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The Women's Health Initiative Postmenopausal Hormone Trials: Overview and Baseline Characteristics of Participants

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INTRODUCTION

The postmenopausal hormone therapy (PHT) component of the Women's Health Initiative (WHI) is composed of two randomized, placebo-controlled, double-blind trials in postmenopausal women aged 50 to 79 years at initial screening, testing the effects of estrogen alone (E-alone) and estrogen plus progestin (E + P) on coronary heart disease (CHD) as the primary outcome, hip and other fractures and colorectal cancer as secondary outcomes, and pulmonary embolism, breast and endometrial cancers as potential risks. The design and rationale of the PHT trials, including general eligibility and exclusion criteria and considerations regarding sample size and statistical power, have been described previously (1).

Postmenopausal hormones have been initiated in menopausal women for the treatment of vasomotor symptoms, mood disturbances, vaginal dryness, and prevention of rapid bone loss for several decades. Despite a paucity of data on effects of initiating hormone use in older women, postmenopausal hormones have also been promoted for the prevention of CHD, osteoporotic fractures, and other diseases that occur years after menopause (2). It is generally recommended (2) that women with a uterus be prescribed a combination of estrogen and progestin to prevent endometrial hyperplasia or cancer, whereas women with a hysterectomy receive unopposed estrogen. The purported benefits of estrogen are assumed to be similar for combined hormones, although relatively few studies have included long-term estrogen plus progestin users, particularly those taking continuous progestin. Reports of greater risk of breast cancer with cyclic estrogen/progestin combinations vs. unopposed estrogen (3, 4) highlight the need to determine the risks and benefits for both estrogen and combined hormones in appropriate clinical populations, including older women.

None of the clinical trials of postmenopausal hormones for cardiovascular endpoints completed previously, e.g., the PEPI study (5), HERS (6), ERA trial (7), or WEST (8), have provided information on the role of hormones in primary prevention of heart disease, nor was there clinical trial evidence that hormones prevent osteoporotic hip fractures (9) or increase breast cancer. A large randomized, controlled trial of postmenopausal hormones involving predominantly women without prior CHD or osteoporosis is needed to determine overall benefits and risks of long-term hormone use. WHI set out to randomize 27,500 ethnically diverse women into such a program for an 8.5-year period. Because women with a uterus were assigned to placebo or estrogen plus progestin, whereas women who had a hysterectomy were assigned to placebo or estrogen alone, the WHI hormone component is designed as two separate trials. Data are therefore presented for the total hormone component, as well as for the two distinct cohorts, i.e., those participating in the E + P trial and those participating in the E-alone trial.

METHODS

Eligibility Criteria and Screening

Details regarding eligibility criteria and the screening process, including hormone component-specific reasons for excluding participants, appear in Hays' article in this issue.

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A combination of age and months of amenorrhea determined eligibility for potential E + P participants who had not undergone hysterectomy. Women waited at least 3 months after a recent hysterectomy to be randomized. Women who were using hormones at initial contact completed a 3-month washout period before continuing screening for the PHT trials. A history of myocardial infarction or stroke within the prior 6 months was an exclusion criterion.

All potential PHT participants received information from trained staff on the objectives, risks, and procedures of the hormone trials. The materials described known potential side effects and risks of active study medications (i.e., breast and endometrial cancer, gallbladder disease, deep venous thrombosis, and pulmonary embolism) and those associated with *not* taking active hormones, including menopausal symptoms and osteoporosis. All participants provided written informed consent.

In addition to other assessments required for all clinical trial participants, PHT participants were required to have a pelvic exam, Pap smear and, for women with a uterus, endometrial aspiration (or transvaginal ultrasound, for women with cervical stenosis). Adherence to placebo during a 28-day (minimum) run-in period was determined by pill count. Women were excluded if they had less than 80% adherence to placebo run-in pills.

Data Collection and Definitions

Questionnaires, physical measurements, blood collection, quality assurance, and statistical procedures for the WHI clinical trial are described in Anderson's article in this issue and in the appendix to Anderson's article. The method for measuring bone mineral density (BMD) at three WHI clinical centers is described in Jackson's article in this issue.

