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REVIEW

Household Air Pollution in the Early Origins of CVD in Developing Countries

Cristina Rabadán-Diehl *, Dewan Alam †, Jill Baumgartner ‡,§

Bethesda, MD, USA; Dhaka, Bangladesh; St. Paul, MN, USA; and Beijing, China

The predisposition for developing cardiovascular disease (CVD) can start as early as our development in the womb where alterations in the intrauterine environment, such as malnutrition, stress, and environmental exposures, result in a higher vulnerability of the offspring to develop diseases later in life. Household air pollution from cooking and heating with wood and other biomass fuels has been shown to contribute to the development of CVD in adults, but the relationship of household air pollution exposure and the early origins of CVD remains largely unexplored. In this paper, we review the evidence linking in utero and/or childhood exposures to tobacco smoke and ambient air pollution exposures with the development of CVD in later life, as well as identify important knowledge gaps and research opportunities.

Cardiovascular diseases (CVD) are the leading contributor to the global burden of disease, accounting for over 17 million deaths in 2004 [1]. The global CVD burden is projected to increase with its distribution continuing to shift toward low- and middle-income countries (LMIC), a progression driven by substantial CVD declines in high-income countries and a sharp rise in CVD in LMIC over the past several decades.

Physiopathological and epidemiologic evidence suggest that precursors of CVD begin very early in life, even though they manifest in adulthood. In 1985, the landmark PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study aimed to improve knowledge of the natural history of atherosclerotic disease in children and young adults in the United States. The objective was to investigate the associations between early signs of atherosclerosis among children and young adults with known risk factors for adult coronary heart disease. A total of 3,000 specimens were collected and fatty streaks, early and advanced atherosclerotic lesions, were identified in adolescents and young adults many years before the occurrence of coronary heart disease [2]. They also found that known risk factors for CVD in adults such as tobacco smoking, obesity, and hypertension were associated with atherosclerotic lesions in adolescents and young adults, supporting the concept that the development of CVD starts in the first decades of life.

Around this same time, British epidemiologist David Barker began gathering evidence on the links between infant health and the later development of disease, in particular identifying a strong correlation between poor maternal nutrition, low birth weight, and the later-life development of CVD in those low birth weight infants [3,4]. This and further studies helped formulate the fetal origins of adult disease hypothesis, better known as the "Barker hypothesis" or the "Developmental Origins of Health and Disease hypothesis" [5,6], which postulates that alterations in the intrauterine environment during pregnancy, particularly undernutrition of the mother, influence the developing fetus and predispose it to the development of diseases in adulthood. In recent decades, both animal and human studies have gathered additional evidence in support of this hypothesis with associations between poor maternal nutrition and other health outcomes in their offspring including diabetes [7], lung diseases [8], cancer [9], and osteoporosis [10]. Other risk factors during pregnancy including maternal

From the *National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; †Centre for Control of Chronic Diseases, International Centre for Diarrheal Disease Research—Bangladesh, Dhaka, Bangladesh; ‡Institute on the Environment, College of Food, Agriculture and Natural Resource Sciences, University of Minnesota, St. Paul, MN, USA; §Department of Building Science, Tsinghua University, Beijing, China. Correspondence: C. Rabadán-Diehl (rabadanc@nhlbi.nih.gov).

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hypertension and diabetes, obesity, stress, and environmental exposures, such as tobacco smoking, have also been correlated with adult disease in offspring.

The increasing CVD trend in LMIC can in part be attributed to demographic and social changes including economic growth and globalization, lifestyle changes with urbanizing societies, and increased life expectancy. Surveillance data from Bangladesh show a several-fold increase in noncommunicable disease mortality over the last 20 years, over 70% of which is attributable to CVD [11]. However, the disproportionate burden of CVD in populations that have been exposed to malnutrition and environmental exposures for generations speaks to a greater role of developmental origins, in particular environmental determinants.

