

Investigating Air Pollution and Atherosclerosis in Humans: Concepts and Outlook

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Abstract

Although ambient particulate matter contributes to atherosclerosis in animal models, its role in atherogenesis in humans needs to be established. This article discusses concepts, study design, and choice of health outcomes to efficiently investigate the atherogenic role of ambient air pollution, with an emphasis on early preclinical biomarkers of atherosclerosis that are unaffected by short-term exposure to air pollution (eg, carotid intima-media thickness [CIMT] and functional performance of the vessel). Air pollution studies using these end points are summarized. The CIMT is currently the most frequently used outcome in this field (6 studies). The continuous nature of CIMT, the lack of short-term variation, its relationship to atherosclerotic changes in the artery wall, its predictive value for coronary heart disease, and the noninvasiveness of the assessment make it a useful candidate for cross-sectional and longitudinal studies investigating the role of air pollution in atherogenesis. (Prog Cardiovasc Dis 2011;53:334-343)

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Abbreviations and Acronyms**A/B ratio** = Ankle/Brachial ratio**AAC** = Aortic atherosclerosis**ABI** = Ankle-brachial index**AHA** = American Health Association**AOC** = Aortic artery calcification**CAC** = Coronary artery calcification**CAD** = Coronary artery disease**CAVI** = Cardio-ankle vascular index**CIMT** = Carotid intima-media thickness**CVD** = Cardiovascular disease**ESCAPE** = European study of cohorts for air pollution effects**LDL** = Low-density lipoprotein**MI** = Myocardial infarction**PAD** = Peripheral artery disease**PM** = Particulate matter

Ambient air pollution causes a range of health problems.¹ A recent review of the current literature published on behalf of the American Health Association concluded that ambient air pollution has a causal relationship to cardiovascular mortality and morbidity.² Evidence is particularly strong for short-term (such as daily) exposure to ambient particulate matter (PM) and subsequent acute effects on a range of outcomes of cardiovascular relevance, including oxidative stress and systemic inflammation; endothelial cell activation and dysfunction; altered blood pressure, heart rate, and heart rate variability; arrhythmia; deregulated coagulation pathways; ischemia; myocardial infarction (MI); and stroke. In line with the latter clinical outcomes, hospital admissions and mortality from cardio-

vascular problems correlate with daily changes of ambient air pollution.³

In addition, living in more polluted areas is linked to higher cardiovascular morbidity and mortality.² If pollution only triggered cardiovascular disease (CVD) events, these studies would also observe significant associations between event frequencies (or life expectancy) and the measure of “long-term” pollution. However, the association observed between long-term exposure to air pollution and death is substantially larger than reported in time series (acute effects).³ This large discrepancy strongly suggests—but does not prove—that air pollution may not only have immediate short-term effects, which are efficiently captured in time-series studies, but also contribute to the underlying long-term CVD pathologies such as coronary artery disease (CAD).⁴

Atherosclerosis is perhaps the most important underlying cardiovascular pathology, leading both to permanent structural and functional changes of arteries and to acute clinical expressions such as an acute myocardial infarction.^{5,6} Whether and how air pollution induces chronic effects on the development and progression of

atherosclerosis, and how acute air pollution-induced effects may be related to the chronic process of atherogenesis has not been thoroughly investigated. Although hypothetical mechanisms are emerging, as emphasized in the American Health Association review² and others,⁷ more research is needed to understand the role of long-term air pollution exposure in atherogenesis. Animal studies provide strong evidence for atherogenic effects of ambient PM.⁸ However, these findings need to be corroborated and quantified in epidemiological research in humans.

The purpose of this article is to discuss the concepts of investigating the atherogenic role of air pollution in humans, to identify and evaluate key study design issues to investigate these effects, and to review and discuss features of various measures of atherosclerosis relevant to air pollution research. A brief summary of the current epidemiological evidence and an outlook on ongoing studies is provided at the end.

