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Post Menopausal Hormones and Measures of Subclinical Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To evaluate whether post menopausal hormones are associated with atherosclerosis.

Methods—We studied the relation of hormone use to coronary calcification and carotid intima-media thickness in a cross-sectional sample of 3,245 post menopausal women, of whom 1,620 had used hormones for various periods. Adjusted associations with three measures of hormone use (ever use, duration, and type of hormone) were estimated by multivariable regression.

Results—The prevalence of coronary calcification was only 4 percentage points lower in women who had ever used hormones than in women who had not (40% versus 44%), and was not monotonically related to longer use: ≤ 2 years: 38%; 2–6 years: 36%; 6–13 years: 41%; >13 years: 48%. Similarly, duration of hormone use did not show a monotonic dose-response relation with the calcium score. Mean differences in carotid intima-media thickness according to categories of years of hormone use and type of hormone ranged from -0.10 mm to $+0.08$ mm, with no consistent patterns. Most adjusted associations were weak and sometimes contrary to our expectation.

Conclusions—We did not find meaningful associations between hormone use and subclinical atherosclerosis—neither to support benefit or harm, nor to support the prevailing theory of “healthy user” bias (namely, inverse associations due to residual confounding).

Keywords

Post menopausal hormones; Atherosclerosis; Coronary calcification; Carotid wall thickness

Introduction

Both observational studies and randomized trials suggest that post menopausal hormone use improves the levels of some risk factors for atherosclerosis, notably the LDL-cholesterol and HDL-cholesterol plasma concentration.(1995;Mendelsohn and Karas, 1999;Nabulsi, et al., 1993;Stevenson, 2004) Observational research has estimated about 40 percent lower risk of clinical coronary heart disease for hormone users relative to nonusers,(Stampfer and Colditz, 1991) but subsequent randomized trials did not produce the expected results—neither in the context of primary prevention(Rossouw, et al., 2002) nor in the context of secondary prevention.(Hulley, et al., 1998) In fact, the risk of myocardial infarction or death from coronary heart disease seemed to increase transiently over the first year of treatment.(Hulley, et al., 1998;Rossouw, et al., 2002)

It is unlikely that continued analysis of existing data will unequivocally explain the conflicting results of randomized trials and observational cohorts. Some animal models suggest that post menopausal hormones are related to the growth of atherosclerotic plaques after menopause. (Adams, et al., 1990; Mikkola and Clarkson, 2002; Mori, et al., 2000) One clinical trial(Hodis, et al., 2001), but not others(Angerer, et al., 2001; Angerer, et al., 2002; Herrington, et al., 2000), showed blunting of progression of atherosclerosis in women randomized to post menopausal hormones, compared to those assigned to a placebo. We investigated the presence and magnitude of the association between the use of post menopausal hormones and subclinical atherosclerosis.

Methods

Study Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center cohort study of subclinical atherosclerosis, its progression, and its clinical sequelae.(Bild, et al., 2002) The cohort comprised 3,213 men and 3,601 women—45 to 84 years old with no clinically apparent cardiovascular disease—who were recruited between 2000 and 2002 from communities in six U.S. locations: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. About 1,100 participants were recruited by each field site from locally available sources, such as lists of residents, lists of dwellings, and random-digit dialing to selected telephone exchanges. In the last few months of the recruitment period, supplemental sources (lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services and referrals by participants) were used to increase the proportions of minorities and elderly subjects. The study was approved by the institutional review board of each participating institution and a consent form was signed by all participants.

We used data from the baseline measurements of the cohort to study the relation between previous use of post menopausal hormones and two measures of subclinical atherosclerosis: coronary calcification and carotid intima-media thickening.

