Air Pollution and Cardiovascular Disease

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Abstract: An escalating body of epidemiologic and clinical research provides compelling evidence that exposure to fine particulate matter air pollution contributes to the development of cardiovascular disease and the triggering of acute cardiac events. There are 3 potential mediating pathways that have been implicated, including "systemic spillover," autonomic imbalance, and circulating particulate matter constituents. Further support that the increased morbidity and mortality attributed to air pollution comes from studies demonstrating the adverse cardiovascular effects of even brief periods of exposure to secondhand smoke. Accordingly, persons with known or suspected cardiovascular disease, the elderly, diabetic patients, pregnant women, and those with pulmonary disease should be counseled to limit leisure-time outdoor activities when air pollution is high. Recognizing the insidious and pervasive nature of air pollution, and the associated odds ratios and population attributable fractions for this widely underappreciated chemical trigger of acute cardiovascular events, may serve to maximize the potential for cardiovascular risk reduction by addressing at least a portion of the 10%-25% incidence of coronary disease that is unexplained by traditional risk factors. (Curr Probl Cardiol 2015;40:207–238.)

Over the past 2 decades, a growing body of epidemiologic and clinical evidence has led to a heightened concern about the potential deleterious effects of environmental air pollution and

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active and passive cigarette smoking on health and their relation to cardiovascular disease (CVD) and stroke. Of special interest are several environmental air pollutants, including carbon monoxide (CO), oxides of nitrogen, sulfur dioxide (SO_2), ozone, lead, secondhand smoke (the single largest contributor to indoor air pollution), and particulate matter (PM). The latter are generally classified by aerodynamic diameter as coarse (PM_{10}, 2.5-10 μm), fine ($PM_{2.5}$, <2.5 μm), or ultrafine ($PM_{0.1}$, <0.1 μm). PM_{10} and especially $PM_{2.5}$, which have been most commonly associated with increased hospitalization and mortality from CVD,[1-4] can be generated from vehicle emissions, tire fragmentation and road dust, industrial combustion, metal processing, construction and demolition activities, residential wood burning, pollens, molds, and forest fires.

According to a 2004 American Heart Association (AHA) scientific statement, exposure to air pollution contributes to the development of CVD.[5] This conclusion was based on a comprehensive review of the scientific literature on air pollution and CVD, with specific reference to 3 lines of pioneering epidemiologic research. First, population-based studies in 20 cities across the United States and in many cities abroad have found the mortality rate from cardiac causes to be elevated on the day following high levels of particulate air pollution.[4] Second, several reports have shown that high levels of particulate air pollution are associated with increased admissions to hospitals for acute coronary syndrome (ACS), including anginal chest pain and acute myocardial infarction (AMI).[6] Third, an especially well-designed investigation, using a case-crossover approach, linked high levels of particulate air pollution in the Greater Boston area with an increased risk of AMI.[7]

Additional compelling experimental evidence has emerged to support the hypothesis that these epidemiologic data truly reflect the deleterious effects of PM on the cardiovascular system. For example, rabbits regularly exposed to PM showed more advanced coronary lesions, increased plaque size, more extensive atherosclerosis in the aorta, and an increase in the volume fraction of lesions comprising lipids (ie, plaques more prone to rupture), as compared with their control counterparts.[8] Other contemporary studies suggest that possible links between acute exposure or chronic exposure, or both, to PM and cardiovascular events may be related to abrupt increases in the rate-pressure product, a key correlate ($r = 0.92$) of myocardial oxygen consumption,[9] fibrinogen, arterial vasoconstriction, inflammatory markers (eg, C-reactive protein), endothelial injury or dysfunction, and decreases in heart rate variability (HRV).[10]

A recent systematic review and meta-analysis reported that all the main air pollutants, with the exception of ozone, were associated with a

short-term increase in the risk of AMI. Depending on the air pollutant, the population attributable fraction (PAF) ranged between 0.6% and 4.5%.[11] Another comparative risk assessment, using a meta-regression analysis, calculated the odds ratios and PAFs for a variety of physical, psychological, and chemical triggers of acute cardiovascular events. Considering the magnitude of risk and the prevalence in the population, air pollution (based on a difference of 30 $\mu g/m^3$ in PM with a diameter < 10 μm [PM_{10}]) was of similar magnitude (PAF, 5%-7%) as other well-documented triggers (eg, vigorous physical exertion, alcohol, coffee, and negative emotions), highlighting the fact that the associated small insidious risks may, over time, have considerable public health relevance.[12] Accordingly, a more recent scientific statement from the AHA concluded that "…the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality."[13]

This review provides a timely update on the population-based and clinical evidence linking air pollution with the development of CVD and acute coronary events, with specific reference to the most recent epidemiologic studies, underlying putative biological mechanisms, the adverse effects of secondhand smoke, and the health implications of exercising in a polluted environment, along with interventions to partially mitigate the adverse health effects of the associated airborne particulates.

Epidemiologic Studies

There is an extremely large epidemiologic literature that provides compelling evidence that exposure to air pollution, especially combustion-related PM and associated pollutants, contribute to CVD and death. Many daily time-series, case-crossover, and related studies have demonstrated small but consistent associations between day-to-day changes in cardiovascular mortality and short-term changes in PM air pollution. Other studies have shown that short-term (one or a few days) changes in PM are associated with cardiovascular hospitalizations, fatal and nonfatal ischemic heart disease events, heart failure, and ischemic stroke. There is also epidemiologic evidence that short-term elevated exposures to PM are associated with subclinical adverse markers related to CVD, including systemic inflammation, vascular or endothelial dysfunction, increased endothelial cell activation and blood coagulation, and decreased HRV.

Epidemiologic studies of long-term exposure to PM (years to decades) indicate even larger cardiovascular health consequences. For example, various prospective cohort studies have demonstrated substantive increases

in the risk of mortality, which were most pronounced for cardiovascular mortality, especially ischemic heart disease mortality. Studies have also indicated that reductions in PM pollution contribute to improvements in cardiovascular and overall health.

The progression of this epidemiologic literature is reflected in previous reviews.[13-15] The objective of this section is to highlight notable advances in our understanding of the effects of PM air pollution on CVD that have come from recent epidemiologic studies. Owing to the large number of recent studies, this overview is highly selective.