Atherosclerosis: conceptual model of disease

To efficiently investigate the long-term effects of air pollution on atherosclerosis, it is first essential to promote a disease model that can explain the full range of atherogenic effects from its very early emergence of arterial wall changes to the late stages of plaque formation leading to arterial stenosis, plaque vulnerability, and, eventually, rupture, which ultimately ends in symptomatic CAD.⁹

The process of atherogenesis follows a life-long pathway, beginning in utero. Systemic and vascular inflammations after increased oxidative stress, endothelial dysfunction, and accumulation of lipids in the vascular wall are early central features of the long-term pathology of the artery wall, resulting in reduced vascular reactivity, arterial stiffening, increase in arterial wall thickness, plaque formation, and arterial stenosis. The process of atherogenesis is often superimposed by acute clinical manifestations, primarily at later stages of the disease process. Vulnerable coronary plaques with lipid-rich necrotic cores but thin fibrous caps are prone to rupture, leading to acute CAD manifestations, for example, acute myocardial infarction. Thrombus formation at carotid plaques is the major cause of cerebral stroke and vascular dementia. Moreover, other atherosclerosis-related diseases, which may or may not lead to an acute event, include peripheral vascular disease and aortic aneurysm.

This life-long process suggests that the degree of atherosclerosis at any point in life reflects a combination of genetic predisposition and a cumulative total exposure to endogenous and exogenous pro- and antiatherogenic factors. Accordingly, subjects of the same age with, for example, hypertension,¹⁰ familial hypercholesterolemia,¹¹ diabetes,¹² obesity,¹³ family history of cardiovascular diseases,¹⁴ poor nutrition, or smoking^{15,16} show more advanced signs of atherosclerosis with thicker artery

walls than those without these risk factors. These differences can be observed during childhood and throughout life.¹⁷ In contrast, reduction of atherogenic risk factors, achieved for example by using lipid-lowering medications^{18,19} or interventions to reduce obesity in children,²⁰ leads to a reduction in the progression of atherosclerosis.

The combination of the aforementioned features results in the proposed disease model shown in Fig 1. According to this model, the total cumulative load of atherogenic risk factors combined with genetic predisposition results in a low, medium, or high atherogenic risk. In turn, atherogenic risk determines where an individual of a certain age falls in the continuum of atherosclerosis (y-axis), the severity of which ranges from “normal” to preclinical and ultimately to clinically relevant levels of atherosclerosis. With increasing advancement of vascular processes, also known as “vascular aging,” the risk of a clinical event and diagnosis of CVD complications steadily increase for any individual.

Air pollution and atherosclerosis: hypothetical pathways and implications for public health and research

The model of the course of atherogenesis from its early, subclinical stages all the way to its clinical manifestation leads to the distinction of 2 relevant time windows of atherosclerosis: (1) the long-term process of atherogenesis,

usually taking years to decades; and (2) the triggering of an acute clinical manifestation (eg, an acute MI). In most cases, the first is a precondition for the second.^{5,6} However, the underlying mechanisms leading to the build-up of atherosclerosis, and those triggering acute events, may not necessarily be the same. Thus, risk factors initiating and promoting atherosclerosis and those triggering events (eg, MI) may be different. Risk factors for the latter are typically short-term in nature such as a short-term increase in blood pressure due to physical or emotional exertion or a transient prothrombotic change due to an infection. Some risk factors even have opposite effects. For example, strenuous exercise is a transient risk factor^{21,22} for acute events, but regular exercise is beneficial in the long term.

Particulate air pollution exposure is suspected to have both capabilities—to induce atherogenesis and to trigger acute events. Therefore, we suggest 2 separate hypotheses. The first hypothesis (H1) assumes that continued long-term exposure to ambient air pollution causes atherogenesis. In keeping with the disease model in Fig 1, individuals with higher exposure would have faster progression of vascular pathologies, reaching the state of clinically relevant atherosclerosis at an earlier age than those with lower exposure to air pollution. This would result, on average, in a shorter life expectancy because of higher cardiovascular mortality. The second hypothesis (H2) assumes that short-term exposure to pollutants may trigger cardiovascular events (in subjects with pre-existing