Household air pollution (HAP) from use of solid fuel (i.e., biomass and coal) for cooking and heating is a major environmental exposure and leading contributor to the global burden of disease [12]. Incomplete combustion of solid fuel emits high levels of air pollution, including known health hazards such as particulate matter, benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons (especially benzo[a]pyrene), radon, trichloroethylene, and tetrachloroethylene [13]. Women and young children in LMIC are particularly vulnerable to HAP exposure as they spend the most time near the domestic hearth [14]. In fact, an estimated 80% of total air pollution exposure occurs indoors, rather than outdoors, in LMIC [15].

Mounting evidence shows an association between HAP and a range of health outcomes including respiratory illnesses in adults and children [16,17], cancer [18], and more recently, cardiovascular outcomes such as higher blood pressure [19,20] in adults. A recent cross-sectional study examined the impact of personal exposure to HAP on blood pressure in school-aged Chinese children [21]. However, no other studies have investigated the potential contribution of HAP exposure in utero or in early childhood to the later development of disease, and in particular CVD, despite the magnitude and increased vulnerability of exposure to HAP in utero (via mother's exposure) and during childhood and growing evidence of CVD impacts from early life ambient air pollution and tobacco smoking exposures. With the increasing global epidemic of CVD in LMIC, there is a pressing need to inform the development of interventions and policies that affect multiple CVD determinants and provide protection over the life course.

In this review, we will present current evidence linking in utero and/or childhood exposures to environmental pollution exposures with the development of CVD later in life, focusing on environmental tobacco smoke and ambient air pollution exposures because they are likely the most relevant to HAP exposures. When we refer to early origins of disease, we are including a time that spans from conception to pre-pubertal age (around 12 years old). We will also identify important knowledge gaps and opportunities for future research.

IN UTERO AND ENVIRONMENTAL EXPOSURE TO PARENTAL TOBACCO SMOKING

The association between in utero tobacco smoke exposure and CVD risk factors in individuals whose mothers smoked during pregnancy is the subject of several recent investigations. A study in the Netherlands [22] looked at the effect of maternal smoking (self-reported by mothers during prenatal visits) on blood pressure (BP) in infant offspring at 2 weeks of age. The analysis showed higher systolic BP (5.4 mm Hg) in infants whose mothers reported smoking during pregnancy. However, observational cohort studies with children ages 4 to 8 years old in other countries found either no effect of in utero maternal smoking on offspring BP [23–27] or even a small increase in systolic BP [28–31]. It is important to note, that most of these observational studies failed to account for post-natal environmental tobacco smoke exposures. However, a cross-sectional study in Germany found a small, but positive relationship between post-natal parental smoking and BP (systolic: 1.0 mm Hg; diastolic: 0.5 mm Hg) in healthy preschool children [32].

Other CVD markers, have been associated with maternal smoking during pregnancy. Aortic intima media thickness (IMT) was significantly greater in a group of 28 Turkish neonates whose mothers smoked during pregnancy [33]. Similar results have been shown for carotid artery IMT in 5-year-olds [34] and young adults [35] exposed to in utero maternal smoking in the Netherlands. Exposure to environmental tobacco smoke was associated with attenuated endothelial function and decreased elasticity of abdominal aorta in pre-pubertal Finnish children [36,37].

In animal models, perinatal tobacco smoke exposure in mice has been shown to increase adult atherogenesis by increasing mitochondrial damage and oxidative stress [38,39]. Similar studies in

nonhuman primates demonstrated low mitochondrial SOD2 activity and decreased SOD2 protein levels, as well as mitochondrial damage as shown by increased levels of mitochondrial deoxyribonucleic acid damage and lower levels of cytochrome oxidase (complex IV) in aortic tissues [40]. Oxidized proteins were significantly higher in monkeys exposed to tobacco smoke in utero. Further, histological analysis of abdominal aortic tissue samples showed indications of early atherogenic changes as indicated by an increased number of cells within the subintima. Together, these animal studies indicate that perinatal tobacco smoke induces in the offspring very early changes at the vascular level by inducing mitochondrial damage and promoting atherosclerosis.

