Epidemiologic Studies of Fatal and Nonfatal Cardiovascular Disease and ETS Exposure from Spousal Smoking

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This article reviews the epidemiologic studies of the association of ischemic heart disease risk and environmental tobacco smoke (ETS) exposure from a spouse who smokes. Seventeen studies (nine cohort, eight case–control) comprising more than 485,000 lifelong nonsmokers and 7,345 coronary heart disease (CHD) events were included in a meta-analysis. Together, these studies include 36% more CHD events and 58% more study subjects than were available for review by the U.S. Occupational Safety and Health Administration (OSHA) in 1994. The relative risk (RR) for fatal or nonfatal coronary events among never smokers married to smokers, compared to those whose spouses did not smoke, was RR = 1.25 (95% confidence interval [95% CI], 1.17–1.33) across the combined studies. This association was statistically similar in men (RR = 1.24; 95% CI, 1.15–1.32) and women (RR = 1.23; 95% CI, 1.15–1.32); in studies of cohort (RR = 1.23; 95% CI, 1.15–1.31) and case–control (RR = 1.47; 95% CI, 1.19–1.81) design; in the United States (RR =1.22; 95% CI, 1.13–1.30) and other countries (RR = 1.41; 95% CI, 1.21–1.65); and in studies of fatal (RR = 1.22; 95% CI, 1.14–1.30) and nonfatal (RR = 1.32; 95% CI, 1.04–1.67) heart disease. In three studies that presented data separately for nonsmokers married to current or former smokers, the association was stronger when the spouses continued to smoke (RR = 1.16, 1.06–1.28) than with former smokers (RR = 0.98; 95% CI, 0.89–1.08). The aggregate data are unlikely to be attributable to chance, publication bias, confounding, or misclassification of exposure. The evidence linking heart disease and ETS exposure from a spouse has become substantially stronger since OSHA first proposed including heart disease in its risk assessment of ETS in 1994. *Key words*: environmental tobacco smoke, heart disease. — *Environ Health Perspect* 107(suppl 6):841–846 (1999). *http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/841-846thun/abstract.html*

This article considers the epidemiologic studies of ischemic heart disease risk and environmental tobacco smoke (ETS) exposure from a spouse who smokes. The individual studies are not discussed in detail. Several comprehensive reviews (*1,2*) have recently considered all the studies, published and unpublished, including the two largest prospective cohort studies published after 1994 (*3,4*) when the U.S. Occupational Safety and Health Administration (OSHA) first proposed regulations on ETS exposure in the workplace (*5*). In this article we summarize the available epidemiologic evidence, discuss its scope and limitations, and consider the extent to which the aggregate data support the hypothesis that ETS causes heart disease. We also address the extent to which epidemiologic studies of ETS from spousal smoking are relevant to workplace exposures.

The findings of epidemiologic studies on the association of ETS and coronary heart disease (CHD) (fatal and nonfatal) should not be interpreted in isolation without considering closely related issues addressed elsewhere in this workshop. Other contributors discuss cross-sectional and longitudinal studies of subclinical vascular disease, experimental studies of the acute effects of ETS in humans and animals, and various approaches to assess confounding and bias in the epidemiologic studies. All these issues are relevant to the interpretation of the epidemiologic data, as they provide support for biologic plausibility. For example, by measuring the acute effects of documented exposures to ETS on platelets, vascular endothelium, and cardiac exercise tolerance in humans, the experimental studies provide insights on the potential mechanisms and the shape of the dose–response curve.

Methods

We identified all potentially relevant epidemiologic studies from comprehensive reviews (*1,2*), reference lists of the individual studies, discussions with colleagues, and from a search through Medline (National Library of Medicine, Bethesda, MD) using the MeSH (medical subject headings) terms smoking, environmental tobacco smoke, and heart disease. To ensure completeness, we reviewed published and unpublished studies of nonfatal myocardial infarction (MI) and/or death from ischemic heart disease (IHD) among lifelong nonsmokers whose potential ETS exposure was defined by the smoking status of the spouses. Ultimately we included nine cohort (*3,4,6–13*) and eight case–control (*14–22*) studies in the overview. Two of the cohort studies (*3,4*) and three case–control studies (*20–22*) were new since OSHA last summarized the literature (*5*).

