Comparison of the Heart and Estrogen/Progestin Replacement Study (HERS) cohort with women with coronary disease from the National Health and Nutrition Examination Survey III (NHANES III)

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Background The Heart and Estrogen/Progestin Replacement Study (HERS) is the first large clinical trial designed to test the efficacy of postmenopausal estrogen/progestin therapy for secondary prevention of coronary heart disease (CHD). To examine the representativeness of the HERS cohort to the general population of postmenopausal women with CHD, we compared the baseline cardiovascular risk factor data from HERS with similar data from women presumed to have CHD from the National Health and Nutrition Examination Survey (NHANES) III.

Methods Age, race, and cardiovascular disease risk factors were compared in the 2763 postmenopausal women younger than 80 years old, with a uterus, and with documented CHD in HERS versus 145 similarly aged women with clinical or electrocardiographic evidence of CHD from phase I of NHANES III.

Results There were fewer current smokers in HERS (13%) than in the NHANES cohort (21.7%, $p = 0.05$). Similarly, a history of hypertension was less prevalent in HERS (58.6%) than in the NHANES cohort (69.3%, $p = 0.03$). Women with fasting triglyceride levels >3.39 mmol/L or fasting glucose levels >16.6 mmol/L were excluded from HERS, resulting in fewer diabetics (22.9% vs 29.5%, $p = 0.26$) and lower serum triglyceride levels (1.88 mmol/L vs 2.25 mmol/L, $p = 0.19$) in HERS versus the NHANES cohort. Systolic and diastolic blood pressure, body mass index, physical activity, and total LDL and HDL cholesterol were not significantly different between the two groups.

Conclusions The HERS cohort had fewer CHD risk factors than women with myocardial infarction or angina in NHANES III, although comparison is hindered by differences in selection criteria. The many women with diabetes and hypertriglyceridemia in the NHANES cohort emphasizes the importance of testing strategies for secondary prevention of CHD in this high-risk subgroup. (Am Heart J 1998;136;115-24.)

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The Heart and Estrogen/Progestin Replacement Study (HERS) is the first large clinical trial of estrogen/progestin therapy for secondary prevention of coronary heart disease (CHD) in postmenopausal women.[1] HERS is important by virtue of the population being studied (postmenopausal women) and the intervention being tested (hormone replacement). Heart disease is the major cause of morbidity and death in men and postmenopausal women in the United States.[2] But because of important unexplained differences between women and men with respect to CHD,[3] more information about women is needed regarding the pathogenesis, prevention, and treatment of CHD to complement the data from studies conducted largely in men during the

last 3 decades. HERS is the first of several large contemporary clinical trials to address this need.

Many observational studies suggest that estrogen users are at lower risk for CHD than nonusers,[1,4,5] and there are a number of biologically plausible mechanisms whereby estrogen could alter the pathogenesis of coronary atherosclerosis.[6-8] However, it has not been established in randomized trials that estrogen replacement reduces clinical coronary events, and it is not known if its beneficial effects are offset by risks of other adverse effects of long-term use. This is especially true for older women with established CHD in whom the risks of estrogen replacement are less well characterized. HERS will quantify both the risks and benefits of estrogen/progestin therapy for secondary prevention of CHD. The large number of postmenopausal women in HERS will also be a source of many additional observations about CHD and other health concerns.

Because of the unique nature of the HERS cohort and the relevance of the primary hypothesis to postmenopausal women, it will be important to know the extent to which HERS results can be generalized to all postmenopausal women with CHD. Unfortunately, there is a paucity of descriptive data on U.S. women with established heart disease for comparison. Furthermore, the data that are available generally come from highly selected groups of women. The National Health and Nutrition Survey (NHANES) III is designed to be a representative sample of the free-living civilian U.S. population and is often drawn on for decisions about national health care policy. Although the total number of women with CHD in NHANES III is small relative to HERS, they still are one of the most representative and important groups against which to compare the HERS women. The validity of this choice for comparison was greatly enhanced by the fact that the same electrocardiogram (ECG) and lipid laboratories were used for both HERS and NHANES III.