Dyslipidemia and obesity are risk factors for the development of CVD. The effects of maternal smoking on her progeny's lipoprotein profile are currently under investigation. A cross-sectional analysis of 4,297 subjects in Brazil found high-density lipoprotein cholesterol differences (2.10 mg/dl; 95% confidence interval [CI]: −3.39 to −0.80) for offspring of smokers compared with offspring of nonsmokers [41]. However, no other cardiovascular risk factors, including BP, were affected in exposed children. Data from animal models have shown either no changes in high- or high-density lipoprotein with tobacco smoke exposure [38] or a significant increase [42]. Interestingly, a study by Ng et al. [42] found that mice exposed to tobacco smoke in utero and fed a high-fat diet gained more weight and experienced a greater increase in their lipoprotein concentrations than unexposed mice on the same high-fat diet, although this effect was only observed in female mice.

The placenta has been shown to be a critical organ in the area of developmental programming [43,44]. Several factors can affect placental development, which could later alter placental function. In the Netherlands, maternal smoking was associated with an increased resistance in uterine, umbilical, and middle cerebral arteries. Fetal and birth weights were reversely correlated with umbilical artery resistance [45]. Several studies examined the relationship between placental function and tobacco smoking, in particular carcinogenic polycyclic aromatic hydrocarbons (PAH), which have been associated with adult CVD [46]. Whether PAH cross the placental–blood barrier remains a subject of current investigation. Several studies indicate that PAH reach both placental and cord blood, and that elevated PAH–deoxyribonucleic acid adducts are correlated with low birth weight and reduced length and head circumference in offspring [47]. Others suggest that tobacco smoking increases placental metabolism of PAH during pregnancy [48], which is indicative of transplacental transport. However, a recent study showed a protective effect of the placental barrier against some tobacco components, including PAH, suggesting an impedance of transplacental transfer of PAH to the fetus [49].

Even though evidence from both animal and epidemiologic studies strongly suggests a relationship between in utero and environmental exposure to tobacco smoke and development of CVD risk factors, the current evidence is scattered and some of the data inconsistent, in particular as it relates to BP.

AMBIENT PARTICULATE MATTER AIR POLLUTION

There is a large and growing body of literature on the relationship between particulate matter (PM) air pollution and CVD outcomes in adults. PM air pollution exposure has been associated with increased risk of myocardial infarction, stroke, and cardiovascular mortality as well as subclinical inflammation [50]. Studies in Italy have reported that exposure to PM and gaseous air pollutants is associated with blood hypercoagulability and deep vein thrombosis, which may cause cardiac events [51,52]. Less intensive exposure to pollutants other than smoking has also been implicated for early origins of adverse cardiovascular outcomes. Carotid artery stiffness has also been shown to be higher among children living in more polluted areas (closer to main road) than in less exposed children [53]. It is likely that exposure to ambient air pollution can initiate atherosclerosis, evoke inflammatory and pro-thrombotic effects, and elevate the risk of CVD in children [54]. Limited evidence suggests possible adult cardiovascular effects of PM pollution from cooking with wood fuel, including higher BP [19,20] and increased risk of diabetes and stroke [55].

Despite the increased vulnerability of children to environmental exposures such as PM air pollution [56], relatively little is known about its effects on cardiovascular and chronic systemic responses in healthy children, with very few studies focusing on the relationship between air pollution and developmental origins. A recent cross-sectional study found no relationship between measured personal PM exposure and BP among Chinese children in households cooking with wood [21]. Studies on pregnant

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women's PM pollution exposures and the subsequent health outcomes of their offspring are lacking, in particular as they relate to HAP and CVD.

Although no studies have been published on the effect of in utero exposure to ambient PM, a recent study in Mexico reported positive associations between short-term ambient PM exposure and day-to-day elevations in inflammatory markers including interleukin 1 in children [57]. Chronic exposure to elevated fine PM (particles <2.5 μg in diameter [$PM_{2.5}$]) was also associated with increased levels of circulating endothelin 1 and elevated mean pulmonary arterial pressure in children [58]. A study in Iran found that previous 7-day exposure to coarse PM (particles <10 μg in diameter [PM_{10}]) was independently associated with worse metabolic insulin sensitivity among 374 children ages 10 to 18 years [59]. This study, along with several in adult populations not reviewed here, suggests that systemic proinflammatory and oxidative responses due to long-term PM air pollution exposure could potentially increase the risk of developing clinically important aspects of the metabolic syndrome, such as diabetes mellitus.

