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Environmental Tobacco Smoke and Coronary Heart Disease in the American Cancer Society CPS-II Cohort

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Abstract

Background Thirteen of 14 epidemiological studies have shown an increased risk of ≈20% for coronary heart disease (CHD) for never-smokers exposed to environmental tobacco smoke (ETS), but this association remains controversial. If true, ETS might account for an estimated 35 000 to 40 000 heart disease deaths per year in the United States.

Methods and Results We have conducted the largest study to date, a prospective study of 353 180 female and 126 500 male never-smokers enrolled in 1982 in the American Cancer Society's Cancer Prevention Study II and followed through 1989. Analyses focused on subcohorts of 309 599 married pairs and of 135 237 subjects concordant for self-reported exposure and exposure reported by each one's spouse. More than 2800 CHD deaths (ICD 410-414) occurred among married pairs; 10% of married men and 28% of married women were married to currently smoking spouses, while 10% and 32%, respectively, were married to former smokers. After controlling for many cardiovascular risk factors, we found 22% higher CHD mortality (rate ratio, 1.22; 95% CI, 1.07 to 1.40) among never-smoking men married to currently smoking wives compared with those married to wives who had never smoked. The corresponding rate ratio for women was 1.10 (0.96 to 1.27). Never-smokers living with former smokers showed no increased risk. When analyses were restricted to subjects whose ETS exposure was classified via both their own self-report and a spouse's report, the rate ratio was 1.23 (1.03 to 1.47) for currently exposed men and 1.19 (0.97 to 1.45) for women.

Conclusions Results are consistent with prior reports that never-smokers currently exposed to ETS have about 20% higher CHD death rates. However, our data do not show consistent dose-response trends and are possibly subject to confounding by unmeasured risk factors.

smoking coronary disease mortality

In 1992, the American Heart Association[1] reviewed the published literature and determined that “the risk of death due to heart disease is increased by about 30% among those exposed to environmental tobacco smoke (ETS) at home and could be much higher in those exposed at the workplace, where higher levels of ETS may be present. Even though considerable uncertainty is a part of any analysis on the health effects of ETS because of the difficulty of conducting long-term studies and selecting sample populations, an estimated 35 000 to 40 000 cardiovascular disease–related deaths and 3000 to 5000 lung cancer deaths due to ETS exposure have been predicted to occur each year.”

There are presently 14 published epidemiological studies (7 cohort, 7 case-control) of heart disease among never-smokers exposed to ETS.[2 3 4 5 6 7 8 9 10 11 12 13 14 15] Almost all these studies showed an increased risk of heart disease for the exposed group (usually defined as currently exposed) compared with the nonexposed group. A number of studies controlled for the principal heart disease risk factors, and several showed a positive dose-response trend according to the level of presumed ETS exposure. All the studies were based primarily on analyses of spousal smoking, ie, never-smokers exposed to ETS from a smoking spouse compared with never-smokers not so exposed; a few also had data on ETS exposure at work or elsewhere. Wells[16] reviewed 12 of these studies in 1994 and conducted a meta-analysis in which he found an overall relative risk of 1.23 (95% CI, 1.12 to 1.35) for heart disease mortality (1.23 for women and 1.25 for men) for ETS exposure from a spouse among never-smokers.

Various experimental and clinical studies also support an ETS–heart disease association and suggest possible mechanisms similar to those for active smoking and coronary heart disease (CHD). Glantz and Parmley[17] reviewed these data, which suggest that ETS causes greater platelet aggregation, increased risk of thrombosis, lower oxygen supply, and greater oxygen demand. A rat model of ischemia and reperfusion suggests that ETS increases myocardial infarct size.[18] Many of these effects are believed to be due to nicotine and carbon monoxide in ETS, but other unidentified agents may also play a role. Analogous to the evidence for mainstream smoking (for which risk drops ≈50% within 1 year of quitting[19]), much of the experimental data that suggest an ETS–heart disease association also support an acute effect of ETS on the heart. In addition, there are also plausible mechanisms of chronic effects, ie, accelerated plaque formation due to endothelial cell damage by ETS, or reduced levels of HDL due to ETS exposure.[20 21] Nonsmoking adolescents exposed to ETS measured by urinary cotinine had significantly lower HDL and lower HDL/LDL ratios than nonsmokers without such exposure.[22] Both cross-sectional and longitudinal observational studies have shown that carotid artery intimal-medial thickness is significantly increased in ETS-exposed subjects, although not as much as in active smokers.[23 24] Taken together, these studies suggest a biologically plausible role for ETS in causing heart disease.

