Socioeconomic Position and Hormone Replacement Therapy Use: Explaining the Discrepancy in Evidence From Observational and Randomized Controlled Trials

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Objectives. We assessed the association between life-course socioeconomic status or position (SEP) and hormone replacement therapy (HRT).

Methods. We conducted a cross-sectional analysis of 4286 women aged 60 to 79 years.

Results. Women experiencing adverse socioeconomic circumstances across the life course were less likely to have used HRT. The associations of childhood socioeconomic measures with HRT use were independent of adult SEP, behavioral risk factors, and physiological risk factors for heart disease.

Conclusions. SEP from across the life course is associated with HRT use. Because the association between early life SEP and HRT is not fully explained by adult risk factors, residual confounding (which is not captured by adjustment for adult variables only) may explain some of the disparity between observational studies and randomized controlled trials in this area. (*Am J Public Health.* 2004; 94:2149–2154)

The disparity between findings from observational studies and randomized controlled trials of the effects of hormone replacement therapy (HRT) on coronary heart disease (CHD)[1–4] has created considerable debate among researchers, practitioners, and postmenopausal women.[5–10] Observational studies have consistently found that use of HRT is protective against CHD, with a meta-analysis of observational studies yielding a summary relative risk for ever use of HRT of 0.56 (95% confidence interval [CI]=0.50, 0.61).[4] By contrast, recent randomized trials among women with established CHD and healthy women have found HRT to be associated with slightly increased risk of CHD or null effects. For example, the large Women's Health Initiative randomized trial found that the hazards ratio for CHD associated with being allocated to HRT was 1.29 (95% CI=1.02, 1.63), after 5.2 years of follow-up.[1]

A number of explanations have been suggested for these disparities. Although some researchers have suggested that the results of the trials were biased because of contamination, and in the case of the Women's Health Initiative, early termination of the arm assessing the effect of combined HRT, the consistency across a number of trials of a null effect makes these explanations unlikely. More plausible explanations are that women who participated in the trials were importantly different from those who participated in the observational studies or that the observational study results were confounded.[5,8,9,11]

Women in the Women's Health Initiative trial were older than the average age at which women take HRT and were more obese than the women who have been included in the observational studies.[1] These women may be more likely to have established atherosclerosis than younger and leaner women and therefore may be more prone to the prothrombotic effects of HRT.[5] However, there was no evidence of interactions of treatment assignment with age, prior hormone use, or body mass index for any cardiovascular outcomes in the Women's Health Initiative.[1,12]

Of particular interest is whether the results in the observational studies are explained by residual confounding. Despite the fact that use of HRT is strongly socially patterned[13] and that socioeconomic status or position (SEP) is associated with CHD,[14] in many observational studies, adjustment for adult SEP has failed to have a marked impact on the HRT–CHD association.[15] However, residual confounding by SEP across the life course may be particularly important.[16,17] SEP in childhood is strongly associated with CHD risk, independent of adult SEP.[14,18] The association between adverse SEP in early life and CHD is in part mediated by adult behavioral and physiological risk factors.[14] Therefore, early life SEP could be an important confounder only if it were associated with HRT use and this association were independent of adult SEP and proximal adult risk factors that in part explain the association between early life SEP and CHD risk.

Our hypothesis was that the protective effect of HRT against CHD found in observational studies is explained at least in part by residual confounding related to early life socioeconomic factors that are not completely captured by adult risk factors. To assess this possibility, the primary aim of this study was to determine whether SEP in early life is associated with HRT use. Furthermore, we aimed to determine whether any association between early life SEP and HRT is fully explained by adult socioeconomic, behavioral, and physiological risk factors. If this association exists, then adequate adjustment for these adult risk factors should be sufficient to capture any potential confounding effect of early life SEP.

METHODS

Data from the British Women's Heart and Health Study were used. Full details of the selection of participants and measurements used in the study have been previously reported.[19,20] Women aged 60 to 79 years were randomly selected from general practitioner lists in 23 British towns. A total of 4286 women (60% of those invited) participated, and baseline data were collected between

April 1999 and March 2001. Local ethics committee approvals were obtained.

