

Chapter 8

Cardiovascular Diseases from Exposure to Secondhand Smoke

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Introduction

Cardiovascular disease is the leading cause of death in the United States (Hoyert et al. 2006). Cardiovascular disease includes coronary heart disease (CHD), which causes the most deaths, and stroke, which ranks as the third leading cause of death (Hoyert et al. 2006). In 2003, CHD was responsible for approximately 480,000 deaths and stroke was responsible for approximately 158,000 deaths (Hoyert et al. 2006). Each year, an estimated 1.2 million Americans experience a new or recurrent heart attack, and an estimated 700,000 people suffer a new or recurrent stroke (American Heart Association 2005). Active smoking is one of the most important modifiable risk factors for both CHD and stroke (U.S. Department of Health and Human Services [USDHHS] 2004). This chapter considers the evidence that links secondhand smoke to these two major outcomes as well as to carotid arterial wall thickness, an indicator of the degree of atherosclerosis. Chapter 2 of this report (Toxicology of Secondhand Smoke) sets out the biologic basis by which exposure to secondhand smoke could increase the risk for CHD and stroke.

The topic of secondhand smoke and CHD was not addressed in the 1986 Surgeon General's

report *The Health Consequences of Involuntary Smoking* (USDHHS 1986). At the time, only a few studies had been published on the association of secondhand smoke with CHD, and the evidence was regarded as too limited to review. Since then, many epidemiologic investigations have been carried out on secondhand smoke exposure and its relationship to CHD and stroke. In fact, both animal and human experimental data, along with clinical studies directed at physiologic consequences of exposure to secondhand smoke, have provided a biologic foundation for interpreting the epidemiologic data (Chapter 2, Toxicology of Secondhand Smoke). The evidence linking secondhand smoke and cardiovascular disease was considered in the 2001 Surgeon General's report *Women and Smoking* (USDHHS 2001). Several earlier reports, including those of the California Environmental Protection Agency (Cal/EPA) (National Cancer Institute [NCI] 1999) and the Australian National Health and Medical Research Council Working Party (NHMRC 1997), had comprehensively reviewed the evidence and concluded that exposure to secondhand smoke does cause CHD.

Coronary Heart Disease

The 2001 Surgeon General's Report

The 2001 report *Women and Smoking* reviewed the 10 cohort and 10 case-control studies on secondhand smoke and CHD that had been published up to 1998 (USDHHS 2001). Since then, additional studies have been published (Tables 8.1 and 8.2). The mean duration of follow-up in the cohort studies ranged from 6 to 20 years. Of the 20 earlier studies, 5 cohort and 4 case-control studies found a statistically significant increase in the risk of CHD from secondhand smoke. Most of the remaining 11 studies also showed an increased risk.

Based on the review of the epidemiologic evidence, the 2001 report reached the following conclusions:

- The data from the existing cohort and case-control studies "...support a causal association between ETS [environmental tobacco smoke] exposure and coronary heart disease mortality and morbidity among nonsmokers" (p. 356).
- Secondhand smoke "...is associated with risk for CHD mortality (fatal events), morbidity (non-fatal events), and symptoms. Most of the data on the association with mortality were from cohort studies, but most of the data on the association with morbidity were from case-control investigations. Nonetheless, the magnitude of association is similar in both sets of results" (p. 356).

Table 8.1 Cohort studies of secondhand smoke exposure and the risk of coronary heart disease (CHD) among nonsmokers

Study	Design/population	Duration of follow-up (years)	Exposure	Findings
Hirayama 1984, 1990	91,540 women Nonsmokers Aged ≥ 40 years 1966–1981 Japan	16	Husband smoked	Death from ischemic heart disease (IHD)
Garland et al. 1985	695 women Lifetime nonsmokers Aged 50–79 years 1974–1983 United States (California)	10	Husband smoked (self-reported)	Death from CHD
Svendson et al. 1987	1,245 married men Lifetime nonsmokers Aged 35–57 years Free of CHD at baseline but at high risk Enrolled in the Multiple Risk Factor Intervention Trial 1973–1982 United States (18 cities)	Average of 7	Wife smoked	Death from CHD
Butler 1988	6,507 Seventh-Day Adventist women married to men also enrolled in the study Aged ≥ 25 years 1976–1982 United States (California)	6	Husband smoked	Death from CHD
Helsing et al. 1988 (not included in the meta-analysis conducted for this 2006 Surgeon General's report)	3,488 men and 12,348 women Lifetime nonsmokers Aged ≥ 25 years 1963 United States (Western Maryland)	12	Cohabitant smoked	Death from CHD
Hole et al. 1989	671 men and 1,784 women Lifetime nonsmokers Aged 45–64 years at baseline 1972–1985 Scotland	Average of 11.5	Cohabitant smoked	Death from IHD
Sandler et al. 1989 (not included in 2001 review)	4,162 White men and 14,873 White women Lifetime nonsmokers in 1963 Aged ≥ 25 years 1963–1975 United States (Maryland)	12	Home exposure from any household member who smoked	Death from CHD
Humble et al. 1990	513 women Lifetime nonsmokers Aged 40–74 years 1960–1980 United States (Georgia)	20	Husband smoked at baseline	Death from CHD

Relative risk (95% confidence interval)	Variables controlled for
1.18 (0.98–1.41)	Age
2.7 (0.59–12.33)	Age, systolic blood pressure, serum cholesterol level, body mass index (BMI), years of marriage
2.23 (0.72–6.92)	Age, blood pressure, serum cholesterol level, body weight, alcohol consumption, level of education
1.4 (0.51–3.84)	Age
Men: 1.31 (1.1–1.6) Women: 1.24 (1.1–1.4)	Age, education, marital status, housing quality
2.01 (1.21–3.35)	Age, gender, social class, diastolic blood pressure, serum cholesterol level, BMI
1.22 (1.09–1.37)	Age, marital status, years of schooling, quality of housing
1.59 (0.99–2.57)	Age, serum cholesterol level, diastolic blood pressure, BMI, and square of BMI

- Higher intensity exposures to secondhand smoke were “associated with a higher risk for CHD in some of these studies, but the differences in risk between levels of ETS exposure were not large” (p. 353).

Since the preparation of the 2001 report, two additional case-control studies of secondhand smoke exposure and CHD have been published (McElduff et al. 1998; Rosenlund et al. 2001), which are also included in Table 8.2. McElduff and colleagues (1998) pooled the CHD cases from two population-based, case-control studies carried out in Newcastle, Australia, and Auckland, New Zealand. The New Zealand component of the study (Jackson 1989) and a portion of the Australian data (Dobson et al. 1991) had been published previously and were included in the 2001 Surgeon General’s report (USDHHS 2001). At both study sites, exposures to secondhand smoke at home and at work were assessed from self-reports. The study included 953 persons with CHD: 670 nonfatal myocardial infarction [MI] patients and 283 persons who had died of coronary disease. After adjusting for age, education, history of heart disease, and body mass index (BMI), McElduff and colleagues (1998) found that women had an increased risk of CHD associated with secondhand smoke (odds ratio [OR] = 1.99 [95 percent confidence interval (CI), 1.40–2.81]). For men, however, the investigators found no association between secondhand smoke and CHD (OR = 1.02 [95 percent CI, 0.81–1.28]).

The case-control study conducted by Rosenlund and colleagues (2001) examined the risk of nonfatal MI associated with secondhand smoke exposure among men and women enrolled in the Stockholm Heart Epidemiology Program—334 lifetime nonsmoking cases and 677 population controls aged 45 through 70 years who resided in Stockholm county. Assessments of exposures to secondhand smoke both at home and at work were based on a mailed questionnaire that also asked about the cumulative time-weighted duration of exposures in both settings, which were expressed as hour-years.¹ After adjusting for age, gender, BMI, hospital catchment area, socioeconomic status (SES), job strain, hypertension, diet, and diabetes mellitus, the OR for MI from an average daily exposure of 20 or more cigarettes smoked by the spouse was 1.58 (95 percent CI, 0.97–2.56). In both men and women,

¹One hour-year equals 365 hours per year, or 1 hour per day for one year.

Table 8.1 Continued

Study	Design/population	Duration of follow-up (years)	Exposure	Findings
LeVois and Layard 1995 (not included in the meta-analysis conducted for this 2006 Surgeon General's report)	88,458 men and 247,412 women Lifetime nonsmokers CPS-I* data 1960 United States	13	Spouse smoked	Death from CHD
Steenland et al. 1996	126,500 men and 353,180 women Lifetime nonsmokers Aged ≥ 30 years CPS-II data 1982–1989 United States	8	Home and workplace exposures and spousal smoking (self-reported)	Death from CHD
Kawachi et al. 1997	32,046 female nurses Lifetime nonsmokers Aged 36–61 years 300,325 person-years† 1982–1992 United States	10	Home or workplace exposure in 1982	Myocardial infarction and death from CHD

Note: All studies appear in both the original review and updated meta-analysis unless otherwise indicated.

*CPS-I = Cancer Prevention Study I, American Cancer Society cohort.

†CPS-II = Cancer Prevention Study II, American Cancer Society cohort.

‡Person-years = Duration of exposure to secondhand smoke (cumulative).

current exposures were associated with a higher risk of MI compared with past exposures. Moreover, the risk of MI decreased consistently with an increase in time since the last exposure.

Compared with persons who had never been exposed to secondhand smoke, persons with combined exposures from home and work showed an OR for MI of 1.55 (95 percent CI, 1.02–2.34) in the highest category of exposure (more than 90 hour-years) (Rosenlund et al. 2001).

Evaluating the Epidemiologic Evidence

Before evidence is accepted for the purpose of drawing a causal inference from epidemiologic studies, several methodologic issues must be addressed. These include, but are not limited to, the possibility of misclassified exposures, the potential for uncontrolled confounding, and publication bias. The biologic plausibility of a causal association should also be addressed. These issues are considered separately in this chapter.

