In December 1992, the US Environmental Protection Agency (EPA) declared that environmental tobacco smoke is a class A human carcinogen, responsible for approximately 3,000 lung cancer deaths per year in nonsmokers (1). Although evidence is still accumulating on the role of passive smoking in coronary heart disease among nonsmokers (2, 3), if this association is real, then the total burden of deaths attributable to passive smoking could be much greater—up to 10–20 times higher—than the risk assessment provided by the EPA.

After the EPA risk assessment, several tobacco companies filed a lawsuit against the Agency, claiming that “various sources of bias, including publication bias... could explain any association claimed by EPA between ETS [environmental tobacco smoke] and lung cancer” (4, p. 133). In the present commentary, we focus on three problems—publication bias, confounding, and measurement error—that could potentially threaten the validity of epidemiologic studies of passive smoking.

**PUBLICATION BIAS**

Publication bias has been described as the “systematic tendency to publish any one type of result, be it positive, negative, or null” (5, p. 1095). In the case of passive smoking, publication bias is a concern if null studies do not get published and consequently fail to be included in meta-analyses such as the EPA risk assessment. The problem is particularly salient when the research is dealing with small effects and authors are reluctant to submit (or journal editors are reluctant to accept) articles with null findings based on low statistical power.

In 1988, Vandenbroucke (6) carried out a formal quantitative assessment of the extent of publication bias in published studies of passive smoking and lung cancer. The author concluded that there was no evidence of publication bias in studies of women, but some evidence for such bias in studies of men. In a response to Vandenbroucke, Wells (7) presented unpublished data from two studies on passive smoking and lung cancer in men. When these unpublished studies were added to the previously reported meta-analysis, the pooled relative risk of lung cancer increased from 1.5 to 1.7. Other authors have also evaluated the extent of publication bias and have concluded that it is unlikely to explain the predominance of positive findings in studies of passive smoking and adverse health outcomes (8, 9). For instance, Bero et al. (9) carried out an exhaustive search for unpublished studies on passive smoking and health effects and concluded that very few such studies had been missed by previous meta-analyses.

The EPA risk assessment was based on a synthesis of 30 epidemiologic studies conducted worldwide, including some unpublished studies (1). Additional studies of passive smoking have continued to be published since the EPA risk assessment, including studies that
indicated an increased risk of lung cancer (10, 11), as well as those that showed no increase in risk (12, 13). In the study by Brownson et al. (12), the odds ratio of lung cancer in those exposed to passive smoking was 1.0 (95 percent confidence interval 0.8–1.2). In the case-control study by Kabat et al. (13), published in the July 15, 1995, issue of the Journal, the odds ratio of lung cancer in women exposed to a spouse’s smoke was 1.08 (95 percent confidence interval 0.60–1.94). Although the point estimates of the odds ratios suggested no association, the upper bound of the 95 percent confidence intervals in both of these studies (12, 13) overlapped the summary relative risk estimate of 1.19 (95 percent confidence interval 1.04–1.35) published by the EPA (1). The study by Kabat et al. (13) had only 30 percent power to detect an odds ratio for lung cancer of 1.5 among passive smokers. Even so, the point estimate of the odds ratio for men exposed to their wives’ smoking was 1.60 (95 percent confidence interval 0.67–3.82).

Thus, the weight of the evidence continues to point to the causal role of passive smoking in lung cancer risk among nonsmokers. Because of the large number of published studies on passive smoking and lung cancer, the results of any single study, such as the one by Kabat et al., are unlikely to tip the overall conclusion one way or the other. Rather, the totality of evidence as presented in a research synthesis (such as meta-analysis) should inform policy and decision making. It is also sound policy for journals such as the American Journal of Epidemiology to continue to publish well-conducted studies with negative or null findings, even if they tend to be underpowered.

