Effects of Estrogen With and Without Progestin on Urinary Incontinence

Susan L. Hendrix, DO
Barbara B. Cochrane, RN, PhD
Ingrid E. Nygaard, MD
Victoria L. Handa, MD
Vanessa M. Barnabei, MD, PhD
Cheryl Iglesia, MD
Aaron Aragaki, MS
Michelle J. Naughton, PhD
Robert B. Wallace, MD
S. Gene McNeeley, MD

Context Menopausal hormone therapy has long been credited with many benefits beyond the indications of relieving hot flashes, night sweats, and vaginal dryness, and it is often prescribed to treat urinary incontinence (UI).

Objective To assess the effects of menopausal hormone therapy on the incidence and severity of symptoms of stress, urge, and mixed UI in healthy postmenopausal women.

Design, Setting, and Participants Women's Health Initiative multicenter double-blind, placebo-controlled, randomized clinical trials of menopausal hormone therapy in 27 347 postmenopausal women aged 50 to 79 years enrolled between 1993 and 1998, for whom UI symptoms were known in 23 296 participants at baseline and 1 year.

Interventions Women were randomized based on hysterectomy status to active treatment or placebo in either the estrogen plus progestin (E + P) or estrogen alone trials. The E + P hormones were 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate (CEE + MPA); estrogen alone consisted of 0.625 mg/d of conjugated equine estrogen (CEE). There were 8506 participants who received CEE + MPA (8102 who received placebo) and 5310 who received CEE alone (5429 who received placebo).

Main Outcome Measures Incident UI at 1 year among women without UI at baseline and severity of UI at 1 year among women who had UI at baseline.

Results Menopausal hormone therapy increased the incidence of all types of UI at 1 year among women who were continent at baseline. The risk was highest for stress UI (CEE + MPA: relative risk [RR], 1.87 [95% confidence interval {CI}, 1.61-2.18]; CEE alone: RR, 2.15 [95% CI, 1.77-2.62]), followed by mixed UI (CEE + MPA: RR, 1.49 [95% CI, 1.10-2.01]; CEE alone: RR, 1.79 [95% CI, 1.26-2.53]). The combination of CEE + MPA had no significant effect on developing urge UI (RR, 1.15; 95% CI, 0.99-1.34), but CEE alone increased the risk (RR, 1.32; 95% CI, 1.10-1.58). Among women experiencing UI at baseline, frequency worsened in both trials (CEE + MPA: RR, 1.38 [95% CI, 1.28-1.49]; CEE alone: RR, 1.47 [95% CI, 1.35-1.61]). Amount of UI worsened at 1 year in both trials (CEE + MPA: RR, 1.20 [95% CI, 1.06-1.36]; CEE alone: RR, 1.59 [95% CI, 1.39-1.82]). Women receiving menopausal hormone therapy were more likely to report that UI limited their daily activities (CEE + MPA: RR, 1.18 [95% CI, 1.06-1.32]; CEE alone: RR, 1.29 [95% CI, 1.15-1.45]) and bothered or disturbed them (CEE + MPA: RR, 1.22 [95% CI, 1.13-1.32]; CEE alone: RR, 1.50 [95% CI, 1.37-1.65]) at 1 year.

Conclusions Conjugated equine estrogen alone and CEE + MPA increased the risk of UI among continent women and worsened the characteristics of UI among symptomatic women after 1 year. Conjugated equine estrogen with or without progestin should not be prescribed for the prevention or relief of UI.

JAMA. 2005;293:935-948 www.jama.com

Menopausal hormone therapy (MHT) consisting of oral estrogen plus progestin or estrogen alone has long been used to treat postmenopausal women and, until recently, was credited with many benefits well beyond the indications for symptomatic relief of hot flashes, night sweats, and vaginal dryness. One of the purported benefits of MHT was to improve the symptoms of urinary incontinence (UI). Biological mechanisms to support this advantage were based on detection of estrogen receptors in various genitourinary tissues, as well as from observational studies and anecdotal reports.[1-5]

A recent Cochrane review assessing the effects of estrogen use for the treatment of UI concluded that treatment consisting of estrogen alone is associated with perceived improvement or cure compared with placebo, but that larger trials were needed.[6] It identified 3 clinical trials comparing treatments of estrogen plus progestin with placebo, including the larger Heart and Es-

See also pp 998 and 1004.

Author Affiliations: Department of Obstetrics and Gynecology, Wayne State University School of Medicine/Hutzel Women's Hospital, Detroit, Mich (Drs Hendrix and McNeeley); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Wash (Dr Cochrane and Mr Aragaki); Department of Obstetrics and Gynecology, Carver College of Medicine (Dr Nygaard) and Department of Epidemiology, College of Public Health (Dr Wallace), University of Iowa, Iowa City; Department of Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore, Md (Dr Handa); Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee (Dr Barnabei); Department of Obstetrics and Gynecology, Washington Hospital Center, Washington, DC (Dr Iglesia); and Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (Dr Naughton).
Corresponding Author: Susan L. Hendrix, DO, Department of Obstetrics and Gynecology, Wayne State University School of Medicine/Hutzel Women's Hospital, Detroit, MI 48201 (shendrix@med.wayne.edu).

trogen/progestin Replacement Study (HERS).[7] The review of these studies only suggested that estrogen plus progestin reduced the likelihood of cure or improvement. With the publication of the HERS results, the practice of using MHT to treat UI was brought into question, but the American College of Obstetricians and Gynecologists, in their response to the results of the Women's Health Initiative (WHI) findings stated, "for genitourinary symptoms associated with menopause, estrogen and progestin have been shown to be beneficial."[8]

The WHI estrogen plus progestin (E + P) and estrogen alone double-blind, placebo-controlled, randomized clinical trials were designed to evaluate the effects of MHT in preventing coronary heart disease and hip fractures in postmenopausal women.[9] Both trials ended prematurely. The E + P trial was stopped after an average of 5.6 years of follow-up because more harm than benefit was observed.[10] The estrogen alone trial was stopped after 7.1 years because an increased risk of stroke was found with no benefit for coronary heart disease, and sufficient information was obtained to provide an overall assessment of the risks and benefits of treatment with estrogen alone.[11]

The primary aim of this analysis was to determine the effects of MHT (E + P or estrogen alone) on the 1-year incidence and severity of symptoms of stress, urge, and mixed UI in healthy postmenopausal women.

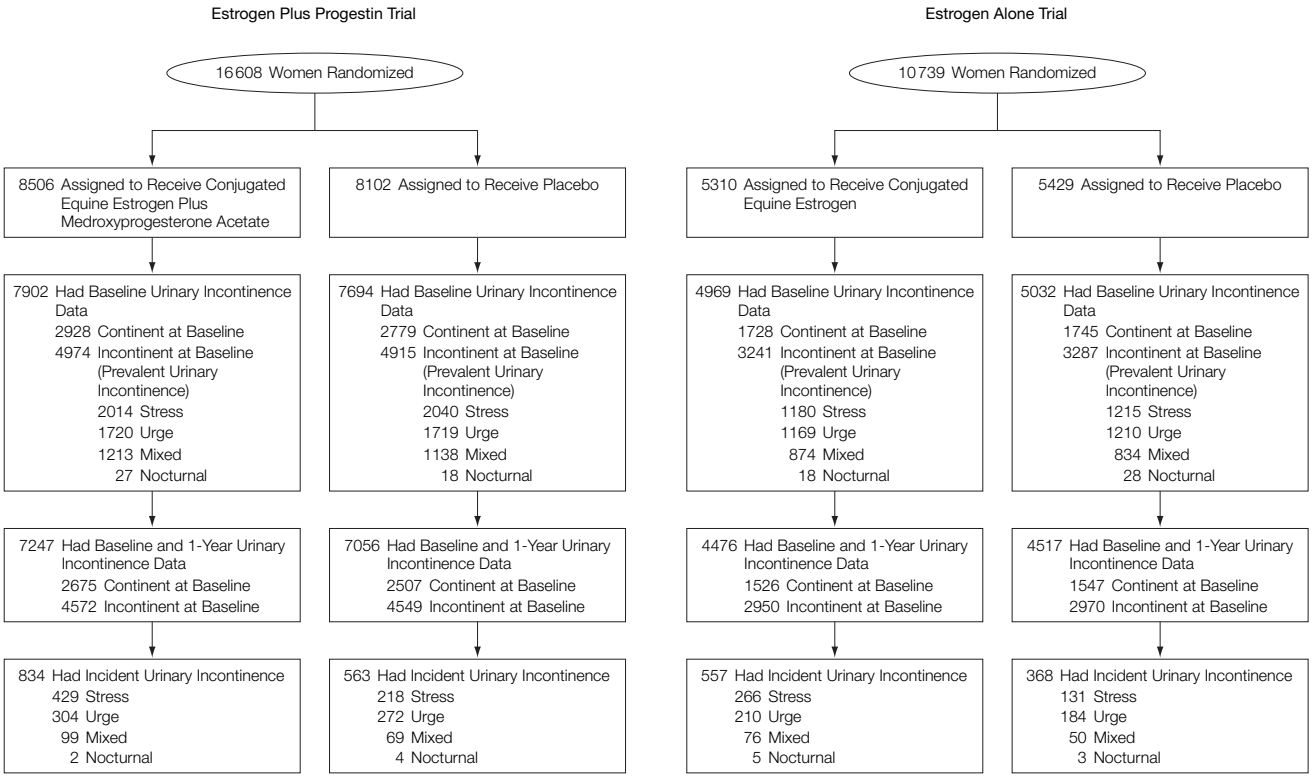
METHODS

Study Population

The WHI hormone trials enrolled 27 347 postmenopausal women from 1993 to 1998 at 40 US clinical centers based on hysterectomy status: 16 608 in the E + P trial, who had not had a hysterectomy; 10 739 in the estrogen alone trial, who had a prior hysterectomy (FIGURE). The WHI used methods to ensure appropriate age distributions and adequate power to test the primary hypotheses, to evaluate intermediate disease outcomes and treatment effects, and to ensure appropriate racial/ethnic group representation.[12] Briefly, women were recruited primarily by mass mailings and other media announcements and were eligible if they were aged 50 to 79 years at entry, postmenopausal, and likely to reside in the study area for 3 years. Women were excluded from the WHI trials for reasons of competing risk, safety, and adherence or retention.