Five publications (*23–27*) were judged to be either duplicative or of uncertain validity and were excluded from the overview. The 1988 report by Helsing et al. (*23*) was dropped in place of the subsequent report in 1989 by Sandler et al. (*11*) on the same population in Washington County, Maryland. Similarly, the report of Gillis et al. (*24*) was replaced in 1989 by the report of Hole et al. (*12*). The cross-sectional study in Scotland in 1995 by Tunstall-Pedoe et al. (*25*) was excluded because of its cross-sectional design. The 1996 article by Steenland et al. (*3*) was used instead of the one by LeVois and Layard (*26*) because it more thoroughly analyzed the American Cancer Society cohort Cancer Prevention Study II (CPS-II). Also excluded was the LeVois and Layard analysis of Cancer Prevention Study I (CPS-I) (*26*) and the Layard case–control analysis of the National Mortality Followback Survey (NMFS) (*27*).

The LeVois and Layard analysis of CPS-I (*26*) was excluded for two reasons. First, neither it nor the accompanying analysis of CPS-II presented separate relative risk (RR) estimates for all nonsmokers married to spouses who currently smoke. By blurring the distinction between current and former ETS exposure, it may have obscured an association between risk of CHD and ETS exposure from a spouse who currently smokes, as occurred in the analysis of CPS-II in the same article (*26*). This concern is plausible because of the known decrease in cardiovascular risk that occurs among active smokers who quit (*28*). A second limitation of the LeVois and Layard analysis of CPS-I (*26*) is that the referent group does not and cannot exclude people exposed to ETS outside the home. In CPS-I, data were not collected with which to identify nonresidential exposure. Neglecting ETS exposure outside the home has greater potential to introduce bias in CPS-I than in CPS-II because smoking at work and in other public places was much more common during the years when CPS-I was conducted (1959–1972) than during the relevant years of CPS-II (1982–1989).

The Layard analysis of the NMFS (*27*) was also excluded because of concerns about validity. NMFS represents a population-based

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sample of all deaths among adults (≥ 25 years of age) in the United States in 1986. However, all information on smoking was obtained from next-of-kin; the comparison group included only deceased persons; and the analyses did not distinguish between spouses who continued to smoke and those who had smoked formerly. Because of these limitations, the results concerning ETS are not informative.

This article uses the term CHD rather than IHD or arteriosclerotic heart disease, although the end points in the individual studies include MI, angina pectoris, and sudden unexpected death in persons with no prior history of CHD. Specific end points are referred to in the text when given by the researchers.

The method used to compute and display the cumulative estimate of the RR and 95% confidence interval (CI) is described by Chappell and Gratt (*29*).

Description of the Epidemiologic Studies

A total of 17 epidemiologic studies (9 cohort, 8 case–control) were included in the overview, as shown in Tables 1 and 2, respectively. These studies were conducted in nine countries of Europe, North America, and Asia and collectively included more than 485,000 people (120,366 men, 364,920 women) and 7,345 CHD events. The studies ranged in size from 8 that included less than 100 CHD events to 2 studies with more than 1,000 events each. The populations generally represented adult, lifelong nonsmokers, 40 years of age and above.

In 16 studies (9 prospective, 7 case–control), there was a suggestion of increased CHD risk associated with ETS exposure from a spouse, the only exception being the 1986 study by Lee et al. (*14*). Figures 1 and 2 illustrate the RR estimates and 95% CI values in the individual cohort and case–control studies, respectively, or in some cases in designated subgroups. Especially in the case–control studies, the 95% CI values were wide and often included the null value of unity. However, as illustrated in Figures 3 and 4, the cumulative RR estimates, based on all of the studies available at the time, were significantly above the null for the cohort studies after 1987 and for the case–control studies after 1991. The RR estimate across all the studies combined was 1.25 (95% CI, 1.17–1.33). The lower bound of the 95% CI is above the null, indicating that the positive association between ETS and CHD is not likely to reflect chance alone.

The RR estimates shown in Figures 1 and 2 were nearly identical in men (RR = 1.24; 95% CI, 1.11–1.39) and women (RR = 1.23;

Table 1. Prospective epidemiologic studies of ischemic heart disease and ETS exposure from a smoking spouse.

