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Genetic modification of the effect of maternal household air pollution exposure on birth weight in Guatemalan newborns

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ABSTRACT

Low birth weight is associated with exposure to air pollution during pregnancy. The purpose of this study was to evaluate whether null polymorphisms of Glutathione S-transferases (GSTs), specifically GSTM1 and GSTT1 genes in infants or mothers, modify the association between high exposures to household air pollution (HAP) from cooking fires and birth weight. Pregnant women in rural Guatemala were randomized to receive a chimney stove or continue to use open fires for cooking. Newborns were measured within 48 h of birth. 132 mother–infant pairs provided infant genotypes ($n = 130$) and/or maternal genotypes ($n = 116$). Maternal null GSTM1 was associated with a 144 g (95% CI, −291, 1) and combined maternal/infant null GSTT1 was associated with a 155 g (95% CI, −303, −8) decrease in birth weight. Although there was a trend toward higher birth weights with increasing number of expressed GST genes, the effect modification by chimney stove use was not demonstrated.

1. Introduction

Low birth weight, a significant cause of infant morbidity and mortality, is associated with maternal exposure to air pollution during pregnancy. Evidence of this association is drawn from at least two dozen studies in developed countries [1–3] where air pollutant concentrations are relatively low and low birth weight (LBW, newborn weight <2500 g) is relatively rare. More than 95% of all LBW infants are born in low income countries [4]. In these countries, approximately 80% of rural households are exposed to a major source of air pollution, smoke inside the home generated by cooking and heating with solid fuels (e.g. wood) [5].

Under these conditions, pregnant women are highly exposed to toxic by-products of combustion from cooking fires, and these maternal exposures impact newborn birth weight. A systematic review with a meta-analysis of five studies that examined the relationship between maternal exposure to solid fuels and birth weight [6–10] found a 38% increased risk of LBW (OR 1.38, 95% CI, 1.25, 1.52) among those exposed to smoke from solid cooking fuel [11]. Two of these studies were conducted in Guatemala [8,10], where 57% of all households [12] and 85% of rural households use wood fuel [5].

Not all pregnant women exposed to air pollution have low birth weight infants. The reason for this may be differential genetic susceptibility. Maternal genetic polymorphisms were found to modify the associations between birth weight and tobacco smoke [13–23] and birth weight and outdoor air pollution exposures [22,24]; several studies even found independent gene effects on birth outcomes [25–27]. Two isoforms of the Glutathione S-transferase super gene family, GSTM1 and GSTT1, have been proposed as candidate genes for susceptibility to inhaled oxidants from air pollutants. The modifying effect that maternal and infant genotypes of GSTM1 and GSTT1 have on exposures to solid fuel smoke and the resulting impact on newborn birth weight are unknown.

Three major air pollutants from solid fuels burned in inefficient, poorly ventilated cookstoves are particulate matter (PM), carbon monoxide (CO) and polycyclic aromatic hydrocarbons (PAHs) [28,29]. The toxicity of PM, a composite mixture of liquid drops and solid particles suspended in air, may be related to the physical and chemical properties of the particles, such as particle size and surface composition [30,31]. For health effects, PM is most commonly classified by the mean aerodynamic diameter of the particle, with smaller particles exerting larger effects. In Guatemala, 48-h kitchen concentrations of $PM_{2.5}$ (PM with aerodynamic diameter <2.5 μm) averaged 636 $\mu g/m^3$ (Standard deviation (SD): 402 $\mu g/m^3$, $n = 50$) in homes using open fires for cooking and 69 $\mu g/m^3$ (SD: 89 $\mu g/m^3$, $n = 49$) in homes using well-maintained chimney stoves [32]. However, even the kitchen concentrations where chimney stoves were

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used exceed the World Health Organization Air Quality Guidelines of 25 $\mu g/m^3$ for $PM_{2.5}$ averaged over a 24-h period [33].

Carbon monoxide (CO) is a product of incomplete combustion released when organic solid fuels, such as wood, are burned with insufficient oxygen supply. Mean CO exposures over a 24-h period have been measured at 2–50 parts per million (ppm) among households that burn solid fuel, and often exceed the 9 ppm standard (in an 8-h period) set by the WHO [34,35]. CO levels in homes using solid fuels are sometimes high enough to result in blood carboxyhemoglobin (COHb) levels between 2.5% and 16%, with upper limits comparable to levels measured in heavy smokers [36–38].

Polycyclic aromatic hydrocarbons (PAHs) are a large class of organic compounds consisting of hydrogen and carbon organized in fused ring structures. PAHs are found on combustion-sourced particles as well as in the vapor phase of combustion emissions. Tobacco smoke is a major source of exposure to PAHs, but cooking and heating with solid fuels is also a major contributor to outdoor and indoor exposures in low resource countries [39–41].

