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# Household air pollution and chronic hypoxia in the placenta of pregnant Nigerian women: A randomized controlled ethanol Cookstove intervention

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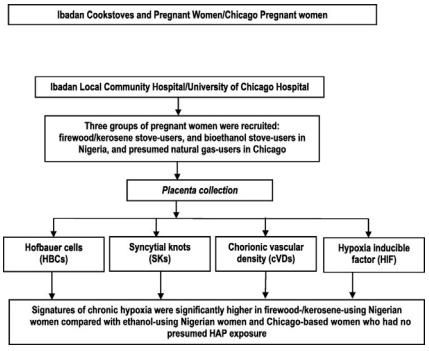
## HIGHLIGHTS

- Effect of household air pollution (HAP) on signatures of chronic hypoxia in placenta was investigated
- Hofbauer cells, syncytial knots, chorionic vascular density and hypoxia-inducible factor were measured in placenta samples
- Pregnant firewood/kerosene and bioethanol stove-users in Nigeria, and presumed natural gas-users in Chicago were recruited
- Chronic hypoxia was significantly higher in firewood-/kerosene-users compared with ethanol-users and Chicago-based women

## GRAPHICAL ABSTRACT

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## ABSTRACT

*Background:* Household air pollution (HAP) is associated with adverse pregnancy outcomes.
*Objectives:* Investigate impact of *in-utero* HAP exposure on placental development and chronic hypoxia.
*Methods:* Markers of chronic placental hypoxia [Hofbauer cells (HBC), syncytial knots (SK), chorionic vascular density (cVD) and hypoxia-inducible factor (HIF)] were stained by hematoxylin-eosin and/or immunohistochemically in placenta samples collected from firewood −/kerosene-users (A,$n = 16$), and ethanol-users (B,$n = 20$) that participated in a randomized controlled intervention trial in Ibadan, Nigeria. A third group of non-smoking and presumed natural gas-using Chicago women (C,$n = 12$) were included in this exploratory pilot to assess for

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possible differences in placenta histology between similar racial groups. All patients had uncomplicated pregnancies and delivered at term.
*Results:* HBC, SK and cVD were significantly increased among firewood-/kerosene-users compared to ethanol-users and natural gas-using Chicago women (HBC medians 5.5, 3.5, and 2.0, respectively; SK means 55.6, 41.8 and 30.1; cVD means 8.8, 6.2, and 5.2; all $p < 0.01$). HIF expression was significantly higher in Group A compared to B and C (all $p < 0.001$).
*Conclusions: In-utero* exposure to HAP is associated with pathologic changes and HIF expression consistent with chronic hypoxia in placenta of firewood/kerosene-users compared to ethanol-users with less HAP exposure and Chicago women with no presumed HAP exposure. Presence of chronic hypoxic signature in placenta of women exposed to HAP has implications for adverse pregnancy complications and future growth and development of the young children. Future larger studies need to focus on HAP exposure and placental disorders like preeclampsia and long-term health impact of *in-utero* exposure to HAP.


## 1. Introduction

Household air pollution (HAP) is the eighth leading risk factor for global disease burden, contributing to 2.9 million yearly premature deaths (Forouzanfar et al., 2016). Nearly 80% of the sub-Saharan population and about 90 million households in Nigeria use biomass as their primary fuel for cooking and energy needs (WHO, 2014), which can adversely impact their health (Olopade et al., 2017; Alexander et al., 2017). Exposure to air pollution has been linked to adverse pregnancy outcomes like stillbirth, preeclampsia, preterm birth, low birth weight, reduced fetal head circumference, miscarriage, and intra-uterine fetal growth retardation (IUGR) (Dadvand et al., 2013; Patelarou and Kelly, 2014; Wylie et al., 2014). Studies on the underlying mechanism that might link exposure to air pollution and pregnancy outcomes are few.