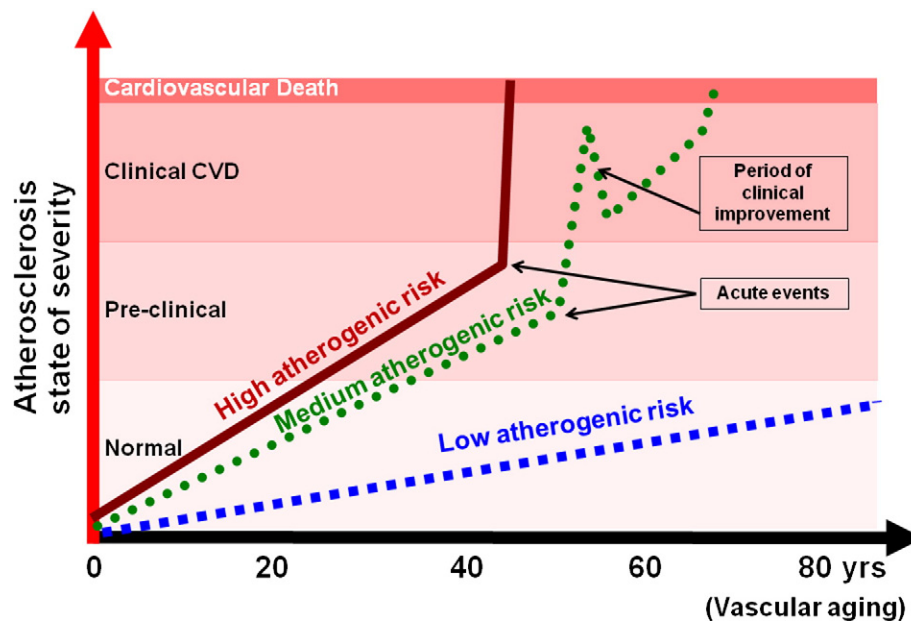


Fig 1. Model of life-time development of atherosclerosis. The continuum of atherosclerosis (y-axis) is categorized into 3 phases (normal, preclinical, and clinical disease manifestation). The total cumulative load of atherogenic risk factors determines individual atherogenic risk level. Examples of low, medium, and high risk are shown. Additional vascular aging increases the risk of developing clinically relevant atherosclerosis. Acute CVD events may be the first manifestation of the underlying but yet unknown preclinical pathology. The “medium atherogenic risk” example shows a period of clinical improvement (eg, because of treatment).

subclinical atherosclerosis). An extensive experimental and epidemiological literature already supports H2, showing that short-term exposure to increased levels of air pollution can trigger cardiovascular events.²

The differentiation between these 2 hypotheses is important when planning and interpreting air pollution research. First, investigation of the 2 hypotheses in humans requires different approaches and study designs. Acute effects of air pollution (H2) are addressed in experiments (chamber studies), panel studies with repeated observations of cardiovascular markers taken in the same subjects, and registry-based case series of cardiovascular outcomes. Statistical analyses focus on exposures to ambient PM during recent hours or days. In contrast, the long-term effects on atherogenesis (H1) require studies that capture the long-term exposure and the resulting level or development of atherosclerosis. In this case, cohort studies assessing both the long-term average exposures of their members and the initiation and progression of atherogenesis are mandated. Analyses of cross-sectional studies may provide important first insights into the contribution of past exposure to ambient air pollution to the current atherosclerotic state.

Because underlying pathologies such as atherosclerosis are in most cases a *conditio sine qua non* for the occurrence of cardiovascular events (eg, MI), strategies that prevent the development of atherosclerosis will be of larger public health relevance than those targeting factors that trigger events. For example, the atherogenic risk load of never-smokers is substantially reduced when compared with a population of smokers. Thus, fewer people in the never-smoker population become susceptible to clinical acute events. Under the H2, air pollution causes the triggering of events among the susceptible; thus, the number of acute events that can be prevented through clean air policies would depend on the number of susceptible people. However, the burden that can be prevented through environmental policies is far larger under H1 because reduction in exposure to air pollution would decrease the pool of subjects with atherosclerosis, thus, those susceptible to cardiovascular events. Accordingly, under H1, air pollution abatement ought to be considered a primary prevention tool of atherosclerosis in much the same way that reduction of salt content in preprocessed food or physical activity are useful prevention strategies. If air pollution is a cause for *both* atherogenesis (H1) and the triggering of events (H2), sustained improvement of air quality would reduce the pool of those susceptible to CVD events *and* the number of acute events among those with underlying atherosclerotic pathologies of any etiology apart from air pollution. As indicated in Fig 1, the superposition of short- and long-term exposures to pollution represents a shortening of the life span, which from the perspective of impact assessment ultimately translates into changes in mortality rates and life expectancy in the population.

