SBP, but was not associated with change in TG or glucose level Change in bioT level was positively associated with change in waist circumference and change in fasting glucose level, but inversely associated with change in HDL

			Change in SHBG level was positively associated with change in HDL level and inversely associated with change in fasting glucose level In fully adjusted models: significant associations of change in bioT (β-coefficient 0.14, $P \leq .01$) and change in SHBG (β-coefficient −0.21, $P \leq .001$) with change in waist circumference; significant associations of change in bioT (β-coefficient −0.48, $P \leq .01$) and change in SHBG (β-coefficient 0.81, $P \leq .001$) with change in HDL; significant association of change in T with change in TG (β-coefficient 1.92, $P \leq .05$); significant associations of change in E_2 (β-coefficient −0.41, $P \leq .01$) with change in SBP In fully adjusted models: no associations of change in E_2 or T and change in waist circumference or change in HDL; no associations of change in SHBG or change in bioT with change in TG or change in SBP; no association of change in E_2 and change in TG; no association of change in T and change in SBP
Kalyani et al,[58] 2009	1612 postmenopausal participants aged 45–84 y of the Multi-Ethnic Study of Atherosclerosis (MESA), free of DM at baseline, median follow-up 4.7 y	Incident type 2 MD based on fasting glucose and/or treatment of DM	After adjustment for age, race/ethnicity, BMI, HOMA-IR, LDL, HDL, TG, SBP, smoking, physical activity, and other factors, there was a significantly greater risk of developing incident DM across higher quartiles of E_2 (HR 1.92 for quartile 4 vs quartile 1, $p_{trend} = 0.01$), and lower quartiles of SHBG (HR 0.52 for quartile 4 vs quartile 1, p_{trend} 0.02) Association between quartile of bioT and risk of incident diabetes (HR 2.45 for quartile 4 vs quartile 1, 95% CI 1.48–4.03) was no longer significant after adjustment No significant associations between DHEA and risk of developing diabetes before or after adjustment

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Table 3
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Longitudinal Studies

Reference	Study Population	Cardiac Risk Factors Examined	Results
Oh et al,[55] 2002	Rancho Bernardo study, 233 women 55–89 y old not using HT, 8-y follow-up	Fasting and after challenge glucose and insulin, incident DM	After adjustment for age, T was correlated with HDL (r = 0.20, $P<.01$) but not with BMI, waist-to-hip ratio, SBP, DBP, or HOMA-IR; bioT was correlated with BMI (r = 0.13, $P<.05$) and DBP (r = 0.16, $P<.05$) but not with waist-to-hip ratio, SBP, HDL, or HOMA-IR; E_2 was correlated with BMI (r = 0.13, $P<.05$) but not with waist-to-hip ratio, SBP, DBP, HDL, or HOMA-IR; and bioE_2 was correlated with BMI (r = 0.21, $P \leq .01$), waist-to-hip ratio (r = 0.20, $P<.01$) and TG (r = 0.22, $P<.01$), but not with SBP, DBP, or TG
Page-Wilson et al,[28] 2009	200 nondiabetic postmenopausal women $\geq$45 y old not using HT in the Women's Health Study of female health professionals, (98 with incident CVD over 2.9 y follow-up, remainder matched controls without CVD)	Hemoglobin A1c	After adjustment for development of CVD and age, ln FAI (β-coefficient 0.02, $P = .0004$), ln FEI (β-coefficient 0.01, $P = .0004$), and ln SHBG (β-coefficient -0.04, $P = .0003$) were significantly associated with ln hemoglobin A1c, but E_2 and T were not significantly correlated with hemoglobin A1c After further adjustment for BMI, associations between FEI and hemoglobin A1c did not persist

Abbreviations: bioE_2, bioavailable E_2; bioT, bioavailable testosterone; BMI, body mass index; DBP, diastolic blood pressure; DHEA-S, DHEA-sulfate; DM, diabetes mellitus; FAI, free androgen index; FEI, free estrogen index; HOMA-IR, homeostatic model assessing insulin resistance; HTN, hypertension; IGT, impaired glucose tolerance; ln, natural log; OR, odds ratio; r, correlation; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; T, testosterone; TG, triglycerides.

with medical record-confirmed CAD[28,29,36] and radiographically-assessed CAD,[33] no association between T and self-reported CVD,[25,39] inverse associations between bioavailable T (bioT) and radiographically-assessed CAD,[35] inverse associations between free T and angiographically-confirmed CAD.[38] A study that lacked detail regarding how MI was ascertained reported no association between T or free T level and MI.[40] Regarding androgens other than T, cross-sectional studies found no associations between androstenedione and self-reported CVD,[25,39] dehydroepiandrosterone (DHEA) level and medical record-confirmed CHD,[34] or DHEA-sulfate (DHEA-S) level and angiographic CAD.[38] A study reported no association between androstenedione, DHEA, or DHEA-S level and MI, but did not provide detail regarding how MI was ascertained.[40]