Data on socioeconomic indicators across the life course included data on the longest held occupation of the participant's father during her childhood, childhood household amenities (i.e., bathroom, hot water, bedroom sharing, and car access), age at completion of full-time education, the longest held occupation of the participant and her spouse, adult housing tenure, car access, and pension arrangements. Childhood social class of each woman was based on her father's longest held occupation and adult social class was based on her husband's longest held occupation or her own longest held occupation for single women.[21] Adult and childhood social class were defined according to the registrar general's classification of occupations (I, II, III nonmanual, III manual, IV, and V, with I indicating professional occupations and V indicating manual unskilled occupations). We repeated the analyses using each woman's own occupation for married women who were not permanent housewives and declared an occupation (74%). The results from these analyses were essentially unaltered from those presented here although, because of reduced numbers, they were less precise. Most of the indicators of SEP were binary variables. For the main analyses, we dichotomized adult and childhood social class into nonmanual (I, II, III nonmanual) and manual (III manual, IV, V) groups to minimize any possible misclassification bias. Pension arrangements were dichotomized as state only or state plus other and adult housing tenure as local authority or other. Age at leaving full-time education was dichotomized around the median value (15 years).

Use of HRT, socioeconomic indicators, age at menopause, history of a hysterectomy or oophorectomy, smoking history, and physical activity were obtained from the self-completed questionnaire and/or the research nurse interview, to which women were requested to bring their current medications.[19,20] Blood samples were taken after a minimum 6-hour fast (except for patients using insulin treatment) using evacuated tubes and were used to determine insulin resistance and lipid levels.[19,20] Blood pressure, weight, height, and waist and hip circumference were measured using standard procedures.[19,20] Coronary heart disease was considered to be present in any woman with a medical record of myocardial infarction (verified with respect to World Health Organization criteria[22]), angina, angioplasty or coronary artery bypass grafting, and/or any woman with a self-report of a physician diagnosis of these.[19]

Of the 4286 participants, 911 (21.0%) stated that they had ever (current and past) used HRT and 368 stated (8.6%) that they were currently using HRT. Of those who had ever used HRT, 43% did not know the name or type of preparation (or gave only vague details such as "tablets" or "patches"), 32% used a combined estrogen–progestogen preparation, 18% used unopposed estrogen, and 7% were not actually using HRT (e.g., tibolone, raloxifene). Of current users, only 9% did not know the name or type, 40% were taking a combined preparation, 39% were taking unopposed estrogen, and 12% were not actually using HRT. Those who had not or were not actually using HRT were categorized as not using HRT; those who did not know the type of HRT that they had used were all assumed to have used HRT. Thus, in the main analysis, 848 women (19.8%) were categorized as ever using HRT, and 323 (7.5%) were categorized as currently using HRT. In a sensitivity analysis, all women who defined themselves as ever (n=911) or currently taking HRT (n=368) were defined as exposed. The results of this sensitivity analysis did not differ substantively from those presented here. All of those who were currently using unopposed estrogen had had a hysterectomy.

Statistical Analysis

Age-adjusted prevalences and 95% confidence intervals for each indicator of SEP are presented for all women in the study and for current, past, and never users of HRT. Multiple logistic regression was used to assess the associations of each individual indicator of SEP with HRT use. For each indicator, 3 logistic regression models were undertaken. In the first, crude associations were assessed. In the second, childhood indicators were adjusted for age (entered as a continuous variable) and adult indicators of SEP (adult social class, car access, local authority housing, and pension arrangements entered as full categorical [indicator] variables, except car access, which is binary). In the third model, all other adult behavioral and physiological risk factors that might capture any association between childhood SEP and HRT use were added to the age- and adult SEP–adjusted model. In this model, systolic blood pressure, high-density lipoprotein cholesterol, triglyceride levels (logged), body mass index, waist-to-hip ratio, and age of menopause were all entered as continuous variables; smoking and physical activity were entered as indicator variables. Homeostasis model assessment scores (insulin resistance) were not estimated for individuals with diabetes, and an indicator variable representing insulin resistance–diabetes was calculated as fifths of homeostasis model assessment scores for nondiabetics together with a sixth category for patients with diabetes.[18] Covariates were decided a priori, rather than being data driven, for example, by stepwise regression.[23] Uptake of HRT has increased over recent decades, and it is possible that as HRT use becomes more widespread, any associations with SEP will be weaker in younger birth cohorts. To assess this possibility, age was dichotomized as 60 to 69 years and 70 to 79 years, and likelihood ratio tests were used to determine statistical evidence for any interactions between age and socioeconomic indicators in their association with HRT use.

