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Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women

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Abstract

***Objectives*—To examine the association between androstenedione, total and bioavailable testosterone, oestrone, and total and bioavailable oestradiol concentrations and the risk of death from cardiovascular and ischaemic heart disease.**

***Design*—19 year old population based prospective study with 99·9% follow up.**

***Setting*—Rancho Bernardo, California.**

***Subjects*—651 postmenopausal women, none taking oestrogen.**

***Main outcome measures*—Concentrations of plasma sex hormones measured by radioimmunoassay in an endocrinology research laboratory. Cardiovascular and ischaemic heart disease deaths assessed by death certificate; 85% of 30% sample validated by record review.**

***Results*—Age adjusted concentrations of sex hormones did not differ significantly in women with and without a history of heart disease at baseline and did not predict cardiovascular death or death from ischaemic heart disease. Most 95% confidence intervals for the age adjusted relative risk of cardiovascular death or death from ischaemic heart disease were narrow, and all included one. Endogenous oestrogen concentrations were not associated with significantly more favourable risk factors for heart disease, and testosterone was not associated with less favourable risk factors.**

***Conclusion*—These prospective data do not support a causal or preventive role for endogenous oestrogens or androgens and cardiovascular mortality in older women.**

Introduction

At every age women have less heart disease than men, and this difference is not explained by any of the classic risk factors for heart disease.[1] In countries with very different death rates from heart disease, diets, and lifestyles, the sex ratio for fatal coronary heart disease in men and women aged 45-69 years shows a surprisingly consistent 2·5 to 4·5-fold excess risk in men,[2] suggesting an endogenous protective trait in women. One obvious candidate is oestrogen.

A cardioprotective role for oestrogen is supported by the observation that the excess risk of cardiovascular disease in women who underwent oophorectomy in young adulthood is prevented by oestrogen.[3] In addition, a large body of observational data shows a significant reduction in the risk of heart disease in women who take oestrogen after a non-surgical menopause.[4,5] The apparent prevention of heart disease in women using exogenous oestrogen is seen when pharmacological doses are given by mouth. It is not known whether physiological concentrations of oestrogen are also associated with a reduced risk of cardiovascular disease. A prospective study of premenopausal women, who are at low risk of cardiovascular disease and have cyclic hormone concentrations, would be difficult. Postmenopausal women have more heart disease and more stable concentrations of their primary oestrogen, oestrone, such that a single assay should reflect hormonal state well enough for epidemiological studies.[6,7]

Only one cross sectional study has reported the relation of circulating oestrone concentrations to heart disease in postmenopausal women; no association was found.[8] To our knowledge, no prospective study has reported the relation of endogenous oestrogen or androgen to cardiovascular disease in women. We describe the absent association of endogenous sex hormones and cardiovascular death in a prospective population based study of postmenopausal women who were followed for 19 years.

Methods

Between 1972 and 1974 all adult residents in Rancho Bernardo, California, were invited to participate in a study of risk factors for cardiovascular disease, and 82% did so. Participants were seen between 7 30 and 11 00 am after a requested 12 hour fast. A standardised questionnaire was completed which included questions about personal and family history of heart disease (heart attack or heart failure), history of cigarette smoking, and current use of oestrogen. Blood pressure was measured with a mercury sphygmomanometer after the participant had been seated for at least five minutes. Height and weight were measured with the participants wearing lightweight clothing without shoes; body mass index (weight (kg)/height $(m)^2$) was used to estimate obesity. Total plasma cholesterol concentration was measured in a Centers for Disease Control standardised lipid research clinic laboratory with an AutoAnalyzer; lipoprotein concentrations were not determined at baseline. Fasting plasma glucose concentration was measured in a hospital diagnostic laboratory with a hexokinase method. Plasma for endogenous sex hormone assays was obtained and frozen at −70°C.

Between 1984 and 1986 sex hormones were measured in an endocrinology research laboratory (S S C Yen) by radioimmunoassay with thawed specimens obtained from postmenopausal women at the 1972-4 venepuncture.[9] Previous work in this laboratory demonstrated no hormone deterioration over 15 years when samples were frozen and stored in

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tightly sealed containers. Bioavailable testosterone and bioavailable oestradiol were determined by using a method modified from Tremblay and Dube.[10] The sensitivity and the between and within assay coefficients of variation, respectively, were 1·8 nmol/l (30 pg/ml), 4% and 8% for androstenedione; 0·1 nmol/l (25 pg/ml), 4% and 10% for testosterone; 26 pmol/l (7 pg/ml), 15% and 16% for oestrone; 18 pmol/l (5 pg/ml), 8% and 12% for oestradiol; 0·03 nmol/l (8 pg/ml), 5·8% and 6·0% for bioavailable testosterone and 4 pmol/l (1 pg/ml), 3·7% and 4·2% for bioavailable oestradiol. Six women with oestradiol concentrations and three with oestrone concentrations below the sensitivity of the assay were excluded from these analyses, as were women who reported use of oestrogen at baseline (n=302). All oestradiol and oestrone concentrations were consistent with postmenopausal status.

