Title
Household Air Pollution and Adverse Fetal, Neonatal and Maternal Outcomes in Low and Middle-Income Countries

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Household Air Pollution and Adverse Fetal, Neonatal and Maternal Outcomes in Low and Middle-Income Countries

by

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DISSERTATION

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Dedication

I dedicate this dissertation to the pregnant women who participated in the HAPIN trial and were willing to share their experiences of loss.

Deep gratitude to my husband, Mark, and the thousand acts of support he lavished on me during this feat. Remember the time in Guatemala during the rainy season when the road was out and we had to cross over a ravine across a rope bridge that was missing most of the planks? That is what these past years have felt like. You carrying my huge backpack, me searching for footing and us trying to make each other laugh. You have always been my anchor in the storm, and calm amongst chaos. Thank you for loving me so well. Also to the 5 little pieces of my heart: Amelia, Sydney, Roger, Hope and Oliver. You are my lights, thank you for expanding my world. Mom, so much of your life has been invested in me. Thank you for making this all possible with the countless hours with the kids and for always supporting me. To Rog, the man in the arena, how fortunate I am to be your sister. Dad, thank you for modeling taking risks and going against the current to achieve your goals. To my family and sibs, thank you for the gift of your lifelong guidance, fellowship and camaraderie.

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Contributions

Younger, A., Alkon, A., Harknett, K., Jean Louis, R., & Thompson, L. M. (2022). Adverse birth outcomes associated with household air pollution from unclean cooking fuels in low- and middle-income countries: A systematic review. *Environmental research*, *204*(Pt C), 112274. doi:10.1016/j.envres.2021.112274

Abstract: Household Air Pollution and Adverse Fetal, Neonatal and Maternal Outcomes in Low and Middle-Income Countries

Ashley Younger

Background: Approximately 3.8 billion people in low- and middle-income countries use unclean fuels as a source of primary cooking fuel as well as for heating. For pregnant women, the toxic chemicals produced by combustion of unclean fuels not only affect women's health directly, but particulate matter and carbon monoxide are absorbed in maternal blood and cross the placental barrier potentially affecting the fetus.

Methods: This dissertation presents three manuscripts. The first is a systematic review examining birth outcomes related to household air pollution (HAP) from type of cooking fuel in low-and middle-income countries. PRISMA 2009 guidelines were used for this systematic review. The inclusion criteria were quantitative, peer reviewed journal articles published within a date range of May 1, 2013-June 12, 2021. The quality of available evidence was evaluated using the Office of Health Assessment and Translation (OHAT) risk of bias rating tool. The reviewed studies presented evidence for an increased risk of low birth weight (LBW), preterm birth (PTB), small for gestational age (SGA), stillbirth, neonatal mortality and reduction in birthweight with unclean fuel use compared to cleaner fuels. The second study's objective was to evaluate the effects of a liquefied petroleum gas (LPG) stove and fuel intervention during pregnancy on congenital anomalies, stillbirth and neonatal mortality using data from the Household Air Pollution Intervention Network (HAPIN) Trial. The HAPIN trial is a randomized controlled trial of LPG stoves and fuel distribution in nearly 3200 households conducted across India, Guatemala, Peru and Rwanda. Participants in the HAPIN Trial were monitored for adverse and serious adverse events. All analyses were performed according to intention-to-treat (ITT)

analysis, and binary outcomes of congenital anomalies, stillbirth and neonatal mortality were compared between the two arms using log binomial models. The third study's objective was to evaluate the effects of a LPG stove and fuel intervention during pregnancy on maternal outcomes of spontaneous abortion, postpartum hemorrhage, hypertensive disorders of pregnancy, and maternal mortality using data from the Household Air Pollution Intervention Network (HAPIN) Trial. All analyses were performed according to intention-to-treat (ITT) analysis, and binary outcomes of spontaneous abortion, postpartum hemorrhage, preeclampsia/eclampsia, and maternal mortality were compared between the two arms using log binomial models.

Results**:** Systematically reviewing the evidence and risk of bias ratings illuminated several gaps in the current literature related to exposure assessment, outcome measurement and adequacy of adjustment for confounding. Results for the second study showed that adverse fetal and neonatal outcomes (congenital anomalies, stillbirth, neonatal mortality) did not differ based on stove type across four country research sites. Pregnant women assigned to the LPG intervention arm had a slightly lower risk of congenital anomaly (RR 0.96, 95% CI: 0.55, 1.70) and neonatal mortality (RR 0.97, 95% CI: 0.53, 1.77) compared to women in the control arm. In regards to stillbirth, pregnant women assigned to the LPG intervention arm had a slightly higher risk of stillbirth (RR 1.01, 95% CI: 0.60, 1.70) compared to women in the control arm. However these results were not statistically significant even after adjusting for maternal education, household food insecurity and bank account. Results for the third study demonstrated adverse maternal outcomes (spontaneous abortion, hypertensive disorders of pregnancy, postpartum hemorrhage and maternal mortality) did not differ based on stove type across the four country research sites. In intention-to-treat analyses we found women assigned to the LPG intervention arm had a higher risk of spontaneous abortion (RR 2.69, 95% CI: 0.71, 10.12) and maternal mortality (RR 1.51, 95% CI:

0.25, 9.03) compared to women in the control arm. Pregnant women assigned to the LPG intervention arm had a lower risk of postpartum hemorrhage (RR 0.84, 95% CI: 0.26, 2.74) and hypertensive disorders of pregnancy (RR 0.84, 95% CI: 0.26, 2.74) compared to women in the control arm. However all results were not statistically significant even after adjusting for maternal education, household food insecurity and bank account.

Conclusion: The systematic review presented evidence for an increased risk of LBW, PTB, SGA, stillbirth, neonatal mortality and reduction in birthweight with solid fuel and kerosene use compared to cleaner fuels like gas and LPG. The HAPIN trial was the first multi-country RCT collecting data on household air pollution and health outcomes on pregnant women across four countries. While the LPG stove intervention did not significantly reduce the relative risk of adverse birth outcomes, women assigned to the LPG intervention arm had a slightly lower risk of congenital anomaly, neonatal mortality, hypertensive disorders of pregnancy and postpartum hemorrhage compared to women in the control arm. Access to sustainable and affordable energy should remain a priority for the global community.

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List of Abbreviations

BC, black carbon

BMI, body mass index

BW, birthweight

CO, carbon monoxide

HAP, household air pollution

HAPIN, Household Air Pollution Intervention Network

IHME, Institute for Health Metrics and Evaluation

IRC, international research center

IUGR, intrauterine growth restriction

LBW, low birth weight

LMICs, low- and middle-income countries

LPG, liquefied petroleum gas

OHAT, Office of Health Assessment and Translation

PM, particulate matter

PPH, postpartum hemorrhage

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTB, preterm birth

SAB, spontaneous abortion

SDGs, Sustainable Development Goals

SGA, small for gestational age

WHO, World Health Organization

Introduction

Background and Significance

Approximately 3 billion people in low- and middle-income countries use solid fuels such as coal, charcoal, wood and dung as a source of primary cooking fuel as well as for heating (World Health Organization [WHO], 2016). The combustion of solid fuels during the heating process releases harmful chemicals such as carbon monoxide and particulate matter (Smith, 1993; WHO, 2007). Cleaner burning, less polluting cooking fuels include liquid petroleum gas (LPG), gases such as biogas/natural gas, electricity and solar (WHO, 2016). Household air pollution (HAP) is the 8th most important contributor to the overall global disease burden (Institute for Health Metrics and Evaluation [IHME], 2018). These health impacts include childhood pneumonia, cardiovascular diseases, chronic obstructive respiratory disease, lung cancer and cataracts (Dherani et al., 2008; Kurmi et al., 2010; Kurmi et al., 2012; Smith et al., 2011; Smith, Mehta & Feuz, 2009).

The use of solid fuels remains widespread despite mounting evidence of harmful health effects (Amegah & Jaakkola, 2016). Over the past 30 years, the number of people using solid fuels for cooking has remained close to 3 billion highlighting the need for improved interventions (Amegah & Jaakkola, 2016; Bonjour et al., 2013). Trends indicate the proportion of the population using solid fuels is declining in Asia, southern Africa and most regions of South America (IHME, 2018). Yet due to population growth and reliance on solid fuel, several countries in sub-Saharan Africa exhibit net increases in the proportion of the population exposed to HAP. In 2014, the WHO issued guidelines for indoor air quality from solid fuel use in order to facilitate research and interventions addressing household air pollution. The WHO 2016 guidelines include recommendations not only against the use of solid household fuels but also kerosene, which is almost as toxic as solid fuels. (WHO, 2016). In 2021, the WHO updated the Global Air Quality Guidelines (AQGs) with even lower limits than prior recommendations for key air pollutants (particular matter, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide) highlighting the threat of air pollution on human health (WHO, 2021).

With the increasing use of solid fuels, there are concerns about the impact of HAP on fetal and maternal health. The body of research connecting the role of household air pollution from solid fuel use with adverse pregnancy outcomes is growing. A systematic review and meta-analysis conducted by Pope et al. (2010) demonstrated an association between household solid fuel use and increased risk of low birth weight (LBW) (OR=1.38; 95% CI: 1.28, 1.52) and stillbirth (OR=1.51; 95% CI: 1.23, 1.85) as well as a reduced mean birth weight of 95.6 g (95% CI:-68.5, -124.7). A more recent review by Amegah et al. (2014) assessed 19 articles published before 2014 on the association between HAP on pregnancy outcomes. The review found that household combustion from solid fuels resulted in a mean reduction in birth weight of 86.4 grams (95% CI: 55.49, 117.37), a 35% increased risk of LBW (EE=1.35, 95% CI: 1.23, 1.48) and 29% increased risk of stillbirth (EE=1.29, 95% CI: 1.18, 1.41). The review concluded that increased risk of preterm birth (PTB) and intrauterine growth restriction (IUGR) were associated with household use of solid fuel (summary effect-estimates of 1.30, 95% CI 1.06, 1.59 for preterm birth and 1.23, 95% CI 1.01, 1.49 for growth restriction). The authors also noted methodological limitations in most of the reviewed studies particularly in direct exposure measurement and called for future research with higher quality evidence on a wide range of adverse pregnancy outcomes. The lack of consistent methodological quality necessitates research that can establish causal inferences between HAP and pregnancy and birth outcomes.

Theory/Biological Plausibility

Women are particularly vulnerable to high exposure levels of HAP since they are primarily responsible kitchen duties; their babies are also vulnerable since they spend time with their mother in the kitchen (Amegah & Jaakkola, 2016; Burnett, 2014; Smith, 2014). Collecting freely available solid fuels can also lead to indirect health risks including assault during firewood collection, insect exposure and musculoskeletal injuries (Oluwole, Otaniyi, Ana, & Olopade, 2012). For pregnant women, the toxic chemicals produced by solid fuel combustion not only affect women's health directly, but particulate matter and carbon monoxide, two important by-products of incomplete combustion, also are absorbed in maternal blood and cross the placental barrier impairing fetal tissue growth through hypoxia/oxidative stress (Li et al., 2003; Pope et al., 2010). Reducing household air pollution has the potential to improve environmental quality for a pregnant woman thereby disrupting pathways for adverse birth outcomes as explained by the Ferguson & Chin model in Figure 1. Ferguson and Chin (2017) examined several biological mechanisms explaining the pathway between environmental chemical and adverse birth outcomes including: inflammation, oxidative stress and endocrine disruption. The authors developed a conceptual model of the biologically plausible mechanistic pathways of particulate matter on preterm birth subtypes of spontaneous labor, preterm premature rupture or membranes, preeclampsia and intrauterine growth restriction (Ferguson & Chin, 2017; Wylie et al., 2017). Environmental contaminants in particular matter are engulfed by phagocytosis resulting in helper T cell activation and release of cytokines resulting in inflammation. Also, toxins can cause epigenetic mutations in DNA methylation initiating intrauterine inflammatory cascades such as cervical ripening, rupture of amniotic sac, placental inflammation and myometrial contractibility. Changes in the mitochondrial membrane permeability caused by environmental toxins lead to impaired antioxidant function related to oxidative stress. These physiological alterations could cause damage in placental membranes and nutrient transport as well as cervical shortening. Environmental contaminants can disrupt endocrine functions that regulate nutrient transfer in pregnancy ultimately leading to poor fetal growth.

Impact and Innovation

Prior studies on the association between HAP and birth outcomes are predominantly observational, unable to demonstrate causation, limited by recall bias and exposure misclassification. (Abusalah, 2018; Amegah et al., 2012; Epstein et al., 2013; Ezeh, Agho, Dibley, Hall, & Page, 2014; Jiang, 2018; Khan et al., 2017; Lakshmi et al., 2014; Milanzi & Namacha, 2017; Nisha, Alam, & Raynes-Greenow, 2014; Patel et al., 2015; Tielsch et al., 2009; Wiley et al., 2014; Wylie et al., 2016; Yucra, Tapia, Steenland, Naeher, & Gonzales, 2014). Previous clean fuel intervention research has focused on biomass-based cookstoves or chimney interventions that have failed to reduce particulate matter exposure levels that potentially correlate with an improvement in health outcomes (Alexander et al., 2018; Thompson et al., 2011).

The purpose of this dissertation research is to determine the impact of reduced household air pollution (HAP) from a liquefied petroleum gas (LPG) stove intervention on the incidence of adverse fetal, neonatal and maternal outcomes among Household Air Pollution Intervention Network (HAPIN) Trial participants. The three manuscripts presented for this dissertation are: (1) Adverse Birth Outcomes Associated with Household Air Pollution from Unclean Cooking Fuels in Low- and Middle-Income Countries: A Systematic Review, (2) Effects of a LPG stove and fuel intervention on adverse fetal and neonatal outcomes: a multi-country randomized controlled trial conducted by the Household Air Pollution Intervention Network (HAPIN) (3)

Effects of a LPG stove and fuel intervention on adverse maternal outcomes: a multi-country randomized controlled trial conducted by the Household Air Pollution Intervention Network (HAPIN).

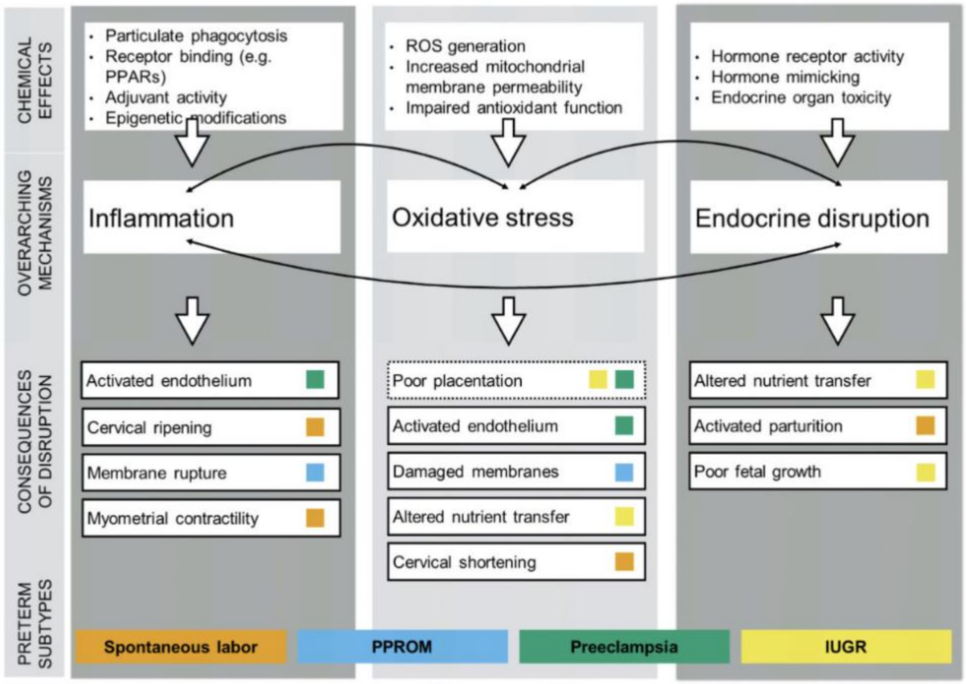

Figure 1: *Potential mechanisms of environmental chemical action in the path to preterm birth (Ferguson & Chin., 2017)*

Abbreviations: Peroxisome proliferator activated receptors (PPARs); Reactive oxygen species (ROS); Preterm premature rupture of the membranes (PPROM); Intrauterine growth restriction (IUGR)

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Chapter 1: Adverse Birth Outcomes Associated with Household Air Pollution from Unclean Cooking Fuels in Low- and Middle-Income Countries: A Systematic Review

1. Introduction

Approximately 3.8 billion people in low- and middle-income countries (LMICs) use unclean fuel for cooking and in 2019 close to 2.3 million people died prematurely due to illnesses attributable to household air pollution (HAP) (Health Effects Institute, 2020). The most recent World Health Organization (WHO) guidelines include recommendations not only against the use of solid household fuels such as coal, charcoal, wood and dung but also kerosene, which are considered highly-polluting (WHO, 2014). Cleaner burning, less polluting cooking fuels are liquid petroleum gas (LPG), gases such as biogas/natural gas, electricity and solar. The combustion of unclean fuels during the heating process releases harmful chemicals such as carbon monoxide and particulate matter that can result in HAP levels 100 times higher than acceptable air quality levels (Smith, 1993; WHO, 2007). According to the Institute for Health Metrics and Evaluation (IHME), HAP is the 8th most important contributor to the overall global disease burden (IHME, 2018). These health impacts include childhood pneumonia, cardiovascular diseases, chronic obstructive respiratory disease, lung cancer and cataracts (Dherani et al., 2008; Kurmi, Arya, et al., 2012; Kurmi, Lam, et al., 2012; Kurmi et al., 2010; Smith et al., 2011; Smith, 2004). A recent impact assessment on the health burden associated with exposure to household air pollution estimated that in 2017, HAP was associated with 1.8 million deaths and 60.9 million disability adjusted life years (DALYs) globally (Lee et al., 2020).