Reasons for exclusion included breast cancer, other invasive cancer in the last 10 years, venous thromboembolism, hypertriglyceridemia, having a medical condition likely to result in death within 3 years, or being unwilling or unable to be randomized to placebo. Menopausal hormone therapy use at baseline required a 3-month washout period before enrollment, and women were excluded if they experienced severe menopausal symptoms at the end of the washout.

Figure. Flow Diagram of Women Included in Analysis of Urinary Incontinence



All participants were required to complete a 4-week placebo run-in with an adherence rate of 80% or greater. At baseline, women completed screening and enrollment questionnaires by interview and self-report, and a physical examination and blood specimen collection were performed. The study was reviewed and approved by the human subjects review committees at each participating institution, and all participants provided written informed consent.

Study Pills

Women randomized in the WHI hormone trials were asked to take a single daily tablet containing a placebo or active medication (estrogen alone participants: 0.625 mg of conjugated equine estrogen [CEE; Premarin, Wyeth Ayerst, St Davids, Pa]; E + P participants: 0.625 mg of CEE plus 2.5 mg of medroxyprogesterone acetate [MPA]). Randomization was performed using a study database distributed by the WHI Clinical Coordinating Center to the local centers; participants were randomized to the active treatment or placebo group in each trial at a 1:1 ratio. The study pill bottles had unique bar codes and computer-based selection to enable double-blinded dispensing.

The study pills were discontinued without unblinding of clinic staff or participants if breast cancer, endometrial pathology (hyperplasia not responsive to treatment, atypia, or cancer), deep-vein thrombosis or pulmonary embolism, malignant melanoma, meningioma, or a triglycerides level of higher than 1000 mg/dL (11.3 mmol/L) was found. The study pills were also discontinued if any nonstudy estrogen or progestin was started.

Baseline Assessment and Follow-up

Baseline questionnaires ascertained comprehensive information on participants, including age, education, occupation, chronic illnesses, time since menopause, parity, breastfeeding history, duration of hormone use, hysterectomy status, constipation, current and past smoking, and physical activity (episodes per week). Participants were asked to categorize their racial or ethnic group by choosing from the following: American Indian/Alaska Native, Asian/Pacific Islander, black/African American, Hispanic, Latino, white, or other. Alcohol consumption and other dietary intake were estimated from a 120-item food frequency questionnaire.[13]

Detailed questions on UI were based on similar items used and validated in previous epidemiological studies[14] and included on a self-administered behavioral and quality of life form (available online at http://www.nhlbi.nih.gov/resources/deca/whios/index.html). Participants who answered yes to the question "Have you ever leaked even a very small amount of urine involuntarily and you couldn't control it?" were categorized as having prevalent UI. Those who answered the question "When do you usually leak urine?" with only "When I cough, laugh, sneeze, lift, stand up or exercise" were considered to have the symptom of stress UI and those who answered with only "When I feel the need to urinate and can't get to the toilet fast enough" to have urge UI. Those who marked both responses were considered to have mixed UI. When a participant responded only "When I am sleeping," she was classified as having only UI at night. Women were classified as continent if they responded, "Not once during the past year" or "no longer leak urine." Prior medical or surgical therapy for UI; details on the route of childbirth, vaginal or Cesarean; or childbirth-related complications were not queried. The baseline questions on UI were repeated at 1 year in all participants and at 3 years in a subsample consisting of 8.6% of participants. The subsample was selected to assess intermediate effects of the interventions (including blood biomarkers), while keeping costs and clinic burden to a minimum. We characterize incident UI as the change from baseline to 1 year. We also report the effect at 3 years in the subsample of the participants.

The WHI participants were asked to bring all current prescription and nonprescription medications to their first screening interview. Clinic interviewers entered the names of each medication from the medicine containers into the WHI database, which assigned drug codes using Medi-Span software.[15] Women reported duration of use for each medication. Information on dose was not captured. Current use of diuretics, anticholinergic medications, α- and β-blockers, and β agonists were recorded. Current and prior use of MHT was ascertained by a detailed interview at baseline that queried women about the type, route of administration, number of pills per day, age when use was initiated, and duration for each hormonal preparation ever taken.

Weight was measured to the nearest 0.1 kg on a balance beam scale with the participant dressed in indoor clothing without shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass index was calculated as weight in kilograms divided by height in meters squared. All women also underwent a standardized baseline pelvic examination. Participants in the E + P trial had an endometrial aspiration or transvaginal uterine ultrasound prior to randomization.

Statistical Analysis

Incident or worsening of symptoms focused on stress, urge, and mixed UI reported at baseline and 1 year. Women stratified by baseline UI were analyzed in the treatment groups to which they were originally randomized according to the intent-to-treat principle. Participants with missing data on UI at baseline or 1 year were excluded from the analyses. Analyses were performed using SAS statistical software (version 9.0, SAS Institute Inc, Cary, NC).

Logistic regression models were fit with UI status (1 = stress, urge, or mixed UI at 1 year; 0 = continent at 1 year) to determine the overall risk of UI among asymptomatic women. Similar logistic regression models were fit to examine risk of developing a particular type of UI at 1 year as opposed to remaining continent. To examine whether CEE + MPA or CEE alone had more substan-

tial effects on UI for particular subgroups of women, we fit a series of logistic regression models. For each model, we included randomization assignment, a baseline characteristic, and the corresponding interaction term. Baseline characteristics corresponding to these subgroups included age; years since menopause; ethnicity; body mass index; prior MHT use and duration; smoking; history of diabetes, asthma, emphysema, or stroke; age at first birth; parity; breast feeding; use of diuretics (carbonic anhydrase inhibitors, loop diuretics, mercurial diuretics, osmotic diuretics, potassium sparing diuretics, thiazides and thiazide-like diuretics, miscellaneous diuretics, or combination diuretics), anticholinergics, α- and β-blockers, β agonists; and alcohol use. Statistical significance of the main effects and interactions were judged by a nominal $\alpha = .05$. Results are expressed as relative risks (RRs).

To determine how MHT affected participants who were incontinent at baseline, changes in self-reported frequency (daily, weekly, monthly, <monthly, not at all), amount (none, barely noticeable, soaked underpants, soaked through to outer clothing), limitations in daily activities (never to very often), and bother/disturbance (not at all to very disturbing) attributed to UI from baseline to 1 year were classified as better, same, or worse. Women's perceptions of inconvenience and bother, as well as impact on activities of daily living, have an important influence on treatment decisions. Preliminary analysis using the response variable indicated little difference between better and same (for example, the odds of reporting a better frequency of UI from baseline to 1 year among participants receiving CEE + MPA compared with placebo was 0.99). For simplicity, the analysis presented herein used the col-

Table 1. General Characteristics of Participants With Urinary Incontinence Data at Baseline and 1 Year*

	No. (%) of Participants			No. (%) of Participants		
	CEE + MPA (n = 7247)	Placebo (n = 7056)	*P* Value†	CEE Alone (n = 4476)	Placebo (n = 4517)	*P* Value†
Age at screening, y						
50-54	854 (11.8)	799 (11.3)	.84	542 (12.1)	555 (12.3)	.97
55-59	1498 (20.7)	1472 (20.9)		773 (17.3)	775 (17.2)	
60-69	3307 (45.6)	3221 (45.6)		2057 (46.0)	2089 (46.2)	
70-79	1588 (21.9)	1564 (22.2)		1104 (24.7)	1098 (24.3)	
Race/ethnicity						
White	6151 (84.9)	5992 (84.9)	.51	3431 (76.7)	3433 (76.0)	.52
Black	458 (6.3)	481 (6.8)		632 (14.1)	694 (15.4)	
Hispanic	341 (4.7)	315 (4.5)		245 (5.5)	234 (5.2)	
Asian/Pacific Islander	177 (2.4)	153 (2.2)		72 (1.6)	63 (1.4)	
American Indian	20 (0.3)	26 (0.4)		34 (0.8)	28 (0.6)	
Unknown	100 (1.4)	89 (1.3)		62 (1.4)	65 (1.4)	
BMI						
Normal (<25)	2237 (31.0)	2198 (31.4)	.88	946 (21.3)	936 (20.9)	.50
Overweight (25 to <30)	2520 (34.9)	2449 (34.9)		1519 (34.1)	1584 (35.3)	
Obese (≥30)	2457 (34.1)	2363 (33.7)		1986 (44.6)	1966 (43.8)	
Moderate or strenuous activity/wk (≥20 min)						
None	1265 (18.2)	1210 (17.5)	.10	938 (21.6)	911 (21.0)	.17
Some	2979 (42.9)	2953 (42.8)		1945 (44.8)	2027 (46.6)	
2 to <4 times	1130 (16.3)	1063 (15.4)		677 (15.6)	617 (14.2)	
≥4 times	1571 (22.6)	1670 (24.2)		778 (17.9)	792 (18.2)	
Smoking						
Never	3595 (50.0)	3500 (50.2)	.72	2301 (51.8)	2257 (50.5)	.30
Past	2875 (40.0)	2751 (39.5)		1705 (38.4)	1737 (38.9)	
Current	715 (10.0)	716 (10.3)		434 (9.8)	474 (10.6)	
Alcohol consumption						
None	801 (11.1)	801 (11.4)	.65	598 (13.5)	595 (13.3)	.97
Ever	1188 (16.5)	1198 (17.1)		1060 (23.9)	1040 (23.2)	
<1/mo	1009 (14.0)	975 (13.9)		638 (14.4)	644 (14.4)	
<1/wk	1440 (20.0)	1328 (19.0)		852 (19.2)	872 (19.5)	
1 to <7 times/wk	1836 (25.5)	1781 (25.4)		889 (20.0)	919 (20.5)	
≥7 wk	925 (12.8)	920 (13.1)		399 (9.0)	412 (9.2)	

Abbreviations: BMI indicates body mass index, calculated as weight in kilograms divided by the square of height in meters; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.
*Subgroup totals may not sum to number randomized in each group because of missing data.
†Based on χ^2 test of association between baseline characteristic and randomization assignment.

lapsed response categories of worse compared with same/better. Logistic regression modeling, similar to the earlier incident analysis, was then performed.