Relative risk (95% confidence interval)	Variables controlled for
1.0 (0.97–1.04)	Age, race
Women: 1.0 (0.98–1.1) Men: 0.97 (0.9–1.1)	Age, race
1.21 (1.06–1.39)	Age, heart disease history, hypertension, diabetes mellitus, arthritis, BMI, level of education, aspirin use, diuretic use, estrogen use, alcohol consumption, exercise, employment status
1.71 (1.03–2.84)	Age, follow-up period, alcohol consumption, BMI, hypertension, diabetes mellitus, hypercholesterolemia, menopausal status, current use of postmenopausal hormones, past use of oral contraceptives, vigorous exercise, saturated fat intake, vitamin E intake, average aspirin use, parental history of myocardial infarction before 60 years of age, father's occupation when participant was 16 years of age

Misclassifying Exposures

Chapter 1 (see “Methodologic Issues”) of this report discussed the need to consider the misclassification of exposures in studies that investigated the effects of secondhand smoke exposure, including CHD and stroke. To validate the questionnaire measures used in the CHD studies, epidemiologic and experimental literature have suggested that exposure biomarkers that are used as the “gold standard” should

reflect both recent and more remote exposures. The 2004 study by Whincup and colleagues (2004) incorporated an independent biochemical validation of secondhand smoke exposures—the current available biomarkers reflect only relatively short-term exposures over a period of days (see “Biomarkers of Exposure to Secondhand Smoke” in Chapter 3). Although short-term exposures may be relevant to CHD, investigators have argued that patterns of risk among active smokers suggest that exposures over the longer term may also be relevant (Wells 1994). Both experimental and epidemiologic findings indicate adverse cardiovascular consequences of immediate and sustained exposures.

Bailar (1999) noted that nonsmokers who develop heart disease may have selectively recalled their exposures to secondhand smoke. However, this criticism applies to case-control studies that relied on retrospective recall rather than to cohort studies. In their meta-analysis, He and colleagues (1999) found that the pooled OR estimate from eight case-control studies was slightly higher (OR = 1.51 [95 percent CI, 1.26–1.81]) than the pooled relative risk (RR) estimate from 10 cohort studies (RR = 1.21 [95 percent CI, 1.14–1.30]). The somewhat higher risks in the case-control studies may reflect recall bias, at least in part, but the pooled estimate is also elevated in the cohort study data, which would not generally be subject to this form of bias.

In addition to the possibility of recall bias in case-control studies, several other types of exposure misclassification may have occurred in the case-control and cohort published studies. For example, Ong and Glantz (2000) suggest that the most important measurement error is likely to be a failure to correct for background exposure to secondhand smoke, as truly unexposed populations are essentially unavailable. Several studies, including Garfinkel (1981), have assessed secondhand smoke exposures from a single source (such as spouses) without considering total exposures in different environments. The effects of secondhand smoke exposures from different sources are likely to be additive because of the qualitative similarity of secondhand smoke in different environments. Thus, not accounting for exposures to background secondhand smoke will bias associations with disease toward the null (Ong and Glantz 2000). In general, nonsmokers are likely to underestimate their true secondhand smoke exposures (Emmons et al. 1992; Bonita et al. 1999). For example, in a study of 663 lifetime nonsmokers and former smokers who attended a cancer screening clinic, Cummings and

Table 8.2 Case-control studies of exposure to secondhand smoke and the risk of coronary heart disease (CHD) among nonsmokers

Study	Year and location of study	Population		Exposure
		Cases	Controls	
Lee et al. 1986	1979–1982 England	41 male and 77 female patients with ischemic heart disease Lifetime nonsmokers and married	133 male and 318 female hospital patients with diseases probably or definitely not related to smoking Lifetime nonsmokers and married	Spouse smoked
He 1989 (not included in the meta-analysis conducted for this 2006 Surgeon General's report)	Years were not reported China	34 female hospital patients Nonsmokers	34 female hospital patients 34 females, population based All nonsmokers	Husband smoked
Jackson 1989 (data included in McElduff et al. 1998 study in the 2006 meta-analysis conducted for this 2006 Surgeon General's report)	1987–1988 New Zealand	44 male and 22 female hospital patients All nonsmokers Myocardial infarction (MI) or death from CHD	84 male and 174 female hospital patients All nonsmokers MI or death from CHD	Home and work exposures combined
Dobson et al. 1991 (data included in McElduff et al. 1998 study in the meta-analysis conducted for this 2006 Surgeon General's report)	1988–1989 Australia (New South Wales)	183 male and 160 female hospital patients MI or death from CHD Nonsmokers	293 male and 174 female hospital patients Nonsmokers Participants in a risk factor prevalence survey	Home and work exposures
La Vecchia et al. 1993	1988–1989 Italy	69 men and 44 women with acute incident MI Lifetime nonsmokers and married Enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-2 Median age: 63 years	217 married hospital controls (161 men, 56 women) Lifetime nonsmokers Admitted for acute diseases not related to any potential cardiovascular disease risk factors in the same network of hospitals Median age: 57 years	Spouse smoked
He et al. 1994	1989–1992 China	59 female patients with nonfatal incident CHD in 3 hospitals Nonsmokers Average age: 58 years	126 patients in the same hospitals or from the community Lifetime nonsmokers Average age: 55 years	Husband smoked and workplace exposure for ≥5 years

Relative risk (95% confidence interval)	Variables controlled for
1.03 (0.65–1.62)	Age, gender, hospital region
1.5 (1.3–1.8)	Alcohol consumption, exercise, personal and family history of CHD, hypertension, hyperlipidemia
MI Men: 1.0 (0.3–3.0) Women: 2.7 (0.6–12.3)	Age, social status, history of CHD
Death from CHD Men: 1.1 (0.2–5.3) Women: 5.8 (1.0–35.2)	
Men: 1.0 (0.5–1.8) Women: 2.5 (1.5–4.1)	Age, history of MI
1.21 (0.57–2.52)	Age, gender, level of education, coffee consumption, body mass index (BMI), serum cholesterol level, hypertension, diabetes mellitus, family history of acute MI
2.36 (1.01–5.55)	Age, hypertension, personality type, total serum and high-density lipoprotein cholesterol level

colleagues (1990) found that 91 percent had detectable levels of cotinine in their urine, even though only 76 percent had reported being exposed to secondhand smoke in the previous four days.

Other types of exposure misclassification than those described above have also been noted in epidemiologic studies (see “Misclassification of Secondhand Smoke Exposure” in Chapter 1). Some self-reported lifetime nonsmokers may have been smokers in the past, and persons more exposed to secondhand smoke may be more likely to have been active smokers in the past. This bias has been considered in relation to lung cancer. Hackshaw and colleagues (1997) found this kind of bias to be of minor importance in studies of secondhand smoke and lung cancer. They also noted that this bias was likely to have a negligible effect on studies of secondhand smoke and CHD because the RR of CHD among active smokers is so much smaller than the RR of lung cancer in active smokers: about a 2-fold to 4-fold increase in risk for CHD and a 20-fold increase in risk for lung cancer compared with the risk among nonsmokers. Moreover, researchers have found the actual extent of this type of misclassification to be minor (Kawachi and Colditz 1996; Howard and Thun 1999). In the Coronary Artery Risk Development in Young Adults Study, a cohort study that involved 5,115 community-dwelling adults aged 18 through 30 years, Wagenknecht and colleagues (1992) confirmed self-reported active smoking with a serum cotinine assay and found that these active smoking rates underestimated the true smoking rate by only 1.3 percent.

However, self-reported exposure to secondhand smoke is also subject to misclassification, which is likely to result in a bias toward the null in estimates of dose-response associations between the intensity of the exposure and CHD risk (Kawachi and Colditz 1996). Over time, the prevalence of secondhand smoke exposure has declined within the United States and in other countries as more people stopped smoking and as workplace restrictions on smoking became more widespread (see “Exposure in the Workplace” in Chapter 4). Cohort studies that assessed secondhand smoke exposures in the 1970s and 1980s, and only once at baseline, would have continued to classify individuals as exposed even though the exposure may have diminished or even ceased during the follow-up period. Some investigators have noted that this type of misclassification tends to result in a bias toward the null in estimates of the relationship between secondhand smoke and CHD (Kawachi and Colditz 1996).

Table 8.2 Continued

Study	Year and location of study	Population		
		Cases	Controls	Exposure
Layard 1995 (not included in the meta-analysis conducted for this 2006 Surgeon General's report)	1986 National Followback Survey United States	475 men and 914 women who died from heart disease	998 men and 1,930 women who died from other causes	Spouse smoked
Muscat and Wynder 1995	1980–1990 United States	68 men and 46 women hospitalized with incident MI in 4 cities Lifetime nonsmokers Average age: 59 years	108 men and 50 women in the same hospitals Lifetime nonsmokers Frequency matched for age, race, year of diagnosis Average age: 58 years	Home, current workplace, and childhood exposures
Tunstall-Pedoe et al. 1995 (not included in the meta-analysis conducted for this 2006 Surgeon General's report)	1984–1986 Scotland	70 men and women aged 40–59 years from general practitioner list Self-reported CHD diagnosis Nonsmokers	2,278 men and women aged 40–59 years from general practitioner list Self-reported CHD diagnosis	Any exposure from someone else in the 3 days before the survey
Ciruzzi et al. 1998	1991–1994 Argentina	336 male and female patients with acute incident MI in 35 coronary care units Median age: 66 years	446 patients in the same hospitals Matched for age, gender, medical center Median age: 65 years	Spouse and children smoked
McElduff et al. 1998 (not included in 2001 review)	1986–1994 Australia and New Zealand	686 male and 267 female patients with fatal or nonfatal MI or unclassifiable coronary death from population register of coronary events Lifetime nonsmokers or former smokers for >10 years	3,189 residents of the same communities participating in independent community-based survey	Home and workplace exposures combined
Rosenlund et al. 2001 (not included in 2001 review)	1992–1994 Sweden	All nonfatal MIs among nonsmoking Swedish citizens aged 45–70 years, residing in study area during 1992–1993 (n = 334; 199 men) Average age: 62 years	401 males and 276 females Lifetime nonsmokers Matched for gender, age, and hospital catchment area	Spouse smoked

Note: All studies appear in both the original review and the meta-analysis conducted for this 2006 Surgeon General's report unless otherwise indicated.