Despite the epidemiological and mechanistic evidence accumulated to date, the ETS–heart disease association is not as well supported as the ETS–lung cancer association. There are fewer epidemiological studies, there are more potential confounders that must be controlled in studies of heart disease, and the increase in heart disease risk due to active smoking is smaller than is the increase in lung cancer risk due to active smoking.

To study a possible ETS–heart disease association further, we analyzed a cohort of 353 180 never-smoking women and 126 500 never-smoking men enrolled in the American Cancer Society's Cancer Prevention Study II (CPS-II). This cohort has provided a wealth of data about active smoking.[25] [26] The number of heart disease deaths analyzed here is as large as the number of deaths in all prior studies of ETS and heart disease mortality combined.

Methods

The American Cancer Society CPS-II cohort consists of 1 185 102 men and women enlisted by American Cancer Society volunteers in 1982.[27] Participants 30 years of age and older were enrolled nationwide. The median age at the time of enrollment was 56 years. Vital status was determined by volunteers or by the National Death Index. By December 1989, 101 519 (8.6%) had died, 1 080 689 (91.2%) were alive, and the remainder had unknown vital status. Death certificates were obtained for 96.8% of decedents and coded by a nosologist to the 9th revision of the International Classification of Disease.

At the time of enrollment, participants completed a four-page questionnaire on their race, medication use, marital status, smoking history, diet, coffee consumption, alcohol intake, physical activity, occupation, height, shift work, weight, history of illnesses, menopausal status, estrogen use, oral contraceptive use, education, exercise, exposure to ETS, and other variables. Indexes of fat and vegetable consumption were derived from the questions on diet.

We excluded all participants who reported having smoked, had unclassifiable smoking data, or lacked information on marital status. Analyses were based on the resulting cohort of 353 180 women and 126 500 men, with 4911 and 3251 deaths from ischemic heart disease, respectively.

We constructed preliminary models using variables identified a priori as potentially related to heart disease. All predictors of heart disease (P<.10) in men or women were included in a final model for both sexes with the use of Cox regression with the full data set. Predictors included in the final model were age, self-reported history of heart disease or taking of heart disease medication, self-reported history of hypertension or hypertension medication, self-reported history of diabetes, self-reported history of arthritis, body mass index (BMI), educational level, aspirin use, diuretic use, alcohol consumption, employment status (currently employed outside the home or not), and exercise. Those with a history of heart disease at baseline (5% to 10%) were kept in the analysis because we thought it possible that the effects of ETS could be apparent particularly in this compromised subset; analyses of the data with and without heart disease at baseline were conducted. All covariates other than exposure were considered as dichotomous (yes or no, any or none) except for the continuous variables of age and BMI and categorical variables for education (less than high school, high school, some college/vocational school, college, postgraduate) and exercise (none, slight, moderate, heavy). Medication use referred to use in the last month.

For covariates (other than exposure) with low levels of missing data (<5%), subjects with missing values were assigned to the most common category for categorical variables (eg, education, with 1% missing). When missing data were more common (eg, estrogen use, 11%), we modeled the missing data as a separate category; if they were no different from the referent group (eg, nonusers), they were assigned to the referents. Missing data for alcohol and medication were assigned “none” if both amount and duration were missing. Missing values of BMI (2% of subjects) were assigned on the basis of average values in the

cohort for a specific age and sex. Subjects with missing data for ETS exposure variables were excluded from the analysis. The principal variables affected by nonresponse were the questions on medication, in which subjects were asked whether they had taken medication in the last month and asked to fill in a “0” if they had not. About 40% of subjects left the questions on diuretics, heart disease medication, and medication for hypertension blank, and about 14% did so for the question on aspirin. The percentage of missing data for these questions did not differ appreciably in the overall cohort between exposed and nonexposed. For heart disease and hypertension, there were separate questions about physician-diagnosed heart disease or hypertension (separate from the questions on medication), and these questions probably captured the necessary information for these potential confounders.