Methods

HERS study population

Postmenopausal women (n = 2763) younger than 80 years old, with a uterus and documented CHD, were recruited to participate in HERS and were enrolled from February 1993 to September 1994 in 18 medical centers across the United States. Potentially eligible women were identified from medical records and responses to media campaigns and direct mailings. Enrollment criteria included one or more of the following: (1) prior documented myocardial infarction (MI) (n = 1068, or 38.7%), (2) documented coronary artery bypass graft surgery (n = 1018, or 36.8%), (3) documented transluminal mechanical revascularization (n = 1081, or 39.1%), or (4) 50% or greater narrowing of one or more major coronary arteries at arteriography (n = 2269, or 82.1%).

Exclusion criteria included a history of deep vein thrombosis or pulmonary embolus, a history of breast cancer or mammogram suggestive of breast cancer, a history of endometrial cancer, an abnormal pap smear or uterine bleeding, endometrial hyperplasia based on an endometrial biopsy or vaginal ultrasound, uncontrolled hypertension (systolic blood pressure ≥200 mm Hg, diastolic blood pressure >105 mm Hg at baseline), uncontrolled diabetes (fasting blood glucose level >16.6 mmol/L), fasting serum triglyceride concentration ≥3.39 mmol/L, alanine aminotransferase more than 1.2 times upper limit of normal, or congestive heart failure (New York Heart Association class IV or severe class III). Women with conditions that might interfere with participation (e.g., alcoholism, drug abuse, or unwillingness to comply) were also excluded.

The screening process for eligibility, medical evaluation, and laboratory testing has been described in detail.[9] In brief, during the preliminary screening visit an initial informed consent was obtained as well as a demographic and medical history, a blood sample for the serum chemistry panel, and assays of follicle-stimulating hormone and estradiol (to confirm the postmenopausal state). A potential participant who met inclusion and exclusion criteria received a detailed information summary and consent form to review and was scheduled for a second screening visit. At the second screening visit, each participant signed the comprehensive informed consent document and had a physical examination, resting supine ECG, a gynecologic examination (including endometrial biopsy), and a mammogram. A placebo run-in period then began to assess willingness and ability to take medication and complete study forms. For subjects who successfully completed the placebo run-in period, a randomization visit was scheduled. At that time, additional information (including a cataloging of concomitant medications) and a blood sample for a fasting lipid profile were obtained. The HERS study protocol was approved by the Institutional Review Board at each clinical site. Overall, 4830 women had a preliminary screening visit, 3464 had a secondary screening visit, and 2766 had a randomization visit. A total of 2763 women were enrolled, resulting in a participation rate of 57% of the population initially screened.

NHANES study population

The NHANES, conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, is designed to produce nationally representative data regarding the civilian, noninstitutionalized U.S. population.[10] NHANES III, a 6-year study from 1988 to 1994, consisted of two phases, each of which was designed as a national probability sample. The first phase, conducted from 1988 to 1991, is the source for the data in this paper. The cardiovascular component of

NHANES III, as with the previous NHANES, was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health.[11]

NHANES III consisted of a home interview followed approximately 2 weeks later by a detailed medical examination in a mobile examination center.[12] There was no upper age limit for inclusion into NHANES III. Participants were asked about their history of heart attack, stroke, and diabetes, and responded to the Rose questionnaire for angina pectoris.[13] Current and past use of cigarettes, lipid-lowering and antihypertensive medications, and insulin were also ascertained. Seated blood pressure was measured three times as part of the initial household interview and three additional times during the subsequent medical examination, using procedures outlined by the American Heart Association.[14] A supine resting ECG and a blood sample for a nonfasting lipid profile also were obtained during the medical examination.

NHANES III analytic sample

We attempted to identify postmenopausal women likely to have CHD in the NHANES III, phase I cohort for comparison. Unlike HERS, NHANES contains less detailed information to classify women according to menopausal status and the presence or absence of CHD. For example, there are no data regarding menstrual bleeding or follicle-stimulating hormone and estradiol concentrations in NHANES III to confirm the postmenopausal state. Although HERS enrolled women who were < 55 years of age if they met other criteria for being postmenopausal, most (96%) were between 55 and 80 years of age. Because other data suggest that 95% of U.S. women are postmenopausal by the age of 55 years,[15] we selected women from NHANES III who were ≥55 years and <80 years of age for comparison.

