# Environmental Tobacco Smoke and Ischemic Heart Disease

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Cohort and case control studies show a 30% excess risk of ischemic heart disease in nonsmokers whose spouses smoke compared with that in nonsmokers whose spouses do not smoke. There is a nonlinear dose-response; the excess risk from actively smoking 20 cigarettes/day is only 80%. Large cohort studies of active smoking support the nonliner dose-response (the excess risk in smokers of 5 cigarettes/day is about 50%). Animal studies show a pronounced vascular effect of environmental tobacco smoke. In experimental studies passive and active smoking have similar effects on platelet aggregation. The collective evidence supports a significant effect of low dose tobacco smoke exposure in causing ischaemic heart disease.


The risk of ischemic heart disease from environmental tobacco smoke exposure is at first sight surprising because it is so large. Meta-analyses have shown a relative risk of about 1.3 (ie, a 30% excess risk) in nonsmokers exposed to environmental tobacco smoke compared with unexposed nonsmokers.[1-5] At the average age at the time of the ischemic heart disease event in these studies (about 65), actively smoking 20 cigarettes per day is associated with an excess risk of only about 80%.[1] The excess risk is therefore about one third that from smoking 20 cigarettes a day, for a tobacco smoke exposure of only 1% of that from 20 cigarettes per day.[6-10] With a linear dose-response relationship, the expected excess risk associated with environmental tobacco smoke exposure would be only 0.8% (1% of the 80% excess risk from smoking 20 cigarettes/d). For lung cancer, by contrast, the dosimetry is linear; the excess risk associated with environmental tobacco smoke exposure is about 1% of that from smoking 20 cigarettes per day, consistent with the exposure.[6]

Some are skeptical of a cause and effect relation because such a nonlinear dose-response relationship seems implausible.[11] But if the relationship were one of cause and effect the attributable risk, in absolute terms, would be substantial. There would be strong grounds for action, including the banning of smoking in public places and working environments (opposed by the tobacco industry because such bans reduce active smoking[12,13]). Also, advising relatives of patients with coronary artery disease not to smoke in their presence should become a necessary part of clinical care (at present, few such relatives refrain from doing this[14]). The problem of the nonlinear dosimetry has tended not to be addressed in previous articles,[11] but resolving it is important.

## Epidemiologic Studies of Environmental Tobacco Smoke Exposure and Ischemic Heart Disease

The best marker of environmental tobacco smoke exposure in epidemiologic studies is a nonsmoker with a spouse who smokes, because this is a simple and objective measure. The blood, urine, or saliva concentration of biochemical markers of tobacco smoke intake (such as cotinine) increase with the number of cigarettes smoked,[15] and from this dosimetry the concentrations of biochemical markers indicate an excess exposure in nonsmokers with spouses who smoke that is equivalent on average to actively smoking about 0.2 cigarettes per day.[6-10] This excess exposure does not all come from the spouse; nonsmokers who live with

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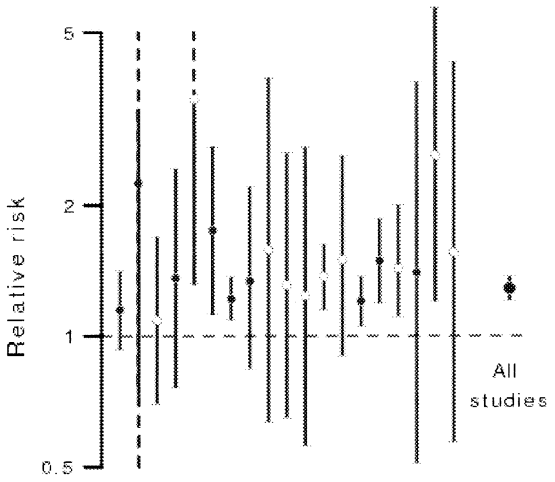


**Fig 1. Relative risk estimates (with 95% CIs) adjusted for age and sex, from 9 prospective studies (●) and 10 case-control studies (○) comparing ischemic heart disease events in lifelong smokers whose spouse currently smoked with those whose spouse had never smoked.**

smokers tend to be more tolerant of environmental tobacco smoke so they do not take steps to avoid it, and their friends may be more likely to smoke. The alternative marker, asking individuals to quantify their exposure (a little, a lot), is unsatisfactory because it is subjective and inaccurate.

