Environmental Tobacco Smoke and Measures of Subclinical Vascular Disease

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Assessing the relationship of exposure to environmental tobacco smoke (ETS) with subclinical measures of atherosclerotic disease supplements the epidemiologic data on fatal and nonfatal cardiovascular events. In addition, such assessment offers the opportunity to study smaller populations (including subgroups within larger studies) through improved statistical precision relative to the analysis of the relationship of ETS and clinical events and provides insights into the mechanisms of the harmful effects of ETS. In this article we review the published literature on the relationship of ETS with several indices of subclinical atherosclerosis including carotid artery intimal-medial thickness, brachial artery endothelial function, and silent cerebral infarctions. In each of these domains, exposure to ETS is associated with evidence of increased subclinical vascular disease. Key words: atherosclerosis, carotid arteries, cerebral infarction. Duplex ultrasonography, smoking, tobacco smoke pollution, vascular endothelium. — Environ Health Perspect 107(suppl 6):837-840 (1999).

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Background

Numerous case-control and cohort studies have established exposure to environmental tobacco smoke (ETS) as a substantial risk factor for the development of clinical coronary events associated with increases of 1.2–1.5 times the risk of those not exposed to ETS (1,2). The findings of case-control studies are subject to specific methodologic concerns, especially information bias. These case-control studies are, however, supported by prospective cohort studies, such as the American Cancer Society CPS-II cohort (3) and the Nurses' Health Study (4), that provide additional information of the association of ETS and clinical coronary disease and allow for adjustment for potential confounding factors. A strength of the epidemiologic data is that studies using different designs (prospective and retrospective, cohort and case-control) in different countries find generally similar results.

Because of the established association of ETS with clinical cardiovascular events (1–4), the role of establishing associations between ETS and subclinical disease may appear illogical. However, the link between ETS and subclinical disease is important for at least three reasons. First, even in the large cohort studies, the number of events is relatively small. For example, the Nurses Health Study with 32,046 participants only presented with 152 clinical coronary events (4). This small number of events limits the statistical power to examine more complex hypotheses, relationships in subgroups, and the potential for effect modification. Many measures of subclinical disease offer increased statistical power, either by providing a continuous (rather than dichotomous or time-to-event measure) outcome measure or by increasing the number of events (by including Asilent events). Second, analysis of subclinical disease outcomes offers insight into the mechanisms underlying the development of clinical coronary events. And finally, analysis of subclinical outcomes allows an assessment of the natural history of the disease process, particularly the early phases. This is an advantage over a study of the final clinical events that generally manifest at older ages, not only by providing an index of the effect of factors at younger ages but also by avoiding potential biases associated with selective mortality and ascertainment (or response) bias (which may result from knowledge of a clinical condition).

There are several mechanistic pathways through which exposure to ETS could affect the development of (subclinical) atherosclerosis. The article by Glantz and Parmley (5) summarizes the potential pathways that a) compromise the myocardium's ability to use oxygen to create adenosine triphosphate that may in turn increase arterial stress, b) increase platelet activity with associated direct impact on atherosclerotic plaque development, and c) decrease endothelial function. These effects are observed in people exposed to ETS in "normal" smoke-filled homes and workplaces.

For all these reasons, there has been growing interest in analysis of subclinical disease in cardiovascular epidemiology. Commonly used subclinical outcomes include a) assessment of the intimal medial thickness (IMT) of the carotid artery using B-mode real-time ultrasound, as an index of systemic atherosclerosis; b) assessment of arterial endothelial function using B-mode ultrasound of the brachial artery, as an index of vascular damage; c) assessment of the presence of silent cerebral infarctions and cortical white matter disease using magnetic resonance imaging; d) assessment of the presence of coronary arterial calcium using electron beam computed tomography scanning, as an index of coronary atherosclerosis; and e) measurement of blood pressure in the ankle, compared to that in the arm, as an index of peripheral vascular disease (6). These measures of subclinical disease are powerful predictors of subsequent incident cardiovascular events. For example, increased IMT is associated with substantial increased risk of incident coronary events (details follow) (7–9), and subclinical infarctions have been associated with an increase in the risk of incident stroke as large as that associated with a clinically pronounced stroke (10). In this article, we review the literature on ETS and selected measures of subclinical cardiovascular disease.

Carotid Ultrasonography

B-mode real-time ultrasound can be used to assess noninvasively the extent of atherosclerosis in arteries close to the skin surface. The carotid artery has received particular attention, initially for its relevance to stroke events. The strong association has been well established between active smoking and advanced atherosclerosis in stroke populations (11,12) and in some populations is the strongest single predictor of atherosclerosis in clinical populations (13).