Coronary Calcification

Coronary calcium was detected and measured by rapid-acquisition computed tomography (CT) of the chest.(Carr, et al., 2005) Of the six field sites, three used an ECG-triggered electron-beam scanner (Imatron C-150, Imatron, San Francisco)(Breen, et al., 1992) and three used prospectively ECG- triggered acquisition at the mid-point of the RR interval with a multi-detector system (Lightspeed, General Electric, Waukesha, WI or Siemens, Volume Zoom, Erlangen, Germany).(Carr, et al., 2000) The latter scanners simultaneously acquired four 2.5 mm slices in each cardiac cycle in a sequential or axial scan mode. To calibrate and standardize

the measurement across study sites and participants, a standard calcium-containing phantom was scanned with the participant; all of the scans were read at the Research and Education Institute of Harbor-University of California, Los Angeles. We used the Agatston score as a measure of coronary calcium.(Agatston, et al., 1990)

Carotid Intima-Media Thickness

The intima-media thickness (IMT) of the common carotid and internal carotid arteries was measured on both sides of the neck using high-resolution B-mode ultrasound (Logiq 700 ultrasound machine, General Electric Medical Systems). Focusing on the distal 1 cm of the common carotid, the carotid bulb, and the proximal 1 cm of the internal carotid, the technician first videotaped a transverse (short-axis) scanning sequence, and tried to identify the site of maximal wall thickening in each segment. Then, five longitudinal images were obtained: the first image was a pulse-wave Doppler measurement of the peak systolic velocity in the internal carotid; the second was a standard lateral view of the common carotid; and the last three images captured the internal carotid artery or bulb from three angles: anterior-oblique, lateral, and posterior-oblique. Images of the internal carotid have centered on a lesion in the proximal segment or in the bulb, if present. Otherwise, the technician focused on the site of maximal wall thickening, preferring to visualize the far arterial wall. All of the scans were centrally read using a standard protocol at the Department of Radiology, New England Medical Center. (O'Leary, et al., 1991) We used the average of maximal wall thickness from all available arterial sites: up to 4 measurements of the common carotid and up to 12 measurements of the internal carotid.

Use of Post menopausal Hormones

Female participants were asked about menopausal status and about past use and present use of post menopausal hormones, including the type of hormones (estrogen and progestin or estrogen alone.) Those who had ever taken hormones reported the age at which they started taking them, and former users reported the age at which they stopped. From these data we calculated the approximate duration of use (in years) before the study exam.

Other Variables

Self-reported information on demographic variables, medical history, use of medications, and smoking was collected by questionnaires. The participants identified themselves as White, Chinese-American, African-American, or Hispanic and reported the number of school years they had completed. Medical history included questions about a physician diagnosis of hypertension, diabetes, hypercholesterolemia, and about the use of medications for these conditions. We also asked a general question about any "ongoing health problem". Questions about smoking enabled us to identify three groups (current, former, and never smokers) and to calculate the variable "pack-years of smoking" (the average number of cigarettes smoked per day times the number of years smoked, divided by 20).

Weight and height were measured while the participant was wearing light clothes and no shoes. Body mass index (BMI) was calculated by dividing the weight (kilograms) by the square of height (meters²). Blood pressure was measured three times in a seated position by a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL) after a 5-minute sitting in a quiet room. We used the average of the last two measurements.

A blood sample was drawn after a 12-hour fast, and the concentrations of total cholesterol, HDL cholesterol, and triglycerides were measured in EDTA plasma. Total cholesterol was measured by the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN). HDL-cholesterol was measured by the same method after precipitation of non-HDL-cholesterol with magnesium-dextran. Triglycerides were measured using Triglyceride GB reagent (Roche

Diagnostics, Indianapolis, IN). The concentration of LDL-cholesterol was calculated according to the Friedewald equation, (Friedewald, et al., 1972) provided that the concentration of triglycerides did not exceed 400 mg/dL. Serum glucose was measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method.

Analysis

To study the association between subclinical atherosclerosis and post menopausal hormones, we contrasted a reference category of women who had never taken them with three measures of hormone use: ever hormone use (regardless of timing and duration), type of hormones (estrogen and progestin, estrogen alone, or an unknown type), and years of use (arbitrarily divided into up to 2 years, 2–6 years, 6–13 years, and over 13 years). Duration of use was strongly correlated with hormone use at the time of the MESA exam. For example, 70% of those who took hormones for a short period (≤ 2 years) were no longer taking them, whereas over 80% of those who took hormones for six years or longer were still using them at the baseline examination. As a result, separation of women who ever used hormones into current users and former users proved inconsequential analytically. On the assumption of a protective effect, former users should have accumulated overall benefit over never users (during their years of hormone use), regardless of when they stopped taking hormones.