Short-Term Exposure, CVD, and Death

Over the past several years, there has continued to be additional daily time-series, case-crossover, and related studies that report associations between short-term exposures to air pollution and CVD and death. One example is a daily time-series mortality study from 16 Chinese cities,[16] which is notable for its size and the extremely high concentrations of air pollution that were observed in most of the cities. Remarkably robust and consistent associations between PM air pollution and total mortality, cardiovascular mortality, and respiratory mortality were observed. By contrast, another study of the effects of short-term exposure used a case-crossover design to assess the association between fine PM and onset of ischemic stroke in the Greater Boston area, a city with relatively low concentrations of air pollution.[17] Onset of ischemic stroke was most strongly associated with traffic-related PM exposures 12-14 hours before the event. Similarly, Mustafić et al[11] conducted a systematic review and meta-analysis of studies of short-term air pollution exposures and myocardial infarction (MI). PM air pollution, along with several other air pollutants (CO, NO_2, and SO_2), were associated with increased risk of MI. Another systematic review and meta-analysis found that short-term exposures to fine PM air pollution, along with the aforementioned pollutants, were associated with increased risk of hospitalization or death due to heart failure.[18] Collectively, these recent studies provide additional evidence that exposure to air pollution for periods of time of less than a day to up to a few days can contribute to increased cardiovascular events and death.

Cohort Studies of Long-Term Exposure

Some of the most important epidemiologic studies of air pollution are cohort-based studies of long-term pollution exposures and mortality. Recent extended follow-up analyses of the Harvard Six-Cities and the

American Cancer Society Cancer Prevention Study II cohorts continue to demonstrate associations between long-term exposure to fine PM and increased risk of cardiovascular and lung cancer mortality.[19-22] Several other recent cohort-based studies have reported PM-mortality associations. For example, associations with long-term exposure to fine PM air pollution and the risk of nonaccidental and cardiovascular mortality was evaluated in a national-level cohort study from Canada.[23] This study is notable because of its size and the relatively low levels of exposure. $PM_{2.5}$ exposures were associated with significant increased risks of nonaccidental and cardiovascular mortality, with the largest effects attributed to ischemic heart disease mortality. In contrast, a cohort study of long-term exposure to air pollution and cardiovascular mortality was conducted in 4 cities in Northern China with considerably higher levels of pollution.[24] Again, long-term exposure to PM pollution was associated with increased cardiovascular mortality, with the largest effects due to ischemic heart disease mortality. A meta-analytic review of the literature of long-term air pollution exposure and mortality has recently been conducted.[25] This review concluded that the overall evidence supports an association between long-term PM exposure and all-cause and cardiovascular mortality. A pooled estimate from the reviewed studies indicate that a 10-$\mu g/m^3$ increment increase in $PM_{2.5}$ is associated with increases of 6% (95% CI: 4%-8%) for all-cause mortality and 11% (95% CI: 5%-16%) for cardiovascular mortality.

The cohort-based studies of long-term PM exposure provide reasonably consistent evidence of PM-mortality associations driven largely by CVD mortality. Moreover, 2 recent related research efforts noted PM-mortality relations, but lesser associations with cardiovascular mortality. A large nationwide English cohort found that air pollution (measured as fine particles, NO_2, and SO_2) was associated with increased mortality.[26] The associations were strongest for respiratory and lung cancer deaths rather than cardiovascular deaths. Comparable results were obtained from a multicenter combined meta-analysis of up to 22 European cohorts (ESCAPE Project). A substantial, statistically significant association between fine PM and natural cause mortality was observed,[27] but in a subanalysis, focused on cardiovascular and related mortality, there was some evidence of a PM-mortality association with cerebrovascular disease mortality but not with CVD generally.[28] However, a subanalysis of acute coronary events using 11 cohorts from the ESCAPE Project reported substantial and statistically significant associations between fine PM and the incidence of acute coronary events, even at pollution levels below current European limits.[29]

Although the overall evidence from cohort-based studies of long-term exposure to PM air pollution suggests that it adversely contributes to disease and death, the relative roles and interactive relationships between respiratory and CVDs and mortality remain unclear. There is emerging epidemiologic evidence that exposure to PM air pollution is strongly related to both cardiovascular and pulmonary disease and that lung disease, especially pulmonary inflammation, contributes to CVD.[30]

Quasi-Experimental Results

Currently, there is growing interest in the use of quasi-experimental or natural experiment studies of air pollution and health. For example, over the past several decades, the United States has made substantial public policy efforts to reduce air pollution, especially in highly polluted cities. This nationwide effort has been treated as a quasi experiment in a study of changes in life expectancy associated with differential reductions in air pollution. Over a 2-decade time period, 1980 through 2000, reductions in fine PM air pollution were associated with significant improvements in life expectancy, even while controlling for changes in socioeconomic, demographic, and smoking variables.[31] Recently, a similar follow-up study found further increases in life expectancy associated with additional reductions in air pollution between 2000 and 2007.[32]

Another novel recent quasi-experimental study exploited a Chinese policy that provided free coal for heating in cities north of the Huai River. Using a formal regression discontinuity design, spatial discontinuities for PM pollution and reduced life expectancy of approximately 5 years were observed.[33] A comparable discontinuity for cardiovascular mortality rates was also observed, suggesting that the spatial discontinuity in life expectancy was largely owing to changes in CVD mortality.

Interventions that led to temporary reductions in air pollution during the 2008 Beijing Olympic Games provided an interesting opportunity for quasi-experimental studies to evaluate the potential associated health benefits. Concentrations of most measured air pollutants were lower during the Olympic intervention period. Using data prospectively collected from a panel of healthy young adults, researchers found that the Olympic intervention-related reductions in air pollution were associated with significant decreases in various biomarkers of inflammation and thrombosis as well as improved measures of cardiovascular physiology.[34,35] Although the clinical significance of these findings is not fully understood, these results suggest that reduced air pollution exposure can enhance cardiopulmonary health.

Atherosclerosis and Vascular Response

As has been previously reported,[13] numerous cross-sectional, cohort, and other studies suggest that exposure to air pollution may contribute to the initiation and progression of atherosclerosis and related diseases, as well as the triggering of acute cardiovascular events in individuals with known or occult CVD. A recent study that evaluated the associations between air pollution and the progression of subclinical atherosclerosis used changes in carotid artery intima-media thickness (CIMT) obtained from pooled data from 5 randomized trials from the Los Angeles, California area.[36] Fine PM and closer proximity to heavy traffic were associated with accelerated progression of atherosclerosis as indicated by larger increases in CIMT. Recent results from the prospective cohort study, Multi-Ethnic Study of Atherosclerosis and Air Pollution, provide further evidence that long-term exposure to air pollution may contribute to the progression of atherosclerosis. Among adults without pre-existing CVD, those with higher exposure to $PM_{2.5}$ had faster rates of CIMT progression. Conversely, improvements in air quality over the study period were associated with slower CIMT progression.[37] Also, using data from the Multi-Ethnic Study of Atherosclerosis and Air Pollution cohort study, long-term ambient exposures to air pollution, specifically $PM_{2.5}$ and oxides of nitrogen, were associated with another marker of subclinical atherosclerosis, increased coronary artery calcification.[38]

Cardiometabolic Disorders

Recent epidemiologic studies provide some evidence that $PM_{2.5}$ exposure may contribute to the development of cardiometabolic conditions.[39] Associations between $PM_{2.5}$ exposures and the prevalence of diabetes or diabetes mortality have been observed in the United States[40] and Canada.[41,42] A cohort study[43] of black women living in Los Angeles found evidence that air pollution, especially traffic-related pollutants, was associated with increased risk of type 2 diabetes and possibly hypertension. A population-based cohort study of nonhypertensive adults from Ontario, Canada,[44] also found that exposure to $PM_{2.5}$ air pollution was associated with a significant increased risk of incident hypertension. A prospective cohort of children, aged 5-11 years, living in 13 Southern California communities was used to evaluate the associations between exposures to traffic-source air pollution and changes in body mass index over time.[45] Robust, statistically significant associations between traffic-source air pollution and increases in body mass index provided evidence that air pollution can heighten the development of obesity, at least in children.