Vital status was determined annually for 99·9% of the cohort to 1992, a 19 year follow up. Death certificates, obtained for all those who died, were coded for underlying cause of death by a certified nosologist using the *International Classification of Diseases*, adapted ninth revision (ICD-9). Cardiovascular disease included codes 400 to 438 and ischaemic heart disease codes 410 to 414. Review of medical records by a panel of cardiologists in a 30% sample of those whose death certificates included a diagnosis of fatal cardiovascular disease confirmed the diagnosis in 85%.

Data were analysed by using SAS.[11] Logarithms of hormone concentrations were used for analysis to account for slightly skewed distributions. Results were similar for untransformed data, which are shown here. Age adjusted mean hormone concentrations were compared between women with and without known heart disease at baseline. All other analyses excluded women with prevalent heart disease. Pearson's partial correlation coefficients were calculated to assess the strength of the association between the hormones and risk factors for cardiovascular disease. Mean hormone concentrations adjusted for age were compared for high and low risk categories of coronary heart disease by using analysis of covariance. The independent contribution of the measured hormones, age, systolic blood pressure, diastolic blood pressure, plasma cholesterol concentration, fasting plasma glucose, obesity, and cigarette smoking to the risk of death from cardiovascular disease or ischaemic heart disease was assessed by using Cox's proportional hazards model.[12] All P values are two tailed. No adjustment was made for multiple comparisons; instead, exact P values are shown in the tables: in the text the term significance refers to $P<0·05$ or 95% confidence intervals that do not include one.

Results

Table I shows that sex hormone concentrations were similar in the 42 women who had and the 651 who did not have heart disease at baseline. Adjustment for body mass index and cigarette smoking did not alter these results (not shown). Women who reported heart disease at baseline were excluded from all the following analyses in case the disease had changed the hormones or risk factors for heart disease.

At baseline the average age of the 651 women without cardiovascular disease was 66·7 years. Table II shows the age specific incidence of fatal cardiovascular disease or ischaemic heart disease after 19 years. Overall, 24% (158) had fatal cardiovascular disease, and 12% (82) had fatal ischaemic heart disease.

TABLE II—*Age specific incidence of fatal cardiovascular disease and ischaemic heart disease after 19 year follow up; Rancho Bernardo postmenopausal women 1972-4 to 1992*

Age (years) at baseline	Total No of deaths	No (%) of deaths from cardiovascular disease	No (%) of deaths from ischaemic heart disease
50-59	87	1 (1·1)	1 (1·1)
60-69	334	63 (18·9)	36 (10·8)
70-79	213	83 (39·1)	40 (18·8)
⩾80	17	11 (64·7)	5 (29·4)
Total	651	158	82

The age adjusted correlations of each sex hormone with each risk factor for heart disease (systolic blood pressure, diastolic blood pressure, cholesterol, triglycerides, fasting plasma glucose, and body mass index) were weak, and only four were significant at $P<0·05$. Androstenedione was positively correlated with total cholesterol (R=0·10) and fasting plasma glucose (R=0·08); total testosterone was negatively correlated with diastolic blood pressure (R=−0·09); and oestrone was negatively correlated with cholesterol (R=−0·09). Bioavailable oestradiol and testosterone were not correlated with any measured risk factor.

Table III shows mean hormone concentrations adjusted for age and body mass index by risk factors for heart disease dichotomised in clinically relevant categories. Women with cholesterol concentrations ⩾6·7 mmol/l and current smokers had significantly higher concentrations of androstenedione than women without these attributes. No concentrations of other sex hormones varied significantly by risk factors.