In addition to assessing the association of each individual life-course indicator of SEP, we assessed the cumulative effect of life-course SEP by generating a life-course SEP score from the 10 dichotomized indicators. Two scores were developed, one in which equal weight was given to each indicator and another in which the inverse of prevalence weights was used. The first score has the advantage of being easy to understand because the score gives the actual number of adverse indicators. The score ranged from 0 (most advantaged position across the life course) to 10 (most disadvantaged position across the life course). Because there were very small numbers in the 0 category (n=77) and in the 10 category (n=57), the 0 category was combined with the 1 category and the 10 category with the 9 category. The second score in which each indictor was weighted by the inverse of its prevalence gave the greatest weight to adverse indicators that were least

TABLE 1—Prevalence of Life-Course SEP Indicators Among All Study Participants and By Use of Hormone Replacement Therapy: British Women's and Heart and Health Study, 1999–2001

		% With Indicator (95% CI)			
	No. With Complete Data on Variable	All Participants (n = 4286)	Nonusers of HRT (n = 3438)	Past Users of HRT (n = 525)	Current Users of HRT (n = 323)
Childhood SEP indicator					
Manual social class	4286	80.0 (78.8, 81.2)	81.4 (80.0, 82.6)	76.0 (72.1, 79.6)	72.1 (66.9, 77.9)
No bathroom in house	4052	38.7 (37.2, 40.2)	41.0 (39.3, 42.7)	31.1 (27.1, 35.3)	28.3 (23.4, 33.7)
No hot water in house	4022	35.3 (33.8, 36.8)	37.3 (35.6, 38.9)	29.1 (25.1, 33.2)	24.9 (20.2, 30.1)
Shared bedroom	3994	52.7 (51.1, 54.3)	54.0 (52.3, 55.8)	48.4 (44.0, 52.9)	46.3 (40.7, 52.0)
No car access	3936	82.6 (81.4, 83.8)	84.1 (82.7, 85.3)	77.6 (73.6, 81.2)	76.2 (71.1, 80.8)
Completed full-time education by age 15 y	3938	88.5 (87.5, 89.5)	89.3 (88.2, 90.4)	87.2 (84.0, 90.0)	82.5 (77.8, 86.6)
Adult SEP indicator					
Manual social class	4286	57.3 (55.8, 58.8)	58.7 (57.1, 60.4)	49.7 (45.4, 50.1)	54.2 (48.6, 59.7)
Local authority housing	4070	13.6 (12.6, 14.7)	15.0 (13.8, 16.2)	9.1 (6.8, 11.9)	7.30 (4.7, 10.8)
No car access	4069	28.9 (27.5, 30.3)	32.5 (30.9, 34.2)	15.1 (12.1, 18.4)	14.6 (10.9, 19.0)
State pension only	3828	28.8 (27.4, 30.3)	30.7 (29.1, 32.4)	23.2 (19.5, 27.2)	18.4 (14.2, 23.3)

Note. CI = confidence interval; HRT = hormone replacement therapy; SEP = socioeconomic position.

prevalent. The resulting weighted score was highly positively skewed, with a range from 0 to 28.9. The 2 composite socioeconomic scores were strongly correlated (Spearman rank correlation coefficient=0.95) and showed identical linear trends in their association with HRT use. Results for the unweighted score only are therefore presented. Likelihood ratio tests were used to assess departure from linearity in the associations between the scores and HRT use.

