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gVIEW

REVIEW

Household Air Pollution from Solid Fuel Use
Evidence for Links to CVD

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More than 3 billion people worldwide continue to depend on solid fuels such as wood, dung, or crop residues for cooking and heating [1]. Use of these fuels in traditional stoves or open fires results in very high levels of household air pollution (HAP), with women and young children bearing a disproportionate burden of the health effects. The World Health Organization estimates that indoor air pollution from solid fuel use accounts for more than 1.9 million (3.3%) of annual deaths, making household air pollution the largest environmental contributor to mortality in the world, even greater than unsafe water and sanitation [2].

Evidence suggests that HAP is associated with increased susceptibility to lung diseases [3], and there is much interest in fuel-efficient, low-emission cook stoves as a way to improve respiratory health and decrease mortality in resource-poor countries. Fewer studies have evaluated the effects of HAP on the cardiovascular system, and only 1 study has examined associations between solid fuel use and self-reported diagnosis of cardiovascular diseases (CVD) [4]. However, combustion-generated aerosols from other sources, and especially fine particulate matter, are considered important causes of CVD and mortality [5].

Whereas CVD mortality has substantially declined in the developed world, there is an emerging CVD epidemic in low- and middle-income countries (LMIC) [6]. The number of CVD deaths in LMIC already exceeds that in high-income countries. The demographic shifts associated with the epidemiologic transition and increased life expectancy in LMIC mean that CVD mortality will become an increasing proportion of deaths. In addition to demographic shifts, changes in conventional risk factors (body mass index, blood pressure, plasma cholesterol, diabetes) are expected to accelerate the increase in CVD [6]. HAP has only recently been recognized as a potentially important and modifiable risk factor for CVD.

We examine the observational evidence for cardiovascular effects of HAP, the experimental evidence for cardiovascular effects of biomass burning, and the evidence from observational and experimental studies of the effects of specific air pollutants found in HAP.

CHARACTERISTICS OF HAP

Inefficient combustion of solid fuels, such as biomass and coal, in household stoves results in products of incomplete combustion including particles, gases, and semivolatile compounds, which together we refer to as HAP. Although the chemical and physical properties of HAP will depend on fuel types and combustion conditions, HAP contains a multitude of compounds that are known toxicants. For

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example, suspended fine particulate matter ([$PM_{2.5}$]; aerodynamic diameter less than 2.5 μm) is a major index of HAP; $PM_{2.5}$ of outdoor origin is a recognized risk factor for cardiovascular morbidity and mortality [5]. Particles emitted from typical solid fuel household stoves are of particular concern because they are predominantly in the size range capable of depositing deeply in the lungs. These ultrafine particles, with aerodynamic diameter less than 100 nm, have been implicated in CVD, partly due to their apparent ability to cross the alveolar membrane and enter circulation, where they can interact directly with the vascular endothelium and cardiac cells [7]. Carbon monoxide (CO) is another major component of HAP [8]. At high doses, CO is an asphyxiant that can have important effects on the cardiovascular system [9,10]. However, even at much lower doses typically found in outdoor air, numerous studies have found an association between short-term variation in outdoor CO levels and increased risk of cardiovascular morbidity [11–15] and mortality [16,17]. Other classes of pollutants found in HAP include hydrocarbons, oxygenated organics, and free radicals [18], many of which have been shown to cause inflammation and oxidative stress. For example, acrolein (propenal) is a toxic unsaturated aldehyde present in wood and coal smoke, secondhand smoke, and other combustion sources, with well-documented adverse cardiovascular effects [19,20].

HAP exposures are of specific concern because of the magnitude and frequency of exposures to these toxic contaminants. The mass concentration of $PM_{2.5}$ is a commonly used metric for assessing exposure to combustion products. As a reference, the World Health Organization's ambient air quality guideline for annual average $PM_{2.5}$ set an upper limit of 10 $\mu g/m^3$ to protect human health [21]. Daily average personal $PM_{2.5}$ exposures among people from households using solid fuels are often in the hundreds of $\mu g/m^3$ [22,24]. Moreover, the intermittency of cooking and fueling of fires can lead to peak exposures of several thousands of $\mu g/m^3$. These daily exposures generally continue throughout life, but can be particularly high during the formative intrauterine and neonatal periods [25].