Passive smoking questions included the number of hours per day exposed to ETS at home, at work, or in other areas. Active smoking questions included a question about tobacco smoking at least daily for 1 year's time (cigarettes only for women, pipes/cigars as well for men). Never-smokers were defined as those answering no to this question. For current smokers of any type of tobacco the amount smoked per day, the age they began smoking, and the total years of smoking were asked for each type of tobacco. For former smokers, additional questions were asked about the age of quitting. The principal exposure variables for the analyses of never-smokers were exposure to ETS on the basis of a spousal report of active smoking (“spousal exposure”) and self-reported current exposure to ETS from cigarettes (at home, work, or other settings).

Spousal exposure was calculated only for those married individuals with spouses also in CPS-II, with valid dates of marriage and with sufficient data on smoking cessation to indicate whether they had smoked during marriage. These restrictions led to “spousal ETS” cohorts of 101 227 for men and 208 372 for women. Analyses considered current and former (versus never) exposure to spousal ETS (any type of tobacco) in the current marriage. Additional analyses were conducted by amount currently smoked by the spouse; for men three categories were used (<20, 20, 21+ cigarettes per day), whereas for women a higher prevalence of exposure and the larger amount smoked by husbands permitted the use of four categories (<20, 20, 21 to 39, 40+ cigarettes per day).

Further analyses for exposure to spousal ETS were made after restrictions of the spousal cohorts to subcohorts of those married only once to spouses who had complete data on duration and amount of cigarette smoking, enabling an analysis of pack-years. For the women, these more detailed analyses were restricted to exposure to ETS from cigarettes and excluded those who also were exposed to pipes or cigars. These analyses were conducted on cohorts numbering 58 530 for men and 99 621 for women.

For self-reported exposure, many subjects were missing data for at least one of the three categories of ETS exposure (home, work, other settings). It is likely that many of these had no exposure. Nevertheless, these were deleted from analyses for that category. Among all never-smoking men, 37.8%, 28.2%, and 42.4% lacked data for self-reported current hours of exposure to ETS at home, work, or other settings, respectively. For women, the corresponding numbers were 44.4%, 48.4%, and 58.5%. In addition, a smaller percentage of subjects had unquantifiable responses such as “little,” “lots,” or they responded with a checkmark. Those with unquantifiable data were considered exposed without quantifiable hours of exposure. Separate analyses were run for self-reported current exposure at home, at work, and in other

settings because the number of those lacking data for these three variables differed. For the analysis of exposure at work, we eliminated those who were not currently employed at baseline. Referent groups for these analyses were those who reported zero hours of exposure at home, work, or other settings.

Finally, we conducted additional analyses for those who indicated current exposure at home and were married to a currently smoking spouse (exposed) compared with those who indicated no current exposure at home and were married to a never-smoking spouse (nonexposed). The motivation for these analyses was that these subjects, who were concordant for two separate measures of ETS exposure at home, would involve the least misclassification of exposure and nonexposure. For example, it is possible that husbands reporting current smoking did not actually smoke at home, or in the presence of their spouses; classifying the wife as exposed on the basis of the husband's smoking status would incorrectly assign her exposure and bias the analysis for spousal ETS toward the null.

Final analyses were conducted via Cox regression, separately for men and women, and stratified by race.[28] The time variable used in the Cox regressions was follow-up time. Proportional hazard assumptions of a constant exposure effect over time were tested by testing the significance of interaction terms between follow-up time and exposure.

Analyses were directed toward determining whether any ETS exposure increased risk of heart disease. If ETS did increase risk, we hypothesized that those currently exposed to ETS would have higher rate ratios than those formerly exposed and that younger subjects would have higher rate ratios than older subjects on the basis of known relations between smoking and heart disease.[19] [29]

Results

Table 1⇓ provides descriptive data on the study subjects used in the spousal cohorts. Generally, the exposed and nonexposed subjects were similar with respect to potentially confounding variables. Women currently or formerly exposed to smoking husbands had a somewhat lower educational level than nonexposed women and were more likely to work outside the home. Men currently exposed to smoking wives had about the same educational level as nonexposed men, but men whose wives were former smokers were better educated and more likely to have white collar jobs. Regarding exposure prevalence, the proportion of never-smoking women exposed to a current smoking (28%) or former smoking (32%) husband was much higher than the proportion of never-smoking men exposed to a current smoking (10%) or former smoking (10%) wife. Furthermore, never-smoking women were exposed to more spousal ETS than never-smoking men, as judged by years of spousal smoking and number of packs per day smoked.