The Atherosclerosis Risk in Communities (ARIC) study was among the first epidemiologic studies to use the IMT of the carotid artery as an index of systemic atherosclerosis in a population-based study of the general population (14). Studies have established that IMT is related to the extent and severity of coronary artery disease (p ≤ 0.0001). However, the strength of the association between carotid and coronary disease is not sufficient so that knowledge of carotid status can reliably predict the coronary status for a specific individual (15). That the correlation is not sufficient for predictive use in individuals is not of particular concern, as the focal nature of atherosclerotic plaques leads to relatively low correlations even between sites.
in the carotid bed (16). That is, the systemic nature of atherosclerosis presents a strong association between arterial beds, but the focal nature of plaques prevents direct clinical prediction between sites for an individual.

Perhaps the most convincing evidence of the relevance of IMT as an index of systemic atherosclerosis is its strong association with subsequent clinical events (7, 9). In the ARIC study, those female participants with IMTs greater than 1,000 μm were at approximately 5 times the risk of subsequent myocardial infarction compared to those with IMTs less than 1,000 μm, whereas men with IM Ts greater than 1,000 μm were at twice the risk (7).

Similarly, the Rotterdam study also showed a 41% increase in stroke risk and a 43% increase in risk for a subsequent myocardial infarction (p = 0.0001 for both) associated with a standard deviation increase in IMT (163 μm) (8). Thickened IMT was also associated with increased risk for coronary events in the Cardiovascular Health Study, where the relative risk of myocardial infarction or stroke (adjusted for age and sex) for the quintile with the highest thickness was approximately 4 times greater than that of the lowest quintile. This association remained significant after adjustment for risk factors (9).

The ARIC study provides strong evidence of increased IMT with increasing exposure to cigarette smoke and for exposure to ETS in particular. In cross-sectional analysis of data from the baseline ARIC visit, there was an 11-μm difference in the average IMT of non-smokers not exposed to ETS (N-E) and non-smokers exposed to ETS (N+E). This estimated difference was increased (17 μm) by adjustment for age, race, and gender (ETS smokers were younger and more likely to be female, both associated with thinner IMT measures), a difference that proved highly statistically significant (p ≤ 0.0001). This difference was reduced to 13 μm but remained statistically significant (p = 0.0027) by further adjustment for the presence of diabetes, hypertension, low-density lipoprotein cholesterol level, education (surrogate for socioeconomic level), fat intake (Keys score), alcohol intake, obesity (body mass index), and leisure-time physical activity. As such, the ARIC study provides clear cross-sectional evidence for an association of ETS with systemic atherosclerosis that is not explained by potential confounders. Although not directly pertinent to this discussion, the IMT measures for past and current smokers were greater than those of nonsmokers (17).

Although exposure to ETS is frequently lifelong, complete and accurate assessment of lifetime exposure to ETS is beyond the scope of most population-based epidemiologic studies. As such, these studies usually resort to assessment and analysis of current measures of ETS exposure. A notable exception to this limitation in the assessment of association of ETS and IMT is the report by Diez-Roux et al. (18). This study assessed current exposure to ETS in a cohort of 2,073 individuals who were subsequently included in the ARIC study. This subsequent ARIC assessment occurred 12–14 years after the initial assessment and included both evaluations of ETS exposure as well as an assessment of IMT. As such, data were available on exposure to ETS at two time points separated by 12–14 years and an ultrasound assessment of atherosclerosis at the later point, allowing analysis of the effect of both current and past ETS exposure with the current extent of atherosclerosis.

Diez-Roux et al. (18) defined four groups of participants in this study: those not exposed to ETS at either exam, those exposed at the first but not the second exam, those exposed at the second but not the first, and those exposed at both exams. Exposure to ETS in one or both periods was associated with increased IMT by a nearly identical amount, suggesting long-term harmful effects of ETS exposure (beyond current exposure). The average IMT of those not exposed in either period was 706 μm; those exposed in the first period only, 731 μm; those exposed in the second period only, 738 μm; and those exposed in both periods, 734 μm. As such, this study reflects the harmful effects of only historical ETS exposure, which are approximately the same as the effect of exposure concurrently with the assessment of atherosclerosis.