In longitudinal studies that confirmed CAD by medical records and/or death certificates, bioT levels did not predict ischemic heart disease death[26] and free T levels were not associated with radiographic coronary artery plaques,[41] but there was a U-shaped curve for the association between bioT and CHD, with the risk of CHD being higher in both the lowest and the highest quintiles of bioT, and lower in the middle quintiles.[43] This U-shaped curve may partially explain the variability in associations between circulating androgen levels and CAD in the cross-sectional studies.

Associations of SHBG level with CAD

In cross-sectional studies outcomes and potential predictors varied across the studies and SHBG levels were not consistently associated with CAD (see **Table 2**). Cross-sectional studies reported inverse association of SHBG with medical record-confirmed CHD events,[31] no association of SHBG level with self-reported CVD,[25] inverse associations between SHBG level and number of radiographic coronary artery plaques,[33] positive associations between SHBG level and coronary artery calcium score,[35] no association between SHBG level and angiographic CAD,[38] no association between SHBG level and self-reported CVD,[39] and inverse associations of SHBG level with medical record-confirmed CVD events that disappeared after adjustment for other cardiac risk factors.[37] A study with unclear methods for ascertainment of MI reported no association between SHBG level and MI.[40]

In longitudinal studies that confirmed CAD by medical records and/or death certificates, one longitudinal study described a U-shaped association between SHBG level and 12-year incidence of MI ascertained from medical records, although the number of study participants was small.[42] In another study, SHBG level was not associated with ischemic heart disease death assessed on death certificates.[27]

Associations of progesterone-related metabolites with CAD

A cross-sectional study found serum pregnenolone level and 17-hydroxypregnenolone level to be associated with significantly lower odds of medical record-confirmed CVD (see **Table 2**).[34]

Association Between Serum Sex Steroid and SHBG Levels and CVD Risk Factors Among Postmenopausal Women

Summary of cardiac risk factors

Specific cardiovascular risk factors examined varied considerably across studies, spanning glucose tolerance testing, a clinical diagnosis of diabetes mellitus (DM), fasting glucose level, body mass index, physical activity, smoking, HDL, total cholesterol, LDL cholesterol, triglycerides, glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, waist circumference, waist-to-hip ratio, and homeostasis model assessing insulin resistance (HOMA-IR) (see **Table 3**). Of the 18 studies, 12 were cross-sectional[25,26,45–54] and 6 were longitudinal.[27,28,55–58]

Associations of circulating estrogens with CAD risk factors

Because the cardiac risk factors examined varied widely across cross-sectional studies, and associations were not consistent across studies, we summarize here the results from longitudinal studies and focus on DM-related associations (see **Table 3**). With regard to studies of DM and insulin resistance, longitudinal studies reported positive associations of circulating E_2 and free E_2 levels with incident DM,[56,58] and no association between E_2 and HOMA-IR.[55] Some associations between FEI and hemoglobin A1c disappeared after adjustment for other risk factors.[28]

Associations of circulating androgens with CAD

Longitudinal studies of DM and insulin resistance reported positive associations of free T and total T with incident DM,[56] association of bioT level with increased odds of developing metabolic syndrome,[57] no correlation of T with HOMA-IR,[55] and positive association between FAI and hemoglobin A1c level (see **Table 3**).[28] However, one longitudinal study reported that associations between bioT level and incident DM disappeared after adjustment for other risk factors.[58]

Associations of SHBG level with CAD

Longitudinal studies of DM and insulin resistance showed inverse correlations of SHBG level with fasting glucose level,[27] a protective association of increases in SHBG level with decreased odds of developing metabolic syndrome,[57] an inverse association of SHBG level with incident diabetes risk,[58] or an inverse association between SHBG level and hemoglobin A1c level (see **Table 3**).[28]

DISCUSSION

In this review, six longitudinal studies reported circulating sex steroid and SHBG levels in relation to incident CAD in postmenopausal women. In these longitudinal studies, circulating estrogen levels were usually not associated with ischemic heart disease death. In one longitudinal study each, associations of bioT with CHD and associations of SHBG level with incidence of MI were U-shaped. The six longitudinal studies did not consistently find associations between estrogen levels and incident DM or insulin resistance, but circulating androgen levels (free T, bioT) were associated with incident DM and metabolic syndrome. In four out of four longitudinal studies, SHBG level was inversely related to both the incidence of metabolic syndrome and the incidence of DM. Many longitudinal studies reported that associations of circulating sex steroid levels and CAD or CAD risk factors disappeared after adjustment for other CAD risk factors, highlighting the difficulty of generalizing results across studies, and raising questions about mechanisms for associations and possible over-adjustment.