A recent extended analysis of the American Cancer Society Cancer Prevention Study II cohort[22] was used to explore the relationships between $PM_{2.5}$ air pollution, cardiometabolic disorders, and cardiovascular mortality. Statistically robust $PM_{2.5}$ associations with all-cause and CVD mortality were observed. Pollution-related cardiovascular mortality was observed for participants with and without cardiometabolic disorders, and there was no evidence that pre-existing cardiometabolic risk factors were effect modifiers for the $PM_{2.5}$-CVD mortality effects. However, the $PM_{2.5}$-CVD mortality associations were relatively large when hypertension or diabetes was noted on the death certificate, as either primary or contributing causes of death—suggesting that the $PM_{2.5}$-CVD mortality associations may be attributed, at least in part, to long-term pollution exposures contributing to the development or exacerbation of cardiometabolic disorders.

Global Burden of Disease

Recently, there has been a systematic effort to provide a comparative risk assessment of the burden of disease and injury attributable to multiple major risk factors known as the Global Burden of Disease Study 2010.[46] The breathing of contaminates such as tobacco smoke (active and secondhand smoking), household air pollution from solid fuels, and ambient PM air pollution, expressed as a percentage of global disability-adjusted life years, were 3 of the top ten leading risk factors in 2010. It was estimated that the latter accounted for approximately 3 million disability-adjusted life years, and that most of the burden of disease was the result of cardiovascular and circulatory diseases (but also included lung cancer and respiratory diseases).

One of the challenges of estimating the burden of disease for $PM_{2.5}$ air pollution is that it requires estimating the exposure-response function across the full range of exposures. Unfortunately, few data are available to identify the shape of the $PM_{2.5}$-mortality exposure-response function at very high levels of exposure common to major cities in China, India, and elsewhere. Integrating information from studies of ambient air pollution, secondhand tobacco smoke, and active smoking provides evidence that the $PM_{2.5}$-mortality exposure respond function for lung cancer mortality is near linear across wide ranges of exposure. The response function for CVD mortality, however, is supralinear (steepest at lower levels of exposure and flattening out at very high levels of exposure).[47,48] Although the estimates of global burden of disease from air pollution are highly dependent on estimates of the shape of the exposure-response function, efforts to

integrate available evidence of the effects of PM air pollution exposure suggest that widespread exposure to combustion-related fine PM air pollution has substantial effect on the global burden of disease.

Biological Mechanisms

During the past several decades, our understanding of the mechanisms whereby PM is capable of triggering acute cardiovascular events and promoting the chronic development of cardiometabolic diseases has been greatly expanded. Beyond the furthering of scientific knowledge, elucidation of the responsible pathways has 2 main pragmatic functions. First, to provide a "causal" basis for the associations between PM and cardiovascular events observed in epidemiologic studies, plausible mechanistic explanations are essential. This information helps to substantiate as well as bolster the foundation of all air-quality regulations worldwide.[49,50] Second, these insights may help foster more effective preventive measures at the public health level as well as potential intervention strategies (eg, lifestyle or pharmacologic approaches) based on a clearer understanding of the responsible pathways. Several publications including the 2010 AHA scientific statement[13] and a 2013 updated contemporary review[15] have expounded on the findings from the vast array of studies. As such, the aims of this section are to provide an overview of the general pathways linking PM with CVDs and thereafter to focus on highlighting major scientific advancements among human studies published during the past few years.

Overview of the General Pathways

Taking the findings from a multitude of experiments together,[13] there appear to be 3 broad "mediating" pathways whereby the inhalation of PM can instigate adverse cardiovascular responses remote from the site of deposition within pulmonary tissues (Fig 1). These include, (1) a "spillover" of proinflammatory or oxidative stress mediators generated in the lungs into the systemic circulation, (2) the instigation of autonomic nervous system imbalance, and (3) the penetration of certain particles or components directly into cardiovascular tissues. However, these pathways are not mutually exclusive. They may be activated at different time frames following PM inhalation and vary in relation to exposure duration and dose and by inhaled particulate sizes or components. Depending on the specific cardiovascular event evoked, different underlying pathway(s) may be responsible. For example, autonomic imbalance is most likely to be involved in the acute genesis of arrhythmias, whereas inflammation and endothelial dysfunction likely play larger roles in the chronic development