Reference	Population	Years	No. of never smokers	End point	Events in men/women	Age-adjusted RR (95% CI)	Adjusted multivariate RR (95% CI)
Hirayama, 1984 (*6*) Hirayama, 1990 (*7*)	Japan	1966–1981	91,540 women	Death	254	1.31 (1.01, 1.69)[a]	1.40)
Garland et al., 1985 (*8*)	Rancho Bernardo, U.S.	1974–1983	695 women	Death	19	2.25[b]	2.7[c]
Svendsen et al., 1987 (*9*)	MRFIT, U.S.	1973–1982	11,245 men	Incidence and death	69	1.48 (0.89–2.47)	1.61 (0.96, 2.71)
Butler, 1988 (*10*)	Spouse pairs		9,378 women		80 women	1.40 (0.51–3.84)[d]	
	AHSMOG	1976–1982	3,488 women		75 men	0.57 (0.14, 2.32)[e]	
			1,489 men	Death	70 women	1.42 (0.94, 2.15)[e]	
Sandler et al., 1989 (*11*)	Maryland, U.S.	1963–1975	4,162 men 14,873 women	Death	370 men 988 women		Men 1.31 (1.05, 1.64)[f] Women 1.19 (1.04, 1.36)
Hole et al., 1989 (*12*)	Scotland	1972–1985	671 men 1,784 women	Death	84 total	1.75[c]	2.01 (1.21–3.35)[c]
Humble et al., 1990 (*13*)	Georgia, U.S.	1960–1980	513 women	Death	76	1.34 (0.84–2.21)[g]	1.59 (0.99–2.57)[g]
Steenland et al., 1996 (*3*)	American Cancer Society, U.S.	1982–1989	101,227 men 208,372 women	Death	2,494 men 1,325 women		Men 1.22 (1.07–1.40) Women 1.10 (0.96–1.27)
Kawachi et al., 1997 (*4*)	Nurses, U.S.	1982–1992	32,046 women	Incidence and death	152		2.11 (1.03–4.33)

AHSMOG, Adventist Health Smog; MRFIT, Multiple Risk Factor Intervention Trial. [a]Spouse smokes 20+ cigarettes per day. [b]Based on only 2 deaths in nonsmokers married to current smokers. [c]Combines people whose spouses smoked formerly and current smokers. [d]Based on only 4 deaths in nonsmokers married to current smokers. [e]Calculated by authors. [f]Household exposure, not spousal. [g]Death from all cardiovascular disease.

Table 2. Case control studies of ischemic heart disease and ETS from spousal smoking.

Reference	Population	End point	Number of cases		Number of controls		Age-adjusted RR (95% CI)	Multivariate adjusted RR (95% CI)
			Men	Women	Men	Women		
Lee et al., 1986[a] (*14*)	Hospital-based, U.K.	Hospitalization IHD	41	77	133	318	1.03 (0.65–1.62)	
He et al., 1989 (*15*)	China	MI or abnormal arteriogram	–	34	–	68	3.00 (1.26, 7.17)	1.50 (0.90, 2.51)
Jackson, 1989 (*16*)	New Zealand	Hospitalization MI	28	11	123	9		Men 1.03 (0.27, 3.90) Women 2.70 (0.57, 12.30)
		Fatal MI	21	112	61	62		Men 1.10 (0.23, 5.20) Women 5.80 (0.95, 35.20)
Dobson et al., 1991 (*17*)	New South Wales, Australia	Fatal or nonfatal	183	160	293	532		Men 0.97 (0.50–1.86) Women 2.46 (1.47–4.13)
LaVecchia et al., 1993 (*18*)	GISSI-2 Italy	Acute MI	69	44	60	125	1.21 (0.57, 2.52)	
He et al., 1994 (*19*) Lam and He, 1997 (20)	China	Hospitalization MI	–	59	–	126		1.24 (0.56, 2.72)
Muscat and Wynder, 1995 (*21*)	Hospital-based American Health Foundation	MI	68	46	108	50		1.5 (0.9–2.6)[b]
Ciruzzi et al., 1998 (*22*)	Hospital-based Argentina	MI	156	180	228	218	1.37 (0.73, 2.59)	1.59 (0.85, 2.96)

Abbreviations: –, no cases or controls for men; GISSI-2, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio. [a]Not specified whether subjects were lifelong nonsmokers. [b]Adult ETS exposure, not necessarily spousal.