Figure 1 shows the results of a meta-analysis of 19 epidemiologic studies comparing risk for ischemic heart disease events (ie, ischemic heart disease death and nonfatal myocardial infarction) in never-smokers whose spouses currently smoke relative to the risk in never-smokers whose spouses had never smoked.[1] Data on former smokers were excluded from the analysis wherever possible. The summary estimate of relative risk was 1.30 (95% confidence interval [CI], 1.22-1.38; $P < .001$).

There was no significant heterogeneity between studies (as can be judged from Fig 1), and the estimate of 1.30 is similar to estimates from other meta-analyses.[2-5] Of the 19 studies, 9 were cohort (prospective) studies and 10 were case-control (retrospective) studies; the studies recorded 6,600 ischemic heart disease events in total. The 19 studies are all such studies published up to 1997,[1,2] apart from 3 studies published by consultants to the tobacco industry[16,17] discussed separately later. In studies published after 1997 (2,600 cases) the odds ratio, if anything, was a little higher than 1.3 (about 1.5 on average).[18-21] In the 19 studies, the estimates were similar in men and women, in cohort and case-control studies, and for fatal and nonfatal ischemic heart disease events.[1,2]

## Studies of Active Smoking and Ischemic Heart Disease

The first logical step in assessing the surprisingly large effect of environmental tobacco smoke exposure is to examine the dose-response relationship in the large cohort studies of active smoking. To support the environmental tobacco smoke evidence, these studies would need to show a disproportionately large risk in light smokers. They do. A meta-analysis of 5 large studies of active smoking and ischemic heart disease showed a comparatively high risk among smokers in the lowest smoking category (about 5 cigarettes/d), and beyond this the further increase in risk, with increasing consumption up to around 30 cigarettes per day, was shallower.[1] Table 1 summarizes the relative risk estimates (defining risk in nonsmokers as 1.0) according to age and 2 levels of smoking (5 and 20 cigarettes/d). The risk estimates associated with smoking decline with age but in each 10-year age group the excess risk associated with smoking 5 cigarettes per day is about half that associated with 20 cigarettes per day, not a quarter. At age 65, for example, it is 50% from 5 cigarettes per day, and 80% from 20 ciga-

**Table 1. Estimated Relative Risk of an Ischemic Heart Disease Event, Compared With That in Unexposed Never-Smokers, From Epidemiologic Studies of Environmental Tobacco Smoke Exposure and of Actively Smoking 5 and 20 Cigarettes Per Day**

| Age at Death (y) | Environmental Tobacco Smoke Exposure | Actively Smoking 5 Cigarettes/d | Actively Smoking 20 Cigarettes/d |
|---|---|---|---|
| 45 | — | 2.5 | 4.5 |
| 55 | — | 1.9 | 3.1 |
| 65 | 1.3 | 1.5 | 1.8 |
| 75 | — | 1.2 | 1.3 |