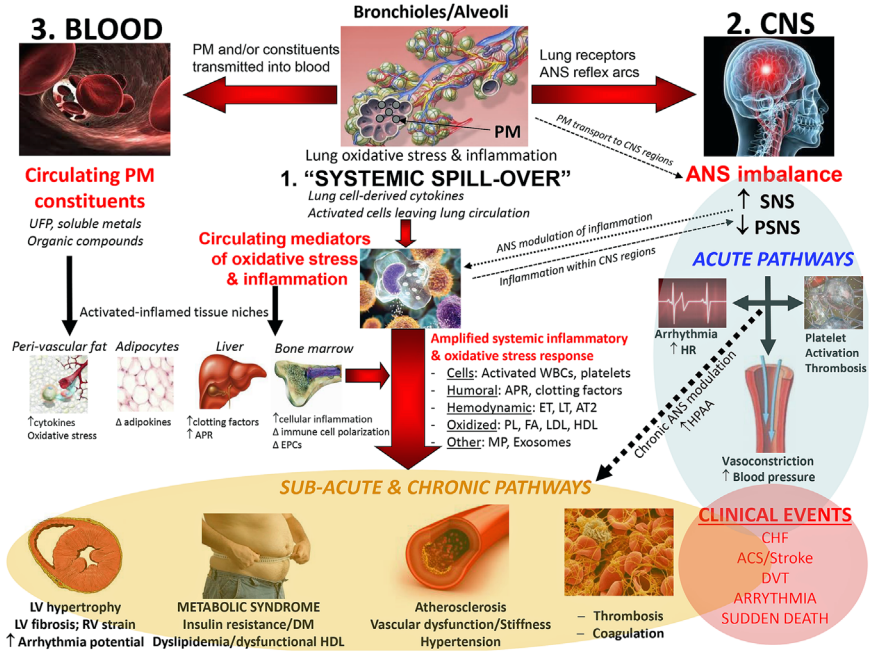

FIG 1. Potential biological mechanisms linking PM with cardiovascular disease and its sequelae. ANS, autonomic nervous system; APR, acute phase response; AT2, angiotensin-2; DM, diabetes mellitus; CHF, congestive heart failure; CNS, central nervous system; DVT, deep venous thrombosis; EPCs, endothelial progenitor cells; ET, endothelins; FA, fatty acids; HDL, high-density lipoproteins; HR, heart rate; LDL, low-density lipoproteins; LT, leukotrienes; LV, left ventricle; PL, phospholipids; PSNS, parasympathetic nervous system; RV, right ventricle; SNS, sympathetic nervous system; UFP, ultrafine particles <100 nm; WBCs, white blood cells. (Color version of figure is available online.)

of atherosclerosis. However, there is likely a large degree of overlap in physiological responses and cross talk between pathways. Underlying susceptibilities and comorbidities may also play a role in determining the preeminent pathways elicited within any individual. Other environmental factors (eg, gaseous copollutants and temperature) may also modify patient-level responses. Ultimately, numerous subclinical physiological alterations induced by PM inhalation including endothelial dysfunction, vasoconstriction, heightened arrhythmia potential, and prothrombotic and coagulant hematologic changes likely determine the actual ostensible cardiovascular event (eg, stroke, heart failure, or ACS) triggered in any single individual (Fig 1).

Pathway no. 1: The deposition of PM, particularly redox-active components (eg, metals and organic carbon compounds), can instigate a nidus of oxidative stress and inflammation in pulmonary tissues.[13]

Pro-oxidant species can be directly generated from certain particles within biological tissues (eg, metals) or from lung-based cells in response to interactions with PM (eg, NADPH oxidase of resident macrophages) or from both. Redox-sensitive pathways (eg, nuclear factor κB) become activated leading to the production of proinflammatory cytokines (eg, IL-6 and Tumor necrosis factor α) and chemokines, which serve to amplify the immune response (as well as the oxidative stress), presumably as part of the coordinated attempt to clear or sequester particles. It has been hypothesized that this response may become maladaptive and may not remain confined within the lungs but "spillover" by the release of an array of mediators into the systemic circulation. The figure illustrates pathway no. 1 and lists many of the circulating factors shown to be elevated by various studies in response to PM exposures. The presumed source of most of these mediators is from lung-based cells (eg, macrophages); however, this remains to be clarified, and the roles of other cells cannot be excluded. Many of these factors can thereafter have direct negative actions on the cardiovascular system (eg, induce vascular oxidative stress and endothelial dysfunction). They may also elicit changes within other organs that amplify the local tissue or systemic cardiovascular-adverse systemic responses such as release of adipocytokines (eg, resistin and adiponectin) and acute phase proteins (eg, C-reactive protein, fibrinogen, and coagulation factors) from adipocytes and hepatocytes, respectively. Pathway no. 1 is believed to typically mediate subacute (several hours to days) and chronic (weeks to years) biological changes leading to CVD sequelae (eg, atherosclerosis, endothelial dysfunction, ventricular hypertrophy, and metabolic disorders). However, this delineation is arbitrary, and acute vascular inflammatory responses may also be able to rapidly trigger plaque instability within hours (instigating ACSs) or potentiate autonomic changes peripherally or via central nervous system inflammation (triggering arrhythmias or heart rate changes) or both.

Pathways nos. 2 and 3: Several types of lung receptors (eg, transient receptor potential) and nerve endings have been shown to "sense" PM or redox-active constituents within the lungs.[13,15] Autonomic afferent reflexes can become activated and thereafter elicit efferent systemic autonomic nervous system responses that represent the integration of various neural pathways. A wide array of studies have shown rapid alterations in heart rate, HRV, blood pressure (BP), and electrocardiographic changes (eg, repolarization abnormalities) likely reflective of an underlying acute autonomic imbalance favoring the sympathetic over the parasympathetic limb.[13,15] Though pathway no. 2 is typically impugned for triggering acute cardiovascular events in the short-term

setting (eg, arrhythmias), it is also possible that persistent sympathetic nervous system hyperactivity may also play a role in the long-term development of chronic diseases states (eg, hypertension and vascular hypertrophy). Finally, a few human experiments have suggested that certain particles (eg, ultrafine PM) or soluble constituents (eg, metals) or both may actually be capable of translocating into the circulation and thereafter directly negatively affecting cardiovascular tissues (pathway no. 3). The plausibility, time course, and relevance of this latter pathway remain controversial.[13]

Recent Advancements from Mechanistic Studies

A large number of experiments have been published during the past few years,[15,51] and this focused review cannot address all of them. Hence, the following sections aim to update and highlight some of the most noteworthy positive study results and findings from human experiments that have enhanced our understanding of the mechanisms related to PM-induced cardiometabolic diseases published since the 2010 AHA scientific statement.[13]

Vasoconstriction and Vascular Dysfunction

Previous studies have shown that PM exposure can evoke acute vasoconstriction and impaired endothelial function.[13,15] However, 2 recent studies have further elucidated how PM influences microvascular tone. In a cross-sectional analysis of 6 US cities from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort ($n = 4607$), Adar et al[52] demonstrated that both short- (ie, prior day) and long-term (ie, 2-year average) ambient $PM_{2.5}$ levels were independently related to reductions in retinal arteriole diameter (ie, decreased central retinal arteriolar equivalent). In a study of healthy adults ($n = 84$) conducted in Belgium, PM_{10} and black carbon levels during the prior day were related to decreases in central retinal arteriolar equivalent values.[53] These experiments support that both recent and long-term exposures to particulate air pollutants, even at present-day low ambient concentrations, are capable of eliciting arteriolar vasoconstriction.

Additional findings from both the MESA ($n = 3040$) and Framingham ($n = 5112$) cohorts have recently shown that long-term exposures to ambient PM levels are associated with chronic vascular endothelial dysfunction.[54,55] Small increases in annual $PM_{2.5}$ levels (interquartile range: 3 $\mu g/m^3$) were linked to a 0.3% reduction in flow-mediated dilatation (FMD) of the brachial artery in MESA study participants.[54] An even smaller interquartile range increase in long-term $PM_{2.5}$ levels

(1.99 μg/m^3) in the Framingham study was also related to blunted FMD as well as hyperemic flow velocity (ie, microvascular vasodilatatory capacity).[55] These studies show that chronic exposure to even low levels of ambient PM can pose observable health risks to both conduit and microvascular endothelial function.

