Ambient and household air pollution: complex triggers of disease

Stephen A. Farmer,1,2* Timothy D. Nelin,3* Michael J. Falvo,3,4 and Loren E. Wold1,5,6

1College of Nursing, The Ohio State University, Columbus, Ohio; 2College of Medicine, The Ohio State University, Columbus, Ohio; 3War-Related Illness and Injury Study Center, Department of Veterans Affairs New Jersey Health Care System, East Orange, New Jersey; 4Rutgers Biomedical and Health Sciences, Newark, New Jersey; 5Department of Physiology and Cell Biology, College of Medicine, The Ohio State University, Columbus, Ohio; and 6Davis Heart and Lung Research Institute, College of Medicine, The Ohio State University, Columbus, Ohio

Submitted 9 April 2014; accepted in final form 10 June 2014

Farmer SA, Nelin TD, Falvo MJ, Wold LE. Ambient and household air pollution: complex triggers of disease. Am J Physiol Heart Circ Physiol 307: H467–H476, 2014. First published June 14, 2014; doi:10.1152/ajpheart.00235.2014.—Concentrations of outdoor air pollution are on the rise, particularly due to rapid urbanization worldwide. Alternatively, poor ventilation, cigarette smoke, and other toxic chemicals contribute to rising concentrations of indoor air pollution. The World Health Organization recently reported that deaths attributable to indoor and outdoor air pollutant exposure are more than double what was originally documented. Epidemiological, clinical, and animal data have demonstrated a clear connection between rising concentrations of air pollution (both indoor and outdoor) and a host of adverse health effects. During the past five years, animal, clinical, and epidemiological studies have explored the adverse health effects associated with exposure to both indoor and outdoor air pollutants throughout the various stages of life. This review provides a summary of the detrimental effects of air pollution through examination of current animal, clinical, and epidemiological studies and exposure during three different periods: maternal (in utero), early life, and adulthood. Additionally, we recommend future lines of research while suggesting conceivable strategies to curb exposure to indoor and outdoor air pollutants.

ADVERSE HEALTH EFFECTS secondary to air pollution exposure have been recognized for over 80 years after several environmental disasters (19). For these reasons as well as significant media attention to global warming and climate change, the harmful effects of outdoor air pollution have received considerable attention and legislative action. However, of the 7 million deaths attributable to air pollution each year [according to the World Health Organization (WHO); http://www.who.int/phe/health_topics/outdoorair/en/], >60% result from indoor air pollution exposure. Air pollution is defined as the contamination of either indoor or outdoor environments by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere (WHO). Economic expansion along with industrial growth and climate change contributes to increased levels of air pollution in developing areas of the world (36). Major constituents of outdoor air pollutants [ozone, carbon monoxide (CO), nitrogen oxides, sulfur oxides, lead, and particulate matter (PM)] are derived from common byproducts of traffic emissions, power plants, industrial processes, and black smoke. Solid fuels in cooking or heating, poor ventilation, tobacco products, and other processes that release gases or particles are primary contributors to indoor air pollution in developing countries. In more developed parts of the world, air conditioning systems, formaldehyde exposure, passive cigarette smoke exposure, and newer sealed office buildings specifically contribute to increased levels of indoor air pollution (68, 90).

PM has been identified as the indicator pollutant responsible for the numerous adverse health outcomes associated with air pollution exposure. A long-standing line of epidemiological evidence outlines a positive association between ambient PM exposure and cardiovascular morbidity and mortality (15, 43, 54, 55). Importantly, adverse health effects are not present only after chronic exposure to high levels of PM air pollution but can occur at levels well below current air quality guidelines (30, 40) and of short duration (7).

Although much research has focused on health outcomes in adulthood, epidemiological studies have similarly demonstrated a strong link between PM exposure and numerous adverse health effects during the early periods of life, such as acute respiratory infections, low birth weight (LBW), and infant mortality (6, 87). Therefore, the focus of the present review is to examine the effects of air pollution exposure at three distinct periods of life: maternal (in utero), early life and childhood, and adulthood. Figure 1 shows the major sources of both indoor and outdoor air pollution and demonstrates the connection between exposure to air pollutants and a number of adverse health effects.

Outdoor Air Pollution

Maternal. The Barker hypothesis (4) suggests that in utero alterations and poor nutrition in early life can affect health outcomes during later time points. The impact of air pollution

* S. A. Farmer and T. D. Nelin contributed equally to this work.