Atherogenesis and outcome measures for epidemiological air pollution studies

The atherogenic process is characterized by a continuum between health and disease (Fig 1). As mentioned, the biologic pathways and risk factors of atherogenesis and the triggering of acute cardiovascular events are not necessarily the same. To understand and distinguish the long-term atherogenic role of long-term exposure to air pollution from short-term effects of exposure, it is essential to choose an outcome measure that reflects the current state of atherosclerosis and the process of atherogenesis. The most direct approach is the measure of atherosclerosis, that is, the ultimate phenotype of interest. Such a “phenomic” approach would be particularly efficient and specific under the hypothesis that air pollutants may contribute in complex ways to a range of mechanisms relevant to atherogenesis. For example, evidence suggests that ambient particles and, in particular, metals on PM contribute to vasoconstriction as a secondary reaction to the release of inflammatory mediators that activate endothelial and smooth muscle cells.²³ Others suggest pollutants lead to endothelial dysfunction or an increase in oxidizability of low-density lipoprotein.²⁴ Although none of these mechanisms alone may be a sufficient cause for atherogenesis, the total atherogenic effect of air pollution may be orchestrated by the combination of these pathways. Thus, a more “distal” measure of the atherogenic phenotype may be the preferred choice.

Given the systemic and long-term nature of atherosclerosis, continuous measures or indicators of atherosclerosis may relate to the functional performance of the conduit arteries or resistance vessels, the morphological characteristics of the arterial wall, or the end-organ involvement. But there is a need to first identify the necessary criteria that make surrogate measures of such complex diseases more or less relevant to air pollution research. We identified 5 main criteria:

1. The marker should measure the *continuous nature* of atherogenesis because atherosclerosis is not a dichotomous condition. Ideally, the level of atherosclerosis should be differentiated at all stages of the development. Repeated measures of the marker would reflect progression (or regression) of the underlying pathology. For example, a diffuse thickening of the intimal layer usually proceeds over years, and its increase can be captured by measurements of the intima-media thickness taken repeatedly in the same place over a time span of several years. Another possibility is to measure the development and progression of plaque and the increase in calcifications within plaques. In contrast, measures of the occurrence of events (such as death, MI, or ischemic stroke) do not characterize the continuous nature of the process.

2. The outcome measure should be a marker of the *long-term load* of atherogenic risk while not being affected by the most recent (eg, yesterday's) pollution. Thus, measures with strong short-term or circadian fluctuations are not ideal candidates, particularly not if the same marker correlates with the daily changes in air pollution, such as endothelial function.²⁴ The occurrence of acute events such as cardiovascular death or MI, which has been shown to be correlated with short-term air pollution in numerous studies, is also not an optimal choice given the established evidence of a causal role of air pollution in triggering these events (ie, acute effects).
3. *Specificity*: The chosen marker should specifically reflect pathologies in the vasculature. Markers of the inflammatory state of the vascular wall would provide specific information, where as general, markers of system inflammation may not only be sufficiently specific but also indicate more proximal inflammatory processes related to air pollution (eg, in the lung). Although atherosclerosis is known to affect ventricular mass, blood pressure, and renal function, there is a range of other pathologies affecting these outcomes as well.
4. *The surrogate measure should have a causal relationship with the disease process, so it can be used to predict clinically relevant outcomes because the latter is of public health relevance.*
5. *Practical issues must be considered*: Because the differences in individual exposures to ambient air pollution tend to be rather small, epidemiological studies on air pollution usually require rather large

sample sizes to observe significant effects. Thus, outcome measurements should be applicable on a large scale and be obtained with an available and affordable method. Ideally, the method should be noninvasive, accurate, and reliable.

Based on these criteria, the following measures of atherogenesis/atherosclerosis of possible use in epidemiological research on effects of ambient air pollution were identified. Table 1 provides scores to these outcomes with regard to the 5 criteria listed above.