The burden of adverse birth outcomes disproportionally occurs in LMICs where 190 million (89%) of the estimated 213 million pregnancies worldwide occur annually (McDonald et al., 2020; Sedgh et al., 2014). Approximately 60% of global preterm births occur in sub-Saharan

African and south Asia each year (Blencowe et al., 2012; McDonald et al., 2020). This translates to about 12% of babies born in LMICs are preterm compared to 9% in higher-income countries (WHO, 2018). In 2015, 1 in every 7 newborns was born with low birthweight (LBW, birthweight <2500g) amounting to 20.5 million LBW babies globally (UNICEF, 2019). The prevalence of LBW in 2015 varied from 7.2% in more developed regions to 13.7% in Africa and 17.3% in Asia (UNICEF, 2019). Every day there are roughly 7,000 newborn deaths and 5,000 stillbirths, 98% of which occur in LMICs (Gibson et al., 2021; Lancet, 2016). These estimates may underestimate actual prevalence of adverse outcomes since many babies are not weighed at birth and births may occur at home or in small clinics without official reporting (Marete et al., 2020; WHO, 2014). Women are particularly vulnerable to high exposure levels of HAP since they are primarily responsible for cooking and tending to the kitchen; children under 5 also have a high exposure and disease risk since they spend much of their time with their mother (Amegah & Jaakkola, 2016; Burnett et al., 2014; Smith et al., 2014). During pregnancy, toxic chemicals produced by unclean fuel combustion adversely affect the health of both the exposed mother and fetus. Particulate matter and carbon monoxide, two important by-products of incomplete combustion, are absorbed in maternal blood and cross the placental barrier impairing fetal tissue growth through hypoxia/oxidative stress (Li et al., 2003; Pope et al., 2010).

The body of research connecting the role of household air pollution from unclean fuel use with adverse pregnancy outcomes in low- and middle-income countries is growing. Ghosh et al. (2021) estimated a global population-weighted mean lowering of 89g of birthweight and 3.4 weeks of gestational age as well as 15.6% of all LBW and 35.7% of all PTB infants attributable to ambient and HAP $PM_{2.5}$ in 2019. A systematic review and meta-analysis conducted by Pope et al. (2010) demonstrated household solid fuel use is associated with an increase in the relative risk of LBW and stillbirth. The systematic review and meta-analysis by Amegah et al. (2014) evaluated 19 articles published before 2014 on the association between HAP and expanded pregnancy outcomes to birthweight, stillbirth, preterm birth, intrauterine growth restriction and miscarriage. The analysis found that household combustion from solid fuels resulted in a statistically significant mean reduction in birthweight of 86.4 grams, a 35% increased risk of LBW and 29% increased risk of stillbirth. The authors also noted methodological limitations in most of the selected studies particularly regarding direct exposure measurement and called for future research with higher quality evidence on a broader range of adverse pregnancy outcomes. Since the publication of Amegah et al. (2014) seven years ago, an expanding field of HAP research has focused on a range of adverse birth outcomes, including three recently published randomized stove intervention trials, necessitating a current review of the new evidence. A comprehensive systematic review, meta-analysis and burden of estimation study by Lee et al. (2020) also limited pregnancy outcomes to birthweight and stillbirth. Specifically, the pooled relative risk was 1.36 for low birthweight, 1.22 for stillbirth and a 149g average reduction of birthweight with use of polluting fuels.

The use of unclean cooking fuels remains widespread despite mounting evidence of harmful health effects (Amegah & Jaakkola, 2016). In 2018, the global population without access to clean cooking fuels and technologies was 2.8 billion with nineteen countries accounting for approximately 80% were in Africa (IEA, 2020). While trends indicate the proportion of the population using unclean fuels is declining in Asia, southern Africa and most regions of South America; several countries in sub-Saharan Africa are exhibiting net increases in the proportion of the population exposed to HAP due to population growth and reliance on unclean fuel (IHME, 2018). To combat these trends, in 2015 all United Nation Member States adopted the 2030 agenda of 17 Sustainable Development Goals (SDGs). SDG 3, 7 and 11 address indicators of disease burden from household and ambient air pollution (Amegah & Jaakkola, 2016; UN, 2015). Table 1.1.

Table 1.1. Sustainable Development Goals and Targets
<u>**SDG 3**</u>: Ensure healthy lives and promote well-being for all at all ages *Target 3.9:* By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination.
<u>**SDG 7:**</u> Ensure access to affordable, reliable, sustainable and modern energy for all *Target 7.1*: By 2030, ensure universal access to affordable, reliable and modern energy services.
<u>**SDG 11:**</u> Make cities and human settlements inclusive, safe, resilient and sustainable *Target 11.6:* By 2030, reduce the adverse per capital environmental impact of cities, including by paying special attention to air quality and municipal and other waste management.

1.1 Objectives and Rationale

This systematic review of the literature updates the evidence by asking: is household air pollution from unclean cooking fuels associated with adverse birth outcomes in low- and middle-income countries? The aims of this systematic review of international articles are 1) to appraise research evidence of an association between household air pollution from unclean cooking fuel and adverse birth outcomes 2) to evaluate the quality of available evidence using the Office of Health Assessment and Translation (OHAT) risk of bias rating tool, and 3) to identify knowledge gaps to inform future research. Since the last systematic review search ended April, 2013, this systematic review synthesizes the current research from 2013-2021 (Amegah et al., 2014).

2. Methods

2.1 Literature Search

We organized this systematic review using the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher et al., 2009).

The design details, analysis and inclusion criteria were preregistered on the International prospective register of systematic reviews. (PROSPERO Registration number: CRD42020152333).

Our inclusion criteria were peer reviewed journal articles published within a date range of May 1, 2013-June 12, 2021 examining birth outcomes related to household air pollution from unclean cooking fuel in low-and middle-income countries. The PECO for the study as defined by Morgan et al. (2018) includes: Participants were pregnant women in low-to middle-income countries; Exposure was household air pollution from unclean cooking fuels; Comparator was the household air pollution from clean cooking fuel; Outcome was adverse birth outcomes. Low- and middle-income countries (Gross National Income per capita <$1,035 to < $4,045 respectively) were chosen since unclean cooking fuels is more likely to be used in these countries (World Bank, 2016). Primary and secondary data analysis studies that investigated the association between household air pollution as a primary exposure and the risk of adverse birth outcomes in the human population were included in the review. Language was restricted to studies written in English and Spanish due to evaluator language ability. Studies were excluded if they addressed topics other than household air pollution from cooking fuels, such as ambient air pollution, used a non-quantitative study design, or evaluated outcomes not related to pregnancy, childbirth or the neonatal period. Studies only available as posters or abstracts were also excluded.

Studies were identified using search strategies within PubMed, EMBASE, CINAHL and Web of Science databases. In the most recent systematic review on HAP and adverse pregnancy outcomes by Amegah et al. (2014) publication dates were constrained to database inception to April 30, 2013; therefore our search, which updates the previous systematic review, included publication dates of May 1, 2013-June 12, 2021. Medical Subject Heading (MeSH) search terms and free text words were systematically combined to identify relevant studies. The search strategy was adapted to each database after adding Boolean operators such as “AND/OR”. Search terms are presented in Table 1.2. After compiling the results from the database searches, the author hand searched for additional relevant articles using references from sourced studies. The last hand search was done June 13, 2021. The full search strategy is included in Supplement Table 1.6.

Table 1.2: *Search Terms*

Exposure		**Outcomes**
MeSH terms	**Free text words**	**MeSH terms**
"Air Pollution, Indoor"	"household air pollution"	"Pregnancy outcome"
Biofuels	"household fuel"	"Pregnancy outcome/adverse effects"
Biomass	"domestic fuel"	"Birth Weight"
Coal	"cooking fuel"	"Infant, Low Birth Weight"
Wood	"cooking smoke"	"Premature Birth"
Kerosene	"solid fuel"	"Infant, Premature"
Cooking	firewood	"Gestational Age"
	"crop residue"	"Infant, Small for Gestational Age"
	"biomass fuel"	Stillbirth
	"biomass smoke"	"Fetal Mortality"
	"wood fuel"	"Fetal Death"
	"wood smoke"	"Perinatal Mortality"
	"charcoal smoke"	"Perinatal Death"
	"unclean fuel"	"Infant Mortality"
		"Abortion, Spontaneous"
		"Maternal Mortality"

2.2 Study Selection

Relevant results were compiled in EndNote 20 and scanned for duplicates. The eligible studies were then organized in the Cochrane Review endorsed online software program Covidence systematic review software (Covidence, 2014). Screening and eligibility assessment were performed by two independent investigators (AY and RJL). First, potential studies were screened by title and abstract using the eligibility criteria. Second, studies were eliminated if they did not address household air pollution or pregnancy, and/or fell outside publication dates. The remaining articles that met inclusion criteria were screened by full text assessment using eligibility criteria with exclusion based on study design and outcome measures. If any disagreements occurred, the two reviewers made joint decisions after discussion of the inclusion eligibility.

2.3 Data Collection and Items

Data were extracted from included studies that were evaluated independently by two investigators (AY and LMT) through full-text review and Covidence software. Extracted variables included author, setting, study design, sample size, measurement and assessment of exposure and outcomes, and covariates used in adjusted models. Adverse birth outcomes extracted for this review are defined as low birth weight (<2500 grams), birthweight, small for gestational age (birthweight<10^{th} percentile), spontaneous abortion (<20 weeks gestation), preterm birth (<37 weeks gestation), stillbirth (≥20 weeks gestation) and neonatal mortality (birth to 28 days). We organized data from each study into three tables: 1) study characteristics, 2) summaries of study results of adverse pregnancy outcomes associated with cooking fuel and, 3) an assessment of risk of bias.

Data were summarized in table form to include birth outcomes related to cooking fuel type. Outcomes were then extracted and reported in adjusted odds (aOR), risk ratios (aRR), hazard ratios (aHR) or posterior means (p.mean) of low birth weight, small for gestational age, spontaneous abortion, preterm birth, stillbirth and neonatal mortality. Birthweight was reported as an adjusted mean difference in grams or kilograms. If data were not adjusted, unadjusted values were presented. Due to the heterogeneity of exposure and outcome reporting, a meta-analysis of findings could not be performed, instead findings were synthesized using a narrative approach into text and tables. The included articles were placed in alphabetical order in Table 1.3 and Table 1.4. Risk of bias ratings for each study are presented in Table 1.5. Figures 3-5 present study design, exposure and outcome assessment measures for grouped outcomes.

2.4 Risk of Bias in Individual Studies

The risk of bias and quality assessment of the included articles was determined by three reviewers (AY, LMT, RJL) utilizing the Office of Health Assessment and Translation (OHAT) tool created by the National Toxicology Program (OHAT, 2015). The OHAT tool was created to evaluate individual study risk of bias or internal validity for human and non-human animal studies. The framework is structured with 11 risk of bias questions or domains with each question applicable for 1 to 6 study design types (animal or human controlled trial, cohort, case-control, cross-sectional, case series). The questions are grouped under 6 types of bias domains: selection, confounding, performance, attrition/exclusion, detection and selective reporting. Finally the questions are rated by selecting among 4 possible answer format options including:

- Definitely Low risk of bias: There is direct evidence of low risk of bias practices
- Probably Low risk of bias: There is indirect evidence of low risk of bias practices OR it is deemed that deviations from low risk-of -bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias.
- Probably High risk of bias: There is indirect evidence of high risk of bias practices OR there is insufficient information (not reported or “NR”) provided about relevant risk of bias practices

- Definitely High risk of bias: There is direct evidence of high risk of bias practices

A conservative approach was taken for studies with insufficient information to judge risk of bias for an individual question by defaulting to the more conservative category as suggested by the OHAT tool instructions.

3. Results

3.1 Study Selection

The literature search identified 553 articles for review. During the selection process, 530 articles were excluded either because they were duplicates (n=122), the abstract indicated they did not meet the screening criteria (n=331), or full text review indicated they did not meet inclusion criteria (n=77). A total of 23 studies were included in the final quantitative synthesis. The PRISMA flow diagram of study selection is depicted in Figure 1.

3.2 Study Characteristics

Twenty-three studies were included in this review with full study characteristics presented in Table 1.3 where they are categorized in alphabetical order and labeled with references 1-23. The selected studies employed various research designs. Fourteen of the studies used cross-sectional designs [2, 4-7, 9, 11-14, 17-19, 21] of which nine analyzed national demographic data such as Demographic and Health Surveys (DHS) [4-7, 11, 12, 14, 17, 18]. Five studies applied cohort design with two utilizing a prospective approach [3, 8, 15, 20, 22]. One study was a case-control design [23] and three studies were randomized control trials (RCT) [1, 10, 16]. The RCT by Katz et al. (2020) summarized the results from two sequential trials. Trial 1 compared vented and traditional stoves while Trial 2 compared vented biomass with LPG stoves. This review only included data from Trial 2. Quinn et al. (2021) presented the exposure-response data of both arms of the Ghana Randomized Air Pollution and Health Study (GRAPHS)

RCT stove intervention. The included studies were conducted in fifteen different countries: Bangladesh, China, Ghana, Guatemala, India, Indonesia, Kenya, Malawi, Nepal, Nigeria, Pakistan, Peru, Sri Lanka, Tanzania, and Zambia. See Supplement Figure 1.5 for a map of global solid fuel use and countries included study settings.

The categorization of cooking fuel varied across studies. A total of six studies focused on HAP from one specific fuel on birth outcomes [1, 2, 10, 13, 19, 21]. Five studies investigated two or more of types of cooking fuels and their individual impact on outcomes [3, 7, 8, 9, 23], while seven studies categorized fuels into two groups of polluting/unclean or clean [6, 12, 14, 15, 17, 18, 20] and three as either solid fuels or non-solid [4, 5, 11]. The clean fuel comparison groups ranged from LPG, gas (biogas/natural gas) and electricity. Kerosene was categorized as a polluting fuel in ten studies [1-3, 6, 7, 9, 14, 15, 17, 20] and a non-polluting fuel in three studies [4, 11, 18]. Islam et al., (2021b) analyzed a gradient of cooking fuels in order to quantify differences in mean birthweight by fuel type.

HAP exposure was either directly or indirectly assessed. Sixteen of the included studies indirectly assessed exposure to household air pollution during pregnancy through interviews or surveys asking about stove and/or fuel type [2, 4-9, 11, 12, 14, 15, 17-21]. Among studies that directly assessed HAP exposure, there were differences in collection timing, location and pollutants measured. Six studies directly measured HAP exposure with three using personal CO and/or PM monitors [1, 16, 22] worn during pregnancy, four measuring PM [3, 10, 13, 22] and three collecting CO kitchen concentrations [10, 22, 23]. The direct measures varied in length of sampling time of exposure collection ranging from 3 consecutive days [1, 3, 13, 22], to 48 hours [16, 23] to two measurements over 21.7 hours [10]. Balakrishan et al. (2015) estimated exposure during each trimester by directly measuring an average of three 24-hour kitchen $PM_{2.5}$

concentration levels as well as a 24-hour kitchen measure of $PM_{2.5}$ in a subset of cohort participants. Mukherjee et al. (2015) recorded the mean direct kitchen PM_{10} exposure of randomly selected households over a three-day period. Wylie et al. (2017) measured personal and kitchen CO exposure levels over a 72-hour period and personal $PM_{2.5}$ exposure during the first and third 24-hours of the CO measurement. Yucra et al. (2014) measured kitchen CO concentrations over a 48-hour period among a specified case and control sub-sample. Two RCT studies collected data on kitchen air pollutant concentrations of $PM_{2.5}$ and CO as well as intervention stove type as a measure of exposure [1, 10]. Alexander et al. (2018) also measured direct personal exposure to $PM_{2.5}$ and CO for three consecutive days during second trimester and third trimester. Quinn et al. (2021) calculated a composite measure of CO exposure using a series of 48-hour-average personal CO monitoring sessions collected during four different points in pregnancy.

In terms of outcomes, birthweight and low birth weight were the most frequently reported health outcomes with twelve studies [1-3, 6-10, 12, 16, 21, 22] and thirteen studies [3, 5, 6, 8, 10, 11, 13, 16-21] respectively. Stillbirth [1, 11, 13-15, 17, 21], and small for gestational age [8, 10, 16, 19-21, 23] were each reported in seven studies each. Preterm birth [1, 10, 16, 17, 20, 21] and neonatal mortality [1, 4, 11, 14, 15, 18] were reported in six studies. Spontaneous abortion was examined as an outcome in three studies [1, 13, 20]. Seven of the twenty-three included studies directly measured birth outcomes [1, 2, 9, 10, 16, 21, 22], seven relied on maternal recall [4, 5, 11, 13, 14, 17, 18], four collected data from medical records [3, 8, 19, 23] while the other five used a combination of interview and medical records [6, 7, 12, 15, 20].