RESULTS

Baseline Characteristics and Prevalence of UI

The study flow for the E + P and estrogen alone trials for women included in this analysis are shown in the Figure. Other flow diagrams have been published previously.[10,11] TABLE 1 and TABLE 2 describe baseline demographic and reproductive

Table 2. Health Characteristics of Participants With Urinary Incontinence Data at Baseline and 1 Year*

	No. (%) of Participants			No. (%) of Participants		
	CEE + MPA (n = 7247)	Placebo (n = 7056)	*P* Value†	CEE Alone (n = 4476)	Placebo (n = 4517)	*P* Value†
Baseline incontinence						
No leaking	2675 (36.9)	2507 (35.5)		1526 (34.1)	1547 (34.2)	
Stress	1844 (25.4)	1884 (26.7)		1074 (24.0)	1086 (24.0)	
Urge	1590 (21.9)	1590 (22.5)	.20	1059 (23.7)	1095 (24.2)	.69
Mixed	1115 (15.4)	1059 (15.0)		800 (17.9)	766 (17.0)	
At night only	23 (0.3)	16 (0.2)		17 (0.4)	23 (0.5)	
Health in general						
Excellent	1399 (19.4)	1321 (18.8)		477 (10.7)	551 (12.2)	
Very good	3179 (44.0)	3133 (44.6)		1735 (38.9)	1671 (37.1)	
Good	2242 (31.0)	2120 (30.2)	.21	1731 (38.8)	1755 (39.0)	.12
Fair	383 (5.3)	430 (6.1)		484 (10.9)	487 (10.8)	
Poor	26 (0.4)	25 (0.4)		29 (0.7)	36 (0.8)	
No. of term pregnancies						
1	574 (7.9)	569 (8.1)		312 (7.0)	374 (8.3)	
2	1647 (22.8)	1480 (21.1)		910 (20.5)	931 (20.7)	
3	1730 (24.0)	1700 (24.2)		968 (21.8)	1088 (24.2)	
4	1218 (16.9)	1256 (17.9)	.22	821 (18.5)	757 (16.9)	.004
≥5	1311 (18.2)	1312 (18.7)		1018 (22.9)	964 (21.5)	
Never pregnant	564 (7.8)	549 (7.8)		316 (7.1)	288 (6.4)	
No term pregnancy	177 (2.5)	159 (2.3)		101 (2.3)	87 (1.9)	
Age at first birth						
Never pregnant	564 (8.6)	549 (8.7)		316 (7.9)	288 (7.1)	
No term pregnancy	180 (2.7)	160 (2.5)		102 (2.6)	89 (2.2)	
<20	948 (14.4)	984 (15.5)	.46	994 (25.0)	1014 (25.0)	.21
20-24	2788 (42.5)	2637 (41.6)		1738 (43.7)	1777 (43.8)	
25-29	1485 (22.6)	1458 (23.0)		655 (16.5)	667 (16.5)	
≥30	600 (9.1)	550 (8.7)		174 (4.4)	218 (5.4)	
Lactation duration, mo						
0‡	3267 (45.6)	3188 (45.7)		2096 (47.7)	2080 (46.8)	
1-6	1849 (25.8)	1801 (25.8)		1227 (27.9)	1234 (27.8)	
7-12	831 (11.6)	785 (11.2)	.96	459 (10.4)	529 (11.9)	.29
13-23	715 (10.0)	693 (9.9)		344 (7.8)	339 (7.6)	
≥24	510 (7.1)	511 (7.3)		269 (6.1)	260 (5.9)	
Duration since menopause, y						
<5	1155 (16.8)	1085 (16.1)		283 (7.4)	268 (6.8)	
5 to <10	1294 (18.9)	1321 (19.6)	.54	411 (10.7)	404 (10.3)	.71
10 to <15	1455 (21.2)	1421 (21.1)		595 (15.6)	612 (15.6)	
≥15	2953 (43.1)	2918 (43.3)		2537 (66.3)	2630 (67.2)	
Hormone use						
Never	5346 (73.8)	5259 (74.6)		2326 (52.0)	2289 (50.7)	
Past	1429 (19.7)	1355 (19.2)	.59	1568 (35.0)	1628 (36.1)	.48
Current	468 (6.5)	440 (6.2)		581 (13.0)	597 (13.2)	
Duration of prior hormone use, y						
Never	5346 (73.8)	5259 (74.5)		2326 (52.0)	2289 (50.7)	
<5	1311 (18.1)	1270 (18.0)		1125 (25.1)	1176 (26.0)	
5 to <10	363 (5.0)	302 (4.3)	.22	394 (8.8)	435 (9.6)	.33
≥10	227 (3.1)	224 (3.2)		631 (14.1)	617 (13.7)	

(continued)

characteristics, medical conditions, and health status characteristics of participants who had baseline and 1-year UI information.

Baseline data on UI was available for 25597 women (93.6% of all WHI participants). Among these women, 16417 or 64.1% (63.4% for E + P trial; 65.3% for estrogen alone trial) reported UI symptoms within the past year at baseline. Stress UI was reported by 41.0% of incontinent women in the E + P trial and

Table 2. Health Characteristics of Participants With Urinary Incontinence Data at Baseline and 1 Year (cont)

	No. (%) of Participants			No. (%) of Participants		
	CEE + MPA (n = 7247)	Placebo (n = 7056)	*P* Value*	CEE Alone (n = 4476)	Placebo (n = 4517)	*P* Value*
Disease or condition						
Diabetes	409 (5.6)	403 (5.7)	.86	426 (9.5)	435 (9.6)	.85
Asthma	463 (6.5)	452 (6.5)	.95	394 (8.9)	352 (7.9)	.09
Emphysema	199 (2.9)	237 (3.5)	.05	181 (4.2)	180 (4.2)	.95
Ulcerative colitis	62 (0.9)	50 (0.7)	.32	60 (1.4)	51 (1.1)	.37
Part of intestines removed	102 (1.5)	101 (1.5)	.97	111 (2.5)	97 (2.2)	.31
Multiple sclerosis	21 (0.3)	19 (0.3)	.77	10 (0.2)	18 (0.4)	.13
Parkinson disease	11 (0.2)	14 (0.2)	.56§	7 (0.2)	9 (0.2)	.80§
Stroke	50 (0.7)	63 (0.9)	.17	60 (1.3)	74 (1.6)	.24
Medication use						
Diuretics (thiazides and loop)	793 (10.9)	805 (11.4)	.38	747 (16.7)	771 (17.1)	.63
Anticholinergics	31 (0.4)	22 (0.3)	.25	21 (0.5)	20 (0.4)	.85
β-Blockers	430 (5.9)	441 (6.3)	.43	372 (8.3)	360 (8.0)	.55
Adrenergic agents	16 (0.2)	22 (0.3)	.29	13 (0.3)	15 (0.3)	.72

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.
*Subgroup totals may not sum to number randomized in each group because of missing data.
†Based on χ^2 test of association between baseline characteristic and randomization assignment.
‡Never pregnant or no term pregnancy.
§Based on a Fisher exact test because of the small number of participants who reported disease.

Table 3. Characteristics Among Women Reporting Stress, Urge, or Mixed Urinary Incontinence at Baseline*

	No. (%) of Women With Incontinence					
	E + P Trial			Estrogen Alone Trial		
Characteristics of Urinary Incontinence	Stress (n = 4054)	Urge (n = 3439)	Mixed (n = 2351)	Stress (n = 2395)	Urge (n = 2379)	Mixed (n = 1708)
Frequency						
<1/mo	1695 (41.8)	1126 (32.7)	483 (20.5)	826 (34.5)	680 (28.6)	241 (14.1)
≥1/mo but <1/wk	1077 (26.6)	1016 (29.5)	596 (25.4)	614 (25.6)	644 (27.1)	369 (21.6)
≥1/wk but <1/d	891 (22.0)	976 (28.4)	761 (32.4)	600 (25.1)	736 (30.9)	594 (34.8)
Daily	391 (9.6)	321 (9.3)	511 (21.7)	355 (14.8)	319 (13.4)	504 (29.5)
Amount						
None	7 (0.2)	8 (0.2)	2 (0.1)	5 (0.2)	5 (0.2)	1 (0.1)
Barely noticeable on underpants	3433 (85.7)	2735 (80.0)	1648 (70.7)	1915 (81.1)	1772 (75.4)	1060 (62.4)
Soaked underpants	508 (12.7)	609 (17.8)	574 (24.6)	376 (15.9)	476 (20.3)	532 (31.3)
Soaked through to outer clothing	58 (1.4)	67 (2.0)	107 (4.6)	65 (2.8)	97 (4.1)	107 (6.3)
Leakage limits activities						
Never	3279 (81.7)	2835 (82.8)	1657 (70.8)	1759 (74.3)	1799 (76.4)	1112 (65.3)
Almost never	579 (14.4)	438 (12.8)	496 (21.2)	426 (18.0)	375 (15.9)	370 (21.7)
Sometimes	124 (3.1)	120 (3.5)	143 (6.1)	138 (5.8)	141 (6.0)	158 (9.3)
Fairly often	20 (0.5)	20 (0.6)	34 (1.5)	33 (1.4)	28 (1.2)	41 (2.4)
Very often	10 (0.2)	9 (0.3)	10 (0.4)	10 (0.4)	11 (0.5)	22 (1.3)
Leakage bothersome						
Not at all	1115 (27.8)	906 (26.5)	371 (15.9)	546 (23.1)	550 (23.4)	214 (12.6)
A little	2022 (50.4)	1658 (48.5)	1051 (44.9)	1143 (48.3)	1092 (46.4)	711 (41.7)
Somewhat	584 (14.6)	559 (16.3)	538 (23.0)	420 (17.7)	419 (17.8)	402 (23.6)
Very	212 (5.3)	220 (6.4)	276 (11.8)	193 (8.2)	219 (9.3)	253 (14.9)
Extremely	79 (2.0)	78 (2.3)	104 (4.4)	65 (2.7)	74 (3.1)	123 (7.2)

Abbreviation: E + P, estrogen plus progestin.
*Subgroup totals may not sum to number randomized in each group because of missing data. $P<.001$ for all comparisons and based on χ^2 test of association between baseline urinary incontinence characteristic and type of urinary incontinence.

