

## PASSIVE SMOKING AND THE RISK OF CORONARY HEART DISEASE — A META-ANALYSIS OF EPIDEMIOLOGIC STUDIES

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### ABSTRACT

**Background** The effect of passive smoking on the risk of coronary heart disease is controversial. We conducted a meta-analysis of the risk of coronary heart disease associated with passive smoking among nonsmokers.

**Methods** We searched the Medline and Dissertation Abstracts Online data bases and reviewed citations in relevant articles to identify 18 epidemiologic (10 cohort and 8 case-control) studies that met pre-stated inclusion criteria. Information on the designs of the studies, the characteristics of the study subjects, exposure and outcome measures, control for potential confounding factors, and risk estimates was abstracted independently by three investigators using a standardized protocol.

**Results** Overall, nonsmokers exposed to environmental smoke had a relative risk of coronary heart disease of 1.25 (95 percent confidence interval, 1.17 to 1.32) as compared with nonsmokers not exposed to smoke. Passive smoking was consistently associated with an increased relative risk of coronary heart disease in cohort studies (relative risk, 1.21; 95 percent confidence interval, 1.14 to 1.30), in case-control studies (relative risk, 1.51; 95 percent confidence interval, 1.26 to 1.81), in men (relative risk, 1.22; 95 percent confidence interval, 1.10 to 1.35), in women (relative risk, 1.24; 95 percent confidence interval, 1.15 to 1.34), and in those exposed to smoking at home (relative risk, 1.17; 95 percent confidence interval, 1.11 to 1.24) or in the workplace (relative risk, 1.11; 95 percent confidence interval, 1.00 to 1.23). A significant dose-response relation was identified, with respective relative risks of 1.23 and 1.31 for nonsmokers who were exposed to the smoke of 1 to 19 cigarettes per day and those who were exposed to the smoke of 20 or more cigarettes per day, as compared with nonsmokers not exposed to smoke ( $P=0.006$  for linear trend).

**Conclusions** Passive smoking is associated with a small increase in the risk of coronary heart disease. Given the high prevalence of cigarette smoking, the public health consequences of passive smoking with regard to coronary heart disease may be important. (N Engl J Med 1999;340:920-6.)

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CORONARY heart disease is the leading cause of death in the United States and other industrialized countries. In 1995, an estimated 481,287 deaths in the United States resulted from coronary heart disease, representing more than 1 of every 5 deaths.<sup>1</sup> In many developing countries, mortality from coronary heart disease has increased rapidly and the disease has become the leading cause of death.<sup>2</sup>

Active cigarette smoking is one of the most important modifiable risk factors for coronary heart disease.<sup>3-5</sup> In the United States, active cigarette smoking results in approximately 100,000 deaths due to coronary heart disease each year.<sup>6</sup> Many epidemiologic studies<sup>7-25</sup> and reviews<sup>26-32</sup> have pointed to the effect of passive smoking on the risk of coronary heart disease. Even so, the extent of the association between passive smoking and coronary heart disease is not fully known. Therefore, we assessed the relation between passive smoking and the risk of coronary heart disease among nonsmokers.

### METHODS

#### Selection of Studies

We searched the Medline data base (from January 1966 through June 1998) for literature with the medical subject headings "tobacco smoke pollution," "coronary disease," and "myocardial infarction" and the key words "passive smoking" and "environmental tobacco smoke." The search was restricted to studies of passive smoking in humans. We also conducted a search of abstracts listed in Dissertation Abstracts Online using the key word "passive smoking," and we performed a manual search of references cited in published original and review articles.<sup>26-32</sup> All the potentially relevant manuscripts were independently reviewed by three investigators. Areas of disagreement or uncertainty were adjudicated by the other investigators. Inclusion was restricted to prospective cohort studies and case-control studies in which the relative risk (or relative odds) of coronary heart disease associated with passive smoking was reported.