3.3 Risk of Bias Within Studies

Within the studies, confounding bias (e.g. unmeasured confounding) and detection bias (e.g. measurement error) in exposure characterization and outcome assessment led to high risk of bias scores. Across the domain of accounting for confounding bias, twelve out of twenty studies (60%) scored ‘probably high risk of bias’ [2, 5, 11-15, 17-20, 23]. The majority of studies in this score category failed to account for important confounding and modifying variables cited in previous literature in either study design or analysis. Risk of bias in exposure characterization revealed seventeen out of twenty-three studies (74%) were either ‘probably high risk’ or ‘definitely high risk’ of bias [1, 2, 4-6, 8-15, 17-20]. Both exposure misclassification related to primary cooking fuel type serving as a proxy for household air pollution and potential recall bias due to self-reported cooking fuel use during pregnancy resulted in high risk of bias scores. Finally, confidence in the outcome was affected by outcome misclassification and measurement error. Evaluation of outcome assessment risk of bias determined seventeen of the twenty-three studies (74%) as either ‘probably high risk’ or ‘definitely high risk’ of bias [1-8, 9-14, 16-18, 23]. Common reasons for higher bias scores include failing to mention questionnaire or instrument validation, objectivity of the outcome assessment and blinding of those who assessed the outcomes. Conversely, a high proportion of the studies scored low risk of bias in the domains of selection and selective reporting bias. Selective bias refers to systematic differences between baseline characteristics of the groups and selective reporting bias is the selective inclusion of outcomes in the publication of the study on the basis of the results (Hutton & Williamson, 2000; Higgins & Green, 2011). The results of the risk of bias assessment are presented in Table 1.5.

3.4 Birthweight, Low Birth Weight and Small for Gestational Age Outcomes

The association of cooking fuel type and birthweight (BW) was reported as adjusted mean difference by twelve studies [1-3, 6-10, 12, 16, 21, 22]. Eight of the twelve studies found statistically significant differences in birthweight based on cooking fuel types. Alexander et al. (2018) conducted a randomized ethanol stove intervention with kerosene/firewood (control) and reported the largest mean birthweight difference of 128 g (95% CI: 20, 236) after adjusting for marital status and BMI [1]. Birthweights were measured by maternal recall [6, 7, 12], hospital records [3, 6-8, 12] and use of a digital scale [1, 2, 9, 10, 16, 21, 22].

Thirteen studies that examined the association of household air pollution exposure from cooking fuel and low birth weight (LBW) (<2500 grams) reported an increased adjusted odds ratio [3, 5, 6, 8, 11, 13, 16, 18-21], adjusted relative risk [10] or parameter posterior mean [17]. Statistically significant estimates of increased adjusted risk for LBW were reported in two studies comparing PM exposure measures [3, 13] and four studies among women using polluting fuel compared to cleaner cooking fuel [5, 8, 18, 19]. Balakrishnan et al. (2015) relied on direct PM exposure measurement methods to detect a significant increase in the odds of LBW with a $10\mu g$/m3 increase in $PM_{2.5}$ (aOR: 1.02, 95% CI: 1.01, 1.04) [3]. Other significant associations of polluting fuel on LBW included coal fuel (aOR: 2.6, 95% CI: 1.1, 6.2) compared with non-solid fuels [5], wood fuel compared with non-solid fuels (aOR: 1.1, 95% CI: 1.0, 1.2) [5], and biomass fuel compared with gas fuels (aOR: 2.51, 95% CI: 1.26, 5.01) (aOR: 2.74, 95% CI: 1.08, 6.96) [8, 19]. Vakalopoulos et al. (2021) also assessed HAP exposure by stove type and HAP levels according to primary and secondary fuel type and ventilation. With this approach the authors reported significant increased risk of LBW with traditional biomass stoves versus clean stoves (aOR: 3.23, 95% CI: 1.17, 8.89).

Outcome assessment for LBW varied across studies. LBW outcomes were obtained from maternal recall of child size at birth [5, 6, 11, 13, 17, 18, 20], hospital records [3, 6, 8, 19, 20] and use of a digital scale [10,16, 21]. For both birthweight and LBW, two studies varied on inclusion of babies weighed at birth [1, 2], 24 hours after birth [21, 22], 48 hours [9] and within 72 hours after birth [10, 16]. Digital scale brand and/or precision of measurement up to 10-gram readability is addressed in three studies [10, 16, 20] while one reports the non-specific scales used on labor units [22] while the last mentions a pediatric weighing machine [9].

The selected seven studies that measured the effect of HAP from cooking fuel on SGA reported outcomes as adjusted odds ratios [8, 16, 19, 20, 21, 23] or adjusted relative risk [10]. Two studies found a statistically significant increased risk of SGA (aOR: 1.87, 95% CI: 1.03, 3.41) and (aOR: 4.53, 95% CI: 1.33, 15.49), respectively among women using biomass versus those who used clean fuel/gas during pregnancy [19, 23]. Compared to cleaner fuel stoves (mainly LPG), traditional biomass stoves also demonstrated a significant association with SGA (aOR: 2.64, 95% CI: 1.27, 4.91) [19]. In determining the outcome of small for gestational age (SGA), one study calculated gestational age using self-reported last menstrual period (LMP) confirmed by ultrasound and digital scale birthweight measurements [8], one only used self-reported LMP and digital scale at birth [10], another relied on birth card records [19] and one study combined digital scale measurements with New Ballard estimations for gestational age [21]. One study categorized SGA with birthweight from hospital records and gestational age from LMP as well as newborn maturity using the Capurro method [23]. The RCT by Quinn et al. (2021) calculated gestational age by ultrasound and birthweight with digital scale within 72hrs of birth [16]. Utilizing WHO methodology, Quinn et al. (2021) also created a country specific curve for birthweight percentiles to accurately capture SGA infants.

3.5 Spontaneous Abortion, Preterm Birth, Stillbirth Outcomes

The impact of cooking fuel on spontaneous abortion (SAB) was reported in three studies who defined SAB as fetal death < 20 weeks gestation and reported as an adjusted odds ratio in two studies [13, 20] and <24 weeks gestation reported as an adjusted risk ratio reported in the third study [1]. While not significant, Weber et al. (2020) found a positive association between unclean fuel use and spontaneous abortion (OR: 2.10, 95% CI: 0/91, 4.81). The authors noted the rate of SAB may be underestimated because women with early miscarriages may not have joined the cohort prior to a SAB event. Mukherjee et al. (2015) found an increased risk of SAB with higher levels of PM_{10} from biomass fuel use (aOR: 3.12, 95% CI: 1.07, 4.17) compared to LPG fuel. SAB outcome assessment was obtained through participant recall [13, 20] and medical records [1, 20].

The outcome of preterm birth (PTB) (birth occurring before 37 weeks gestation) was ascertained by six studies and reported in adjusted risk ratios [1, 10], adjusted odds ratios [16, 20, 21] and parameter posterior mean [17]. In a cross-sectional study by Wylie et al. (2014), cooking with wood fuel was significantly associated with an increased risk of PTB (aOR: 2.29, 95% CI: 1.24, 4.21) compared to PTB in the gas fuel group. The authors only looked at a dichotomous measurement of primary cooking fuel and did not capture variability in possible use of multiple fuels, or stove stacking. PTB outcomes were collected from maternal recall [17], hospital records [20], new Ballard estimation [21] and field workers at delivery for the RCT studies [1,10, 16].

Seven studies examined the outcome of stillbirth reported in adjusted odds ratios [11, 13-15, 17, 21] and relative risk [1]. The dating of stillbirth varied from fetal death after 24 weeks [1], 28 weeks [11, 13], to any pregnancy that did not result in the birth of a live child including miscarriage [17]. Patel et al. (2015) differentiated stillbirths by macerated (death before onset of labor) and non-macerated (presumed intrapartum death). Both categories of stillbirth demonstrated significantly higher odds of stillbirth comparing with polluting fuels verses cleaner fuels. Stillbirth outcome assessment was obtained through maternal recall [11, 13, 14, 17] and medical records [1, 15, 21].

3.6 Neonatal Mortality Outcomes

The association between unclean cooking fuel and neonatal mortality was reported as increased odds ratio in four studies [11, 14, 15, 18], increased hazard ratio in one study [4] and a risk ratio in a RCT study [1]. Neonatal mortality outcomes were defined as death between birth and 28 days of age by four studies [1, 4, 11, 18], separated into early neonatal mortality (0-6 days) by one study [14] and categorized as very early (0-2 days) and later neonatal mortality (3-28 days) by another study [15]. Cooking with polluting fuels was significantly associated with an increased risk of very early neonatal mortality (aOR:1.82, 95% CI: 1.47, 2.22), early neonatal mortality (aOR 1.46, 95% CI: 1.01, 2.10), and neonatal mortality (aOR:1.38, 95% CI: 1.14, 1.67) compared to households cooking with clean fuels [14, 15, 18]. Five studies relied on maternal recall for reporting neonatal mortality outcomes [4, 11, 14, 15, 18] while one study used hospital records [1].

4. Discussion

We found an association between adverse birth outcomes and HAP from cooking fuels in low- and middle-income countries in our systematic review. The reviewed studies presented evidence for an increased risk of low birth weight (LBW), preterm birth (PTB), small for gestational age (SGA), stillbirth, neonatal mortality and reduction in birthweight with solid fuel and kerosene use compared to cleaner fuels like gas and LPG. This review builds upon the systematic review by Amegah et al. (2014) noting the methodologic drawbacks around the lack of personal exposure monitoring methods and potential for outcome measurement bias. The field of exposure science has progressed to include more studies on a variety of birth outcomes beyond birthweight including three recently published randomized clean stove/fuel intervention trials. This change was evidenced by the increase in available studies meeting selection criteria with outcomes including SAB, SGA, PTB, stillbirth and neonatal mortality. Systematically reviewing the evidence illuminated several gaps in the current literature related to exposure assessment, outcome measurement and adjustment for confounders.

First, variability in the exposure assessment and lack of direct or personal exposure assessment during pregnancy and the neonatal period contributed to difficulty in interpreting results and comparing statistics across studies. The measurements of direct personal or kitchen exposure varied in PM size fraction, inclusion of CO exposure measures, sampling time and approach to capturing exposure during pregnancy. Failing to assess exposures over different times scales using integrated exposure measurements may underestimate true exposure (Clark et al., 2013; Ezzati et al., 2000). These longer, more time-integrated approaches capture variability of cooking and non-cooking exposures in the household (Clark et al., 2013). Wylie et al. (2017) observed a seasonal pattern of personal exposure to CO related to a hypothesized increase use of kerosene during the rainy season. Alexander et al. (2018) also noted personal $PM_{2.5}$ exposure levels were lower during the rainy season vs the dry season which complicated the effect of the intervention on exposure levels. Assessing HAP exposure during the first trimester, which may be critical periods for outcomes like spontaneous abortion, can deepen our understanding of mechanisms of PM exposure on fetal development. Quinn et al. (2021) began enrollment around 10+ weeks of gestation and monitored personal CO exposure over four 72-hour sessions. Additionally, Balakrishnan et al (2018) utilized serial measurements of 24-h household $PM_{2.5}$

concentrations across all three trimesters as the primary measure of exposure. Inaccurate quantification of exposure that does not objectively measure exposure data across all trimesters can lead to underestimation of the relationship between HAP and adverse birth outcomes (Pope et al., 2010). These observations highlight the need for original data collection incorporating personal exposure monitoring, cooking behaviors and ideally biomarkers of exposure (Amegah et al., 2014; Clark et al., 2013).

Household emissions from other pollutants such as trash burning, tobacco smoke, ambient air pollution and fuels for lighting and heating all contribute to HAP, making it more difficult to distill the effects of exposure from cooking fuels. The exposure classification also fluctuated between studies that aggregated fuel types into clean or polluting while others compared specific fuels or stove types and their impact on birth outcomes. While using reported primary fuel or stove type as the assessment of exposure is inexpensive, the approach can lead to exposure misclassification, if households use multiple stoves and fuel types, and cannot produce an accurate exposure-response association (Clark et al., 2013). Exposure misclassification can occur when studies focusing on primary fuel use overlook the practice of stove stacking, the use of a combination fuels or using traditional stoves next to clean stoves, and therefore misrepresent the impact of clean fuel cooking practices on personal exposure (Ruiz-Mercado & Masera, 2015; Shankar et al., 2020). Rather than focusing on adoption of primary use of clean fuels, studies should also focus on the discontinuation of traditional stoves and incorporation of monitoring of stove usage to understand changes in behavior. The higher risk of bias scores resulting from exposure misclassification due to self-report or inadequate measurement underscore how errors in exposure characterization can attenuate, strengthen or even invert the true relationship (OHAT, 2015; White, 2003).

Kerosene in particular poses a unique issue in fuel type classification with several studies placing kerosene as a polluting fuel and others as clean fuel. Amegah et al. (2014) noted a similar categorization discrepancy of kerosene in their review. Kerosene is a liquid fuel distilled from petroleum oil and is often advocated as a cleaner alternative to solid fuel in settings where LPG, gas and electricity are too expensive or not available (Lam et al., 2012). The WHO established air quality guidelines (AQG) for indoor particulate matter concentrations not to exceed 35 μg PM2.5/m3 and a review by Lam et al. (2012), concluded kerosene-fueled stoves elevate indoor PM concentrations well above WHO guidelines (WHO, 2006). Kerosene fuel not only emits high quantities of PM, but the ultrafine particle size is much small than the diameter of solid fuel PM ensuring deep lung and vascular deposition (Lam et al., 2012). These discrepancies in exposure classification may affect the validity of the results.

Nine of the included studies utilized population-level DHS data [4-7, 11, 12, 14, 17, 18] and sixteen conducted interviews to assess HAP exposure [2, 4-9, 11, 12, 14, 15, 17-20]. Collecting data via survey relies on self-report often from births within 5 years of the survey leading to reporting and recall biases (Odo et al., 2021). DHS collects information on cooking fuel as a proxy to estimate HAP but does not include questions on non-cooking sources of pollution like lighting and heating contributing to exposure misclassification. Recently, the WHO created a harmonized survey questions for monitoring household energy use and SDG indicators to be incorporated in future DHS-style surveys as a means to monitor SDG indicators (WHO, 2019).

Second, assessing birth outcomes also exhibited variability across studies. The potential for maternal recall bias was reflected in the high risk of bias scores in outcome assessment. Ideally newborns birthweight is measured within the first hours of delivery before postnatal weight loss occurs (Marete et al., 2020). Because infants are expected to lose 5-10% of their weight in the first week of life, timely measurement using a well-calibrated scale measuring within 10g increments for categorizing low birth weight and SGA is particularly important (Gladstone et al., 2021; Macdonald et al., 2003; Thompson et al., 2011). Training of field workers in reliable anthropometry methods is also essential for obtaining accurate categorizations of LBW and SGA babies. Imprecision in calculation of birthweight by rounding (>10g), scale calibration or maternal recall can lead to digit bias and potential misclassification of birth outcomes like LBW (WHO, 2005).

In high poverty areas where unclean fuel use is prevalent, and where infants are born at home, or in hospitals using imprecise scales, accurate measurement of birthweight is intermittent and may influence birth outcome associations with HAP in studies analyzing secondary data (Pope et al., 2010). Stillbirth outcomes varied in definition as fetal death ≥20 weeks gestation by one study [15], ≥ 24 weeks in one study [1], ≥28 weeks in three studies [11, 13, 14], infant delivered without any sign of life [21] and any pregnancy that did not result in the birth of a live child including miscarriages [17]. Also, cases of stillbirth and neonatal mortality that occur in the home may not be recorded in hospital records or demographic survey data mitigating the true effect of HAP on serious adverse birth outcomes. Additionally, analyses of live births as the study population for adverse birth outcomes may be impacted by live-birth bias. Recognizing that an estimated 30-40% of fertilized eggs will not result in viable gestation, selective analysis of live births could lead to bias in the observed association vs an actual causal relationship (Neophytou et al., 2021; Raz et al, 2018)

Finally, the range of study designs added to the complexity of interpreting significant associations between HAP and birth outcomes. Most of the included studies are observational using cross-sectional, cohort or case-control designs with six analyzing large national DHS data. Only three studies were RCTs and neither utilized the measure of blinding of exposure or outcome in their study designs. The selected RCTs exhibited strengths and limitations. Alexander et al., (2018) demonstrated accurate health outcome assessments, conducted personal exposure and stove use monitoring while controlling for season in the exposure-response relationship. However, the small sample size (n=324) may have lacked adequate power to detect smaller effects on outcomes. The authors mention the lack of reliable exposure assessments across both the second and third trimester as well as no measurements conducted during the first trimester. Katz et al. (2020) did not conduct personal exposure monitoring and by not measuring infant weight at birth within 24 hours lacked adequate outcome assessment. The high ambient air pollution levels may also have modified the association between HAP and birth outcomes in both studies. Quinn et al. (2021) conducted repeated CO measures among a large sample size (n=1288) using gold standard personal exposure monitoring methods in an attempt to distill the exposure-response relationship of the GRAPHS Trial cookstove intervention. Birth outcomes were directly measured by field workers within 72 hours of birth using standardized anthropometric methods. The authors originally intended to include a single 72 hr $PM_{2.5}$ exposure assessment but the data did not pass assurance/quality control checks. A recently launched RCT, Household Air Pollution Intervention Network (HAPIN) trial, is a multi-country trial to assess the effect of a randomized LPG stove intervention on maternal, child, and adult health outcomes (Clasen et al., 2020). The investigators plan on using repeated 24-h personal and indirect measure of PM and CO as well as black carbon to capture exposure-response associations.

None of the studies included in this review cited a theoretical framework explaining the mechanisms relating HAP to adverse birth outcomes. Capturing the multidimensional nature of socioeconomic status (SES) requires thoughtful justification for included socioeconomic factors and adequate adjustment for poverty as an explanatory pathway influencing health outcomes (Braveman et al., 2005). Except for RCT designed studies where randomization can remove confounding factors in groups, controlling for poverty and SES varied widely across studies.

The main strength of this systematic review was the organization of a breadth of outcome variables into adverse birth outcomes. This format clearly identified significant main findings. The search was conducted in two languages across four databases and built upon references from the two previous reviews (Amegah et al., 2014; Pope et al., 2010). Limitations of the review include a lack of grey literature. The search resulted in studies conducted in only 15 countries and the reviewer may have missed key outcomes specific to other countries. Also, the chosen outcome measures and type of cooking fuels for each study were highly variable making it difficult to compare statistics across studies.