Table 4. Incident Urinary Incontinence at 1 Year in Women Asymptomatic at Baseline*

	No. (%) of Participants				No. (%) of Participants			
	CEE + MPA (n = 2675)	Placebo (n = 2507)	RR (95% CI)	*P* Value†	CEE Alone (n = 1526)	Placebo (n = 1547)	RR (95% CI)	*P* Value†
Stress Urinary Incontinence								
Total participants	429 (16.0)	218 (8.7)	1.87 (1.61-2.18)	<.001	266 (17.4)	131 (8.5)	2.15 (1.77-2.62)	<.001
Age at screening, y								
50-54	34 (10.0)	35 (11.4)	0.90 (0.58-1.40)	<.001	28 (13.5)	26 (11.7)	1.13 (0.69-1.86)	.002
55-59	86 (14.3)	49 (8.6)	1.63 (1.18-2.27)		49 (18.4)	20 (7.7)	2.32 (1.42-3.77)	
60-69	227 (18.4)	102 (8.9)	2.11 (1.70-2.62)		130 (18.5)	69 (9.5)	2.10 (1.60-2.74)	
70-79	82 (16.4)	32 (6.6)	2.59 (1.77-3.81)		59 (16.9)	16 (4.8)	3.91 (2.31-6.60)	
Duration since menopause, y								
<5	51 (12.8)	42 (10.9)	1.21 (0.83-1.77)	.005	12 (13.0)	15 (15.2)	0.95 (0.47-1.90)	.02
5 to <10	68 (14.5)	42 (8.7)	1.70 (1.19-2.44)		21 (14.6)	9 (6.6)	2.18 (1.04-4.57)	
10 to <15	97 (18.6)	47 (9.3)	2.00 (1.45-2.77)		35 (18.0)	17 (8.4)	2.01 (1.17-3.44)	
≥15	165 (16.5)	69 (7.2)	2.33 (1.79-3.03)		139 (17.0)	61 (7.1)	2.56 (1.93-3.39)	
Hormone use								
Never	304 (15.4)	158 (8.3)	1.87 (1.57-2.24)	.008	144 (17.2)	66 (7.9)	2.25 (1.72-2.95)	.55
Past	106 (19.7)	38 (8.2)	2.41 (1.71-3.41)		96 (17.8)	46 (8.4)	2.24 (1.62-3.10)	
Current	19 (12.1)	22 (15.3)	0.85 (0.48-1.50)		26 (17.1)	19 (11.7)	1.60 (0.93-2.75)	
Smoking								
Never	235 (16.9)	113 (8.9)	1.93 (1.57-2.38)	.46	130 (16.5)	66 (8.0)	2.23 (1.69-2.93)	.82
Past	161 (16.3)	78 (8.5)	1.95 (1.52-2.51)		108 (19.5)	54 (10.1)	1.98 (1.47-2.67)	
Current	33 (11.9)	24 (8.7)	1.42 (0.87-2.33)		26 (15.2)	10 (5.7)	2.56 (1.28-5.12)	
Diabetes								
Absent	411 (16.2)	203 (8.5)	1.94 (1.66-2.27)	.10	249 (17.6)	118 (8.4)	2.19 (1.79-2.69)	.48
Present	18 (13.3)	14 (11.4)	1.11 (0.58-2.11)		17 (15.0)	13 (9.4)	1.72 (0.88-3.36)	
β-Blocker use								
Absent	411 (16.1)	215 (9.1)	1.81 (1.55-2.11)	.03	238 (16.9)	120 (8.3)	2.14 (1.75-2.63)	.92
Present	18 (13.8)	3 (2.3)	6.69 (2.03-22.05)		28 (23.5)	11 (11.2)	2.11 (1.12-3.98)	
Urge Urinary Incontinence								
Total participants	304 (11.4)	272 (10.8)	1.15 (0.99-1.34)	.06	210 (13.8)	184 (11.9)	1.32 (1.10-1.58)	.003
Age at screening, y								
50-54	37 (10.9)	28 (9.1)	1.18 (0.75-1.88)	.46	14 (6.7)	18 (8.1)	0.85 (0.44-1.66)	.05
55-59	49 (8.1)	55 (9.6)	0.90 (0.63-1.30)		24 (9.0)	28 (10.7)	0.94 (0.56-1.57)	
60-69	145 (11.8)	120 (10.5)	1.26 (1.01-1.58)		101 (14.4)	81 (11.1)	1.49 (1.14-1.95)	
70-79	73 (14.6)	69 (14.2)	1.20 (0.89-1.61)		71 (20.3)	57 (17.0)	1.45 (1.07-1.98)	
Duration since menopause, y								
<5	40 (10.0)	32 (8.3)	1.25 (0.80-1.93)	.89	11 (12.0)	9 (9.1)	1.37 (0.60-3.12)	.35
5 to <10	48 (10.2)	46 (9.5)	1.17 (0.80-1.70)		15 (10.4)	12 (8.8)	1.26 (0.62-2.58)	
10 to <15	54 (10.4)	50 (9.9)	1.17 (0.81-1.67)		19 (9.8)	30 (14.8)	0.74 (0.43-1.26)	
≥15	134 (13.4)	124 (13.0)	1.17 (0.93-1.46)		130 (15.9)	108 (12.6)	1.46 (1.16-1.84)	
Hormone use								
Never	225 (11.4)	208 (11.0)	1.14 (0.96-1.36)	.89	113 (13.5)	96 (11.5)	1.33 (1.03-1.70)	.58
Past	63 (11.7)	54 (11.6)	1.16 (0.83-1.62)		77 (14.3)	75 (13.7)	1.23 (0.92-1.64)	
Current	15 (9.6)	10 (6.9)	1.38 (0.65-2.96)		20 (13.2)	13 (8.0)	1.81 (0.94-3.49)	
Smoking								
Never	149 (10.7)	138 (10.8)	1.11 (0.89-1.37)	.84	113 (14.3)	93 (11.2)	1.47 (1.14-1.89)	.42
Past	120 (12.1)	103 (11.2)	1.20 (0.94-1.53)		71 (12.8)	66 (12.3)	1.19 (0.87-1.62)	
Current	33 (11.9)	28 (10.2)	1.24 (0.77-1.98)		22 (12.9)	23 (13.2)	1.06 (0.62-1.81)	
Diabetes								
Absent	290 (11.4)	249 (10.4)	1.21 (1.03-1.41)	.03	196 (12.1)	171 (12.1)	1.30 (1.08-1.58)	.78
Present	14 (10.4)	23 (18.7)	0.59 (0.32-1.09)		14 (9.4)	13 (9.4)	1.46 (0.72-2.96)	
β-Blocker use								
Absent	286 (11.2)	258 (10.9)	1.13 (0.97-1.33)	.34	196 (13.9)	171 (11.8)	1.34 (1.11-1.62)	.53
Present	18 (13.8)	14 (10.6)	1.57 (0.82-3.00)		14 (11.8)	13 (13.3)	1.06 (0.53-2.13)	

(continued)

Table 4. Incident Urinary Incontinence at 1 Year in Women Asymptomatic at Baseline* (cont)

	No. (%) of Participants				No. (%) of Participants			
	CEE + MPA (n = 2675)	Placebo (n = 2507)	RR (95% CI)	*P* Value†	CEE Alone (n = 1526)	Placebo (n = 1547)	RR (95% CI)	*P* Value†
Mixed Urinary Incontinence								
Total participants	99 (3.7)	69 (2.8)	1.49 (1.10-2.01)	.01	76 (5.0)	50 (3.2)	1.79 (1.26-2.53)	.001
Age at screening, y								
50-54	7 (2.1)	3 (1.0)	2.11 (0.55-8.06)	.26	7 (3.4)	7 (3.2)	1.07 (0.38-2.99)	.04
55-59	21 (3.5)	20 (3.5)	1.05 (0.58-1.91)		5 (1.9)	8 (3.1)	0.69 (0.23-2.06)	
60-69	45 (3.6)	33 (2.9)	1.46 (0.94-2.26)		40 (5.7)	24 (3.3)	2.05 (1.25-3.35)	
70-79	26 (5.2)	13 (2.7)	2.24 (1.17-4.30)		24 (6.9)	11 (3.3)	2.63 (1.32-5.25)	
Duration since menopause, y								
<5	13 (3.3)	10 (2.6)	1.32 (0.59-2.96)	.73	5 (5.4)	0	2.62 (0.94-7.30)	.46
5 to <10	15 (3.2)	11 (2.3)	1.53 (0.71-3.29)		2 (1.4)	6 (4.4)	0.36 (0.07-1.74)	
10 to <15	18 (3.5)	15 (3.0)	1.31 (0.67-2.56)		8 (4.1)	10 (4.9)	0.89 (0.36-2.20)	
≥15	42 (4.2)	29 (3.0)	1.58 (0.99-2.50)		49 (6.0)	29 (3.4)	2.11 (1.35-3.30)	
Hormone use								
Never	73 (3.7)	54 (2.8)	1.43 (1.01-2.02)	.49	35 (4.2)	30 (3.6)	1.36 (0.85-2.18)	.15
Past	18 (3.3)	13 (2.8)	1.39 (0.69-2.79)		34 (6.3)	15 (2.7)	2.65 (1.47-4.79)	
Current	8 (5.1)	2 (1.4)	3.64 (0.79-16.79)		7 (4.6)	5 (3.1)	1.75 (0.57-5.35)	
Smoking								
Never	50 (3.6)	29 (2.3)	1.75 (1.12-2.74)	.52	44 (5.6)	21 (2.5)	2.57 (1.55-4.27)	.05
Past	41 (4.1)	34 (3.7)	1.26 (0.81-1.96)		30 (5.4)	22 (4.1)	1.51 (0.89-2.58)	
Current	8 (2.9)	4 (1.5)	2.12 (0.65-6.95)		2 (1.2)	6 (3.4)	0.38 (0.08-1.86)	
Diabetes								
Absent	93 (3.7)	68 (2.9)	1.43 (1.06-1.95)	.24	70 (5.0)	46 (3.3)	1.76 (1.23-2.53)	.81
Present	6 (4.4)	1 (0.8)	5.01 (0.61-40.81)		6 (5.3)	4 (2.9)	2.07 (0.60-7.11)	
β-Blocker use								
Absent	92 (3.6)	68 (2.9)	1.39 (1.02-1.89)	.09	73 (5.2)	48 (3.3)	1.81 (1.27-2.58)	.81
Present	7 (5.4)	1 (0.8)	8.56 (1.07-68.38)		3 (2.5)	2 (2.0)	1.48 (0.25-8.60)	