Three potentially relevant studies were excluded from analysis.<sup>25,33,34</sup> The first was a cross-sectional survey.<sup>25</sup> The second did not provide valid data on passive smoking, and the case and control groups were not comparable.<sup>33</sup> The results of the third study, an analysis of the data from the American Cancer Society Cancer Prevention studies I and II,<sup>34</sup> conflicted with the findings of a more careful analysis of the same data conducted by Steenland and colleagues.<sup>15</sup>

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**TABLE 1.** CHARACTERISTICS OF 10 COHORT STUDIES OF PASSIVE SMOKING AND THE RISK OF CORONARY HEART DISEASE AMONG NONSMOKERS.

STUDY	YEAR AND LOCATION OF STUDY	POPULATION	EXPOSURE	OUTCOME*	DURATION OF FOLLOW-UP (YR)	VARIABLES CONTROLLED FOR
Hirayama <sup>7,8</sup>	1984, Japan	91,540 women; age, ≥40 yr	Husband's smoking	Death due to CHD	16	Age
Garland et al. <sup>9</sup>	1985, California	695 women; age, 50–79 yr	Husband's self-reported smoking	Death due to CHD	10	Age, systolic blood pressure, serum cholesterol level, body-mass index, and years of marriage
Svendsen et al. <sup>10</sup>	1987, United States	1245 men; age, 35–57 yr†	Wife's smoking and workplace exposure	MI and death due to CHD	6–8	Age, blood pressure, serum cholesterol level, body weight, alcohol consumption, and level of education
Butler <sup>11</sup>	1988, California	6507 Seventh-Day Adventist women; age, ≥25 yr	Husband's smoking	Death due to CHD	6	Age
Butler <sup>11</sup>	1988, California	4098 male and 2334 female Seventh-Day Adventists; age, ≥25 yr‡	Home and workplace exposure	Death due to CHD	6	Age and sex
Sandler et al. <sup>12</sup>	1989, Maryland	19,035 men and women; age, ≥25 yr	Home exposure	Death due to CHD	12	Age, sex, marital status, level of education, and quality of housing
Hole et al. <sup>13</sup>	1989, Scotland	2455 men and women; age, 45–64 yr	Cohabitant's smoking	Death due to CHD	11.5	Age, sex, socioeconomic status, diastolic blood pressure, serum cholesterol level, and body-mass index
Humble et al. <sup>14</sup>	1990, Georgia	513 women; age, ≥40 yr	Husband's smoking	Death due to CHD	20	Age, serum cholesterol level, diastolic blood pressure, body-mass index, and square of body-mass index
Steenland et al. <sup>15</sup>	1996, United States	479,680 men and women; age, ≥30 yr§	Home and workplace exposure and spouse's self-reported smoking	Death due to CHD	7	Age, sex, heart disease, hypertension, diabetes mellitus, body-mass index, level of education, aspirin use, diuretic use, estrogen use, alcohol consumption, exercise, and others
Kawachi et al. <sup>16</sup>	1997, United States	32,046 female nurses; age, 36–61 yr	Home and workplace exposure	MI and death due to CHD	10	Age, alcohol consumption, body-mass index, hypertension, diabetes mellitus, hyperlipidemia, estrogen-replacement therapy, exercise, saturated-fat intake, vitamin E intake, use of aspirin, parental history of MI, and others

\*CHD denotes coronary heart disease, and MI myocardial infarction.

†Subjects were enrolled in the Multiple Risk Factor Intervention Trial.

‡Subjects were enrolled in the Adventist Health Smog Study.

§Subjects were enrolled in the American Cancer Society Cancer Prevention Study II.

**Data Abstraction**

All the data were independently abstracted in triplicate by means of a standardized protocol and data-collection form by three investigators, each of whom was unaware of the coding system used by the other two. Disagreements were resolved by discussion. Recorded characteristics of the studies were as follows: first author's name and year of publication, study design (prospective cohort study or case-control study), characteristics of the study subjects (sample size, sampling methods, and distribution according to age, sex, and race), measures of outcome and exposure, duration of follow-up (for prospective cohort studies), confounding factors that were controlled for by matching or adjustment, and the relative risk (or relative odds) of coronary heart disease associated with passive smoking and its standard error, overall and in each subgroup, according to sex and the site of exposure (home or workplace).