EVIDENCE FROM OTHER RELEVANT AIR POLLUTION EXPOSURES

Ambient outdoor air pollution (AOP), secondhand smoke (SHS), and HAP share several important common aspects. Each of these pollutant mixtures contains fine and ultrafine particles and is composed of combustion-based pollutants containing redox-generating chemicals (e.g., oxygenated organic compounds) capable of eliciting adverse responses in biological systems [5,26–28]. All 3 pollutant mixtures contain gaseous and vapor phase copollutants that may exert effects in addition to the particulate phases [5,26–28]. The numerous adverse biological responses that have been shown to occur in response to exposures to AOP and SHS have been reviewed in detail elsewhere [5,26] and are only mentioned briefly here as they may relate to findings on HAP effects.

Epidemiological evidence is strong that both AOP and SHS increase cardiovascular morbidity and mortality. The evidence for both these sources of combustion-generated air pollution has been deemed strong enough to support the implementation of public health campaigns and regulatory policies to prevent CVD in many parts of the world. Whereas there are important differences between HAP and these other pollutant mixtures, the similarities in exposure characteristics and components suggest that HAP is likely also associated with increased CVD risk and underscore the need for research efforts in this area.

EVIDENCE FOR CARDIOVASCULAR EFFECTS OF HAP

Cardiovascular mortality and clinical events. Whereas the major concern is that HAP exposure is a risk factor for major adverse cardiovascular events (sudden death, myocardial infarction, stroke, etc.), there has been only 1 study that has directly examined this association [4]. Lee et al. [4] found that household use of solid fuels was associated with increased risk of self-reported coronary heart disease (odds ratio [OR]: 2.58, 95% confidence interval [CI]: 1.53 to 4.32) and diabetes (OR: 2.48, 95% CI: 1.59 to 3.86), and being in the highest tertile of duration of solid fuel use compared with the lowest tertile was associated with past stroke (OR: 1.87, 95% CI: 1.03, 3.38).

There is compelling observational and experimental evidence that outdoor air pollution generally [29] and fine particulate air pollution specifically [5] are causally linked with increased risk of cardiovascular events. SHS is also consistently linked with cardiovascular mortality and morbidity [30–32]. The evidence for these CVD effects of SHS is supported by the substantial reductions in cardiovascular events that have been observed

following bans on smoking in workplaces and restaurants [33–36].

Blood pressure and risk of hypertension. A number of cross-sectional epidemiologic studies have reported increased arterial blood pressure and hypertension associated with solid fuel use and HAP exposures (Table 1). In a population-based study of 14,068 Chinese adults, self-reported ever use of solid fuels (biomass or coal) was associated with a 1.7-fold (95% CI: 1.4 to 2.1) increased prevalence odds of hypertension, and the risk of hypertension increased with duration of solid fuel use [4]. In a cross-sectional study of Indian women, Dutta et al. [37] found the prevalence of hypertension (systolic blood pressure [SBP] $\geq$140 mm Hg or diastolic blood pressure [DBP] $\geq$90 mm Hg) was 30% among solid fuel users and 11% among liquid petroleum gas (LPG) users. The prevalence odds for hypertension was 1.41 (95% CI: 1.22 to 2.08) times greater for women with kitchen $PM_{2.5}$ above the median of the study population. Among 123 Nicaraguan women, Clark et al. [23] found increased, although not statistically significant, SBP and DBP associated with personal measurements of CO exposure; associations with kitchen levels of $PM_{2.5}$ and CO were weaker. Baumgartner et al. [24] measured personal $PM_{2.5}$ among several hundred Chinese women from rural Yunnan using biomass fuels. They found 1.5 mm Hg higher SBP (95% CI: 0.6 to 2.6) and 0.3 mm Hg higher DBP (95% CI: −0.3 to 0.9) associated with doubling of $PM_{2.5}$ during the previous 24 h.

The most compelling evidence for an effect on hypertension comes from a randomized exposure intervention study (RESPIRE [Randomized Exposure Study of Pollution Indoors and Respiratory Effects]) in Guatemala comparing a chimney woodstove to the traditional open fire among households with a pregnant woman or infant <4 months of age. After the randomized intervention had occurred, women from both arms of this trial were recruited for a cardiovascular substudy [22]. Women with the chimney stove intervention had 3.7 mm Hg lower (95% CI: −8.1 to 0.6) SBP and a 3.0 mm Hg lower (95% CI: −5.7 to −0.4) DBP than with those in women with the traditional open fire. In a longitudinal comparison of women before and after receiving chimney stoves, similar improvements in SBP and DBP associated with the improved chimney stove intervention were observed.