5. Conclusion

This review demonstrates the current evidence on the relationship of HAP from cooking fuel on adverse and serious adverse birth outcomes. The lack of consistent methodological quality limited the validity of the evidence, and more research is needed to establish a causal relationship between HAP and birth outcomes. A deeper understanding of the pathways of HAP exposure via maternal factors remains an area of future research. The UN Sustainable Development Goals support evidence-based policy and their progress over the next ten years may influence political will in low- and middle-income countries to improve access to clean household energy solutions (Amegah et al., 2014). Considering the Sustainable Development

Goals, the findings from this review will continue to guide researchers and policy makers to identify opportunities to address household air pollution for vulnerable populations internationally.

Table 1.3: *Study Characteristics*

	First author and Publication Year	Geographic Location	Setting	Design	Sample Size	Exposure	Outcome	Covariate Adjustment
1	Alexander, 2018	Ibadan, Nigeria	Urban	RCT Stove Intervention	324 pregnant women	Ethanol stove and free fuel intervention, maternal personal CO and $PM_{2.5}$ exposure in second and third trimester	BW, PTB, SAB, Stillbirth, Neonatal Mortality	Marital status, BMI
2	Arinola, 2018	Ibadan, Nigeria	Urban	Cross-sectional	72 pregnant women	Liquified natural gas (LNG) vs kerosene	BW	Family income, maternal age, maternal education level, multivitamin consumption during pregnancy, number of children.
3	Balakrishnan, 2018	Tamil Nadu, India	Urban and rural	Prospective Cohort	1,286 pregnant women	Kitchen $PM_{2.5}$ concentrations	BW, LBW	Season of conception, maternal age, maternal BMI, history of previous LBW child, gestational age, infant sex, birth order.
4	Ezeh, 2014	Nigeria	National	Cross-sectional	30,726 births	Type of cooking fuel	Neonatal Mortality	Place of residence, wealth index, maternal age, maternal education, maternal working status, breastfeeding. child size, child's gender.
5	Haider, 2016	Bangladesh	National	Cross-sectional	8,753 live births	Type of cooking fuel	LBW	Wealth index, residence, location of kitchen, maternal age, maternal education, maternal BMI, antenatal care, pregnancy intention, birth order, sex of child.
6	Islam, 2021a	India	National	Cross-sectional	93,721 full-term singleton births	Type of cooking fuel	BW, LBW	Household wealth index, place of residence, environmental tobacco smoke, maternal age, maternal education, maternal social group, maternal weight, maternal anemia status, maternal tobacco use, antenatal care, pregnancy intention, sex of the child, child birth order.

	First author and Publication Year	Geographic Location	Setting	Design	Sample Size	Exposure	Outcome	Covariate Adjustment
7	Islam, 2021b	India	National	Cross-sectional	8602 full-term singleton births	Gradient of type of cooking fuel	BW	Household wealth index, place of residence, environmental tobacco smoke, place of cooking, maternal age, maternal education, maternal social group, maternal underweight, maternal anemia status, birth interval, antenatal care, sex of the child, child birth order.
8	Jiang, 2015	Lanzhou, China	Urban	Cohort	9,895 pregnant women	Type of cooking fuel	BW, LBW, SGA	Family income, smoking and ventilation, maternal age, maternal education, maternal weight gain, vitamin supplement during pregnancy, preeclampsia, caesarean section, parity, gestational weeks.
9	Kadam, 2013	India	Urban	Cross-sectional	328 women	Type of cooking fuel	BW	Maternal weight gain, breakfast, evening snacks.
10	Katz, 2020	Nepal	Rural	RCT Stove Intervention	907 pregnant women	LPG stove and free fuel intervention (trial 2)	BW, LBW, SGA, PTB	Rainfall and temperature on day of measurement.
11	Khan, 2017	Bangladesh	National	Cross-sectional	22,789 women	Type of cooking fuel	LBW, Stillbirth, Neonatal Mortality	Place of residence, region, socio-economic status, maternal age, maternal education, breastfeeding, sex of child.
12	Milanzi, 2017	Malawi	National	Cross-sectional	9124 households	Type of cooking fuel	BW	Wealth index, place of residence, maternal age, maternal education, maternal BMI, maternal religion, sex at birth, birth order.
13	Mukherjee, 2015	India	Rural	Cross-sectional	404 women	Type of cooking fuel, kitchen $PM_{2.5}$ exposure	LBW, SAB, stillbirth	Socioeconomic status, BMI, environmental tobacco smoke.
14	Nisha, 2018	Bangladesh	National	Cross-sectional	Stillbirth: 27,237 pregnancies Neonatal mortality: 35,052 births	Type of cooking fuel	Stillbirth, Neonatal Mortality	Residence, wealth index, kitchen location, survey year, maternal age, education, BMI, working status, birth order.

	First author and Publication Year	Geographic Location	Setting	Design	Sample Size	Exposure	Outcome	Covariate Adjustment
15	Patel, 2016	India, Pakistan, Kenya, Zambia, Guatemala	Rural	Prospective cohort	65,912 pregnant women	Type of cooking fuel	Stillbirth, Neonatal Mortality	Maternal education, antenatal care, delivery attendant, parity, infant sex.
16	Quinn, 2021	Ghana	Rural	RCT Stove Intervention	1,414 pregnant women	Maternal personal CO exposure	BW, LBW, SGA, PTB	Maternal age, BMI, maternal ethnicity, adequacy of antenatal care visits (4 or more visits versus fewer), parity, infant sex, placental malaria
17	Roberman, 2021	Nigeria	National	Cross-Sectional	41,821 women	Type of cooking fuel	LBW, PTB, Stillbirth	Wealth quintile, region, smoking status, maternal age, maternal education.
18	Suryadhi, 2019	Indonesia	National	Cross sectional	36,842 women	Type of cooking fuel	LBW, Neonatal Mortality	Residential area, maternal age, maternal education, child age, sex at birth.
19	Vakalopoulos, 2021	Sri Lanka	Urban and rural	Cross-sectional	445 live births	Type of cooking fuel, stove type, ventilation	LBW, SGA	Household monthly income, education, area, use of incense, use of vaporizer for mosquitos, exposure to second-hand tobacco smoke, chimney.
20	Weber, 2020	Accra, Ghana	Urban	Cohort	819 pregnant women	Type of cooking fuel	LBW, SAB, PTB	Socioeconomic status, maternal age, maternal education, maternal BMI.
21	Wylie, 2014	Central and East India	Urban and rural	Cross-sectional	1744 pregnant women	Type of cooking fuel	BW, LBW, SGA, PTB, Stillbirth	Propensity score, cohort, presence of windows, time spent cooking, maternal age, BMI, gravidity, hypertension at delivery, hemoglobin at delivery, fever in week prior to delivery.
22	Wylie, 2017	Dar es Salaam, Tanzania	Urban	Prospective Observational Cohort	239 pregnant women	Maternal personal CO and $PM_{2.5}$ exposure, kitchen $PM_{2.5}$	BW	Household asset index, urban neighborhood, housing, parent trial and year of measurements, maternal age, maternal BMI, compliance with prenatal vitamins, parity, sex of infant.
23	Yucra, 2014	Huancavelica and Abancay, Peru	Urban and rural	Case-control	202 full term births	Kitchen CO measurements	SGA	Maternal education level, parity.

BW-birthweight, CO-carbon monoxide, LBW-low birth weight, PM-particulate matter, PTB-preterm birth, SAB-spontaneous abortion, SGA-small for gestational age

Table 1.4: *Adverse Birth Outcomes Associated with Cooking Fuel Type*

	First author and Publication Year	Exposed Group	Comparator Group	Exposure Assessment	Outcome Assessment	Results
1	Alexander, 2018	Kerosene/firewood stove	Ethanol stove intervention	Stove intervention, direct personal CO and PM measure (3 days during second and third trimester)	Newborn weighed with digital scale at birth, medical records.	**Birthweight** Adjusted mean difference: 128g (95% CI: 20, 236) Spontaneous Abortion aRR 0.4 (95% CI 0.04, 3.1) Preterm Birth aRR 0.6 (95% CI: 0.3, 1.3) Stillbirth aRR 0.6 (95% CI: 0.2, 1.9) Neonatal Mortality aRR 0.4 (95% CI: 0.1, 1.4)
2	Arinola, 2018	Kerosene	LNG	Interview	Newborn weighed with digital scale at birth	**Birthweight** Adjusted mean difference: -0.326 kg ± 0.155 (SE)
3	Balakrishnan, 2018	Kerosene, biomass, $PM_{2.5}$ concentration	LPG, $PM_{2.5}$ concentration	Interview, direct kitchen $PM_{2.5}$ measure (24-hour)	Medical records	**Birthweight** Adjusted mean difference: *10µg/m3 increase in $PM_{2.5}$* 4 g (95% CI: 1.08, 6.76) **Low Birth Weight** aOR: ***10µg/m3 increase in $PM_{2.5}$*** 1.02 (95% CI: 1.005, 1.041); *kerosene* 1.22 (95% CI: 0.69, 2.13); *biomass* 1.44 (95% CI: 0.94, 2.21)
4	Ezeh, 2014	Solid fuel (coal/ lignite, charcoal, wood, crop waste, dung straw/shrubs/grass)	Non-solid fuel (electricity, LPG, natural gas, biogas, kerosene)	2013 Nigeria Demographic and Health Survey (NDHS)	NDHS Household recall	Neonatal Mortality aHR: 1.01 (95% CI: 0.73, 1.26)
5	Haider, 2016	Solid fuel (coal, wood, straw/crop)	Non-solid fuel (electricity/gas)	2011 Bangladesh Demographic and Health Survey (BDHS)	BDHS maternal recall of baby size	**Low Birth Weight** aOR: ***coal*** 2.6 (95% CI: 1.1, 6.2); ***wood*** 1.1 (95% CI: 1.0, 1.2); *straw/crop* 1.1 (95% CI: 1.0, 1.3)
6	Islam, 2021a	Unclean cooking fuel (wood, animal dung, agricultural byproducts/ residues/wastes, straw/shrubs/grass, kerosene, charcoal, coal/lignite)	Clean cooking fuel (LPG, biogas, electricity, no food cooked in house)	2015-2016 National Family Health Survey (NFHS)	NFHS maternal recall of baby size, health card	**Birthweight** Adjusted mean difference: 80g (95% CI: NR) Low Birth Weight aOR: 1.03 (95% CI: 0.97, 1.08)
7	Islam, 2021b	Biomass, kerosene, charcoal/coal/lignite,	LPG/gas, biogas, electricity	2015-2016 National Family Health Survey (NFHS)	NFHS maternal recall, health card	**Birthweight** Adjusted mean difference (ref electricity): ***biogas*** -165g (95%CI: NR); ***kerosene*** -138 g (95% CI: NR); ***biomass*** -123g (95% CI:NR); ***coal/ligate/charcoal*** -116 g (95% CI: NR); ***LPG*** -48 g (95% CI: NR)

	First author and Publication Year	Exposed Group	Comparator Group	Exposure Assessment	Outcome Assessment	Results
8	Jiang, 2015	Coal, biomass fuel	Gas fuel	Interview	Medical records	**Birthweight** Adjusted mean difference: ***coal*** -73.31 g (95% CI: -119.77, - 26.89); ***biomass*** -87.84 g (95% CI:-10.76, -164.46) **Low Birth Weight** aOR: *coal* 1.09 (95% CI: 0.67, 1.78); ***biomass*** 2.51 (95% CI: 1.26, 5.01) Small for Gestational Age aOR: *coal* 1.27 (95% CI: 0.90, 1.80), *biomass* 1.22 (95% CI 0.70, 2.08)
9	Kadam, 2013	Wood fuel (including crop residue and dung), LPG+wood, kerosene	LPG	Interview	Newborn weighed with scale within 48 hours of delivery	Birthweight Adjusted mean difference: *wood* -204 g (95% CI: NR); *LPG + wood* -112g (95% CI: NR); *kerosene* -52 g (95% CI: NR)
10	Katz, 2020	Biomass stove with chimney (trial 2)	LPG	Stove intervention, direct kitchen CO and $PM_{2.5}$ measure (2 days, 21.7-hours/day)	Newborn weighed with digital scale within 72 hours of birth, medical records.	Birthweight Adjusted mean difference: -37g (95% CI: -122, 47) Low Birth Weight aRR: 1.34 (95% CI: 0.97, 1.86) Small for Gestational Age aRR: 0.98 (95% CI: 0.79, 1.21) Preterm Birth aRR: 1.28 (95% CI: 0.81, 2.01)
11	Khan, 2017	Solid fuel (coal/ lignite, charcoal, wood, crop waste, dung straw/shrubs/grass)	Clean fuel (electricity, LPG, natural gas, biogas, kerosene)	2007, 2011, 2014 Bangladesh National Health Survey (BDHS)	BDHS maternal recall	Low Birth Weight aOR: 0.96 (95% CI: 0.81, 1.13) Stillbirth aOR 1.09 (95% CI: 0.86, 1.37) Neonatal mortality aOR 1.03 (95% CI: 0.80, 1.33)
12	Milanzi, 2017	High pollution fuel (charcoal, wood, crops, straw, dung)	Low pollution fuel (LPG, electricity, biogas)	2010 Malawi Demographic and Health Survey (MDHS)	MDHS maternal recall, health card	Birthweight Adjusted mean difference: -92 g (95% CI: -320.4, 136.4)
13	Mukherjee, 2015	Biomass fuel PM_{10} concentration	LPG PM_{10} concentration	Survey, direct kitchen PM_{10} measure (3 days, 8hr/day)	Maternal recall	**Low Birth Weight** aOR: 6.82 (95% CI: 3.34, 10.51) **Spontaneous Abortion** aOR: 3.12 (95% CI: 1.07, 4.17) **Stillbirth** aOR: 3.06 (95% CI: 1.14, 7.83)

	First author and Publication Year	Exposed Group	Comparator Group	Exposure Assessment	Outcome Assessment	Results
14	Nisha, 2018	Polluting fuel (charcoal, wood, kerosene, crops, coal/lignite, dung, straw/shrubs/grass)	Clean fuel (biogas, electricity, LPG, natural gas)	2004, 2007, 2011, 2014 Bangladesh Demographic Health Survey (BDHS)	BDHS maternal recall	Stillbirth aOR 1.25 (95% CI: 0.85, 1.84) **Early Neonatal Mortality** aOR 1.46 (95% CI: 1.01, 2.10)
15	Patel, 2016	Polluting fuel (kerosene, charcoal, coal, wood, straw, crop waste, dung).	Clean fuel. (electricity, biogas, LPG, natural gas)	Interview	Interview, hospital records	**Macerated stillbirth** aOR 1.66 (95% CI: 1.23, 2.25) **Non-macerated stillbirth** aOR 1.43 (95% CI: 1.15, 1.85) **Very early neonatal mortality** aOR 1.82 (95% CI: 1.47, 2.22) Later neonatal mortality aOR 1.28 (95% CI: 0.91, 1.76)
16	Quinn, 2021	CO exposure-response across both study arms	CO exposure-response across both study arms	Direct personal CO monitoring (Four 48-hour-average CO measurements)	Newborn weighed with digital scale within 72 hours of birth, medical records by community based field workers.	**Birthweight** Adjusted mean difference: ***1ppm increase*** -53.4g (95% CI: -84.8,-21.9) Low Birth Weight aOR: 1.14 (95% CI: 0.97, 1.33) Small for Gestational Age aOR: 1.14 (95% CI: 0.98, 1.32) Preterm Birth aOR: 0.92 (95% CI: 0.71, 1.2)
17	Roberman, 2021	Unclean cooking fuel (animal dung, charcoal, kerosene, wood, coal, straw/shrubs/grass)	Clean cooking fuel (LPG, biogas, natural gas, electricity)	2018 Nigeria Demographic and health Survey (NDHS)	NDHS maternal recall	Low Birth Weight p.mean: -0.09 (95% CrI: -0.31, 0.10) Preterm Birth p.mean: -0.01 (95% CrI: -0.33, 0.31) **Stillbirth** p.mean: 0.14 (95% CrI: 0.08, 0.20)
18	Suryadhi, 2019	Polluting fuel (coal, lignite, charcoal, straw/shrubs/grass wood)	Clean fuel (gas, kerosene, propane/natural biogas, electricity)	2012 Indonesian Demographic Health Survey (IDHS)	IDHS maternal recall	**Low Birth Weight** aOR 1.62 (95% CI: 1.38, 1.90) **Neonatal Mortality** aOR 1.38 (95% CI: 1.14, 1.67)
19	Vakalopoulos, 2021	Biomass fuel, traditional biomass stove, improved biomass stove, HAP exposure (very high, high, moderate)	Clean fuel (LPG, biogas, electricity), clean energy stove, HAP exposure (low)	Interview	Health card	**Low Birth Weight:** aOR: ***biomass*** 2.74 (95% CI: 1.08, 6.96); ***traditional biomass stove*** 3.23 (95% CI: 1.17, 8.89); *improved biomass stove* 2.11 (95% CI: 0.80, 5.53); ***very high HAP*** 4.63 (95% CI: 1.54, 13.93).**Small for Gestational Age:** aOR: ***biomass*** 1.87 (95% CI: 1.03, 3.41); ***traditional biomass stove*** 2.64 (95% CI: 1.27, 4.91); *improved biomass stove* 1.26 (95% CI: 0.78, 3.06); *very high HAP* 1.76 (95% CI: 0.75, 4.13)