We modeled coronary calcium in two ways: First, we created a binary variable that indicated the presence or absence of coronary calcium (score > 0 versus score $= 0$) and then fit modified Poisson regression models with robust variances. (Zou, 2004) From these models, we computed adjusted proportion ratios (adjusted “prevalence ratios”) of coronary calcification and their 95% confidence intervals. Second, we excluded observations of a zero score, and fit linear regression models in which the log of the calcium score was the dependent variable. From these models, we computed adjusted geometric mean ratios (GMR), the multiplicative counterpart of adjusted arithmetic mean differences, and 95% confidence intervals. (The absolute value of $100 \times (\text{GMR} - 1)$ may be interpreted as the percentage difference in the calcium score per one unit increment of the predictor.) To study the association of post menopausal hormones with carotid atherosclerosis, we fit linear regression models using mean IMT of the common carotid arteries, or mean IMT of the internal carotid arteries, as the dependent variable.

Each type of regression model was fit with three sets of independent variables: 1) a measure of hormone use (unadjusted association); 2) a measure of hormone use and “potential confounders” (model 1); and 3) a measure of hormone use, potential confounders, and presumed effects of hormone use on causal pathways to atherosclerosis (model 2). 95% confidence intervals are shown for all associations. SAS® was used for analysis.

Results

Of 3,601 women who took part in the baseline study exam, 1,625 (45%) had never taken post menopausal hormones, 593 (16%) had taken them in the past, and 1,027 (29%) were still taking them. The remainder 356 women (10%) were excluded because they were pre menopausal ($N=203$), or because they did not provide information on hormone use ($N=153$). We were able to compute the duration of use for 98% of hormone users, but the type of hormone remained unknown in about one third.

Table 1 shows the unadjusted associations between each measure of hormone use and demographic or clinical variables. Women who used hormones tended to be slightly younger than women who did not (except for those who took hormones for many years.) Hormone users were more likely to be White; with a greater than high school education; and with a lower BMI. With few exceptions, measures of glucose metabolism, the cholesterol profile, and blood pressure showed a more desired distribution among hormone users than among never users.

In contrast, women who took hormones were more likely to have smoked than women who did not and were as likely (or even more likely) to report having an ongoing health problem. Similar trends were sometimes evident when long-term users of hormones were compared with short-term users. On several variables, women who took estrogen and progestin (and women who took hormones of an unknown type) differed from never users more than did women who took estrogen alone.

Over 40% of the women had measurable coronary calcification (Agatston score >0). The prevalence was only 4 percentage points lower in women who had ever used hormones (40%) than in women who had not (44%), and there was no inverse, graded relation with years of use (Table 2). Multivariable adjustment by either model essentially nullified the weak associations between coronary calcification and all three measures of hormone use.

Similar results were obtained by modeling the log of coronary calcium among the 1,377 women with any evidence of calcification (Table 3). Ever use of post menopausal hormones was associated with an 18% lower coronary calcium score than never use, but duration of hormone use did not show a monotonic dose-response relation with the calcium score. Again, after multivariable adjustment, any remaining association was weak and sometimes inconsistent with our expectation. In other analyses (not shown), we examined the relation between coronary calcification and duration of hormone use among current users. The results were similar. Likewise, we found no evidence of the hypothesized associations among younger women (age ≤ 55), or statistical evidence of multiplicative interactions with smoking, diabetes, or hypertension (data not shown).

Table 4 and Table 5 show, respectively, the relation of common carotid IMT and internal carotid IMT to hormone use. Both before adjustment and after adjustment, the estimated mean differences were small and not always in the expected direction. The results did not differ according to the type of hormones taken.

Discussion

In this cross-sectional study, there was no consistent relation between use of post menopausal hormones and either carotid intima-media thickness or presence or extent of calcified coronary plaques.