In HERS, the presence of CHD was carefully documented for every participant based on ECG data and review of medical records. Although detailed ECG data also were available in NHANES III, medical records documenting prior MIs, revascularization procedures, and coronary angiography were not collected. Therefore, for the purposes of this comparison, we defined women in NHANES III as likely to have CHD if they had angina according to the Rose questionnaire or evidence of prior MI based on a combination of the clinical history and ECG findings. Exertional chest pain defined by the Rose questionnaire is a strong and independent predictor of CHD death in older women.[16]

Many women in HERS without a prior MI had nonetheless undergone coronary angiography and successful revascularization treatment for coronary disease. Thus despite angiographic evidence of coronary disease, they were asymptomatic and without ECG or historical evidence of MI at baseline. Since prior coronary angiography data were not available in NHANES III, such women in the NHANES III cohort could not be identified for inclusion in the analytic subset. Therefore, for some analyses, the HERS cohort was stratified according to whether the evidence for CHD was based on ECG and history of prior MI (as in NHANES III) or based solely on coronary anatomic considerations.

Table I. NHANES algorithm for assessing the probability of MI

Probability	Minnesota code Q wave	Repolarization abnormalities*	History of MI
Definite			
	1.1	+/–	+
	1.2	+/–	+
	1.3†	+	+
	1.0	+	+
	1.1	+	–
Probable			
	1.3	–	+
	1.0	–	+
	1.1	–	–
	1.2	+	–
Possible			
	1.2	–	–
	1.3	+	–
Not considered MI			
	1.3	–	–
	1.0	+	–

Positive (+) means the finding is present in one or more anatomic distributions (anterior, inferior, lateral). Negative (–) means the finding is not present or is missing.
*Includes Minnesota codes 4.1, 4.2, 5.1, 5.2.
†Includes Minnesota codes 1.26 and 1.28.

ECG analyses

ECGs from both cohorts were analyzed at the Epidemiological Cardiology Research Center (EPICARE), Department of Public Health Sciences, Wake Forest University School of Medicine. Digital ECGs were processed with the NOVACODE ECG analysis program,[17,18] which has algorithms for ECG classifications according to the Minnesota Code.[19] Classification categories used herein were based on Minnesota codes 1 (Q and QS waves), and 4 and/or 5 (repolarization abnormalities). A hierarchic scheme using questionnaire data on the history of MI together with the Minnesota Code classification was used to categorize the likelihood of MI at four levels: (1) definite, (2) probable, (3) possible MI, and (4) no MI (Table I). Women in both cohorts with a definite, probable, or possible MI or history of angina by Rose questionnaire were defined as having CHD.

Lipid and lipoprotein analyses

All lipid and lipoprotein analyses for both HERS and NHANES III were performed in the Johns Hopkins University Lipid Research Clinic Laboratory with the standardized methods of the Centers for Disease Control and Prevention.[20] Cholesterol was measured enzymatically with a commercially available reagent mixture (Cholesterol/HP, Boehringer Mannheim Diagnostics, Indianapolis, Ind.) and is based on the method of Allain et al.[21] Triglycerides were analyzed

Table II. Evidence of coronary heart disease in the HERS and NHANES III cohorts

Evidence of CHD*	HERS		NHANES III		
	n	(%)	*n*	(%)	*p* Value
MI	1676	(60.7)	16	(11.0)	<0.001
Angina	294	(10.6)	129	(89.0)	<0.001
Neither†	716	(25.9)	0	(0)	NA
Unable to classify‡	77	(2.8)	0	(0)	NA
Total	2763	(100)	145	(100)	

NA, Not applicable.
*Using the NHANES III classification scheme. Classifications are mutually exclusive with preference to MI over angina, that is, if a woman had evidence of both, she was counted in the MI group only.
†Coronary disease, however, was confirmed through medical record review, including cardiac catheterization, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery reports.
‡Due to missing data.

enzymatically with commercially available reagents (A-gent Triglycerides Reagent Set, Abbott Laboratories, Chicago, Ill.; triglycerides/GPO, Boehringer-Mannheim Diagnostics). HDL cholesterol was measured in supernatants after precipitation of apolipoprotein B–containing lipoproteins with heparin/manganese chloride and removal of excess Mn^{+2} by precipitation with sodium bicarbonate.[22] LDL cholesterol was calculated only for persons with fasting triglyceride levels ≤3.39 mmol/L using the equation developed by Friedewald et al[23]: LDL cholesterol = Total cholesterol – (HDL cholesterol – triglycerides/5), in which triglycerides/5 is taken as a measure of VLDL cholesterol. All concentrations are expressed in mmol/L.