95% CI, 1.15–1.32). Similarly, these estimates were statistically equivalent (95% CI values broadly overlapping) in the cohort studies (RR = 1.23; 95% CI, 1.15–1.31) and in the case–control studies (RR = 1.47; 95% CI, 1.19–1.81). The association between ETS and CHD risk was also similar in the studies with fatal CHD as the end point (RR = 1.22; 95% CI, 1.14–1.30) to that in the studies of nonfatal MI (RR = 1.32; 95% CI, 1.04–1.67), and in the studies conducted in the United States (RR = 1.22; 95% CI, 1.13–1.30) to those conducted in other countries (RR = 1.41; 95% CI, 1.21–1.65).

Three studies reported the association between ETS and CHD separately for nonsmokers married to current smokers and those married to former smokers (*3,10,18*). We examined whether the association between ETS and heart disease was stronger when the spouses continued to smoke, as the association between smoking and heart disease declines after successful cessation (*28*). The pooled RR estimate for nonsmokers whose spouses had formerly smoked was 0.98 (95% CI, 0.89–1.08), whereas the estimate for nonsmokers whose spouses still smoked was 1.16 (95% CI, 1.06–1.28), supporting the hypothesis that current ETS exposure may cause cardiovascular disease.

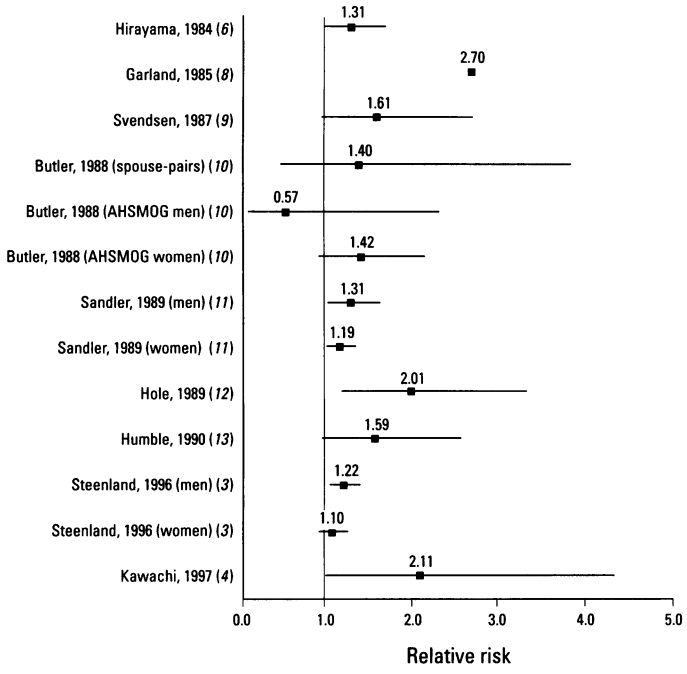

Figure 1. Spousal environmental tobacco smoke and coronary heart disease: cohort studies (listed by first author).

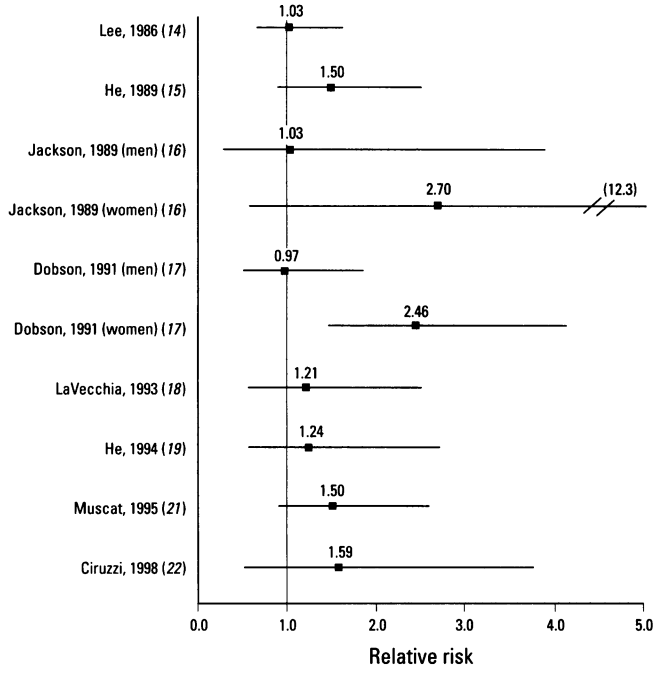

Figure 2. Spousal environmental tobacco smoke and coronary heart disease: case–control studies (listed by first author).