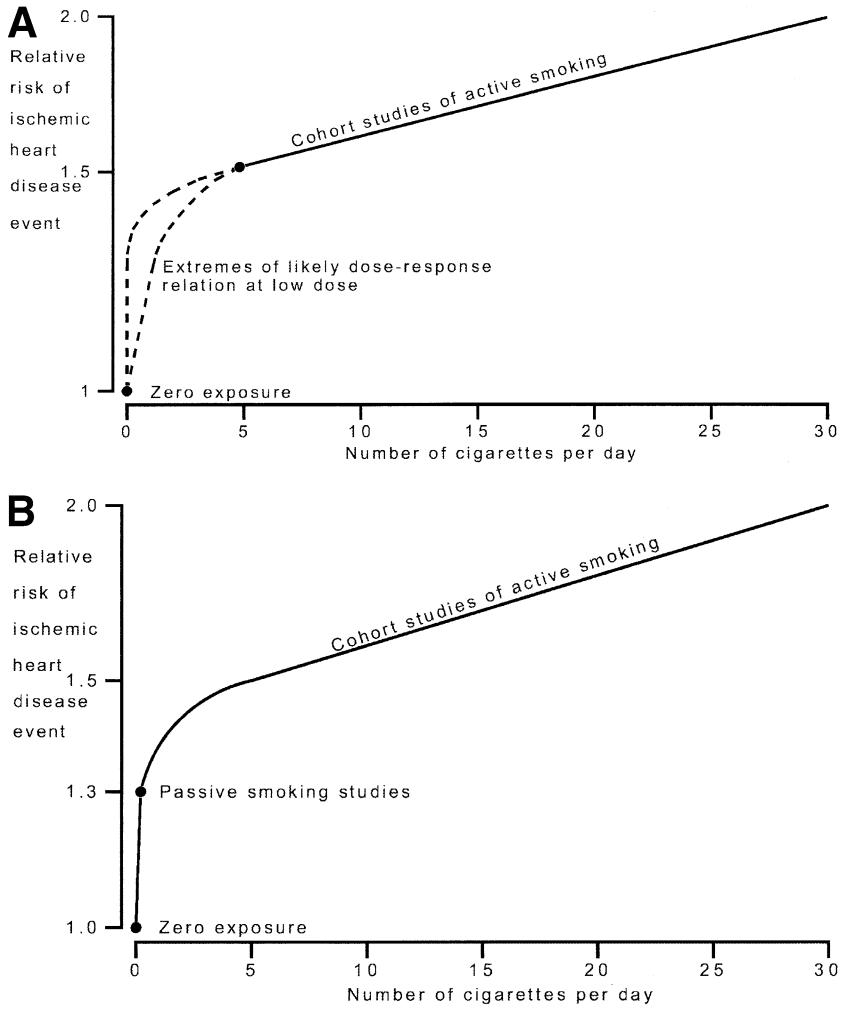


**Fig 2. The dose-response relationship between cigarette smoking and risk for ischemic heart disease events. (A) Summation of evidence from a meta-analysis of 5 large cohort studies of active smoking,[1] (B) combined with the summary estimate from the studies of environmental tobacco smoke exposure (taken to be equivalent to actively smoking 0.2 cigarettes per day[6-10]).**

rettes per day. Figure 2A shows the dose-response relationship between smoking from 5 to 30 cigarettes per day and ischemic heart disease events at age 65 from the meta-analysis of cohort studies of active smoking. These studies provide no estimate of risk from fewer than 5 cigarettes per day, but they establish that the dose-response must be nonlinear. The dotted lines in Figure 2A show the extremes of the likely relationship (based on maintaining a reasonably smooth dose-response curve). Any line within this range implies a significant excess risk for environmental tobacco smoke exposure. The conclusion from the studies of active smoking is that there is an excess risk for ischemic heart disease from low-dose exposure, and the risk associated with environmental tobacco smoke exposure will be much greater than that expected from, say, 1% of the excess risk from smoking 20 cigarettes per day.

The average age at the time of the ischemic heart disease events in the environmental tobacco smoke studies in Fig 1 was about 65, and the associated relative risk of 1.3 also is shown in Table 1. In Figure 2B this estimate is used to fix the dose-response relationship at low dose, combining the data from the studies of environmental

tobacco smoke exposure (plotting this at the equivalent of 0.2 cigarettes per day[6-10]) and the data from studies of active smoking. The reconciliation of the dose-response evidence from active smoking and the risk estimate from environmental tobacco smoke exposure is crucial in concluding that environmental tobacco smoke is a cause of ischemic heart disease.

## Additional Estimates of Risk for Environmental Tobacco Smoke

Further estimates of the risk for ischemic heart disease associated with environmental tobacco smoke exposure in nonsmokers comes from 3 sources. Workplace exposure in different combinations of studies was associated with an excess risk of between 11% and 50% ($P < .05$).[2,22] Carotid artery ultrasound measurements have shown that the excess intimal and medial thickness (a measure of atheromatous disease), compared with the baseline value in unexposed nonsmokers, was about half as great in nonsmokers living with a smoker as in smokers (0.17 v 0.30 mm).[23] Endothelium-dependent arterial dilatation (in the brachial artery) was reduced to a similar extent in nonsmokers exposed to environmental tobacco smoke and in smokers, compared with the baseline value in unexposed nonsmokers (endothelial dysfunction being an important early feature of the atherogenic process).[10] All these studies therefore confirm a pronounced effect at low dose.