**Statistical Analysis**

Relative risk was used as a measure of the relation between passive smoking and the risk of coronary heart disease. For case-

control studies, the relative odds were used as a surrogate measure of the corresponding relative risk. Because the absolute risk of coronary heart disease is low, the relative odds approximate the relative risk. Before data were pooled, relative risks from individual studies were transformed to their natural logarithms, or log (RR<sub>i</sub>), to stabilize the variances and to normalize the distributions.<sup>35</sup> The overall log (RR) was estimated as

$$\log (RR) = \sum w_i \times \log (RR_i) \div \sum w_i$$

where w<sub>i</sub> is a weight that consists of the reciprocal of the variance of the log (RR<sub>i</sub>). The homogeneity of log (RR<sub>i</sub>) across the k studies was tested by using Woolf's  $\chi^2$  statistic<sup>36</sup>:

$$\chi^2 = \sum w_i [\log (RR_i) - \log (RR)]^2, \text{ with } df = k - 1.$$

The variance of the natural logarithm was derived from the confidence interval provided in the study or was calculated by means of standard formulas.<sup>36</sup> Ninety-five percent confidence intervals were approximated by natural-logarithm transformation and were expressed again by natural-antilogarithm transformation of the data. The z statistic was calculated, and a two-tailed P value

**TABLE 2.** CHARACTERISTICS OF EIGHT CASE–CONTROL STUDIES OF PASSIVE SMOKING AND THE RISK OF CORONARY HEART DISEASE AMONG NONSMOKERS.\*

STUDY	YEAR AND LOCATION OF STUDY	CASE PATIENTS	CONTROLS	EXPOSURE	VARIABLES CONTROLLED FOR
Lee et al. <sup>17</sup>	1986, England	118 male and female patients with ischemic heart disease in 10 hospital regions	451 hospital patients	Spouse's smoking	Age, sex, and hospital region
He et al. <sup>18</sup>	1989, China	34 female patients with CHD	34 hospitalized patients and 34 community residents	Spouse's smoking for $\geq 5$ yr	Age, ethnicity, occupation, area of residence, hypertension, hyperlipidemia, alcohol consumption, exercise, and family history of MI
Jackson <sup>19</sup>	1989, New Zealand	39 male and female patients with CHD	235 residents of the same community	Home and workplace exposure (self- or surrogate-reported)	Age, sex, socioeconomic status, and history of ischemic heart disease
Dobson et al. <sup>20</sup>	1991, Australia	343 male and female patients with MI or death due to CHD in the community	825 randomly selected residents of the same community	Home and workplace exposure	Age, sex, and history of heart disease
La Vecchia et al. <sup>21</sup>	1993, Italy	90 male and female patients with acute MI†	194 patients in the same network of hospitals	Spouse's smoking	Age, sex, level of education, coffee consumption, body-mass index, serum cholesterol level, hypertension, diabetes mellitus, and family history of acute MI
He et al. <sup>22</sup>	1994, China	59 female patients with CHD in 3 hospitals	126 patients in the same hospitals or from the community	Husband's smoking and workplace exposure	Age, hypertension, personality type, serum total and high-density lipoprotein cholesterol level
Muscat and Wynder <sup>23</sup>	1995, United States	114 male and female hospitalized patients with incident MI in 4 cities	158 patients in the same hospitals	Home and workplace exposure	Age, sex, race, level of education, hypertension, and calendar year
Ciruzzi et al. <sup>24</sup>	1998, Argentina	336 male and female patients with acute MI in 35 coronary care units	446 patients in the same hospitals	Spouse's and children's smoking	Age, sex, level of education, body-mass index, hyperlipidemia, history of diabetes or hypertension, and family history of CHD

\*CHD denotes coronary heart disease, and MI myocardial infarction.

†Patients were enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II.

