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# Commentary: How acute and reversible are the cardiovascular risks of secondhand smoke?

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Could eating in a smoky restaurant precipitate an acute myocardial infarction in a non-smoker? As unlikely as this sounds, a growing body of scientific data suggests that this is possible. In this context, the results of the observational study in Helena, MT are provocative: hospital admissions for acute myocardial infarction declined by about 40% during the six months in which a comprehensive local ordinance on clean air was in effect, and rebounded after the ordinance was suspended.[1]

Given the small size and observational design of the study, these findings might be discounted or even disregarded altogether. However, the study focuses attention on an interesting subset of literature on secondhand smoke and its consequences. We now have a considerable amount of epidemiological literature and laboratory data on the mechanisms by which relatively small exposures to toxins in tobacco smoke seem to cause unexpectedly large increases in the risk of acute cardiovascular disease.[2-7]

### Secondhand smoke causes coronary heart disease

Exposure to secondhand smoke increases the risk of fatal and non-fatal coronary heart disease in non-smokers by about 30%.[2 5 8 9] Because coronary heart disease is a leading cause of death in many countries, even relatively small increases in risk from this one factor can result in a large population burden of disease attributable to exposure to tobacco smoke.[10 11] While the substantial cardiovascular risks posed by active smoking are now almost universally accepted, the tobacco industry and some other observers continue to question the idea that secondhand smoke can cause cardiovascular disease and death.[12–15] Notwithstanding the substantial clinical and experimental evidence regarding the adverse cardiovascular effects of exposure to secondhand smoke, some have argued that an association between low level environmental exposures and health outcomes should be more critically evaluated, particularly when the relative risk for the exposure is below 2.0.[14 15] In addition, the risk of coronary heart disease associated with the typical self reported level of exposure to secondhand smoke (for example, that of a non-smoker living with a smoker) can seem disproportionate. It is more than one third of the risk associated with smoking 20 cigarettes a day, even though the measured exposure to tobacco smoke among non-smokers is only about 1% of the exposure from smoking 20 cigarettes a day.[2 4 5 16]

This observation differs from the case for lung cancer, where the excess risk for exposure to secondhand smoke reflects a more linear dose-response effect in comparison with the risk from smoking 20 cigarettes a day.[2 4 5 17] While the epidemiological pattern of risks for coronary heart disease might seem inconsistent with the data on measured exposures, the emerging understanding of the mechanisms by which exposure to toxins in tobacco smoke increases the risk of acute myocardial infarction provides a biologically plausible explanation of the data.[3–7 16 18 19]

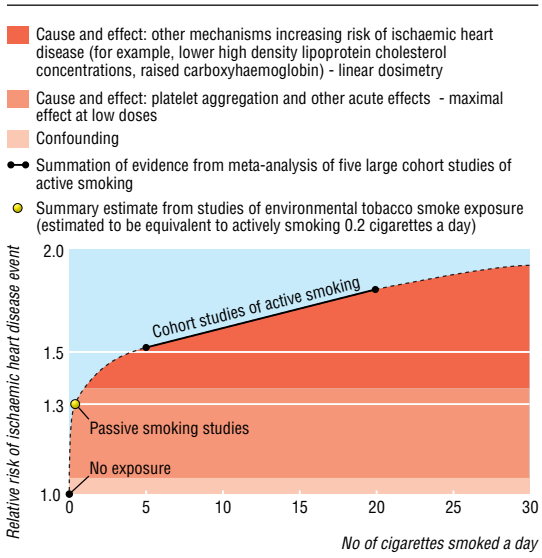
### Even small exposures to tobacco smoke rapidly increase the risk

A substantial body of epidemiological and laboratory data indicates that, unlike the case with lung cancer, the risk of acute myocardial infarction and coronary heart disease associated with exposure to tobacco smoke is non-linear at low doses, increasing rapidly with relatively small doses such as those received from secondhand smoke or actively smoking one or two cigarettes a day.[3 4 5] At higher levels of exposure from active smoking (for instance, five to 20 cigarettes a day), the risk of coronary heart disease increases more slowly and in a more linear way.[2 8 9] Consistent with the epidemiological findings both for active smoking at lower numbers of cigarettes a day and for exposure to secondhand smoke, laboratory data suggest that even small exposures significantly and rapidly increase platelet aggregation and induce other arterial and haemodynamic changes.[5–7 16 18 19] An acute myocardial infarction is commonly precipitated by the activation and aggregation of platelets and the resulting formation of a thrombus or clot that obstructs the arterial blood supply to part of the heart.[4 5]

Other mechanisms that increase the overall risk of acute myocardial infarction and coronary heart disease, such as reduced high density lipoprotein cholesterol and increased carboxyhaemoglobin concentrations, have been shown to have a more linear dose-response relation with exposure to tobacco smoke.[5] Secondhand smoke has a small effect on several of these other mechanisms, but the risk they impart is much more substantial for the dose of toxins delivered by active smoking (for example, from smoking five or more cigarettes a day).