Only a few observational studies have examined the relation of post menopausal hormones to coronary calcification as measured by CT. Three groups reported an inverse association, (Akhrass, et al., 2003; McLaughlin, et al., 1997; Shemesh, et al., 1997) one group reported no association, (Schisterman, et al., 2002) and one group concluded that post menopausal hormones played the role of an effect modifier of LDL-cholesterol but were not associated with coronary calcification. (Kuller, et al., 1999) Of the three studies that reported an inverse association, the first study was small (N=78); (Shemesh, et al., 1997) the second might have not adjusted rigorously for confounders; (McLaughlin, et al., 1997) and the third applied numerous statistical assumptions to derive the estimates and their standard errors. (Akhrass, et al., 2003) The latter study, however, reported an odds ratio of 0.5 for having a calcium score greater than 400 (the top 5th percentile or so) for current users of post menopausal hormones (versus a group that included former users), and “maximum benefit of HRT on the CAC score... after 23 yr of therapy” (Akhrass, et al., 2003) (from a model that imposed a quadratic dose-response function). Recently, an ancillary study of the Women’s Health Initiative (of women who had undergone hysterectomy) found lower coronary calcium scores in those who received estrogen as compared with those who received placebo. (Manson, et al., 2007)

Over a dozen observational studies have examined the relation of post menopausal hormones to carotid intima-media thickness, a measure of early carotid atherosclerosis that correlates

moderately with coronary atherosclerosis. At least eight groups concluded that their results had corroborated the protective effect hypothesis;(Dubuisson, et al., 1998; Griewing, et al., 1999; Jonas, et al., 1996; Liang, et al., 1997; Mihmanli, et al., 2002; Sator, et al., 1998; Takahashi, et al., 2004; Westendorp, et al., 1999) four reported qualified or equivocal results; (Baron, et al., 1998; Le Gal, et al., 2003; Moreau, et al., 2002; Tremollieres, et al., 2000) and one group reported no association(Nabulsi, et al., 1996) (from the largest study to date.) Of two relevant trials in postmenopausal women, one found slower progression of carotid intima-media thickness in recipients of estrogen than in recipients of placebo,(Hodis, et al., 2001) whereas the other found no such difference between recipients of estrogen (combined with standard or low-dose progestin) and untreated controls.(Angerer, et al., 2001)

Much debate has been generated by the sharp contrast between the results of randomized trials of post menopausal hormones (no cardiac benefit; possible harm) and pre-trial subjective probabilities (almost 100% certainty of some cardiac benefit).(Barrett-Connor, 2004; Grady and Hulley, 2001; Harman, et al., 2004; Michels, 2003; Piantadosi, 2003; Stampfer, 2004; Whittemore and McGuire, 2003) The contrasting results have fueled skepticism about the science of epidemiology, and might have amplified naive beliefs in the “ultimate truth” of randomized trials. In retrospect, the story of post menopausal hormones reads like a helpful reminder of the conjectural nature of scientific knowledge—including the “definitive” knowledge generated by a large randomized trial.(Garbe and Suissa, 2004)

One camp of critics has assumed false results from observational studies, suggesting three key explanations for previous findings: (1) “healthy user” bias—a collective term for unknown (and therefore untestable) confounding paths; (2) confounding, or residual confounding, by socioeconomic status; (3) inability to estimate the relative risk during the first year of taking the hormones (possibly attributed to transient prothrombotic effects).(Barlow, 1997; Hoibraaten, et al., 2001; van Baal, et al., 2000) Others have proposed, in response, two key explanations for the diverging results of the trials: (1) coronary events might have been preferentially ascertained in hormone users, possibly due to the high frequency of unblinding; (2) the treatment was initiated too late in the postmenopausal period, having failed to replicate the timing of a typical prescription (as properly captured by observational studies of incident disease). During the 1980s, for example, post menopausal hormones were usually prescribed in the peri-menopausal period to alleviate symptoms of estrogen deficiency, and not at a mean age of 63 years(Rossouw, et al., 2002) or 67 years.(Hulley, et al., 1998)

At the core of the last explanation lies a general theory of effect modification: the effect of post menopausal hormones on coronary heart disease could vary quantitatively or even *qualitatively* according to variables such as chronological age, “menopausal age” (years since the menopause), and the severity of coronary atherosclerosis. For instance, starting to take a low dose of post menopausal hormones shortly after the decline of endogenous hormones, rather than 15 years later on, might slow the formation of early atherosclerotic lesions without increasing the risk of early thrombo-embolic events.