Address for reprint requests and other correspondence: L. E. Wold, The Ohio State Univ., 603 Davis Heart and Lung Research Institute, 473 12th Ave., Columbus, OH 43210 (e-mail: Loren.Wold@osumc.edu).

http://www.ajpheart.org

H467
that insults during the developmental period as well as lower
discussed throughout the review, there is increasing evidence

Fig. 1. Air pollution can be broadly separated into two distinct categories: indoor and outdoor. Classification of air pollution depends on the source; the fact that outdoor air pollution can influence indoor air quality should also not be overlooked. A number of adverse health effects have been associated with exposure to air pollution throughout life. Adverse health effects caused by fetal exposure to air pollution, both indoor and outdoor, can significantly affect the health of the individual throughout life. While the sources of air pollution vary, the health complications associated with exposure to increased levels of these pollutants seem to be universal. LBW, low birth weight; IUGR, intrauterine growth restriction.

exposure and its negative effect on fetal growth continue to be
a focus of current research. Studies have shown associations
between exposure and negative birth outcomes including, but
not limited to, LBW, preterm birth, reduced birth length, and
congenital anomalies (71, 80). These studies, with varying
methods and results, hypothesized that exposure to air pollution
has a direct, negative effect on fetal health and growth. For
example, Estarlich et al. (17) investigated the link between
exposure to nitrogen dioxide (NO₂) and benzene, metrics for
traffic-generated pollution, and anthropometric measures at
birth. The authors found that a 10-µg/m³ increase in NO₂
exposure was correlated with a 0.09-mm decrease in birth
length and a 22-g reduction in birth weight. In a separate birth
cohort study conducted in Valencia, Spain (3), exposure to
NO₂ above 40 µg/m³ during the first trimester was associated
with a decrease in birth length of −0.27 cm [95% confidence
interval (CI): −0.51 to −0.03] and a reduction in birth weight
of 40.3 g (95% CI: −96.3 to 15.6). The same study (3) reported
a significant decrease in head circumference for exposures to
concentrations of NO₂ above 40 µg/m³.

Similar birth outcomes have been observed secondary to PM
exposure. Dadvand et al. (14) demonstrated that a 10-µg/m³
increase in respirable PM (PM₁₀) and fine PM (PM₂.₅) exposure
during gestation was associated with an increased incidence
of LBW [combined random effects odds ratio (OR): 1.10, 95% CI: 1.03–1.18]. A separate study (41) conducted
over a 9-yr period in the United States measured exposure to
PM₂.₅ 30 and 90 days before delivery, respectively. The
study found that an increase of 10-
µg/m³ PM₂.₅ was associated with a decrease in birth weight of
8.80 g (95% CI: −10.32 to −4.44) and 9.20 g (95% CI: 15.00
to −3.30) for 30 and 90 days before delivery, respectively. As
discussed throughout the review, there is increasing evidence
that insults during the developmental period as well as lower
birth weight can contribute to cardiopulmonary issues later in
life.

Early life and childhood. The prevalence of childhood
asthma diagnoses continues to increase, and early life exposure
to constituents of outdoor air pollution is associated with an
increased frequency of childhood asthma and other respiratory
diagnoses (38). Clark et al. (12) explored the incidence of
asthma in southwestern British Columbia to determine possible
links between exposure to outdoor air pollution and the develop-
ment of childhood asthma. They showed that the incidence
or risk of asthma diagnosis was positively correlated with
exposure to the major traffic pollutants nitric oxide (NO), NO₂,
CO, and black carbon. This suggests that early life exposure to
traffic pollutants places children at a higher risk of developing
asthma.

In addition to effects on the respiratory system, other inves-
tigators have studied metabolism as a target for air pollution
exposure in children. Thiering et al. (76) recorded fasting blood
glucose samples from 397 school-aged children (~10 yr old)
and estimated their exposure to traffic-related air pollution
using regression models. The authors found a 17% increase in
insulin resistance (95% CI: 5.0–30.3) per 2 SD increases in
NO₂. The results of this study also demonstrated an 18.7%
increase in insulin resistance (95% CI: 2.9–36.9) per 2 SD
increase in ambient PM₁₀ levels. These data demonstrate that
outdoor air pollution may trigger metabolic adaptations that
precede the development of cardiovascular disease.

Adulthood. Numerous diseases and adverse health events
are associated with exposure to outdoor air pollution during adult-
hood. Strong associations between outdoor air pollution expo-
sure and stroke have been explored in multiple recent studies.
A 5-yr study (89) in Japan found that exposure to outdoor air
pollution could increase the risk of hemorrhagic stroke and
ischemic stroke mortality. Maheswaran et al. (50) conducted a
study to determine the effects of air pollution on stroke mortality and found that an increase of 10 μg/m³ in both NO₂ and PM_{10} exposure was correlated with a 28% (95% CI: 11–48%) and 52% (6–118%) increased risk of death, respectively.