	First author and Publication Year	Exposed Group	Comparator Group	Exposure Assessment	Outcome Assessment	Results
20	Weber, 2020	Polluting fuel (firewood, charcoal, kerosene or crop residue/sawdust)	Clean fuel (LPG, electricity)	Interview	Hospital records, interview	Low Birth Weight aOR 1.05 (95% CI: 0.57, 1.93) Spontaneous Abortion aOR: 2.10 (95% CI: 0.91, 4.81) Small for Gestational Age aOR 1.43 (95% CI: 0.40, 4.89) Preterm Birth aOR: 1.01 (95% CI: 0.48, 2.10)
21	Wylie, 2014	Wood fuel	Gas fuel	Interview	Newborn weighed with digital scale within 24 of birth, Ballard estimation for gestational age, health records	Birthweight Adjusted mean difference: -14 g (95% CI: -93, 66) Low Birth Weight aOR 0.95 (95% CI: 0.58, 1.57) Small for Gestational Age aOR 0.53 (95% CI: 0.23, 1.19) **Preterm Birth** aOR 2.29 (95% CI: 1.24, 4.21) Stillbirth aOR 2.06 (95% CI: 0.08, ∞)
22	Wylie, 2017	$PM_{2.5}$ and CO concentrations	$PM_{2.5}$ and CO concentrations	Interview, direct personal CO (72hr) and $PM_{2.5}$ (48hr), kitchen $PM_{2.5}$ (48hr) measure	Newborn weighed with digital scale within 24 of birth	**Birthweight** Adjusted mean difference: ***$PM_{2.5}$ per interquartile increase*** -0.15kg (95% CI: -0.3, 0.00); *CO per interquartile increase* -0.02 kg (95% CI: 0.11, 0.08)
23	Yucra, 2014	Biofuel, biofuel+gas, kitchen CO levels	Gas fuel	Interview, direct kitchen CO measure (48hr)	Medical records	**Small for Gestational Age** aOR: **biofuel** 4.53 (95% CI: 1.33, 15.49); *biofuel+gas* 2.1 (95% CI: 0.80, 5.55); *CO top tertile level* 3.53 (95% CI:-0.69, 0.63)

Statistically significant results in bold. aOR-adjusted odds ratio, aHR-adjusted hazard ratio, aRR-adjusted relative risk, CO-carbon monoxide, HAP-household air pollution, LPG-liquified petroleum gas, NR-not reported, p.mean-posterior mean, PM-particulate matter

Table 1.5: *OHAT Risk of Bias Heat Map*

Risk of Bias Question	Alexander, 2018	Arinola, 2018	Balakrishnan, 2018	Ezeh, 2014	Haider, 2016	Islam, 2021a	Islam, 2021b	Jiang, 2015	Kadam, 2014	Katz, 2020	Khan, 2017	Milanzi, 2017	Mukherjee, 2015	Nisha, 2018	Patel, 2016	Quinn, 2021	Roberman, 2021	Suryadhi, 2019	Vakalopoulos, 2021	Weber, 2020	Wylie, 2014	Wylie, 2017	Yucra, 2014
Randomization	++									++						+							
Allocation concealment	++									-						+							
Comparison groups		+	++	++	++	+	++	++	++		++	++	++	++	++		+	++	-	+	++	++	+
Confounding (design/analysis)		-	++	+	-	+	+	+	--		-	-	-	-	-		-	-	-	-	++	+	-
Blinding of researchers	--									--						--							
Attrition/missing outcome data	+	++	++	++	++	+	+	+	++	-	++	++	+	+	+	+	--	+	+	-	++	+	++
Exposure characterization	-	--	+	-	-	-	+	-	--	-	-	--	-	-	--	+	-	-	-	--	+	++	+
Outcome assessment	-	-	-	-	--	-	-	+	--	-	-	-	-	-	+	-	--	-	++	+	++	++	-
Outcome reporting	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	-	++	++	++	++	++	+
Other threats	-	--	+	-	-	-	-	-	--	-	--	--	-	-	-	+	--	-	-	+	++	+	-

Key:

Definitely low risk of bias	++
Probably low risk of bias	+
Probably high risk of bias	-
Definitely high risk of bias	--
Not Applicable	

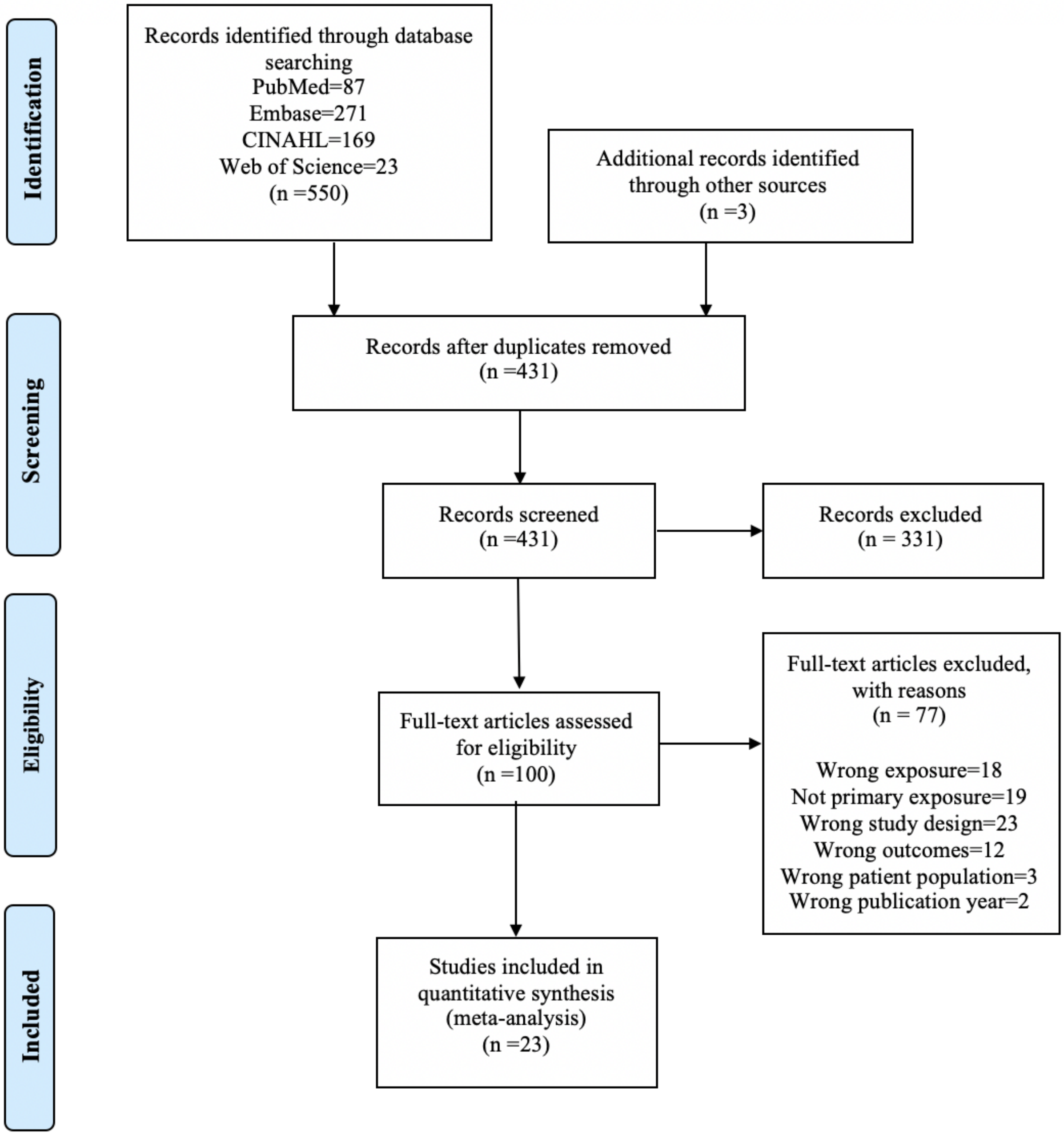


Figure 1.1: *PRISMA Flow Diagram*

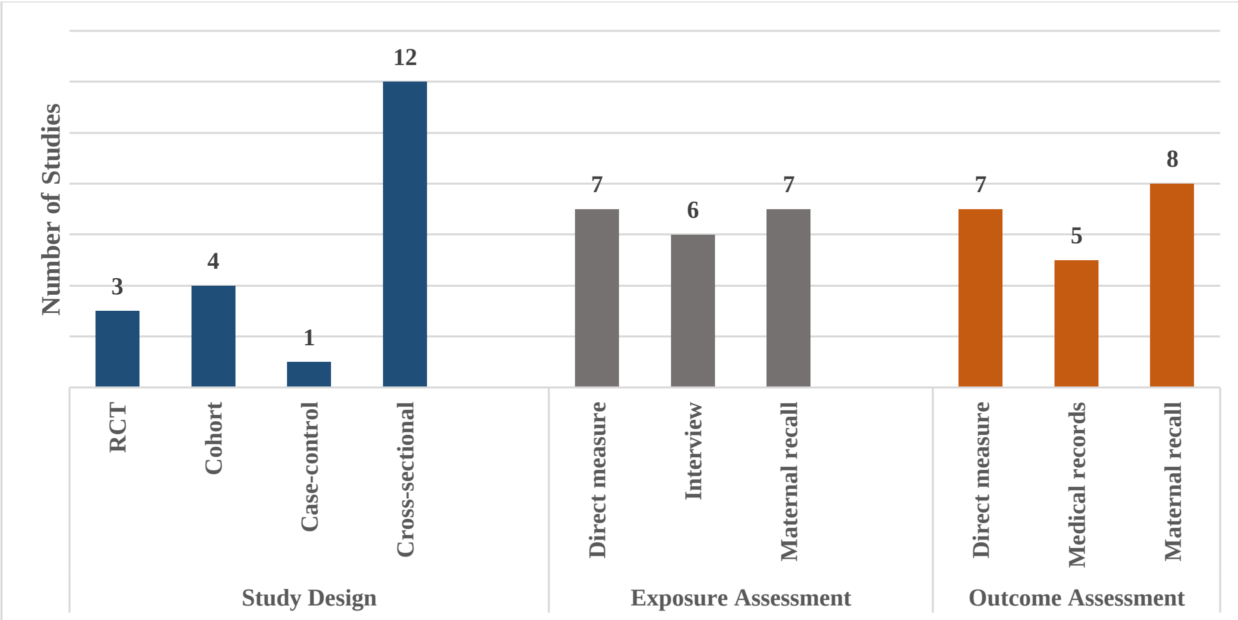


Figure 1.2: *Study design, exposure and outcome assessment measures for outcomes of birthweight, low birthweight and small for gestational age*

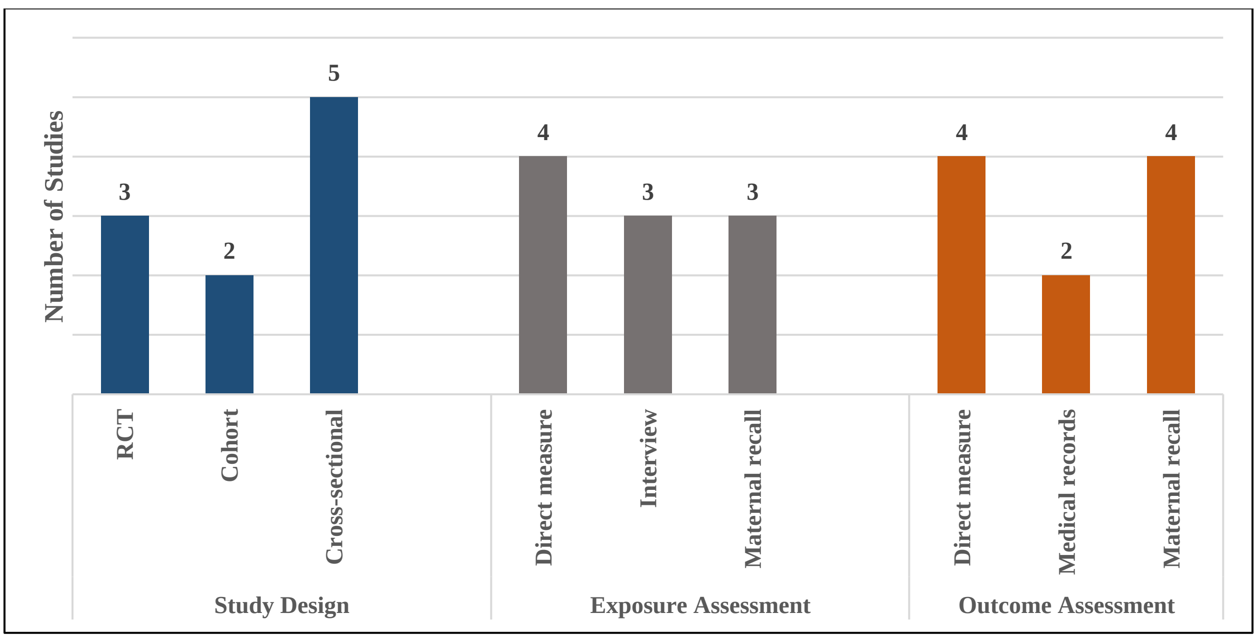


Figure 1.3: *Study design, exposure and outcome assessment measures for outcomes of stillbirth, preterm birth and spontaneous abortion*

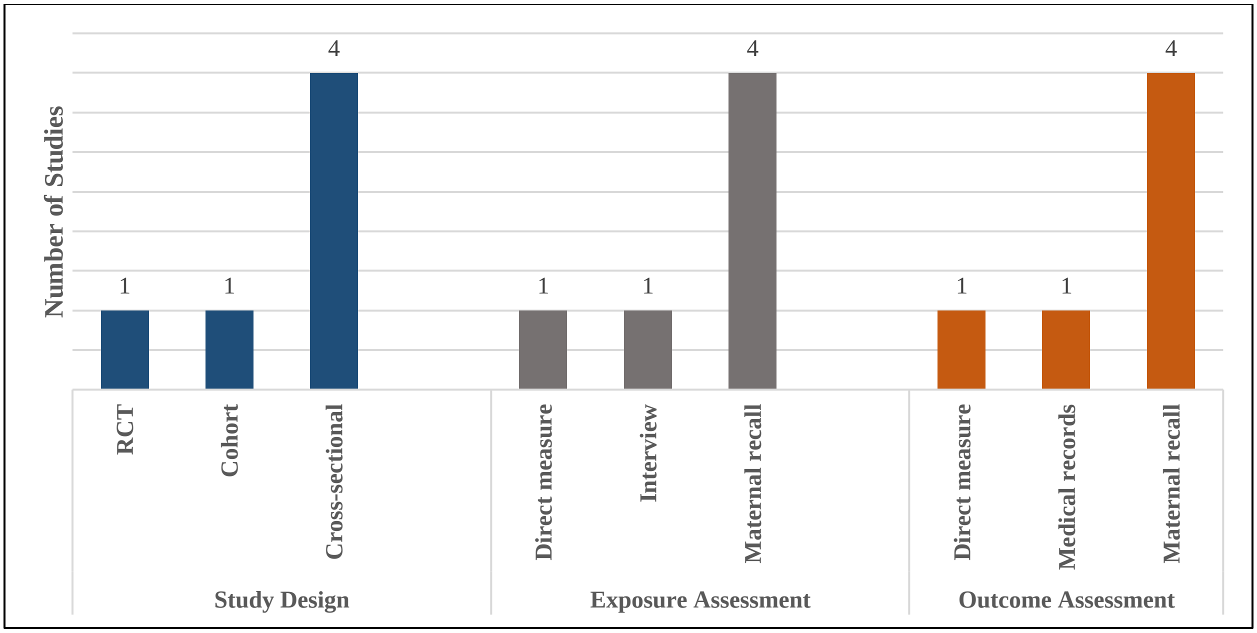


Figure 1.4: *Study design, exposure and outcome assessment measures for outcomes of neonatal mortality*

Supplement Table 1.6: *Search Term and Strategy List*
Date of Search: June 12, 2021

PubMed
May 1, 2013-June 12, 2021

#	Searches	Results
1	"Air Pollution, Indoor"[Mesh] OR "Biofuels"[Mesh] OR "Biomass"[Mesh] OR "Coal"[Mesh] OR "Wood"[Mesh] OR "Charcoal"[Mesh] OR "Kerosene"[Mesh] OR "Cooking"[Mesh] OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR "crop residue" OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke" OR "unclean fuel"	51,024
2	"Pregnancy outcome"[MESH] OR "Pregnancy Outcome/adverse effects"[Mesh] OR "Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature"[Mesh] OR "Gestational Age"[Mesh] OR "Infant, Small for Gestational Age"[Mesh] OR "Fetal Mortality"[Mesh] OR "Fetal Death"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Perinatal Death"[Mesh] OR "Stillbirth"[Mesh] OR stillbirth* OR "Abortion, Spontaneous"[Mesh] OR "Maternal Mortality"[Mesh]	73,277
3	("Air Pollution, Indoor"[Mesh] OR "Biofuels"[Mesh] OR "Biomass"[Mesh] OR "Coal"[Mesh] OR "Wood"[Mesh] OR "Charcoal"[Mesh] OR "Kerosene"[Mesh] OR "Cooking"[Mesh] OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR "crop residue" OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke" OR "unclean fuel") AND ("Pregnancy outcome"[MESH] OR "Pregnancy Outcome/adverse effects"[Mesh] OR "Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature"[Mesh] OR "Gestational Age"[Mesh] OR "Infant, Small for Gestational Age"[Mesh] OR "Fetal Mortality"[Mesh] OR "Fetal Death"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Perinatal Death"[Mesh] OR "Stillbirth"[Mesh] OR stillbirth* OR "Abortion, Spontaneous"[Mesh] OR "Maternal Mortality"[Mesh])	88