Randomization

Eligible women who had a hysterectomy had to be willing to be randomly assigned to take either placebo pills or pills containing 0.625 mg of conjugated equine estrogens (CEE) each day. In the original design, women with a uterus had to be willing to be randomized to placebo pills, pills containing 0.625 mg CEE combined with 2.5 mg of medroxyprogesterone acetate (MPA) daily, or unopposed 0.625 mg CEE pills each day. In December 1994, when PEPI trial results indicated that unopposed estrogen was associated with an unexpectedly high incidence of complex endometrial hyperplasia (5), randomization of women with a uterus to unopposed estrogen was stopped, and 331 women who had been randomized to unopposed estrogen were unblinded and changed to E + P. Thereafter, women with a uterus were randomized to take either placebo pills or pills containing 0.625 mg CEE and 2.5 mg MPA each day.

RESULTS

From November 1993 through October 1998, 27,347 women were enrolled in the postmenopausal hormone therapy component (99.4% of goal); 16,608 (60.7%) had a uterus (E + P cohort), while 10,739 (39.3%) had a hysterectomy (E-alone cohort). PHT participants' age distribution was: 50 to 59 years, 32.3%; 60 to 69 years, 45.2%; and 70 to 79 years, 22.5% (mean age was 63.6 and 63.3 years in the E-alone and E + P cohorts, respectively). 19.5% of PHT participants identified themselves as women from specific racial/ethnic groups other than White (Table 1). A much higher proportion of Black, Hispanic, and American Indian women were younger than 60 years and a much lower proportion were 70 to 79 years old, compared with White women. Minority women, particularly Blacks, represented a greater proportion of women in the E-alone (hysterectomy) cohort than in the E + P cohort. The percentages of women with a hysterectomy were: Whites, 36.7%; Blacks, 59.0%; Hispanics, 42.4%; Asian/Pacific Islanders, 31.1%; and American Indians, 57.3%.

The majority of PHT women had schooling beyond high school, with over 30% having a college degree. Only 10.5% were current smokers. Alcohol intake was low, with only 4.8% of E + P women and 3.2% of E-alone women consuming an average of two or more alcoholic drinks per day. Overall, women in the E + P cohort were more highly educated, had higher family incomes, were more physically active, and were more likely to take calcium supplements than women in the E-alone cohort. Dietary calcium intake (not shown) was 664 ± 352 mg/day (mean ± standard deviation) for E + P participants and 613 ± 337 mg/day for E-alone women, with little variation across age groups.

Only 26.7% of hormone component participants were normal or underweight, while 38.2% were obese (Table 2). A higher percentage of women in the E-alone cohort (44.6%) were obese, compared with the E + P cohort (34.1%), and a much lower proportion of E-alone women were normal weight. Mean waist circumference was 91.6 ± 13.8 cm for women in the E-alone cohort and 88.0 ± 13.8 cm for those in the E + P cohort. One-third of PHT participants had ever been told by a doctor that they had hypertension, and the proportion with a systolic blood pressure above 140 mm Hg increased substantially across the age groups in both the E-alone and E + P cohorts. A quarter of all PHT women were being treated for high blood pressure and nearly 14% had high cholesterol requiring pills. A higher percentage of women in the E-alone cohort had high blood pressure and reported being treated for hypertension, diabetes, and high cholesterol than those in the E + P cohort. Only a small percentage of PHT participants reported a prior heart attack, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty

TABLE 1. Baseline demographic and general health characteristics of WHI Postmenopausal Hormone Therapy participants by hysterectomy[a] status and age at screening