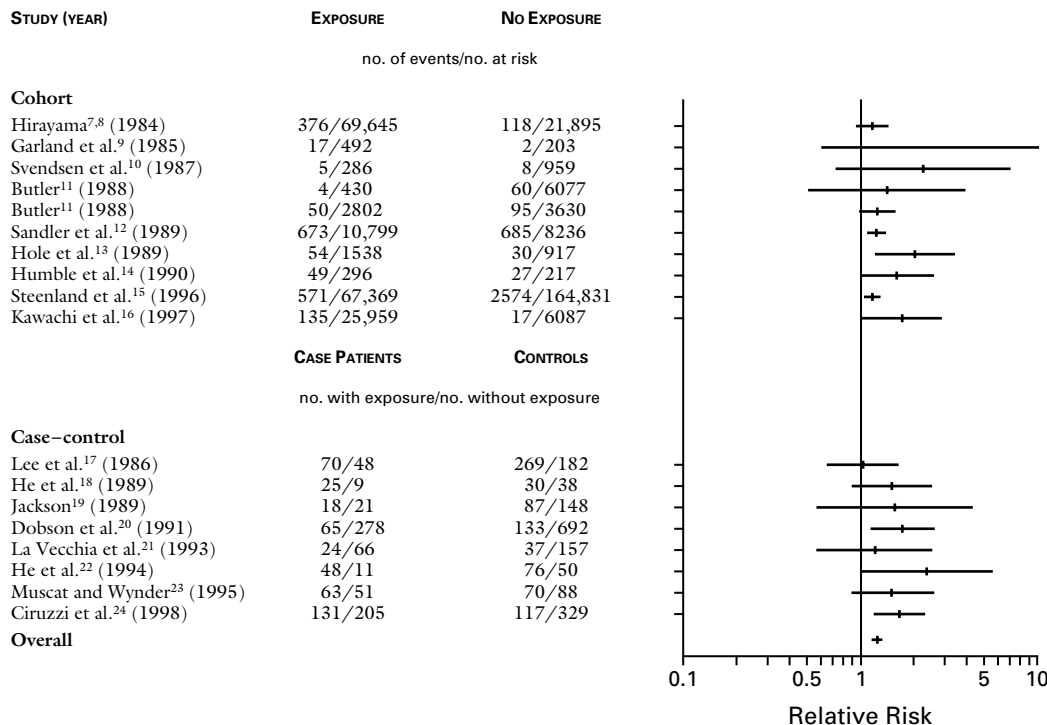
of less than 0.05 was considered to indicate statistical significance. Linear regression analysis was used to test the dose–response relation between the degree of exposure to smoke (cigarettes per day) and the log relative risk and between the duration of exposure (years) and the log relative risk, with weighting by the reciprocal of its variance.

To estimate the robustness of our findings with respect to different assumptions, we conducted a sensitivity analysis. We used both a fixed-effects model and a random-effects model to calculate the pooled relative risk.<sup>37</sup> Because these two approaches yielded virtually identical overall estimates, we present only the results obtained with the fixed-effects model. We also examined the influence of various exclusion criteria on the overall relative risk.

The potential for publication bias was examined by constructing a “funnel plot” in which variance was plotted against log relative risk.<sup>38</sup> In addition, the association between variance and standardized log relative risk was analyzed by rank correlation with use of the Kendall tau method. If small studies with negative results were less likely to be published, the correlation between variance and log relative risk would be high; in the absence of publication bias, no significant correlation between variance and log relative risk would be evident.<sup>38</sup>

## RESULTS

We included 10 prospective cohort studies and 8 case–control studies in our meta-analysis. The characteristics of the study subjects and the designs of the cohort studies are presented in Table 1. Of the 10 cohort studies, 8 were conducted in the United States. The number of subjects ranged from 513 in the Evans County Study<sup>14</sup> to 479,680 in the American Cancer Society Cancer Prevention Study II.<sup>15</sup> Passive exposure to smoking at home was measured in all the cohort studies, but only four measured workplace exposure. In all the cohort studies, the outcome was myocardial infarction or death due to coronary heart disease. The mean follow-up period ranged from 6 to 20 years. The potentially confounding effects of age and sex were controlled for in all the cohort studies, whereas only six controlled for blood pressure or hypertension, body weight or body-mass index, and serum cholesterol level or hyperlipidemia.