EMBASE,
January 1, 2013-June 12, 2021

#	Searches	Results
1	'indoor air pollution'/exp OR 'biofuels'/exp OR 'biomass'/exp OR 'coal'/exp OR 'wood'/exp OR 'charcoal'/exp OR ‘kerosene’/exp OR 'cooking'/exp OR 'household air pollution' OR 'household fuel' OR 'domestic fuel' OR 'cooking fuel' OR 'cooking smoke' OR 'solid fuel' OR firewood OR ‘crop residue’ OR 'biomass fuel' OR 'biomass smoke' OR 'wood fuel' OR 'wood smoke' OR 'charcoal smoke' OR ‘unclean fuel’	79,565
2	‘Pregnancy outcome’/exp OR ‘Pregnancy Outcome/adverse effects’/exp OR ‘Birth Weight’/exp OR ‘Infant, Low Birth Weight’/exp OR ‘Premature Birth’/exp OR ‘Infant, Premature’/exp OR ‘Gestational Age’/exp OR ‘Infant, Small for Gestational Age’/exp OR ‘Fetal Mortality’/exp OR ‘Fetal Death’/exp OR "Perinatal Mortality’/exp OR ‘Perinatal Death’/exp OR ‘Stillbirth’/exp OR stillbirth* OR ‘Abortion, Spontaneous’/exp OR ‘Maternal Mortality’/exp	195,627
3	('indoor air pollution'/exp OR 'biofuels'/exp OR 'biomass'/exp OR 'coal'/exp OR 'wood'/exp OR 'charcoal'/exp OR ‘kerosene’/exp OR 'cooking'/exp OR 'household air pollution' OR 'household fuel' OR 'domestic fuel' OR 'cooking fuel' OR 'cooking smoke' OR 'solid fuel' OR firewood OR ‘crop residue’ OR 'biomass fuel' OR 'biomass smoke' OR 'wood fuel' OR 'wood smoke' OR 'charcoal smoke' OR ‘unclean fuel’) AND ('pregnancy outcome'/exp OR 'pregnancy outcome/adverse effects' OR 'birth weight'/exp OR 'infant, low birth weight'/exp OR 'premature birth'/exp OR 'infant, premature'/exp OR 'gestational age'/exp OR 'infant, small for gestational age'/exp OR 'fetal mortality'/exp OR 'fetal death'/exp OR 'perinatal mortality'/exp OR 'perinatal death'/exp OR 'stillbirth'/exp OR stillbirth* OR 'abortion, spontaneous'/exp OR 'maternal mortality'/exp)	271

CINAHL

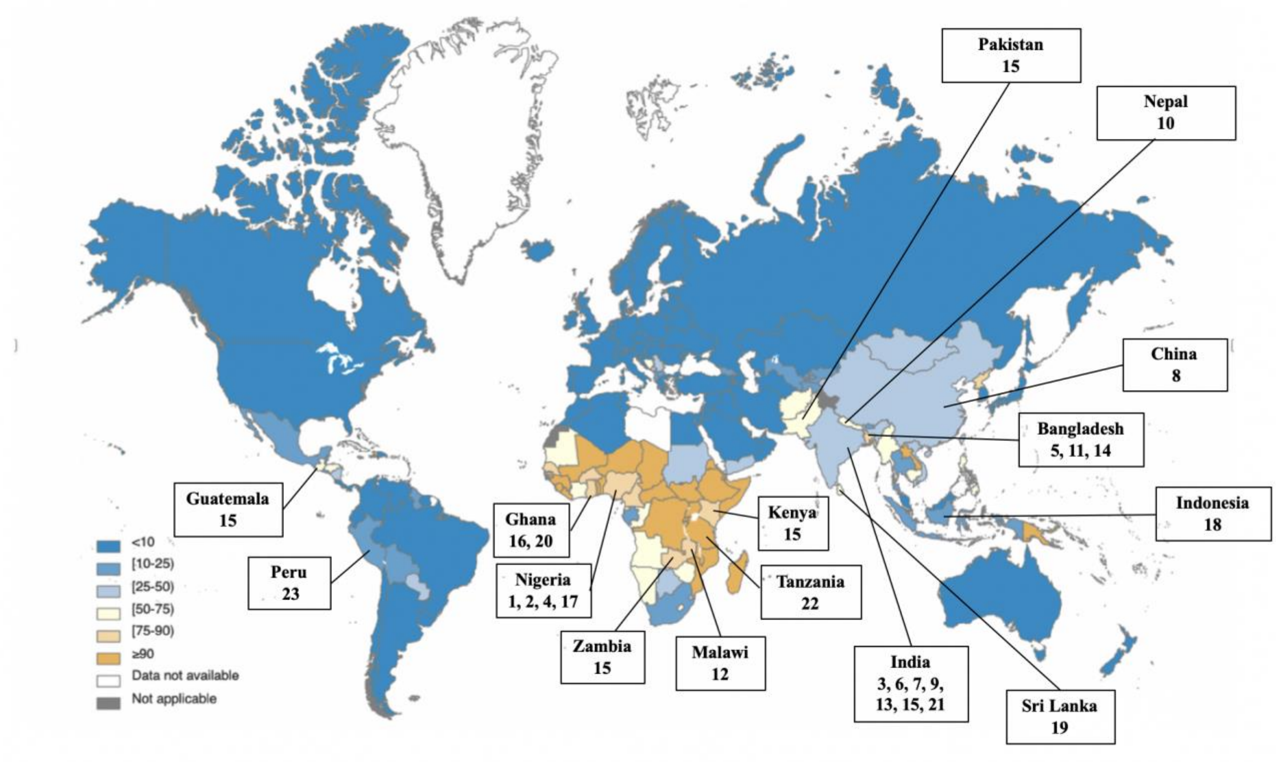
January 1, 2013-June 12, 2021

#	Searches	Results
1	"Indoor air pollution" OR "Biofuels" OR "Biomass" OR "Coal" OR "Wood" OR "Charcoal" OR "Kerosene" OR "Cooking" OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR "crop residue" OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke" Or "unclean fuel"	16,067
2	"Pregnancy outcome" OR "Birth Weight" OR "Low Birth Weight" OR "Premature Birth" OR "Premature Infant" OR "Gestational Age" OR "Small for Gestational Age" OR "Fetal Mortality" OR "Fetal Death" OR "Perinatal Mortality" OR "Perinatal Death" OR "Stillbirth" OR "Spontaneous Abortion" OR "Maternal Mortality"	48,510
3	("Indoor air pollution" OR "Biofuels" OR "Biomass" OR "Coal" OR "Wood" OR "Charcoal" OR "Kerosene" OR "Cooking" OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR "crop residue" OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke" OR "unclean fuel") AND ("Pregnancy outcome" OR "Birth Weight" OR "Low Birth Weight" OR "Premature Birth" OR "Premature Infant" OR "Gestational Age" OR "Small for Gestational Age" OR "Fetal Mortality" OR "Fetal Death" OR "Perinatal Mortality" OR "Perinatal Death" OR "Stillbirth" OR "Spontaneous Abortion" OR "Maternal Mortality")	169

Web of Science

January 1, 2013-June 12, 2021

#	Searches	Results
1	"Air Pollution, Indoor"[Mesh] OR "Biofuels"[Mesh] OR "Biomass"[Mesh] OR "Coal"[Mesh] OR "Wood"[Mesh] OR "Charcoal"[Mesh] OR “Kerosene”[Mesh] OR "Cooking"[Mesh] OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR “crop residue” OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke” OR “unclean fuel”	11,601
2	“Pregnancy outcome”[MESH] OR "Pregnancy Outcome/adverse effects"[Mesh] OR "Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature"[Mesh] OR "Gestational Age"[Mesh] OR "Infant, Small for Gestational Age"[Mesh] OR “Fetal Mortality"[Mesh] OR "Fetal Death"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Perinatal Death"[Mesh] OR "Stillbirth"[Mesh] OR stillbirth* OR "Abortion, Spontaneous"[Mesh] OR "Maternal Mortality"[Mesh]	7,358
3	("Air Pollution, Indoor"[Mesh] OR "Biofuels"[Mesh] OR "Biomass"[Mesh] OR "Coal"[Mesh] OR "Wood"[Mesh] OR "Charcoal"[Mesh] OR “Kerosene”[Mesh] OR "Cooking"[Mesh] OR "household air pollution" OR "household fuel" OR "domestic fuel" OR "cooking fuel" OR "cooking smoke" OR "solid fuel" OR firewood OR “crop residue” OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke” OR "unclean fuel") *AND* (“Pregnancy outcome”[MESH] OR "Pregnancy Outcome/adverse effects"[Mesh] OR "Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Premature"[Mesh] OR "Gestational Age"[Mesh] OR "Infant, Small for Gestational Age"[Mesh] OR “Fetal Mortality"[Mesh] OR "Fetal Death"[Mesh] OR "Perinatal Mortality"[Mesh] OR "Perinatal Death"[Mesh] OR "Stillbirth"[Mesh] OR stillbirth* OR "Abortion, Spontaneous"[Mesh] OR "Maternal Mortality"[Mesh])	23



Supplement Figure 1.5: *Countries Included Study Settings with Proportion of the Population with Primary Reliance on Polluting Fuels and Technology for Cooking (%)*

Modified from: Global Health Observatory, World Health Organization (2021). Proportion of the Population with Primary Reliance on Polluting Fuels and Technology for Cooking [Data visualization]. Retrieved from https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-phe-population-with-primary-reliance-on-polluting-fuels-and-technologies-for-cooking-proportion

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Chapter 2: Effects of a LPG stove and fuel intervention on fetal and neonatal outcomes: a multi-country randomized controlled trial conducted by the Household Air Pollution Intervention Network (HAPIN)

1. Introduction

Globally, 3.8 billion people are exposed to household air pollution (HAP) from the burning of solid fuels for cooking (Health Effects Institute [HEI], 2020; Ghosh et al. 2021). In 2019, HAP exposure contributed to approximately 2.3 million deaths, the majority of which occurred in the regions of South Asia (36%), sub-Saharan Africa (30%) and Southeast Asia, East Asia and Oceania (28%) (HEI, 2020). Research findings show HAP exposure is related to illness across the lifespan including childhood pneumonia, cardiovascular diseases, chronic obstructive respiratory disease, lung cancer and cataracts (Dherani et al., 2008; Gordon et al., 2014; Kurmi et al., 2012; Kurmi et al., 2012, Kurmi et al., 2010; Smith et al., 2011; Smith, 2004). In an effort to further protect population health, the World Health Organization (WHO) revised the Global Air Quality Guidelines (AQGs) of 24-hour mean fine particulate matter ($PM_{2.5}$, with a diameter of 2.5 microns or less), reducing levels from 25 $\mu g/m^3$ in 2005 to 15 $\mu g/m^3$ in 2021 (WHO, 2021).

The incomplete combustion of solid cooking fuel releases pollutants such as particulate matter (PM), carbon monoxide (CO), and sulfur dioxide (SO_2) that can adversely impact health. The two mostly commonly measured pollutants in HAP studies are PM and CO. Several physiologic mechanisms related to these two pollutants have been postulated as harmful to the gestating fetus or the newborn such as oxidative stress, DNA methylation and endocrine disruption (Li et al., 2018). $PM_{2.5}$ can penetrate lung barriers and enter the pregnant woman's or the newborn's blood stream. Due to the ability of particulate matter to cross the placenta and pathological changes such as chronic placental hypoxia and thrombotic lesions, exposure to HAP during pregnancy can negatively affect fetal growth and development (Dutta et al., 2017; Kannan et al., 2006; Wylie et al , 2017). By reducing the oxygen carrying capacity of maternal hemoglobin, CO decreases oxygen delivery to fetal tissue affecting fetal growth and development (Amegah et al., 2014; Salam et al., 2005). Three systematic reviews and meta-analyses reported associations between exposure to unclean cooking fuel during pregnancy and adverse birth outcomes including reductions in birth weight, increased risk of low birthweight and stillbirth (Amegah et al., 2014; Lee et al., 2020; Pope et al., 2010).

The WHO estimates 295,000 newborns die each year due to congenital anomalies (WHO, 2020). Congenital anomalies are structural or functional disorders that occur during pregnancy and impact chronic illness and disability. While primary prevention includes folic acid supplementation, the mechanisms behind congenital anomalies may be impacted by conditions of poverty including air pollution and dietary factors (Hall & Solehdin, 1998; Ravindra et al., 2021). It has been hypothesized that maternal exposure to environmental risk factors, including air pollutants, may contribute to the incidence of abnormal fetal development by promoting oxidative stress (Kampa & Castanas, 2008). Prenatal exposure to indoor air pollution from cooking smoke was also a risk factor for cleft lip and/or palate in children in a population-sampled case-control study across 7 low-resource countries (Auslander et al., 2020). Women who reported cooking over open fire during pregnancy were 49% more likely to have a child with a cleft lip or palate even after adjusting for country, maternal age, paternal education, family history of cleft palate, rural/urban, alcohol intake during pregnancy and smoking variables. A recent systematic review and meta-analysis by Ravindra et al. (2021) reported that prenatal exposure to ambient $PM_{2.5}$ and NO_2 significantly increased the prevalence of pulmonary valve stenosis, $PM_{2.5}$ with tetralogy of Fallot, SO_2 with ventral septal defect and cleft lip/cleft palate, and O_3 with increased prevalence of limb defects. Most of the studies included in the review relied on ambient air pollutant concentrations measured at stationary monitoring stations and lacked measures of indoor air pollution or personal measures of exposure to air pollution. Multiple studies included in the review included covariates such as socio-economic status, maternal age, alcohol, smoking, and folate deficiency. The authors called for improved methods of exposure assessment during pregnancy to identify other contributing factors to congenital malformations due to air pollutants.

Stillbirth is defined as an infant born with no signs of life after a certain gestational age. The WHO defines stillbirth as the death of a baby before or during birth on or after 28 weeks of pregnancy (WHO, 2020). Whereas in the United States, the Center for Disease Control (CDC) National Center for Health Statistics defines stillbirth as a fetal death that occurs after 20 weeks of pregnancy and before or during delivery (CDC, 2020). The United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) estimated 2 million stillbirths occur annually with 84% occurring in low- and middle-income countries (LMICs) (UN IGME, 2020). These data likely underrepresent the global prevalence of stillbirths due to poor quality or incomplete health registries, variability in the definition of stillbirth and misclassification of early neonatal deaths as stillbirths (UN IGME, 2020). In their systematic review and meta-analysis, Amegah et al. (2014) reported a 29% increased risk of stillbirth from solid fuel use (EE 1.29, 95% CI: 1.18, 1.41). The prospective cohort study surveying pregnant women across 5 LMICs by Patel et al. (2015) examined whether HAP from polluting cooking fuels was associated with stillbirth. Compared to households cooking with clean fuels, both macerated (death before onset of labor) and non-macerated (presumed intrapartum death) stillbirth demonstrated significantly higher odds among household using polluting fuels (aOR 1.66, 95% CI: 1.23-2.25) (aOR 1.43, 95 % CI

1.15-1.85), after adjusting for site, lack of maternal education, nulliparity, 3 or more prior births, no antenatal care, and male sex. However, Alexander et al. (2018) conducted a randomized controlled trial (RCT) in Nigeria comparing an ethanol stove intervention to continued use of kerosene/firewood. No statistically significant difference in stillbirth outcomes were found between the intervention and control arms (EE 0.6, 95% CI: 0.2, 1.9).

Neonatal mortality is defined as infant death within the first 28 days of life (WHO, 2020). According to estimates from the WHO, 2.4 million infants died in the first month of life in 2019 (WHO, 2020). Identifying pathways for accelerated reduction of newborn mortality is a pressing goal for achieving the Sustainable Development Goals (SDGs) by 2030 (Gibson et al., 2021). Several studies have explored the association of environmental factors such as HAP exposure during pregnancy with increased risk of neonatal mortality. Using data from the 2012 Indonesian Demographic Health Survey, Suryadhi et al. (2019) found an increased risk of neonatal death for children exposed to high levels of pollution from solid fuel use (OR 1.38, 95% CI: 1.14, 1.67). A prospective cohort study in rural India, Pakistan, Kenya, Zambia and Guatemala also reported households using polluting fuels increased the risk of very early neonatal mortality (aOR 1.82, 95%CI: 1.47, 2.22) (Patel et al., 2015). In contrast, a study using the Bangladesh Demographic Health Survey from 2004-2014 did not find an effect from exposure to polluting cooking fuel on increased odds of neonatal mortality compared to clean fuels such as electricity, LPG and gas (aOR 1.25, 95% CI: 0.85, 1.84) (Nisha et al., 2018). Additionally the RCT by Alexander et al. (2018) did not detect a statistically significant difference in neonatal mortality between the intervention (ethanol stove) and control arms (EE 0.4, 95% CI: 0.1, 1.4).

Since 2014, evidence for the association between HAP and adverse birth outcomes continues to build but findings have not been consistent. Prior research is primarily cross-sectional and unable to establish a causal relationship between unclean fuel use during pregnancy on fetal and neonatal outcomes. The quality of the evidence is limited by variability in exposure assessment, residual and unmeasured confounding, and inconsistency in assessing birth outcomes (Younger et al., 2021). The recent trials have yielded mixed results making it difficult to conclude that there are significant associations between HAP and birth outcomes. Randomized controlled trials allow causal inferences to be drawn on the effect of an intervention to reduce HAP exposures during pregnancy on specific birth outcomes.

The Household Air Pollution Intervention Network (HAPIN) Trial is a randomized controlled trial (RCT) of LPG stoves and continuous, free fuel distribution with behavioral reinforcement to encourage LPG use in intervention homes in four low- and middle-income countries: India, Guatemala, Peru and Rwanda. The HAPIN Trial is the first multi-country RCT collecting a vast amount of high-quality personal air pollution data and health outcomes on pregnant women, their infants and older adult women living in 3200 households. The HAPIN Trial's overall objective is to investigate the effect of a randomized LPG stove and fuel intervention on health in four diverse LMIC populations, determine the exposure-response relationships for HAP and health outcomes as well as measure targeted and exploratory biomarkers of exposure/health effects.