High exposures to combustion by-products may impact fetal growth by several mechanisms, including interference with transplacental delivery of oxygen, which may cause fetal growth retardation, a form of LBW. Due to physical characteristics (e.g. large surface area) and chemical composition (e.g. PAHs adhering to surface of particle), small particles ($\leq PM_{2.5}$) can induce oxidative stress, which causes local inflammation in the maternal pulmonary system, leading to both short-term and chronic damage to the lung [42]. Lung damage decreases maternal oxygen exchange, ultimately affecting oxygen transport to the fetus. In addition, the smallest particles can be transported from the lung across the alveolar-capillary membrane into the blood circulation, where they may exert effects on the cardiovascular system [43]. PAHs are transported by diffusion across membranes in the respiratory and gastrointestinal tract and are absorbed into the bloodstream. PAHs are capable of crossing the placenta [44,45]. Umbilical cord blood PAH-DNA adducts have been associated with decreased fetal growth, after adjusting for maternal environmental tobacco smoke exposures in China [46], Krakow, and New York [47,48]. Carbon monoxide is a potent fetotoxicant that binds with both maternal and fetal hemoglobin, forming carboxyhemoglobin and making oxygen less available for oxygenating tissue (such as the placenta). Exposures to low, constant CO in utero, as measured by maternal carboxyhemoglobin, produce large decrements in oxygen tension in the fetal blood stream [49]. In animal models, maternal exposure to ambient concentrations of elevated CO has been associated with poor fetal development including reduced birth weight [50–52].

Air pollutants are damaging xenobiotic substances in and of themselves, but they also induce harmful endogenous by-products of oxidative stress [53,54]. Genes that modulate oxidative stress are good candidates for investigating the interaction between air pollution and adverse human health. Glutathione S-transferases (GSTs) are a family of detoxifying enzymes that play an important role in protecting cells from reactive oxygen species (ROS), which can cause oxidative stress. GST enzymes conjugate ROS with glutathione, thus allowing the detoxification and excretion of harmful substances, such as ROS. A recent systematic review found suggestion of gene-environment interactions between outdoor air pollution and GST polymorphisms on respiratory lung function, but evidence for specific pollutants acting in concert with specific genes was not conclusively determined [55]. The complete deletion of both alleles (null polymorphism) confers absence of an important detoxifying enzyme, thus potentially increasing individual susceptibility to air pollutants.

Our aim was to evaluate whether the null polymorphisms of GSTM1 and GSTT1 genes in infants or mothers would modify the association between exposure to household air pollution (HAP) from wood fuel use and newborn birth weight. Our a priori hypothesis was that between the low and high HAP exposure groups, we would find differences in birth weight in mothers and/or infants with null genotypes compared to those with non-null genotypes. This is a sub-study of a larger birth cohort reported elsewhere [10], which found that rural, Guatemalan mothers randomized to receive a wellmaintained chimney stove during pregnancy had a 39% reduction in personal exposures to carbon monoxide and had infants who weighed 89 g more than infants whose mothers used open fires during pregnancy. Here we report on the cohort of pregnant women and children who participated in two studies that measured the impact of a randomized chimney stove on child pneumonia and pulmonary growth: the RESPIRE (Randomized Exposure Study of Pollution Indoors and Respiratory Effects) study [56] and the follow-up study CRECER (Chronic Respiratory Effects of Early Childhood Exposure to Respirable Particulate Matter) [57].

2. Materials and methods

2.1. Study population

The study population, located in 23 rural communities in the Western highlands of Guatemala, consists of primarily indigenous Mam-speaking women and children. The majority of the households in these communities used wood fuel for cooking during the study period. Between October 2002 and May 2003, 266 pregnant women who used open fires were enrolled into the RESPIRE study; half were randomized to receive a vented chimney stove. Among women recruited during pregnancy, 254 singleton, healthy newborns were born (five miscarriages, four stillbirths, two pregnancies with multiple gestations, and one child with Down syndrome were excluded). We were able to measure birth weight on 224 (88%) newborns within 1 week and 190 (75%) within 48 h of a home delivery. Between January 2007 and October 2008, a subset of these mothers and their children continued to participate in the follow-up study, CRECER. They provided saliva samples for DNA extraction. Our final sample includes those who had birth weight measured at less than 48 h during the RESPIRE study ($n = 190$) and 132 mother–infant pairs who provided infant genotypes ($n = 130$) and/or maternal genotypes ($n = 116$) during the CRECER follow-up study. Demographic characteristics and exposure data for women and infants in the present analysis were not statistically different from the 254 pregnant women who originally enrolled in the RESPIRE stove intervention trial or the 190 women who had infants weighed in their home within 48 h of birth [10].

The study received approval from the institutional review boards at the University of California, Berkeley and the Universidad del Valle in Guatemala and was conducted in accordance with international guidelines for the protection of human subjects. Before collection of saliva DNA, all adult subjects provided written consent for the use of DNA for research purposes. The mother of the child provided consent for herself and for her child. All children were between 5 and 7 years of age at the time of salivary DNA collection. Local Mam-speaking trained fieldworkers explained the study in simple terms and all questions were answered before consent was signed.

2.2. Birth weight

Recruitment and follow-up of pregnant women and birth weight measurement of their newborns has been described previously [10]. Birth weight was measured in grams using a calibrated Siltec BS1 baby scale with 10-g readability (model 0309, Dogain Instruments, Inc.; Santa Clara CA, USA).