In NHANES III, serum total and HDL cholesterol were measured in all women regardless of fasting status. Serum triglycerides, however, were measured in a statistically representative half sample of persons who were asked to fast for 12 hours and to be examined the next morning, consistent with the guidelines recommended by the National Cholesterol Education Program Adult Treatment Panel for lipoprotein analysis.[24] For analyses of the triglycerides, only results for women examined in a fasting state (at least 9 hours without eating) were used.

Statistical analysis

All data are presented as a mean or percentage ± standard error. For data from the HERS cohort, standard errors are estimated with standard techniques.[25] For data from NHANES III, the means and standard errors were estimated with a weighting scheme, based on the sampling strategy used, to ensure that the results were representative of the entire U.S. population. The weighted point and variance estimates were calculated using SUDAAN.[26] Statistical significance of comparisons between HERS and NHANES data was calculated using *t* tests for continuous variables and normal approximation tests for dichotomous variables. In both cases, the weighted standard errors were used for the NHANES data.

Results

Study populations

The HERS cohort consisted of 2763 women. The NHANES III cohort consisted of 145 women who met the criteria for CHD, from a total of 1186 women aged 55 to 79 years (inclusive) from phase I of NHANES III. The NHANES III women were enrolled, on average, 4 years earlier than the HERS women (1988 to 1991 versus 1993 to 1994). Unlike the NHANES III women, the HERS women were required to have an intact uterus and to not be taking hormone replacement at enrollment. Table II shows the distribution of types of evidence for CHD in the two study populations. In HERS, most women (60.7%) had historical and electrocardiographic evidence of a prior MI. In contrast, only 11% of NHANES III women had similar evidence of MI ($p < 0.001$). Almost 90% of the NHANES III cohort was classified as having CHD based solely on responses to the Rose angina questionnaire versus approximately 11% in the HERS cohort ($p < 0.001$). An additional 15.7% of the HERS participants had Rose angina plus historical and electrocardiographic evidence of MI (data not shown).

Comparison of cardiovascular risk factors

Table III shows the cardiovascular risk factor data from both cohorts. Despite the inclusion of a few women in HERS younger than age 55 years, the mean age of the two cohorts was virtually identical. Although 13% of the HERS cohort were current smokers compared with 21.7% in the NHANES III cohort ($p = 0.05$), HERS participants were more likely to have smoked at some time in their lives than were NHANES participants (62.0% vs 52.4%, $p = 0.07$). More women in NHANES III reported a history of hypertension ($p = 0.03$); however, blood pressure at the time of the examination was similar in the two groups.

Approximately 30% of women in the NHANES III cohort reported having diabetes versus roughly 23% in HERS ($p = 0.26$). Some diabetic women were excluded from HERS because of the entry requirement of a fasting blood glucose level <16.6 mmol/L and a serum triglyceride concentration of ≤3.39 mmol/L at baseline. The body mass index was nearly equal in the two groups of women. A greater proportion of HERS women reported being more physically active than comparably aged women in NHANES III (41.4% versus 33.0%), but this difference was not statistically significant.

Fasting mean triglyceride concentrations were slightly higher in the NHANES III cohort, although the

Table III. Comparison of risk factors in HERS and NHANES III women with coronary heart disease

	HERS		NHANES III		
	n	**Mean or % (SE)**	***n***	**Mean or % (SE)**	***p* Value**
Sample size	2763		145		
Age (y)	2763	66.7 (0.1)	145	67.2 (0.7)	0.48
Non-white (%)	312	11.3 (0.6)	38	10.6 (3.1)	0.82
Smoking status					
Current (%)	360	13.0 (0.6)	29	21.7 (4.4)	0.05
Former (%)	1712	62.0 (0.9)	70	52.4 (5.2)	0.07
Never (%)	1051	38.0 (0.9)	46	47.2 (5.2)	0.08
Hypertension					
History (%)	1619	58.6 (0.9)	90*	69.3 (4.8)	0.03
SBP (mm Hg)	2763	135.0 (0.4)	145	137.3 (1.5)	0.14
DBP (mm Hg)	2762	73.1 (0.2)	145	72.3 (1.0)	0.43
Diabetes†	634	22.9 (0.8)	44*	29.5 (5.8)	0.26
BMI (kg/m^2)	2757	28.6 (0.1)	145	28.8 (0.7)	0.78
Physical activity‡					
More active (%)	1144	41.4 (0.9)	42	33.0 (5.0)	0.10
Less active (%)	700	25.3 (0.8)	42	27.8 (5.1)	0.63
Lipids (mmol/L)					
TC	2759	5.92 (0.02)	132	6.09 (0.16)	0.30
LDL	2752	3.75 (0.02)	46	3.53 (0.21)	0.30
HDL	2752	1.30 (0.01)	130	1.36 (0.05)	0.23
TG	2759	1.87 (0.01)	53	2.25 (0.29)	0.19