	E + P						E-alone						Total								
	50–59 (N = 5522)		60–69 (N = 7510)		70–79 (N = 3576)		50–59 (N = 3310)		60–69 (N = 4852)		70–79 (N = 2577)		E + P (N = 16,608)			E-alone (N = 10,739)			Total (N = 27,347)		
Characteristic	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD
Race/Ethnicity																					
American Indian	0.5		0.3		0.2		0.8		0.7		0.5		56	0.3		75	0.7		131	0.5	
Asian/Pacific Islander	2.4		2.0		2.2		1.6		1.5		1.5		363	2.2		164	1.5		527	1.9	
Black	9.7		5.9		4.0		20.1		14.4		9.8		1124	6.8		1617	15.1		2741	10.0	
Hispanic	8.9		4.3		2.2		10.2		5.4		2.1		888	5.3		655	6.1		1543	5.6	
White	77.0		86.2		90.0		65.8		76.7		84.6		13,945	84.0		8082	75.3		22,027	80.5	
Unknown	1.5		1.3		1.4		1.5		1.2		1.5		232	1.4		146	1.4		378	1.4	
Education																					
0–8 years	2.8		2.3		1.5		3.3		3.2		2.7		379	2.3		329	3.1		708	2.6	
Some high school	3.9		4.3		5.5		5.5		7.2		7.8		735	4.5		724	6.8		1459	5.4	
High school diploma/GED	16.5		22.1		18.8		20.5		24.6		22.3		3222	19.5		2421	22.8		5643	20.8	
School after high school	39.1		38.2		40.0		45.6		42.7		42.2		6415	38.9		4621	43.4		11,036	40.7	
College degree or higher	37.7		33.1		34.2		25.2		22.4		25.1		5753	34.9		2543	23.9		8296	30.6	
Family income																					
<$10,000	6.5		4.8		5.3		8.5		8.8		8.0		857	5.5		864	8.5		1721	6.7	
$10,000–$19,999	10.2		15.5		21.3		14.4		19.7		26.5		2348	15.0		1989	19.7		4337	16.8	
$20,000–$34,999	21.8		29.3		32.5		24.7		31.0		33.6		4316	27.5		2999	29.7		7315	28.3	
$35,000–$49,999	20.6		22.4		19.6		19.7		20.7		16.0		3329	21.2		1947	19.3		5276	20.4	
$50,000–$74,999	21.5		16.6		14.0		19.1		13.0		10.6		2773	17.7		1447	14.3		4220	16.4	
$75,000 +	19.4		11.4		7.4		13.5		6.9		5.3		2075	13.2		866	8.6		2941	11.4	
Marital status																					
Never married	5.2		3.6		3.6		3.9		2.8		2.9		686	4.1		337	3.2		1023	3.8	
Divorced/Separated	23.6		15.1		9.7		26.9		18.4		10.5		2774	16.8		2038	19.1		4812	17.7	
Widowed	7.5		18.5		37.5		8.4		21.1		39.7		3137	19.0		2316	21.7		5453	20.0	
Presently married/Living as married	63.6		62.8		49.1		60.7		57.7		46.9		9945	60.1		5984	56.1		15,929	58.5	
Smoking																					
Never smoked	46.8		49.5		55.3		47.4		50.1		58.0		8177	49.8		5428	51.1		13,605	50.3	
Past smoker	38.1		41.1		39.5		37.8		39.4		37.2		6519	39.7		4075	38.4		10,594	39.2	
Current smoker	15.2		9.5		5.2		14.8		10.5		4.9		1718	10.5		1113	10.5		2831	10.5	
Alcohol intake																					
Never drinker	10.1		11.7		13.7		12.6		14.0		14.6		1910	11.6		1455	13.7		3365	12.4	
Past drinker	17.2		16.3		18.3		23.3		24.5		23.8		2807	17.0		2547	23.9		5354	19.7	
Current drinker	72.7		72.0		68.0		64.1		61.6		61.6		11,761	71.4		6633	62.4		18,394	67.8	
Physical activity																					
No activity	19.8		18.1		16.3		25.4		21.7		17.1		2783	18.2		2124	21.7		4907	19.6	
Some activity	42.6		43.1		43.0		44.1		45.7		48.3		6556	42.9		4485	45.8		11,041	44.1	
2–< 4 episodes/wk of moderate + activity	14.8		15.6		17.7		14.1		14.7		15.0		2415	15.8		1428	14.6		3843	15.3	
4 + episodes/wk of moderate + activity	22.8		23.1		23.1		16.4		17.9		19.6		3512	23.0		1747	17.9		5259	21.0	
Dietary energy (kcal)[b]		1606 ± 645		1547 ± 576		1474 ± 544		1582 ± 668		1514 ± 607		1443 ± 551	16,049		1550 ± 593	10,250		1517 ± 614	26,299		1537 ± 602
Calcium as single supplement (including antacids)																					
No	81.1		76.4		71.6		85.7		81.0		78.7		12,776	76.9		8737	81.4		21,513	78.7	
Yes	18.9		23.6		28.4		14.3		19.0		23.6		3832	23.1		2002	18.6		5834	21.3	

[a]Women with a uterus comprised the E + P cohort, and those with a hysterectomy at randomization comprised the E-alone cohort.
[b]Means and standard deviations were computed on the log scale and back-transformed values are reported.