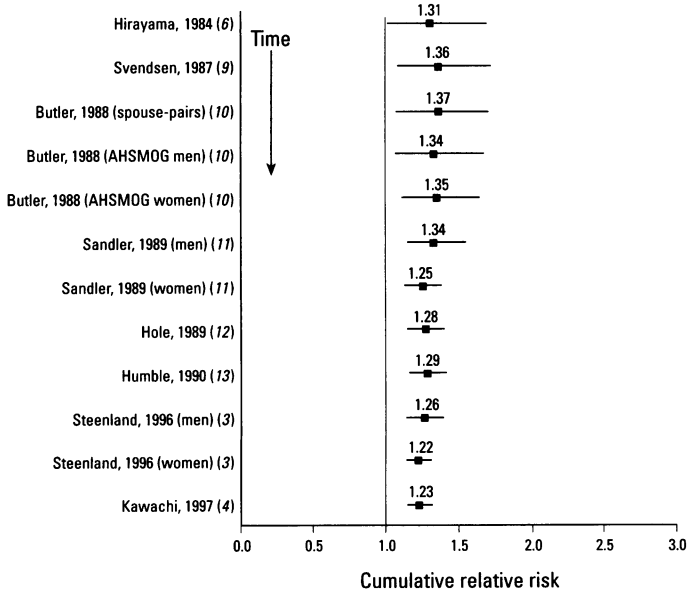

Figure 3. Cumulative relative risk and 95% confidence interval for spousal environmental tobacco smoke and coronary heart disease: cohort studies (listed by first author).

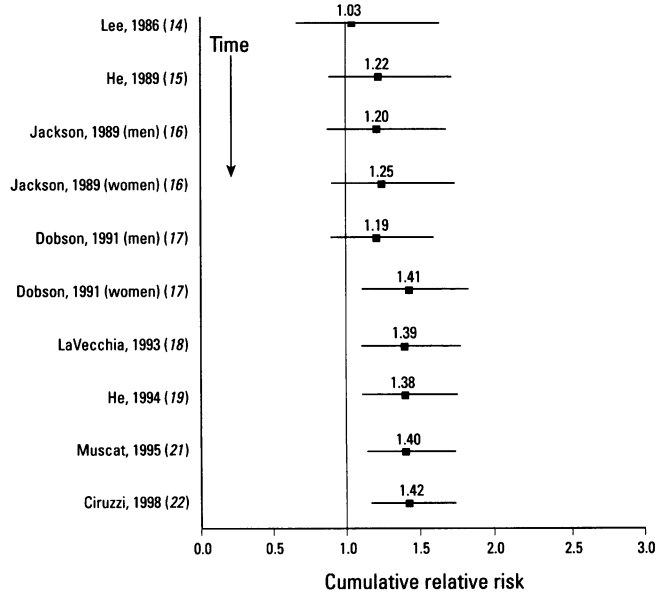

Figure 4. Cumulative relative risk and 95% confidence interval for spousal environmental tobacco smoke and coronary heart disease: case–control studies (listed by first author).

Seven studies examined the association between ETS and CHD by the number of cigarettes smoked daily by the spouse (*3,9,12,13, 18,19,22*). Of these, six (*9,12,13,18,19,22*) found higher RR estimates when the spouse smoked more cigarettes per day. Four (*3,4,10,19*) of the five (*3,4,10,19,21*) studies that examined the association between ETS and CHD by years of spousal smoking found some evidence of higher RR estimates with longer potential exposure.

No consistent differences were seen between the age-adjusted and multivariate-adjusted RR estimates, diminishing concern about residual confounding. Of seven studies that presented both the age-adjusted and the multivariate-adjusted RR estimates (*3,4,9,12, 13,18,22*), four showed an increase in the RR estimate when adjusted for multiple factors besides age (*9,12,13,22*), whereas three showed a decrease in the RR (*3,4,18*).