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Table 1.

Descriptive Variables for Never-Smokers in Spousal Cohorts

Tables 2 through 4⇓⇓⇓ provide the results of analyses of CHD mortality by spousal (Tables 2⇓ and 3⇓) and self-reported (Table 4⇓) ETS exposure. Table 2⇓ indicates that both men and women exposed to cigarette smoke from currently smoking spouses had small increases in risk of death from heart disease compared with those not so exposed (relative risks, 1.22 and 1.10, respectively). Confidence intervals for the observed relative risks excluded the null value of 1.00 for men and were borderline for women. Excess risks were similar but slightly higher for analyses restricted to subjects with heart disease at baseline or to subjects <65 years of age. When analyzed by amount of current smoking exposure, categorical analysis did not show increasing trends in risk with increasing amount smoked by the spouse for either men or women. Exposure to former smokers did not entail any excess risk for either men or women.

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Table 2.

Results for Spousal Cohorts

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Table 3.

Results for Spousal Subcohorts With Single Marriage and Data on Amount and Duration of Exposure to Smoking During Marriage

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Table 4.

Results for Self-Reported Exposure to Environmental Tobacco Smoke From Cigarettes

Table 3⇑ gives the results for the subcohort of married men and women who were married only once and whose spouses had adequate data to determine duration of smoking and amount currently smoked. For men with wives who had smoked during the marriage, there was a positive trend of increased risk with increased years of exposure. However, rate ratios decreased with increasing pack-years of exposure. Women with husbands who smoked showed positive trends for both duration of exposure and pack-years of exposure. For both men and women, risks were somewhat higher in those <65 years of age at baseline.

Table 4⇑ provides results for self-reported exposure to ETS. Both men and women showed slightly increased risks for home exposure (rate ratios, 1.15 and 1.07, respectively). These findings parallel the findings for spousal exposure. These risks for home exposure were increased in subjects <65 years of age at baseline (1.34 for men, 1.18 for women). Self-reported exposure at work or in other settings did not show significant consistent increases in risk. Separation of subjects by blue collar versus white collar jobs

revealed that male blue collar workers (n=16 568; 199 deaths) had a risk ratio of 1.36 (1.01 to 1.83) for self-reported ETS exposure at work, whereas male white collar workers (n=45 267; 456 deaths) had no excess risk (risk ratio, 0.95). For women, neither blue collar (n=12 667; 47 deaths) nor white collar employees (n=81 844, 213 deaths) showed much increased risk with ETS exposure at work (risk ratios, 1.02 and 1.11, respectively).

Table 5⇓ presents the analysis for subjects concordant between self-report and spousal report for exposure or for nonexposure to current cigarette smoke at home. These data probably involve the least amount of misclassification of any of the analyses presented. Men show a 23% excess risk and women a 19% excess risk for heart disease death for the currently exposed versus the nonexposed. For women, there are some indications of increased risk for those with increased hours of exposure on the basis of self-report or with the highest reported amount smoked by the spouse, but trends were not consistent. Inverse trends by intensity were observed for men. For men, the overall rate ratio of 1.23 increased to 1.42 for those <65 years of age at baseline, whereas for women there was only a slight corresponding increase. The effect of ETS exposure was concentrated among those without heart disease at baseline.

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Table 5.

Analyses for Subjects Concordant for Both Self-Reported Current Exposure to Cigarettes and Exposure to Cigarettes Based on Spouse Report

Discussion

Our study had several important strengths. The prospective design, which assessed exposure defined at baseline, avoids possible reporting biases that can occur in retrospective studies. Our analyses were based on a number of heart disease deaths as large or larger than all other prior studies combined, increasing our precision in estimating an effect. Spousal smoking was reported by the spouses themselves, potentially leading to less misclassification of exposure. Another strength is that we had two sources of exposure data available (self-report and report by the spouse), although ≈40% of study subjects were missing self-reported data. The principal limitations of our study include a crude assessment of exposure at baseline only and inability to control for confounding by certain cardiovascular risk factors.