Our results indirectly contribute to both sides of the debate. On the one hand, we found no evidence of an inverse association of post menopausal hormones with atherosclerosis which would suggest a favorable effect—in accord with the results of the primary prevention trial. On the other hand, we found no evidence of “healthy user” bias either—namely, a “spurious” inverse association—which should be present (due to residual confounding) after adjustment for known confounders. If residual confounding bias has indeed generated non-causal associations in previous cohort studies, it has probably spared our cross-sectional sample (unless negative confounding has masked a *detrimental* effect of post menopausal hormones on atherosclerosis.) Moreover, detected confounding was modest and inconsequential: most crude associations did not differ much from adjusted associations.

One limitation of our study was self-reported data, and not detailed enough to allow examination of dose or exact formulation. In addition, we did not assess compliance to hormone therapy. Nonetheless, if our results reflect the truth, they suggest that the effect of post menopausal hormones on atherosclerosis is either “precisely null” or small— perhaps too small to be of pathophysiological importance, or too small to be estimated by our measures of atherosclerosis, or both. A small effect or “precisely no effect” may be explained, in turn, by well-known opposing effects of post menopausal hormones on risk factors for atherosclerosis: some effects are favorable (for example, on LDL-cholesterol and HDL-cholesterol) whereas others are not (for example, on C-reactive protein and triglycerides). (1995;Cushman, et al., 1999;Stevenson, 2004) Notwithstanding the shortcomings of observational studies, it will be of interest to repeat the present analysis when data on IMT and particularly calcium progression in MESA become available, especially focusing on women using hormones in peri- or immediate post-menopause.

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Demographic and clinical variables by hormone use (ever versus never), years of hormone use, and type of hormone: the Multi-Ethnic Study of Atherosclerosis, USA, 2002–2002

Table 1

Variable	Hormone use		≤2 (N=498)	Years of hormone use*			Estrogen (N=655)	Type of hormone Estrogen and progestin (N=399)	Unknown (N=566)
	Never used (N=1,625)	Ever used (N=1,620)		2–6 (N=344)	6–13 (N=358)	>13 (N=389)			
Age (years, mean±SD)	65±10	63±9	62±10	60±9	63±8	68±8	64±9	62±8	63±9
Ethnicity (%)									
White	28	49	39	44	56	59	40	56	54
Chinese	15	8	12	9	5	4	6	8	9
African-American	32	27	27	27	25	28	38	23	16
Hispanic	26	17	23	21	14	9	16	13	21
Education (%)									
Less than high school	26	14	22	12	10	10	16	12	15
High school	22	20	18	23	19	21	22	17	20
More than high school	52	66	60	65	70	68	62	71	65
Body mass index (mean±SD)	29±6	28±6	28±6	28±6	28±6	28±6	29±6	28±6	28±6
Smoking status (%)									
Currently smoke	11	12	12	14	14	9	14	12	11
Formerly smoke	25	34	26	31	39	43	30	36	39
Never smoke	64	53	62	55	47	47	57	52	50
Pack-years of smoking (percentiles: 0th, 75th, 95th)	0, 7, 45	0, 13, 46	0, 5, 36	0, 10, 46	1, 18, 48	0, 18, 53	0, 13, 42	0, 10, 44	0, 15, 51
Reported diabetes (%)	12	10	11	8	9	10	12	8	9
Taking diabetes medication (%)	11	8	9	7	8	8	10	6	7
Glucose (mg/dl, mean±SD)	105±32	99±24	102±29	99±24	98±19	97±20	102±24	99±26	97±22
HDL-cholesterol (mg/dl, mean±SD)	54±14	59±16	56±15	59±17	60±16	62±16	58±16	58±16	61±17
LDL-cholesterol (mg/dl, mean±SD)	122±33	114±31	120±33	114±30	112±29	110±29	116±32	118±31	110±29
Taking cholesterol medication (%)	17	19	17	16	18	22	21	15	19
Reported hypertension	43	44	44	40	40	50	51	38	39
Taking hypertension medication (%)	36	38	36	37	36	46	46	31	35
Systolic blood pressure (mean±SD)	130±24	127±22	126±22	124±22	126±22	130±23	130±23	126±22	123±21
Diastolic blood pressure (mean±SD)	70±10	69±10	69±10	69±10	68±9	68±10	70±10	69±10	68±10
Reported ongoing health problems (%)	75	77	75	75	80	78	72	77	83