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate; RR, relative risk.
*Subgroup totals may not sum to number randomized in each group because of missing data.
†Calculated from a logistic regression model.

36.7% of those in the estrogen alone trial; urge UI, 34.8% in the E + P trial and 36.4% in the estrogen alone trial; and mixed UI, 23.8% in the E + P trial and 26.2% in the estrogen alone trial. Finally, UI only at night was reported by 0.5% of E + P trial participants and 0.7% of estrogen alone trial participants. There were no differences in participant characteristics by baseline hormone use. Participants with mixed UI tended to have leakage more frequently and tended to report more impact on quality of life in terms of activity limitations and bother attributed to UI (TABLE 3).

Women with missing UI data at baseline or 1 year in both MHT trials were more likely to be younger, to be from a racial/ethnic minority group, to consume less alcohol, and to be less healthy (ie, more sedentary, poorer self-reported health, and more likely to have emphysema or Parkinson disease). For the estrogen alone trial, women with missing UI data were more likely to report asthma, while E + P trial women with missing UI data were more likely to report being closer to menopause, obese, and a current smoker and to have a history of colitis (data available from authors on request).

Participant Follow-Up

At 1 year, vital status was known for 99.9% of participants, including 0.2% who were deceased and 0.1% who were lost to follow-up. During the first year, 9.7% of women receiving CEE + MPA and 6.6% receiving placebo stopped taking study pills for various reasons. Overall, the rate of adherence (taking 80% of the pills) to the study protocol was 74% in the CEE + MPA group and 81% in the placebo group at 1 year.

For the estrogen alone trial at 1 year, vital status was known for 100% of participants, including 0.4% who were deceased. During the first year, study pills were stopped for various reasons by 8.4% of women randomized to CEE alone and 8.0% of women randomized to placebo. Overall, 77.4% of women randomized to CEE alone and 81.4% of women randomized to placebo were adherent (taking at least 80% of pills) at 1 year.

Incident UI

For those women who were asymptomatic at baseline, MHT was associated with an increased incidence at 1 year of (1) any UI (E + P trial: 834 vs 563 cases [RR, 1.39; 95% confidence interval {CI}, 1.27-1.52]; estrogen alone trial: 557 vs 368 cases [RR, 1.53; 95% CI, 1.37-1.71]); (2) stress UI (E + P: 429 vs 218 cases [RR, 1.87; 95% CI, 1.61-2.18]; estrogen alone: 266 vs 131 cases [RR, 2.15; 95% CI, 1.77-2.62]); and (3) mixed UI (E + P: 99 vs 69 cases [RR, 1.49; 95% CI, 1.10-2.01];

estrogen alone: 76 vs 50 cases [RR, 1.79; 95% CI, 1.26-2.53]) (TABLE 4). A significant effect of hormones on urge UI was not observed in the E + P trial (304 vs 272 cases [RR, 1.15; 95% CI, 0.99-1.34]), but an increase in risk was observed in the estrogen alone trial (210 vs 184 cases [RR, 1.32; 95% CI, 1.10-1.58]).

When comparing amount, degree of bother, and limitations, there were no differences by treatment group for either estrogen alone or E + P trial participants, except for degree of bother in those treated with estrogen alone. In this subgroup analysis, rates of bother were a little, not at all, or somewhat (29% for CEE alone compared with 8% for placebo), very (41% vs 55%) and extremely disturbing (30% vs 37%, respectively) ($P = .04$).

Table 4 includes RRs by subgroups corresponding to interactions that were significant at $P<.05$ for stress, mixed, or urge UI. Older women and women who have been postmenopausal for a longer duration tended to be at higher risk for MHT effects on incident stress UI ($P<.001$ for CEE + MPA and $P=.002$ for CEE alone with respect to interaction with age). Similar age trends can be seen for urge and mixed UI for estrogen alone ($P\leq.05$). Although the interactions between prior MHT use and CEE + MPA, diabetes and CEE + MPA, and smoking and CEE alone achieved nominal statistical significance ($P<.05$) in modifying the risk for stress, urge, and mixed UI, respectively, these findings are within the realm of chance in that there does not appear to be any pattern between UI types or MHT treatments or any biological mechanism explaining these findings. Table 4 displays the main comparisons of interest (a total of 2 trials × 3 types of UI × 18 baseline characteristics = 108 comparisons made; complete data available on request).

Interaction for stress UI and CEE + MPA is probably a chance finding for small groupings such as women who used β-blockers. Ethnicity, body mass index, duration of prior hormone use, asthma, emphysema, stroke, age at first birth, parity, breastfeeding, use of thiazide or loop diuretics, anticholinergics, calcium channel blockers, opiates, sedatives, or alcohol did not substantially alter the effect of MHT on the incidence of stress UI. No subgroups of women were identified to be at significantly higher or lower risk of incident urge or mixed UI. Subgroup analyses did not show a significant effect of race/ethnicity on the effect of MHT on UI (data available on request).

Because of the slight imbalance of baseline characteristics and treatment assignment in Table 1 and Table 2 (ie, emphysema by CEE + MPA assignment and parity by estrogen alone assignment), we also adjusted for emphysema in a sensitivity analysis. The RR for stress UI changed from 1.87 to 1.88, the RR for urge UI changed from 1.15 to 1.13, and the RR for mixed UI changed from 1.49 to 1.48. Adjustment for parity in the regression models corresponding to the estrogen alone trial did not change any of the RRs.

To account for different definitions of UI, we performed a sensitivity analysis and found that the risk of incident UI due to MHT was robust to multiple definitions of UI (ie, increasing the frequency threshold used to define UI; TABLE 5). For example, if we change the definition for UI from "within the last year" to "more than once a week," the RR for stress UI changes slightly from 1.87 (95% CI, 1.61-2.18) to 2.28 (95% CI, 1.91-2.73). Therefore, regardless of whatever definition of UI is thought to be clinically meaningful, these results still apply.

Table 5. Sensitivity Analysis of Definitions of Incident Urinary Incontinence at 1 Year in Asymptomatic Women

Frequency of Urinary Incontinence at Baseline and 1 Year	Relative Risk (95% Confidence Interval)	
	CEE + MPA vs Placebo	CEE Alone vs Placebo
Stress		
Within last year	1.87 (1.61-2.18)	2.15 (1.77-2.62)
>1/mo but <1/wk	1.93 (1.67-2.23)	2.21 (1.85-2.65)
≥1/wk but <1/d	2.28 (1.91-2.73)	2.59 (2.10-3.18)
Daily	2.48 (1.84-3.33)	2.39 (1.75-3.27)
Urge		
Within last year	1.15 (0.99-1.34)	1.32 (1.10-1.58)
>1/mo but <1/wk	1.12 (0.97-1.30)	1.36 (1.15-1.61)
≥1/wk but <1/d	1.02 (0.87-1.20)	1.31 (1.08-1.59)
Daily	1.12 (0.84-1.49)	1.36 (1.01-1.83)
Mixed		
Within last year	1.49 (1.10-2.01)	1.79 (1.26-2.53)
>1/mo but <1/wk	1.69 (1.35-2.11)	1.83 (1.42-2.36)
≥1/wk but <1/d	1.72 (1.40-2.12)	1.99 (1.58-2.50)
Daily	1.73 (1.33-2.24)	2.17 (1.66-2.85)

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.

Worsening of Prevalent UI

For those women who reported UI (stress, urge, or mixed) at baseline, MHT increased the likelihood of worsening amount of UI (TABLE 6; CEE + MPA: RR, 1.20 [95% CI, 1.06-1.36]; CEE alone: RR, 1.59 [95% CI, 1.39-1.82]); worsening frequency of UI (TABLE 7; CEE + MPA: RR, 1.38 [95% CI, 1.28-1.49]; CEE alone: RR, 1.47 [95% CI, 1.35-1.61]); and worsening limitations in daily activities related to UI (TABLE 8; CEE + MPA: RR, 1.18 [95% CI, 1.06-1.32]; CEE alone: RR, 1.29 [95% CI, 1.15-1.45]). Menopausal hormone therapy also increased the likelihood of worsening degree of bother or disturbance attributed to UI (TABLE 9; CEE + MPA: RR, 1.22 [95% CI, 1.13-1.32]; CEE alone: RR, 1.50 [95% CI, 1.37-1.65]).