Several recent experiments have provided important insights into the biological mechanisms of how air pollutants actually elicit systemic vascular changes. In an elegant protocol involving the nitric oxide (NO) clamp method and the forearm infusion of NO inhibitors, Langrish et al[56] provided convincing evidence that the vascular dysfunction acutely elicited by diesel exhaust is mediated by reduced NO bioavailability, likely as a consequence of excess consumption within the vasculature. The detrimental actions of whole diesel exhaust were already shown by this group to be principally caused by inhalation of the particulate component (ie, particle traps abrogated the endothelial dysfunction) rather than from the gaseous copollutants.[57] Wauters et al[58] expounded on these findings in a series of studies involving skin laser Doppler flow and the iontophoresis of pharmacologic agents. Diesel exhaust acutely impaired NO-dependent (not independent) skin microvascular vasodilatation. Endothelial cells incubated with serum from diesel-exposed subjects produced higher levels of reactive oxygen species. Collectively, these studies provide compelling evidence that the acute vascular dysfunction prompted by diesel exhaust is caused by impaired endothelial-dependent vasodilatation owing to blunted NO bioavailability secondary to systemic oxidative stress generated from the inhaled particulate constituents. It is plausible that these vascular responses, including acute arteriolar vasoconstriction and endothelial dysfunction, may play pivotal roles in the genesis of acute myocardial ischemia and chronic CVDs.[13]

Increased BP and Hypertension

Although air pollution has been linked to higher BP levels in the past,[13] several recent studies have provided novel insights into the hemodynamic alterations induced by PM. In controlled exposure studies, diesel exhaust increased BP by 4.4 mm Hg within several hours,[59] though it was recently shown that coarse PM (aerodynamic diameter ranging from 2.5-10 μm) is also capable of eliciting similar degrees of BP elevations (3-4 mm Hg) during a 2-hour exposure period.[60] Increases in BP have also been linked to ambient air pollutant exposures in several recent trials conducted in Beijing, including personal-level black carbon during the prior 10 hours,[61] background levels of PM_{10} during the prior few days,[61,62] and changes in

regional $PM_{2.5}$ levels during the Olympic games.[35] Further studies conducted in several different countries have added to the evidence that longer-term exposures to air pollutants are also linked to elevations in BP.[63-67] Perhaps most importantly, mounting evidence supports that living in regions with higher levels of air pollution is linked to an increased prevalence and incidence of overt hypertension.[43,44,68] For example, new-onset hypertension was shown to increase by 13% per 10-$\mu g/m^3$ elevation in long-term ambient $PM_{2.5}$ concentrations among individuals (n = 35,303) living in the relatively clean environment of Ontario, Canada. Hence, not only can air pollution increase BP but also longer-term exposures may play a role in the development of a chronic hypertensive-disease state per se.

The mechanisms underlying the acute and chronic elevations in BP have been outlined previously.[13] Recent findings from a controlled human exposure study (eg, reduced HRV metrics) corroborate that an activation of the sympathetic nervous system is likely an important factor.[60] Additional novel observations from a cohort of 359 adults living in Switzerland suggest that impaired renal sodium excretion may also be involved.[69] It is likely that a compilation of endothelial dysfunction, arterial vasoconstriction and vascular hypertrophy, and autonomic imbalance favoring sympathetic nervous system hyperactivity, along with other potential factors (eg, impaired sodium handling), are involved in the pathobiology.[13] Regardless of mechanistic details, these results support that air pollution could instigate cardiovascular events (in particular strokes and heart failure) via an acute elevation in BP as well as by the long-term promotion of a prohypertensive state.

Insulin Resistance and Diabetes

Since the 2010 AHA statement, additional evidence has accrued linking PM exposures with insulin resistance and a heightened risk for developing diabetes.[39] It was recently shown that higher ambient $PM_{2.5}$ levels over a 5-day period in Southeastern Michigan were associated with a worsening of insulin sensitivity (ie, higher homeostasis model assessment of insulin resistance values) among 25 healthy adults.[70] The study findings supported that autonomic imbalance may have been involved in the underlying mechanisms, as altered HRV metrics were associated with the increases in higher homeostasis model assessment of insulin resistance levels. Results from 2 additional studies in Germany also support that higher ambient PM levels can worsen insulin resistance and diabetes control.[71,72] Similar to hypertension, long-term PM exposure may also potentiate the risk for

developing overt diabetes.[39] Chen et al[41] demonstrated in a population living in Ontario, Canada, ($n = 62{,}012$) that diabetes incidence is increased by 11% per 10-μg/m^3 elevation in long-term ambient $PM_{2.5}$ levels. Persistent autonomic imbalance, inflammation within insulin-sensitive tissues (eg, fat cells), altered adipocytokine expression, hepatic steatosis, and endoplasmic reticulum stress have all been implicated in the pathophysiology.[39] These findings suggest that metabolic insulin resistance and the development of an overt diabetic state owing to chronic air pollution exposure may place individuals at greater risk for future cardiovascular events.

Atherosclerosis

Chronic exposure to higher levels of PM can be capable of potentiating the development of systemic atherosclerosis.[13] A few notable trials during the past few years have added further evidence supporting the veracity of this proatherosclerotic effect. Annual average exposure to higher levels of black carbon (per 0.26-μg/m^3 elevation), a marker of traffic-related PM, was associated with a 1.1% increase in CIMT in a cohort of elderly men living in the Boston area.[73] Several measures of traffic exposure were similarly associated with increased CIMT among 2780 adults living in Girona, Spain.[74] Perhaps the most influential recent findings come from additional analyses of the MESA study.[37] Among 5362 adults living in 6 US cities, higher residential air pollution levels were associated with a greater progression of CIMT on repeat ultrasound testing (5.0 μm/year per 2.5-μg/m^3 increase in $PM_{2.5}$). Moreover, individuals living in regions that enjoyed reductions in ambient $PM_{2.5}$ levels benefited from significantly slower degrees of CIMT progression. These findings provide some of the most compelling evidence that long-term exposure to particulate air pollution has a meaningful effect on the risk for developing systemic atherosclerosis in humans.

Animal studies have elucidated some of the underlying biological pathways involved including systemic inflammation, vascular oxidative stress, activation of innate and adaptive immunity, and dysfunction of high-density lipoprotein functionality.[13] Deciphering the relevant mechanisms in human studies is more difficult. However, a recent report has shown that estimated long-term traffic exposure, as well as measured carbon load within airway macrophages, was independently associated with increases in circulating plasma oxidized low-density lipoprotein particle concentrations among 79 adults.[75] This suggests that oxidation of lipoproteins may be involved in the underlying mechanisms, in addition

to systemic inflammation, as both responses play key roles in the genesis of atherosclerosis.[13] Collectively, these studies support that long-term air pollution exposures may promote the development and progression of atherosclerosis and its sequelae, including a heightened risk for acute cardiovascular events.