There appear to be certain subgroups at greater risk of blood pressure effects from HAP. Age-dependent effects were found in a Chinese study [24] that showed strong direct associations between blood pressure and personal $PM_{2.5}$ among women >50 years of age, whereas nonsignificant associations among women $\leq$50 years of age were many times smaller for SBP and in the opposite direction for DBP. Lee et al. [4] found a stronger association between hypertension and household solid fuel use among men and women $\geq$40 years than in younger adults, but this difference was small and not statistically significant ($p = 0.34$). The study in India of HAP and blood pressure included only women up to 41 years of age [37], whereas the study in Guatemala included only women over 38 years of age [22], and neither of these studies report whether effect modification by age was assessed. Lee et al. [4] report a stronger association with hypertension among never-smokers compared with smokers, whereas other studies found no evidence of effect modification by smoking [22] or excluded smokers [23,24,37]. Lee et al. [4] found a stronger HAP association between HAP and hypertension among women than among men, and all other studies have included only women.

Several epidemiologic studies have reported outdoor particulate air pollution to be associated with hypertension and blood pressure. The American Heart Association statement on cardiovascular effects of particulate air pollution reports that increased daily ambient fine particulate air pollution is linked to acutely increased systemic arterial blood pressure, and that long-term particulate exposures (months to years) may alter basal blood pressure levels and induce vascular remodeling [5]. Furthermore, the association of AOP with increased heart rate is another mechanism by which air pollution may increase cardiovascular workload [5].

Endothelial function and alterations in vasomotor tone. Blood vessel endothelial dysfunction encompasses a series of alterations in vessel contractibility, coagulation cascades, and inflammatory mediators that result in pathophysiologies relevant to CVD [38].

Observational studies have shown an association between HAP and endothelial dysfunction. In a cross-sectional study, Buturak et al. [39] found lower flow-mediated dilation (5% vs. 11%), suggesting reduced endothelial function, and lower endothelium-independent dilation (14% vs. 22%), indicating reduced smooth muscle cell function, among adults reporting chronic exposure to animal dung smoke compared with those using LPG. This novel finding is interesting because flow-mediated dilation and other markers of endothelial function have been shown to be important

Table 1. Studies of blood pressure or hypertension and household air pollution

Study/location	Population	Design/analysis	Exposure variable	Key findings (95% CI)	Comments
McCracken et al. [22], Guatemala	120 rural women Age >38 yrs, mean (range): 53 (12) yrs Mean SBP/DBP = 105/68 mm Hg	Repeated measures, between-groups comparison nested within randomized control trial.	Chimney stove vs. open fire.	Chimney associated with SBP −3.7 (−8.1 to 0.6) and DBP −3.0 (−5.7 to −0.4) mm Hg.	Personal $PM_{2.5}$ means for chimney and open fire: 102 and 264 μg/m^3, respectively.
McCracken et al. [22], Guatemala	55 subjects from above	Repeated measures, compared same subjects before-and-after stove intervention.	Chimney stove vs. open fire.	Chimney associated with SBP −3.1 (−5.3 to −0.8) and DBP −1.9 (−3.5 to −0.4) mm Hg.	Personal $PM_{2.5}$ means for chimney and open fire: 174 and 273 μg/m^3, respectively.
Dutta et al. [37], India	480 women Age median (range): 33.5 (22−41) yrs 20% with hypertension	Cross-sectional, biomass fuel-users compared with age-matched controls using LPG.	Biomass fuel vs. LPG.	Hypertension prevalence 29.5% vs. 11% ($p < 0.05$).	No adjustment for confounding. Excluded family history of CVD. Kitchen 8-h $PM_{2.5}$ means for biomass and LPG 156 and 52 μg/m^3, respectively.
Dutta et al. [37], India	As above	Cross-sectional, association between kitchen levels and hypertension.	Mean of 8-h $PM_{2.5}$ measures on 3 consecutive days per subject. Variability due to group difference of 104 μg/m^3 plus SD 63 and 27 in biomass and LPG, respectively.	OR 1.41 (1.22 to 2.08) for hypertension associated with $PM_{2.5}$ above the median versus below the median.	Adjusted for education, family income, and kitchen location.
Clark et al. [23], Nicaragua	123 women in semirural setting Age mean (SD): 35 (16) yrs Mean SBP/DBP = 121/76 mm Hg	Cross-sectional.	48-h indoor $PM_{2.5}$, indoor CO, and personal CO mean (SD): 1354 (1275) μg/m^3, 26 (25) ppm, and 2.4 (2.5) ppm, respectively.	Each 2 ppm increase in personal CO associated with 1.89 (−0.48 to 4.26) mm Hg increase in SBP and 0.5 mm Hg (−1.12 to 2.13) in DBP.	Adjusted for age, BMI, secondhand smoke exposure, and education (3 categories).
Baumgartner et al. [24], China	280 rural women Age ≥25 yrs, mean (range): 52 (25-90) yrs Mean SBP/DBP = 120/72 mm Hg 13% hypertensive	Repeated measures study in winter and summer.	24-h personal $PM_{2.5}$ median (IQR): 52 (61) and 120 (105) μg/m^3 in the summer and winter, respectively.	1 log-unit increase in $PM_{2.5}$ associated with 2.2 mm Hg higher SBP (0.8 to 3.7) and 0.5 higher DBP (−0.4 to 1.3).	196 subjects measured in both seasons. Adjusted for age, waste circumference, physical activity, SES, salt intake, time of day, day of week, and average ambient temperature.
Lee et al. [4], China	14,068 adults, 54% women. age ≥18 yrs, mean (SD): 49 (17) yrs 19% hypertensive	Cross-sectional and retrospective analyses of random selection from census track data.	Ever used solid fuel (coal or biomass) and duration of use.	Ever use of solid fuel associated with a 1.7 (95% CI: 1.4 to 2.1) increased odds of hypertension. Associations were stronger among subjects ≥40 yrs, women, and never smokers.	Associations stratified by age are both lower than main effect, suggesting residual confounding by age.