TABLE 2. Baseline medical history status of WHI Postmenopausal Hormone Therapy participants by hysterectomy[a] status and age at screening

	E + P						E-alone						Total								
	50–59 (N = 5522)		60–69 (N = 7510)		70–79 (N = 3576)		50–59 (N = 3310)		60–69 (N = 4852)		70–79 (N = 2577)		E + P (N = 16,608)			E-alone (N = 10,739)			Total (N = 27,347)		
Medical History	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD
Body mass index (BMI), kg/m^2		28.9 ± 6.3		28.6 ± 5.8		27.5 ± 5.2		31.2 ± 6.7		30.2 ± 6.0		28.6 ± 5.4	16,520		28.5 ± 5.4	10,672		30.1 ± 6.2	27,192		29.1 ± 6.0
Underweight (<18.5)	0.5		0.6		1.1		0.2		0.4		0.6		118	0.7		39	0.4		157	0.6	
Normal (18.5–24.9)	29.5		28.0		34.6		16.8		19.5		26.3		4940	29.9		2167	20.3		7107	26.1	
Overweight (25.0–29.9)	33.3		36.1		36.6		32.0		34.4		38.9		5826	35.3		3707	34.7		9533	35.1	
Obesity I (30.0–34.9)	20.8		22.0		19.1		26.2		26.1		23.3		3467	21.0		2716	25.4		6183	22.7	
Obesity II (35.0–39.9)	10.1		9.0		6.8		15.1		13.1		7.9		1475	8.9		1332	12.5		2807	10.3	
Obesity III (≥40)	5.7		4.2		1.8		9.7		6.6		2.9		694	4.2		711	6.7		1405	5.2	
Systolic blood pressure (mm Hg)																					
≤120	51.2		34.7		23.4		43.0		29.2		21.5		6270	37.8		3394	31.6		9664	35.3	
>120–140	37.0		43.7		43.4		41.5		44.9		42.3		6873	41.4		4641	43.2		11,514	42.1	
>140	11.9		21.6		33.2		15.6		25.9		36.2		3465	20.9		2704	25.2		6169	22.6	
Diastolic blood pressure (mm Hg)																					
<90	91.7		92.4		94.5		88.9		91.3		94.1		15,385	92.6		9799	91.3		25,184	92.1	
≥90	8.3		7.6		5.5		11.1		8.7		5.9		1223	7.4		938	8.7		2161	7.9	
History of hypertension																					
Never hypertensive	78.5		68.3		68.3		67.2		58.2		52.9		10,609	70.0		5762	59.7		16,371	66.0	
Untreated hypertensive	7.6		8.6		8.8		11.4		10.0		9.4		1266	8.4		993	10.3		2259	9.1	
Treated hypertensive	13.9		23.1		29.9		21.3		31.8		37.7		3271	21.6		2903	30.1		6174	24.9	
Treated diabetes (pills or shots)																					
No	96.1		95.4		95.0		93.3		91.8		92.2		15,864	95.6		9907	92.3		25,771	94.3	
Yes	3.9		4.6		5.0		6.7		8.2		7.8		734	4.4		821	7.7		1555	5.7	
Treated hypercholesterolemia (pills)																					
No	93.6		85.0		82.7		90.7		83.2		80.6		13,107	87.3		8147	84.8		21,254	86.3	
Yes	6.4		15.0		17.3		9.3		16.8		19.4		1906	12.7		1460	15.2		3366	13.7	
History of MI																					
No	99.4		98.1		96.6		98.7		96.8		94.7		16,312	98.2		10,402	96.9		26,714	97.7	
Yes	0.6		1.9		3.4		1.3		3.2		5.3		296	1.8		337	3.1		633	2.3	
History of CABG/PTCA																					
No	99.7		98.7		97.1		99.0		97.6		96.6		16,191	98.7		10,345	97.8		26,536	98.3	
Yes	0.3		1.3		2.9		1.0		2.4		3.4		215	1.3		234	2.2		449	1.7	
History of stroke																					
No	99.6		99.3		98.3		99.2		98.3		97.4		16,470	99.2		10,571	98.4		27,041	98.9	
Yes	0.4		0.7		1.7		0.8		1.6		2.6		138	0.8		168	1.6		306	1.1	
Family history of breast cancer																					
No	85.3		84.5		82.5		82.5		82.6		82.3		13,256	84.3		8309	82.5		21,565	83.6	
Yes	14.7		15.5		17.5		17.5		17.4		17.7		2461	15.7		1763	17.5		4224	16.4	
History of fracture at age 55+[b]																					
No	95.8		84.8		73.8		95.2		84.8		76.1		11,317	84.6		7168	84.5		18,485	84.6	
Yes	4.2		15.2		26.2		4.8		15.2		23.9		2057	15.4		1319	15.5		3376	15.4	

MI, myocardial infarction.
[a]Women with a uterus comprised the E + P cohort, and those with a hysterectomy at randomization comprised the E-alone cohort.
[b]Applies only to participants age 55 and older at baseline.