When we assessed worsening of UI by type of UI (urge, stress, and mixed) at baseline, overall worsening was independent of type of UI. The exception to this was the effect of CEE + MPA on worsening of frequency, for which the RR was 1.41 (95% CI, 1.21-1.64) for stress UI; 1.15 (95% CI, 1.02-1.30) for

urge UI; and 1.58 (95% CI, 1.41-1.77) for mixed UI. In the estrogen alone trial, the effect on worsening of amount and degree of bother differed by type of UI at baseline (RR for amount was 2.18 [95% CI, 1.69-2.81] for stress UI; 1.27 [95% CI, 1.02-1.58] for urge UI; and 1.49 [95% CI, 1.17-1.90] for mixed UI; RR for degree of bother was 1.65 [95% CI, 1.42-1.93] for stress UI; and 1.21 [95% CI, 1.04-1.40] for urge UI; 1.78 [95% CI, 1.48-2.14] for mixed UI), but all types of UI were worsened by CEE alone. Because MHT worsened symptoms for all 3 types of UI, subgroup analysis of UI worsening was performed by combining all 3 types of UI, thereby limiting the number of comparisons to a manageable amount.

A sensitivity analysis showed that the risk of increased amounts of urine leakage due to MHT use (quantified in our study by how much urine had soaked through underpants or outer clothing) was robust to amount of protection used. For example, if we only included participants whose protection (none, mini-pad, menstrual pad, diaper, or other) at baseline either stayed the same or increased at 1 year (eg, using mini-pads at baseline and diapers at 1 year), worsening of amount was relatively unchanged (RR, 1.20; 95% CI, 1.06-1.36) in our main analysis and among participants whose protection at baseline remained the same or increased (RR, 1.24; 95% CI, 1.09-1.42) at 1 year.

Subgroup analysis among women receiving CEE alone compared with placebo showed that incontinent women who were older ($P=.004$) and had a lower body mass index ($P=.002$) had more leakage. Tables 6 through 9 show selected subgroups, most of which achieved a nominal level of statistical significance (a total of 2 treatments × 4 types of worsening × 18 baseline characteristics = 144 comparisons made; complete data available on request). Similar but more modest trends were seen for CEE + MPA with older and thinner women experiencing increased amounts of urine leakage.

Among women receiving CEE alone compared with placebo, women who were older ($P<.001$) and had a lower body mass index ($P<.001$) had an increased frequency of UI. Similar trends were seen in the E + P trial. Limitations were increased for women who were younger ($P=.01$) and further from menopause ($P<.001$). Degree of bother increased for older women closer to menopause who were receiving CEE + MPA or CEE alone. Race/ethnicity did not modify the effect of MHT on UI (data available on request).

Prior hormone use, duration of use, and treatment assignment had some nominally significant interactions at $P<.01$, but no coherent pattern emerged. Participants with no prior hormone use were more likely to be bothered by UI at 1 year than at baseline. Smoking, diabetes, asthma, or diuretic use had no significant interaction with the effect of CEE + MPA or CEE alone on UI symptoms.

Table 6. Urinary Incontinence at 1 Year in Women Symptomatic at Baseline and Stratified by Baseline Characteristics: Effect on Amount

	CEE + MPA vs Placebo		CEE Alone vs Placebo	
	RR (95% CI)	*P* Value*	RR (95% CI)	*P* Value*
Overall	1.20 (1.06-1.36)	.004	1.59 (1.39-1.82)	<.001
Age at screening, y				
50-54	0.85 (0.54-1.35)	.01	1.13 (0.74-1.73)	.004
55-59	0.88 (0.65-1.19)		1.31 (0.94-1.83)	
60-69	1.36 (1.13-1.64)		1.58 (1.29-1.94)	
70-79	1.33 (1.04-1.70)		2.04 (1.56-2.65)	
BMI				
Normal (<25)	1.51 (1.16-1.96)	.08	2.24 (1.54-3.26)	.002
Overweight (25 to <30)	1.16 (0.93-1.44)		1.88 (1.48-2.40)	
Obese (>30)	1.09 (0.90-1.33)		1.31 (1.09-1.58)	
Smoking				
Never	1.13 (0.94-1.36)	.004	1.46 (1.20-1.77)	.39
Past	1.48 (1.20-1.81)		1.80 (1.45-2.24)	
Current	0.69 (0.46-1.05)		1.67 (1.06-2.63)	
Duration since menopause, y				
<5	0.76 (0.53-1.08)	.004	1.18 (0.63-2.24)	.32
5 to <10	1.25 (0.93-1.68)		1.43 (0.91-2.25)	
10 to <15	1.03 (0.76-1.38)		1.92 (1.27-2.90)	
≥15	1.42 (1.18-1.71)		1.61 (1.35-1.91)	
Hormone use				
Never	1.25 (1.08-1.45)	.57	1.58 (1.30-1.92)	.92
Past	1.09 (0.82-1.47)		1.61 (1.29-2.00)	
Current	1.01 (0.62-1.65)		1.59 (1.04-2.42)	
Duration of prior hormone use, y				
Never	1.25 (1.08-1.45)	.30	1.58 (1.30-1.92)	.50
<5	1.14 (0.83-1.56)		1.39 (1.08-1.79)	
5 to <10	0.74 (0.43-1.27)		2.02 (1.19-3.43)	
≥10	1.40 (0.69-2.82)		1.88 (1.30-2.72)	
Diabetes				
Absent	1.22 (1.07-1.39)	.47	1.50 (1.30-1.74)	.03
Present	1.02 (0.65-1.62)		2.40 (1.58-3.63)	
Asthma				
Absent	1.29 (1.12-1.47)	<.001	1.61 (1.39-1.86)	.87
Present	0.55 (0.34-0.88)		1.64 (1.05-2.57)	
Diuretic use				
Absent	1.26 (1.10-1.45)	.07	1.60 (1.38-1.86)	.69
Present	0.91 (0.65-1.26)		1.52 (1.08-2.16)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate; RR, relative risk.
*Calculated from logistic regression model.

UI at 3 Years

To determine the longer-term effect of MHT on UI, we examined data in an 8.6% subsample of participants (oversampled for minorities) at 3 years. For the E + P trial, the subsample of participants at 3 years consisted of 775 participants receiving active treatment and 736 receiving placebo. The subsample in the estrogen alone trial consisted of 577 participants receiving active treatment and 612 participants receiving placebo.

Estrogen Plus Progestin

At 1 year, women in the CEE + MPA subsample compared with placebo had a RR of 1.33 (95% CI, 0.99-1.79) for UI, which was similar to the entire CEE + MPA sample (RR, 1.39; 95% CI, 1.27-1.52). Continent women in the CEE + MPA subsample continued to be at higher risk for UI at 3 years. For the participants in the CEE + MPA subsample who were continent at baseline and 1 year, 39 (25.5%) of 153 receiving CEE + MPA reported incident UI at 3 years compared with 26 (14.1%) of 185 women who were receiving placebo (RR, 1.81; 95% CI, 1.16-2.84). Most women who had incident UI at 1 year still had UI at 3 years (51 [70.8%] of 72 receiving CEE + MPA and 40 [70.2%] of 57 receiving placebo; $P = .94$ for difference in remaining incontinent by treatment group).

Estrogen Alone

Women in the CEE alone subsample had a RR of 1.66 (95% CI, 1.19-2.32) for UI at 1 year, which was similar to the RR of 1.53 (95% CI, 1.37-1.71) for the entire CEE alone sample. Participants receiving CEE alone tended to be at higher risk, albeit not significantly so, than participants receiving placebo at 3 years, with 27 (28.1%) of 96 who were continent at baseline and 1 year reporting incident UI at 3 years compared with 26 (19.1%) of 136 who were receiving placebo (RR, 1.47; 95% CI, 0.92-2.36). Most women who had incident UI at 1 year still had UI at 3 years. Of the participants who reported incident UI at 1 year, 43 (71.7%) of 60 women who were receiving CEE alone and 26 (68.4%) of 38 receiving placebo were also incontinent at 3 years ($P = .73$).

COMMENT

In this randomized clinical trial of MHT in a group of healthy postmenopausal women, treatment with daily tablets of 0.625 mg of conjugated equine estrogen (CEE alone) or 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (CEE + MPA) increased new onset UI among continent women and worsened the characteristics of UI among already incontinent women. This effect persisted through 3 years. Although these findings are based on 1 specific type, route of administration, and dosage of estrogen (with or without progestin), they are consistent with findings from an observational study that reported use of several different formulations of E + P and estrogen alone and suggested an increased risk of UI associated with MHT.[16] To our knowledge, this is the first randomized trial to demonstrate that estrogen alone increased UI.

Table 7. Urinary Incontinence at 1 Year in Women Symptomatic at Baseline and Stratified by Baseline Characteristics: Effect on Frequency

	CEE + MPA vs Placebo		CEE Alone vs Placebo	
	RR (95% CI)	*P* Value*	RR (95% CI)	*P* Value*
Overall	1.38 (1.28-1.49)	<.001	1.47 (1.35-1.61)	<.001
Age at screening, y				
50-54	1.20 (0.93-1.53)	.07	1.03 (0.79-1.35)	<.001
55-59	1.31 (1.10-1.55)		1.15 (0.93-1.43)	
60-69	1.41 (1.26-1.56)		1.56 (1.37-1.78)	
70-79	1.47 (1.27-1.70)		1.78 (1.51-2.10)	
BMI				
Normal (<25)	1.51 (1.32-1.73)	.17	1.89 (1.54-2.32)	<.001
Overweight (25 to <30)	1.36 (1.21-1.54)		1.59 (1.37-1.83)	
Obese (>30)	1.32 (1.17-1.50)		1.27 (1.12-1.44)	
Smoking				
Never	1.41 (1.27-1.57)	.83	1.54 (1.36-1.74)	.38
Past	1.35 (1.21-1.52)		1.43 (1.25-1.64)	
Current	1.35 (1.07-1.71)		1.25 (0.95-1.66)	
Duration since menopause, y				
<5	1.15 (0.95-1.40)	.01	1.27 (0.85-1.90)	.08
5 to <10	1.30 (1.09-1.56)		1.36 (1.03-1.80)	
10 to <15	1.38 (1.17-1.62)		1.14 (0.88-1.46)	
>15	1.47 (1.32-1.64)		1.54 (1.38-1.72)	
Hormone use				
Never	1.40 (1.29-1.53)	.57	1.47 (1.30-1.66)	.03
Past	1.34 (1.14-1.57)		1.62 (1.40-1.87)	
Current	1.24 (0.91-1.69)		1.14 (0.89-1.46)	
Duration of prior hormone use, y				
Never	1.40 (1.29-1.53)	.02	1.47 (1.30-1.66)	.66
<5	1.53 (1.28-1.83)		1.53 (1.29-1.82)	
5 to <10	1.07 (0.77-1.49)		1.55 (1.15-2.09)	
≥10	0.87 (0.61-1.24)		1.35 (1.08-1.68)	
Diabetes				
Absent	1.38 (1.28-1.49)	.98	1.48 (1.35-1.62)	.78
Present	1.36 (1.03-1.79)		1.44 (1.08-1.90)	
Asthma				
Absent	1.40 (1.30-1.51)	.10	1.50 (1.37-1.64)	.25
Present	1.09 (0.83-1.45)		1.25 (0.91-1.72)	
Diuretic use				
Absent	1.43 (1.32-1.54)	.03	1.51 (1.37-1.66)	.32
Present	1.11 (0.90-1.36)		1.34 (1.09-1.63)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate; RR, relative risk.
*Calculated from logistic regression model.