BMI, body mass index; CI, confidence intervals; CO, carbon monoxide; CVD, cardiovascular disease; DBP, diastolic blood pressure; LPG, liquid petroleum gas; OR, odds ratios; PM, particulate matter; ppm, parts per million; SBP, systolic blood pressure; SES, socioeconomic status.

predictors of CVD incidence and prognosis [40,41]. An important limitation of this study is the lack of adjustment for potential confounders, as the exposed group was from a rural area, whereas the unexposed group was from an urban area.

In a randomized crossover study in a community in British Columbia, Canada with outdoor air pollution primarily from residential wood combustion, Allen et al. [42] found air filtration, which reduced indoor $PM_{2.5}$ from 11 to 5 $\mu g/m^3$ and levoglucosan (a marker of wood smoke) from 127 to 33 ng/m^3, was associated with a 9.4% (95% CI: 0.9 to 18) increase in reactive hyperemia index in 45 healthy adults, indicating improved endothelial function. Also in a randomized, double-blind, crossover study of nonsmokers with 2 consecutive 48-h in-home exposures to either particle-filtered or nonfiltered air, Brauner et al. [43] found that air filtration was associated with improved microvascular function, measured as peripheral artery tone after ischemia, and that the concentration of potassium in $PM_{2.5}$ was inversely associated with microvascular function. This is an interesting observation because potassium is associated with particles from biomass combustion.

In experimental animal studies, acrolein, an important component of HAP, results in endothelial dysfunction after inhalation [44].

Among the numerous adverse subclinical responses shown to occur with AOP are changes in vascular function, such as endothelial dysfunction and vasoconstriction [5]. Even very brief (30 to 60 min) SHS exposures have been observed to induce endothelial changes [45,46].

Effects on markers of subclinical atherosclerosis. Few studies have been conducted to look at subclinical atherosclerosis as a result of HAP. The cross-sectional study by Buturak et al. [39] did not find evidence of an association between chronic biomass smoke exposure, mostly from animal dung burning, and carotid intima media thickness (CIMT), a marker for subclinical atherosclerosis. This study was limited by the lack of comparability among exposure groups and small sample size. Moreover, it is unclear whether the effects of animal dung smoke are similar to those of more common types of biomass fuel, such as wood.

Fine particulate matter pollution in outdoor air has been associated with subclinical atherosclerosis. In the HNR (Heinz Nixdorf Recall) study, median CIMT was analyzed in 3,380 participants and increases in $PM_{2.5}$ (4.2 $\mu g/m^3$) and PM_{10} (6.7 $\mu g/m^3$) and a decrease in distance to high traffic (1,939 m) were associated with 4.3% (95% CI: 1.9% to 6.7%), 1.7% (95% CI: −0.7% to 4.1%), and 1.2% (95% CI: −0.2% to 2.6%) increases in CIMT, respectively [47].

Experiments with animal models and humans as well as epidemiological studies consistently find that SHS exposure leads to induction of endothelial dysfunction and other early features of atherogenesis after short-term exposures and the progression of atherosclerosis with long-term exposures [26,48,49].