The objective of this paper is to investigate if adverse fetal and neonatal outcomes (congenital anomalies, stillbirth, neonatal mortality) differ based on stove type across the four country sites within the HAPIN Trial. We hypothesized that the relationship between the LPG intervention would reduce personal exposures to HAP during pregnancy and would thus reduce the incidence of adverse fetal and neonatal outcomes, compared to women in the control arm who continued to cook over traditional fires.

2. Methods

2.1 Trial design and study settings

The HAPIN trial is a randomized controlled trial of LPG stoves and free fuel distribution with behavioral reinforcement in the intervention arm conducted in nearly 3200 households from September 2016 to June 2021 across four low-and middle-income countries: India (2 study sites), Guatemala, Peru (6 study sites) and Rwanda. Participating households were followed for an average of 18 months from time of enrollment through the first year of infant's life. Fidelity and adherence to LPG stove use were evaluated using stove and fuel delivery records, questionnaires, visual observations and temperature-logging stove use monitors (SUMs) that continuously monitored traditional stoves in intervention homes throughout the trial. Results showed that among participants in the LPG intervention arm, 96% reported cooking exclusively with LPG at the two follow-up visits during the prenatal period. Among those who retained the traditional stove (68.6%), the majority (59.5%) did not use them as detected via SUMs (Quinn et al., 2021). The study protocol is available at ClinicalTrials.gov Identifier: NCT02944682 and study methods are detailed in a comprehensive study design paper (Clasen et al., 2020).

2.2 Participant recruitment and enrollment

In cooperation with local ministries of health (MoH) authorities, eligible pregnant women were identified at antenatal clinics. At each research site, 800 pregnant women (aged 18 to <35 years, 9 to <20 weeks gestation confirmed by ultrasound) who used traditional biomass stoves for cooking were recruited (Clasen et al., 2020). Half of the participating households in each site were randomly assigned to receive an LPG cookstove and a 18-month supply of free fuel delivered to their home (intervention arm). Education and behavioral reinforcements occurred in intervention homes that continued to use traditional stoves. The other half (control arm) were anticipated to continue cooking with solid biomass fuels. Figure 1 presents the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Moher et al., 2010).

Informed consent was obtained from all study participants that met eligibility requirements using standard procedures. Participants were able to withdraw from the study at any time. The consent forms and study protocol were reviewed and approved by institutional review boards (IRBs) or ethics committees at Emory University (00089799), Johns Hopkins University (00007403), Sri Ramachandra Institute of Higher Education and Research (IEC-N1/16/JUL/54/49) and the Indian Council of Medical Research– Health Ministry Screening Committee [5/8/4-30/(Env)/Indo-US/ 2016-NCD-I], Universidad del Valle de Guatemala (146-08-2016/ 11-2016) and Guatemalan Ministry of Health National Ethics Committee (11-2016), Asociacion Benefica PRISMA (CE2981.17), London School of Hygiene and Tropical Medicine (11664-5), Rwandan National Ethics Committee (No. 357/RNEC/2018), and Washington University in St. Louis (201611159).

2.3 Randomization and intervention

The Emory University data management core assembled randomization lists and sent the assignments to the participating international research centers in sealed tamper-proof envelopes. The randomization list was further stratified into two sites in India and six sites in Peru. Trained study field staff visited the homes of eligible participants and randomized participants into intervention and control after participants selected one of six envelopes provided to them. The intervention households received a high-quality, locally available LPG stove and a continuous supply of free LPG fuel for 18 months. Field staff encouraged exclusive stove use during fuel deliveries and details of the behavior change program have been published (Williams et al., 2020). Control households received international research center (IRC) specific compensations approved by the IRBs or ethics committees during the study, with the option to receive an LPG stove at the end of the study when the child reached 12 months of age (Quinn et al., 2019).

2.4 Data collection and outcome measures

A total of 3195 pregnant women were randomized to the intervention (1590) or control arm (1605) as seen in Figure 1. A baseline survey was administered by a trained, local field worker or nurse following recruitment and informed consent. This baseline survey included questions about cooking behaviors, household characteristics, socioeconomic and demographic info, medical and obstetric history, physical activity, dietary diversity, and household food insecurity. Field workers also measured resting blood pressure in triplicate, and weight and height in duplicate, of enrolled pregnant women at this visit (Clasen et al., 2020). Additional home study visits occurred two additional times before birth, at 24-28 weeks and 32-36 weeks gestation. At these visits, trained local fieldworkers repeated many of the same procedures that occurred at the baseline visit.

Over the course of the 18-month trial, participants were monitored for adverse events (AEs) and serious adverse events (SAEs). AEs and SAEs were defined according to standard definitions used in clinical trials (OHRP, 2007). The definition used for AEs is: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. The definition used for SAEs is an adverse event that: 1) results in death (we divided this into "death" and "stillbirth"); 2) is life threatening, or places the participant at immediate risk of death from the event as it occurred; 3) results in or prolongs hospitalization; 4) causes persistent or significant disability or incapacity; 5) results in congenital anomalies or birth defects; or 6) is another condition which investigators judge to represent significant hazards.

Standardized Operating Procedures (SOPs) for AE and SAE reporting were reviewed at the beginning of the trial with local project managers and fieldworkers at all IRCs. Step-by-step instructions for the AE and SAE case report forms were provided as well. At each regular study visit, fieldworkers asked participants about symptoms or situations that fit AE and SAE definitions that may have occurred since the last study visit. At some IRCs, participants were also asked to call or visit local project offices or contact fieldworkers if any adverse event occurred between these interval visits, such as the loss of a pregnancy or a hospitalization. Whenever an event occurred, the fieldworker collected detailed information on the appropriate case report form (AE or SAE) in REDCap™. If any health condition was ongoing and required medical attention, a referral to the nearest health center or hospital was made. When fieldworkers returned to the office, reports were reviewed by a local project manager for complete data. SAEs were then sent to the research project manager at Emory (AL) via a secure REDCap™ server hosted by Emory University, who reviewed the reports and requested follow-up information as needed. SAEs were reported to IRB and ethics committees per institutional guidelines. A database of the SAEs was also periodically sent to the trial's data safety monitoring board (DSMB) for review.

After the gestational visits, a birth visit occurred. As soon as participants went into labor, they called the project office. Within 24 hours, fieldworkers met the participants at the clinic, hospital or home to collect birth, or in some cases stillbirth, information. Participants were also asked to call or visit our local project offices or contact our fieldworkers if any serious adverse event occurred between these interval visits, such as the loss of a pregnancy or a hospitalization.

Here we define stillbirth as a fetal death ≥ 20 weeks gestation; neonatal mortality as the death of any live-born infant in first 28 completed days of life; and congenital anomaly is any structural or functional anomalies that occur during intrauterine life. All of these events are considered to be a SAE and would be reported on a SAE form. A priori, before the unblinding of data, we designated stillbirth and neonatal death as secondary outcomes and congenital anomalies as an exploratory outcome to the HAPIN primary outcome of birthweight.

2.5 Statistical analysis

First, we conducted preliminary analyses of baseline data summarized by frequencies and percentages for categorical variables and by means and standard deviation (SD) for continuous variables; missing data are reported separately. Second, outcomes were compared using two sample t-tests for continuous variables and chi-square tests for categorical variables. Third, we used intention-to-treat (ITT) analyses according to the randomized allocation. Binary outcomes of stillbirth, neonatal death, and congenital anomalies were compared between the intervention and control arms using log binomial regression models. For all binary outcomes, we performed two-tailed hypothesis tests at an α-level of 0.05, and calculated risk ratios. We also created a composite score by summing reported congenital anomalies, stillbirths and neonatal deaths into one binary adverse neonatal and fetal outcome. The composite score accounted for multiple outcomes in the same participant (example: congenital anomaly and stillbirth). Analyses accounted for the randomization stratum (two in India and six strata in Peru based on number of sites) by combining strata-specific differences using inverse-variance weighting. Primary analyses of stove type related to each of the outcomes were conducted with unadjusted and adjusted models. The adjusted models controlled for the baseline differences found between the intervention and control arms.

3. Results

3.1 Baseline characteristics

Baseline characteristics are detailed by intervention versus control arms in Table 2.1. The mean gestational age of enrollment was 15.4 (SD 3.1) weeks overall and was similar across the 4 country sites indicating the majority of the women were enrolled in the second trimester (Supplemental Table 2.4). The maternal age group of less than 20 years old made up 12.5% while most of the included women were in either the 20-24 (37.4%) and 25-29 (31.8%) age groups. Approximately a third of women were distributed across each category of education levels that were divided into no formal education (32.5%), primary completed (34.2%) to secondary completed (33.3%). Over half of the participants (56.2%) fell into the low category in the minimum dietary diversity score yet over half reported being food secure in the household food insecurity categories (56.1%). The overall mean body mass index (BMI) for pregnant women at enrollment was 23.2 (SD 4.1) and 38.4% were nulliparous.

A majority of the pregnant women reported iron (60.1%) and folate (56.0%) supplementation. The overall mean hemoglobin was 12.5 (SD 1.9). Stratification by IRC revealed India's mean hemoglobin in both the intervention (10.3, SD 1.2) and control arms (10.4, SD 1.3) are classified as anemia in pregnancy (WHO, 2011). Conversely, Peru's mean hemoglobin levels from the intervention (14.3, SD 1.3) and control arms (14.3, SD 1.2) were higher than the overall. In terms of household assets, 87.1% of participant households owned a mobile phone but only 41.5% had a bank account. While all included women were non-smokers to meet inclusion criteria, 10.5% reported a smoker in their household. Chi-square testing revealed randomization resulted in balanced arms except for the categories of maternal education, household food insecurity and bank account. Statistical analyses adjusting for these three variables were performed in addition to unadjusted analyses. Additionally, baseline characteristics were compared within each country site by arms and imbalances were found in Guatemala (no vitamin intake), India (nulliparity), Peru (BMI), Rwanda (maternal education, dietary diversity, household food insecurity, color tv, bank account, household smoking).

3.2 Fetal and Neonatal Outcomes

Fetal and neonatal outcomes by study arm are presented in Table 2.2. Among the 3195 pregnant women in the study, there were 47 congenital anomalies (23 intervention, 24 control), 56 stillbirths (28 intervention, 28 control), and 41 neonatal deaths (20 intervention, 21 control). Table 3 displays results of fetal and neonatal outcomes by study arm stratified by international research center. Among the 800 pregnant women enrolled in Guatemala, 22 congenital anomalies (9 intervention, 13 control), 14 stillbirths (9 intervention, 5 control), and 11 neonatal deaths (5 intervention, 6 control) were reported. The India IRC included 799 pregnant women and 11 congenital anomalies (7 intervention, 4 control), 18 stillbirths (10 intervention, 8 control), and 7 neonatal deaths (4 intervention, 3 control) were reported. Within the Peru IRC, 798 pregnant women participated and reported 8 congenital anomalies (5 intervention, 3 control), 8 stillbirths (2 intervention, 6 control), and 10 neonatal deaths (4 intervention, 6 control). Among the 798 pregnant women from the Rwanda IRC there were 6 congenital anomalies (2 intervention, 4 control), 16 stillbirths (7 intervention, 9 control), and 13 neonatal deaths (7 intervention, 6 control). Across IRCs Guatemala reported the highest number of congenital anomalies (22), India had the highest reported stillbirths (18) and Rwanda recorded the most neonatal mortalities (13).

The overall incidence of congenital anomalies was 1.45% in the intervention arm (23/1590) and 1.50% in the control arm (24/1605). Compared to the control arm, the unadjusted relative risk of congenital anomaly among women randomized to the intervention was 0.96 (95% CI: 0.55, 1.70) (Table 2.2). After adjusting for maternal education, household food insecurity and bank account, it was 0.89 (95% CI: 0.50, 1.59). The analysis showed a slightly lower risk for the intervention arm, although the association was not significant. The highest incidence of congenital anomalies occurred in Guatemala with 2.25% in the intervention arm and 3.25% among controls.

The overall incidence of stillbirth was 1.76% in the intervention arm (28/1590) and 1.74% in the control arm (28/1605). Compared with the control arm, the unadjusted relative risk of stillbirth among women randomized to the intervention was 1.01 (95% CI: 0.60, 1.70). After adjusting for control variables, the relative risk decreased to 0.93 (95% CI: 0.54, 1.59). Both models were not statistically significant. India reported the highest incidence of stillbirth in the intervention arm at 2.50% compared to 2.01% among controls. Peru reported a stillbirth incidence of 0.51% for the intervention arm compared to 1.49% in the control arm. Rwanda reported a stillbirth incidence of 1.78% for the intervention arm compared to 2.23% in the control arm.

The overall incidence of neonatal mortality was 1.26% in the intervention arm (20/1590) and 1.31% in the control arm (21/1605). Compared with the control arm, the unadjusted relative risk of neonatal mortality among women randomized to the intervention was 0.97 (95% CI: 0.53, 1.77) and 0.99 (95% CI: 0.54, 1.82) after adjusting for control variables. Both models did not show a significant association. The incidence of neonatal mortality was highest in the intervention arm in Rwanda with 1.78% compared to 1.49% in the control arm. The lowest incidence was reported among the control arm in India at 0.75% versus 1.00% in the intervention arm.

Finally, the proportion of overall adverse fetal and neonatal composite outcomes (congenital anomaly, stillbirth and neonatal mortality) was 3.08% in the intervention arm (49/1590) and 3.68% in the control arm (59/1605). Compared with the control arm, the unadjusted relative risk of a composite adverse fetal and neonatal outcome among women randomized to the intervention was 0.84 (95% CI: 0.58, 1.22). The adjusted model slightly decreased the relative risk to 0.81 (95% CI: 0.55, 1.18) but remained statistically insignificant. The country site with the highest incidence of combined adverse outcomes was reported in Guatemala among the control arm with 4.50% compared to 3.75% in the intervention arm. The lowest incidence was occurred among the intervention arm in Peru at 1.77% versus 3.23% among controls.

4. Discussion

The HAPIN trial was the first multi-country RCT collecting valid and reliable personal air pollution data on household air pollution and health outcomes on pregnant women across 3195 households. We found that adverse fetal and neonatal outcomes (congenital anomalies, stillbirth, neonatal mortality) did not differ based on stove type across the four country research sites. In intention-to-treat analyses we found women assigned to the LPG intervention arm had a slightly lower risk of congenital anomaly (RR 0.96, 95% CI: 0.55, 1.70) and neonatal mortality (RR 0.97, 95% CI: 0.53, 1.77) compared to women in the control arm. However these results were not statistically significant even after adjusting for maternal education, household food insecurity and bank account. In regards to stillbirth, women assigned to the LPG intervention arm had a slightly higher risk of stillbirth (RR 1.01, 95% CI: 0.60, 1.70) which was reduced after controlling for maternal education, household food insecurity and bank account (aRR 0.93, 95% CI: 0.54, 1.59) but both analyses were not statistically significant. The unadjusted relative risk of the adverse fetal and neonatal composite outcome (congenital anomaly, stillbirth and neonatal mortality) among women randomized to the intervention was 0.84 (95% CI: 0.58, 1.22) and the adjusted model decreased to 0.81 (95% CI: 0.55, 1.18).

Outcomes with small sample sizes can contribute to inadequate power for detecting meaningful differences between arms. A previous randomized stove intervention trial by Alexander et al. (2018) investigated the impact of cooking with ethanol fuel on adverse birth outcomes that included both stillbirth and neonatal mortality. The trial randomized 324 pregnant women in Ibadan, Nigeria to either continue cooking with a kerosene/firewood stove (control) versus cooking with a study-provided ethanol stove (intervention). While there were more stillbirths (3 intervention, 7 control), and neonatal deaths (2 intervention, 5 control) in the control arm, given the small number of events, the differences were not statistically significant. The results are attributed to a low rate of stillbirths accounting for 3.1% (10/324) and neonatal mortality 2.2% (7/324) which did not generate enough power. Our study had an even smaller incidence of reported stillbirths at 1.75% (56/3195) and neonatal mortality at 1.28% (41/3195). While the results supported the protective effect of the LPG intervention arm, the small number of cases contributed to the lack of power and our ability to detect an effect of the intervention on the adverse birth outcomes included in this study. Interestingly, the composite outcome exhibited the largest difference in incidence (3.08% intervention versus 3.68% control) and the lowest relative risk with strongest support for the protective effect of the LPG intervention compared to the individual adverse outcomes (RR 0.84; 95% CI: 0.58, 1.22). This may suggest that the relative risk was lowest when we combined the number of outcomes since we had more power to detect differences among the rare outcomes.

A recognized limitation of the Nigerian trial was the inability to collect more than one $PM_{2.5}$ exposure assessment in 51% of the participating households and thus the study did not cover both the dry and rainy seasons. Ambient air pollution levels may have masked the household differences since available exposure monitoring data was only gathered indoors. The Ghana Randomized Air Pollution and Health Study (GRAPHS) measured lower personal $PM_{2.5}$ exposures among 1414 pregnant women randomized to receive an LPG stove compared to women in the control arm (continued traditional biomass use), but found no difference in neonatal mortality (Jack et al. 2021). The GRAPHS study did not enroll participants until the second trimester of pregnancy. While reporting an uptake of the stove intervention, the authors hypothesized that the stove intervention failed to reduce exposures enough to improve health outcomes possibly due to high housing density and/or continuing to use traditional biomass stoves alongside LPG. Randomization occurred at the community level, crowded neighborhood smoke contributed to overall exposure and the implemented exposure assessment could not differentiate emissions by source.