RESULTS

Most women provided data on each of the socioeconomic indicators, with details of pension arrangements being the variable with the greatest amount of missing data (3828 [89%] women provided data for this indicator). There were no significant differences in SEP indicators or risk factor distributions between women with complete data on all indicators and those with some missing data (all P values >.25). Table 1 shows the prevalence of each indicator of SEP for all study participants and by HRT use.

Table 2 shows the results of logistic regression analyses for the associations of each indicator of childhood SEP with HRT use. In general, childhood indicators of SEP were more strongly associated with HRT use than adult indicators, although the single strongest association was with adult car access. All indicators of childhood SEP were associated with reduced odds of ever and current use of HRT even with adjustment for adult SEP and a full range of adult behavioral and physiological risk factors, although the association of completing full-time education before age 15 years with ever use of HRT and of sharing a bedroom with current HRT did not reach conventional levels of 5% statistical significance. There was no statistical evidence of any interactions between age and any indicators of SEP in their associations with HRT use (all P values >.3). There was a cumulative effect of life-course SEP on HRT use as demonstrated by strong linear trends across the composite score (Table 3) for both ever and current use of HRT.

Among the 3496 women with complete data on all indicators of SEP, 514 (15.5%) women had CHD, and the prevalence of CHD did not differ between women with these complete data and all women in the cohort (P=.23). Table 4 shows the association of ever and current use of HRT with prevalent CHD and the effect on this association of adjustment for life-course SEP and all other adult risk factors, and also the effect on this association of adjustment for just adult SEP (all indicators of adult SEP) and adult risk factors. In crude analyses, both ever use and current use of HRT are associated with a protective effect. When adjustment is made for life-course SEP (using the cumulative life-course socioeconomic score) and adult behavioral and physiological risk factors, both of these associations are reversed to slight increases in risk (although both are nonsignificant at the conventional 5% level). When adjustment is made just for all indicators of adult SEP together with adult behavioral and physiological risk factors, the results are attenuated but still suggest some benefit of HRT (although again not significant at the conventional 5% level).

DISCUSSION

In this cohort of British women aged 60 to 79 years, adverse socioeconomic indicators from across the life course were associated with use of HRT. Indicators of socioeconomic deprivation in childhood were associated with a reduced odds of using HRT, and these associations were independent of adult SEP, behavioral risk factors, and physiological risk factors. Because childhood SEP is independently associated with CHD,[14,18] our findings suggest that the protective effect of HRT use found in observational studies may be attributable to residual confounding. The logic behind this argument starts from the conflicting evidence between observational studies and trials. Well-conducted trials should not be affected by confounding, and therefore residual

TABLE 2—Associations Between Use of Hormone Replacement Therapy and Indicators of SEP Across the Life Course, With Adjustment for Potential Confounding and Mediating Variables: British Women's Heart and Health Study (n = 3496),[a] 1999–2001