1. Measures based on morphological characteristics of the arterial wall

Carotid intima-media thickness (CIMT): CIMT is the most validated technique for measurement of progression of atherosclerosis (clinical trials). The CIMT is assessed noninvasively by real-time, high-resolution, B-mode ultrasound imaging coupled with automatic data processing systems. It relies on the identification of a characteristic double-line pattern of the artery wall. Digitized image processing and automated reading procedures averaging multiple, simultaneously obtained automatic measurements allow an investigator-independent measurement of the mean CIMT. Although detailed protocols regarding measurement technique and analysis are readily available, the optimal site of measurement remains controversial (common carotid, bifurcation, internal carotid, posterior [far] or anterior [near wall]). In advanced atherosclerosis, the presence of plaque may perturb the characteristic double-line, leading to ambiguity regarding the inclusion of plaque area in the measurement. A comparison between studies can be difficult, because of different procedures and reading protocols. The CIMT has been used in longitudinal

Table 1

Scoring with regard to 5 criteria determining the usefulness of the outcome measure to investigate long-term atherogenic effects of ambient air pollution in epidemiological studies

	Continuous Measure	Marker for Long-Term Effects	Specific for Artery Wall Pathology	Predict CVD	Practical Issues (Low Costs; Low Invasiveness)
Morphological characteristics of the arterial wall					
CIMT	++	++	++	+	++
CAC	+	++	++	++	+
AOC	+	++	++	+	+
Retinal vessel diameter	++	+	+	0	++
Measures based on functional performance of the vessel					
ABI	++	+	+	+	++
Orbital blood flow velocity	++	+	+	0	++
Arterial stiffness, compliance, elasticity	++	+	++	+	++
Measures based on end-organ involvement					
Renal function	++	+	0	+	++
Ventricular mass	++	++	0	+	+
MI	0	0*	++	N/A	++
Cardiovascular death/mortality	0	0*	+	N/A	++

Scores are assigned relative to other outcome measures. Most appropriate features are scored with ++. A 0 score means that the outcome is not a good choice for the respective criterion. For a description of the outcome measures, see text.

* Marker for short-term effects of air pollution.

studies to assess the effect of clinical interventions, but the change in CIMT was not always correlated with the degree of clinical benefits.²⁵ The related outcome measure of carotid plaque, which can be assessed with the same instrumental technique, but for which less standardized reading protocols are available, has not been evaluated in air pollution studies so far.

Coronary artery calcification (CAC): CAC is a quantitative continuous marker of coronary atherosclerosis which is associated with prevalence and incidence of cardiovascular disease. It is a better predictor of cardiovascular events than traditional risk factors, C-reactive protein, or CIMT.^{26,27} Calcified plaques can be detected in early stages of atherosclerosis, but soft plaque without calcium will not be detected, and most of the population younger than 50 years do not have detectable calcium despite an increased cardiovascular risk. The CAC can accurately and reproducibly be measured using electron-beam or multidetector computed tomography. Different procedures for the quantification of the calcium burden have been proposed, the most frequently used being the Agatston score.²⁸ Although it is a continuous outcome measure, the high prevalence of no detectable calcifications, especially in the young and in women, pose methodological challenges.

Aortic artery calcification (AOC): AOC is an established measure of systemic atherosclerosis.²⁹ It is associated with traditional cardiovascular risk factors, atherosclerosis of the carotid and coronary arteries, and cardiovascular morbidity and mortality.^{30–32} Compared with CAC, prevalence and extent of abdominal aortic calcifications are greater in age groups older than 50 years, which improves statistical qualities of this measure. Measurement techniques are similar as for CAC but can represent costly instrumentation and high radiation exposure.

Retinal vessel diameter: Retinal vessel diameter is assessed by retinal photography and provides a noninvasive measure to investigate microvascular atherosclerotic disease that may lead to mirror microvascular disease in the brain and other end organs. Generalized arteriolar narrowing is related to carotid plaque, inflammation, and carotid artery stiffness.^{33,34} The retinal microvascular abnormalities are associated with subclinical as well as clinical stroke.³⁵ It is a method that has no risk-related measurements and has a high reproducibility when using digitized retinal photography.