As shown in tables IV and V plasma sex hormones did not predict fatal cardiovascular disease or ischaemic heart disease. Similar results were found in Cox's proportional hazards model adjusted for age, blood pressure, cigarette smoking, cholesterol, obesity, and glucose. In this model only age (each five year increase) (relative risk=1·42; 95% confidence interval 1·24 to 1·67) and increased concentration of fasting plasma glucose (>7·78 mmol/l) (3·04; 1·45 to 6·37) were significantly and independently associated with fatal cardiovascular disease and ischaemic heart disease. No pattern to suggest any association between hormone concentration and cardiovascular disease was seen in another analysis restricted to women whose death occurred in the first seven years after blood was obtained for hormone assays. Stratification of all analyses by postmenopausal use of oestrogen during follow up also did not alter the results.

TABLE I—*Age adjusted mean (SE) and median (interquartile range) of hormone concentrations by history of heart disease at baseline*

Hormone	History of heart disease at baseline (n=42)		No history of heart disease at baseline (n=651)		P value
	Mean (SE)	Median (interquartile range)	Mean (SE)	Median (interquartile range)	
Androstenedione (nmol/l)	2·10 (0·15)	2·02 (1·42 to 2·76)	2·11 (0·04)	1·94 (1·43 to 2·69)	0·91
Testosterone (nmol/l)	8·57 (1·51)	7·49 (4·96 to 8·88)	9·29 (0·38)	7·56 (5·29 to 10·89)	0·65
Oestrone (pmol/l)	132·0 (32·4)	116·5 (92·5 to 159·1)	143·3 (8·3)	114·7 (85·1 to 159·1)	0·73
Oestradiol (pmol/l)	65·5 (9·5)	40·4 (29·4 to 66·1)	56·6 (2·4)	42·2 (29·4 to 66·1)	0·37
Bioavailable oestradiol (pmol/l)	27·7 (9·5)	22·0 (14·7 to 33·0)	32·7 (2·3)	25·7 (14·7 to 36·7)	0·61
Bioavailable testosterone (nmol/l)	42·9 (7·5)	31·9 (15·6 to 48·5)	39·1 (1·9)	32·9 (20·8 to 49·2)	0·63

*P values are based on logged data.

TABLE III—*Mean (SE) concentrations of sex hormones adjusted for age and body mass index by category of risk factor for coronary heart disease*

Risk factor	Androstenedione (nmol/l)	Testosterone (nmol/l)	Oestrone (pmol/l)	Oestradiol (pmol/l)	Bioavailable estradiol (pmol/l)	Bioavailable testosterone (nmol/l)
Systolic blood pressure (mm Hg):						
<140 (n=307)	2·06 (0·060)	92·1 (5·92)	151·8 (12·86)	57·4 (3·35)	31·3 (3·57)	36·1 (2·74)
≥140 (n=344)	2·15 (0·056)	92·6 (5·51)	136·5 (11·97)	56·5 (3·11)	34·5 (3·44)	42·0 (2·64)
P value	0·20	0·85	0·38	0·80	0·57	0·13
Diastolic blood pressure (mm Hg):						
<95 (n=573)	2·10 (0·043)	92·6 (4·18)	144·6 (9·11)	57·2 (2·36)	32·7 (2·54)	38·3 (1·96)
≥95 (n=78)	2·25 (0·115)	95·4 (11·32)	133·7 (24·64)	53·1 (6·50)	34·6 (7·22)	45·3 (5·37)
P value	0·20	0·81	0·68	0·55	0·80	0·22
Cholesterol (mmol/l):						
<6·5 (n=373)	2·01 (0·052)	87·7 (5·14)	154·5 (11·18)	60·3 (2·93)	32·3 (2·82)	38·1 (2·16)
≥6·5 (n=278)	2·26 (0·061)	100·0 (6·03)	128·0 (13·01)	52·1 (3·38)	34·3 (4·53)	41·6 (3·56)
P value	0·00	0·12	0·16	0·16	0·70	0·43
Fasting plasma glucose (mmol/l):						
<7·8 (n=629)	2·11 (0·041)	92·8 (3·99)	143·1 (8·69)	56·7 (2·26)	32·9 (2·44)	39·3 (1·88)
≥7·8 (n=22)	2·20 (0·217)	94·7 (21·21)	148·8 (46·43)	58·2 (11·92)	33·0 (11·98)	36·5 (9·54)
P value	0·69	0·93	0·90	0·90	0·99	0·78
Body mass index* (kg/m²):						
<27 (n=527)	2·14 (0·044)	95·8 (4·34)	142·9 (9·45)	55·4 (2·46)	32·5 (2·64)	39·7 (2·03)
≥27 (n=124)	1·99 (0·091)	79·7 (8·94)	145·3 (19·42)	61·6 (5·03)	34·5 (5·53)	36·5 (4·40)
P value	0·14	0·11	0·91	0·27	0·75	0·52
History of smoking:						
Never/past (n=505)	2·04 (0·045)	91·81 (4·45)	147·9 (9·71)	56·28 (2·53)	30·91 (2·66)	38·96 (2·05)
Current (n=143)	2·63 (0·087)	96·87 (8·59)	126·7 (18·51)	58·42 (4·78)	41·18 (5·59)	40·02 (4·45)
P value	0·001	0·31	0·69	0·60	0·10	0·83