**Figure 1.** Relative Risks of Coronary Heart Disease Associated with Passive Smoking among Nonsmokers in 18 Epidemiologic Studies. The horizontal bars represent the 95 percent confidence intervals. The relative risk in the study by Garland et al.<sup>9</sup> was 14.9.

Most of the eight case-control studies were conducted outside the United States (Table 2). The number of case subjects enrolled in these studies ranged from 34 to 343, and the corresponding number of control subjects ranged from 68 to 825. In four studies, passive smoking was assessed both at home and in the workplace; in the other four, it was assessed only at home. Matching or adjustment was performed for a variety of potential confounders.

Figure 1 shows the relative risk (and 95 percent confidence intervals) of coronary heart disease associated with passive smoking in each study and overall. All the relative risks were greater than 1, but only 7 of the 18 were statistically significant. As compared with nonsmokers who were not exposed to smoke, nonsmokers exposed to passive smoking had an overall relative risk of coronary heart disease of 1.25 (95 percent confidence interval, 1.17 to 1.32) (Table 3).

This estimate changed very little after studies with different inclusion criteria had been excluded. For example, after the exclusion of an outlier study with an extremely large relative risk,<sup>9</sup> the overall relative risk was reduced only slightly, to 1.24. After three studies that were available only as dissertations were excluded,<sup>11,19</sup> the overall relative risk did not change. When the analysis was confined to the 14 studies that used myocardial infarction, death due to coro-

**TABLE 3.** OVERALL RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH PASSIVE SMOKING AMONG NONSMOKERS IN STUDIES THAT USED DIFFERENT EXCLUSION CRITERIA.\*

STUDIES INCLUDED IN ANALYSIS	NO. OF STUDIES	RELATIVE RISK (95% CI)	P VALUE
All studies	18	1.25 (1.17-1.32)	<0.001
All studies except one outlier study†	17	1.24 (1.17-1.32)	<0.001
Peer-reviewed studies‡	15	1.25 (1.17-1.33)	<0.001
Studies that used death from MI or CHD as an outcome measure§	14	1.24 (1.17-1.32)	<0.001
Studies that controlled for important CHD risk factors¶	10	1.26 (1.16-1.38)	<0.001

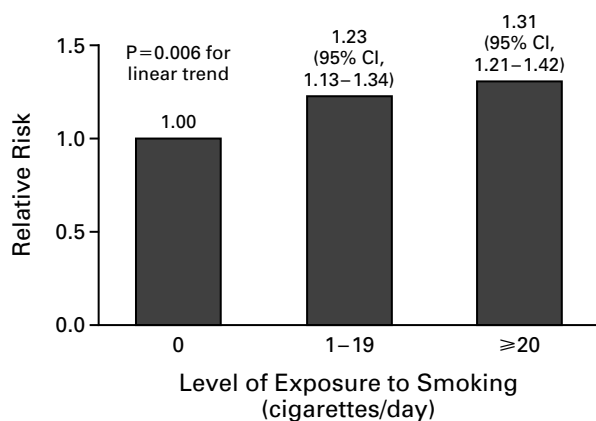
\*CI denotes confidence interval, MI myocardial infarction, and CHD coronary heart disease.

†The study by Garland et al.<sup>9</sup> was excluded because it had an extremely large relative risk.

‡Studies by Butler<sup>11</sup> and Jackson<sup>19</sup> were excluded.

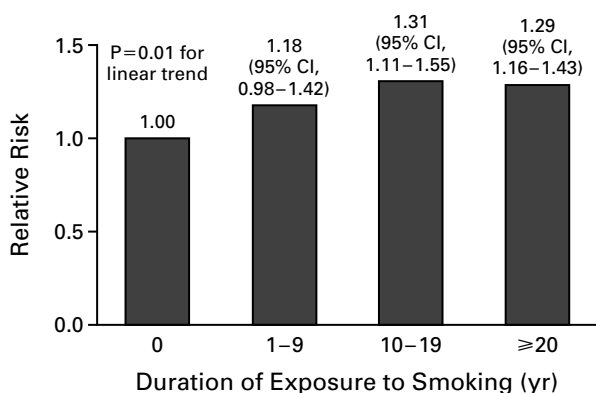
§Studies by Lee et al.,<sup>17</sup> Jackson,<sup>19</sup> and He et al.<sup>22</sup> were excluded.