2. Measures based on functional performance of the vessel

Ankle-brachial index (ABI): ABI is a continuous marker for the degree of subclinical peripheral atherosclerosis and correlates well with cardiovascular risk factors. It relies on the physiologic blood pressure increase in the distal arteries compared with the more proximal segments. A hemodynamically relevant stenosis of the arterial lumen proximal to the distal measurement leads to a decrease in

the ABI that correlates well with the severity of the stenosis.³⁶ The ratio of average systolic blood pressure in the bilateral brachial arteries and the dorsalis pedis and posterior tibial arteries is measured by the Doppler technique; however, there is no widely accepted standardized protocol for the calculation of this index. The ABI can be used to assess the prevalence of peripheral arterial disease in asymptomatic individuals, usually by dichotomizing the continuous measure at a predefined value.

Orbital blood flow velocity: This is a measure that allows for detecting hemodynamic changes in the central vessels of the carotid circulation, using the dampening of the Doppler effect distal to a hemodynamically significant stenosis. It is, therefore, a measure of the conduit function of the retrobulb (ophthalmic artery, central retinal artery) and the internal carotid artery. Orbital blood flow velocity is assessed noninvasively with high-resolution color Doppler ultrasonography, using specific software for the measurement of flow velocity of the orbital arteries such as the ophthalmic, central retinal, and posterior ciliary arteries. The flow velocities (systolic peak velocity and end-diastolic velocity) and pulsatility indices (A/B [Ankle/Brachial] ratio and resistance index) have been shown to be related to the degree of carotid stenosis.³⁷

Arterial stiffness, arterial compliance, or arterial elasticity: These measures are based on the degree to which a vessel distends during the application of pressure during systole. This ability to distend can reflect either structural or functional changes in the arterial wall, depending on the location within the vascular system. Increased stiffness of the aorta and large conduit arteries mainly results from an altered structure of the vessel wall because of an increase in collagen. In medium-sized conduit arteries, endothelial production of nitrogen oxide and resulting smooth muscle relaxation play an increasing role in determining the stiffness. In the microvasculature, the main determinant of stiffness is smooth muscle tone, regulated by vasoactive substances released from the endothelium. Changes in the small arteries and the microvasculature occur earlier in the disease process than in the larger arteries.³⁸ Different methods for assessing arterial stiffness exist, most of them involving ultrasound imaging or tonometry and the simultaneous noninvasive measurement of blood pressure. In some of these measures, a relationship with incidence of cardiovascular events in selected populations has been shown.^{39,41} Information on longitudinal changes and their determinants is limited. The multitude of measurement techniques and the complexity of physiologic interpretation, instrument requirements, and personnel requirements have limited comparisons between studies.

3. Measures based on end-organ involvement

Urinary albumin excretion: Urinary albumin excretion reflects impaired endothelial function in the renal glomerula. It has been hypothesized that it is also a marker of vascular damage throughout the vasculature.⁴²

Table 2
Basic characteristics of published epidemiological studies on air pollution and atherosclerosis using any of the markers of atherosclerosis listed in Table 1