Relative risk (95% confidence interval)	Variables controlled for
Men: 1.0 (0.7–1.3) Women: 1.0 (0.8–1.2)	Age, race
2.4 (1.1–4.8)	Age, housing, tenure, cholesterol level, diastolic blood pressure
1.5 (0.9–2.6)	Age, gender, race, level of education, hypertension, year of diagnosis
1.68 (1.2–2.37)	Age, gender, race, level of education, BMI, hyperlipidemia, history of diabetes or hypertension, family history of CHD, exercise
1.41 (0.73–2.71)	Age, education, history of CHD, BMI
1.37 (0.9–2.09)	Age, gender, hospital catchment area, BMI, socioeconomic status, job strain, hypertension, diet, diabetes mellitus

Controlling for Confounding

If individuals who are exposed to secondhand smoke have greater exposures to other factors that increase their risk of CHD, then potential confounding by these risk factors has to be taken into account. This section reviews the studies that examined the distribution of coronary risk factors between exposed and unexposed persons. The differences found between the two groups in cardiovascular risk factors, such as diet, were not large enough to explain the observed associations between secondhand smoke and CHD risk.

Using data from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Follow-up Study, Matanoski and colleagues (1995) examined the dietary and behavioral characteristics of 3,896 nonsmoking women in relation to secondhand smoke exposures. These investigators found that women exposed to secondhand smoke from their spouses were more likely than women whose husbands did not smoke to report lower levels of education, higher alcohol consumption, a lower intake of vitamin supplements, and a lower dietary intake of vitamin A, vitamin C, and calcium. A limitation of this study was that the dietary assessment (from the 1971 to 1975 NHANES I) preceded the secondhand smoke exposure assessment (1982–1984 NHANES I Follow-up Study) by about 10 years.

Thornton and colleagues (1994) studied 9,003 British adults from the Health and Lifestyle Survey and found that compared with unexposed nonsmokers, nonsmokers exposed to secondhand smoke in the home were more likely to report low educational qualifications and employment in blue-collar manual occupations. Nonsmokers exposed to secondhand smoke were also more likely than unexposed nonsmokers to consume fried foods, to be more overweight, and to report a lower intake of fruits, salads, and breakfast cereals.

Koo and colleagues (1997) carried out an international study to examine the characteristics of women who were lifetime nonsmokers with or without smoking husbands. The authors studied 530 women from Hong Kong, 13,047 from Japan, 87 from Sweden, and 144 from the United States. In all four locations, wives of smoking husbands generally ate less healthy diets, with a tendency toward more fried foods and less fresh fruit, compared with wives of nonsmoking husbands. The investigators also noted that wives with

nonsmoking spouses had other lifestyle traits, including the avoidance of obesity, dietary cholesterol, and alcohol. Emmons and colleagues (1995) examined the dietary behaviors of 10,833 nonsmoking men and women who were surveyed as part of the Working Well Trial, and found that secondhand smoke exposure in the workplace was associated with lower intakes of vitamin C, fruits, and vegetables (but not of other micronutrients).

In contrast to the studies mentioned above, three other reports—one in the United States and two in Europe—have suggested a more limited potential for confounding in studies of secondhand smoke and heart disease (Steenland et al. 1998; Curtin et al. 1999; Forastiere et al. 2000). Steenland and colleagues (1998) studied the distribution of coronary risk factors among 3,338 lifetime nonsmokers aged 17 years or older who were representative of all U.S. lifetime nonsmokers in the 1988–1991 NHANES (NHANES III). The study examined the following cardiovascular risk factors: diabetes, sedentary behavior, alcohol consumption, serum cholesterol, high-density lipoprotein (HDL) serum cholesterol, systolic and diastolic blood pressure, blood pressure medication, serum triglycerides, BMI, estimated daily grams of dietary fat, the estimated percentage of daily kilocalories from fat, and a log of estimated dietary carotene (Steenland et al. 1998). After adjusting for age, gender, race, and education, the investigators found no significant differences between exposed and unexposed persons in any of the 13 cardiovascular risk factors. The only exception was dietary carotene, which was lower among the exposed group than among the unexposed group. One strength of this study was the availability of serum cotinine measurements, which had a geometric mean value of 0.48 nanograms per milliliter (ng/mL) in the exposed group and 0.12 ng/mL in the unexposed group. For adults aged 40 years or older (the highest risk category for heart disease), the study also noted an inverse linear trend between serum cotinine levels and HDL cholesterol ($p < 0.001$), indicating one possible mechanism for an effect of secondhand smoke exposure.

Curtin and colleagues (1999) carried out a survey of 914 female lifetime nonsmokers in Geneva, Switzerland, that included the administration of a semiquantitative food frequency questionnaire. The authors found that the association between secondhand smoke and dietary habits varied according to the source of the exposure. When women exposed to secondhand smoke at home were compared with unexposed women, the investigators found that dietary patterns did not differ. However, women

exposed to secondhand smoke at work ate smaller amounts of fiber, cereals, vegetables, and lean meat, and had a lower intake of iron and beta-carotene than did unexposed women (Curtin et al. 1999).

Forastiere and colleagues (2000) conducted a cross-sectional study of 1,938 nonsmoking women in four areas of Italy. Medical examinations were carried out and urinary cotinine levels were measured. Nonsmoking women married to smokers were compared with unexposed women across a variety of factors, including SES, physician-diagnosed hypertension, hypercholesterolemia, diabetes, diet, BMI, waist:hip ratio, triceps skinfold thickness, systolic and diastolic blood pressure, plasma antioxidant vitamins (alpha and beta-carotene, retinol, L-ascorbic acid, alpha-tocopherol, and lycopene), total serum and HDL cholesterol, and triglycerides. The investigators found that women married to smokers were more likely to be less educated than women married to nonsmokers, and the husbands of exposed women were also less educated than the husbands of unexposed women (Forastiere et al. 2000). Compared with women married to nonsmokers, women married to smokers were also significantly less likely to eat cooked (OR = 0.72 [95 percent CI, 0.55–0.93]) or fresh (OR = 0.63 [95 percent CI, 0.49–0.82]) vegetables more than once a day. The prevalence of all other variables did not differ. Overall, the investigators concluded that once studies on the health effects of secondhand smoke control for socioeconomic differences, the possibility of confounding is minimal.

Even in studies that found differences in dietary habits between exposed and unexposed nonsmokers, the actual magnitude of the differences was quite modest (Law et al. 1997). Several epidemiologic studies of secondhand smoke exposure and CHD, however, were able to adjust for a range of potential confounding factors. Seven out of 11 published cohort studies were able to control for major cardiovascular risk factors, including blood pressure (or hypertension), serum cholesterol (or hyperlipidemia), and BMI (Table 8.1); only 4 out of the 10 case-control studies controlled for blood pressure and cholesterol (Table 8.2).

Because of the differences in these potential confounding factors between exposed and unexposed lifetime nonsmokers, some investigators have observed that adjusting for other cardiovascular risk factors leads to a modest attenuation of the RR of CHD. In one meta-analysis, He and colleagues (1999) obtained an overall RR of 1.26 when they confined their pooling procedure to the 10 studies that adjusted for major CHD risk factors (blood pressure, serum

cholesterol, and BMI). In some studies, such as the Nurses Health Study, investigators controlled for a wide range of potential confounders, including age, alcohol consumption, BMI, physical activity, hypertension, diabetes mellitus, hypercholesterolemia, menopausal status, use of estrogen replacement therapy, past use of oral contraceptives, parental history of heart disease, use of aspirin, and vitamin E and saturated fat intake (Kawachi et al. 1997). After adjusting for the major CHD risk factors, Kawachi and colleagues (1997) found only a modest effect on the RR of CHD from secondhand smoke (a reduction from 1.97 to 1.71). Similarly, in the American Cancer Society Cancer Prevention Study II (CPS-II) cohort, Steenland and colleagues (1996) compared adjustments for age, education, high blood pressure, diabetes, diet, physical activity, and BMI with age adjustment alone and found that the RR estimate for age adjustment alone was reduced from 1.31 to 1.19 in men, and from 1.25 to 1.23 in women.

The studies on secondhand smoke and CHD risk have been reported over a span of several decades and have been carried out in multiple countries. The observed increase in risks is likely attributable to exposures across most of the last century, a time period when the epidemiologic characteristics of CHD changed sharply. Recent cross-sectional studies indicate that persons exposed to secondhand smoke tend to have a less favorable CHD risk factor profile than persons with fewer or no exposures. The relevance of these current patterns of correlation to past exposures is uncertain and the studies may not be readily generalizable to other populations (e.g., Hirayama's cohort in Japan).

Studies that have considered potential confounding factors have observed small reductions in the RR. Some residual confounding can never be excluded, but uncontrolled confounding can be set aside as the sole explanation for the increased RR observed with secondhand smoke exposure.

Workplace Secondhand Smoke Exposure and Risk of Coronary Heart Disease

There is no biologically plausible reason to hypothesize that the risk of CHD from exposures to secondhand smoke would differ across exposure settings (Kawachi and Colditz 1999). The effects of home and workplace exposures are expected to be additive. Workplace exposures also represent background exposures for studies that only inquired about home exposures (and vice versa), and the failure to account for the totality of exposures in different settings would

bias associations with CHD in the direction of the null, as noted earlier in this discussion.