TABLE 3. Baseline gynecologic history status of WHI Postmenopausal Hormone Therapy participants by hysterectomy[a] status and age at screening

	E + P			E-alone			Total					
	50–59 (N = 5522)	60–69 (N = 7510)	70–79 (N = 3576)	50–59 (N = 3310)	60–69 (N = 4852)	70–79 (N = 2577)	E + P (N = 16,608)		E-alone (N = 10,739)		Total (N = 27,347)	
Gynecologic History	%	%	%	%	%	%	N	%	N	%	N	%
Number of live births												
Never pregnant	8.5	7.1	8.0	6.7	6.2	7.5	1288	7.8	713	6.7	2001	7.4
None	3.4	2.0	2.4	2.9	2.1	2.7	422	2.6	262	2.5	684	2.5
1	10.5	7.2	7.8	9.7	6.9	8.3	1389	8.4	862	8.1	2251	8.3
2–4	66.0	62.0	63.0	65.0	59.9	61.2	10,503	63.5	6589	61.8	17,092	62.9
5+	11.6	21.7	18.8	15.7	24.9	20.3	2928	17.7	2237	21.0	5165	19.0
Age at first birth, (y)[b]												
Never had term pregnancy	4.0	2.2	2.8	3.2	2.2	2.9	400	2.9	237	2.7	637	2.8
<20	20.6	16.7	8.9	36.4	27.5	14.7	2236	16.4	2417	27.3	4653	20.7
20–29	66.8	72.8	72.9	56.7	65.6	73.8	9670	70.8	5737	64.8	15,407	68.4
30+	8.6	8.2	15.4	3.6	4.7	8.7	1344	9.8	469	5.3	1813	8.1
Total oral contraceptive duration, (y)												
Non-user	36.2	60.4	82.0	36.8	65.1	87.6	9466	57.0	6634	61.8	16,100	58.9
<5	33.9	20.8	9.2	36.4	20.7	7.9	3765	22.7	2409	22.4	6174	22.6
5–<10	16.1	8.2	3.6	15.1	7.2	2.5	1634	9.8	914	8.5	2548	9.3
10+	13.8	10.5	5.3	11.7	7.0	2.1	1743	10.5	782	7.3	2525	9.2
Age at hysterectomy, (y)												
<40				55.5	36.6	25.5			4249	39.8	4249	39.8
40–49				38.3	46.2	41.8			4556	42.7	4556	42.7
50+				6.2	17.2	32.7			1872	17.5	1872	17.5
Bilateral oophorectomy												
No	99.8	99.6	99.6	64.0	57.5	56.2	16,474	99.7	5890	59.3	22,364	84.5
Yes	0.2	0.4	0.4	36.0	42.5	43.8	53	0.3	4049	40.7	4102	15.5
History of PHT use[c]												
Never	70.5	75.1	74.5	49.4	50.7	52.8	12,192	73.4	5447	50.8	17,639	64.6
Past, <5 years ago	11.8	6.4	3.1	13.5	8.5	4.5	1243	7.5	975	9.1	2218	8.1
Past, 5–<10 years ago	4.0	4.9	1.9	6.6	4.8	3.3	659	4.0	535	5.0	1194	4.4
Past, 10+ years ago	1.4	7.1	17.5	9.2	21.7	31.3	1233	7.4	2159	20.1	3392	12.4
Current	12.3	6.4	3.1	21.3	14.3	8.1	1273	7.7	1608	15.0	2881	10.5
Total PHT duration, years												
< 5	76.9	68.4	64.0	57.8	52.0	52.3	3118	70.6	2853	53.9	5971	61.5
5–<10	18.3	17.7	16.7	22.1	18.1	15.6	783	17.7	995	18.8	1778	18.3
10+	4.8	13.9	19.3	20.2	29.8	32.1	514	11.6	1444	27.3	1958	20.2
History of E-alone use[3]												
Never	93.7	89.2	80.7	52.2	52.7	53.8	14,756	88.9	5664	52.8	20,420	74.7
Past/Current	6.3	10.8	19.3	47.8	47.3	46.2	1845	11.1	5061	47.2	6906	25.3
History of E + P use[3]												
Never	74.5	83.0	91.7	94.0	95.5	97.7	13,620	82.0	10,261	95.6	23,881	87.3
Past/Current	25.5	17.0	8.3	6.0	4.5	2.3	2984	18.0	477	4.4	3461	12.7

PHT, postmenopausal hormone therapy; E-alone, estrogen alone; E + P, estrogen + progestin.
[a]Women with a uterus comprised the E + P cohort, and those with a hysterectomy at randomization comprised the E-alone cohort.
[b]Applies only to participants who have ever been pregnant.
[c]Based on estrogen and progesterone pills and patches only (creams and shots excluded). Episodes less than 3 months are excluded.