BMI, Body mass index; *DBP,* diastolic blood pressure; *SBP,* systolic blood pressure; *TC,* total cholesterol; *TG,* triglycerides.
*Based on responses from 132 subjects.
†Self-report of physician-diagnosed diabetes.
‡Physical activity based on response to the question: "Compared to other women your age, how would you describe your level of activity: less active, about the same, or more active?"

difference did not reach statistical significance (p = 0.19). When the NHANES cohort was further limited to those women with triglyceride levels ≤3.39 mmol/L (the HERS entry requirement), the difference between the two cohorts in triglyceride levels was negligible (1.88 mmol/L for HERS vs 2.25 mmol/L for NHANES, p = not significant). HDL concentrations in the two cohorts were very similar. Total and LDL cholesterol levels in the two cohorts were not significantly different. Thus, with the exception of current smoking and a history of hypertension which were more prevalent in NHANES women, there were no significant differences between the two cohorts. However, there were trends toward greater proportions of sedentary women and women with diabetes and hypertriglyceridemia in the NHANES cohort than in HERS.

When the HERS cohort was limited to those women who met the criteria for NHANES CHD, only two risk factor variables were significantly different between the two groups (Table IV). In the HERS subset there were more current and former smokers (p = 0.03) and fewer participants who had never smoked (p = 0.03) than in the NHANES cohort. In contrast, there were fewer women in the HERS subset with a history of hypertension than in NHANES III (p = 0.03).

HERS women with CHD but no prior MI or angina

In NHANES III, women were classified as having CHD if they had evidence of a prior MI or Rose angina. When this definition was applied to the HERS cohort 71.3% were classified as having NHANES CHD. The remainder of the HERS women had evidence of CHD based on coronary anatomy alone. To better characterize these women with documented CHD not identified by the NHANES algorithm, HERS women with and without NHANES CHD were compared (Table IV). HERS women without NHANES CHD were slightly older and more likely to be white (p < 0.001 for both). They were also less likely to be current smokers (p = 0.003) or past smokers (p < 0.001) and less likely to have diabetes (p < 0.01). They reported more physical activity than HERS participants with angina or evidence of MI (p < 0.001). These data suggest that current estimates of CHD prevalence in women based on NHANES data may underestimate the true prevalence of CHD. However, the women

Table IV. Comparison of HERS women with and without NHANES criteria for CHD

	With NHANES CHD		Without NHANES CHD		
	n	**Mean or % (SE)**	***n***	**Mean or % (SE)**	***p* Value**
Sample size	1970		793		
Age (y)	1970	66.4 (0.2)	793	67.4 (0.2)	<0.001
Non-white (%)	246	12.5 (0.7)	66	8.3 (1.0)	<0.001
Smoking					
Current (%)	280	14.2 (0.8)	80	10.1 (1.1)	0.003
Former (%)	1264	64.2 (1.1)*	448	56.5 (1.8)	<0.001
Never (%)	706	35.8 (1.1)*	345	43.5 (1.8)	<0.001
Hypertension					
History (%)	1161	58.9 (1.1)*	458	57.8 (1.8)	0.60
SBP (mm Hg)	1970	135.0 (0.4)	793	136.0 (0.7)	0.20
DBP (mm Hg)	1969	73.2 (0.2)	793	72.9 (0.3)	0.45
Diabetes	478	24.3 (1.0)	156	19.7 (1.4)	<0.01
BMI (kg/m^2)	1964	28.7 (0.1)	793	28.3 (0.2)	0.08
Physical activity†					
More active (%)	768	39.0 (1.1)	376	47.4 (1.8)	<0.001
Less active (%)	567	28.8 (1.0)	133	16.8 (1.3)	<0.001
Lipids (mmol/L)					
TC	1967	5.92 (0.02)	792	5.90 (0.04)	0.56
LDL	1961	3.75 (0.02)	791	3.75 (0.03)	1.00
HDL	1961	1.30 (0.01)	791	1.31 (0.01)	0.36
TG	1967	1.88 (0.01)	792	1.86 (0.003)	0.45