Epidemiological studies show associations between chronic CO exposure, a major component of HAP, and increased CIMT [9], but these studies have not clearly distinguished the effects of CO and other correlated pollutants. Experiments with animal models have not implicated CO in the pathways leading to atherosclerosis [51]. A 2009 report from the Institute of Medicine concludes that, overall, the data indicate that CO at concentrations present in SHS is unlikely to initiate atherogenesis [52].

Polycyclic aromatic hydrocarbons, including benzo[a]pyrene and 1,3-butadiene, found in high concentrations in the vapor phase of biomass fuel smoke, have been shown to accelerate atherosclerotic plaque development in cockerels [50]. Oral administration of acrolein has been shown to increase atherosclerosis in susceptible animals [19].

Effects on markers of coagulation. Alterations in coagulability using circulating markers have been extensively validated as surrogate markers of CVD risk. Ray et al. [53] measured blood markers of platelet and leukocyte activation in 165 women from eastern India who cooked solely with wood, dung, and agricultural wastes and compared it with 155 women who cooked with LPG. The investigators reported increased activation of platelets and leukocytes and increased formation of leukocyte-platelet aggregates in the biomass group versus the LPG group. These findings suggest that alterations in blood rheology favoring coagulation and a prothrombotic condition are associated with biomass fuel use. However, compared to women in the biomass group, women in the LPG group were significantly healthier, were less likely to live with smokers or use smokeless tobacco, and had significantly higher family income.

In a follow-up study in the same region, Dutta et al. [37] evaluated platelet activation in 244 women who cooked with biomass fuel and 236 women who cooked with LPG and found statistically significantly higher measures of platelet activation (e.g., platelet p-selectin expression) in the biomass group.

In a controlled exposure study, Barregard et al. [54] exposed 13 men and women to wood smoke for 4 h in a laboratory setting and observed increased

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plasma levels of factor VIII and the ratio of factor VIII to von Willebrand factor compared with after exposure to 4 h of laboratory air. These results suggest potential effects of acute exposure to wood smoke on the coagulation cascade. In contrast, Ghio et al. [55] exposed 10 men and women to filtered air and then to wood smoke for 2 h and found no changes in blood levels of markers of thrombosis, including von Willebrand factor, D-dimer, plasminogen, plasminogen activator-1, and tissue plasminogen activator. The effects of longer exposures on these biomarkers were not evaluated.

Reed et al. [56] exposed rats and mice to realistic environmental levels of wood smoke for 1 week and found modest increases in platelet numbers, but no other notable cardiovascular effects. No consistent effects were observed when coal smoke was considered instead [57].

Fine particulate matter pollution in outdoor air is associated with prothrombotic alterations, such as platelet activation and elevations in procoagulant factors (e.g., tissue factor, fibrinogen), and enhanced global metrics of thrombosis formation have been shown to occur in response to ambient air pollution [5]. Inhalation of acrolein, an unsaturated aldehyde in HAP, results in platelet activation and a prothrombotic state in mice [58].

Effects on oxidative stress and inflammation. Inflammation and oxidative stress mechanisms are the central pathophysiological mechanisms in atherosclerosis and have been used previously as surrogate markers to provide supportive evidence for CVD risk factors. Barregard et al. [54] described the first controlled human exposure to wood smoke that evaluated physiological changes directly relevant to CVD. Healthy humans were exposed to wood smoke at 240 to 280 $\mu g/m^3$ during 2 4-h sessions 1 week apart, relatively low cumulative exposures compared with those experienced daily by many women in LMIC households [59]. Immediately, 3 and 20 h after exposure, the participants had elevated levels of serum amyloid A. This acute-phase protein, a predictor of cardiovascular risk [60,61], increases rapidly during various conditions associated with inflammation and is thought to play a role in atherosclerosis [61]. After removal of 1 outlier, this controlled human exposure experiment also showed increased urinary excretion of 8-iso-prostaglandin $F_{2\text{-alpha}}$, a major isoprostane and marker of free radical–mediated lipid peroxidation. The investigators suggest this effect may be directly caused by oxidative stress or may be associated with inflammation via induction of cytokines due to free radicals or oxidative stress.

In a subsequent report on this study, Barregard et al. [62] presented further evidence of lipid peroxidation, indicated by elevated levels of malondialdehyde in breath condensate. They also presented evidence of inflammation in the distal airways, indicated by increased fraction of exhaled nitric oxide at exhalation flow rate 270 ml/s ($FENO_{270}$) 3 h after exposure. Moreover, they found increased Clara cell protein 16 in serum 20 h after exposure. Because this protein is secreted in the lungs, the investigators attribute increased serum levels to increased permeability of the air-blood barrier. Dubick et al. [63] found evidence of oxidative stress in the lungs but not the hearts of rats acutely exposed to high doses of wood smoke. Pulmonary inflammation from HAP may lead to systemic inflammation that could affect the cardiovascular system.