Two consultants to the tobacco industry, LeVois and Layard,[16,17] have published analyses of 3 sets of data. One was a separate analysis of one of the cohort studies of environmental tobacco smoke exposure and ischemic heart disease in Figure 1,[24] and 2 were analyses of data not published elsewhere.[16,17] They reported a combined relative risk estimate from the 3 analyses of 1.00 with a narrow 95% CI (0.97-1.04).[17] This negative result is statistically inconsistent with the estimate of 1.30 (1.22-1.38) from Figure 1, so the 2 groups of studies cannot be combined as separate valid estimates. One of the studies must be flawed. We believe the estimate from the 19 studies to be the valid one because (1) LeVois and Layard included never-smokers married to former smokers (about half the deaths),[17] which substantially inflated study size but diluted the estimate of risk (because former smokers' own risk is not materially increased,[1] so that of their spouses cannot be); and (2) there were specific problems in the analyses of each of the 3 individual analyses.[25] In the first, for example, LeVois and Layard confirmed the 20% increased risk shown in the independent analysis of the same cohort study by the owners of the data,[17,24] but diluted it by including never-smokers married to former smokers and negated it by claiming an implausible significantly reduced risk in never-smokers married to former smokers, a surprising inconsistency from the independent analysis of the same data.

Another negative report was published by Enstrom and Kabat,[26] who also received funding from the tobacco industry. These investigators performed an analysis of data from the American Cancer Society's Cancer Prevention Study I, a large cohort study based on residents of 25 US states who were recruited in 1959 and originally followed-up for 12 years. The new analysis was based on a subset (residents of California) who were followed-up for 40 years. It showed no difference in ischemic heart disease mortality in nonsmokers according to whether the spouse was a current smoker or a nonsmoker in 1959 (relative risk, 0.94; 95% CI, 0.85-1.05). It was based on 1,400 heart disease deaths, compared with 6,600 events in the meta-analysis[1] and 2,600 in the other studies published since 1997 showing positive associations. The most likely reason for this negative result is that over the 40-year follow-up from 1959, a large proportion of people who smoked in 1959 would have subsequently given up, so the exposure to the nonsmoking spouse would have diminished greatly. This, plus the fact that many of the couples will have divorced or separated over the 40-year period, will greatly reduce the expected excess risk in nonsmokers married to smokers in 1959 because the excess risk from ischemic heart disease in active smokers is largely reversed within a few years of stopping smoking and the same would be expected in passive smoking. A subsidiary analysis, based on 1972 smoking histories, had smaller numbers and a wide confidence interval (relative risk, 1.06; 0.90-1.25), and even in this analysis there were nearly 30 years of follow-up. The negative result is therefore not surprising.

## Can the Association Be Explained Through Confounding?

Confounding might partly or wholly explain the association between environmental tobacco smoke exposure and ischemic heart disease if, for example, the saturated fat content of the diet was substantially higher in nonsmokers who lived with smokers. Strong evidence against this is that the evidence from studies of environmental tobacco smoke exposure and from those of active smoking fit so well. One would have to conclude that the greater part of the association between active smoking and ischemic heart disease was not cause and effect, and this has been considered carefully and excluded by numerous expert committees.

Examination of data on other cardiovascular risk factors indicates that the smoking association is not materially subject to confounding. Blood pressure is similar in smokers and nonsmokers in cross-sectional studies.[1] Body weight is lower in smokers (associated with lower cardiac risk). Serum total and low-density lipoprotein cholesterol is higher in smokers, but the effect is small; on average, low-density lipoprotein cholesterol is 0.07 mmol/L higher in smokers,[27] associated with only a 3% excess risk of ischemic heart disease.[28] Fruit and vegetable consumption is lower in smokers; the average difference was also associated with an excess risk of ischemic heart disease of about 3%.[1,29] Confounding overall might therefore account for a relative risk of about 1.06 in smokers (an excess risk of 3% +3% = 6%).

Any confounding effect in nonsmokers exposed to environmental tobacco smoke is likely to be smaller. In cross-sectional studies of never-smokers according to whether or not the spouse smoked, the differences in serum cholesterol, blood pressure, and body mass index were imperceptible.[1] Adjusting the epidemiologic studies in Figure 1 for blood pressure, serum cholesterol, body mass index, and social class did not reduce the relative risk estimates.[1] There were differences in fruit and vegetable consumption, but they were smaller than those between smokers and nonsmokers.[1]

Further evidence against confounding as an explanation comes from a meta-analysis of estimates from 3 large cohort studies on the excess risk of ischemic heart disease in men who had stopped smoking for 20 or more years. The risk decreased to nearly background level—to a relative risk of 1.06 compared with never-smokers. This indicates either that there is no confounding (if the excess risk associated with smoking did not entirely reverse after 20 years), or that if the excess risk was entirely reversible, the effect of confounding does not exceed an excess risk of 6%.