¶Studies by Hirayama,<sup>7,8</sup> Butler,<sup>11</sup> Sandler et al.,<sup>12</sup> Lee et al.,<sup>17</sup> Jackson,<sup>19</sup> Dobson et al.,<sup>20</sup> and Wynder<sup>23</sup> were excluded.



**Figure 2.** Pooled Relative Risks of Coronary Heart Disease Associated with Various Levels of Exposure to Spouse's Smoking among Nonsmokers.

Data were obtained from Hirayama,<sup>78</sup> Svendsen et al.,<sup>10</sup> Sandler et al.,<sup>12</sup> Hole et al.,<sup>13</sup> Steenland et al.,<sup>15</sup> He et al.,<sup>18,22</sup> and La Vecchia et al.<sup>21</sup> CI denotes confidence interval.



**Figure 3.** Pooled Relative Risks of Coronary Heart Disease Associated with Various Durations of Exposure to Spouse's Smoking among Nonsmokers.

Data were obtained from Butler,<sup>11</sup> Steenland et al.,<sup>15</sup> Kawachi et al.,<sup>16</sup> He et al.,<sup>18,22</sup> Muscat and Wynder,<sup>23</sup> and Ciruzzi et al.<sup>24</sup> CI denotes confidence interval.

nary heart disease, or both as end points, the overall relative risk was 1.24. When the analysis was confined to the 10 studies that adjusted for important risk factors for coronary heart disease, such as age, sex, blood pressure, body weight, and serum cholesterol, the overall relative risk was 1.26.

The relative risk of coronary heart disease increased significantly with exposure to a higher level or a longer duration of passive smoking (Fig. 2 and 3). For example, as compared with nonsmokers who were not exposed to smoke, nonsmokers who were exposed to 1 to 19 cigarettes per day and to 20 or more cigarettes per day had relative risks of coronary

heart disease of 1.23 (95 percent confidence interval, 1.13 to 1.34) and 1.31 (95 percent confidence interval, 1.21 to 1.42), respectively ( $P=0.006$  for linear trend). Likewise, as compared with nonsmokers who were not exposed to cigarette smoke, nonsmokers who were exposed to a spouse's smoke for 1 to 9 years, 10 to 19 years, and 20 or more years had relative risks of coronary heart disease of 1.18 (95 percent confidence interval, 0.98 to 1.42), 1.31 (95 percent confidence interval, 1.11 to 1.55), and 1.29 (95 percent confidence interval, 1.16 to 1.43), respectively ( $P=0.01$  for linear trend).

A significant increase in the relative risk of coronary heart disease associated with passive smoking was consistently found when the data were analyzed according to the type of study, sex, and place of exposure (Table 4). The relative risks found in prospective cohort studies were slightly less than the corresponding relative odds found in case-control studies. The relative risks were not significantly different for men and women or for exposure at home and exposure in the workplace.

There was no evidence of publication bias in our study. The Kendall tau correlation coefficient for the standard error and the standardized log relative risk was 0.24 ( $P=0.16$ ) for all 18 studies. When a study with an extreme value was excluded,<sup>9</sup> the Kendall tau correlation coefficient for the standard error and the standardized log relative risk was reduced to 0.19 ( $P=0.28$ ).