Enhanced Coagulation and Thrombosis

Previous studies have shown that air pollution exposures are related to several metrics of increased thrombosis potential, activated platelets, and heightened blood coagulation tendencies.[13,15] Recent experiments have corroborated and expanded our knowledge in this regard. For example, Lucking et al[57] demonstrated that the particulate components of diesel exhaust (not gases) are responsible for the enhanced ex vivo thrombus formation using the Badimon chamber technique as well as for the reduction in tissue-type plasminogen activator release following bradykinin infusion during controlled pollution exposures. It was also recently reported among 137 diabetic patients living in Belgium that 2-hour increases in ambient PM_{10} levels were associated with a rapid augmentation of platelet activation measured by the PFA-100 analyzer.[76] Similar metrics of platelet activation (ie, increases in circulating CD40L) were shown to occur in relation to higher levels of ambient ultrafine PM during the prior day in Rochester, New York.[77]

The mechanisms responsible for these prothrombotic changes have not been completely elucidated. However, it has been hypothesized, based on prior experimental data, that inhaled particles may rapidly and directly activate platelets and promote thrombosis, independent from the instigation of systemic inflammatory responses.[78,79] This may involve direct actions on platelets of particulate constituents reaching the blood or inflamed lung endothelial cells secreting adhesion molecules that activate circulating platelets in a P-selectin–dependent manner or both. Local activation of tissue factor or release of tissue factor–bearing microparticles from the lung cells or both may also be involved in the pathobiology.[78,79]

Enhanced coagulation potential has also been associated with air pollution exposures,[13] including recent studies demonstrating increased risk for venous thrombosis, perhaps owing to ambient coarse PM concentrations.[80,81] The sum effect of multiple small changes in hepatic expression of acute phase proteins (eg, fibrinogen) and coagulation factors may underlie these responses.[79] However, Tarantini et al[82] have recently shown that hypomethylation of inflammatory genes may be involved. An assay of endogenous thrombin-generation potential increased in

association with PM_{10} levels among 63 steel workers exposed to high air pollution levels. Interestingly, activation (ie, reduced methylation) of NO synthase-3 and endothelin-1 genes mediated these procoagulation changes. Thus, these results support that augmented thrombotic-coagulation potential may heighten the risk for acute cardiovascular events among susceptible individuals.

Autonomic Imbalance, HRV, Electrocardiographic Changes, and Arrhythmias

Altered HRV was among the first adverse biological responses shown to occur in relation to air pollution exposures.[13] A large body of literature supports that PM is capable of disturbing cardiac autonomic balance. In 2012, a meta-analyses of 29 epidemiologic studies involving 18,667 subjects demonstrated that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with significant reductions in time (eg, standard deviation of normal-to-normal R wave intervals) and frequency domain (low and high frequency) metrics of HRV.[83] These physiological changes support that inhaled pollutants generally alter autonomic balance in favor of heightened sympathetic activity. The pathways responsible for these changes have not been fully elucidated but have been hypothesized to represent a systemic stress response or an integrated neural reflex response mediated by the activation of vagal afferents by various lung receptor subsets.[13] Irrespective of the mechanistic details, blunted HRV belies a perturbation of cardiac autonomic balance that may represent a plausible means whereby inhaled PM can trigger arrhythmias, sudden cardiac death, or hemodynamic changes (eg, elevated heart rate and BP) that favor myocardial ischemia.

Several recent studies have also shown that PM can detrimentally alter electrocardiographic repolarization.[84-87] These ion channel disturbances can potentiate the milieu for significant arrhythmias among at-risk patients. Indeed, several pathologic changes in heart rhythm, including the onset of atrial fibrillation, ventricular tachycardia, and premature ventricular contractions, have been associated with ambient air pollutants.[88-90] Finally, a novel study conducted in Brazil has recently demonstrated that during the season of sugarcane burning and increased ambient PM, systolic BP was elevated in relation to heightened peripheral sympathetic nerve activity as directly measured by microneurography.[91] These findings provide the first direct and most substantive evidence that PM inhalation may play a role in augmenting sympathetic nervous system outflow. In summary, there is compelling evidence that derangements in HRV are induced by air

pollution exposures. These adverse changes may be related to central or peripheral autonomic imbalance, increasing the likelihood of acute cardiovascular events, including threatening arrhythmias.

Cardiovascular Effects of Secondhand Smoke: Vastly Underestimated

Further support that the increased cardiovascular morbidity and mortality that are attributed to air pollution comes from studies of the effects of environmental tobacco smoke. Interestingly, despite what would be expected from a comparison of the doses of toxins delivered, the effects of even brief (minutes to hours) passive smoking are, on average, 80%-90% as large as those from chronic active smoking.[92] A provocative report, highlighting the adverse effects of low doses of passive tobacco smoke exposure and the immediate effect it has on the cardiovascular system, emphasized that never smokers increased their risk of coronary heart disease by $\sim$30% if they lived with a smoker.[92]

Numerous studies now suggest that the cardiovascular system is highly sensitive to the toxins in secondhand smoke. Even short-term exposure to secondhand smoke increases platelet activation,[93] causes transient endothelial dysfunction,[94] promotes atherosclerotic plaque development,[95] and augments infarct size in experimental animals.[96] Previous research has also shown that exposure to the secondhand smoke of just 1 cigarette per day accelerates the progression of atherosclerosis.[97] Even brief periods of passive smoke exposure can lead to acute vascular injury characterized by mobilization of dysfunctional endothelial progenitor cells with blocked NO production, increased endothelial microparticles and vascular endothelial growth factor levels, and decreased FMD.[98] Although the latter returned to baseline at 2.5 hours, markers of vascular injury persisted for $>$24 hours. Collectively, these data suggest that even brief exposure to real-world levels of secondhand smoke can have adverse acute (Table 1) and chronic effects on the cardiovascular system, especially the coronary circulation.[92,98] According to a widely cited retrospective analysis of data from 192 countries, secondhand smoke was responsible for an estimated 603,000 deaths worldwide, and approximately 63% of these deaths were owing to ischemic heart disease.[99]

Reduced Cardiac Events Related to Smoking Bans

Reductions in acute cardiovascular event rates have been reported in several large US cities and countries that have banned smoking in public

TABLE 1. Acute effects of secondhand smoke on the cardiovascular system: Mechanisms of action*