Study	Population	Age Range of Study Population	End point	Exposure	Unit of Exposure	Main Result
Künzli et al, 2005 ⁴⁵	798 participants from 2 clinical trials	≥40 y	CIMT	Annual residential PM _{2.5}	10 μg/m ³ PM _{2.5}	4.2% increase (95% CI, -0.2 to 8.9)
Erdogmus et al, 2006 ⁴⁶	61 highway toll collectors, 48 controls, Turkey	Range, 24-56 y; mean, 36.2 y	CIMT	Occupational traffic exposure	Exposure vs no exposure	0.8 (SD, 0.2) vs 0.6 mm (SD, 0.1) (unadjusted)
Diez Roux et al, 2008 ⁴⁷	5172 subjects, Multi-Ethnic Study of Atherosclerosis	Range, 45-84 y; mean, 62 y	CIMT	20-y average residential PM ₁₀	21 μg/m ³ PM ₁₀	3% increase (95% CI, 1%-5%)
Lenters et al, 2010 ⁴⁸	750 subjects of the Atherosclerosis Risk in Young Adults Study	Range, 27-30 y; mean, 28.4 y	CIMT	Annual residential PM _{2.5} ; proximity to traffic	5 μg/m ³ PM _{2.5}	No association
Bauer et al, 2010 ⁴⁹	3380 participants, Heinz Nixdorf Recall Study, Germany	Range, 45-75 y; mean, 60 y	CIMT	Annual residential PM _{2.5} ; residential proximity to high traffic	4.2 μg/m ³ PM _{2.5} (interdecile range); 1,939 m (interdecile range)	4.3% (95% CI, 1.9-6.7%); 1.2% (95% CI, -0.2%-2.6%)
Künzli et al, 2010 ⁵⁰	1503 participants from 5 clinical trials	≥40 y (one study ≥30)	CIMT progression (longitudinal)	Annual residential PM _{2.5} ; proximity to traffic	10 μg/m ³ PM _{2.5} ; 100 m to major road	2.53-mm progression per y (95% CI, 20.31-5.38)
Erdogmus et al, 2007 ⁵¹	20 highway toll collectors, 20 controls, Turkey	Range, 24-56 y; mean, 36.2 y	Peak systolic flow in ophthalmic artery	Occupational traffic exposure	Exposure vs no exposure	36.8 (SD, 2.2) vs 33.2 cm/s (SD, 2.4) (unadjusted)
Hoffmann et al, 2007 ⁵²	4494 participants, Heinz Nixdorf Recall Study, Germany	Range, 45-75 y; mean, 60 y	CAC	Annual residential PM _{2.5} ; residential proximity to high traffic	3.91 μg/m ³ PM _{2.5} ; ≤50 vs >200 m	17.2% increase (95% CI, -6-46); OR, 1.63 (95% CI, 1.14-2.33)
Hoffmann et al, 2009 ⁵³	4302 subjects, Heinz Nixdorf Recall Study, Germany	Range, 45-75 y; mean, 60 y	ABI	Annual residential PM _{2.5} ; residential proximity to high traffic	3.91 μg/m ³ PM _{2.5} ; ≤50 vs >200 m	No association; -0.024 (95% CI, -0.047 to -0.001)
			Prevalence of PAD	Annual residential PM _{2.5} ; residential proximity to high traffic	3.91 μg/m ³ PM _{2.5} ; ≤50 vs >200 m	OR, 0.87 (95% CI, 0.57-1.34); OR, 1.77 (95% CI, 1.01-3.10)
Diez Roux et al, 2008 ⁴⁷	5172 subjects, Multi-Ethnic Study of Atherosclerosis	Range, 45-84 y; mean, 62 y	ABI	20-y average residential PM ₁₀	21 μg/m ³ PM ₁₀	Absolute difference, 0.001 (95% CI, -0.010-0.012)
			Prevalence of any CAC	20-y average residential PM ₁₀	21 μg/m ³ PM ₁₀	OR, 1.02 (95% CI, 0.81-1.30)
Allen et al, 2009 ⁵⁴	1147 subjects, Multi-Ethnic Study of Atherosclerosis	Range, 45-84 y; mean, 62 y	Prevalence of AAC	2-y annual residential PM _{2.5} ; residential proximity to high traffic	10 μg/m ³ PM _{2.5} ; ≤100 m from highway or ≤50 m from major road	OR, 1.06 (95% CI, 0.96-1.16); No association
Iannuzzi et al, 2010 ⁵⁵	52 participants	Range, 6-14 y	Arterial stiffness; CIMT	Distance from road	Within 300 m to major road	Absolute difference 1.58 (P = .007); No association
Lenters et al, 2010 ⁴⁸	750 subjects of the Atherosclerosis Risk in Young Adults Study	Range, 27-30 y; mean, 28.4 y	Arterial stiffness	Annual residential PM _{2.5} ; proximity to traffic	5 μg/m ³ PM _{2.5}	No association
Wu et al, 2010 ⁵⁶	17 mail carriers	Range, 22-46 y; mean, 32.4 y	Arterial stiffness (CAVI)	Occupational traffic exposure	Interquartile range (7.2 μg/m ³ PM _{1<2.5})	2.5% increase in CAVI (95% CI, 0.3-4.8)

All studies are cross-sectional analyses with regard to the mentioned end point unless stated otherwise. In all studies, end points were measured in adults.