Law and Wald have produced a conceptual model that integrates epidemiological risk data for ischemic heart disease or coronary heart disease for active exposure and exposure to secondhand smoke (figure).[5] In this model, it is estimated that a large proportion, and particularly the more acute aspects, of the risks from exposure to the toxins in tobacco smoke come close to peaking at relatively low levels of exposure, increasing little with exposure to higher levels of active smoking.[5] Research has identified the likely mechanisms, including thrombosis, endothelial dysfunction, and inflammation, by which smoking causes acute cardiovascular events.[3–7 16 18 19]

A recent epidemiological study found that, compared with unexposed non-smokers, non-smokers exposed to secondhand smoke had higher blood chemistry values related to these types of mechanisms—including white blood cells, C reactive protein, homocysteine, fibrinogen, and oxidised low density lipoprotein cholesterol concentrations—and




Dose-response association between exposure to tobacco smoke toxins and ischaemic heart disease (adapted from Law and Wald[5])

that the values for these biomarkers of inflammation were similar to those observed in active smokers.[20] Additionally, laboratory data suggest that even 30 minutes of exposure to a typical dose of secondhand smoke induces changes in arterial endothelial function in exposed non-smokers of a magnitude similar to those measured in active smokers.[21] Finally, data on smokers indicate that the risks of sudden death and acute myocardial infarction decline within days or months after smoking cessation.[2–3 5 22] Hence, these data and reviews of the laboratory findings on mechanisms[3–7 16 18 19] indicate that short term reductions in acute myocardial infarction events after reductions in exposure to low doses of toxins in tobacco smoke are biologically plausible.

### Smoke-free policies effectively reduce exposure

The US Surgeon General has concluded that exposure to secondhand smoke is a common public health hazard that is completely preventable.[23] Exposures can be dramatically reduced by eliminating smoking in all enclosed public places and workplaces [24–27] and by encouraging smokers to adopt smoke-free rules in their homes and cars.[28] Primarily due to the changes in smoke-free policies in the United States, cotinine concentrations (a tobacco specific biomarker of exposure) decreased substantially among non-smokers from 1991-4 to 1999-2000, dropping 58% for children, 55% for adolescents, and 75% for adults.[29] However, even with this reduction in exposure, the current estimate is that in the United States secondhand smoke still causes over 35 000 deaths from coronary heart disease each year.[30]

### Need for replication of results

Although the results of the study by Sargent and colleagues[1] are consistent with the literature on the risks of acute myocardial infarction associated with secondhand smoke, the study has some important limitations. Firstly, it contains no data on actual exposures to secondhand smoke among residents or cases, and thus no data on the changes in exposure to secondhand smoke that may have occurred after the

policy was implemented. It might be reasonable to assume that levels of important smoke toxins within public places in Helena covered by the ordinance dropped dramatically. This effect has been observed in other locations where similar policies have been implemented, with air quality measurements showing 80-90% declines in public places.[25–27] Even if such declines also occurred in Helena, some proportion of non-smokers would still have been exposed in their homes, cars, or other enclosed places not covered by the ordinance. Thus, without more data, the proportion of non-smokers in Helena among whom exposures were significantly reduced during the six months that the ordinance was in effect cannot be known.

A second concern is that the geographical isolation of the city, while making this type of study feasible, also resulted in a small number of admissions for acute myocardial infarction. As reported elsewhere, the typical number of acute myocardial infarction events per month before the ordinance was only about six or seven and was highly variable, with the actual number per month ranging from none to about 10-12.[31] Although conservative statistical analyses were applied to these data, due to the small number of events and the lack of data on changes in active smoking, random variation and factors other than secondhand smoke exposure may have contributed to the findings.

