Study occurred among women who both started hormone therapy and experienced a myocardial infarction during the same 2-year interval, and that the overall hazard ratio estimate increased only from 0.71 to 0.76 if these events were classified as occurring among women on hormone therapy, using the WHI hazard ratio estimate for the first 2 years of hormone therapy use. This is a useful piece of information, but it does not fully address the issue of potential bias in the Nurses' Health Study from their reporting methods.

Women who started hormone therapy and subsequently stopped use prior to their biennial snapshot of hormone therapy are presumably regarded as nonusers throughout the follow-up period in the Nurses' Health Study analyses. In community studies, as many as 60 percent of women who initiate hormone therapy discontinue their use within 2 years, with about 20 percent discontinuation within the first 6 months of use. If discontinuation rates of this magnitude apply also to the Nurses' Health Study, where estrogen plus progestin use was quite common, then the coronary heart disease rates in the estrogen plus progestin user group could be underestimated and coronary heart disease rates in the nonuser group could be overestimated by this additional source of misclassification. Our own simulation studies, described more fully elsewhere (6), contaminated the randomization assignment in the WHI estrogen plus progestin trial by the type of misclassification rates just mentioned, and we found that trial evidence for an early elevation in coronary heart disease risk disappeared or was substantially reduced by such misclassification, with much of the downward bias derived from data on short-term hormone therapy users who were permanently misclassified as nonusers. It would be helpful if Dr. Willett and colleagues could explore this additional source of potential bias in the Nurses' Health Study context.

Dr. Willett and colleagues go on to offer the perspectives that ''age at initiation and duration of hormone therapy use are sufficient to explain the ostensibly discordant findings for hormone therapy use and coronary heart disease between the WHI trial and observational studies'' (1, p. 1067) and even that the ''WHI findings, taking into account the age at initiation and duration of hormone therapy use, support the validity of findings from observational studies relating hormone therapy use to reduced coronary heart disease risk'' (1, p. 1067). We agree that the time from hormone therapy initiation may be an important element underlying this apparent discrepancy; in fact, this was the main point of our paper (2). However, we do not think that WHI data should be used to support an argument of coronary heart disease risk reduction with estrogen plus progestin, even among younger women. As shown in the WHI paper by Manson et al. (5), over an average 5.6-year intervention period, there was no evidence for interaction of the coronary heart disease hazard ratio with age at hormone therapy initiation ($p = 0.36$). The hazard ratio estimate was 1.27 for the estrogen-plus-progestin versus placebo group among women 50–59 years of age at randomization, very similar to the estimate of 1.24 for the overall estrogen-plus-progestin trial cohort.

Recent analyses (7) provide corresponding analyses to those given in our article (2) for estrogen alone using data

FIVE AUTHORS REPLY

We thank Willett et al. (1) for responding to our article (2) on a potential bias in Nurses' Health Study findings on combined estrogen plus progestin postmenopausal hormone therapy and coronary heart disease. We suggested that the use of only a biennial snapshot of current hormone therapy use could have led to a downward bias in hazard ratio estimates from the Nurses' Health Study (3), in view of the elevation in coronary heart disease risk in the first few years following hormone therapy initiation observed in the Women's Health Initiative (WHI) estrogen plus progestin trial (4, 5). Dr. Willett and colleagues responded that only 17 of 1,342 coronary heart disease cases in the Nurses' Health

from both the WHI clinical trial and the cohort study. Once again, the WHI clinical trial has too few women in the group aged 50–59 years at enrollment for a definitive analysis, but the available data are somewhat suggestive of an interaction of the estrogen-alone coronary heart disease hazard ratio with age at initiation ($p = 0.07$), with possibly more favorable results among younger women (8, 9). Note, however, that the enrollees aged 50–59 years in the WHI estrogen-plus-progestin trial, and especially in the estrogen-alone trial, differ from older enrollees in many factors including ethnicity, obesity, and age at hysterectomy (10), so that issues of effect modification may contribute to this nonsignificant interaction. Additionally, it should be remembered that hazard ratio estimates for both estrogen plus progestin and estrogen alone were substantially increased by control for standard coronary risk factors in both the WHI observational study (2, 7) and the Nurses' Health Study (11). Our comparisons of WHI clinical trial and observational study results suggest some residual confounding for each of coronary heart disease, stroke, and venous thromboembolism. Hence, allowances should be made for residual confounding in the interpretation of observational study results of these associations. Confounding may be a particular issue among younger women, where coronary heart disease rates are relatively low and risk factors less well documented.

WHI investigators welcome additional data and discussion of the health benefits and risks of these important preparations, and we again thank Dr. Willett and colleagues for their thoughtful input.

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Conflict of interest: Dr. Barbara V. Howard is a consultant for Merck, the Egg Nutrition Council, and General Mills. She lectures for Schering-Plough and has received support in the form of drug donations from Pfizer, Merck, and Schering-Plough.

REFERENCES

1. Willett WC, Manson JE, Grodstein F, et al. Re: "Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial." (Letter). Am J Epidemiol 2006;163:1067–8.
2. Prentice RL, Langer R, Stefanick ML, et al. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol 2005;162:404–14.
3. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary presentation of cardiovascular disease. Ann Intern Med 2000;133:933–41.
4. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
5. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523–34.
6. Prentice RL, Pettinger M, Anderson GL. Statistical issues arising in the Women's Health Initiative. Biometrics 2005; 61:899–911; discussion 911–41.
7. Prentice RL, Langer RD, Stefanick ML, et al. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. Am J Epidemiol 2006;163:589–99.
8. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–12.
9. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease. The Women's Health Initiative. Arch Intern Med 2006;166:357–65.
10. Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol 2003;13(suppl):S78–86.
11. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health 2006;15: 35–44.

Ross L. Prentice[1], Marcia L. Stefanick[2], Barbara V. Howard[3], David Barad[4], and Lewis Kuller[5] (e-mail: rprentic@fhcrc.org)
[1] *Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA*
[2] *Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA*
[3] *Medstar Research Institute, Hyattsville, MD*
[4] *Department of Obstetrics and Gynecology, Albert Einstein School of Medicine, Bronx, NY*
[5] *Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA*

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