The baseline prevalence of UI in the WHI participants is consistent with some, but not all, past epidemiological studies. An earlier review of studies described prevalence rates ranging from 17% to 50% for UI symptoms within the past 12 months.[17] Use of a detailed assessment tool for measuring UI may have provided a slightly different estimate of overall UI prevalence or its subtypes in our study sample.[18] However, rates in our study are consistent with more recent studies that also defined UI broadly as any leakage of urine in the last 12 months. These studies have identified prevalence rates ranging from 41% to 72% in community-dwelling, midlife, and older women.[19-25]

For several decades, estrogen has been 1 of several treatments for UI in women. This practice was based on assumptions about biological mechanisms, associations of various symptoms with menopause, and small uncontrolled trials. The lower urinary tract shares a common embryologic origin with the genital tract, the urogenital sinus, and estrogen and progesterone receptors are present in the vaginal epithelium, the urethra, and bladder trigone.[1-4] Estrogen loss after menopause causes atrophy throughout the genital tract, which may lead to itching, burning, dryness, and dyspareunia. Coexistent symptoms, including urinary frequency, urgency, UI, and recurrent urinary tract infections, were thought to be related to atrophy of the urinary tract. Because MHT has a beneficial effect on vaginal mucosa, in particular in improving symptoms of atrophic vaginitis,[26] clinicians suggested that MHT might also improve UI.

Table 8. Urinary Incontinence at 1 Year in Women Symptomatic at Baseline and Stratified by Baseline Characteristics: Effect on Limitations

	CEE + MPA vs Placebo		CEE Alone vs Placebo	
	RR (95% CI)	*P* Value*	RR (95% CI)	*P* Value*
Overall	1.18 (1.06-1.32)	.002	1.29 (1.15-1.45)	<.001
Age at screening, y				
50-54	1.13 (0.78-1.62)	.35	1.16 (0.82-1.64)	.01
55-59	1.17 (0.89-1.53)		0.85 (0.64-1.12)	
60-69	1.11 (0.95-1.31)		1.42 (1.19-1.68)	
70-79	1.34 (1.09-1.66)		1.49 (1.20-1.86)	
BMI				
Normal (<25)	1.33 (1.06-1.67)	.22	1.28 (0.95-1.72)	.84
Overweight (25 to <30)	1.17 (0.96-1.42)		1.26 (1.03-1.55)	
Obese (>30)	1.10 (0.93-1.29)		1.29 (1.10-1.51)	
Smoking				
Never	1.30 (1.11-1.53)	.24	1.30 (1.10-1.53)	.19
Past	1.08 (0.91-1.29)		1.39 (1.15-1.66)	
Current	1.08 (0.78-1.50)		0.94 (0.64-1.36)	
Duration since menopause, y				
<5	0.94 (0.70-1.26)	.25	0.78 (0.46-1.33)	<.001
5 to <10	1.25 (0.96-1.62)		0.84 (0.58-1.22)	
10 to <15	1.29 (1.00-1.67)		1.18 (0.84-1.64)	
≥15	1.20 (1.03-1.41)		1.43 (1.23-1.65)	
Hormone use				
Never	1.16 (1.02-1.31)	.17	1.32 (1.12-1.55)	.17
Past	1.13 (0.88-1.44)		1.39 (1.14-1.68)	
Current	1.89 (1.16-3.07)		1.00 (0.74-1.35)	
Duration of prior hormone use, y				
Never	1.16 (1.02-1.31)	.57	1.32 (1.12-1.55)	.45
<5	1.26 (0.97-1.63)		1.39 (1.11-1.73)	
5 to <10	1.60 (0.94-2.72)		0.97 (0.67-1.41)	
>10	0.94 (0.53-1.66)		1.26 (0.92-1.71)	
Diabetes				
Absent	1.20 (1.07-1.34)	.47	1.27 (1.13-1.44)	.47
Present	1.04 (0.71-1.52)		1.46 (1.03-2.08)	
Asthma				
Absent	1.18 (1.05-1.32)	.68	1.30 (1.15-1.47)	.80
Present	1.09 (0.76-1.58)		1.22 (0.86-1.75)	
Diuretic use				
Absent	1.24 (1.10-1.40)	.07	1.30 (1.15-1.48)	.83
Present	0.90 (0.68-1.20)		1.24 (0.95-1.60)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate; RR, relative risk.
*Calculated from logistic regression model.

Epidemiological studies have reported higher rates of UI in middle-aged women, and it was postulated that estrogen deficiency was associated with both menopause and with UI.[5] However, in a large cross-sectional Study of Osteoporotic Fractures, estrogen use by postmenopausal women was associated with an almost 2-fold increased risk of daily UI, after adjusting for various factors.[14] These findings, reported in 1996, had little impact on subsequent treatment recommendations, and estrogens continued to be viewed as a viable treatment for UI.[27-29]

Early uncontrolled case series analyses suggested a benefit of estrogen, in various forms, on urinary tract symptoms and urodynamic findings. However, clinical trials of the effect of estrogen therapy on UI have had mixed results. Most were small and of short duration, and the majority showed no improvement in the number of incontinent episodes per week.[30-34] In some of these trials, various combinations of pharmacological agents along with estrogen were used to treat UI, and benefit could be attributed to combination therapy, not simply to estrogen alone.[35] In 1 of the few randomized trials assessing the impact of combined hormone therapy on UI as the primary outcome, 83 women received cyclic hormone therapy compared with placebo.[36] After 3 months of cyclic hormone therapy,

there were no differences in clinical or quality-of-life variables between the treated and untreated groups. In the largest randomized clinical trial to date prior to WHI, measures of UI and frequency were obtained from women with heart disease.[7] Of 1525 women who reported at least weekly UI, the use of combined E + P increased the severity and frequency of urge and stress UI.

A meta-analysis of 28 trials of various hormone preparations with a total of 2926 women (sample sizes ranging from 16 to 1525 women) assessed the effect of estrogen treatment on UI.[6] In the 15 trials that compared a total of 374 women randomized to estrogen and 344 to placebo, subjective cure and improvement rates were higher in women receiving estrogen for both urge UI (35/61 vs 16/58 on placebo) and stress UI (46/107 vs 29/109). In contrast, based largely on the HERS results, the authors concluded that estrogen plus progestin therapy was associated with reduced subjective cure or improvement of UI. Like HERS, we found that estrogen plus progestin therapy increased the risk of UI. However, our results found similar increased risk in women taking estrogen alone.

In light of the biological plausibility that MHT would improve UI, it is important to consider recent advances in basic science research to understand the mechanisms by which hormone treatment could worsen this condition. Although basic science in this area is limited, a recent placebo-controlled, randomized clinical trial of estrogen alone sheds light on this issue. Women receiving 2 mg of oral estradiol valerate over 6 months showed significant decreases in total periurethral collagen.[37] Profound effects on collagen metabolism were observed and included stimulation of collagen degradation via increased matrix metalloproteinase-2 activity. Urethral closure is dependent on the integrated action of the suburethral vaginal wall, the pubourethral ligaments, the pubococcygeus muscles, and the paraurethral connective tissues. For all of these structures, connective tissue is a crucial element. Consequently, damage in the paraurethral connective tissue connecting these structures to one another and to the urethra will cause ineffective urethral closure, thus setting the stage for UI. Further research evaluating the effects of estrogen alone compared with estrogen plus progestin on various biological mechanisms, such as collagen metabolism, may provide important additional insights on the mechanisms of action of these preparations on UI.