Of the published studies on secondhand smoke and CHD, four case-control studies (Dobson et al. 1991; He et al. 1994; Muscat and Wynder 1995; Rosenlund et al. 2001) and three cohort studies (Svendensen et al. 1987; Steenland et al. 1996; Kawachi et al. 1997) examined the relationship between secondhand smoke exposure in the workplace and CHD risk. The point estimates of the RR for CHD in these studies exceeded 1.0 in six of the seven studies (ranging from 1.2 to 1.9), but the estimates were not statistically significant.

Wells (1998) carried out a meta-analysis of the same six published studies reviewed by Kawachi and Colditz (1999), along with two additional unpublished doctoral dissertations (Butler 1988; Jackson 1989). These eight studies yielded a pooled RR estimate of 1.18 (95 percent CI, 1.04–1.34) for secondhand smoke exposures at work. Two more studies of secondhand smoke and CHD followed these reviews by Wells (1998) and Kawachi and Colditz (1999). The case-control study by McElduff and colleagues (1998) summarized earlier in this chapter reported ORs for CHD from workplace secondhand smoke exposures of 1.31 (95 percent CI, 0.95–1.80) for men and 0.58 (95 percent CI, 0.27–1.24) for women. The case-control study by Rosenlund and colleagues (2001) reported ORs for MI from workplace secondhand smoke exposures of 1.39 for men (95 percent CI, 0.86–2.25) and 1.31 for women (95 percent CI, 0.62–2.79).

Biologic Plausibility of the Magnitude of the Association

Despite estimated exposure levels equivalent to smoking only one-half or one cigarette per day, the estimated increase in risk of CHD from exposure to secondhand smoke is 25 to 30 percent above that of unexposed persons. The magnitude of this association may seem surprisingly large compared with the known association between active smoking and CHD, which is between a twofold and fourfold increase in risk among current smokers of 20 cigarettes per day (Bailar 1999; Howard and Thun 1999).

However, extrapolations from published studies of active smoking yield estimates of CHD risk from exposure to secondhand smoke that are not substantially different from observed risks in epidemiologic studies of secondhand smoke and CHD (Law et al. 1997; Howard and Thun 1999). For example, Howard and Thun (1999) used linear regression to describe the relationship between daily cigarette use and CHD mortality, based on seven studies summarized in the

1983 Surgeon General's report *The Health Consequences of Smoking: Cardiovascular Disease* (USDHHS 1983) that documented CHD risk in relation to the number of cigarettes smoked per day. Assuming that involuntary smokers had been exposed to the equivalent of 0.75 cigarettes per day (the midpoint of the interval between one-half and one cigarette per day), the authors found that the expected CHD mortality ratio ranged from 1.13 to 1.47 across the seven studies, with an overall average of 1.32 (Howard and Thun 1999). This finding was similar to the pooled RR estimated from the published studies of secondhand smoke and CHD.

Some investigators, however, have argued that quantitative extrapolations based on risks for CHD in active smokers are uncertain (Howard and Thun 1999; Steenland 1999). The underlying concept of deriving a "cigarette equivalent" risk factor for CHD from secondhand smoke exposure by linear extrapolation appears biologically inappropriate, particularly in the context of the experimental evidence reviewed in Chapter 2 (see "Heart Rate Variability"). Furthermore, calculating equivalence based on relative exposures to nicotine or to its metabolite cotinine may not be biologically appropriate because the particular components of secondhand smoke that are most relevant for an increased risk of CHD have not yet been identified. For example, an experimental study conducted by Sun and colleagues (2001) found that rabbits exposed to smoke from standard nicotine-containing cigarettes versus smoke from nicotine-free cigarettes during a 10-week period had a similar extent of arterial lipid deposits. Thus, constituents besides nicotine may play a more important role in the damaging effects of secondhand smoke.

Additionally, some of the mechanisms linking tobacco smoke exposure to CHD risk appear to have nonlinear relationships with dose. The effect of tobacco smoke on platelet aggregation provides one plausible and quantitatively consistent mechanism for the association between secondhand smoke and CHD, but the findings on active and involuntary smoking imply a nonlinear relationship (Glantz and Parmley 1991, 1995; Law et al. 1997). In a summary of the experimental evidence on smoking and platelet aggregation, Law and colleagues (1997) found that the acute effects of secondhand smoke were similar to the effects of active smoking. Based on extrapolations from epidemiologic evidence relating a given increase in platelet aggregation to a risk of CHD, the estimated immediate increases in risk attributable to the effects on platelet aggregation were 43 percent for active smoking and 24 percent for involuntary smoking (Law et al. 1997).

An additional plausible mechanism of damage caused by secondhand smoke involves acute endothelial dysfunction (Glantz and Parmley 2001; Otsuka et al. 2001). Normal endothelial cells promote vasodilation and inhibit atherosclerosis and thrombosis, partly mediated by the release of nitric oxide (Glantz and Parmley 2001). Dysfunctional cells, on the other hand, contribute to vasoconstriction, atherogenesis, and thrombosis. Otsuka and colleagues (2001) demonstrated that just 30 minutes of exposure to secondhand smoke compromised the endothelial function in the coronary arteries of healthy non-smokers, as indexed by the coronary flow velocity reserve, to an extent that was indistinguishable from habitual smokers.

Publication Bias

Publication bias refers to the tendency for investigators to submit manuscripts and for editors to accept them based on the statistical significance and direction of the association (positive rather than negative) found in study results. Overall, there is little evidence to suggest that publication bias attributable to the omission of unpublished data significantly affected the conclusions of the published reviews or meta-analyses of the evidence on CHD. Comprehensive reviews of the evidence linking secondhand smoke to CHD, including the 1997 Cal/EPA report on *Health Effects of Exposure to Environmental Tobacco Smoke* (NCI 1999), the 2001 Surgeon General's report (USDHHS 2001), and the meta-analysis by He and colleagues (1999), have included unpublished studies. In some cases, investigators provided a quantitative estimate of the likelihood of publication bias. For example, of the 19 studies reviewed by Law and colleagues (1997) on secondhand smoke and CHD, 8 indicated a statistically significant association (a probability for each of less than 1 in 40 if there were no association). The total number of studies needed to generate this result by chance would be more than 300 (8×40); that is, the number of unpublished studies would need to be improbably large. In their meta-analysis, He and colleagues (1999) summarized 18 cohort and case-control studies and performed a rank correlation analysis of the association between standard error and log RR. If small studies with negative results were less likely to be published, the correlation between the standard error and log RR would be high, suggesting publication bias. The Kendall tau correlation coefficient for the standard error and the standardized log RR was 0.24 ($p = 0.16$) for all 18 studies, providing little evidence for publication bias. When one study with

an extreme value was excluded (Garland et al. 1985), the Kendall tau correlation coefficient for the standard error and the standardized log RR was further reduced to 0.19 ($p = 0.28$).

The possibility that publication bias has affected meta-analyses of the literature on CHD has also been raised because two meta-analyses excluded studies conducted by consultants to the tobacco industry (Lee 1998; LeVois and Layard 1998). Specifically, several meta-analyses of secondhand smoke and CHD carried out by Law and colleagues (1997), Wells (1998), He and colleagues (1999), and Thun and colleagues (1999) excluded the CPS-I and CPS-II analyses by LeVois and Layard (1995) and the National Mortality Followback Survey (NMFS) analyses by Layard (1995). Both studies suffer from serious methodologic flaws (USDHHS 2001). In the case-control study by Layard (1995), the quality of information on spousal secondhand smoke exposure was uncertain because the exposure categories did not capture whether the spousal exposure was a current or former exposure or whether the spousal exposure was from a current or previous marriage. In addition, all of the NMFS participants had died and exposure data for both case and control groups were obtained from next of kin; 18 percent of the surrogate respondents were not even first-degree relatives. Another flaw was that an estimated 50 percent of the deaths in this study that were attributable to CHD were excluded because of missing information on marital status or spousal smoking behaviors or both.

Methodologic flaws in the cohort analyses of CPS-I and CPS-II data by LeVois and Layard (1995) were also noted in the 2001 Surgeon General's report (USDHHS 2001). The investigators did not distinguish between current exposures from spousal secondhand smoke and former exposures, nor did they separately report the effect of current spousal smoking on the risk of CHD. In a more careful analysis of the CPS-II data, Steenland and colleagues (1996) showed that exposure to current spousal smoking was associated with an increased risk of CHD among both men and women. Using the same data set, Law and colleagues (1997) noted that the estimated RR of CHD from spousal smoking reported by LeVois and Layard (1995) (RR = 1.0 [95 percent CI, 0.87–1.04]) was inconsistent with the estimate reported by Steenland and colleagues (1996) (RR = 1.21 [95 percent CI, 1.06–1.38]). Because both results cannot be correct, Law and colleagues (1997), He and colleagues (1999), and others

rejected the analyses by LeVois and Layard (1995) as less valid than the analysis by Steenland and colleagues (1996).

Previous Reviews of the Evidence

Numerous published reviews, including meta-analyses, summarize the epidemiologic studies of secondhand smoke and CHD (Table 8.3). As the 2001 Surgeon General's report stated, "Although few of the risk estimates in individual studies were statistically significant, pooled estimates from meta-analyses showed a significant, 30-percent increase in risk for CHD in relation to ETS exposure" (USDHHS 2001, p. 356). Two additional reviews of secondhand smoke exposure and CHD were published during the review process preceding the publication of the 2001 Surgeon General's report but were not mentioned in that report: the 1997 Cal/EPA report (NCI 1999) and the 1997 Australian NHMRC Working Party Report (NHMRC 1997) on the health effects of involuntary smoking.

The Cal/EPA report reviewed 10 cohort studies and 8 case-control studies of secondhand smoke and CHD. Although the report did not provide a pooled estimate of RR across the published studies, it concluded that the "epidemiological data...in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers" (NCI 1999, p. 425). Furthermore, the report concluded that "an overall risk of about 30 percent is supported by the collective evidence and is within range of risk estimates observed for active smoking and CHD" (NCI 1999, p. 425).