Oxidative damage, whether by direct action of SHS components on target organs or indirectly through stimulation of inflammatory responses of immune cells, is thought to be a critical step on a pathway leading to damage of the vascular endothelium. After accounting for dietary intake, SHS exposure is associated with lower levels of plasma antioxidants, such as beta-carotene and vitamin C, which provide protection against free radicals [64]. Nonsmokers exposed for 3 h to high levels of side stream smoke had significantly increased migration of stimulated neutrophils and release of reactive oxidants by neutrophils [65].

AOP is associated with activation of systemic innate immune responses (e.g., elevated cytokines and activated cellular immune responses) and cardiovascular tissue oxidative damage [5].

Effects on electrocardiographic markers. Prior studies of HAP exposure have examined alterations in ST-segment changes on electrocardiograms as well as heart rate variability (HRV) measures as surrogate markers of CVD risk. In a substudy within RESPIRE in Guatemala, McCracken et al. [66] found that replacement of open fires with chimney stoves led to a statistically significant reduction in the relative risk of having a 30-min average ST-segment below −1.0 mm. Although these changes were in relatively young and healthy adults and may not be construed as evidence of clinical ischemia, these changes suggest alterations in repolarization in response to HAP exposure. McCracken et al. [66] found no evidence to suggest an effect of chimney stove replacement on time-domain or frequency-domain measures of HRV.

In contrast, Ghio et al. [55] exposed 10 men and women in the laboratory to filtered air and then to wood smoke for 2 h and found no evidence of changes in myocardial repolarization as assessed by corrected QT interval, P-wave complexity, T-wave complexity, QRS complexity, or corrected QT dynamics. Comparison to other studies is difficult because the investigators did not report any measures of ST-segment changes and the clinical or physiologic significance of these measures of complexity of the P-wave, T-wave, and QRS complex are unknown. Ghio et al. [55] did find an 11.2% increase in the normalized high-frequency ($p = 0.07$) component of HRV, a 19.4% increase in the ratio of the high-frequency to low-frequency components ($p = 0.10$), and a 16.8% decrease in maximal heart rate ($p = 0.016$) immediately following exposure to wood smoke as compared to immediately after air exposure, but no evidence of changes in time-domain measures of HRV.

The gas phase of wood is known to contain high concentrations of free radicals and radical precursors [67], which may produce toxicity via production of reactive oxygen species in the airways, leading to inflammation and stimulation of afferent nerves of the autonomic nervous system. Acute CO poisoning, which occurs at much higher CO levels, has historically been associated with myocardial ischemia [68] and the development of cardiac arrhythmias, including conduction disorders, atrial and ventricular fibrillation, and atrial and ventricular premature beats [69,70]. Fine particulate air pollution has been associated with reduced heart rate variability in controlled exposures of animals, controlled exposure of healthy adults and those with chronic obstructive pulmonary disease, and observational studies in the community. Ambient particulate matter has also been associated with increased arrhythmias, cardiac repolarization abnormalities, and myocardial ischemia. These studies are summarized in recent reviews [5]. Supporting evidence is also found from SHS exposures that have been shown to reduce heart rate variability after short-term exposure [71].

Effects on myocardial stretch. Exposure to wood smoke and other forms of HAP have long been implicated in the development of cor pulmonale and right heart dysfunction, especially in LMIC. As Pandey describes in this issue of *Global Heart* [72], case series form the bulk of the evidence of this linkage. Brain (B-type) natriuretic peptide (BNP) is a hormone released primarily from ventricular myocytes in response to myocardial stretch [73]. Plasma BNP levels have been shown to correlate well with left ventricular end-diastolic pressure and New York Heart Association classification of symptoms, can be used to discriminate pulmonary from cardiac causes of dyspnea in prospective studies, and are associated with greater mortality [74,75]. BNP levels also correlate negatively with right ventricular ejection fraction and 6-min walk distance, and positively with mean pulmonary arterial pressure and right ventricular end-diastolic pressure [76,77], even in the absence of left-sided heart disease [78]. There has been one study examining the effect of exposure to HAP on plasma BNP level as a marker of myocardial stretch and right ventricular function. In a cross-sectional case-control study of 39 women with, and 31 women without exposure to HAP, Emirolgu et al. [79] assessed pulmonary and ventricular function and BNP levels. They found that women with a reported history of exposure to HAP (167 ± 107 h/year) had worse measures of right ventricular size and function and higher BNP levels than did women without HAP exposure, in addition to worse indices of pulmonary function. BNP levels were significantly correlated with right ventricular end-diastolic volume and pulmonary arterial systolic pressure, but not with other measures of right-sided structure and function (e.g., such as right atrial dimensions, tricuspid annular plane systolic excursion). Due to the cross-sectional nature of this study, it is not possible to identify the causal pathway to elevated BNP levels and whether impaired lung function is a mediator or a confounder. Moreover, socioeconomic status of cases and control subjects were not reported. Despite these limitations, the investigators conclude that right ventricular function is impaired in women exposed to HAP and that BNP levels may be helpful to monitor these patients.