Prenatal exposures to ambient $PM_{2.5}$ have been linked to low birth weight, and a recent study [60] in the United States found that certain chemical constituents of $PM_{2.5}$, in particular those emitted from fuel oil combustion, were more strongly associated with lower birth weight than PM from other sources. Maternal exposure to HAP from biomass combustion has also been reported to be associated with low birth weight and pre-term delivery [61,62], with a recent meta-analysis estimating that as much as 21% of global low birth weight is attributable to HAP exposure during pregnancy [63]. Such a strong contribution of HAP to poor fetal growth has implications for CVD risks later in life as already discussed in this paper. Biological mechanisms for explaining how exposure to air pollutants affect birth outcomes (low birth weight/intrauterine growth retardation/pre-term delivery) have been reviewed elsewhere [64], suggesting that processes such as oxidative stress, inflammation, endothelial dysfunction, hemodynamic responses, and disturbances of rheological factors are likely to be involved.

An animal study looking at the effects of PM air pollution on placental morphology found that fetal weights were lower in the offspring of air pollution–exposed mice. There was also a decrease in placental weight with a change in morphology, including reduced volumes, calibers, and surface areas of maternal blood spaces but greater capillary surfaces and diffusive conductance in the fetus [65]. These changes could be interpreted as fetoplacental adaptations to maintain and expand oxygen and nutrient delivery to the growing fetus because maternal blood delivery to the placenta seems to be compromised. The actual mechanism involved in those changes remains to be elucidated.

INSIGHTS FROM OTHER ENVIRONMENTAL POLLUTANTS

Methylmercury (MeHg) and lead are two widespread environmental pollutants that have been linked to cardiovascular effects in infants and children, although as with maternal and environmental tobacco smoking, the data are inconsistent. Adult lead exposure is an established risk factor for hypertension and CVD in older age; however, the role of prenatal and childhood lead exposure in cardiovascular risk is unclear. Prenatal lead exposure measured using cord blood was associated with elevated systolic BP and peripheral vascular resistance in a cohort of 122 children followed from birth to 9.5 years old in the United States [66], whereas in a cohort in Mexico (age 7 to 15 years) showed no association between mother's cord lead levels and offspring BP [67]. The timing of fetal dose in these studies remains unclear as cord lead represents fetal exposure just prior to delivery, rather than throughout the entire pregnancy.

There are only a few studies on the association between MeHg exposure and cardiovascular risk in children. MeHg and BP associations have been identified in several child populations. In the Faroese cohort, Sørensen et al. [68] observed associations between prenatal (cord blood) MeHg exposure and increased BP, with slightly weaker relationships observed with maternal hair MeHg. However, the study was repeated in the same cohort at age 14 years and the effect of prenatal MeHg exposure on BP was no longer apparent [69]. In the Seychelles Child Development Study, prenatal MeHg exposure was associated with increased diastolic BP in boys at age 15 years [70] with no effect observed in girls or with systolic BP for either sex.

Associations between MeHg and heart rate variability have also been observed in children [69,71] although the direct significance of decreased heat rate variability in young children for later development of CVD is unknown. Prenatal (cord blood) MeHg exposure was associated with a 47% decrease in heat rate variability, but it had no effect on heart

rate [69]. The investigators suggest that these effects are attributable to the action of MeHg on the parasympathetic nervous system. In a case-control study, subjects with Minamata disease (from mercury poisoning) had a significantly decreased pulse pressure and lower parasympathetic nervous activity than control subjects did, although BP did not differ between groups [72]. They also had a significantly elevated resting heart rate, but heat rate variability did not differ between groups. Similar to Sørensen et al. [68], Oka et al. [72] proposed that a parasympathetic nervous system dysfunction occurred after prenatal MeHg exposure. Overall, evidence of cardiovascular effects of MeHg exposure is not very strong. However, the few studies on this topic suggest that prenatal exposure may have a role in the development of cardiovascular complications during adult life.