The cross-sectional association of larger IMT with greater exposure to cigarette smoke is consistent with previously unpublished results from the Insulin Resistance Atherosclerosis Study (IRAS). The design and methods for this population-based epidemiologic study have been reported elsewhere (19). Briefly summarized, 1,625 participants were evaluated in four clinical centers, with detailed assessment of IMT, smoking history, and potential confounders. The average IMT was estimated in this population for N-E, N+E, past smokers not exposed to ETS (P-E), past smokers exposed to ETS (P+E), and current smokers (C) after adjustment for age, ethnicity, sex, obesity (body mass index), hypertension, low-density and high-density lipoprotein levels, triglyceride levels, diabetes status, alcohol intake, socioeconomic status (indexed by education), and physical activity (indexed by total energy expenditure). In the common carotid artery, there was a step-wise relationship with increasing exposure to cigarette smoke from 810 μm for N-E, to 813 μm for N+E, to 829 μm for P-E, to 845 μm for P+E, and finally to 863 μm for C. In the internal carotid artery the relationship was reversed for N-E (881 μm) and N+E (864 μm) but was otherwise ordered from 892 μm for P-E, to 939 μm for P+E, and finally 990 μm for C. Other large epidemiologic studies addressing the relationship of smoking and IMT have addressed only the impact of active smoking and have failed to provide a description of the effect of ETS (20–22).

In addition to the cross-sectional association between ETS and IMT, the ARIC study also examined longitudinal association between exposure to ETS and the progression (worsening) of atherosclerosis (23). In a longitudinal analysis, exposure (in this case ETS) is assessed prior to the determination of the outcome (worsening of atherosclerosis), thereby avoiding concerns of the temporal sequencing of the exposure and outcome. After adjustment for age, race, sex, baseline IMT, hypertension, low-density lipoprotein levels, previous coronary heart disease, diabetes, dietary fat intake (Keys score), socioeconomic status (education), leisure-time physical activity, and alcohol use, the estimated progression rate for N–E was 25.9 μm over a 3-year follow-up compared to 31.6 μm for N+E, 32.8 μm for P–E, 38.8 μm for P+E, and 43.0 μm for C. The average increase in progression rate associated with ETS exposure (across nonsmokers and past smokers) was 5.9 ± 2.3 μm over a 3-year period (a 20% increase), a difference that was statistically significant (p = 0.01). In addition, subgroups of the population were identified as particularly susceptible to increased exposure to cigarette smoke. Specifically, the magnitude of the increase in progression rate associated with exposure to cigarette smoke (either active or ETS) was approximately twice the increases observed among nondiabetic subjects. The average progression of atherosclerosis among participants with hypertension also appeared to be at a faster rate than that of their normotensive counterparts.

These data, largely reflecting the results of the ARIC study, indicate that exposure to ETS is associated with greater levels and faster progression of atherosclerosis, indicating a potential mechanism of the association of ETS and clinical coronary events.

Endothelial Function

Endothelial damage has been hypothesized to be one of the early steps in the process of atherogenesis and is likely to be an important early marker of vascular damage (24). Endothelial function can be assessed by measuring the dilatation of the brachial artery following hyperemia of the forearm induced by a pneumatic tourniquet (25).

Celemajer et al. (26) have reported the association of endothelial function and exposure to cigarette smoke in 26 N–E, 26 N+E, and 26 C. These groups did not differ by age, gender, blood pressure, cholesterol, or vessel
size. The flow-mediated percent dilation of the N–E was 8.2 ± 3.1, which was substantially greater than that of the N+E (3.1 ± 2.7%). The dilation for N+E was even nonsignificantly less than that of C (4.4 ± 3.1%), a group previously shown to have substantially impaired endothelial function (27). Finally, among the N+E, there was a clear dose–response relationship with increasing exposure to ETS, with those with light exposure (1–3 hr/day) showing a 4.1 ± 2.2% response compared to a 3.1 ± 2.2% response among those with moderate exposure (4–6 hr/day) and a 1.8 ± 2.0% response among those with heavy exposure (more than 6 hr/day). Woo et al. (28) have reported similar results among Caucasians in Australia and England but found no association between smoking (active or ETS) and endothelial function in a Chinese population.

Hence, at least in Caucasian populations, there appears to be an association between ETS exposure and endothelial function, an early indicator of arterial damage.

Silent Cerebral Infarctions

The advent of widespread magnetic resonance imaging capability allows the assessment of silent cerebral infarctions (SCIs) to be extended from neurologic patients to population-based cohorts. Between 10 and 40% of patients with transient ischemic attacks have SCIs (29), and in neurologic populations the prognosis for patients with SCIs is suggested to be nearly as poor as for those with clinically manifest strokes (10).