Increased platelet aggregability
Endothelial dysfunction
Mobilization of dysfunctional endothelial progenitor cells with blocked nitric oxide production
Increased endothelial microparticles and vascular endothelial growth factors
Decreased flow-mediated dilation
Increased inflammation and infection
Accelerated atherosclerosis
Low high-density lipoprotein cholesterol levels
Plaque instability
Increased oxidized low-density lipoprotein cholesterol levels
Increased oxidative stress and decreased antioxidant defense
Decreased myocardial energy production
Increased insulin resistance
Altered autonomic tone
Decreased parasympathetic stimulation to the heart
Increased arterial stiffness
Outcome measures
Increased infarct size
Decreased heart rate variability
Increased malignant ventricular arrhythmias
Increased number of stenotic coronary arteries

Adapted with permission from Barnoya and Glantz[92] and Heiss et al.[98]
*These mechanisms, rather than isolated stressors, interact with each other to disproportionately increase the risk of atherosclerotic CVD and its clinical manifestations.

places. Several years ago, researchers reported a significant decrease in AMI hospitalizations after implementing a comprehensive smoke-free ordinance in public buildings and workplaces in a geographically isolated community, Pueblo, Colorado (risk ratio = 0.73, 95% CI: 0.63-0.85).[100] No significant reductions in AMI rates were observed among residents outside city limits or in an external control group (El Paso County). Even after adjusting for seasonal trends, the differences among groups persisted. Of note, the 27% (95% CI: 37%-15%) reduction in the incidence of AMI observed in Pueblo was similar in magnitude to the 40% decline (95% CI: 64%-1%) in hospital admissions during a smoking ordinance previously reported within Helena, Montana city limits.[101]

Since the end of March 2006, smoke-free legislation was implemented in all enclosed public places throughout Scotland. To assess the effect of the smoking prohibition, researchers evaluated the number of patients admitted with ACS to 9 Scottish hospitals during the 10-month period

preceding the passage of the legislation and during the same period the following year. Overall, the number of hospital admissions for ACS decreased by 17%—as compared with a 4% reduction in England (which had no such legislation during the same period) and an average annual decrease of 3% in Scotland, and a maximum yearly decrease of 9%, during the decade preceding the study.[102] The number of prevented admissions for ACS involving nonsmokers accounted for 67% of the reduction and appeared to be greater among women than men.

More recently, investigators reported that initial implementation of a smoke-free law (which exempted casinos) in Gilpin County, Colorado, was followed by a 22.8% drop in ambulance calls from locations other than casinos, but no significant change in calls from casinos.[103] After 2 years, when the law was expanded to casinos, a 19.1% drop in ambulance calls from casinos was observed, with no changes in calls originating outside casinos.[103] Because the magnitudes of the reduction in ambulance calls were similar when these 2 venues (general community and casinos) were made smoke free, 2 important conclusions emerged: first, clinicians should counsel their patients, especially those with known or suspected CVD, to avoid smoky environments (eg, bars and casinos), and second, policy makers should ensure that all public environments are smoke free.

Another opportunity to examine the effect of a public smoking ban on the incidence of hospital admissions owing to ST-segment elevation MI (STEMI) was recently provided by an analysis of the Bremen, Germany STEMI Registry. Comparing data before and after the smoking ban, investigators noted a 16% decrease in the total number of respective STEMI hospital admissions. A 26% decline in hospital admissions owing to STEMIs was exclusively found in nonsmokers, whereas in smokers the incidence of STEMIs was essentially unchanged (Fig 2).[104]

Health Effects of Exercising in Air Pollution

Although regular physical activity and a moderate-to-high level of cardiorespiratory fitness are important components of a healthy lifestyle,[105] many of the most accessible forms of exercise, such as walking, running, and bicycling, often occur outdoors. Accordingly, such activities can increase exposure to unhealthy airborne pollutants, including PM, ozone, and CO. Higher levels of CO may also decrease the oxygen-carrying capacity of arterial blood, adversely affecting aerobic capacity and exercise performance. When the exercise duration or intensity is increased, the choice of location for exercise should also take into account the air quality, as these modulators can affect the burden of inhaled pollutants.

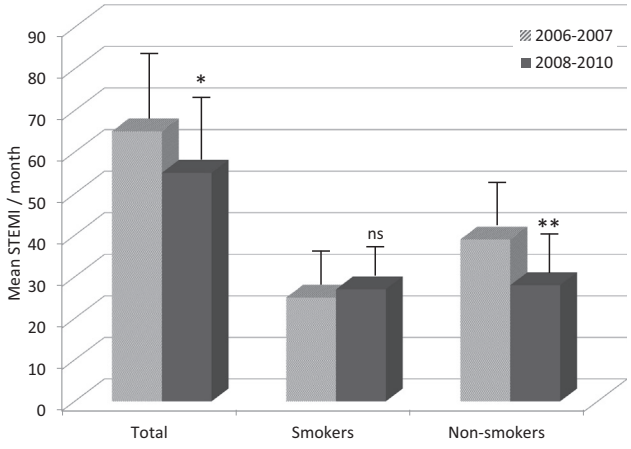

FIG 2. Number of patients admitted with STEMI per month, before and after the smoking ban in public areas was implemented. *A 16% reduction from 2006-2007 to 2008-2010 ($P < 0.01$). **A 26% reduction from 2006-2007 to 2008-2010 ($P < 0.01$). (Adapted with permission from Schmucker et al.[104])

This scenario presents the challenge of balancing the beneficial effects of lifestyle physical activity, structured exercise, or both, along with the adverse effects of air pollution on health.

In a seminal study, Mills et al,[106] using a double-blind, randomized, crossover study of 20 men with a history of MI, examined the effect of filtered air vs dilute diesel exhaust, at a level comparable to what might be routinely experienced when driving in traffic, on the cardiovascular response to a standardized workload during cycle ergometry. During each exposure period, patients exercised at workloads corresponding to 5-7 metabolic equivalents (1 metabolic equivalent = 3.5 mL O_2/kg/min) for two 15-minute periods, separated by 15-minute rest periods. Although the heart rate response to exercise was not significantly different across exposure periods, electrocardiographic evidence of myocardial ischemia, manifested as ST-segment depression, was significantly greater during exposure to diesel exhaust than during filtered air. Although the mechanisms linking air pollution exposure to the increased evidence of myocardial ischemia observed in this study were unclear, silent ischemia has been reported to be highly arrhythmogenic.[107] These findings may help to explain the reported association between transient exposure to higher levels of ambient air pollution and the onset of acute cardiovascular events, especially during periods of superimposed vigorous physical exertion. Considering the cardioprotective effect of regular physical activity, and its established role in attenuating the large spikes in relative cardiovascular

risk that can occur with unaccustomed strenuous physical exertion,[108] the associated risk of exercise may be reduced by exercising in areas away from dense traffic.