These data were also obtained and analyzed recently by LeVois and Layard (1995)[30] as part of a larger analysis of alleged publication bias in this field. These authors analyzed ETS exposure from a spouse, using a data set with ≈18 000 more women and 2000 more men than did we, possibly due to different definitions of “known” spousal smoking data. These authors reported finding no increased CHD risk for those exposed to ETS from a spouse, an interpretation with which we disagree. LeVois and Layard emphasized the results for “any” spousal exposure to ETS, which dilutes the effects among current smokers by including former smokers. They did not report “current” as a separate single category, although they did report results for current smokers by categories of amount smoked. They also did not

use any of the data on self-reported exposure to ETS or consider data in which self-reported current exposure to ETS at home was concordant with spousal reports of current smoking. These last data (see Table 5⇑) are those that we believe are likely to be the least misclassified and therefore the most accurate.

Overall, our results are consistent with previous literature in finding a small increase in risk (≈20%) for never-smokers exposed to ETS at home. Our findings are reasonably consistent whether exposure was determined by smoking habits reported by the spouse or via self-reported exposure or when both sources of exposure definition were used together. This last analysis was the least likely to suffer from misclassification of exposure, which could bias results toward the null, obscuring a small excess in heart disease risk.

Our findings were slightly stronger for persons <65 years of age at baseline, among whom the background risk of fatal CHD due to causes other than smoking is low.[29] Approximately 5% to 10% of our cohort reported heart disease at baseline. For most analyses, there were no marked differences in findings for those with or without heart disease at baseline. However, for men in the concordant pair analysis, the effect was largely limited to those free of heart disease at baseline.

Our findings could be consistent with either an acute or chronic effect of ETS on the heart. The excess risk was largely confined to persons whose ETS exposure was ongoing at the time of the baseline interview and was not apparent in those formerly exposed to ETS. This suggests that the risk due to ETS exposure, if causal, may predominantly reflect short-term effects. It may be that the effect of ETS on the heart is similar to that of mainstream smoking and largely disappears within 5 years.[19] However, in our analyses of a subcohort with good quantitative data on spousal smoking in the past (Table 3⇑), we did find significant increasing trends in risk with increasing duration of exposure to spousal smoking for men and women and with increasing pack-years of exposure for women. These trends might indicate a chronic effect. We did some additional analyses restricting follow-up to the first 3 years after baseline, under the assumption that some percentage of the exposed would become nonexposed because their spouse might give up smoking, and if there were a predominantly acute effect, it might be more apparent during the beginning of follow-up. However, the association between ETS and heart disease death was not stronger during the first 3 years of follow-up.

Both misclassification and confounding could have biased our findings. Several types of misclassification are of concern. First, it is possible that some of our self-reported never-smokers were actually current smokers; if these were more likely to report ETS exposure and also to have higher heart disease rates, such “smoking-status” misclassification would bias our results upward. However, this type of misclassification is of much less concern for heart disease than for diseases more strongly linked to mainstream smoking, such as lung cancer. Furthermore, recent data from a large random sample of US adults indicates that only ≈1.3% of self-reported nonsmokers had levels of serum cotinine high enough to suggest they were in fact current smokers.[31] This low level of misclassification is unlikely to have any effect on estimated rate ratios in our study. A second type of misclassification is misclassification of exposed/nonexposed status among our never-smokers. If such misclassification were the same for those who went on to develop disease and those who did not (nondifferential), as is likely, it would tend to bias our results downward. Regarding our principal exposure variable, exposed or not exposed at home, there was likely to be only a low level of exposure misclassification in the analysis in which exposure status was

concordant from two sources (self-report and spousal report). However, it is likely that some of our "exposed" subjects in fact had less actual exposure to ETS than some of our "nonexposed" subjects, given our lack of data on actual intensity of exposure and the known overlap of cotinine distributions between nonsmoking populations reporting current ETS exposure and those reporting no current ETS exposure.[32] Furthermore, our data on exposure status were obtained only at one point in time. Hence, some downward bias in our findings may exist because of this type of misclassification. Finally, misclassification of level or intensity of ETS exposure, which affects dose-response analysis, is likely to be relatively high because our measures of intensity were again based on reports at one point in time and relied on self-reported hours per day or on amount of cigarette smoking reported by the spouse; both these measures are surrogates for actual intensity levels and have been shown to be only weakly correlated with cotinine measurement (correlations on the order of 0.2 to 0.3).[32] [33] Assuming this misclassification of intensity to be nondifferential, it is likely to have produced a bias against observing positive dose-response trends.