Criticisms of the Epidemiologic Studies

The epidemiologic studies of heart disease and ETS exposure from a spouse who smokes have been criticized for several of the same reasons as have the studies of ETS and lung cancer. The three criticisms most commonly raised concern publication bias, confounding, and misclassification of exposure (*30–39*). These concerns have been responded to extensively in the scientific literature (*1,40–46*) and in regulatory hearings (*2*). It is nevertheless important to discuss these issues systematically in the context of all currently available studies.

Publication Bias

The concern that negative (null) studies of ETS and disease are less likely to be submitted or accepted for publication has been expressed repeatedly (*26,27,30,31,39*). However, the idea that selective publication introduces a major bias into the ETS–heart disease literature has become progressively less plausible over time for two reasons. First, the published literature is now sufficiently large that additional studies have minimal impact on the aggregate findings (Figures 3, 4). Second, 14 years have elapsed since Hirayama first publicized the hypothesis that ETS causes heart disease (*6*), which allows ample time for important negative studies to be discovered (*42*). A systematic review by Misakien and Bero found only a 2-year delay in publication of studies with statistically insignificant results, compared to those with statistically significant results (*44*).

A related criticism is that the analyses of CPS-I by LeVois and Layard (*26*) and the analysis of the NMFS by Layard (*27*) should not have been excluded from meta-analyses (*31*). As has been pointed out, the excluded studies encompass two-thirds of the total number of CHD events in all the studies (*31*). Unfortunately, these two studies must be disqualified because they do not meet the fundamental criterion of validity to be considered. Retaining the studies would enhance the statistical precision of the meta-analysis but would undermine its validity.

Confounding

It is conceivable that one or several risk factors for heart disease may be associated with marriage to a smoker, and that these, rather than ETS itself, may account for the greater CHD risk among nonsmokers whose spouses smoke. Confounding is of genuine concern because the RR estimate is between 1.0 and 2.0, the range at which confounding is difficult to exclude with certainty in observational studies, and the end point is heart disease, which is influenced more than lung cancer by factors other than tobacco smoke (*42*).

The best approach to assess the potential for confounding in these studies is to examine the extent to which the RR estimates change when adjusted for risk factors other than age. All epidemiologic studies of CHD and spousal smoking have controlled for age and sex; most have also adjusted for other medical parameters; and a few have adjusted extensively for socioeconomic and dietary correlates of ETS. A strength of the Nurses' Health study was the availability of longitudinally collected information on diet, alcohol consumption, physical activity, body mass index, and other factors associated with ETS exposure that also affect heart disease. Adjusting for 12 factors other than age in the Nurses' Health study caused only a small reduction in the association between spousal smoking and CHD (*4*). The RR estimate associated with all incident MIs among the nurses exposed to passive smoke decreased from 1.97 (95% CI, 1.20–3.24) to 1.71 (95% CI, 1.03–2.84), a 13% reduction (*4*).

Concern about confounding is further reduced by the results of five other studies that show both age-adjusted and multivariate RR estimates for CHD associated with spousal smoking (*3,12,13,18,22*). In three of these studies the RR estimate increased after multivariate adjustment (*12,13,22*); in the remaining two (*3,18*), the RR estimate decreased slightly, as it did in the Nurses' Health Study (*4*). Apart from the Nurses' Health Study, only the American Cancer Society CPS-II analysis (*3*) controlled directly for diet and alcohol consumption. The RR estimate for men decreased from 1.25 to 1.23 with multivariate adjustment; the estimate in women decreased from 1.31 to 1.19. In no study is there a large or systematic reduction in the RR estimate after factors such as education and cholesterol are controlled for. Thus, other studies with minimal information to adjust for potential confounders are unlikely to over- or underestimate seriously the true RR associated with spousal smoking. After adequate control for all measured confounders the RR is still significantly above the null (*1*).