In a large cohort (n = 1,265,058) study (9) of subjects over the age of 30 yr who had lived in Rome for at least 5 yr, both NO₂ and PM_{2.5} were shown to be associated with an increase in nonaccidental mortality. The authors demonstrated a hazard ratio of 1.03 (95% CI: 1.02–1.03) per 10-μg/m³ increment of NO₂ and a hazard ratio of 1.04 (95% CI: 1.03–1.05) per 10-μg/m³ increment of PM_{2.5}. The strongest association existed between exposure to outdoor air pollutants and ischemic heart diseases. A 10-μg/m³ increase in PM_{2.5} exposure was related to a hazard ratio of 1.10 (95% CI: 1.06–1.13). Two separate studies in New York and Houston implicated PM exposure in the development of acute cardiovascular events. Silverman et al. (63) found that a 10-μg/m³ elevation in PM_{2.5} exposure increased the risk of out-of-hospital cardiac arrest (OHCA) for time series (RR = 1.06, 95% CI: 1.02–1.10) and case-crossover (RR = 1.04, 95% CI: 0.99–1.08) analyses. In Houston, TX, researchers found that 2 days before the onset of OHCA, a 6-μg/m³ average increase in exposure to PM_{2.5} existed (1.046, 95% CI: 1.012–1.082) (16). In a similar study, Wichmann et al. (83) showed that an increase in PM_{2.5} and PM_{10} increased the risk of OHCA events. These data demonstrate the heterogeneous threat that PM exposure poses to certain adult populations, with exposure exacerbating a number of negative cardiovascular conditions.

Related research demonstrated that exposure to air pollution is also linked to arrhythmias and myocardial infarctions (MIs). Link et al. (48) followed patients with known cardiac disease and implantable cardioverter defibrillators for an average of 1.9 yr and documented incidences of atrial fibrillation in association with acute exposure to air pollution. They found that for each 6.0-μg/m³ increase in PM_{2.5} concentration 2 h before the event, the odds of atrial fibrillation increased by 26% (95% CI: 8–47%). This study further strengthened the hypothesis that PM exposure can trigger sudden cardiac events. Previous studies (49, 78) have demonstrated that exposure to traffic pollution, especially NO₂ and PM_{2.5}, is associated with an increased incidence of acute MI. A study conducted by Koton et al. (42) strengthened these claims by demonstrating an increase in PM_{2.5} exposure of 10 μg/m³ resulted in increased hazard ratios of 1.3 (95% CI: 0.8–2.1) for death and 1.5 (95% CI: 1.1–1.9) for multiple recurrences of MI, heart failure, and stroke in patients that had suffered a previous MI. It has become increasingly clear that enhanced exposure to outdoor air pollutants can trigger the onset of acute cardiovascular events and implies the need for further research to explore outdoor air pollution exposure in high-risk populations.

Since 2001, >2.5 million United States military personnel have been deployed to Iraq and Afghanistan and were likely exposed to poor air quality during their deployment. At multiple locations in the deployment environment, PM_{10} and PM_{2.5} levels have been shown to consistently exceed occupational and military exposure guidelines (51). In fact, levels of PM_{2.5} are ~10-fold greater in the deployment environment than those observed at rural and urban monitoring sites in the United States (51). Geological dust, smoke from burning trash (i.e., “burn pits”), and industrial processing facilities were identified as the primary air pollution sources. It remains unclear whether these exposures are associated with long-term health effects; however, several epidemiologic studies have raised concerns. For example, acute respiratory illnesses have been reported to occur in 40–70% of military personnel during deployment (57, 69). Compared with nondeployed, deployed military personnel have higher rates of newly reported respiratory symptoms (14% vs. 10%) (65) as well as a greater frequency of new onset asthma (73). Clinical case series of rare pulmonary diseases, such as constrictive bronchiolitis (52) and acute eosinophilic pneumonia (62), have also been reported in this population and have been suggested to be the result of military exposures. The potential health effects related to deployment-related ambient air pollution exposure is an emerging area of concern that warrants close attention.

### Indoor Air Pollution

**Birth.** A well-documented line of research suggests a strong correlation between in utero exposure to indoor air pollution and a number of adverse health outcomes (1, 26, 46, 82). During the last 5 yr, a number of studies have explored connections between exposure to indoor air pollution and negative health outcomes at birth, including LBW, stillbirth, and preterm birth. Many of these studies specifically analyzed the relationship between in utero exposure to indoor air pollutants and adverse birth outcomes. As introduced above, the Barker hypothesis (4) revealed that insults to the health of the fetus can alter the health of the individual not only at that time but also later in life (23). One study (23) examined the effects of cigarette smoke and exposure to volatile organic compounds and showed that women exposed to secondhand smoke exhibited increased odds of LBW (adjusted OR: 1.36, 95% CI: 0.85–2.18) and preterm birth (adjusted OR: 1.27, 95% CI: 0.95–1.70) compared with unexposed women for full-term labors. A separate meta-analysis explored the relationship between indoor air pollution exposure and the incidence of LBW and stillbirth (56). For standardization, this meta-analysis examined exposure to indoor air pollutants resulting from solid fuel in open fires and showed that exposure to indoor air pollution was positively associated with an increase in LBW (OR: 1.38, 95% CI: 1.25–1.52) and stillbirth (OR: 1.51, 95% CI: −0.68.5 to −124.7). These data support the hypothesis that exposure to indoor air pollutants during pregnancy can cause a number of adverse birth outcomes.

These studies demonstrated a connection between adverse pregnancy outcomes and exposure to indoor air pollutants, highlighting a link between poor ventilation and the persistence of indoor air pollution. Further studies should focus on the potential effects of installation of ventilation mechanisms in rural and urban areas. Table 1 shows a summary of clinical studies that explored the effects of indoor and outdoor air pollution during the early stages of life, from in utero to birth.