In summary, little of the 30% excess risk of ischemic heart disease exposure is attributable to confounding.

## Can the Association Be Explained Through Bias?

As with confounding, any bias sufficient to account for the environmental tobacco smoke association is unlikely because it would need to affect the studies of active smoking as well. Publication bias in the epidemiologic studies of environmental tobacco smoke exposure is unlikely because 8 of the 19 individual studies in Figure 1 were statistically significantly positive; the total pool of studies needed to generate 8 statistically significant studies by chance would exceed 320 ($8 \times 40$), of which only 19 were published, which is highly improbable. In addition, the exclusion of smaller studies (<100 events) from the analysis did not affect the relative risk estimate, and selective publication is more likely to affect small studies. Misclassification bias (whereby some people who claim never to have smoked were in fact former or current smokers and thereby at greater risk for ischemic heart disease and more likely to have spouses who smoked) has been found to be of minor importance in studies of lung cancer.[6] It will be negligible in studies of ischemic heart disease because the relative risk in smokers is so much smaller than for lung cancer (about 2 v 20).

## Mechanisms of Effect

Cigarette smoking increases the risk for ischemic heart disease events through several mechanisms, including increasing plasma fibrinogen, reducing high-density lipoprotein cholesterol, increasing carboxyhemoglobin, and increasing platelet stickiness and aggregation. Evidence indicates that environmental tobacco smoke does not significantly alter the first 3 of these. But there is evidence that it has a pronounced effect on the fourth, platelet

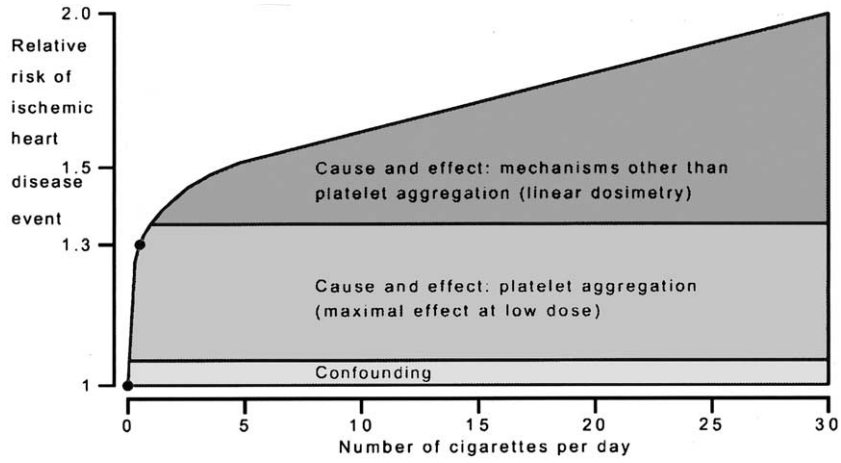


**Fig 3. Dose-response relationship between tobacco smoke and ischemic heart disease events (as in Fig 2), compartmentalized into separate associations attributable to confounding, cause and effect maximal at low dose, and cause and effect with linear dosimetry.**

aggregation. A cause and effect relationship between platelet aggregation and ischemic heart disease is shown by the effect of aspirin in reducing platelet aggregation and decreasing cardiac risk, and a cohort study has shown an association between the 2.[1,30] Experimental studies in which platelet aggregation was measured before and after 20 minutes of exposure to environmental tobacco smoke, and before and after actively smoking 1 or 2 cigarettes, showed a similar effect of the 2 exposures on platelet aggregation.[1] From the association between platelet aggregation and ischemic heart disease events shown in the cohort study, the excess risk associated with low-dose tobacco exposure was about one third—similar to the estimate from the epidemiologic studies.[1]

Figure 3 reproduces the dose-response relationship between tobacco smoke and ischemic heart disease shown in Figure 2, and compartmentalizes it into portions attributable to confounding, to cause and effect maximal at low dose (owing to effects of tobacco smoke on platelet aggregation), and to cause and effect with linear dosimetry that has little effect at low dose (owing to effects of tobacco smoke on fibrinogen, high-density lipoprotein cholesterol, and other mechanisms).