An indirect way of assessing confounding is to compare the prevalence of known risk factors for heart disease among nonsmokers married to smokers to that of nonsmokers whose spouses do not smoke. The largest of such studies compared 26,000 nonsmoking U.S. nurses who reported exposure to ETS at home or work with 6,000 who reported no ETS exposure (*42*). The age-adjusted prevalence of self-reported hypertension, diabetes, and increased cholesterol was slightly (1–3%) higher among ETS-exposed nurses than among the unexposed. Similarly, the differences in body mass index, dietary carotenoid intake, and alcohol consumption were small between the ETS-exposed and ETS-unexposed persons in the Third National Health and Nutrition Survey (NHANES-III) (*45*). Steenland et al. (*45*) found that the positive associations between serum cotinine and body mass index and the negative correlation with dietary carotenoids were greatly diminished by adjusting for age, sex, race, and education. Earlier studies of the prevalence of cardiovascular risk factors in relation to spousal smoking were too small to be informative (*47–50*).

Not all factors associated with ETS exposure in the epidemiologic studies would influence the RR estimate in the same direction. Whereas adjusting for the lower consumption of fruits and vegetables and the higher body mass index of ETS-exposed persons would plausibly increase the RR estimate, adjusting for the more prevalent consumption of alcoholic beverages would decrease the estimate. It is an oversimplification to assume that residual confounding only exaggerates the association between ETS and heart disease.

Misclassification of Exposure

A small fraction of respondents who describe themselves as never smokers may actually be current or former smokers. This is the only type of misclassification that would cause the association between ETS and heart disease to be overestimated, and it is uncommon. Only about 1.3% of self-reported never smokers in NHANES-III had levels of serum cotinine high enough to suggest that they were in fact current smokers (*51*). The impact of misclassifying some current smokers among the never smokers is much smaller in studies of ETS and heart disease than when studying ETS and lung cancer because the association between active smoking and heart disease is weaker than the association between active smoking and lung cancer (*52*).

A second type of misclassification involves misclassification of ETS exposure

among the never smokers. Typically this would result in random misclassification of exposure and underestimation of the RR (*42*). The analysis of the American Cancer Society CPS-II study found the RR estimates to be most consistent between men and women in subanalyses in which exposure status was concordant from two sources (self- and spousal report), which minimized misclassification of ETS exposure (*3*).

Relevance of the Studies of Spousal Smoking to Workplace Exposure

The studies of heart disease among nonsmokers married to smokers are relevant to understanding the potential hazards of ETS exposure at work in several ways. These studies encompass over 118,000 men and 269,000 women from all parts of the United States as well as a large number of nonsmokers from other countries. Most of the cardiovascular events in these studies occurred after age 40 in men and after menopause in women, as is true in the general population. Cigarettes, rather than pipes or cigars, are the predominant source of ETS in both residential and occupational settings. Although factors such as the number of people smoking, the volume of the polluted space, the ventilation rate, the size of the room, and the duration of exposure may cause differences in the concentration of ETS in the home and in the workplace, these differences do not negate the qualitative and quantitative similarities of the exposure (*53*). Certain factors render ETS exposure in the workplace more hazardous than ETS exposure at home. For example, greater physical activity, higher respiratory rates, and/or the presence of other industrial air contaminants may all exacerbate the toxicity of ETS in the workplace (*53*).

Nonsmokers married to a spouse who smokes may also incur greater ETS exposure from other household residents, in the workplace, or in other public settings (*45*). Any additional ETS exposures that occur do not invalidate the relationship between ETS and heart disease, however, but only overestimate the risk caused by spousal smoking alone.

Previous Consensus Reviews

Seven expert panels have formally reviewed all the available evidence on ETS and heart disease (*1,2,54–58*) (Table 3). The review by Law et al. (*1*) is included because it was commissioned and then reviewed by a public health consensus group in the United Kingdom (*58*). As seen in Table 3, the conclusions regarding the causal relationship between ETS and heart disease have become progressively stronger between 1986 and 1997 as the epidemiologic, clinical, and experimental studies have accumulated. These reviews are broader than meta-analyses of epidemiologic studies (*59,60*) in that they also consider a broad array of experimental and clinical studies of active smoking and ETS exposure.

Summary

The 17 epidemiologic studies discussed in this overview provide consistent evidence that adult nonsmokers married to smokers have higher risks of CHD than those whose spouses do not smoke. All but one of the studies considered acceptable for inclusion in this overview found greater risk of MI and/or death from CHD among nonsmokers married to current smokers than in those married to nonsmokers. In three studies, CHD risk was higher when the spouse continued to smoke than when the spouse quit smoking. Risk was also higher when the spouse smoked more cigarettes per day in six of the seven studies that assessed this.