**Early life and childhood.** Approximately half of the global population (~3 billion people) uses biomass fuels (e.g., wood, charcoal, and crop residues) for energy needs (WHO). Exposure to these household pollutants during early life can have negative effects on health (1, 21, 66, 72). The rising incidence of asthma diagnoses and developmental issues are of particular concern as more data now support a relationship between indoor air pollution exposure and the prevalence of these conditions.
Increased exposure to indoor air pollutants may be implicated in the development of asthma (32). In both urban and rural environments, this study (32) demonstrated that exposure to acetaldehyde and toluene was significantly associated with a higher risk of asthma (OR: 2.73, 95% CI: 1.28–5.83, and OR: 2.15, 95% CI: 1.01–4.58, respectively). A long-term study of an infant cohort by Raaschou-Nielsen et al. (58) explored the effects of exposure to indoor air pollution and wheezing, a symptom that may progress into asthma later in life. This study did not demonstrate a systematic association between the risk for wheezing symptoms and levels of indoor air pollutants. These results may suggest that indoor air pollution is not causally related to the initial onset of wheezing; rather, this exposure may trigger and worsen symptoms of previously developed asthma (35).

Roy et al. (60) investigated indoor air pollution exposure and its effects on lung function among children in four Chinese cities. Exposure to coal combustion was associated with 16.5 ml/yr lower forced expiratory volume in 1 s (33%, P < 0.001) and 20.5 ml/yr lower forced vital capacity (39%, P < 0.001) growth. The authors effectively demonstrated that household coal combustion, a component of indoor air pollution, may impair lung function. A study (67) in highland Guatemala investigated the relationship between reduced exposure to indoor air pollution and incidence of pneumonia in children. This study found that children living in homes with chimneys experienced significantly reduced exposure from 2.2 to 1.1 ppm CO, on average, compared with homes with open wood fires. This 50% reduction in exposure was associated with a significant reduction in physician-diagnosed pneumonia (RR: 0.82, 95% CI: 0.70–0.98).

Exposure to indoor air pollution in utero and in early life periods must be understood in a larger context. The Barker hypothesis implicates in utero development as a major determinant for a number of chronic diseases later in life (39). Therefore, future lines of research should focus on long-term studies to further elucidate the connection between indoor air pollution exposure, fetal and in utero development, and the onset of chronic disease later in life. The effects of these clinical studies are shown in Table 2 alongside the effects of similar outdoor air pollution clinical studies discussed above.

**Adulthood.** Numerous adverse health outcomes have been associated with long-term exposure to indoor air pollution during adulthood (8, 18, 20, 66). These effects range from decreased cardiovascular health to chronic bronchitis and DNA damage. A majority of the studies dealt with populations from developing regions of the world where indoor air pollutants accumulated due to combustion fuels used in cooking and cleaning coupled with poor ventilation. This section focuses specifically on the adverse health conditions reported among adult populations after exposure to indoor air pollution.

A study (47) conducted in Taipei, China, measured improvements in cardiovascular health after a reduction in exposure to indoor air pollution. The authors demonstrated that increased high-sensitivity C-reactive protein (a marker of inflammation), 8-hydroxy-2-deoxyguanosine (demonstrative of oxidative stress), and fibrinogen (present in high concentration in the inflammatory response) levels and a decrease in heart rate variability (reduced heart rate variability has been shown to be a predictor of MI) were associated with increased levels of indoor air pollutant particles. These data reveal that exposure to indoor air pollution is positively correlated with inflammation, oxidative stress, and cardiac dysfunction (79). Another study (79) demonstrated that exposure to wood smoke increases arterial stiffness and decreases heart rate variability. Positive associations exist between the use of solid fuel, chronic obstructive pulmonary disease (OR: 2.80, 95% CI: 1.85–4.0), and chronic bronchitis (OR: 2.32, 95% CI: 1.92–2.80) (44).

A 1-log μg/m³ increase in PM$_{2.5}$ exposure was associated with a 2.2 mmHg higher systolic blood pressure (95% CI: 0.8–3.7, P = 0.003) and 0.5 mmHg higher diastolic blood pressure (95% CI: −0.4 to 1.3, P = 0.31) among 280 women in Yunnan, China exposed to indoor air pollution (5). Women aged 50 yr or older demonstrated an even greater response to PM$_{2.5}$ exposure. The National Institutes of Health have identified high blood pressure as a precursor to a number of negative cardiovascular events, so the link between indoor air pollution exposure and elevated blood pressure may indirectly have an effect on a host of related adverse health outcomes.