TABLE 4. Baseline characteristics of WHI Postmenopausal Hormone Therapy and Bone Mineral Density participants by hysterectomy[a] status and age at screening

	E + P				E-alone				Total					
	50–64 (N = 553)		65–79 (N = 472)		50–64 (N = 518)		65–79 (N = 419)		E + P (N = 1025)		E-alone (N = 937)		Total (N = 1962)	
Characteristic	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD	N	%	Mean ± SD
Total hip BMD (WHO criteria)																	
Normal	60.8		39.7		66.4		38.9		511	51.0		498	54.0		1009	52.4	
Osteopenic	37.1		50.9		30.6		51.0		436	43.5		367	39.8		803	41.7	
Osteoporotic	2.1		9.4		3.0		10.1		55	5.5		57	6.2		112	5.8	
Hip scan (g/cm^2)		0.87 ± 0.13		0.79 ± 0.12		0.90 ± 0.13		0.81 ± 0.13	1024		0.84 ± 0.13	934		0.86 ± 0.14	1958		0.85 ± 0.14
Spine scan (g/cm^2)		0.97 ± 0.15		0.92 ± 0.17		0.98 ± 0.16		0.95 ± 0.16	1004		0.95 ± 0.16	911		0.97 ± 0.16	1915		0.96 ± 0.16
Whole body scan (g/cm^2)		1.02 ± 0.10		0.96 ± 0.09		1.03 ± 0.10		0.98 ± 0.10	1025		0.99 ± 0.10	937		1.01 ± 0.11	1962		1.00 ± 0.10
Lean body mass +BMC (kg)		41.0 ± 5.9		38.8 ± 4.8		41.8 ± 5.9		39.5 ± 5.6	1016		40.0 ± 5.5	928		40.7 ± 5.9	1944		40.3 ± 5.7
Fat body mass (kg)		33.6 ± 11.8		31.2 ± 10.1		37.2 ± 12.0		34.1 ± 10.5	1016		32.5 ± 11.1	928		35.8 ± 11.4	1944		34.1 ± 11.4

BMD, bone mineral density; WHO, World Health Organization; BMC, bone mineral content.
[a]Women with a uterus comprised the E + P cohort, and those with a hysterectomy at randomization comprised the E-alone cohort.

(PTCA), or stroke, with a higher percentage of E-alone participants reporting these than E + P subjects. About 16% of PHT participants reported having a female relative who had breast cancer, with a slightly higher proportion of E-alone women reporting this than E + P women.

Over 80% of PHT women reported two or more live births and nearly 20% had five or more (Table 3). Women in the E-alone cohort were more likely to have had first births before age 20 and less likely to have them after age 30 than women in the E + P cohort. Only a small percentage of older women in either the E-alone or E + P cohorts reported ever using oral contraceptives (OC), particularly for more than 5 years. Mean OC duration was 5.6 ± 5.4 years for all E + P women and 4.8 ± 4.9 years for all E-alone women. A higher proportion of women aged 50 to 59 years were taking postmenopausal hormones at the initial screening visit compared with older women, thereby requiring a 3-month wash-out, particularly for women who were eventually enrolled in the E-alone trial. The proportion of women in the E + P cohort who had never used hormones was much higher than in the E-alone group. In both cohorts, a much higher proportion of women aged 70 to 79 years had stopped using hormones 10 or more years ago and a higher percentage had used hormones for 10 or more years in duration, compared with younger women. Lifetime duration of hormone use was 4.1 ± 4.8 years for women in the E + P cohort and 7.0 ± 7.5 years for women in the E-alone cohort. Older women reported lower rates of combined estrogen/progestin use compared with the younger women in both cohorts, particularly in the E + P cohort. A higher fraction of older women reported prior use of unopposed estrogen in the E + P cohort compared with the younger E + P participants.

In each ethnic group, women in the E-alone cohort were more likely to report no physical activity (except in American Indians), to be obese and have high blood pressure, and to report being treated for hypertension, diabetes, and high cholesterol, compared with women in the E + P cohort. In Blacks, Hispanics, and Whites, women in the E-alone cohort reported having a history of prior myocardial infarction, CABG/PTCA, and/or stroke at a higher frequency than women in the E + P cohort (see appendix to Hays' article). Also, in each ethnic group, a higher percentage of the women in the E-alone cohort had five or more live births, first births before age 20, and had used postmenopausal hormones ever and for 10 or more years.