	OR (95% CI) for Ever Use of HRT Compared With Never Use			OR (95% CI) for Current Use of HRT Compared With Never Use		
	Crude	Adjusted for Age and Adult/Childhood SEP[b]	Adjusted for Age, Adult/Childhood SEP, and Other Adult Risk Factors[c]	Crude	Adjusted for Age and Adult/Childhood SEP[b]	Adjusted for Age, Adult/Childhood SEP, and Other Adult Risk Factors[c]
Childhood SEP indicator						
Manual social class	0.63 (0.52, 0.76)	0.72 (0.59, 0.88)	0.72 (0.58, 0.89)	0.60 (0.46, 0.79)	0.67 (0.51, 0.89)	0.66 (0.49, 0.89)
No bathroom in house	0.68 (0.57, 0.81)	0.73 (0.61, 0.88)	0.73 (0.60, 0.88)	0.67 (0.52, 0.87)	0.66 (0.50, 0.88)	0.68 (0.51, 0.91)
No hot water in house	0.71 (0.59, 0.85)	0.79 (0.66, 0.96)	0.78 (0.64, 0.95)	0.66 (0.50, 0.87)	0.70 (0.53, 0.93)	0.69 (0.51, 0.93)
Shared bedroom	0.77 (0.66, 0.91)	0.84 (0.71, 1.00)	0.84 (0.70, 1.00)	0.77 (0.61, 0.97)	0.81 (0.63, 1.05)	0.79 (0.61, 1.03)
No car access	0.67 (0.55, 0.82)	0.74 (0.60, 0.91)	0.73 (0.58, 0.91)	0.70 (0.53, 0.93)	0.71 (0.53, 0.96)	0.68 (0.50, 0.92)
Completed full-time education by age 15 y	0.72 (0.56, 0.91)	0.83 (0.65, 1.07)	0.80 (0.61, 1.02)	0.60 (0.43, 0.82)	0.68 (0.48, 0.96)	0.65 (0.45, 0.93)
Adult SEP indicator						
Manual social class	0.71 (0.61, 0.83)	0.90 (0.76, 1.08)	0.93 (0.77, 1.12)	0.86 (0.68, 1.08)	1.16 (0.90, 1.50)	1.30 (0.99, 1.71)
Local authority housing	0.61 (0.46, 0.80)	0.70 (0.52, 0.95)	0.76 (0.55, 1.05)	0.56 (0.36, 0.88)	0.71 (0.45, 1.13)	0.81 (0.49, 1.32)
No car access	0.51 (0.41, 0.63)	0.55 (0.44, 0.69)	0.58 (0.45, 0.74)	0.57 (0.41, 0.79)	0.67 (0.48, 0.95)	0.74 (0.51, 1.06)
State pension only	0.67 (0.55, 0.81)	0.78 (0.64, 0.97)	0.81 (0.65, 1.01)	0.59 (0.44, 0.81)	0.74 (0.54, 1.02)	0.76 (0.55, 1.07)

Note. OR = odds ratio; CI = confidence interval; HRT = hormone replacement therapy; SEP = socioeconomic position.
[a]Number for whom complete data were available on all SEP indicators and all covariates included in the final model.
[b]Childhood SEP indicators are adjusted for adult SEP indicators (social class, housing tenure, car access, pension arrangements); adult SEP indicators are adjusted for childhood SEP indicators (social class, bathroom in house, hot water in house, bedroom sharing, car access, and age at leaving full-time education).
[c]Other adult risk factors: systolic blood pressure, high-density lipoprotein cholesterol, triglyceride levels, diabetes, body mass index, waist-to-hip ratio, age at menopause, hysterectomy/oophorectomy, physical activity, and smoking.

TABLE 3—Association of Cumulative Life-Course SEP Score with Ever With Current Use of Hormone Replacement Therapy: British Women's and Heart and Health Study (n = 3496), 1999–2001

Cumulative Life-Course SEP Score (No. of Adverse Indicators)	No.	OR (95% CI) of Ever Use HRT Compared With Never Use		OR (95% CI) of Current Use HRT Compared With Never Use	
		Crude Association	Fully Adjusted Association[a]	Crude Association	Fully Adjusted Association[a]
0-1	425	1.00	1.00	1.00	1.00
2	393	0.91 (0.66, 1.26)	0.93 (0.66, 1.31)	0.97 (0.63, 1.50)	0.94 (0.59, 1.49)
3	500	0.88 (0.65, 1.19)	0.91 (0.66, 1.27)	0.81 (0.54, 1.24)	0.78 (0.49, 1.22)
4	517	0.76 (0.56, 1.03)	0.73 (0.52, 1.02)	0.66 (0.43, 1.02)	0.59 (0.37, 0.95)
5	455	0.69 (0.50, 0.96)	0.72 (0.51, 1.02)	0.56 (0.35, 0.89)	0.54 (0.33, 0.90)
6	457	0.54 (0.39, 0.76)	0.52 (0.34, 0.75)	0.46 (0.28, 0.76)	0.48 (0.29, 0.82)
7	353	0.45 (0.30, 0.67)	0.41 (0.26, 0.65)	0.53 (0.30, 0.94)	0.56 (0.30, 1.03)
8	226	0.26 (0.15, 0.47)	0.23 (0.12, 0.44)	0.34 (0.15, 0.77)	0.25 (0.10, 0.65)
9-10	170	0.23 (0.11, 0.49)	0.25 (0.12, 0.55)	0.23 (0.07, 0.75)	0.27 (0.08, 0.92)
P linear trend		<.001	<.001	<.001	<.001
P nonlinearity		.49	.39	.97	0.93