The 1997 NHMRC Working Party report considered 22 analyses from 16 studies of secondhand smoke and CHD, with 17 of the 22 analyses indicating some increase in the risk of coronary events among nonsmokers exposed to secondhand smoke; in 8 of the studies, the results were statistically significant. Rather than conducting a quantitative meta-analysis, the NHMRC Working Party report summarized the data using a median RR corresponding to the interquartile range (NHMRC 1997). The median estimate of 1.24 (interquartile range, 1.02 to 1.62) was consistent with the pooled estimate of a 25 to 30 percent increase in risk of CHD reported in other comprehensive meta-analyses (Table 8.3).

Table 8.3 Meta-analyses of secondhand smoke exposure and coronary heart disease

Study	Design	Findings	
		Outcome	Pooled relative risk (95% confidence interval)
Wells 1994	7 cohort studies (Garland et al. 1985; Svendsen et al. 1987; Butler 1988; Hole et al. 1989; Sandler et al. 1989; Hirayama 1990; Humble et al. 1990)	Nonfatal coronary events	Women 1.51 (1.16–1.97) Men 1.28 (0.91–1.81) Combined 1.42 (1.15–1.75)
	5 case-control studies (Lee et al. 1986; He 1989; Jackson 1989; Dobson et al. 1991; He et al. 1994)	Fatal coronary events	Women 1.23 (1.11–1.36) Men 1.25 (1.03–1.51) Combined 1.23 (1.12–1.35)
Law et al. 1997	9 cohort studies (Garland et al. 1985; Svendsen et al. 1987; Butler 1988; Hole et al. 1989; Sandler et al. 1989; Hirayama 1990; Humble et al. 1990; Steenland et al. 1996; Kawachi et al. 1997)	All coronary events	Combined women/men 1.30 (1.22–1.38)
	10 case-control studies (Lee et al. 1986; He 1989; Jackson 1989; Dobson et al. 1991; Lee 1992; La Vecchia et al. 1993; He et al. 1994; Muscat and Wynder 1995; Tunstall-Pedoe et al. 1995; Ciruzzi et al. 1998)		
Wells 1998	9 cohort studies (Garland et al. 1985; Svendsen et al. 1987; Butler 1988; Hole et al. 1989; Sandler et al. 1989; Hirayama 1990; Humble et al. 1990; Steenland et al. 1996; Kawachi et al. 1997)	Nonfatal coronary events	Home exposure only 1.50 (1.23–1.83) Spousal exposure only 1.38 (1.02–1.61) Workplace exposure 1.32 (1.01–1.72)
	9 case-control studies (Lee et al. 1986; He 1989; Jackson 1989; Dobson et al. 1991; La Vecchia et al. 1993; He et al. 1994; Muscat and Wynder 1995; Tunstall-Pedoe et al. 1995; Ciruzzi et al. 1998)	Fatal coronary events	Home exposure only 1.25 (1.12–1.40) Spousal exposure only 1.21 (1.09–1.35) Workplace exposure 1.14 (0.99–1.32)
He et al. 1999	10 cohort studies (Hirayama 1984; Garland et al. 1985; Svendsen et al. 1987; Butler 1988; Hole et al. 1989; Sandler et al. 1989; Hirayama 1990; Humble et al. 1990; Steenland et al. 1996; Kawachi et al. 1997)	All coronary events	Women 1.24 (1.15–1.34) Men 1.22 (1.15–1.34) Combined 1.25 (1.17–1.32) Cohort data 1.21 (1.14–1.30) Case-control data 1.51 (1.26–1.81) Home exposure 1.17 (1.11–1.24) Workplace exposure 1.11 (1.0–1.23)
	8 case-control studies (Lee et al. 1986; He 1989; Jackson 1989; Dobson et al. 1991; La Vecchia et al. 1993; He et al. 1994; Muscat and Wynder 1995; Ciruzzi et al. 1998)		
Thun et al. 1999	10 cohort studies (Hirayama 1984; Garland et al. 1985; Svendsen et al. 1987; Butler 1988; Hole et al. 1989; Sandler et al. 1989; Hirayama 1990; Humble et al. 1990; LeVois and Layard 1995; Steenland et al. 1996)	All coronary events	Women 1.23 (1.15–1.32) Men 1.24 (1.15–1.32) Combined 1.25 (1.17–1.33)
	8 case-control studies (Lee et al. 1986; He 1989; Jackson 1989; Dobson et al. 1991; La Vecchia et al. 1993; He et al. 1994; Muscat and Wynder 1995; Ciruzzi et al. 1998)	Nonfatal coronary events	Combined women/men 1.32 (1.04–1.67)
		Fatal coronary events	Combined women/men 1.22 (1.14–1.30)

Updated Meta-Analysis of Exposure to Secondhand Smoke and Cardiovascular Disease

This meta-analysis updates the 1999 synthesis by He and colleagues (1999) of the literature covering the association between secondhand smoke exposure and cardiovascular disease. Articles on this association in nonsmokers published between June 1998 (the cutoff date for the He and colleagues [1999] paper) and April 2002 were identified through a search of PubMed using the Medical Subject Headings (MeSH) terms tobacco smoke pollution, CHD, and myocardial infarction and the keywords passive smoking and environmental tobacco smoke. The search was limited to English-language studies and yielded two additional studies compared with the previous meta-analysis.

All of the English-language studies included in previous meta-analyses, along with the two new studies, were abstracted and reviewed for inclusion in this meta-analysis. Five papers were excluded from the analysis (Jackson 1989; Dobson et al. 1991; Layard 1995; LeVois and Layard 1995; Tunstall-Pedoe et al. 1995). The articles by Jackson (1989) and Dobson and colleagues (1991) were excluded because they reported data that were reanalyzed in one of the more recent papers (McElduff et al. 1998). The paper by Tunstall-Pedoe and colleagues (1995) was excluded because of its cross-sectional design. The analyses by Layard (1995) and LeVois and Layard (1995) were excluded because of methodologic issues in exposure measurement. Layard's (1995) analysis of data from the 1986 NMFS was based on surrogate reports of exposure. LeVois and Layard (1995) used data from CPS-I and CPS-II; the CPS-II data were analyzed by Steenland and colleagues (1996) and the CPS-I data were insufficient for classifying exposure. The sensitivity of the results when these last three studies were excluded was tested and found not to produce significant differences.

For all of the studies, the estimates used were after adjustments for major cardiovascular disease risk factors, if available. If data were presented separately for women and men or for different exposure levels, they were pooled using random effects models. All quantitative pooling was carried out with Stata (version 7); results presented are for random effects models.

The meta-analysis included nine cohort studies (Table 8.1) and seven case-control studies (Table 8.2). All but two of the cohort studies were conducted in the United States; in contrast, only one of the case-control studies was conducted in the United States.

Six studies included only women, nine studies included both genders, and one study included only men. All study participants were nonsmokers, and in all but three studies they were lifetime nonsmokers. Those three studies either explicitly included former smokers or did not specify whether the nonsmokers had ever smoked (Hirayama 1984; Butler 1988; McElduff et al. 1998). Most of the studies (15) used in the updated meta-analysis documented self-reported exposures to secondhand smoke in the home either from a spouse or a cohabitant. Four studies also reported exposures at work separately from other settings, whereas two studies did not specify the different exposure sources. All but one of the cohort studies reported on the effect of exposure to secondhand smoke on fatal CHD (five) or on ischemic heart disease (IHD) (three). In addition, one cohort study combined fatal CHD and nonfatal acute MI. Four of the case-control studies used nonfatal acute MI as their outcome, one used nonfatal CHD, one used fatal and nonfatal acute MI, and one used nonfatal IHD.

Figure 8.1 provides the findings of the 16 studies included in the meta-analysis, along with the overall pooled estimate (RR = 1.27 [95 percent CI, 1.19–1.36]). The individual RR estimates cover a relatively narrow range, but the CIs are quite wide for the smaller studies.

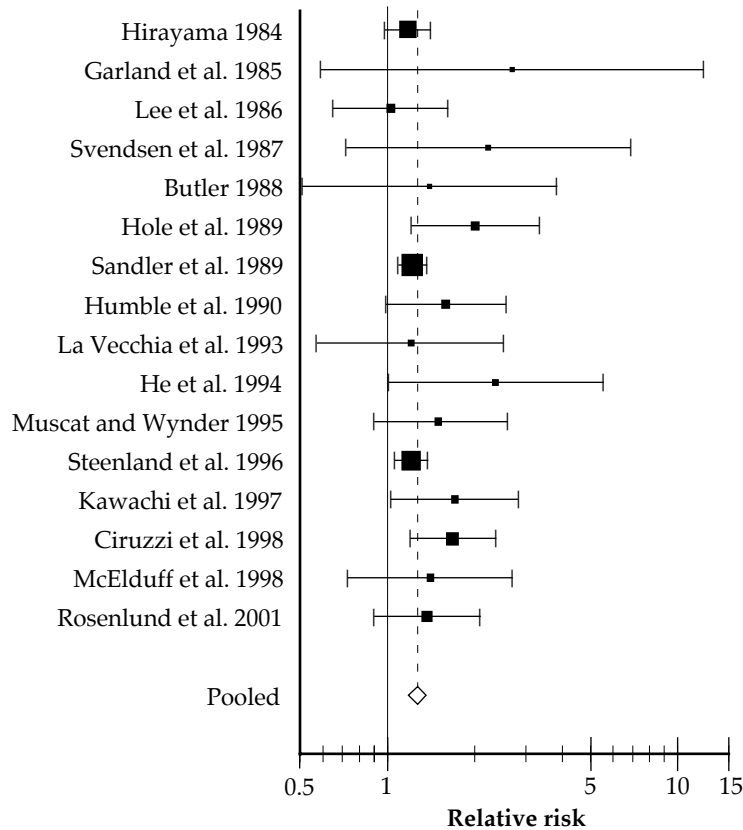
Variations in the pooled estimates were examined by place of exposure, gender, outcome, study design, and level of adjustment for potential confounding factors (Figure 8.2). Interpretation of these stratified analyses is limited by the precision of the estimates. Nonetheless, point estimates are similar for men and women and by exposure venue. The stringency of adjustment for potential confounding also has little effect on the estimates. The pooled estimate for the case-control studies is somewhat higher than for the cohort studies.