Mondal et al. (53) explored the connections between chronic exposure to biomass smoke and genotoxicity. Compared with the control group, individuals exposed to high levels of biomass smoke exhibited increased incidences of micronucleated cells in both bucal and airway epithelial cells (3.5 vs. 1.7, P < 0.001, and 4.54 vs. 1.86, P < 0.001, respectively). Biomass users exhibited increased ROS generation, decreased levels of
The literature demonstrates a correlation between exposure to both indoor and outdoor air pollutants and adverse health effects including stroke, out-of-hospital cardiac arrest (OHCA), elevated blood pressure, decreased heart rate variability, wheezing, myocardial infarction, and cardiovascular-associated morbidity and mortality. Adverse health effects of air pollution exposure are present in both indoor and outdoor settings and many areas across the globe, demonstrating an extensive relationship between air pollutants and adverse health effects.

### Table 2. Summary of data showing effects of both outdoor and indoor air pollutants and the negative health effects on early childhood life

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al. (12)</td>
<td>Southwest British Columbia, Canada</td>
<td>Outdoor</td>
<td>There was an increased risk of asthma diagnosis with early life exposure to traffic pollutants: the adjusted OR was 1.08 (95% CI: 1.04–1.12) for a 10-µg/m³ increase in nitric oxide, 1.12 (95% CI: 1.07–1.17) for a 10-µg/m³ increase in NO₂, and 1.10 (95% CI: 1.06–1.13) for a 100-µg/m³ increase in CO</td>
</tr>
<tr>
<td>Thiering et al. (76)</td>
<td>Germany</td>
<td>Outdoor</td>
<td>There was an increased insulin resistance with a 2-SD increase exposure to NO₂ of 17% (95% CI: 5.0–30.3) and PM₁₀ of 18.7% (95% CI: 2.9–36.9)</td>
</tr>
<tr>
<td>Raaschou-Nielsen et al. (58)</td>
<td>Denmark</td>
<td>Indoor</td>
<td>There was no association found between exposure to NO₂, NO₃, formaldehyde, or PM₂.₅ and risk of wheezing symptoms</td>
</tr>
<tr>
<td>Roy et al. (60)</td>
<td>China</td>
<td>Indoor</td>
<td>Exposure to indoor coal combustion resulted in a forced expiratory volume in 1 s of 16.5 mL/yr lower (33%, P &lt; 0.001) and forced vital capacity of 20.5 mL/yr lower (39%, P &lt; 0.001)</td>
</tr>
<tr>
<td>Smith et al. (67)</td>
<td>Guatemala</td>
<td>Indoor</td>
<td>Homes using chimneys reduced exposure to CO from 2.2 to 1.1 ppm. There was a reduction in physician diagnosed pneumonia of RR = 0.82 (95% CI: 0.70–0.98)</td>
</tr>
<tr>
<td>Jackson et al. (35)</td>
<td>Multiple countries</td>
<td>Indoor</td>
<td>Exposure to indoor air pollutants was significantly associated with severe acute lower respiratory infections (OR: 1.57, 95% CI: 1.06–2.31)</td>
</tr>
</tbody>
</table>

Summary of data showing effects of both outdoor and indoor air pollutants and the negative health effects on early childhood life.

The data suggest that exposure to both outdoor and indoor pollutants can increase diagnoses of asthma, exacerbate already diagnosed asthma, decrease lung function, and increase insulin resistance. CO, carbon monoxide; NOₓ, nitrite/nitrate; PM₁₀, respirable PM.

#### Animal Models

Animal studies can be used to explore the effects of exposure to both indoor and outdoor air pollution. Recent animal studies have reinforced the association between exposure to SOD, and decreased total antioxidant status. These results demonstrated how chronic biomass exposure may lead to a depleted antioxidant defense mechanism, ultimately resulting in DNA and chromosomal damage.

While exposure to indoor air pollution in early life can cause a plethora of adverse developmental effects, exposure during adulthood is significantly associated with a number of negative health conditions. Exposure can also be markedly decreased by the advent of initiatives such as the installation of proper ventilation and decreased tobacco consumption indoors. Table 3 shows a comparison of the indoor air pollution clinical studies explored above with the outdoor air pollution studies previously discussed.

### Table 3. Summary of the epidemiological and clinical data outlining the effects of exposure to indoor and outdoor air pollution during adulthood