Note. OR = odds ratio; CI = confidence interval; HRT = hormone replacement therapy; SEP = socioeconomic position.
[a]Fully adjusted association: systolic blood pressure, high-density lipoprotein cholesterol, triglyceride levels, type 1 diabetes, body mass index, waist-to-hip ratio, age at menopause, hysterectomy/oophorectomy, physical activity, and smoking.

confounding in the observational studies is a persuasive explanation for the difference. Our belief is that observational studies did not adequately adjust for SEP from across the life course. This belief is supported by the findings in this study in the following ways. First, the fact that childhood SEP is associated with HRT use, independent of adult SEP, behavioral risk factors, and physiological risk factors, suggests that adjusting for these proximal risk factors will not take fully into account the effect of early life SEP on HRT use. Second, we have shown a cumulative effect of SEP from across the life course, indicating that not only does life-course SEP need to be accounted for but that a single measure of SEP also is unlikely to be adequate. Finally, although these cross-sectional data are not ideal for assessing HRT–CHD associations, our analysis of this association also supports our hypothesis. The crude associations were consistent with previous observational studies.[4] When we adjusted for 4 indicators of adult SEP and all adult risk factors, the association attenuated but still suggested some protective effect; this adjusted result was consistent with adjusted results in previous observational studies.[4] When we adjusted for SEP across the life course, together with adult risk factors, HRT use was associated with a slightly increased risk of CHD, consistent with evidence from randomized controlled trials.[1]

Our response rate (60%) is moderate but consistent with other baseline data collected in large epidemiological surveys.[24] Respon-

TABLE 4—Association of Ever and Current Use of Hormone Replacement Therapy with Coronary Heart Disease, Adjustment for Life-Course SEP, and Other Adult Risk Factors and Adjustment Just for Adult Indicators of SEP and Other Adult Risk Factors: British Women's and Heart and Health Study (n = 3496), 1999–2001

	OR (95% CI) of CHD		
	Crude	Adjusted for Life-Course Cumulative SEP Score and Adult Behavioral and Physiological Risk Factors[a]	Adjusted for Adult Indicators of SEP and Adult Behavioral and Physiological Risk Factors[b]
Ever vs never use of HRT	0.66 (0.53, 0.83)	1.09 (0.81, 1.45)	0.87 (0.67, 1.13)
Current vs past or never use of HRT	0.74 (0.54, 1.02)	1.15 (0.78, 1.70)	0.84 (0.59, 1.15)

Note. OR = odds ratio; CI = confidence interval; HRT = hormone replacement therapy; SEP = socioeconomic position; CHD = coronary heart disease.
[a]Adjusted for life-course cumulative SEP score, systolic blood pressure, high-density lipoprotein cholesterol, triglyceride levels, type 1 diabetes, body mass index, waist-to-hip ratio, age at menopause, hysterectomy/oophorectomy, physical activity, smoking, and low-fat diet.
[b]Adjusted for adult social class, car access as an adult, housing tenure as an adult, pension arrangements, systolic blood pressure, high-density lipoprotein cholesterol, triglyceride levels, type 1 diabetes, body mass index, waist-to-hip ratio, age at menopause, hysterectomy/oophorectomy, physical activity, and smoking.

ders were younger and less likely to have had a stroke than nonresponders, although CHD prevalence was similar among responders and nonresponders.[19] The social class distribution of the British Women's Heart and Health Study is similar to that found for the 1991 census for England and Wales (57% manual social class in British Women's Heart and Health Study vs 55% of women aged 65 and older in the 1991 census), which provides some evidence to suggest that our sample is not affected by selection bias based on SEP.