FUTURE RESEARCH DIRECTIONS AND OPPORTUNITIES

Collectively, these studies on environmental pollutants such as tobacco smoke and ambient PM air pollution support the notion that early life HAP exposure may be an important determinant of adult CVD risk and a contributor to the growing burden of CVD in LMIC. Yet assessing this potential relationship presents a major challenge given the likely complex interactions between HAP exposure and nutritional and genetic factors, the temporal variation in HAP exposure concentrations and doses over the life course, and the considerable logistical constraints of conducting research in the low-resource settings where HAP is most common. Having identified the gaps in our knowledge, we suggest some areas for further research that can shed light on HAP exposure at different developmental points, assess the potential magnitude of this risk, and delineate specific mechanisms by which pollution exposure affects CVD.

Longitudinal birth cohort studies are one design for detecting and evaluating the impact of HAP on children's health by following their development from conception through early childhood, adolescence, and into adulthood. Most birth cohort studies on environmental pollution have been launched in developed countries and are relatively rare in LMIC, where pollution exposures tend to be highest and may pose an even larger health burden. However, recent large birth cohorts in Bangladesh on in utero/neonatal arsenic exposure [73] illustrate their feasibility and utility in low-resource settings. Though costly and often logistically complex, the collection of extensive data and specimens starting from the pre-conception or prenatal period and into childhood provides the unique opportunity to quantify the cardiovascular impacts of early life HAP exposure, identify underlying mechanisms, and shed light on the impacts of interactions between HAP exposure and other environmental and epigenetic changes over time.

Intervention studies such as RESPIRE, a randomized trial looking at the effect of HAP on respiratory function in women and children under 2 years of age [74,75] and the Intermediate Technology Development Group studies [76] can be further extended to evaluate cardiovascular outcomes such as blood pressure, potential inflammatory biomarkers, and carotid artery IMT in relation to the change in HAP exposure with the intervention. Another opportunity is to use a natural experiment of long-term exposure to solid versus clean fuel, like the one existing in rural Matlab, Bangladesh. Leveraging existing cohort studies that already involve collection of important, related variables is cost-effective and allows for a faster evaluation of cardiovascular outcomes that otherwise may be difficult in long-term prospective study designs.

Another major challenge is obtaining accurate in utero, neonatal, and childhood exposure measurements and, in particular, estimating inhaled exposure dose. Day-to-day changes in human behavior coupled with substantial variability in spatial and temporal pollutant levels limit the accuracy of stationary samplers as a proxy for maternal or child exposure. Personal PM exposure monitoring is more accurate, but most monitors are too large and/or heavy for children to carry for long periods. In fact, past epidemiologic studies on HAP in pregnant women have all relied on proxy measurements of PM pollution exposure [77] and just 2 studies have measured personal PM pollution exposure in children [78,79]. The development and validation of robust, lightweight PM monitors is an important step. Further, biomarker analysis may also provide sensitive tools to trace even subtle changes in exposure and dose in mothers before conception, during pregnancy, and in children after birth. Several recent studies indicate that biological tissues such as blood and urine samples [80–84] may provide information that reflects the dose of HAP exposure from wood and other biomass combustion during pregnancy or at birth, as well as during childhood. However, further research that identifies appropriate biomarkers for HAP exposure assessment and also

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demonstrates the feasibility of measuring these biomarkers in remote, low-resource settings is needed.

The importance of the detrimental effects of HAP to the health of women and children globally has been acknowledged by the U.S. government and the United Nations Foundation. Together, in 2010, they formed the Global Alliance for Clean Cookstoves, an innovative public–private partnership whose mission is "to save lives, improve livelihoods, empower women, and combat climate change by creating a thriving global market for clean and efficient household cooking solutions" [85]. Recent funding opportunities include research on cook stoves and child survival, with special focus on adverse pregnancy outcomes and low birth weight, and severe respiratory illness in young children. Initiatives like this allow the research community to examine the role of HAP in the early origins of diseases and will provide the evidence needed for effective interventions that will ultimately improve the health of people in LMIC.

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