* Unknown for 31 women who reported having used hormones
Percentages may not add to 100 because of rounding

Table 2

Prevalence and prevalence ratios of coronary calcification (Agatston score>0) by hormone use (ever versus never), years of hormone use, and type of hormone: the Multi-Ethnic Study of Atherosclerosis, USA, 2000–2002

	Hormone use		Years of hormone use		>13 (N=389)	Estrogen (N=655)	Type of hormone Estrogen and progestin (N=399)	Unknown (N=566)
	Never used (N=1,625)	Ever used (N=1,620)	≤2 (N=498)	2–6 (N=344)				
Prevalence	44%	40%	38%	36%	48%	42%	38%	40%
Prevalence ratio	Reference	0.91 (0.84–0.99)	0.86 (0.74–0.96)	0.82 (0.69–0.94)	1.09 (0.95–1.21)	0.95 (0.86–1.06)	0.86 (0.84–0.98)	0.91 (0.80–1.01)
95% confidence limits								
Model 1*								
Adjusted prevalence ratio	Reference	0.97 (0.90–1.04)	0.96 (0.85–1.07)	1.03 (0.89–1.18)	0.92 (0.82–1.03)	0.97 (0.88–1.08)	0.96 (0.84–1.10)	0.96 (0.86–1.07)
95% confidence limits								
Model 2**								
Adjusted prevalence ratio	Reference	1 (0.92–1.08)	0.95 (0.84–1.06)	1.07 (0.93–1.23)	0.98 (0.87–1.10)	0.99 (0.90–1.10)	0.98 (0.86–1.12)	1.01 (0.91–1.13)
95% confidence limits								

* Covariates that are not assumed to be effects of hormones: age, ethnicity, education, smoking status, pack-years of smoking, body-mass index, systolic blood pressure, use of anti-hypertension medications

** Covariates from model 1 and covariates that are presumed effects of hormones: glucose, diabetes (taking medication), HDL-cholesterol, LDL-cholesterol and taking cholesterol medication

Geometric mean and geometric mean ratio of coronary calcium (Agatston score when >0) by hormone use (ever versus never), years of hormone use, and type of hormone among 1,377 women with coronary calcification: the Multi-Ethnic Study of Atherosclerosis, USA, 2000–2002

Table 3

	Hormone use		Years of hormone use			>13 (N=186)	Estrogen (N=278)	Type of hormone Estrogen and progestin (N=151)	Unknown (N=226)
	Never used (N=722)	Ever used (N=655)	≤2 (N=187)	2–6 (N=123)	6–13 (N=145)				
Geometric mean	61	50	57	35	56	53	54	51	47
Geometric mean ratio	Reference	0.82	0.93	0.57	0.92	0.87	0.89	0.84	0.77
95% confidence limits		(0.68–0.99)	(0.70–1.23)	(0.40–0.79)	(0.66–1.24)	(0.65–1.15)	(0.69–1.12)	(0.61–1.13)	(0.58–0.99)
Model 1*	Reference	0.93	1.13	0.81	1.04	0.76	0.93	1.08	0.84
Adjusted geometric mean ratio		(0.78–1.12)	(0.87–1.48)	(0.59–1.12)	(0.77–1.41)	(0.58–1.01)	(0.74–1.18)	(0.80–1.45)	(0.65–1.09)
95% confidence limits									
Model 2**	Reference	0.94	1.13	0.82	1.04	0.77	0.93	1.09	0.85
Adjusted geometric mean ratio		(0.78–1.13)	(0.86–1.49)	(0.59–1.13)	(0.76–1.41)	(0.58–1.02)	(0.74–1.19)	(0.80–1.46)	(0.65–1.10)
95% confidence limits									

* Covariates that are not assumed to be effects of hormones: age, ethnicity, education, smoking status, pack-years of smoking, body-mass index, systolic blood pressure, use of anti-hypertension medications

** Covariates from model 1 and covariates that are presumed effects of hormones: glucose, diabetes (taking medication), HDL-cholesterol, LDL-cholesterol, and taking cholesterol medication