*Age-adjusted only

TABLE IV—*Age adjusted mean hormone concentration by 19 year mortality and relative risk (95% confidence interval) for cardiovascular disease in women from Rancho Bernardo*

Hormone	Died from cardiovascular disease (n=176)	Alive, or died from causes other than cardiovascular disease (n=475)	P value*	Relative risk (95% confidence interval)
Androstenedione (nmol/l)	2·14	2·11	0·74	1·00 (0·99 to 1·01)
Testosterone (nmol/l)	8·81	9·43	0·53	1·00 (0·99 to 1·03)
Oestrone (pmol/l)	154·4	139·8	0·49	1·70 (0·37 to 2·98)
Oestradiol (pmol/l)	56·2	56·8	0·92	1·27 (0·79 to 2·03)
Bioavailable oestradiol (pmol/l)	32·0	33·1	0·85	0·98 (0·94 to 1·02)
Bioavailable testosterone (nmol/l)	37·8	39·5	0·72	0·98 (0·95 to 1·02)

*For comparison of hormone concentrations.

TABLE V—*Age adjusted mean hormone concentrations by 19 year mortality and relative risk (95% confidence interval) for ischaemic heart disease in women from Rancho Bernardo*

	Died from ischaemic heart disease (n=93)	Alive or died from causes other than ischaemic heart disease (n=558)	P value*	Relative risk (95% confidence interval)
Androstenedione (nmol/l)	2·08	2·12	0·76	1·00 (0·99 to 1·01)
Testosterone (nmol/l)	9·26	9·29	0·98	1·01 (0·99 to 1·03)
Oestrone (pmol/l)	135·4	144·5	0·73	0·32 (0·03 to 2·97)
Oestradiol (pmol/l)	54·3	57·0	0·69	1·06 (0·89 to 1·19)
Bioavailable oestradiol (pmol/l)	28·1	33·6	0·44	0·94 (0·84 to 1·06)
Bioavailable testosterone (nmol/l)	39·8	39·0	0·89	1·34 (0·58 to 1·83)

*For comparison of hormone concentrations.

Nested case-control analyses matched on date of visit and season of sampling also showed no association with fatal cardiovascular disease or ischaemic heart disease (data not shown).

Discussion

In this prospective community based study of postmenopausal women neither endogenous oestrogens nor any other measured sex steroid was related to the subsequent risk of death from cardiovascular disease. These results agree with those from the cross sectional study reported by Cauley and colleagues, who studied 87 postmenopausal women admitted for cardiac catheterisation and found no difference in serum oestrone concentrations in women with or without coronary artery occlusion.[8] Similar to the results reported here they also found that the primary predictors of angiographically defined coronary artery disease in older women were age and diabetes; cholesterol concentration and blood pressure contributed little to their multivariate model.

Oestrone concentrations in our sample of women were weakly and inversely related to total plasma cholesterol; another study found no relation between cholesterol and endogenous oestrone concentration.[13] In our study neither oestrone nor oestradiol was related to other risk factors for heart disease, including obesity. These results differ from other studies in which obese women had higher oestrogen concentrations than lean women,[6] probably because only 100 of our women were obese (body mass index >28). Although high density lipoprotein cholesterol was not measured at baseline in our study, there was no association of endogenous oestrone or oestradiol with high density lipoprotein cholesterol in a 15% random sample of women in this cohort (unpublished).

A large amount of literature suggests that exogenous oestrogen is associated with a reduced risk of cardiovascular disease and more favourable levels of several risk factors for heart disease.[4,5] We therefore postulated that endogenous oestrogen would also be cardioprotective. Why are these results at variance with expectations? Possibly the use of only a single hormone assay to describe each woman's endogenous sex hormone status was inadequate to describe her usual hormone status. Oestradiol, a more potent oestrogen than oestrone, has wide variation between individual subjects, such that a single assay characterises an individual rather poorly.[6,7] On the other hand, oestrone, the primary oestrogen in postmenopausal women, has less variation than other biological variables which have been shown to predict cardiovascular disease, including plasma cholesterol.[6,7]