BMD measurements of the subsample of PHT participants who had DEXA tests (i.e., those randomized at the three bone density centers) are presented in Table 4 for E + P, E-alone, and combined. While most features of this subsample are similar to the entire PHT cohort, some modest differences are noted. The mean age for the total BMD subsample was 63.7 years and 47.4% of women had a hysterectomy. Compared with the total PHT cohort, the subsample included smaller proportions of women who had ever

smoked or reported no physical activity, but also smaller proportions of women who reported either 2 to 3 or 4 or more 20-minute exercise bouts per week. The subsample also included a greater proportion of women who had never used postmenopausal hormones, with those who had used them having done so for a shorter duration. As in the total sample, within the BMD subsample, women in the E-alone cohort were less physically active, had a higher body mass index, and were more likely to have used postmenopausal hormones ever and to have used them 10 or more years and for a longer duration than women in the E + P trial. Despite these differences, and small differences in dietary calcium and use of calcium supplements, bone density did not differ markedly between women in the E-alone and E + P BMD subsamples at the hip, spine, or whole body. A smaller proportion of women in the E + P cohort BMD subsample met the WHO criteria (10) for normal BMD at the hip (<1 SD below the mean of young normal women), yet a smaller percentage were osteoporotic (>2.5 SD below the mean), compared with the women in the E-alone cohort BMD subsample.

Differences in levels of selected blood analytes in the 8.6% subsample between women in the E + P cohort (N = 1319) and E-alone cohort (N = 992) included higher levels of fasting triglycerides, slightly lower HDL and HDL-2 cholesterol levels, and slightly higher insulin levels in the women in the E-alone subsample compared with the E + P subsample (Table 5).

DISCUSSION

The initial WHI design assumed 55% of women (15,125) would be assigned to E + P or placebo and 45% (12,375) would be assigned to E-alone or placebo for an average of 9 years. Nearly 1500 more women were recruited into the E + P arm than originally planned, but over 1600 fewer were randomized into the E-alone arm. Average follow-up was planned for 8.5 years. Age goals were nearly achieved; primarily due to closure of age cells for White women aged 50 to 59 years before recruitment ended. The ethnic distribution among PHT participants is similar to the percentage in the US census for women aged 50 to 79 years: Whites, 86.3%; Blacks, 9.6%; Hispanic, 5.1%; Asian-Pacific Islander, 2.0%; American Indian 0.5%; and other 1.6% (11). This is considerably more diverse than most previous hormone trial cohorts (5–7). The percentage of women in the PHT component with a hysterectomy is 39.3%. Hysterectomy, one of the most common surgeries performed in the US (12), has been reported in approximately 40% of US women over 40 years (13). Hysterectomy surveillance data indicate that annual rates of hysterectomy in the US do not differ by race, although the reasons for this surgery and the age at which it is performed do differ across ethnic groups, with Blacks and Hispanics having the surgery at younger ages than Whites (13, 14, 15). Differences in the proportion of women with a uterus across the WHI ethnic groups may be a consequence of the recruitment process, which restricted entry of White women by age but not of minority women, resulting in a higher proportion of younger minority women.

The family household income and the percentage of PHT women with a college degree or higher exceeds that of women of this age in the general population (11). The smoking rate is lower (11), as is the percentage of PHT women reporting no participation in leisure-time physical activity (24.8%) per week, which was thirty to fifty percent for women of this age in NHANES III (16). On the other hand, the percentage that was achieving the level of activity recommended by the US Surgeon General (accumulation of

TABLE 5. Baseline blood analytes from WHI Postmenopausal Hormone Therapy participants by hysterectomy[a] status

	Hysterectomy status					
	E + P (N = 1319)		E-alone (N = 992)		Total (N = 2311)	
Blood analyte[b,c]	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Total cholesterol (mg/dl)	1318	222 ± 37.1	991	226.5 ± 41.3	2309	223.7 ± 38.2
LDL-C (mg/dl)	1297	134.7 ± 32.9	970	137.3 ± 37.8	2267	135.7 ± 34.9
HDL-C (mg/dl)	1313	55.3 ± 13.6	987	54.2 ± 13.8	2300	54.9 ± 13.8
HDL-2 (mg/dl)	1276	16.4 ± 7.0	963	15.9 ± 6.7	2239	16.2 ± 7.0
HDL-3 (mg/dl)	1276	38.2 ± 7.9	964	37.8 ± 8.3	2240	38.1 ± 8.1
Triglyceride (mg/dl)	1318	130.9 ± 59.4	991	144.1 ± 67.3	2309	135.7 ± 63.6
Lp (a) (mg/dl)	1299	16.0 ± 17.2	974	16.1 ± 17.2	2273	16.0 ± 17.5
Fibrinogen (mg/dl)	1269	301.5 ± 56.2	960	305.6 ± 62	2229	303.1 ± 58.1
Glucose (mg/dl)	1315	98.4 ± 19	989	101.9 ± 23.9	2304	99.7 ± 21.1
Insulin (μlU/ml)	1280	10.0 ± 4.9	971	11.0 ± 5.5	2251	10.4 ± 5.3