CONFOUNDING IN STUDIES OF PASSIVE SMOKING

A growing number of studies have addressed the issue of systematic differences in health characteristics of individuals exposed to passive smoking compared with those not exposed (14–18). The study by Matanoski et al. (18), which appeared in the July 15, 1995, issue of the Journal examined the dietary and behavioral characteristics of 3,896 nonsmoking women from the first National Health and Nutrition Examination Survey in relation to exposure to passive smoking. The study found that, compared with women whose husbands did not smoke, women exposed to spouses’ smoke were more likely to report lower education, to drink more alcohol, and to report lower consumption of vitamin supplements, as well as of dietary vitamin A, vitamin C, and calcium (18). Similarly, a study of 9,003 British adults from the Health and Lifestyle Survey (17) found that nonsmokers exposed to passive smoking in the home were more likely to report no educational qualifications and to work in blue-collar manual occupations. Compared with unexposed individuals, passive smokers were also more likely to consume fried foods, to be more overweight, and to report lower intake of fruits, salads, and breakfast cereals (17).

Since numerous studies have suggested that diet may influence the risk of lung cancer (19–22), studies of passive smoking and lung cancer should control for potential confounding by dietary habits. Yet few studies have addressed this issue (23, 24). The magnitude of confounding produced by dietary factors on lung cancer risk is estimated to be relatively modest (14, 15). For example, both Sidney et al. (14) and Le Marchand et al. (15) estimated that the relative risk of lung cancer with passive smoking would drop from 2 to about 1.8 after controlling for differences in dietary intake of beta-carotene between passive smokers and nonsmokers. Nonetheless, confounding could pose a genuine problem, since the pooled relative risks of lung cancer based on overviews of passive smoking studies range from 1.3 to 1.4 (25, 26).

Confounding poses a potentially even greater problem in studies of coronary heart disease compared with lung cancer, since coronary heart disease is much more multifactorial in etiology than lung cancer. The failure of many studies to control for confounding may be one of the reasons for continuing uncertainty about the role of passive smoking in coronary heart disease. The risks of heart disease in passive smokers have been estimated to range between 1.2 to 1.3, on the basis of pooled data from 12 published studies (3). Again, only a minority of studies have adjusted for potential confounding by a range of cardiovascular risk factors. Data from the Nurses’ Health Study, an ongoing cohort of 121,701 middle-aged and older US women, illustrate the potential for confounding by passive smoking status. Table 1 shows the age-adjusted distribution of cardiovascular risk factors according to passive smoking exposure among 32,046 never-smokers in the cohort, who answered a questionnaire in 1982 concerning exposure to passive smoking at home or at work. Never-smokers exposed to passive smoking at home or work consistently exhibited a less favorable profile of cardiovascular risk factors compared with women who were not exposed (table 1).

In the Nurses’ Health Study, adjustment for the variables shown in table 1 resulted in an attenuation of the relative risk for total incident coronary heart disease among women exposed to passive smoke, from 1.97 (95 percent confidence interval 1.20–3.24) to 1.71 (95 percent confidence interval 1.03–2.84) (27). Thus, failure to control for the effects of confounding
TABLE 1. Age-standardized distributions of cardiovascular risk factors among 32,046 never smokers in the Nurses' Health Study, 1982

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Passive smoking status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not exposed</td>
</tr>
<tr>
<td>No.</td>
<td>6,109</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>16.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>5.3</td>
</tr>
<tr>
<td>Postmenopausal hormone use (%)</td>
<td>19.7</td>
</tr>
<tr>
<td>Past use of oral contraceptives (%)</td>
<td>46.4</td>
</tr>
<tr>
<td>Parental history of myocardial infarction before age 60 years (%)</td>
<td>12.2</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>3.6</td>
</tr>
<tr>
<td>Vigorous exercise at least once a week (%)</td>
<td>43.8</td>
</tr>
<tr>
<td>Highest quintile of vitamin E intake (%)</td>
<td>18.6</td>
</tr>
<tr>
<td>Highest quintile of saturated fat intake (%)</td>
<td>15.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7</td>
</tr>
<tr>
<td>Father in blue-collar occupation (%)</td>
<td>20.9</td>
</tr>
</tbody>
</table>