Abbreviations as in Table III.
*$p < 0.03$ when compared with NHANES women with CHD.
†Based on the question "Compared to other women your age, how would you describe your level of activity: less active, about the same, or more active?"

with coronary disease not classified as having CHD by the NHANES algorithm appear to be a healthier subset of women, and presumably at lower risk for CHD events.

Discussion

The HERS cohort has fewer risk factors for coronary disease than similarly aged women from NHANES III with evidence of MI or angina, although not dramatically so. Specifically, the HERS women are less likely to be current smokers and to have a history of hypertension. There were also trends toward fewer proportions of HERS women who are sedentary or who have diabetes or hypertriglyceridemia. On the other hand, other important risk factors such as LDL and HDL cholesterol levels and systolic and diastolic blood pressure readings were not different between the two groups.

Some of the differences between the HERS and NHANES III cohorts are probably caused by the HERS selection criteria that excluded women with uncontrolled hypertension or diabetes. However, the HERS cohort may also be healthier than the general U.S. population of women with CHD because of a "healthy volunteer" effect.[27,28] Subjects who participate in clinical trials frequently differ from the general population. In some cases, people who are willing to participate in a clinical trial are healthier than nonparticipants.[29] Such a difference raises questions about whether the same benefits (and risks) observed in the clinical trial can be expected in the general population in which the intervention will be ultimately used. It is not uniformly true, however, that participants in clinical trials have a different outcome than nonparticipants. In the Coronary Artery Surgery Study (CASS), survival of participants in the clinical trial was identical to that seen in a registry of similar nonparticipating subjects.[30]

Another problem with selection bias in volunteer subjects is a lower-than-expected event rate in the control group. If not prospectively considered, this factor can decrease the study's power to detect the treatment effect of interest. In planning HERS, it was assumed that 5% of women per year assigned to the placebo group would have fatal and nonfatal MIs. Since the start of the trial, however, dramatic and favorable changes have occurred in the recommendations for management of acute and chronic CHD.[24,31,32] The extent to which the healthier nature of the cohort or secular changes in CHD treatment will

influence the overall event rate or the response to treatment remains to be seen.

Diabetic women were not explicitly excluded from HERS; however, women with the metabolic sequelae of poorly controlled diabetes (including elevated fasting glucose or triglyceride concentrations and, to a lesser extent, uncontrolled hypertension) were ineligible. This exclusion is consistent with clinical practice, where estrogen is often withheld from diabetic women with preexisting hypertriglyceridemia for fear of exacerbating their triglyceride disorder.[33] As a result, there was a slightly smaller proportion of diabetic women in HERS than in NHANES III, although this difference was not significant. Estrogen raises triglyceride levels by increasing the production of large VLDL particles, which are preferentially taken up directly by the liver rather than being converted to LDL.[34] Thus, the atherogenicity of estrogen-associated elevations in triglyceride levels may not be as great as with other triglyceride disorders. The large number of diabetic women in HERS (n = 634) will provide much needed information about triglyceride metabolism and the prospects for secondary prevention in diabetic women, whose risk for MI and CHD death is among the highest of any subgroup in the population.

This study highlights the deficiencies in the number and quality of descriptive data on U.S. women with CHD before HERS. For example, although phase 1 of NHANES III included approximately 15,000 people 2 months of age and older, only 1186 women aged 55 to 80 years had ECGs. Despite a relatively high unweighted CHD prevalence of 12.2%, this resulted in only 145 women with CHD. Other large epidemiologic cohorts also have relatively few women with established CHD and, in some cases, such as the Nurses Health Study,[35] they also had certain unique selection biases. With the exception of the most recent trials of lipid lowering[36,37] and thrombolytic therapy,[38,39] trials of interventions for secondary prevention of cardiovascular disease have also included very few women. Of the three major trials of medical versus surgical therapy for coronary disease, the European Cooperative Study,[40] the Veterans Administration Study,[41] and CASS,[42] only CASS included women (79, or 9.7% of 780 randomly assigned subjects). The CASS registry fortunately included a larger number of women (n = 2737) with angiographically defined CHD. Much of what we know about angina, exercise treadmill testing, and angiographically defined coronary disease in women was derived from the CASS data set, which is now more than 25 years old.