Dose-Response Analysis

Methods

Studies from the overall meta-analysis that provided measures of association stratified by the intensity of exposure to secondhand smoke, determined by the number of cigarettes smoked per day by a cohabitant, were used to generate pooled estimates for the dose-response analysis (Table 8.4). Although most studies categorized the daily number of cigarettes as none, 1 to 19, and 20 or more, several studies used the categories none, 1 to 14, and 15 or more.

Figure 8.1 Relative risks of coronary heart disease associated with secondhand smoke exposure among nonsmokers*



Note: The horizontal bars represent the 95% confidence intervals (CIs), and the size of the box for each study reflects each study's weight in the pooled estimate, with a larger box indicating a larger weight.

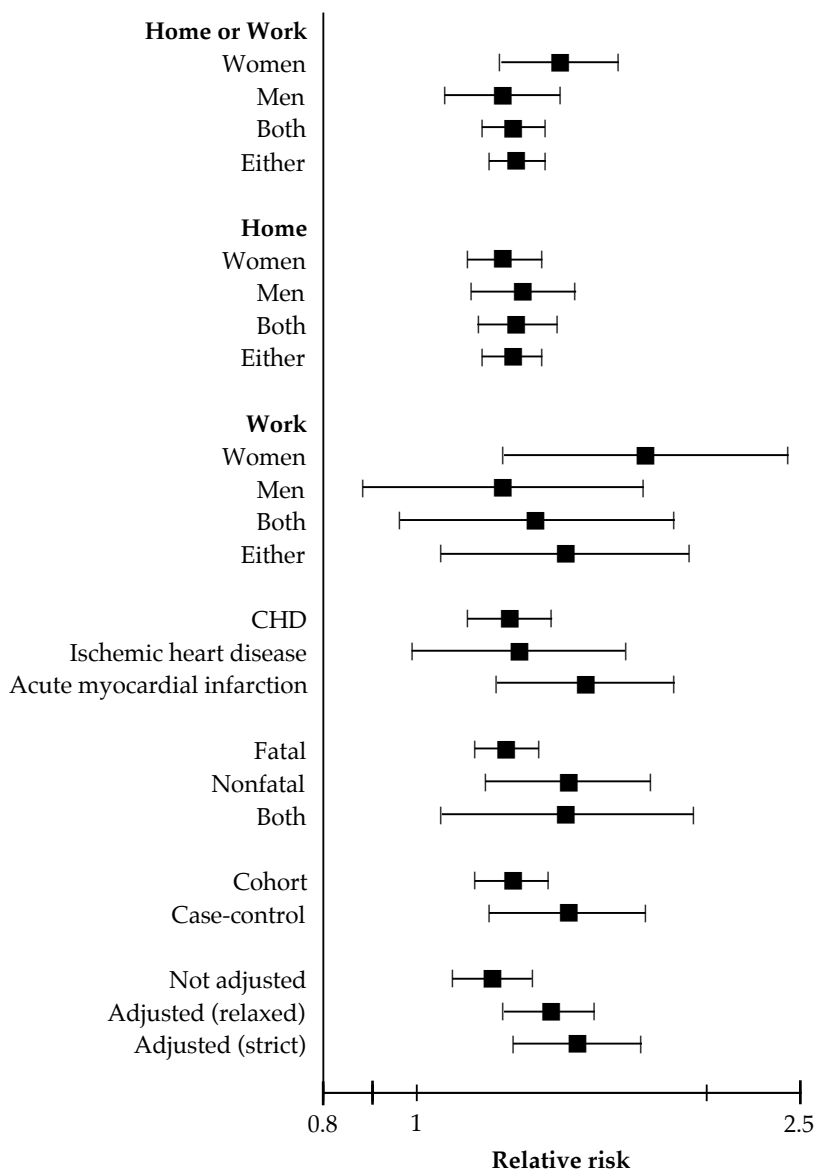
*Pooled estimate = 1.27 (95% CI, 1.19–1.36), the dashed line.

For the purpose of pooling as many studies as possible in this analysis, levels of exposure were categorized as none, low to moderate, and moderate to high. Categories of 1 to 19 and 1 to 14 cigarettes per day were therefore combined, as were categories of 20 or more and 15 or more cigarettes per day. Similar to the main analysis, adjusted measures of association were used when available. If confidence limits were not provided in a paper, they were estimated using standard methods appropriate for the study design. Papers that presented separate estimates for men and women were combined using random effects models. Pooled estimates were also calculated using random effects models. All calculations were carried out in Stata (version 7).

Results

Of the 19 studies, 8 included measures of association determined by the number of cigarettes smoked per day by a cohabitant, usually a spouse (Table 8.4). There were four cohort studies (Svendsen et al. 1987; Hole et al. 1989; Hirayama 1990; Steenland et al. 1996) and four case-control studies (La Vecchia et al. 1993; He et al. 1994; Ciruzzi et al. 1998; Rosenlund et al. 2001). The RR of CHD increased slightly with exposure to a higher level of secondhand smoke (Figure 8.3). Compared with unexposed nonsmokers, nonsmokers exposed to levels of secondhand smoke ranging from low to moderate (1 to 14 or 1 to 19 cigarettes per day) had a RR of 1.16 (95 percent

Figure 8.2 Pooled relative risks of coronary heart disease (CHD) associated with secondhand smoke exposure among nonsmokers in various subgroups



Note: Data are provided in detail in Tables 8.1 and 8.2. Stratified by gender for any exposure and for home and work exposures separately, by diagnosis (CHD, ischemic heart disease, acute myocardial infarction), by outcome (fatal or nonfatal), by study design (cohort or case-control), and whether the estimates were adjusted for important CHD risk factors (strict included several CHD risk factors, relaxed included at least one risk factor).

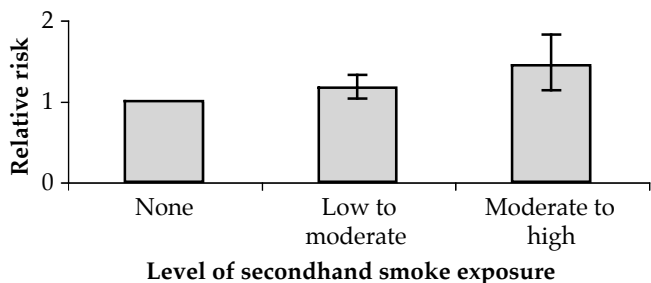
Sources: Hirayama 1984, 1990; Garland et al. 1985; Lee et al. 1986; Svendsen et al. 1987; Butler 1988; Helsing et al. 1988; He 1989; Hole et al. 1989; Jackson 1989; Sandler et al. 1989; Humble et al. 1990; Dobson et al. 1991; La Vecchia et al. 1993; He et al. 1994; Layard 1995; LeVois and Layard 1995; Muscat and Wynder 1995; Tunstall-Pedoe et al. 1995; Steenland et al. 1996; Kawachi et al. 1997; Ciruzzi et al. 1998; McElduff et al. 1998; Rosenlund et al. 2001.

Table 8.4 Studies included in the dose-response meta-analysis and pooled results

Study	Low to moderate exposure		Moderate to high exposure	
	Cigarettes/day	Relative risk (95% confidence interval)	Cigarettes/day	Relative risk (95% confidence interval)
Svendson et al. 1987	1–19	0.90 (0.02–6.70)	>19	3.21 (0.71–11.98)
Hole et al. 1989	1–15	2.09 (0.60–7.23)	>15	4.12 (1.21–14.05)
Hirayama et al. 1990	1–19	1.08 (0.9–1.3)	>19	1.3 (1.06–1.6)
La Vecchia et al. 1993	1–14	1.13 (0.45–2.82)	>14	1.3 (0.5–3.4)
He et al. 1994	6–20	1.61 (0.49–5.34)	>20	3.56 (0.81–15.58)
Steenland et al. 1996	1–19	1.31 (1.06–1.62)	>19	1.14 (0.97–1.34)
Ciruzzi et al. 1998	1–20	1.24 (0.61–2.52)	>20	4.03 (0.99–16.32)
Rosenlund et al. 2001	1–19	1.02 (0.73–1.42)	>19	1.58 (0.97–2.56)
Pooled results	Fixed effects:	1.16 (1.03–1.32)		1.26 (1.12–1.42)
	Random effects:	1.16 (1.03–1.32)		1.44 (1.13–1.82)

CI, 1.03–1.32). Nonsmokers exposed to levels ranging from moderate to high (≥ 15 or ≥ 20 cigarettes per day) had a RR of 1.44 (95 percent CI, 1.13–1.82) compared with unexposed nonsmokers. These estimates are similar to those of He and colleagues (1999), who found that nonsmokers exposed to 1 to 19 cigarettes per day had a RR of 1.23 (95 percent CI, 1.13–1.34), and nonsmokers exposed to 20 or more cigarettes per day had a RR of 1.31 (95 percent CI, 1.21–1.42). The differences between the two results are attributed to the studies used in the pooling and to the use of random effects models for this report. (He and colleagues [1999] reported results of fixed effects models.)

Figure 8.3 Pooled relative risks of coronary heart disease associated with various levels of exposure to secondhand smoke among nonsmokers



Note: None, low to moderate (1–14 or 1–19 cigarettes per day), and moderate to high (≥ 15 or ≥ 20 cigarettes per day).

Stroke

Six studies (four case-control, one cross-sectional, and one cohort) have examined the association between secondhand smoke and risk of stroke (Table 8.5). These studies did not address the risk for specific types of stroke. Two of the six published studies found a statistically significant increase for the risk of stroke among involuntary smokers (Sandler et al. 1989; Bonita et al. 1999).