Abbreviations: 95% CI, 95% confidence interval; AAC, aortic atherosclerosis; CAVI, cardio-ankle vascular index; OR, odds ratio; PAD, peripheral artery disease; PM_{2.5}, particulate matter with dynamic diameter up to 2.5 micrometer; PM₁₀, particulate matter with dynamic diameter up to 10 micrometer.

Urinary albumin is a sensitive and specific measure that can be easily applied in the clinical or research setting. Urinary albumin excretion is associated with an increased risk for renal failure, heart disease, stroke, peripheral artery disease, and cardiovascular mortality.^{38,43} On the other hand, reduction in proteinuria does not predict improvement in cardiovascular outcomes. This limits the value for the investigation of disease progression. Although readily available in many large studies, its association with air pollution has been investigated only once so far.⁴⁴

In theory, the association between air pollution and atherosclerosis might also be investigated using any of the typical features of atherogenesis such as endothelial dysfunction, lipid oxidation, or disintegration of the extracellular matrix. However, acute and chronic effects of air pollution are difficult to disentangle in each of these cases because these pathophysiologic features are also relevant in triggering CVD events. We therefore did not include these markers in the list of candidates. Similarly, because none of the metabolic markers of inflammation are specific for atherosclerosis per se, a “metabolic” approach may not be specific enough to investigate the air pollution-atherogenesis hypothesis.

State of evidence and outlook

Table 2 lists all epidemiological studies published so far using any of the above listed measures of atherosclerosis in relation to markers of long-term exposure to ambient air pollution. Although all preclinical outcomes listed in Table 1 have been used to explore associations with ambient air pollution in these studies, only a few measures have been taken into consideration in more than one study. Carotid intima-media thickness is a well-validated technique for the measurement of progression of atherosclerosis in clinical trials. In conjunction with its noninvasiveness, CIMT is particularly attractive for air pollution studies. Within the air pollution literature, CIMT is the only outcome for which longitudinal data (ie, CIMT progression) have been used, reporting positive correlations with traffic-related air pollution.⁵⁰ The CIMT measured at any point in life reflects the total atherogenic burden of the past. To the extent that air pollution studies derive some estimates of total past exposures to ambient air pollution, causal associations between exposure and CIMT may be inferred even from cross-sectional studies. However, cross-sectional studies do not address the contribution of pollution to the progressive development of atherosclerosis. Longitudinal studies with repeated measures should remain the gold standard to which we aspire to understand the causal link between air pollution exposure and atherogenesis.

In respiratory health, the development of lung function has been successfully used to investigate the effects of air

pollution at various ages, with strong evidence from the Children’s Health Studies and others for a causal role of air pollution in the development of lung function in childhood.^{57,58} Similarly, it will be of interest to see whether air pollution affects atherogenesis at all ages and how early in life this effect may be observed. Improvements in air pollution levels have resulted in enhanced development of children’s lungs and in a slower decline in lung function among adults.⁵⁹ We hypothesize that a reduction of long-term exposure to air pollution results in a similar deceleration of atherogenesis, but this remains to be explored.

A few studies are currently under way to address these questions at various ages and/or in larger samples than those published to date. The activity within the European Study of Cohorts for Air Pollution Effects (ESCAPE, www.escapeproject.org) is of special relevance because it reflects a standard approach to characterizing subjects’ exposure to traffic-related pollution, handling modification and confounding effects, and conducting meta-analyses of the association between pollutants and level of CIMT within and across 4 participating studies.

Conclusion

Although a few studies indicate a possible causal atherogenic role of ambient pollution, this role needs further investigation in epidemiologic studies. To accomplish this objective, proper choice of markers of atherosclerosis or atherogenesis is crucial. We have identified a set of markers we believe are good candidates for this purpose, placing particular emphasis on CIMT, which is an attractive candidate for investigating the hypothesis of long-term effects of air pollution on atherogenesis. Ongoing studies will also provide insights into the relevance of age and a range of covariates in the manifestations of atherogenic effects of air pollution.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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