We studied only 0.625 mg/d of conjugated equine estrogens (estrogen alone trial) or 0.625 mg/d of conjugated equine estrogens plus 2.5 mg/d of medroxyprogesterone acetate (E + P trial). Therefore, our ability to generalize these findings to women taking other MHT formulations is limited. We cannot address the impact of surgery for UI or changes in treatment over time because we did not collect those data. Analysis of smaller subgroups for some categories (eg, women aged 50-54 years), although of inter-

Table 9. Urinary Incontinence at 1 Year in Women Symptomatic at Baseline and Stratified by Baseline Characteristics: Effect on Degree of Bother

	CEE + MPA vs Placebo		CEE Alone vs Placebo	
	RR (95% CI)	*P* Value*	RR (95% CI)	*P* Value*
Overall	1.22 (1.13-1.32)	<.001	1.50 (1.37-1.65)	<.001
Age at screening, y				
50-54	0.94 (0.72-1.23)	<.001	0.94 (0.70-1.27)	<.001
55-59	0.98 (0.81-1.18)		1.09 (0.87-1.36)	
60-69	1.29 (1.15-1.46)		1.74 (1.51-2.00)	
70-79	1.44 (1.22-1.70)		1.70 (1.43-2.02)	
BMI				
Normal (<25)	1.33 (1.13-1.56)	.42	1.68 (1.36-2.08)	.06
Overweight (25 to <30)	1.17 (1.01-1.35)		1.63 (1.40-1.91)	
Obese (>30)	1.20 (1.06-1.37)		1.37 (1.20-1.57)	
Smoking				
Never	1.31 (1.16-1.47)	.14	1.46 (1.28-1.66)	.73
Past	1.17 (1.03-1.33)		1.57 (1.36-1.82)	
Current	1.02 (0.80-1.30)		1.59 (1.18-2.14)	
Duration since menopause, y				
<5	0.93 (0.75-1.14)	<.001	0.94 (0.63-1.39)	.002
5 to <10	1.10 (0.91-1.33)		1.63 (1.17-2.26)	
10 to <15	1.39 (1.14-1.70)		1.06 (0.80-1.41)	
≥15	1.37 (1.22-1.55)		1.67 (1.49-1.87)	
Hormone use				
Never	1.30 (1.18-1.43)	.02	1.50 (1.31-1.71)	.76
Past	1.10 (0.92-1.32)		1.53 (1.32-1.78)	
Current	0.84 (0.60-1.17)		1.45 (1.12-1.88)	
Duration of prior hormone use, y				
Never	1.30 (1.18-1.43)	.03	1.50 (1.31-1.71)	.62
<5	1.12 (0.93-1.35)		1.55 (1.30-1.84)	
5 to <10	0.77 (0.52-1.15)		1.72 (1.25-2.38)	
>10	0.91 (0.56-1.50)		1.34 (1.06-1.69)	
Diabetes				
Absent	1.22 (1.12-1.33)	.98	1.52 (1.38-1.68)	.56
Present	1.21 (0.87-1.69		1.35 (1.02-1.78)	
Asthma				
Absent	1.23 (1.13-1.34)	.25	1.53 (1.39-1.69)	.21
Present	1.02 (0.74-1.41)		1.24 (0.88-1.74)	
Diuretic use				
Absent	1.24 (1.14-1.35)	.41	1.52 (1.38-1.69)	.47
Present	1.10 (0.88-1.39)		1.40 (1.12-1.75)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate; RR, relative risk.
*Calculated from logistic regression model.

est, may have unstable estimates and therefore were not performed. Further research on the effects of different estrogen formulations on pathophysiological changes associated with UI is needed.

In conclusion, these results from a large, double-blind, placebo-controlled, randomized clinical trial, conducted in multiple centers with an ethnically diverse group of healthy postmenopausal women, indicate that MHT use does not confer protection against any type of UI. On the contrary, both CEE alone and CEE + MPA increased risk of new onset UI among continent women and worsened the characteristics of UI among symptomatic women. Considerations regarding the use of hormone therapy by postmenopausal women for any duration should incorporate the current findings into the established risks and benefits of these agents.

Author Contributions: Dr Hendrix had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hendrix, Nygaard, Naughton, Wallace.
Acquisition of data: Hendrix, Wallace, McNeeley.
Analysis and interpretation of data: Hendrix, Cochrane, Nygaard, Handa, Barnabei, Iglesia, Aragaki, Naughton, Wallace.
Drafting of the manuscript: Hendrix, Cochrane, Nygaard, Barnabei, Iglesia, Aragaki, Wallace.
Critical revision of the manuscript for important intellectual content: Hendrix, Cochrane, Nygaard, Handa, Barnabei, Iglesia, Aragaki, Naughton, Wallace, McNeeley.
Statistical analysis: Nygaard, Aragaki.
Obtained funding: Hendrix, Wallace.
Administrative, technical, or material support: Hendrix, Cochrane, Naughton, McNeeley.
Study supervision: Hendrix, Barnabei.
Financial Disclosure: Dr Hendrix has received research funding from Lilly. None of the other authors reported any disclosures.
Funding/Support: The National Heart, Lung, and Blood Institute funds the Women's Health Initiative program. Wyeth-Ayerst provided the study pills (active and placebo).
Role of the Sponsor: The National Heart, Lung, and Blood Institute participated in the design, conduct, and oversight of the trial and reviewed this report. Wyeth-Ayerst provided study pills only and had no involvement in the design or conduct of the trial.
Acknowledgment: The Women's Health Initiative (WHI) Steering Committee gratefully acknowledges the dedicated efforts of the investigators and staff, who are listed at http://www.whi.org. The WHI also recognizes the WHI participants for their extraordinary commitment to the WHI program. We thank Andrea LaCroix, PhD, for her critical evaluation and review of the manuscript.

REFERENCES

1. Schreiter F, Fuchs P, Stockamp K. Estrogenic sensitivity of alpha-receptors in the urethra musculature. *Urol Int*. 1976;31:13-19.
2. Saez S, Martin PM. Evidence of estrogen receptors in the trigone area of human urinary bladder. *J Steroid Biochem*. 1981;15:317-320.
3. Iosif CS, Batra S, Ek A, Astedt B. Estrogen receptors in the human female lower urinary tract. *Am J Obstet Gynecol*. 1981;141:817-820.
4. Batra SC, Iosif CS. Progesterone receptors in the female lower urinary tract. *J Urol*. 1987;138:1301-1304.
5. Iosif CS, Bekassy Z. Prevalence of genito-urinary symptoms in the late menopause. *Acta Obstet Gynecol Scand*. 1984;63:257-260.
6. Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women. *Cochrane Database Syst Rev*. 2003;2:CD001405.
7. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T; HERS Research Group. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. *Obstet Gynecol*. 2001;97:116-120.
8. Response to the Women's Health Initiative Results by the American College of Obstetricians and Gynecologists. June 3, 2003. Available at: http://www.acog.com/member_access/misc/whiResponse.cfm. Accessed December 10, 2004.
9. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61-109.
10. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
11. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701-1712.
12. Hays J, Hunt JR, Hubbel A, et al. The Women's Health Initiative: recruitment methods and results. *Ann Epidemiol*. 2003;13:S18-S77.
13. Patterson RE, Kristal AR, Tinker AF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;3:178-187.
14. Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D. Urinary incontinence in older women: who is at risk? study of Osteoporotic Fractures Research Group. *Obstet Gynecol*. 1996;87:715-721.
15. *MDDB Product Line Documentation Manual.* San Bruno, Calif: First DataBank Inc; 2000.
16. Grodstein F, Fretts R, Lifford K, Resnick N, Curhan G. Association of age, race, and obstetric history with urinary symptoms among women in the Nurses' Health Study. *Am J Obstet Gynecol*. 2003;189:428-434.
17. Thom DH, Brown JS. Reproductive and hormonal risk factors for urinary incontinence in later life: a review of the clinical and epidemiologic literature. *J Am Geriatr Soc*. 1998;46:1411-1417.
18. Resnick NM, Beckett LA, Branch LG, Scherr PA, Wetle T. Short-term variability of self report of incontinence in older persons. *J Am Geriatr Soc*. 1994;42:202-207.
19. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF; Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. *Obstet Gynecol*. 1999;94:66-70.
20. Hunskaar S, Burgio K, Diokno A, Herzog AR, Hjalmas K, Lapitan MC. Epidemiology and natural history of urinary incontinence in women. *Urology*. 2003;62(suppl 1):16-23.
21. Muscatello DJ, Rissel C, Szonyi G. Urinary symptoms and incontinence in an urban community: prevalence and associated factors in older men and women. *Intern Med J*. 2001;31:151-160.
22. Novielli KD, Simpson Z, Hua G, Diamond JJ, Sultana C, Paynter N. Urinary incontinence in primary care: a comparison of older African-American and Caucasian women. *Int Urol Nephrol*. 2003;35:423-428.
23. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstet Gynecol*. 2002;100:1230-1238.
24. Swithinbank LV, Donovan JL, du Heaume JC, et al. Urinary symptoms and incontinence in women: relationships between occurrence, age, and perceived impact. *Br J Gen Pract*. 1999;49:897-900.
25. Uustal Fornell E, Wingren G, Kjolhede P. Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiological study. *Acta Obstet Gynecol Scand*. 2004;83:383-389.
26. Griebling TL, Nygaard IE. The role of estrogen replacement therapy in the management of urinary incontinence and urinary tract infection in postmenopausal women. *Endocrinol Metab Clin North Am*. 1997;26:347-360.
27. Andersson KE, Appell R, Cardozo LD, et al. The pharmacological treatment of urinary incontinence. *BJU Int*. 1999;84:923-947.
28. Butler RN, Maby JI, Montella JM, Young GPH. Urinary incontinence: primary care therapies for the older woman. *Geriatrics*. 1999;54:31-44.
29. Sarkar PK, Rich AES. Management of urinary incontinence. *J Clin Pharm Ther*. 2000;25:251-262.
30. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis: first report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol*. 1994;83:12-18.
31. Judge T. The use of quinestradol in elderly incontinent women: a preliminary report. *Gerontol Clin (Basel)*. 1969;11:159-164.
32. Wilson PD, Faragher B, Butler B, et al. Treatment with oral piperazine oestrone sulphate for genuine stress incontinence in postmenopausal women. *Br J Obstet Gynaecol*. 1987;94:568-574.
33. Jackson S, Shepherd A, Brookes S, Abrams P. The effect of oestrogen supplementation on postmenopausal urinary stress incontinence: a double-blind placebo-controlled trial. *Br J Obstet Gynaecol*. 1999;106:711-718.
34. Rufford J, Hextall A, Cardozo L, Khullar V. A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14:78-83.
35. Ahlstrom K, Sandahl B, Sjoberg B, Ulmsten U, Stormby N, Lindskog M. Effect of combined treatment with phenylpropanolamine and estriol, compared with estriol treatment alone, in postmenopausal women with stress urinary incontinence. *Gynecol Obstet Invest*. 1990;30:37-43.
36. Fantl JA, Bump RC, Robinson D, McClish DK, Wyman JF; The Continence Program for Women Research Group. Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet Gynecol*. 1996;88:745-749.
37. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. *BJOG*. 2002;109:339-344.