by dietary and other health habits may result in a modest, although potentially noteworthy, inflation of the relative risk estimates. On the other hand, there is no compelling evidence that the excess risk of coronary heart disease reported in existing studies of passive smoking can be completely explained by confounding. In the meta-analysis by Wells (3), which did not include data from the Nurses' Health Study, restriction of the analysis to the five studies that best controlled for confounding variables resulted in a pooled relative risk estimate for coronary heart disease mortality of 1.7 (95 percent confidence interval 1.3–2.3).

A final point to consider is the extent to which present patterns of confounding reflect past patterns of exposure. Passive smokers tend to have lower socioeconomic status compared with those not exposed to tobacco smoke (table 1). Social-class gradients in many health risk behaviors (such as smoking, obesity, and hypertension) have become steeper during the past 20 years (28). Hence, it is possible that the differences in risk factors between passive smokers and those not exposed to tobacco smoke could be widening over time. Adjustment for current patterns of confounding will not take account of such temporal trends. Yet, the incidence of major diseases linked to passive smoking—lung cancer and coronary heart disease—at least partly reflects patterns of cumulative exposure. If the risk factor differences between passive smokers and those not exposed to tobacco smoke were indeed less marked in the past, then adjustment for current patterns of behavior will result in overcontrol for confounding. The corollary to this point is that prospective investigations of passive smoking and disease should regularly update information on exposure to risk factors, since the degree of confounding may actually increase during follow-up.

MEASUREMENT OF EXPOSURE TO PASSIVE SMOKING

In epidemiologic studies of passive smoking, exposure is most frequently estimated by questionnaires. Self-reported current exposure to passive smoking has been found to correlate modestly (Pearson coefficients ranging between 0.2 and 0.5) with biochemical markers such as salivary (29) and urinary (30) cotinine (table 2). However, self-reports can explain only at most 30 percent of the total variance in urinary or salivary cotinine concentrations (table 2), suggesting that questionnaires may not accurately estimate total passive smoking exposure. The exception to the pattern suggested by the studies in table 2 is that by Jarvis et al. (31), which reported that 44 percent of the variance in salivary cotinine among 569 schoolchildren could be explained by level of parental smoking. In that instance, exposure was highly specific to one setting, the home. Some caution is required in the interpretation of the data summarized in table 2, since it is acknowledged that there is wide between-individual variation in the half-life of cotinine even after controlled doses of environmental tobacco smoke exposure, presumably reflecting differential metabolism of nicotine (32).

Exposure to passive smoking is ubiquitous. In a study of 663 never- and former smokers attending a cancer screening clinic, 91 percent had detectable levels of cotinine in their urine, even though only 76 percent of subjects reported exposure to passive smoking in the previous 4 days (30). In the same study, 84 percent of the subjects who did not live with a smoker had detectable cotinine levels (30). Misclassification of exposure is especially likely to occur when studies fail to ascertain exposures outside the home. Of the more than a dozen studies of passive smoking and coronary heart disease, only a handful have assessed...
exposure at work or in other social settings (27, 33-36). Yet, most exposure assessment studies agree that exposure at work is comparable with, and often greater than, exposure at home due to the higher density of smokers at work (37-39). Although the introduction of smoking restriction policies in workplaces has reduced exposure, failure to ascertain exposure outside the home may substantially underestimate overall exposure to passive smoking (39).

One criticism of the studies of passive smoking and lung cancer is that a dose-response relation between exposure and outcome has not been consistently demonstrated (40). Comparing the results of different studies is somewhat complicated because different measures of "dose" have been adopted, including measures of intensity (e.g., number of cigarettes smoked per day by spouses); combined intensity and duration measures (e.g., pack-years); and pure duration measures (e.g., number of years lived with a spouse who smokes). In fact, the majority of studies that examined intensity of exposure have found that the relative risks of lung cancer increased with the daily number of cigarettes smoked by spouses (1). By contrast, the duration of environmental tobacco smoke exposure to lung cancer risk has been much less convincingly demonstrated. Although the point estimates of relative risks are generally greater than 1.0 for any duration of exposure, few studies have found a dose-response gradient between years of passive smoking and lung cancer incidence. Part of the explanation for this inconsistency may be the low reliability of self-reported duration of exposure to passive smoking.