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yourifuji and Kashima (89)</td>
<td>Japan</td>
<td>Outdoor</td>
<td>There was a risk ratio of 10-µg/m³ increase in PM of 1.014 for hemorrhagic stroke and 1.016 for ischemic stroke</td>
</tr>
<tr>
<td>Maheswaran et al. (50)</td>
<td>London, England</td>
<td>Outdoor</td>
<td>A 10-µg/m³ increase in PM and NO₂ resulted in 52% and 28% increased stroke mortality, respectively</td>
</tr>
<tr>
<td>Cesaroni et al. (9)</td>
<td>Rome, Italy</td>
<td>Outdoor</td>
<td>The hazard ratio for mortality was 1.03 for a 10-µg/m³ increase NO₂ and 1.04 for a 10-µg/m³ increase PM₂.₅</td>
</tr>
<tr>
<td>Silverman et al. (63)</td>
<td>New York, NY</td>
<td>Outdoor</td>
<td>The relative risk of an OHCA after a 10-µg/m³ increase in PM₂.₅ was 1.06</td>
</tr>
<tr>
<td>Ensor et al. (16)</td>
<td>Houston, TX</td>
<td>Outdoor</td>
<td>The relative risk of an OHCA after a 6-µg/m³ increase in PM was 1.046</td>
</tr>
<tr>
<td>Link et al. (48)</td>
<td></td>
<td>Outdoor</td>
<td>Increased odds of atrial fibrillation of 26% after a 6-µg/m³ increase in PM₂.₅</td>
</tr>
<tr>
<td>Koton et al. (42)</td>
<td>Israel</td>
<td>Outdoor</td>
<td>There was an adjusted hazard ratio of 1.3 for death and 1.5 for myocardial infarction after a 10-µg/m³ increase in PM₂.₅</td>
</tr>
<tr>
<td>Wichmann et al. (83)</td>
<td>Copenhagen, Denmark</td>
<td>Outdoor</td>
<td>Increased percent chance of an OHCA of 4% after PM₂.₅ exposure and 5% after PM₁₀ exposure</td>
</tr>
<tr>
<td>Unosson et al. (79)</td>
<td>Helsinki, Finland</td>
<td>Indoor</td>
<td>Wood smoke exposure resulted in arterial stiffness and decreased heart rate variability</td>
</tr>
<tr>
<td>Kurmi et al. (44)</td>
<td>Multiple countries</td>
<td>Indoor</td>
<td>ORs after biomass smoke exposure of 2.80 for chronic obstructive pulmonary disease and 2.32 for chronic bronchitis</td>
</tr>
<tr>
<td>Baumgartner et al. (5)</td>
<td>Yannen, China</td>
<td>Indoor</td>
<td>Systolic blood pressure was 2.2 mmHg higher after a 1-log µg/m³ increase in PM₂.₅ and diastolic blood pressure was 0.5 mmHg</td>
</tr>
<tr>
<td>Smith-Sivertsen et al. (64)</td>
<td>Guatemala</td>
<td>Indoor</td>
<td>The relative risk was 0.42 for wheezing after a 61.6% CO exposure reduction</td>
</tr>
<tr>
<td>Mondal et al. (53)</td>
<td>India</td>
<td>Indoor</td>
<td>Biomass smoke exposure resulted in an increased incidence of micronucleation</td>
</tr>
</tbody>
</table>

The literature demonstrates a correlation between exposure to both indoor and outdoor air pollutants and adverse health effects including stroke, out-of-hospital cardiac arrest (OHCA), elevated blood pressure, decreased heart rate variability, wheezing, myocardial infarction, and cardiovascular-associated morbidity and mortality. Adverse health effects of air pollution exposure are present in both indoor and outdoor settings and many areas across the globe, demonstrating an extensive relationship between air pollutants and adverse health effects.
indoor and outdoor air pollution and negative health outcomes. Animal models represent an important subset of the current research as exposure conditions can be simulated under many conditions. The concentration and components of air pollution can be manipulated in each study for the desired specificity and scope. The specific role that air pollution plays in the development of cardiovascular disease has been studied extensively using animal models. Research in this arena supports past and current human cohort studies that detailed associations between exposure to outdoor air pollution and a decrease in functional cardiovascular physiology.

Outdoor air pollution. The process of cardiac remodeling potentiated by chronic hypertension or acute MI acts as a major risk factor in the development of heart failure. Fibrosis, accompanied by myocyte hypertrophy, is a pathological process that can lead to decreased cardiac function (27). Ying et al. (88) exposed 8-wk-old male C57BL/6 mice to PM2.5 at concentrations 10 times ambient levels for 12 wk. Mice were then dosed (0.75 mg·kg⁻¹·day⁻¹ in 0.15 mol/l NaCl and 0.01 N acetic acid) with ANG II for 14 days to simulate renovascular hypertension. The authors found that exposure to PM2.5 significantly enhanced cardiac collagen deposition in ANG II-treated mice and increased systolic blood pressure in PM2.5-treated mice after 1 wk of infusion with ANG II compared with their filtered air counterparts. They also noted that RhoA activity was increased due to PM2.5 exposure (88).

Ischemia-reperfusion-related injuries cause myocardial damage that ranges from temporary and mild to permanent and severe. Meyer et al. (52) used an adult male Wistar rat model to demonstrate that prolonged CO exposure at levels resembling an urban environment was associated with severe, deleterious myocardial injury. The results of their study suggest that prolonged CO exposure may negatively affect SOD and glutathione peroxidase levels, ultimately leading to incapacitated intracellular Ca²⁺ handling. Popowich et al. (57) isolated aortic vascular smooth muscle cells from p53⁻/⁻ and p53⁻/⁻ mouse strains to explore the role of NO in vascular smooth muscle damage. Their study reported that ROS mediate NO-induced vascular smooth muscle apoptosis and showed that p53 protects vascular smooth muscle cells from NO-induced apoptosis by clearing intracellular ROS. These results demonstrate the prominent, deleterious role of ROS in myocardial and vascular injury and suggest possible mechanisms by which prolonged exposure to urban air pollution initiates long-term damage.