We encountered challenges in interpretation of results because of substantial heterogeneity across studies regarding how CAD outcomes were ascertained or defined and tremendous diversity regarding which sex steroid levels were measured (eg, free, total, bioavailable). Moreover, many older studies used assays that did not have adequate sensitivity to detect the very low E_2 levels characteristic of postmenopausal women, obscuring the ability to detect associations between very low E_2 levels and subsequent development of CAD. Finally, serum sex steroid levels do not capture the entire hormonal milieu at the tissue level. Many, if not most, publications did not address the influence of body fat or fat distribution on hormone levels and CVD risk.

Despite these caveats, there is adequate reason to seek evidence for associations of circulating estrogen levels and CAD. Estrogen receptors (ERs) exist in the vascular endothelium, vascular smooth muscle, and adventitial cells of humans.[59] This localization of ERs may explain why brachial artery flow-mediated dilation (assessed by

ultrasound) is inversely associated with years since menopause.[60] Moreover, in postmenopausal women, brachial artery flow-mediated dilation was positively associated with serum E_2 level.[61]

Estrogen has both genomic and nongenomic effects on endothelial and vascular smooth muscle cells.[62] Estrogen stimulates gene transcription and estrogen-regulated genes themselves encode transcription factors.[59] Adding yet another layer of complexity to the study of endogenous estrogen's link with CAD, the vascular endothelium contains polymorphisms in the genes encoding ERs and truncated forms of ERα and ERβ.[59] These polymorphisms may influence the development of CHD by influencing ER binding. Also, polymorphisms in ER may also influence development of CHD by influencing E_2 levels themselves. For example, in the Framingham Heart Study, postmenopausal carriers of the ESR2 (CA)n long allele (vs short/long or short/short allele), and the rs1256031C allele (vs T/T), had moderately higher E_2 levels.[63] Finally, ERα polymorphisms have been linked with lipoprotein metabolism in postmenopausal women.[64] ERβ expression is increased in women with CAD.[59]

Beyond the genes themselves, modification of genes, such as occurs with gene methylation, should be considered as potential factors influencing the effects of endogenous estrogen on the heart such that the same genetic code can result in different phenotypic effects depending on the degree of gene methylation. In human right atrium, there is an age-related increase in ERα gene methylation, and human internal mammary arteries contain significant levels of ERα gene methylation.[65] Moreover, ERα gene methylation is increased in coronary atherosclerotic plaques compared with normal proximal aortic tissue.[65]

In the future, even if ovarian senescence-associated hormonal changes are confirmed to be associated with CAD in cohort studies of postmenopausal women, there may be other components explaining the gender differences in CAD patterns. Theoretically, gender differences in heart disease mortality rates with age could be due to adverse influences of menopause, or to protective effects of the premenopausal circulating hormonal milieu. To explore this question, a recent study analyzed ischemic heart disease mortality in England, Wales, and the United States among three birth cohorts: 1916 to 1925, 1926 to 1935, and 1936 to 1945.[66] The study compared associations between mortality rates and age modeled under two alternative assumptions: a linear relationship, or a proportional (logarithmically-associated) relationship. The proportional age-related changes in ischemic heart disease mortality fit the longitudinal mortality data better than absolute age-related changes in mortality did, suggesting that acceleration in heart disease mortality among men ceased at around age 45, whereas the CHD association in women did not change at the age of menopause—although the expected postmenopausal decrease in breast cancer risk after age 50 was readily apparent. These observations suggest that the reason postmenopausal women have CVD risks more like those of older men is not explained by female estrogen deficiency but by the decreasing risk in surviving old men.[66] This paper also shows similar decreases in CVD mortality in both sexes during the past three decades despite the ongoing obesity epidemic, which could be due to behavior change and medication use. This will certainly make it more difficult to understand hormones and women's health in the future, and suggests the potential added value of previous cohort studies when data were collected before widespread medical or lifestyle interventions.

SUMMARY

In conclusion, the associations of circulating androgens and SHBG with CHD, incident DM, and metabolic syndrome in longitudinal studies of postmenopausal

women are of great interest and are clearly worthy of future study. Unfortunately, limited information exists regarding the biologic mechanisms underlying these associations. The few longitudinal studies did not support the existence of notable associations between circulating estrogen levels and CAD incidence in postmenopausal women.

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