Several studies have addressed the reliability of passive smoking recall using test-retest designs (40-42). In a lung cancer case-control study, Pron et al. (40) approached 117 control subjects 6 months after their initial interview and found good agreement for both residential passive smoke exposure (88 percent concordance, kappa = 0.66) and occupational exposure (73 percent concordance, kappa = 0.46). In contrast to the assessment of recent passive smoking exposure, self-reported duration of exposure has been

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**TABLE 2. Validation studies of self-reported exposure to passive smoking, using cotinine concentrations as the gold standard**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Self-reported measure of exposure</th>
<th>Gold standard</th>
<th>Correlation*</th>
<th>Amount of variance explained†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings et al. (30)</td>
<td>663 never- and former smokers</td>
<td>No. of exposures (home, work, other) over previous 4 days</td>
<td>Urinary cotinine</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>Coultas et al. (41)</td>
<td>149 nonsmokers</td>
<td>No. of smokers to whom exposed in previous 24 hours</td>
<td>Urinary cotinine</td>
<td>0.21-0.24</td>
<td>Not given</td>
</tr>
<tr>
<td>Coultas et al. (55)</td>
<td>20 nonsmokers in 10 homes</td>
<td>No. of hours exposed</td>
<td>Urinary cotinine</td>
<td>0.29-0.32</td>
<td>Not given</td>
</tr>
<tr>
<td>Delfino et al. (56)</td>
<td>258 nonsmokers</td>
<td>No. of hours and smokers to whom exposed in previous 24 hours</td>
<td>Salivary cotinine</td>
<td>Not given</td>
<td>0.23</td>
</tr>
<tr>
<td>Riboli et al. (57)</td>
<td>1,369 nonsmoking women from 15 centers worldwide</td>
<td>Cumulative duration of exposure from spouse, work, and other settings in previous 3 days</td>
<td>Urinary cotinine</td>
<td>0.4-0.5 in 9 participating centers</td>
<td>Not given</td>
</tr>
<tr>
<td>Emmons et al. (29)</td>
<td>186 nonsmokers</td>
<td>Total minutes of exposure in previous 7 days; no. of smokers to whom exposed at home and work</td>
<td>Salivary cotinine</td>
<td>0.36-0.42</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* Pearson (or Spearman) correlation coefficient between self-reported measure and gold standard.† R² values in regression models, with the self-reported measure of exposure as the predictor variable and cotinine levels as the dependent variable.
found to be much less reliable (40). In the study by Pron et al., a correlation coefficient of 0.25 was found between the reported duration of exposure to spousal smoking at the initial and repeat interviews. Consequently, a dose-response relation with duration of passive smoking has been difficult to detect in studies of lung cancer (43, 44), as well as those of coronary heart disease (27).

The assessment of lifetime exposure to passive smoking may be particularly problematic, given that there is little correlation between exposure during childhood and exposure in adulthood, either at home or at work (45). No study has attempted to validate self-reported duration of passive smoke exposure, since there does not as yet exist a biomarker that could integrate exposure over long periods of time and provide an estimate of total internal dose.

Most types of errors in exposure estimates tend to bias associations in the direction of the null. Notwithstanding the limitations of questionnaire assessments, studies of passive smoking have yielded generally consistent findings of excess risk for lung cancer, coronary heart disease, and other health outcomes. Nonetheless, the assessment of passive smoking exposure could benefit from standardization; in particular, every study should attempt to ascertain exposure in the workplace.