Our study is cross-sectional and so may be affected by reverse causality and survivor bias. In the association of early life SEP with HRT use, reverse causality is not an issue, and for adult SEP it is difficult to imagine HRT use having an effect on socioeconomic circumstances. Our results for the association between HRT and CHD are consistent with those from prospective cohort studies.[4] Survivor bias would be important for the association between childhood SEP and HRT use if the association between these 2 among women who died prematurely was either null or in the opposite direction to that presented here (i.e., women from poor SEP were more likely to use HRT). Although this cannot be ruled out, it seems unlikely.

We have no information on how women who were prescribed HRT were screened by their physicians, and it is likely that confounding by indication also will have biased previous observational studies.[11] That is, doctors may have been less likely to prescribe HRT to women who were at greater risk of CHD because of obesity, high blood pressure, or other CHD risk factors. To some extent, this may be controlled for by adjustment for these adult risk factors, but adjustment for life-course SEP may capture this effect to a greater extent by reflecting these exposures over the life course. However, our study is not suitable for fully examining the importance of confounding by indication in the HRT–CHD associations.

Our study cohort consisted of women who were born in Great Britain between 1919 and 1940, and the results may not be generalizable to women from other countries and those from different birth cohorts. For example, a study of women born in 1946 in Great Britain found no association between childhood SEP and HRT use.[25] Because observational studies of the protective effect of HRT were largely conducted on cohorts born before the 1940s,[4] our results have relevance for the current debate about the disparities between observational and trial results but do not necessarily mean that for all populations childhood SEP will be associated with HRT use.

Data on HRT use were confirmed by review of medication among current users and by self-report for past users, which may have led to some misclassification for the ever use category. Over two fifths (43%) of women who stated that they had ever used HRT were unable to name the preparation, and 4% who named their preparation were using a related but nonhormonal preparation such as raloxifene. However, the results of this study were consistent for current use of HRT (where actual preparations were checked at the interview) and ever use (where some misclassification is likely). Furthermore, most other observational studies have relied on self-report of HRT use only and are likely to have included some women who were using nonhormonal preparations, as in this study. Finally, our results for the association between HRT use and CHD are consistent with previous prospective studies that have used either self-report or medical record data.[4]

We have not assessed all factors that may affect HRT use and CHD risk and may thus have confounded the associations presented in earlier observational studies. For example, ethnicity may determine HRT use and is associated with CHD risk. Over 99% of women in this study were White; we were therefore unable to determine the effect of ethnicity on HRT use in this study.

Childhood SEP may affect future use of HRT by means of a number of mechanisms, including the individual's attitudes toward health, preventive treatment, and natural physiological processes such as menopause and aging, gained from their parent's attitudes toward these; the ability to access health care; and discrimination based on patient characteristics. Although the actual mechanisms are not discernible from our data, it is plausible that adult attitudes toward the use of HRT and access to HRT are formed by SEP in earlier life.

The importance of our results is in the contribution that they make to the debate concerning disparities in observational and trial evidence. We believe that these results support the trial evidence of no protective effect. Our results also have general implications for observational epidemiological studies. Future observational studies, in this and other areas, should aim to collect (even retrospectively) in-

formation on socioeconomic circumstances from across the life course to be able to adjust as fully as possible for potential confounding factors. Sensitivity analyses to assess the possibility of residual confounding should also become routine practice in observational epidemiology.[26,27] In addition, specificity of association should be considered.[26,28] As long ago as 1986, Diana Petitti pointed out in observational studies that HRT was apparently equally protective against accidental and violent deaths as it was against death resulting from cardiovascular disease.[29] She pointed out that given the lack of any biologically plausible link between HRT and these external causes of death, both associations should be considered to be attributable to residual confounding.[29] We have discussed approaches to strengthening inferences from observational studies in detail elsewhere.[30,31] ■

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Contributors

All authors developed the study aim. S. Ebrahim and D.A. Lawlor managed data collection, storage, and cleaning for the British Women's Heart and Health Study. D.A. Lawlor undertook the analysis and coordinated writing of the article. All authors contributed to writing the article. D.A. Lawlor acted as guarantor.

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Human Participant Protection

The British Women's Heart and Health Study has ethics approval from UK local ethics committees in each town in which the study participants reside.

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