As demonstrated throughout the review, numerous epidemiological studies have provided a connection between PM exposure and cardiopulmonary morbidity. Mahne et al. (51) explored the link between exposures to environmentally persistent free radicals (EPFR), a component of PM, and decreased cardiac function. Their study used healthy male Sprague-Dawley rats to demonstrate that inhalation 1,2-dichlorobenzene (an EPFR) was associated with a decrease in stroke volume, cardiac output, and stroke work, three components of left ventricular function. Inhalation of 1,2-dichlorobenzene also increased pulmonary artery pressure and decreased end-diastolic volume and pressure. These data suggest that inhalation of EPFRs increases pulmonary vascular resistance and decreases cardiac function while concomitantly creating a state of increased inflammation both systemically and in the heart.

Our laboratory (84) demonstrated that mice exposed to concentrated PM2.5 over a period of 9 mo demonstrated decreased cardiac function. Male mice that were exposed to PM2.5 showed higher rates of cardiac remodeling characterized by increases in both left ventricular end-systolic and end-diastolic diameters compared with filtered air-exposed control mice. The authors also found that PM2.5-exposed mice showed decreased systolic posterior wall thickness, and isolated cardiomyocytes showed a significant decrease in percent peak shortening, an increase in time to 90% peak shortening, and time to 90% relengthening. PM2.5-exposed mice demonstrated increased levels of collagen type I and decreased levels of sarco(endo)plasmic reticulum Ca²⁺-ATPase 2a. This could suggest an alteration that promotes Ca²⁺ reuptake into the sarcoplasmic reticulum, which is again consistent with an incipient heart failure phenotype. These data were the first to assess the cardiac effects of exposure to long-term air pollutants.

Similar mouse studies have implicated diesel exhaust (DE) in the development of atherosclerotic events. Bai et al. (2) exposed apolipoprotein E knockout mice to DE with a PM concentration of 200 μg/m³ and to filtered air for 7 wk. This exposure significantly enhanced inducible NO synthase expression 4-fold in the thoracic aorta and 1.5-fold in the heart. A two-fold increase of NF-κB activity after exposure to DE was also found and positively correlated with inducible NO synthase expression ($R^2 = 0.5998$). In a later study, Bai et al. (2) exposed apolipoprotein E knockout mice to DE at 200 μg/m³ of PM and to filtered air for 7 wk. Cyclooxygenase expression in the thoracic aorta ($P < 0.01$) and aortic root ($P < 0.03$) was significantly increased, indicating an increased inflammatory response. As this knockout mouse is involved in atherosclerosis development, the authors hypothesized that DE exposure could enhance atherosclerosis, which could eventually lead to pollution-associated cardiovascular morbidity and mortality.

Indoor air pollution. Cigarette smoke has long been known to contribute to the generation of indoor air pollution. Literature has linked secondhand tobacco smoke exposure to compromised immune function (70), endothelial dysfunction (74), impaired lung function (45), high blood pressure (28), and atherosclerosis (31). Gentner et al. (22) used rat models to demonstrate that secondhand tobacco smoke exposure altered the cilia/mucus pattern of heart rate and blood pressure, increased pulse wave dP/dt, and increased inactivation of NO. Chen et al. (10) showed that short-term secondhand smoke exposure reduced heart rate variability and increased arrhythmia in mouse models.

Significant associations between chronic tobacco use, hypertension, oxidative stress, decreased levels of NO, endothelial dysfunction, and cardiac remodeling in mouse models have been well established (75). Polycyclic aromatic hydrocarbons comprise a large portion of the toxic makeup of cigarette smoke. Rennie et al. (59) exposed female mice to polycyclic aromatic hydrocarbons before conception, perfused fetoplacental arterial trees with a contrast agent, and imaged the vasculature. Vessel tortuosity and reduced vascularization in the fetoplacental arterial tree after maternal exposure to polycyclic aromatic hydrocarbons characterized the results of the study. Interestingly, others (13) have shown that glutathione-S-transferases (GSTs) protected against endothelial dysfunction by demonstrating that GST-P⁻/⁻ mice exhibited an exaggerated...
response to tobacco smoke compared with GST-P+/+ mice (13). CO also constitutes a large portion of indoor air pollution in the urban setting, and many studies have indicated CO exposure in the development of a number of adverse health outcomes. Chronic CO exposure exacerbated myocardial ischemia-reperfusion injuries characterized by augmented post-ischemic ventricular arrhythmias, impaired recovery of myocardial function, and increased infarct size (60 ± 5% vs. 33 ± 2% of the ischemic zone) (52).