The lack of association could reflect seasonal or diurnal variation in endogenous oestrogen concentrations, but matching on season of sampling and date of visit did not alter the results, and all blood was obtained from fasting subjects in the morning. There was no evidence of hormone instability in frozen plasma, and the average concentrations of oestrone and oestradiol measured here were within the normal range observed in fresh samples from postmenopausl women studied in the same laboratory. Some investigators have remarked on the limited sensitivity of the oestrogen assays; in this laboratory only six women had oestradiol and three women had oestrone concentrations below the level of sensitivity. Although a larger sample might have shown an association, the power to detect a significant difference in mean hormone concentration between the group with and without ischaemic heart disease was 98% for total testosterone and 84% for bioavailable testosterone. In cardiovascular death, the power was 92% for total oestradiol

Key messages

- Age adjusted concentrations of sex hormone did not differ significantly in women with and without a history of heart disease at baseline and did not predict death from cardiovascular or ischaemic heart disease
- Most 95% confidence intervals for age adjusted relative risk of death from these diseases were narrow, and all included one
- Endogenous oestrogen concentrations were not associated with significantly more favourable risk factors for heart disease, and testosterone was not associated with less favourable risk factors
- These prospective data do not support a causal or preventive role for endogenous oestrogens or androgens in cardiovascular disease in older women

and 85% for bioavailable oestradiol. Diagnoses on death certificates are always suspect, but the cause of death in Rancho Bernardo was confirmed by a panel of cardiologists in 85% of women for whom validation was sought. Although it is possible that oestrogen prevents only non-fatal heart disease, this was not suggested by our cross sectional analysis, by the previously reported angiographic study,[8] or by observational studies of exogenous oestrogen.[4,5]

Although there was a long interval between hormone assessment and the outcome, we think this is unlikely to explain the absent association for two reasons: firstly, oestrogen concentrations decrease little after the menopause,[14,15] and, secondly, analysis restricted to women whose death from cardiovascular disease occurred within seven years of the time blood was obtained for hormone assay also showed no trend in the direction of protection (or harm).

Finally, oestrogen concentrations in postmenopausal women may be below those required to prevent atherosclerosis, and possibly only premenopausal concentrations are cardioprotective. We cannot exclude this possibility, but the absence of a change in the slope of cardiovascular death rates around age 50 (the age of menopause)[16,17] speaks against this possibility.

In summary, this prospective study, like the cross sectional study reported by Cauley *et al*,[8] does not support the hypothesis that endogenous oestrogens prevent cardiovascular disease in postmenopausal women. Further studies are needed.

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Correction

FcεRI-β polymorphism and risk of atopy in a general population sample

A printer's error occurred in this paper by M R Hill and colleagues (23 September, pp 776-9). In table I the italic headings "*Paternally inherited FcεRI-β Leu 181/Leu 183*" and "*Maternally inherited FcεRI-β Leu 181/Leu 183*" should be transposed.

BMJ audit: time to decisions and publication

We aim to make a decision on publication within eight weeks (56 days); to reject papers that are unsuitable for external peer review within two weeks (14 days); and to publish a paper within eight weeks of acceptance.

Between 1 January and 30 June this year we made a decision within 56 days for 72% of all papers submitted (1514/2095) and for 41% of those we accepted (87/210). We accepted 53% (112) within 66 days (10 days over target), and the mean time to accept a paper was 69 days. We met our target of rejecting papers without peer review within 14 days for 22% of papers (279/1258); 56% (706) were rejected within 24 days (10 days over target), and the average time to reject such papers was 26 days. We published 38% (80) of papers within eight weeks of acceptance; 60% (125) were published within 10 weeks, and 76% (159) within 12 weeks. A comparison with previous audits is shown in the table below.

Results of "BMJ" audits. Values are percentages unless stated otherwise

	Decision within 56 days		Accepted papers		Rejected papers			Publication times after acceptance		
Audit	All papers	Accepted papers	Decision within 66 days	Mean time to acceptance (days)	Decision within 14 days	Decision within 24 days	Mean time to reject without peer review (days)	Within 8 weeks	Within 10 weeks	Within 12 weeks
1993:										
Jan-June	88	73	85	41	37	76	19	38	72	95
July-Dec	86	62	75	50	40	84	18	27	66	85
1994:										
Jan-June	88	64	76	48	40	84	18	13	24	57
July-Dec	83	64	73	51	46	73	21	40	67	87
1995:										
Jan-June	72	41	53	69	22	56	26	38	60	76