Lee and colleagues (1986) carried out a hospital-based, case-control study in 10 regions in the United Kingdom. Involuntary smoking was classified according to self-reported secondhand smoke exposures at home, at work, during travel, and during leisure time. A secondhand smoke exposure score (ranging from 0 to 12) was based on a linear summation of the self-reported intensity of an exposure in each setting (0 = not at all; 1 = little; 2 = average; 3 = a lot). Participants were also asked whether their spouses had smoked cigarettes for the duration of their marriage (yes/no). The study included 92 persons who had suffered a stroke, but the authors did not define the diagnostic criteria used for stroke. Persons recruited as controls were hospitalized patients treated in medical, thoracic surgery, and radiotherapy wards and were matched to stroke patients for gender, age, and hospital region. Overall, the study did not find an association between exposure to spousal secondhand smoke and stroke (OR = 0.90 [95 percent CI, 0.53–1.52]). The OR of stroke among patients with a high secondhand smoke exposure score (ranging from 5 to 12) was 2.18 (95 percent CI, 0.86–5.48) compared with those with a low score (0 or 1).

Donnan and colleagues (1989) carried out a case-control study in four hospitals in Melbourne, Australia; a strength of this study was that 98 percent of the stroke cases were confirmed by a computerized tomography (CT) scan. Cases with a first-ever stroke (256 men, 166 women), including transient ischemic attack (TIA), were matched to 422 neighborhood controls. Self-reported exposures to spousal or parental smoking of at least a one-year duration were used to classify the exposure. Eighty-eight cases of stroke occurred among lifetime nonsmokers. The OR of stroke for lifetime nonsmokers with a smoking spouse was 1.6 (95 percent CI, 0.6–3.9). No association was found between exposures to parental smoking and stroke (OR = 1.0 [95 percent CI, 0.5–2.1]). The ORs were adjusted for hypertension, high cholesterol,

alcohol intake, history of MI, and any use of oral contraceptives.

Sandler and colleagues (1989) carried out a 12-year follow-up study of a cohort of 19,035 lifetime nonsmokers who had been identified through a 1963 private census of households in Washington county, Maryland. Investigators ascertained deaths that occurred in the cohort by matching the census to death certificates, with causes of death on the death certificate coded according to the *International Classification of Diseases*, 7th revision (World Health Organization [WHO] 1957). No further information was available to confirm cases of stroke. Investigators calculated the sum of smoking histories of all smokers in the household for a household tobacco smoke exposure score that was used to assess secondhand smoke exposures. The score did not measure the total secondhand smoke exposure because the number of cigarettes smoked per day outside of the home was not specified. Of the 14,873 female and 4,162 male lifetime nonsmokers in the study, 64.2 percent of the women and 30.0 percent of the men reported secondhand smoke exposures. After adjusting for age, marital status, housing quality, and education, the RRs of stroke mortality were 0.97 for men (95 percent CI, 0.65–1.46; based on 33 exposed cases) and 1.24 for women (95 percent CI, 1.03–1.49; based on 297 exposed cases) (Sandler et al. 1989).

Howard and colleagues (1998b) analyzed findings of magnetic resonance imaging (MRI) scans on 1,737 participants aged 55 through 70 years who had been selected from two of the four U.S. communities in the Atherosclerosis Risk in Communities (ARIC) Study. The study included 444 lifetime nonsmokers who were classified as not exposed to secondhand smoke by the definition used and 348 exposed lifetime nonsmokers. The disease outcome in this cross-sectional study was the prevalence of silent cerebral infarction (SCI), which was defined by standardized criteria on the MRI scans; SCI is an indicator of cerebrovascular disease. Acceptable interrater reliability was reported for the detection of lesions and the interpretation of scans. Involuntary smoking was defined as self-reported current exposure to secondhand smoke for one or more hours per week. The authors adjusted their risk estimates for a number of potential confounding factors, including hypertension, HDL cholesterol and triglyceride levels,

Table 8.5 Epidemiologic studies of secondhand smoke exposure and stroke

Study	Design	Population	Case definition	Relative risk (95% confidence interval)	Variables controlled for
Lee et al. 1986	Case-control Hospital-based	Men 4 cases 33 controls Women 8 cases 18 controls United Kingdom	Data were not reported	Spousal secondhand smoke 0.90 (0.53–1.52) All sources of secondhand smoke 2.18* (0.86–5.48)	Age, gender, marital status
Donnan et al. 1989	Case-control Hospital cases and community controls	88 cases and 88 matched controls Lifetime nonsmoking men and women Australia	Incident stroke and transient ischemic attack (98% confirmation by computerized tomography [CT] scan)	Spousal secondhand smoke 1.6 (0.6–3.9) Parental secondhand smoke 1.0 (0.5–2.1)	Age, gender, hypertension, high cholesterol, alcohol intake, history of heart attack, any use of oral contraceptives
Sandler et al. 1989	Cohort study with 12-year follow-up	4,162 men and 14,873 women Lifetime nonsmokers United States	<i>International Classification of Diseases</i> codes from death certificates, 7th revision	Secondhand smoke exposure in the home Men 0.97 (0.65–1.46) Women 1.24 (1.03–1.49)	Age, marital status, housing quality, education
Howard et al. 1998b	Cross-sectional study of Atherosclerosis Risk in Communities Study participants	444 lifetime nonsmokers not exposed to secondhand smoke and 348 lifetime nonsmokers exposed to secondhand smoke United States	Prevalent silent cerebral infarction	All sources of secondhand smoke Prevalence odds ratio = 1.06 (0.64–1.75)	Age, gender, race, hypertension, high-density lipoprotein cholesterol and triglyceride levels, diabetes mellitus, dietary fat, exercise, body mass index, alcohol consumption
Bonita et al. 1999	Case-control Hospital cases and community controls	215 cases and 1,336 controls among nonsmokers, including former smokers who quit >10 years ago New Zealand	Incident stroke based on World Health Organization criteria	Secondhand smoke exposure in the home Men 2.10 (1.33–3.32) Women 1.66 (1.07–2.57) Combined 1.82 (1.34–2.49)	Age, gender, hypertension, diabetes, history of heart disease
You et al. 1999	Case-control Hospital cases and community controls	149 cases and 210 controls Lifetime nonsmoking men and women Australia	Incident stroke verified by CT scan	Spousal secondhand smoke 1.70 (0.98–2.92) Parental secondhand smoke 0.78 (0.48–1.26)	Age, gender, education, hypertension, diabetes mellitus, history of heart disease

*Comparing the highest level of exposure with the lowest (see Lee et al. 1986, Table V, p. 102).

diabetes mellitus, dietary fat intake, leisure time physical activity, BMI, and alcohol intake. The investigators calculated an adjusted prevalence OR of 1.06 for SCI for those classified as exposed to secondhand smoke (95 percent CI, 0.64–1.75) compared with unexposed nonsmokers. There was no relationship between hours of exposure to secondhand smoke and SCI (Howard et al. 1998b).

Bonita and colleagues (1999) carried out a population-based, case-control study of secondhand smoke and stroke in Auckland, New Zealand. Diagnostic criteria and methods for the 215 nonsmoking persons aged 35 through 74 years with first-ever acute stroke were defined according to WHO guidelines. The 1,336 nonsmoking controls were community-dwelling participants drawn from a 1993–1994 cross-sectional survey of cardiovascular risk factors carried out in the same city. The investigators determined exposures to secondhand smoke by asking patients and controls the same questions and characterized an exposure as a household member who regularly smoked cigarettes in their presence, or a coworker who smoked in the same indoor room in their presence for more than 1 year during the past 10 years. Risks were assessed among lifetime nonsmokers combined with long-term former smokers. Exposure to secondhand smoke was associated with an increased risk among men (crude OR = 2.10 [95 percent CI, 1.33–3.32]) and women (crude OR = 1.66 [95 percent CI, 1.07–2.57]). Overall, the risk of stroke was 1.82 (95 percent CI, 1.34–2.49)

for involuntary smokers with adjustment for several potential confounding factors. The nonsmokers in this study (both cases and controls) included former smokers who had stopped smoking for more than 10 years. No attempt was made in this study to distinguish secondhand smoke exposures at home, at work, or elsewhere (Bonita et al. 1999).

One case-control study in Australia compared 452 hospitalized cases of first-ever ischemic stroke and 452 gender-matched neighborhood controls (You et al. 1999). Ischemic stroke was defined as the acute onset of a focal neurologic deficit that lasted more than 24 hours and that was verified by CT (excluding hemorrhage). Involuntary smoking was defined as living with a father, mother, or spouse who smoked at least one cigarette per day. To estimate the OR, You and colleagues (1999) controlled for educational attainment, history of CHD, hypertension, and diabetes mellitus, and then excluded current and former smokers. There were 154 participants who had suffered a stroke and 213 with no history of a stroke among the lifetime nonsmokers; missing values in either cases or controls bring the numbers to 149 cases and 210 controls used in the analysis. The adjusted OR of stroke for lifetime nonsmokers exposed to spousal smoking was 1.70 (95 percent CI, 0.98–2.92). No association was found for exposures to parental smoking (OR = 0.78 [95 percent CI, 0.48–1.26]) (Table 8.5). These studies were not pooled in this report because of their small number and the heterogeneity of their methods.

Subclinical Vascular Disease

A number of studies have been published linking secondhand smoke exposure to measures of subclinical vascular disease. These studies offer insights into the mechanisms underlying the relationship between exposures to secondhand smoke and the development of clinical coronary and cerebrovascular events (Howard and Wagenknecht 1999). Five different types of subclinical vascular outcomes that have been studied in humans in relation to secondhand smoke include the following:

- assessing intimal-medial thickness (IMT) of the carotid artery using B-mode ultrasound as an

index of systemic atherosclerosis (Howard et al. 1994, 1998a; Diez-Roux et al. 1995);

- assessing flow-mediated arterial endothelial function using B-mode ultrasound of the brachial artery as an index of vascular damage (Celermajer et al. 1996; Lekakis et al. 1997; Raitakari et al. 1999);
- assessing coronary endothelial dysfunction using a quantitative coronary angiography to measure the extent of impairment of acetylcholine-induced coronary artery dilatation (Sumida et al. 1998);

- assessing coronary flow velocity reserve using noninvasive transthoracic Doppler echocardiography (Otsuka et al. 2001); and
- assessing aortic elastic properties before and after involuntary smoking with the aortic pressure-diameter relation (Stefanadis et al. 1998, 1999).