## DISCUSSION

Passive cigarette smoking is associated with a smaller increase in the relative risk of coronary heart disease than is active cigarette smoking. For example, in the Cancer Prevention Study II, the risk of coronary heart disease was 1.7 times as high among men who smoked as among those who did not (95 percent confidence interval, 1.6 to 1.8); the corresponding increase in risk among women was by a factor of 1.6 (95 percent confidence interval, 1.4 to 1.7).<sup>39</sup> In our analysis, the increase in the relative risk of coronary heart disease among passive smokers as compared with nonsmokers was 1.25 (95 percent confidence interval, 1.17 to 1.32). However, because of the high prevalence of passive cigarette smoking at home and in the workplace, a substantial number of coronary events occur, with implications for public health.<sup>40</sup>

Several studies have suggested that the increased risk of coronary heart disease associated with passive smoking may be due to confounding effects of lifestyle and diet.<sup>41,42</sup> Passive smokers were more likely than nonsmokers to consume diets with fewer vegetables and fruits and more fat and were less likely to take antioxidant vitamin supplements.<sup>43-46</sup> However, clinical trials have indicated that beta carotene and vitamin E supplementation does not reduce the

**TABLE 4.** OVERALL RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH PASSIVE SMOKING AMONG NONSMOKERS, ACCORDING TO THE DESIGN OF THE STUDY AND THE CHARACTERISTICS OF THE PARTICIPANTS.

VARIABLE	NO. OF STUDIES	RELATIVE RISK (95% CI)*	P VALUE
Study design			
Cohort	10	1.21 (1.14–1.30)	<0.001
Case-control	8	1.51 (1.26–1.81)	<0.001
Sex†			
Male	9	1.22 (1.10–1.35)	<0.001
Female	15	1.24 (1.15–1.34)	<0.001
Passive exposure to smoking			
Home	18	1.17 (1.11–1.24)	<0.001
Workplace	8	1.11 (1.00–1.23)	0.05

\*CI denotes confidence interval.

†Two studies did not report results according to sex.

risk of coronary heart disease in persons who do not have a history of myocardial infarction.<sup>47,48</sup> In our analysis, the pooled relative risk of coronary heart disease associated with passive smoking for studies that adjusted for important confounding factors for coronary heart disease (such as age, sex, body weight, blood pressure, and serum cholesterol level) was virtually identical to the pooled relative risk for all the studies. In keeping with our findings, Law and colleagues have suggested that differences in diet between passive smokers and nonsmokers account for only 1 to 3 percent of the difference in their risk of coronary heart disease.<sup>31</sup>

Our findings are unlikely to be due to misclassification of outcomes. The pooled relative risk for studies in which the end points were myocardial infarction, death due to coronary heart disease, or both was similar to the pooled relative risk for all studies. Likewise, our findings are unlikely to result from publication bias, as was suggested in one report.<sup>34</sup> The pooled relative risk for published studies is identical to that obtained by pooling relative-risk estimates for all the available studies, including dissertations. In addition, correlation analysis of the standard error and the log relative risk does not support the possibility of publication bias.

Several mechanisms may increase the risk of coronary heart disease in persons exposed to environmental tobacco smoke. The acute effects of passive smoking include increases in the heart rate at rest, blood pressure, and blood levels of carboxyhemoglobin and carbon monoxide.<sup>49,50</sup> Other effects are an increase in the ratio of serum total cholesterol to high-density lipoprotein cholesterol, a decrease in the serum level of high-density lipoprotein cholesterol,<sup>50</sup> an increase in platelet aggregation, and endothelial-cell damage.<sup>51</sup> Abnormal platelet aggregation is an independent risk factor for coronary heart

disease.<sup>26,28,29,52</sup> There is also evidence that passive smoking may contribute to atherosclerosis by sensitizing neutrophils, causing their activation and subsequent oxidant-mediated tissue damage.<sup>53</sup>

According to the Third National Health and Nutrition Examination Survey, about 43 percent of non-smoking children and 37 percent of nonsmoking adults are exposed to environmental tobacco smoke in the United States.<sup>40</sup> The high prevalence of passive smoking in the general population has implications for public health. To achieve a meaningful reduction in the burden to society of coronary heart disease, both passive and active cigarette smoking must be targeted.

Many children are regularly exposed to cigarette smoke at home or in other environments, such as child-care facilities and schools.<sup>40</sup> The only safe way to protect nonsmokers from exposure to cigarette smoke is to eliminate this health hazard from public places and workplaces, as well as from the home.

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