## Animal Experiments as Evidence for Causality

Eight animal studies from 3 different research groups on 4 separate animal species have all shown pronounced vascular toxicity of environmental tobacco smoke.[31-38] The exposure in these studies came from simultaneous combustion of

**Table 2. Animal Experiments: Results of 8 Studies Comparing Vascular Toxicity in Animals Exposed and Unexposed to Environmental Tobacco Smoke**

| Study | No. of Animals | | Method of Assessing Vascular Toxicity | Result | |
|---|---|---|---|---|---|
| | Exposed | Unexposed | | Exposed | Unexposed |
| Prentice[31] | 5 | 5 | Size of infarct after ligating one coronary artery, as % of area of risk | 46% | 24% |
| Zhu,[32] 1994 | 12 | 12 | | 61% | 34% |
| Zhu,[33] 1996 | 15 | 15 | | 61% | 51% |
| Shu,[34] 2002 | 21 | 21 | | 57% | 37% |
| Penn,[35] 1993 | 30 | 12 | Plaques in aorta: size (units) | 7 | 4 |
| Penn,[36] 1994 | 30 | 10 | | 5 | 3 |
| Zhu,[37] 1993 | 32 | 32 | % of surface area | 52% | 30% |
| Sun,[38] 1994 | 16 | 16 | % of surface area | 60% | 45% |

**Table 3. Low-Dose Tobacco Smoke Exposure and Ischemic Heart Disease Events: Summary of Evidence**

| | | |
|---|---|---|
| Association | Nonsmokers living with smokers: increased risk | 30% |
| | Expected increased risk from low dose exposure from studies of active smoking | 30% |
| Confounding | Increased risk in smokers from dietary differences | 6% |
| | Increased risk 20 years ater stopping smoking | 6% |
| Bias | Publication bias | Improbable |
| | Misclassification bias | Negligible |
| Causality | Experimental effect on platelet aggregation | Pronounced |
| | Vascular toxicity in animal experiments | Pronounced |

between 1 and 10 cigarettes in a room in which the animals were housed, typically for 30 hours per week for 6 weeks. The vascular toxicity was measured in 2 different ways, as the infarct size after ligating one coronary artery (a measure of disease in the other coronary arteries because the collateral circulation will determine the size of the infarct), or as the area of atheromatous plaques in the aorta. The results of these studies are summarized in Table 2. Although these measures cannot be translated into estimates of coronary risk in humans, the differences between exposed and control animals were pronounced in every study. It has been suggested that the environmental tobacco smoke exposure in these studies was so intense as to mimic active smoking, but in one of the studies at least, care was taken to ensure that the exposure was no higher than that typical of environmental tobacco smoke exposure in humans.[36] It is difficult to interpret these results in any other way than as indicating cause and effect.

## Conclusions

The evidence reviewed here is summarized in Table 3. Perhaps most important, the large cohort studies of active smoking and ischemic heart disease show nonlinear dosimetry with a disproportionately large risk at low levels of tobacco smoke intake; it is not only the studies of environmental tobacco smoke exposure and ischemic heart disease that show the association. Confounding cannot explain more than a small part of the association in either set of studies. There is no recognized material source of bias, and it is difficult to conceive of any plausible source of confounding or bias that could affect the studies of both active and passive smoking. Direct evidence in favor of causality comes from the experimental effect of environmental tobacco smoke on platelet aggregation, and the animal experiments.

The case for a cause and effect relationship despite the surprising size of the effect rests on the jigsaw-like way in which unrelated pieces of evidence fit together. In the light of all the evidence, we believe that there is no satisfactory alternative interpretation of the evidence than that environmental exposure to tobacco smoke causes an increase in risk for ischemic heart disease events of about 30%. This is equivalent to a substantial absolute excess risk because heart disease is so common in people with no exposure to tobacco smoke.

Tobacco smoke is a serious environmental hazard, and one that is avoided easily. The evidence warrants further action in preventing smoking in public buildings and enclosed working environments. The hazard in the home requires greater public education so that smokers recognize the risk to which they expose members of their family. Most important of all, clinicians should advise families of patients with known coronary artery disease not to smoke in their presence.

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