Although the ever-present small risks of air pollution have considerable public health relevance,[12,109] it is especially important that persons with chronic diseases, the elderly, diabetic patients, pregnant women, and those with pulmonary disease be advised to limit outdoor activities (including exercise) when pollution is high. Persons with asthma and patients with coronary disease should be particularly careful to avoid the aforementioned airborne pollutants by considering upwind and downwind conditions. Moreover, runners and walkers should be counseled to avoid main roads, exercise in the early morning hours (when PM concentrations are lowest), and avoid exercising in smog or areas of high industrial combustion or traffic density.[110] Ways in which exercisers can partially mitigate the adverse health effects of air pollution exposure during outdoor activity are detailed elsewhere, and briefly summarized in Table 2.[111-121] Nevertheless, studies suggest that the beneficial effects of exercise outweigh the adverse effects of air pollution,[122] and that regular moderate-to-vigorous physical activity reduces the likelihood of air pollution–related mortality.[122,123]

Conclusions

Recent epidemiologic evidence that exposure to air pollution contributes to CVD and death continues to grow (Fig 3).[124,125] Numerous reports have further elucidated the mechanisms whereby air pollution may, over time, accelerate the development of atherosclerotic CVD and its clinical consequences. It is hypothesized that the inhalation of PM can instigate adverse cardiovascular responses via 3 potential mediating pathways: a "spillover" of proinflammatory or oxidative stress mediators generated in the lungs into the systemic circulation; the incitement of autonomic nervous system imbalance, characterized by sympathetic predominance; and, the penetration of certain particles or components directly into the cardiovascular tissues. Conversely, there is also increasing evidence that reducing air pollution can have a profound and favorable effect on population health.

Further support that the increased morbidity and mortality attributed to air pollution comes from studies demonstrating that the cardiovascular system is highly sensitive to the toxins in secondhand smoke. According to a provocative report,[92] the adverse cardiovascular effects of even brief periods of passive smoking are, on average, 80%-90% as large as those from chronic smoking. Moreover, nonsmokers increased their risk of

TABLE 2. Potential strategies to minimize the adverse health effects of exercising in air pollution

Habitually sedentary individuals, in particular, should avoid unaccustomed, vigorous physical activity, especially during exposure to high levels of airborne pollutants.[112]
Reduce the overall risk of cardiovascular events by increased lifestyle physical activity, regular structured exercise, enhanced cardiorespiratory fitness, or combinations thereof. The primary beneficiaries of an exercise program are those individuals who move from the least fit, least active population cohort (bottom 20%), to the next lowest quintile (ie, below average fitness).[105,113]
Among persons with heart disease, high cardiorespiratory fitness, a normal-to-overweight body habitus, and a resting bradycardia (HR <70 bpm) appear to decrease the effects of air pollution on BP.[114,115]
Exercisers should consider a diet rich in antioxidants, antioxidant supplements, or both, as these may help protect against the acute effects of ozone on lung function and lung injury.[116,117]
Wearing a facemask during exercise has been shown to attenuate adverse cardiovascular responses (eg, increased BP, decreased HRV, and ST-segment depression) in persons with and without heart disease.[118,119]
Pretreatment with montelukast (a leukotriene antagonist) 6-8 h before exercise reduces the deleterious effects of air pollution on postexercise FMD[120] and selected spirometry measures (eg, forced expiratory volume$_1$) in those with exercise-induced bronchoconstriction.[121]
Exercisers should follow EPA updates and local air-quality forecasts and plan workouts accordingly. This is especially important for "at-risk" individuals, including those with known cardiovascular or respiratory disease or both.
During the summer months, exercising in the morning should be encouraged to minimize afternoon ozone exposure.[111]

bpm, beats per minute; EPA, Environmental Protection Agency.

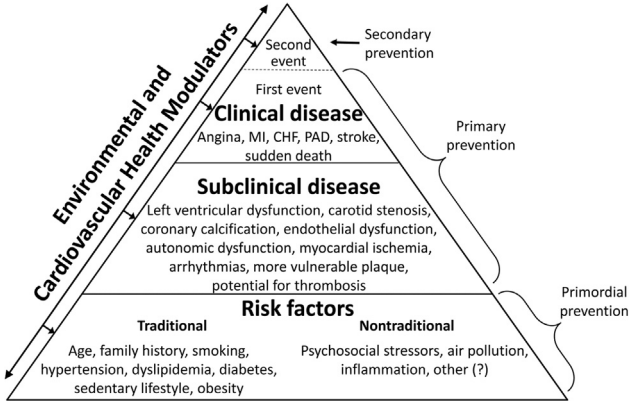

FIG 3. The evolutionary CVD pyramid. Prevention can be divided into 3 types: primordial (prevention of risk factors); primary (treatment of risk factors); and secondary (prevention of recurrent cardiovascular events), which can be modulated by traditional and nontraditional risk factors, including psychosocial stressors, air pollution, and inflammatory triggers. Recognizing the latter (ie, nontraditional risk factors) may maximize the potential for cardiovascular risk reduction by addressing at least a portion of the 10%-25% incidence of coronary disease that is unexplained by traditional risk factors.[125] (Adapted with permission from Franklin and Cushman.[124])

coronary heart disease by ~30% if they lived with a smoker. Collectively, these studies, and other recent reports,[100-104] suggest that community adoption of a smoke-free environment has the potential to rapidly improve the cardiovascular health status of its citizens while simultaneously reducing hospital admissions, and that the population majority (non-smokers) are most likely to benefit from such legislation.

The choice of location for outdoor exercise should take into account the air quality, as the immediate environment can affect the burden of inhaled pollutants. It is especially important that persons with CVD, the elderly, diabetics, pregnant women, and those with pulmonary disease be advised to limit outdoor activities (including structured exercise) when air pollution is high.[110] Nevertheless, studies suggest that the beneficial effects of regular exercise outweigh the adverse health effects of exposure to air pollution, especially when interventions to partially mitigate these effects are embraced.[122,123] The Environmental Protection Agency provides daily information about ozone and PM levels for >150 cities at www.epa.gov/airnow. Complete avoidance of air pollution is impossible, especially in major metropolitan areas, but strategies that reduce potential sources (eg, vehicle emissions, smoking bans, industrial combustion, and construction and demolition activities) should be implemented using current Environmental Protection Agency standards and more widespread adoption of potentially protective public laws or policies.

Comments

Rahimtoola, S.H.

Stanton A. Glantz, Ph.D, University of California, San Francisco, CA, stated "*It is a very well done manuscript*".

The authors have lucidly presented the various aspects of pollutants in the air that contribute to ill health. They have presented the particulate matters that are involved, described those who are at higher risk for morbidity and mortality, and have emphasized the underappreciated chemical triggers of disease(s) especially for cardiovascular events. This excellent manuscript provides an experts' knowledge that should be valuable reading to all people especially to those in the health-care related fields.

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