The placenta is the most specialized organ of pregnancy (Gude et al., 2004) and normal pregnancy requires sufficient placentation and functioning, impairment of which may result in maternal and fetal complications (Salafia et al., 2006; Ness and Sibai, 2006). Evidence suggests that *in utero* exposure to particulate matter (PM) with a diameter less than or equal to 2.5 μm ($PM_{2.5}$) affects normal fetal development in humans because of the suboptimal intrauterine environment (Ballester et al., 2010). *In utero* exposure to carbon monoxide (CO) caused severe fetal damage in a 22-year-old pregnant woman who was exposed to carbon monoxide poisoning at 30 weeks of gestation due to a fire in her home (Delomenie et al., 2015). Exposures to CO (Liu et al., 2003; Salam et al., 2005) and sulphur dioxide (Liu et al., 2003; Ha et al., 2001) are positively associated with fetal growth retardation. $PM_{2.5}$, CO, oxides of nitrogen (NOx) and sulphur (SOx), formaldehyde, benzene, benz(a)pyrene (Smith, 2000) and several endocrine disruptors (Wu et al., 2002; Wang et al., 2005) are hazardous pollutants that are components of biomass smoke, which lead to HAP. Perturbations *in utero*-placental exchange of nutrients and oxygen due to these exposures may program the fetus in such a way that the risk of developing cardiovascular disease and diabetes in adult life may increase (Ramadhani et al., 2006; Jansson and Powell, 2007). Placenta forms the interface between fetal and maternal circulation and plays a critical role in the regulation of fetal growth and development through controlled nutrient supply. Systemic inflammation and oxidative stress play important mechanistic roles in mediating the harmful effects of HAP (Dutta et al., 2012) and may play a significant role in the process of regulating fetal growth and development. The hypoxia inducible factor (HIF), a transcription factor that responds to changes in oxygen tension and hypoxia in the placenta, ultimately leading to proper placental development (Fryer and Simon, 2006), may also be a key player. Chronic hypoxia has been shown to impair fetal nutrition and growth by causing hypoperfusion of the placenta (Jakoubek et al., 2008). This may cause critical injury to vital organs (Hutter et al., 2010a) that is causally implicated in fetal growth restriction and preeclampsia (Zamudio et al., 2007) and slows fetal growth (Hutter et al., 2010b). Presence of Hofbauer cells, syncytial knots and chorionic vascular density are signatures of chronic hypoxic placental injury (Stanek, 2012; Stanek, 2013a).

Fundamental mechanisms by which PM exposure may impair fetal growth and development are poorly understood. Therefore, we sought to undertake this pilot study to investigate whether the presence of the signature markers of chronic placental hypoxia (Hofbauer cells, syncytial knots, chorionic vascular density) and expression of HIF, which is intricately involved in regulating and responding to hypoxia, were higher among the firewood/kerosene stove users who were exposed to higher levels of HAP compared to the ethanol stove-users who had reduced exposure to HAP in Ibadan, Nigeria. The Nigerian samples were obtained from a subgroup of pregnant women who participated in a large, randomized control trial that investigated the impact of transitioning from firewood or kerosene to ethanol as cooking fuel on pregnancy outcomes. Furthermore, as a supplement to this study, we investigated and compared the same endpoints among African American women from Chicago who were selected based on their racial similarity with the Nigerian women. The Chicago women typically cook with natural gas and were presumed to have no HAP exposure. Hence, this pilot study was undertaken to explore if *in-utero* HAP exposure affects placenta function or chronic hypoxia.

## 2. Methods

### 2.1. Study design, eligibility criteria and subject recruitment

This study is part of a larger randomized control trial (RCT; registered on ClinicalTrials.gov: NCT02394574) that was conducted in Ibadan, Nigeria from June 2013 to October 2015. Details of subject recruitment are provided in our earlier publications (Olopade et al., 2017; Alexander et al., 2017). Briefly, 324 apparently healthy women who were <18 weeks gestational age were enrolled in the parent study. Parturients who cooked regularly with firewood/kerosene and did not have high-risk pregnancy (multiple gestations, uncontrolled maternal hypertension, maternal age > 35 years for their first delivery, three or more prior miscarriages, or a prior cesarean section) were included. Pregnant women that met entry criteria were recruited and randomized to the ethanol (E) or control (C) arm. Those in the E group were given a CleanCook ethanol stove (CLEANCOOK Sweden AB) and an initial supply of fuel on a home visit between 16 and 18 weeks gestational age (GA). Written consent was obtained from participants at recruitment. The Institutional Review Boards (IRB) of the University of Ibadan and the University of Chicago approved the study protocol.

For the current ancillary study, placenta samples of 36 Nigerian women from the parent trial were studied. African American participants from Chicago ($N = 12$) were selected in order to reflect a similar racial demographic with the Nigerian women. Of the 36 samples from Nigerian women, 16 women used firewood/kerosene for cooking and 20 had been using ethanol CleanCook stoves at the time of sample collection.