Table 4

Arithmetic mean and arithmetic mean difference of common carotid intima-media thickness (mm) by hormone use (ever versus never), years of hormone use, and type of hormone: the Multi-Ethnic Study of Atherosclerosis, USA, 2000–2002

	Hormone use		≤2 (N=490)	Years of hormone use		>13 (N=385)	Estrogen (N=643)	Type of hormone Estrogen and progestin (N=392)	Unknown (N=562)
	Never used (N=1,602)	Ever used (N=1,597)		2–6 (N=336)	6–13 (N=355)				
Arithmetic mean	0.87	0.85	0.83	0.82	0.85	0.91	0.88	0.84	0.84
Arithmetic mean difference	Reference	–0.01 (–0.02, 0.00)	–0.04 (–0.06, –0.02)	–0.05 (–0.07, –0.03)	–0.02 (–0.04, 0.00)	0.04 (0.02, 0.06)	0.01 (–0.01, 0.03)	–0.03 (–0.05, –0.01)	–0.03 (–0.05, –0.01)
95% confidence limits									
Model 1*									
Adjusted mean difference	Reference	0.00 (–0.01, 0.01)	–0.01 (–0.03, 0.01)	0.00 (–0.02, 0.01)	0.00 (–0.02, 0.02)	0.02 (0.00, 0.04)	0.01 (–0.01, 0.02)	0.00 (–0.02, 0.01)	–0.01 (–0.02, 0.01)
95% confidence limits									
Model 2**									
Adjusted mean difference	Reference	0.01 (–0.01, 0.02)	–0.01 (–0.03, 0.01)	0.00 (–0.02, 0.02)	0.01 (–0.01, 0.03)	0.03 (0.01, 0.05)	0.01 (0.00, 0.03)	0.00 (–0.02, 0.02)	0.00 (–0.01, 0.02)
95% confidence limits									

* Covariates that are not assumed to be effects of hormones: age, ethnicity, education, smoking status, pack-years of smoking, body-mass index, systolic blood pressure, use of anti-hypertension medications

** Covariates from model 1 and covariates that are presumed effects of hormones: glucose, diabetes (taking medication), HDL-cholesterol, LDL-cholesterol, and taking cholesterol medication

Table 5

Arithmetic mean and arithmetic mean difference of internal carotid intima-media thickness (mm) by hormone use (ever versus never), years of hormone use, and type of hormone: the Multi-Ethnic Study of Atherosclerosis, USA, 2000–2002

	Hormone use		Years of hormone use		>13 (N=382)	Estrogen (N=636)	Type of hormone Estrogen and progestin (N=388)	Unknown (N=548)
	Never used (N=1,573)	Ever used (N=1,572)	2–6 (N=334)	6–13 (N=345)				
Arithmetic mean	1.04	1.03	0.94	1.03	1.12	1.10	0.99	0.98
Arithmetic mean difference	Reference	–0.01 (–0.05, 0.03)	–0.10 (–0.17, –0.03)	–0.01 (–0.08, 0.06)	0.08 (0.01, 0.15)	0.06 (0.01, 0.11)	–0.05 (–0.12, 0.02)	–0.06 (–0.12, 0.00)
95% confidence limits								
Model 1*								
Adjusted mean difference	Reference	–0.01 (–0.05, 0.03)	–0.03 (–0.10, 0.03)	–0.01 (–0.08, 0.05)	–0.03 (–0.10, 0.03)	0.03 (–0.02, 0.08)	–0.02 (–0.09, 0.04)	–0.05 (–0.11, 0.00)
95% confidence limits								
Model 2**								
Adjusted mean difference	Reference	0.00 (–0.04, 0.04)	–0.02 (–0.09, 0.05)	0.00 (–0.06, 0.07)	–0.02 (–0.08, 0.05)	0.03 (–0.02, 0.08)	–0.01 (–0.08, 0.05)	–0.04 (–0.09, 0.02)
95% confidence limits								

* Covariates that are not assumed to be effects of hormones: age, ethnicity, education, smoking status, pack-years of smoking, body-mass index, systolic blood pressure, use of anti-hypertension medications

** Covariates from model 1 and covariates that are presumed effects of hormones: glucose, diabetes (taking medication), HDL-cholesterol, LDL-cholesterol, and taking cholesterol medication