Published evidence suggests that exposure to secondhand smoke is damaging for each type of subclinical vascular outcome. This section reviews the evidence on secondhand smoke in relation to carotid arterial wall thickness.

Carotid Intimal-Medial Thickness

Carotid IMT, assessed by B-mode ultrasound, is an established predictor of clinical events, including MI and stroke (Bots et al. 1997; Chambless et al. 1997; O'Leary et al. 1999). All three published studies linking secondhand smoke to an increased carotid IMT have used data from the ARIC Study (Howard et al. 1994, 1998a; Diez-Roux et al. 1995). In a cross-sectional analysis of data from the baseline ARIC assessment of 5,113 nonsmokers, Howard and colleagues (1994) found a difference of 11 micrometers (μm) in the average IMT of unexposed compared with exposed nonsmokers. This difference increased to 13 μm ($p = 0.003$) after adjusting for age, race, gender, education, hypertension, diabetes mellitus, low-density lipoprotein cholesterol level, fat intake, alcohol consumption, BMI, and leisure time physical activity. Among exposed male nonsmokers, there was a statistically significant dose-response relationship between the number of hours of the exposure and carotid IMT ($p = 0.03$). No dose-response relationship was observed among unexposed female nonsmokers.

Diez-Roux and colleagues (1995) assessed IMT in relation to current and past exposures to secondhand smoke in a cohort of 2,073 persons who were included in the ARIC Study. The participants had information available on secondhand smoke exposure in 1975 and

in 1987–1989. The authors defined four groups of lifetime nonsmokers: (1) those not exposed to secondhand smoke at either exam, (2) those exposed at the first but not at the second exam, (3) those exposed at the second but not at the first exam, and (4) those exposed at both exams. Exposure at one or both exams was associated with a nearly identical increase in IMT. This finding suggests that secondhand smoke has long-term harmful effects on atherosclerosis. The average IMT was 706 μm ($\pm 13 \mu\text{m}$) for those not exposed in either period, 731 μm ($\pm 22 \mu\text{m}$) for those exposed in the first period only, 738 μm ($\pm 11 \mu\text{m}$) for those exposed in the second period only, and 734 μm ($\pm 12 \mu\text{m}$) for those exposed in both periods (Diez-Roux et al. 1995).

Finally, the ARIC Study examined the longitudinal association between secondhand smoke and the progression of IMT (Howard et al. 1998a). During a three-year follow-up period, the IMT progression rate was 31.6 μm for exposed lifetime nonsmokers and 25.9 μm for unexposed lifetime nonsmokers. The estimates of IMT progression were adjusted for the same demographic and coronary risk factors as in the cross-sectional report by the same investigators (Howard et al. 1994). Among lifetime nonsmokers and former smokers combined, exposure to secondhand smoke was associated with an adjusted IMT progression rate of 5.9 μm over three years ($\pm 2.3 \mu\text{m}$; $p = 0.01$). In proportional terms, this rate amounted to a 20 percent increase in IMT, which was nearly one-third of the size of the corresponding rate of progression among current smokers. No dose-response pattern was detected, however, between an increase in weekly hours of exposure and increased IMT progression rates.

The evidence on CHD and stroke are considered separately in this section; however, the underlying pathogenetic mechanisms by which involuntary smoking increases risk are shared. For both outcomes, progression of atherosclerosis and increased risk for thrombosis are relevant. The finding that exposure to secondhand smoke increases IMT is supportive of a causal role for secondhand smoke exposure for both CHD and stroke.

Evidence Synthesis

Secondhand Smoke and Coronary Heart Disease

Epidemiologic studies published since the 1986 Surgeon General's report (USDHHS 1986) demonstrate convincingly that secondhand smoke is associated with an increased risk for CHD. The results of both case-control and cohort studies carried out in multiple populations consistently indicate about a 25 to 30 percent increase in risk of CHD from exposure to secondhand smoke. Additionally, cross-sectional and prospective studies convincingly demonstrate an association between exposure to secondhand smoke and the progression of carotid arterial IMT. The excess risk is unlikely to be explained by a measurement error with resulting exposure misclassification or uncontrolled confounding. One type of measurement error, the failure to correct for background secondhand smoke exposure, would lead to an underestimation of the association. Because exposures to secondhand smoke in different environments are presumed to be additive, studies that assess exposures in only one setting will underestimate the true, overall association. Although few studies have addressed CHD risk from secondhand smoke exposure in the workplace, there is no biologically plausible reason to suppose that the effect of secondhand smoke exposure at work differs from the effect of exposures in the home environment.

When interpreting the epidemiologic data, researchers must also consider the possibility that the association reflects uncontrolled confounding. Several cross-sectional studies show differing profiles of cardiovascular risk factors in secondhand smoke-exposed versus unexposed persons. However, an association has been consistently observed in multiple populations, and a number of studies have considered potential confounding factors in the analysis. Whereas some degree of residual confounding can never be fully excluded, the consistency of the association of secondhand smoke exposure with CHD risk and the persistence of an association with controls for confounding weigh heavily against residual confounding as the sole explanation.

A substantial body of experimental evidence supports the biologic plausibility of an association of CHD risk with secondhand smoke exposure. Secondhand smoke exposure adversely affects platelet

function and endothelial function. In animal models, secondhand smoke exposure produces atherosclerosis in the coronary arteries.

Current exposures to secondhand smoke appear to be more harmful than past exposures, and several studies suggest a higher risk of CHD from exposures of higher intensities. At least one study suggests that the risk declines as more time elapses since the last exposure.

Compared with the effects of active smoking, the magnitude of the association between secondhand smoke and CHD seems large. This finding can be reconciled, however, with experimental data from both human and animal studies showing that acute effects of secondhand smoke on platelet aggregation as well as on endothelial dysfunction are nonlinear (Chapter 2, Toxicology of Secondhand Smoke).

Secondhand Smoke and Stroke

The evidence is more limited for an association between secondhand smoke and stroke, although the biologic plausibility of an association with stroke risk is supported by the same evidence considered for CHD. The findings of the epidemiologic studies of CHD are complementary to those of stroke. Four case-control studies, one cross-sectional study, and one cohort study have addressed the association between secondhand smoke and the risk of stroke. In these studies, exposures to secondhand smoke were assessed either through self-reports (Lee et al. 1986; Donnan et al. 1989; Howard et al. 1998b; Bonita et al. 1999), or through the use of living in a household with other smokers as an indicator (Sandler et al. 1989; You et al. 1999). In addition to the possibility of measurement error, recall bias may be a problem in case-control studies that assess involuntary smoking with participant reports.

Four of the six studies measured and adjusted for potential confounding variables such as hypertension and diabetes (Donnan et al. 1989; Howard et al. 1998b; Bonita et al. 1999; You et al. 1999). Measures of exposure differed across the studies. Of the six studies, two reported a statistically significant increase in the risk of stroke among involuntary smokers (Sandler et al. 1989; Bonita et al. 1999). Two other studies reported elevated risks of stroke from exposures to spousal

smoking, but the lower 95 percent CI was below unity for both studies (Donnan et al. 1989; You et al. 1999).

The six published studies also varied in their definition of stroke. Lee and colleagues (1986) did not define diagnostic criteria, whereas Donnan and colleagues (1989) included cases of TIA. Sandler and colleagues (1989) studied only stroke deaths based on death certificates; Howard and colleagues (1998b) examined SCI using MRI scans. The published studies of secondhand smoke exposure and stroke are still too

few and too heterogeneous in their methods and their exposure and outcome measures to warrant a pooled analysis.

Given the established causal associations between active cigarette smoking and stroke and between involuntary smoking and CHD, an association between secondhand smoke and stroke is biologically plausible. There is a need for further research, especially more cohort studies, before a causal association can be inferred.

Conclusions

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women.
2. Pooled relative risks from meta-analyses indicate a 25 to 30 percent increase in the risk of coronary heart disease from exposure to secondhand smoke.
3. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke.
4. Studies of secondhand smoke and subclinical vascular disease, particularly carotid arterial wall thickening, are suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and atherosclerosis.

Overall Implications

Cal/EPA has estimated that 46,000 (a range of 22,700 to 69,600) cardiac deaths in the United States each year are attributable to secondhand smoke exposures at home and in the workplace (Cal/EPA 2005). Thus, the estimated exposures in these two environments can potentially produce a substantial burden of avoidable deaths. Because researchers have identified workplaces as predominant sites for exposure to secondhand smoke (Chapter 4, Prevalence of Exposure to Secondhand Smoke), the estimated pooled RR for workplace exposures suggests that secondhand smoke represents a significant occupational hazard. Following a modified risk assessment approach adopted in 1994 by the U.S. Occupational Safety and Health Administration, Steenland (1999) estimated that as a

result of secondhand smoke exposures in the workplace, the excess risk of death from heart disease by 70 years of age was 7 per 1,000 (95 percent CI, 1–13 per 1,000). On the basis of current estimates of exposures to secondhand smoke in U.S. workplaces, Steenland further estimated that these exposures had caused 1,710 excess deaths from CHD annually among non-smoking workers aged 35 through 69 years.

This review identified several areas for further research. Mechanistic studies that further refine the dose-response relationships and mechanisms of acute responses of the cardiovascular system to secondhand smoke exposure should be carried out. Additional epidemiologic studies of stroke are also needed.

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