The role of ozone-initiated monoterpene reaction products, characteristic of many office environments, has been investigated for its role in the onset upper airway irritation (86). The authors specifically explored acute upper airway irritation, airflow limitation, and pulmonary irritation in the alveolar region. Their study exposed mice to five common ozone reaction products for 60-min time periods, mimicking the time and concentration of exposure in an office environment. The authors effectively demonstrated that exposure does not significantly contribute to upper airway irritation. Synthetic musk, an ingredient in many personal care products, also contributes to indoor air pollution. Shi et al. (61) performed a microarray analysis of gene expression in mouse embryonic stem cells after exposure to synthetic musk. The study found 2,879 differentially expressed genes of the 45,037 transcripts in the microarray, highlighting the potential influence of synthetic musk on embryonic development. Another study (34) showed that chronic oral exposure to acrolein, an aldehyde pollutant, caused dilated cardiomyopathy in mice. The effects of human exposure to acrolein should be studied further to investigate possible connections between chronic exposure, cardiomyopathy, and heart failure.

Volatile organic compounds (VOCs) may cause multiple chemical sensitivity reactions in humans and are constituents of indoor air pollution in the domestic setting. Wang et al. (81) exposed male Kunming mice to filtered air and four types of VOC mixtures (formaldehyde, benzene, toluene, and xylene). Markers of oxidative stress, cellular infiltration, cytokine production, neurotrophin, and substance P were examined in the bronchoalveolar lavage fluid. VOC exposure was significantly correlated with an increase in NO synthase, GSH, and IL-6 concentration. However, interferon-γ (representative of the innate immune inflammatory response) and substance P were significantly decreased. These data implied that VOC exposure may induce airway inflammation via NO signaling pathways, supporting the hypothesis that NO-derived oxidants are characteristic of the response to vascular injury. Wolkoff et al. (85) alternatively demonstrated that chronic, low-level exposure to VOCs did not significantly cause airway irritation and airflow limitation. This may suggest that prolonged exposure to elevated levels of VOCs is required to trigger the milieu of adverse outcomes. Another important consideration in future research is to delineate the effects of mouse strain and compare outcomes to clinically related data as well as explore the concentration of ambient VOCs and time of exposure required to elicit airway irritation.

Limitations

Indoor and outdoor PM levels are continuously on the rise in industrialized nations; however, we are now beginning to understand the causal effects of increased exposure and disease progression. Several limitations are present in the data presented in this review, including the inability to adequately compare animal data obtained in varying strains of mice with human data. Another concern is the varying concentrations of indoor and outdoor pollutants throughout the world. It is also impossible to compare the constituents of indoor versus outdoor PM since their source is likely not the same. These limitations will only be understood with further research.

Conclusions

A growing body of epidemiological studies has demonstrated air pollution’s negative effects on human health. Adverse health outcomes include declines in physiological function of the cardiovascular and respiratory systems and increases in diagnoses of respiratory wheezing/asthma, OHCAs, MI, and overall cardiovascular morbidity and mortality. The exact mechanisms by which PM contributes to these health conditions remain ambiguous; however, arterial stiffening, inflammation, and oxidative stress pathways are likely involved. Future research efforts using appropriate animal models may prove beneficial in determining a pathophysiological mechanism responsive to air pollution exposure.

In addition to pathophysiological mechanisms, future studies should continue to design ways to mitigate air pollution levels. A vast amount of literature has already demonstrated the usefulness of implementing certain pollution control mechanisms on diminishing the incidence of adverse health effects. The application of chimney woodstoves significantly decreased the amount of indoor air pollution generated from biomass burning and is associated with a lessened incidence of negative health outcomes (11, 37, 64). A 50% decrease in indoor air pollution levels accompanied a national tobacco ban in New Zealand (77). Numerous studies have characterized the negative effects resulting from exposure to high levels of outdoor air pollutants (25, 80). For instance, Invernizzi et al. (33) demonstrated that the black carbon concentration is a highly relevant metric of traffic pollution; future studies could investigate how reductions in black carbon emissions improve health. Similar studies have also shown that outdoor air pollution negatively affected the quality of indoor air. Other studies should explore ways to mitigate these effects as indoor and outdoor air pollution are intrinsically related (24, 29).

Current evidence sets the groundwork for future studies assessing the effectiveness of policies aimed at improving air quality. As developing countries continue to develop, combustible biomass is used as fuel, roadways develop, and traffic patterns grow, exposure to air pollutants will continue to rise. Based on our evaluation of the current literature, the health implications associated with pollution exposure should be considered in the development of future policies concerning reductions in both PM and gaseous pollutants worldwide.

GRANTS

This work was supported in part by a Teacher Fellowship from the American Physiological Society Frontiers in Physiology program (to S. A. Farmer), National Institutes of Health Grants R01-ES-019923 and R01-NR-012618 (to L. E. Wold), a Bennett Memorial Scholarship from the College of Medicine at the Ohio State University (to T. D. Nelin), and Department of Veterans Affairs Rehabilitation Research and Clinical Science Research and Development Services Grants I121RX001079 and I121CX000797 (to M. J. Falvo).

AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00235.2014 • www.ajpheart.org
H474 AMBIENT AND HOUSEHOLD AIR POLLUTION

DISCLAIMER
The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES
33. Jackson S, Mathews K, Punic D, Falconer R, Rudan I, Campbell H, Nair H. Risk factors for severe acute lower respiratory infections in...