Upward bias from positive confounding also could affect our results, given the many known risk factors for heart disease and the relatively small effect we observed. The literature on ETS and cardiovascular risk factors suggests that among never-smokers, the ETS-exposed may be less educated, eat less healthful diets, and drink more alcohol than nonexposed smokers, although there are few large studies and findings are not consistent.[34] [35] The potential for confounding in our study was reduced by controlling for a large number of variables including age, education, self-reported hypertension and diabetes, medication for hypertension, alcohol, diet, physical activity, and BMI. CPS-II has a relatively homogeneous population, which diminishes the potential for major differences between the exposed and nonexposed groups. To evaluate potential residual confounding by measured risk factors, we conducted additional analyses with only age in the model for the concordant subcohort in Table 5⇑. The rate ratio for exposed women was 1.31 and for exposed men was 1.25. Control over measured confounders decreased these rate ratios to 1.19 and 1.23, respectively, suggesting a low degree of confounding and therefore a low potential for residual confounding by measured risk factors. On the other hand, we had no data on cholesterol, lipid-lowering drugs, or measured blood pressure and could not control for these variables.

Confounding as the result of unmeasured or uncontrolled risk factors is also not likely to explain the small but measurable increase in CHD risk that is associated with ETS in many different studies of different design and in different countries, many of which also were able to control for the principal cardiovascular risk factors.

The lack of positive dose-response trends in many of our analyses neither supports nor convincingly refutes a causal association. There are several reasons why a consistent positive dose-response might not be observed. People who are more highly exposed and ill may selectively remove themselves from exposure. In analyses based on married pairs and spousal reports, it is possible that the heaviest smokers had died, so their surviving never-smoking spouse (potentially at higher risk) was not included in the study. As discussed above, potential misclassification of exposure limits our ability to examine dose-response trends. Although this study is large, the number of heart disease deaths in subgroups of the population is small, exacerbating the problem of misclassification. Finally, Glantz and Parmley[17] suggest that some of the effects of cigarette smoke on the heart may reach a saturation point, so a monotonic dose-response effect may not exist.

We did not generally find an increase in CHD risk associated with ETS exposure at work or in other settings. When we analyzed the data separately for blue collar and white collar workers, we found an excess risk for blue collar men for ETS exposure at work (rate ratio, 1.36; 1.01 to 1.83) but not for white collar men (rate ratio, 0.95; 0.79 to 1.16). For women there were few differences between blue collar and white collar workers. Self-reported exposure outside the home (eg, work or other settings) may involve greater misclassification than spousal or domestic exposure, given the wide variety of workplace and other social settings and the lack of information from the questionnaire regarding intensity or duration of exposure. If ETS exposure at home were a risk factor for heart disease, one would expect ETS exposure at work or other settings also to be a risk factor, although perhaps not measurable by our crude definitions of exposure. An objective measure of ETS exposure across all settings, incorporating intensity and duration of exposure, would be the ideal measure but is not available in our data or in other existing studies of ETS and heart disease.

Summary

Our findings point to a modestly elevated risk for heart disease due to ETS exposure among never-smokers. Our study is consistent with other studies, is controlled for a number of known cardiovascular risk factors, and parallels the data for active smoking in being somewhat stronger in younger individuals and in showing a predominantly acute effect. On the other hand, the observed relative risks are small and could be due to confounding by unmeasured risk factors; also, positive dose-response relationships among the exposed are generally not present. Other factors that make any interpretation difficult include problems in accurately measuring exposure and limited precision for estimates in subgroups in which the number of heart disease deaths is small. These problems are typical of observational studies of ETS and heart disease mortality. It is likely that future research that will reveal more information about this association will require carefully designed prospective clinical studies of intermediate end points (eg, platelet aggregation, carotid artery thickness) accompanied by repeated serial objective measurements of exposure, integrated across all sources of exposure. Such studies will also need to assess change in cardiovascular risk factors such as blood pressure and cholesterol.

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