The association between cigarette smoking, ETS exposure, and the presence of SCIs in the general population was recently evaluated in the ARIC study (30). Overall, 11% of this middle-age population has silent cerebral infarctions. Cigarette smoking was among the most powerful predictors of prevalent SCIs. Current smokers had an 88% increase in the risk of SCIs after control for age, race, sex, hypertension, diabetes, high-density lipoprotein and triglyceride levels, alcohol use, obesity (body mass index), leisure-time physical activity, and dietary fat intake (Keys score). Past smokers have a 16% increase in the risk of prevalent SCIs. ETS exposure was also studied. Compared to the N–E group, the N+E group has a 6% increase (p > 0.05) in the likelihood of SCIs. The overall trend for increased risk of SCIs with increased exposure to cigarette smoke proved statistically significant (p = 0.029).

Other Measures of Subclinical Disease

To our knowledge there is no literature on or analysis of the relationship of ETS with other important measures of subclinical disease such as measures of peripheral vascular disease, coronary calcium by electron beam-computed tomography, or left ventricular function by echocardiogram or electrocardiogram. Clearly, further research is needed on ETS and other measures of subclinical disease.

Summary

The association of ETS with subclinical indices of atherosclerosis is based largely on associations observed in the ARIC population. In atherosclerosis, the ARIC data appear to strongly support an association in both cross-sectional and longitudinal analyses. However, this association is supported by previously unreported data (and non-peer-reviewed) reported here from the IRAS study. Although the association of ETS exposure and IMT thickening is based largely on the ARIC study, the strength of the association and its persistence in both cross-sectional and longitudinal analysis augment other evidence that ETS exposure causes cardiovascular injury. Similarly, the association of ETS with endothelial function is strongly supported by the magnitude of its effect and the existence of a dose–response function within the N+E group. The association of ETS with SCIs is weaker (a nonsignificant 6% increase in risk). However, the effect is in the anticipated direction and is consistent with the pattern of effects observed for atherosclerosis of the carotid artery. Although evidence of an ETS effect on atherosclerosis and endothelial function appears strong, it is based on a single report; confirmation would substantially strengthen the argument for the existence of an effect. More important, significant other domains of subclinical disease remain unaddressed.

Using subclinical measures of atherosclerosis to assess the relationship of ETS exposure and atherosclerosis does not address the most challenging aspect of the assessment of risk associated with ETS—the assessment of the exposure itself. One major shortcoming of these reports is the possibility of misclassification bias when assessing ETS, particularly over the lifetime of those exposed. In addition, the widespread nature of ETS exposure makes it difficult to ensure the nonexposure of the reference group. However, these shortcomings should, on average, tend to make the identification of an association more difficult (i.e., bias toward the null hypothesis of no association).

In relatively small populations, subclinical measures of atherosclerosis can be used to establish an association with ETS. For example, a relationship between ETS exposure and endothelial functioning using only 52 subjects (26), a slight increase in the prevalence of SCIs associated with ETS exposure with only 1,737 subjects (30), and a difference in progression rates of carotid atherosclerosis were established between 4,298 participants exposed to ETS and 3,660 not exposed (23). This is in contrast to the substantial study size that would be required to establish an association of ETS with incident clinical events. Specifically, the optimal prospective study design (smallest sample size) would be to follow a population of never smokers with a 50% exposure to ETS for incident events. If the anticipated hazard ratio associated with ETS exposure were 1.3, then a population of sufficient size to provide 611 incident events would be required to provide even 80% power (31). In Framingham, Massachusetts, the risk of a heart attack in an 8-year period was 471/1,000 in men and 8/1,000 in women (32). In a population that is 50% female, this corresponds to an annual incidence rate of approximately 0.3%. At this incidence rate, a total of 203,667 person-years of exposure would be required to provide 611 events, clearly a substantial undertaking.

The differences in subclinical measures of atherosclerosis are small between those individuals exposed to ETS and those not exposed. However, the long-term clinical impact of such small differences in subclinical measures of atherosclerosis has been established. Such small differences in IMT of the carotid artery are powerful and independent predictors of new coronary heart disease events (7–9), and subclinical infarctions have been associated with an increase in the risk of incident stroke as large as that associated with a clinically pronounced stroke (10). As such, although these associations should be interpreted with caution, they suggest that a higher cardiovascular risk is associated with ETS exposure. Additional work to assess the relationship of ETS with other indices of subclinical atherosclerosis should be encouraged.

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