Although some authors have advocated a combination of questionnaire and biologic markers as the best approach to accurately assess exposure to passive smoking (30, 41), it is unclear which marker should be used as the most representative of passive smoke exposure (46). For example, although cotinine is generally regarded as the most sensitive and specific marker for tobacco smoke exposure, little is understood about the relations of cotinine levels with specific tobacco constituents that are most relevant for specific health outcomes of interest (46). The effects of secondhand tobacco smoke on the cardiovascular system are unlikely to be caused by a single component of smoke (such as nicotine, of which cotinine is the principle metabolite), but rather by a combination of elements, including carbon monoxide, polycyclic aromatic hydrocarbons, and other, not fully specified elements in the smoke (47). Similar limitations apply to studies of lung cancer, where cotinine levels will not necessarily provide information about the uptake, metabolic activation, intensity, or long-term duration of exposure to carcinogens.

Developments in “molecular epidemiology” may eventually pave the way for more sensitive and specific exposure assessment, especially in the field of cancer. The uptake and metabolism of all three major classes of carcinogens in tobacco smoke—nitro-

### STUDIES OF SUBCLINICAL CARDIOVASCULAR OUTCOMES

A number of studies have begun to investigate the relations of passive smoking to markers of subclinical cardiovascular outcomes. Two studies (52, 53), based in the Atherosclerosis Risk in Communities Study, reported an association between passive smoking and carotid artery intimal-medial thickness (IMT). In the first study (52), based on cross-sectional data in 12,953 women and men, passive smoking was defined by self-reported exposure to at least 1 hour of tobacco smoke per week. Using B-mode ultrasound, a gradient was found in IMT by smoking status: never smokers not exposed to passive smoke had the lowest IMT (mean = 0.701 mm), followed by never smokers exposed to passive smoke (0.711 mm), former smokers (0.772 mm), and current smokers (0.775 mm). After adjustment for age, race, and gender, there was a significant difference (p < 0.0001) in IMT of 0.017 mm comparing passive smokers with nonsmokers. This magnitude of difference in IMT was equivalent to the difference associated with 7 mmHg of systolic blood pressure, 1.5 years of chronologic age, or 0.7 mmol/liter (27 mg/dl) of total plasma cholesterol in this population (52). A second report (53), based on follow-up of a sample of 2,073 participants in the Atherosclerosis Risk in Communities Study cohort, examined the relation of passive smoking in 1975 and 1987–1989 to carotid wall thickness in 1987–1989. Although carotid wall thickness was not assessed at the beginning of follow-up (in 1975) and the results were not statistically significant, passive smoking (compared with no environmental tobacco smoke) did appear to be linked to increased wall thickness 12–14 years later.

Finally, a study of 78 healthy teenagers and young adults found that those exposed to passive smoking for at least 1 hour daily exhibited early arterial damage, as assessed by endothelium-dependent brachial artery dilatation (54). There was a dose-response relation between intensity of exposure to passive smoking and the degree of endothelial dysfunction (54).

Although they are not exempt from publication bias, confounding, and measurement error, studies based on subclinical outcomes may provide a better understanding of the mechanisms linking passive smoking to...
cardiovascular disease and thereby provide additional support for the hypothesis.

CONCLUSION

In this commentary, we have focused on three types of problems that beset epidemiologic studies of the health effects of passive smoking. Publication bias and confounding are especially problematic when dealing with weak associations (relative risks of the order of 1.5) Although there is little evidence for publication bias in studies of passive smoking and adverse health effects, authors, peer reviewers, and editors all share the responsibility to ensure that well-conducted negative studies continue to be published. The need to control for confounding is imperative, especially since passive smokers have repeatedly been found to have a less favorable health profile compared with those not exposed. The third problem is measurement error. Exposure to passive smoking is ubiquitous, which makes it difficult to carry out an accurate and comprehensive assessment. This widespread exposure also makes passive smoking a potentially important public health problem. Even modest associations, if valid, can give rise to a heavy burden of illness and death attributable to passive smoking.

REFERENCES