[a]Women with a uterus comprised the E + P cohort, and those with a hysterectomy at randomization comprised the E-alone cohort.
[b]Means and standard deviations were computed on the log scale and back-transformed values are reported.
[c]Means and standard deviations are weighted by the overall CT and OS ethnic distribution.

30 minutes of exercise on most, preferably all, days of the week) was also lower than the NHANES III sample (16). The percentage of obese women was considerably higher in the PHT cohort than the national averages of 28.9%, 24.8%, and 20.0% for US women aged 50 to 59, 60 to 69, and 70 to 79 years, respectively (17). The mean daily intake of dietary calcium was above the average intake of 571 mg/day for women aged 50 to 70 years in the US (18); however, this amount is less than the recommended intake of 1200 mg/day of calcium in this age group (19).

PHT women appeared to be at fairly low risk for CHD, when compared with risk profiles identified by systematic screening (20). Hypertension was reported by fewer PHT women than women in the general population, ranging from 38% to 68% in 50- to 79-year-old White women, and from 47% to 78% in Black women of this age (21). Diabetes was also reported less often by PHT women than the 10.4% reported for 65- to 74-year-old women in the general population (22), as was high cholesterol requiring pills (23). Prevalence of self-reported stroke and prior myocardial infarction were also lower than what was reported by women aged 55 to 79 years in NHANES III (24).

The two cohorts within the PHT component differ in most characteristics described here. Since hysterectomy status may influence a woman's willingness to be randomized to placebo or active hormones, differences between the E + P and E-alone cohorts cannot be attributed to having a hysterectomy as these differences may merely represent some selection biases. Because population studies and clinical trials do not generally provide demographic, lifestyle, or medical characteristics by hysterectomy status, it is difficult to determine whether differences seen between women with and without a uterus in WHI reflect those of the general population. However, the characteristics of each cohort may influence the outcome of each trial, so it is important to recognize the differences between the cohorts of women participating in the E-alone and the E + P trials. In particular, it should be clear that these are two separate trials, involving two distinct study populations that are receiving different treatments. In general, women in the E-alone trial were at higher risk for CHD than the E + P cohort at baseline. They were more obese, less active, and had a slightly higher incidence of pre-existing cardiovascular disease. A high percentage, though not the majority, of WHI women in the E-alone cohort reported a bilateral oophorectomy, which is often performed in the context of a hysterectomy as a means of preventing ovarian cancer (25). Bilateral oophorectomy, but not hysterectomy, has been associated with greater risk for CHD in several studies (26, 27).

It is anticipated that comparisons between the E + P and E-alone cohorts will be done in secondary analyses. The fact that women are randomized to active or placebo hormones in each cohort will enable us to control for differences between their respective placebo groups, as well as the measured confounders noted in this paper. While this cannot replace a direct randomized comparison, it will provide much stronger evidence regarding the relative merits of these two regimens than any other type of observational study.

The WHI hormone trials will eventually be considered in relationship to study populations of other randomized trials of hormone use, both completed (5, 6, 7, 28, 29) and underway. Blood analytes in the WHI subsample generally reflect higher coronary risk than in the younger PEPI cohort (5) and lower risk than in the HERS secondary prevention trial (6). For example, mean fasting plasma fibrinogen, triglycerides, and glucose were higher, and HDL-cholesterol was lower, in the WHI subsample than in PEPI, whereas HDL-cholesterol was higher and triglycerides were lower in the WHI subsample than in HERS.

The WHI PHT component is distinguished by the size and diversity of its cohort and as a primary prevention trial with multiple clinical outcomes. Beyond differences between age and ethnic groups, the current report emphasizes the differences between WHI women with a uterus assigned to E + P or placebo and women with a hysterectomy assigned to E-alone or placebo, which will have a bearing on the interpretation of the final results.

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