Finally, the observed effect (a decline of an average of 16 admissions for acute myocardial infarction for a six month period) was substantially greater than what might be expected. With smokers accounting for 38% of the admissions, we can estimate that about 25 admissions ($40\times0.62=24.8$) were among former and never smokers during the equivalent six month period before the ordinance. Even assuming that the proportion of acute myocardial infarction cases among smokers was fairly constant across time, that all non-smokers were frequently exposed to secondhand smoke in public places, that virtually all this exposure was eliminated by the ordinance, and that all coronary heart disease risk related to this exposure was immediately reversed among non-smokers (that is, that risk dropped from 1.3 to 1.0), the maximum impact on admissions for acute myocardial infarction would be predicted to be about 18-19% ($0.30\times24.8=7.44$; $7.44/40=18.6\%$) during the six months that the ordinance was in effect. Taking all of the above assumptions and issues into consideration, a more conservative estimate of the predicted reduction in acute myocardial infarction events might be 10-15%. The authors suggest that the smoke-free ordinance may also have reduced exposure to secondhand smoke among smokers, as well as encouraging smokers to stop smoking or reduce consumption. No data are provided to support this suggestion, but such changes in active smoking could have contributed to some declines in admissions for acute myocardial infarction. Recent reviews and studies have found that the implementation of smoke-free policies typically reduces consumption and promotes cessation among smokers.[23–25 32–34]

The small number of acute myocardial infarction events in this study produced a wide 95% confidence interval in the analysis that includes the conservative estimate of a 10-15% reduction. The width of the confidence interval underscores the importance of additional, larger studies that could replicate the findings of the Helena study[1] and provide more stable estimates of the effect size. Because it would be unethical to conduct a randomised trial that assigned adults at high risk of cardiovascular disease to either frequent exposure to secondhand smoke or no exposure and then compared their rates of acute myocardial infarction, we must rely on observational studies. Sargent et al's study suggests that future observational studies should be conducted in larger geographical areas where "before-after" trend analysis and the comparisons with "control" areas can be performed with adequate power to detect even a 10% reduction in acute myocardial infarction events. Additionally, future observational analyses should seek to obtain data on actual exposure to secondhand smoke before and after policy changes in order to document how much exposures have declined among residents overall and among non-smokers admitted for acute myocardial infarction.

**People at risk of coronary heart disease should avoid exposure to secondhand smoke**

Even without future studies or replications of these findings[1] the data are sufficient to warrant caution regarding exposure to secondhand smoke.[2 23–24] Clinicians should be aware that such exposure can pose acute risks, and all patients at increased risk of coronary heart disease or with known coronary artery disease should be advised to avoid all indoor environments that permit smoking.[3 5 16] Additionally, the families of such patients should be counselled not to smoke within the patient's home or in a vehicle with the patient. In addition to its impact on heart disease, exposure to secondhand smoke causes lung cancer in non-smokers, respiratory infections and asthma in children, and even death in exposed infants.[2 17 30] As the US Surgeon General and the US Community Preventive Service Task Force have noted,[2 23 24] much of this important health risk is preventable by the implementation of comprehensive smoke-free policies similar to the policy that was implemented in Helena for six months. Additional studies are needed to confirm how much the exposure to the toxins in tobacco smoke among non-smokers at risk for acute myocardial infarction and coronary heart disease can be reduced by the implementation of such comprehensive smoke-free policies and to confirm that such reductions in exposure can decrease rates of acute myocardial infarction. If future studies replicate the positive results from the Helena study, the public health implications would be dramatic; thousands of acute myocardial infarction events among non-smokers in countries around the world could potentially be prevented each year.

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# Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study

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## Abstract

**Objective** To examine the relation between the normal range of serum aminotransferase concentration and mortality from liver disease.
**Design** Prospective cohort study.
**Setting** Korea Medical Insurance Corporation study with eight years' follow up.
**Participants** 94 533 men and 47 522 women aged 35-59 years.
**Main outcome measure** Mortality from liver diseases according to death certificate.
**Results** There was a positive association between the aminotransferase concentration, even within normal range (35-40 IU/l), and mortality from liver disease. Compared with the concentration <20 IU/l, the adjusted relative risks for an aspartate aminotransferase concentration of 20-29 IU/l and 30-39 IU/l were 2.5 (95% confidence interval 2.0 to 3.0) and 8.0 (6.6 to 9.8) in men and 3.3 (1.7 to 6.4) and 18.2 (8.1 to 40.4) in women, respectively, The corresponding risks for alanine aminotransferase were 2.9 (2.4 to 3.5) and 9.5 (7.9 to 11.5) in men and 3.8 (1.9 to 7.7) and 6.6 (1.5 to 25.6) in women, respectively. According to receiver operating characteristic curves the best cut-off values for the prediction of liver disease in men were 31 IU/l for aspartate aminotransferase and 30 IU/l for alanine aminotransferase.
**Conclusion** People with slightly increased aminotransferase activity, but still within the normal range, should be closely observed and further investigated for liver diseases.



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