These findings are supported by the observation that AOP is related to heart failure exacerbations and elevated right-sided cardiac pressures [80,81]. Prolonged AOP exposures have also been shown to promote left ventricular hypertrophy [5].

Nieman et al. [82] found that acute exposure to wood smoke profoundly but transiently increased pulmonary vascular resistance in experimental dogs. Additionally, oral administration of acrolein in rats resulted in hemodynamic derangements that led to dilated cardiomyopathy [20].

DISCUSSION

HAP is considered a major global health problem, and until now, it was primarily seen as a risk factor

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for respiratory disease outcomes. Exposures to combustion-generated pollutants from other sources, such as automobiles and smoking, have been shown to increase the risk of CVD events and mortality. We reviewed literature on studies of subclinical, physiological changes associated with HAP exposure that may represent increased susceptibility to CVD. The most important evidence to date relates to the impacts of HAP exposure on blood pressure and hypertension, which have now been reported in 5 studies from Central America and Asia, including 1 stove intervention study and others with personal exposure measures and fairly rigorous adjustment for potential confounding bias. Other studies have found associations with nonspecific ST-segment depression, endothelial dysfunction, blood coagulation, systemic inflammation and oxidative stress, and increased myocardial stretch (Fig. 1).

The strength of evidence from these studies varies considerably. The RESPIRE cardiovascular substudy, which was nested within a randomized trial of an improved cooking stove and also measured within-subject changes in blood pressure before and after the intervention, provided strong evidence that reducing biomass smoke exposure lowers blood pressure. Chamber experiments with controlled wood smoke exposures among humans have provided clear evidence of several effects, including systemic oxidative stress and inflammation and increased coagulation of the blood, and weaker and unexpected evidence regarding increased high-frequency HRV. Among the observational epidemiological studies of HAP and CVD effects, few studies actually measured HAP exposure, with most assigning exposure based on fuel type. Confounding is an important potential limitation of several studies because use of cleaner fuels typically depends on socioeconomic status [83], which is associated with several CVD risk factors.

The value of the surrogate markers evaluated in past HAP studies for predicting clinically meaningful CVD events is not always clear. The effect of HAP on blood pressure is important because blood pressure is a known determinant of CVD risk [84]. The findings from RESPIRE are particularly valuable because they show a long-term improvement in blood pressure resulting from a stove intervention. Whereas a person's typical blood pressure determines CVD risk, the relevance of short-term changes in blood pressure for CVD is less clear. Similarly, the importance of short-term changes in inflammation and endothelial function are less clear than would be chronic effects on these parameters.

Given the limited epidemiological evidence specifically linking HAP with cardiovascular events, it is instructive to consider epidemiologic and mechanistic observations linking cardiovascular events with exposures to other air pollutant mixtures that have been more extensively studied, such as AOP and SHS [5,26]. As has been summarized under each physiologic endpoint in this review, preliminary mechanistic and short-term studies that have examined the effects of HAP appear to suggest similarities to the health effects of AOP and SHS. These similarities aside, there are important differences in composition that may render the cardiovascular effects of HAP different from those seen with AOP and SHS.

There is a well-established linear dose-response relationship between AOP levels and the risk for CVD events (e.g., myocardial infarction, stroke, and hospitalization for heart failure exacerbation) and no evidence of a threshold below which the cardiovascular effects abate [5,85,86]. When pooling AOP, SHS, and active smoking studies together, an interesting log-linear relationship emerges, wherein the exposure-response relationship is steep at levels typical for AOP, with the slope tapering off dramatically at levels seen with SHS and active smoking [85]. Given the nature and concentration of particles encountered with HAP (i.e., levels between SHS and active smoking), it is reasonable to suppose that HAP exposures would cause an intermediate level of adverse cardiovascular health effects with respect to these 2 exposure types or at the very least cause effects that are comparable to AOP [86].