Inference about whether the association between CHD and spousal smoking is causally related to ETS involves issues discussed elsewhere in this workshop. Important questions are whether bias and confounding can be

Table 3. Consensus reviews of coronary heart disease and environmental tobacco smoke.

Year	Author, reference	Studies	Pooled RR	Conclusions/comments
1986	Centers for Disease Control (*54*)	4	–	"Further studies on the relationship between involuntary smoking and cardiovascular diseases are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease."
1986	National Research Council (*55*)	4	–	"Further experimental and observational studies should be conducted to assess the effect of long-term and acute ETS exposure on cardiac function, blood pressure, and angina in nonsmokers."
1991	U.S. National Institute for Occupational Safety and Health (*56*)	7	–	"Recent evidence also suggests a possible association between exposure to ETS and an increased risk for heart disease in nonsmokers." "NIOSH has determined that the collective weight of evidence is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers."
1992	Taylor et al. (*57*)	Cites reviews		"The effects of environmental tobacco smoke on cardiovascular function, platelet function, neutrophil function, and plaque formation are the probable mechanisms leading to heart disease. The risk of death due to heart disease is increased by about 30% among those exposed to environmental tobacco smoke at home and could be much higher in those exposed at the workplace, where higher levels of environmental tobacco smoke may be present."
1994	U.S. Occupational Safety and Health Administration (*5*)	11	RRs range from 1.24 to 3.0	Used RR from Helsing (1.24 [females] and 1.31 [males]) to calculate attributable risk. "The Agency estimates that there will be between 2,094 and 13,000 deaths from heart disease per year among nonsmoking American workers exposed to ETS in the workplace. When considered over a working lifetime, this translates into an excess death rate of approximately between 7 and 16 cases of heart disease per thousand attributed to workplace exposure to ETS. Clearly, this risk is significant in itself and combined with the lung cancer risk, the significance of risk is very great."
1997	California Environmental Protection Agency (*2*)	18	–	"Epidemiologic data are supportive of causal association between ETS exposure from spouses and CHD mortality in nonsmokers."
1997	Law et al. (*1*); Report of the Scientific Committee on Tobacco and Health (*58*)	19	1.30 (1.22, 1.38) with dietary consideration 1.23 (1.14, 1.33) (*1*)	"Breathing other people's smoke is an important and avoidable cause of IHD, increasing a person's risk by a quarter." (*1*)

NIOSH, U.S. National Institute for Occupational Safety and Health.

excluded with reasonable certainty, whether it is biologically plausible that ETS causes heart disease in nonsmokers, and whether ETS exposures that are approximately 1% those of active smokers could conceivably cause an increase in CHD risk 30–50% of that caused by active smoking. All these questions directly affect the interpretation of the epidemiologic data but are beyond the scope of this article.

Certain points can be made, however, based on the data presented. Both chance and publication bias can essentially be excluded as plausible explanations for the observed finding. It has been 15 years since Hirayama first hypothesized that ETS might cause heart disease (*6*). The analyses included in this overview represent a 36% increase in CHD events and a 58% increase in nonsmokers above the data considered by OSHA in its 1994 proposed regulation of ETS in the workplace (*5*), yet the results are virtually unchanged. There are now sufficient published or otherwise available data on this topic that the findings will not change substantively if additional small, unpublished studies are discovered in the future.

A major strength of the epidemiologic data on CHD in relation to spousal smoking is that the results are remarkably consistent despite differences in locale, study population, investigators, and design. Of course, consistency does not guarantee causality. It is certainly possible that the same or similar biases could be replicated across studies. However, adjusting for measured potential confounders in these studies (*3,4,9,12,13,18*) does not consistently weaken the association. Furthermore, nonsmokers married to smokers may not only have less healthy dietary patterns and engage in less physical activity but they may also drink alcoholic beverages more regularly, which may partially offset the other behaviors with respect to heart disease.

The magnitude of the association between ETS and heart disease has been challenged as being at once too low to exclude confounding and too high to be biologically plausible (*31*). Addressing the criticisms regarding bias, confounding, and biologic plausibility requires that the epidemiologic data be considered together with the clinical and experimental data and not in isolation. Furthermore, OSHA should define the level of scientific certainty required to include heart disease as an end point in its risk assessment.

References and Notes

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