Thus, despite being slightly healthier than the general population of women with CHD, the HERS cohort will be one of the largest contemporary groups of postmenopausal women with CHD studied to date. The large body of additional data collected in HERS beyond that required to test the primary hypothesis should facilitate additional studies that will enhance our understanding of CHD and other health concerns in postmenopausal women.

There are also limits on the degree to which any cohort can claim to be truly representative of the entire population, regardless of the size of the cohort. Even in the most well-planned efforts, as in NHANES, there are practical limitations that are difficult to overcome. For example, only 66.4% of women aged 50 to 79 invited to participate in the mobile examination center screening actually came in to have an ECG and to give a blood sample for lipid profile determination (unpublished data, National Center for Health Statistics, Centers for Disease Control and Prevention, 1992). Adjustments for nonresponse in the NHANES III survey do not reveal evidence of bias from nonresponse (Ezzati and Khare, unpublished data, 1992); however, the possibility of a healthy volunteer bias among the subgroup of older women with CHD remains plausible.

An additional limitation of the NHANES III survey and other epidemiologic studies has to do with the sensitivity and specificity of classification of CHD in women. NHANES III was constrained to the simple questionnaire and ECG data that were feasible to collect in large numbers of subjects. However, our comparison suggests that use of the NHANES CHD classification to identify individuals with CHD may underestimate the prevalence of the disease because of a sizable number of subjects who have been successfully treated with medical or revascularization therapy but have not yet had a Q-wave MI.[43] This underestimation may be particularly important in women, who are less likely than men either to report typical angina with CHD[44] or acute MI[45] or to have electrocardiographically documented Q waves develop after MI.[46] In HERS, for example, 74.6% of women with documented CHD were free of angina at baseline.

There are also questions about the specificity of the NHANES III classification for CHD in women. Most women in NHANES III designated as having CHD

were so classified because of anginal symptoms. Some studies have shown that angina is less predictive of coronary angiographic disease[47] or subsequent CHD events in women than in men.[48,49] Thus the NHANES III CHD cohort may contain some women who do not have true coronary artery disease. However, this is unlikely to be the case in the NHANES cohort because, on average, the NHANES women had a less favorable CHD risk factor profile than the HERS cohort, a group of women with unequivocal coronary artery disease. NHANES III was not specifically designed to study individual disease states in detail; nonetheless, many important health policy decisions are influenced by NHANES III data. In future NHANES surveys, more questions about medical and revascularization therapies for CHD and less reliance on anginal symptoms may significantly improve the ability to identify women with coronary artery atherosclerosis.

This study set out to compare the HERS cohort with a similar group of women with CHD from NHANES III. Questions regarding sample size, representativeness, and sensitivity and specificity of CHD classification in the NHANES III data may limit the value of this comparison. Nonetheless, the highly stratified, multistage probability sampling strategy used in NHANES III provides the best opportunity to assess how representative the HERS cohort is of the broader group of postmenopausal women with CHD in the United States who may want to use the results of the HERS trial to guide decisions about use of hormone replacement therapy. Thus it is encouraging that, despite the exclusion criteria and a possible healthy volunteer effort in HERS, the two cohorts are generally quite similar with respect to CHD risk factor profiles. An important outcome from this study is the demonstration of how little data are currently available on women with CHD in the United States. Data from the HERS trial will provide a major increment in this regard. The relatively large number of diabetic subjects in the NHANES cohort highlights the need for information about the effects of hormone replacement regimens and other forms of therapy for prevention of CHD in this high-risk subgroup. HERS, with more than 600 diabetic women, will provide critical information about the risks and benefits of hormone therapy in these patients. Finally, the data from this study reveal opportunities to enhance the sensitivity and specificity of the NHANES detection of CHD, the primary cause of morbidity and death in postmenopausal women in the United States.

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