In sum, we believe that the indirect evidence of CVD effects from HAP, including the numerous adverse responses known to be induced by other combustion-generated air pollutants (i.e., SHS and AOP), the similarities in pollutant characteristics and exposure conditions, and the evidence of a generalized dose-response relationship between particulate air pollution and CVD add to evidence from the existing few studies examining adverse cardiovascular effects induced by HAP. Together, this totality of evidence is compelling that HAP is likely to be hazardous to cardiovascular health.

Although providing stronger direct evidence for the role of HAP in the development of CVD is challenging because of the field conditions in

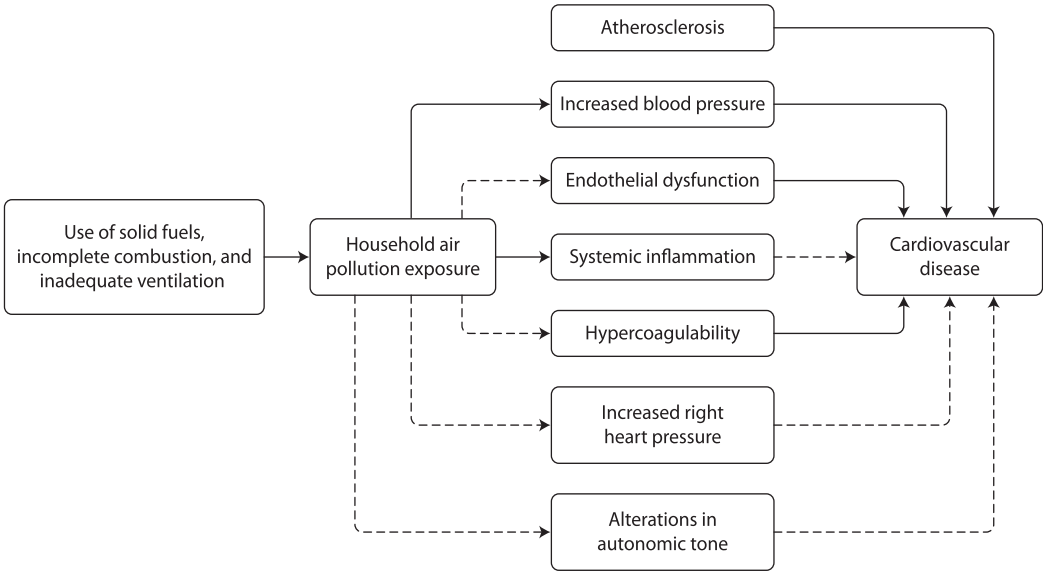

Fig. 1. Schematic representation of hypothesized mechanisms for relationship between household air pollution (HAP) and cardiovascular disease (CVD). Solid lines represent stronger evidence and dashed lines represent weaker evidence. Strong evidence for the link between HAP and surrogate outcomes means it is based on randomized controlled trials or carefully conducted observational studies with adequate control for confounders and valid exposure assessment. Strong evidence for the link between surrogate outcomes and CVD means that these markers are widely accepted as determinants of CVD. The absence of an arrow means there is no evidence of a relationship from HAP studies.

many LMIC, including the typically lacking or incomplete data on exposures and health outcomes, HAP-related research also presents a unique opportunity for improved understanding of the effects of air pollution from combustion sources. Fortunately, there are relatively simple solutions to reduce HAP exposures. Cleaner sources of household energy, such as gas and electricity, have already been adopted by approximately one-half the world's population and are associated with substantially lower levels of HAP exposure, even in communities with high prevalence of solid fuel use [87,88]. Ventilation has been shown to be a major determinant in some areas [87], and biomass stove interventions, by improving combustion efficiency and venting emission out of the home, can provide substantial reductions in exposure that can be maintained over time [25].

CONCLUSIONS

Epidemiological and toxicological evidence suggest that HAP affects the cardiovascular system in ways that may lead to increased CVD risk. It is debatable whether basing major policy decisions on these studies alone would be prudent, and research in this area needs be strengthened. However, the indirect evidence from studies of AOP and SHS, similar mixtures of combustion-generated pollutants, and the known effects of several HAP constituents suggest that HAP may be an important population-attributable risk factor for CVD and provide ample reason for promotion of preventive interventions to reduce HAP exposures, particularly among poor, vulnerable populations whose primary risk for eventual mortality is through cardiovascular causes.

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