The null results from the HAPIN trial do not seem to be attributed to inadequate exposure measurement or LPG stove uptake. The HAPIN trial captured HAP exposure using 24-hr personal and indirect measurements of $PM_{2.5}$, CO and black carbon and the trial recruited 50-60 pregnant women a month per IRC over 12 months which would have accounted for seasonal effects (Clasen et al., 2020). Tracked changes in ambient $PM_{2.5}$ concentrations and regional air quality with measurements within each IRC were also recorded. The HAPIN trial exhibited high compliance of the LPG intervention uptake through the use of measured stove use monitors and reduced exposure to (Johnson et al., 2021). The WHO target for annual average $PM_{2.5}$ exposure was recently reduced from 35 μg/$m^3$to 25μg/m^3. Perhaps the intervention failed to reduce exposure sufficiently to impact birth outcomes.

Considering the first trimester is crucial for fetal development, interventions to improve birth outcomes may have a larger impact on birth outcomes if initiated early in pregnancy or even during the preconception period (Jack et al., 2021). Brain, spine, cardiac tissues begin to form in the first twelve weeks of pregnancy along with the placenta, internal organs, cartilage and limbs (American College of Obstetricians and Gynecologists, 2020). The effect of biomass PM_{10} compared to LPG PM_{10} levels on stillbirth outcomes was examined in a cross-sectional study by Mukherjee et al. (2015) in rural West Bengal, India. The study design aimed to account for the effects of cumulative PM_{10} exposure from either biomass or LPG before conception on adverse reproductive outcomes. Researchers collected kitchen PM_{10} over 3 days on 404 women between the ages of 21-43 years old in rural India who in the past 5 years cooked exclusively with biomass fuels compared to LPG. A significant association was observed between cumulative biomass smoke exposure and stillbirth (OR 2.1, 95 % CI: 1.21–4.35). The mean gestational age for enrollment and receipt of the LPG intervention for the HAPIN trial was 15.4 weeks (SD 3.1) and the mean maternal age at baseline was 25.4 years (SD 4.5). Pregnant women were recruited from health centers during antenatal care visits which may have biased results to better outcomes since participants may have been healthier at baseline.

According to the review and meta-analysis by Ravindra et al. (2021), prenatal exposure to $PM_{2.5}$ and NO_2 significantly increased the prevalence of congenital anomalies. Yet most of the 26 studies included in the review relied on ambient air pollutant concentrations measured at stationary monitoring stations and lack measures of indoor air pollution or personal exposure to air pollution. A case-control study included both mothers with fetuses diagnosed with congenital health disease (CHD) and mothers with normal fetuses from 6 hospitals in Northwest China explored the association between cooking stoves used during pregnancy and CHD. Data on stove type and use during pregnancy was self-reported by the enrolled mothers. The study found after adjusting for covariates, coal stoves (OR 2.38, 95% CI: 1.43, 3.95) and firewood (OR 6.74, 95% CI: 3.03, 15.00) were associated with a higher risk for CHD in their offspring compared to gas stoves (Zhao et al., 2021). Interestingly, the study found that higher cooking frequency with gas stoves was also associated with increased risk of CHD compared to lower cooking frequency with gas stoves (OR 2.38, 95% CI*:* 1.43, 3.95). Yet despite the reduction in HAP exposure, our study found pregnant women assigned to the LPG intervention arm did not have a significantly lower risk of congenital anomaly (RR 0.97; 95% CI 0.54, 1.72). This trend remained when the analysis was stratified by IRC (See Table 3).

The HAPIN trial LPG intervention did demonstrate a significant reduction in individual pollutant exposure to $PM_{2.5}$, black carbon, and CO (Johnson et al., 2021). Despite a good exposure contrast in CO/PM, NO_2 was not a measured pollutant. A recent study measured 48-hour kitchen area NO_2 concentrations within a randomized controlled trial of LPG stoves vs biomass among 100 participants in the Peruvian Andes (Kephart et al., 2021). Results showed kitchen area NO_2 concentration were lower within the LPG intervention arm compared to the biomass-using control arm. But within the LPG intervention arm, 69% of 24-hour kitchen area samples exceeded WHO indoor annual guidelines. These results imply there may be potential health risks associated with LPG-related NO_2 emissions and ventilation is an important factor in stove promotion.

Our study has several strengths. The HAPIN trial was one of the largest and first multi-country RCTs using a standardized protocol to assess the effect of a LPG stove intervention on exposure to HAP and adverse birth outcomes. The coordination by field workers, researchers and participants was executed at a high level of competency, resulting in low loss to follow-up, high compliance to stove use and remarkable tracking of adverse outcomes even throughout the COVID-19 pandemic. Multiple exposure assessments post-baseline collected in 24-hr periods provided comprehensive exposure assessment of $PM_{2.5}$ and CO.

This study has several limitations. The study sites chosen for the HAPIN trial were all rural and low-income and thus it becomes challenging to untangle the impact of nutrition and poverty, which may have overwhelmed any protective effects of improved HAP from the LPG intervention, on the outcomes. Pregnant women were recruited from prenatal clinics and may be healthier than other women in the community who do not seek or have access to antenatal care. Enrollment occurred in the second trimester, limiting the length of reduced HAP exposure and potentially missing important first trimester fetal and placental developmental windows that would have benefited from the intervention. Field workers visited both control and intervention households and therefore were unblinded by study arm. A number of potential covariates were missing from data collection including number of prenatal visits, household density, use/compliance to new/unmonitored biomass stoves in LPG homes, or acquisition of LPG stoves in control homes. This study was limited to ITT, and an exposure-response analysis may show trends that are not apparent based on ITT. However, given the good contrast in exposure reductions between intervention and control arms, and adequate randomization, we feel the ITT illustrates the story adequately.

5. Conclusion

The HAPIN trial was the first multi-country RCT collecting data on household air pollution and health outcomes on pregnant women across four countries. While the LPG stove intervention did not significantly reduce the relative risk of adverse birth outcomes, women assigned to the LPG intervention arm had a slightly lower risk of congenital anomaly and neonatal mortality compared to women in the control arm. Enrolling and introducing the LPG intervention to pregnant women in the second trimester may be too late in fetal development to detect a protective effect. Other factors related to poverty and access to adequate prenatal care may play a more important role in improving health outcomes. However, access to sustainable and affordable energy should remain a priority for the global community. Forthcoming HAPIN trial papers will examine effects on child stunting and pneumonia during infancy, and a range of secondary outcomes including early child development.

Table 2.1: *Demographic characteristics at baseline by control and intervention arm*

	Control N = 1,605	**Intervention** N= 1,590	**Overall** N= 3,195[1]
Gestational week at enrollment, mean (SD)	15.3 (3.2)	15.5 (3.1)	15.4 (3.1)
Maternal age in years, N (%)			
<20	209 (13.0)	189 (11.9)	398 (12.5)
20-24	579 (36.1)	616 (38.7)	1,195 (37.4)
25-29	517 (32.2)	500 (31.5)	1,017 (31.8)
30-35	300 (18.7)	285 (17.9)	585 (18.3)
Highest level of education Completed, N (%)*			
No formal education	558 (34.8)	481 (30.3)	1,039 (32.5)
Primary completed	533 (33.2)	558 (35.1)	1,091 (34.2)
Secondary completed	514 (32.0)	550 (34.6)	1,064 (33.3)
Minimum dietary diversity, Category (score)[2], N (%)			
Low (<4)	906 (56.4)	890 (56.0)	1,796 (56.2)
Medium (4-5)	533 (33.2)	496 (31.2)	1,029 (32.2)
High (>5)	165 (10.3)	203 (12.8)	368 (11.5)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
Household food insecurity Category (score)[3]*, N (%)			
Food secure	863 (53.8)	930 (58.5)	1,793 (56.1)
Mild (1, 2, 3)	448 (27.9)	416 (26.2)	864 (27.0)
Moderate (4, 5, 6) / Severe (7, 8)	272 (16.9)	220 (13.8)	492 (15.4)
Missing	22 (1.4)	24 (1.5)	46 (1.4)
Height in cm, mean (SD); N missing	152.1 (6.0); 4	152.3 (6.2); 8	152.2 (6.1); 12
Body mass index (kg/m^2), mean (SD); N missing	23.1 (4.0); 7	23.3 (4.1); 12	23.2 (4.1); 19
Nulliparous[4], N (%)			
Yes	589 (36.7)	639(40.2)	1,228 (38.4)
No	1,014 (63.2)	947(59.6)	1,961 (61.4)
Missing	2 (0.1)	4 (0.3)	6 (0.2)

	Control N = 1,605	Intervention N= 1,590	Overall N= 3,195[1]
Vitamin Intake[5], N(%)			
Multiple micronutrient tablets	198 (12.3)	181 (11.4)	379 (11.9)
Iron	974 (60.7)	947 (59.6)	1,921 (60.1)
Vitamin A	15 (0.9)	10 (0.6)	25 (0.8)
Folate	911 (56.8)	877 (55.2)	1,788 (56.0)
Other	46 (2.9)	44 (2.8)	90 (2.8)
None	314 (19.6)	342 (21.5)	656 (20.5)
Maternal hemoglobin, mean (SD); N missing	12.5 (1.9); 13	12.4 (1.9); 17	12.5 (1.9); 30
Number of people sleeping in house, mean (SD); N missing	4.3 (2.0); 0	4.3 (2.0); 1	4.3 (2.0); 1
Owns household assets, N (%)			
Color television	783 (48.8)	774 (48.7)	1,557 (48.7)
Radio	721 (44.9)	734 (46.2)	1,455 (45.5)
Mobile phone	1,395 (86.9)	1,388 (87.3)	2, 783 (87.1)
Bicycle	409 (25.5)	365 (23.0)	774 (24.2)
Bank account*	628 (39.1)	697 (43.8)	1,325 (41.5)
Someone in household Smokes[6], N (%)	181 (11.3)	153 (9.6)	334 (10.5)

*p<0.05; SD, standard deviation
[1]N=3,200 women were randomized; 5 women were deemed ineligible after randomization
[2]Adapted from Food and Agriculture Organization of the United Nations Minimum Diet Diversity for Women (FAO 2016b)
[3]The Food Insecurity Experience Scale, developed by the Food and Agriculture Organization of the United Nations, http://www.fao.org/3/as583e/as583e.pdf
[4]Nulliparous defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond; miscarriages can have occurred in a woman who is nulliparous.
[5] Vitamins taken in the past 12 months
[6]Someone in the household other than the pregnant woman smokes; pregnant women were all non-smokers based on eligibility criteria

Table 2.2: *Effects of the intervention on congenital anomalies, stillbirth, neonatal mortality and composite outcome* (N=3195)*

Outcome	Intervention (n=1590)	Control (n=1605)	Relative Risk	95% CI	Adjusted Relative Risk	95% CI
Congenital Anomalies						
Yes	23 (1.45%)	24 (1.50%)	0.96	(0.55, 1.70)	0.89	(0.50, 1.59)
No	1567 (98.6%)	1581 (98.5%)				
Stillbirth						
Yes	28 (1.76%)	28 (1.74%)	1.01	(0.60, 1.70)	0.93	(0.54, 1.59)
No	1562 (98.24%)	1577 (98.26%)				
Neonatal Mortality						
Yes	20 (1.26%)	21 (1.31%)	0.97	(0.53, 1.77)	0.99	(0.54, 1.82)
No	1570 (98.74%)	1584 (98.69%)				
Composite Outcome						
Yes	49 (3.08%)	59 (3.68%)	0.84	(0.58, 1.22)	0.81	(0.55, 1.18)
No	1541 (96.92%)	1546 (98.32%)				

*Overall model adjusted for maternal education, household food insecurity and bank account

Table 2.3: *Effects of the intervention on congenital anomalies, stillbirth, neonatal mortality and composite outcome by country site, N (%)*

Outcome	Guatemala		India		Peru		Rwanda	
	Intervention (n=400)	Control (n=400)	Intervention (n=400)	Control (n=399)	Intervention (n=396)	Control (n=402)	Intervention (n=394)	Control (n=404)
Congenital Anomaly								
Yes	9 (2.25)	13 (3.25)	7 (1.75)	4 (1.00)	5 (1.26)	3 (0.75)	2 (0.51)	4 (0.99)
No	391 (97.75)	387 (96.75)	393 (98.25)	395 (99.00)	391 (98.74)	399 (99.25)	392 (99.49)	400 (99.01)
Stillbirth								
Yes	9 (2.25)	5 (1.25)	10 (2.50)	8 (2.01)	2 (0.51)	6 (1.49)	7 (1.78)	9 (2.23)
No	391 (97.75)	395 (98.75)	390 (97.50)	391 (97.99)	394 (99.49)	396 (98.51)	387 (98.22)	395 (97.77)
Neonatal Mortality								
Yes	5 (1.25)	6 (1.50)	4 (1.00)	3 (0.75)	4 (1.01)	6 (1.49)	7 (1.78)	6 (1.49)
No	395 (98.75)	394 (98.50)	396 (99.00)	396 (99.25)	392 (98.99)	396 (98.51)	387 (98.22)	398 (98.51)
Composite Outcome								
Yes	15 (3.75)	18 (4.50)	13 (3.25)	11 (2.76)	7 (1.77)	13 (3.23)	14 (3.55)	17 (4.21)
No	385 (96.25)	382 (95.50)	387 (96.75)	388 (97.24)	389 (98.23)	389 (96.77)	380 (95.45)	387 (95.79)

Supplemental Table 2.4: *Demographic characteristics at baseline by intervention and control arm for each IRC (N=3,195)*[1]

	Guatemala		India		Peru		Rwanda	
	I* N=400	C N=400	I N=400	C N=399	I N=396	C N=402	I N=394	C N=404
Gestational week at enrollment, mean (SD)	14.4 (3.0)	14.2 (3.1)	16.1 (3.0)	16.0 (3.1)	15.8 (3.3)	15.6 (3.4)	15.6 (2.8)	15.4 (2.7)
Maternal age, years, N (%)								
<20	64 (16.0)	58 (14.5)	62 (15.5)	66 (16.5)	40 (10.1)	59 (14.7)	23 (5.8)	26 (6.4)
20-24	168 (42.0)	156 (39.0)	192 (48.0)	190 (47.6)	151 (38.1)	135 (33.6)	105 (26.6)	98 (24.3)
25-29	110 (27.5)	121 (30.3)	117 (29.3)	113 (28.3)	130 (32.8)	127 (31.6)	143 (36.3)	156 (38.6)
30-35	58 (14.5)	65 (16.3)	29 (7.3)	30 (7.5)	75 (18.9)	81 (20.1)	123 (31.2)	124 (30.7)
Highest level of education achieved, N (%)								
No formal education	189 (47.3)	192 (48.0)	130 (32.5)	155 (38.9)	15 (3.8)	20 (5.0)	**147 (37.3)**	**191 (47.3)**
Primary completed	160 (40.0)	152 (38.0)	116 (29.0)	111 (27.8)	131 (33.2)	103 (25.6)	**151 (38.3)**	**167 (41.3)**
Secondary completed	51 (12.8)	56 (14.0)	154 (38.5)	133 (33.3)	249 (63.0)	279 (69.4)	**96 (24.4)**	**46 (11.4)**
Minimum dietary diversity, Category (score)[2], N (%)								
Low (<4)	279 (69.9)	268 (67.0)	315 (78.8)	306 (76.7)	46 (11.6)	41 (10.2)	**250 (63.5)**	**291 (72.2)**
Medium (4-5)	104 (26.1)	115 (28.8)	73 (18.3)	81 (20.3)	203 (51.3)	234 (58.2)	**116 (29.4)**	**103 (25.6)**
High (>5)	16 (4.0)	17 (4.3)	12 (3.0)	12 (3.0)	147 (37.1)	127 (31.6)	**28 (7.1)**	**9 (2.2)**

	Guatemala		India		Peru		Rwanda	
	I* N=400	C N=400	I N=400	C N=399	I N=396	C N=402	I N=394	C N=404
Household food insecurity Category (score)[3], N (%)								
Food secure	225 (56.3)	215 (53.8)	324 (81.0)	321 (80.5)	210 (53.0)	202 (50.3)	**171 (43.4)**	**125 (30.9)**
Mild (1, 2, 3)	126 (31.5)	129 (32.3)	54 (13.5)	60 (15.0)	128 (32.3)	146 (36.3)	**108 (27.4)**	**113 (28.0)**
Moderate (4, 5, 6) / Severe (7, 8)	43 (10.8)	52 (13.0)	19 (4.8)	17 (4.3)	53 (13.4)	47 (11.7)	**105 (26.7)**	**156 (38.6)**
Missing	6 (1.5)	4 (1.0)	3 (0.8)	1 (0.3)	5 (1.3)	7 (1.7)	**10 (2.5)**	**10 (2.5)**
Height in cm, mean (SD); missing	148.6 (5.0); 1	148.2 (5.7); 0	151.0 (5.9); 0	151.2 (5.3); 0	152.7 (4.6); 6	152.6 (4.5); 4	156.9 (6.0); 1	156.2 (5.7); 0
Body mass index (kg/m^2), mean (SD); N missing	23.9 (3.4); 3	23.7 (3.3); 2	19.8 (3.3); 0	19.6 (3.1); 0	**26.3 (3.6); 6**	**25.8 (3.6); 4**	23.3 (3.5); 3	23.5 (3.3); 1
Nulliparous[4], N (%)								
Yes	119 (29.8)	108 (27.0)	**245 (61.3)**	**214 (53.6)**	154 (38.9)	156 (38.8)	121 (30.7)	111 (27.5)
No	281 (70.3)	292 (73.0)	**155 (38.8)**	**185 (46.4)**	239 (60.3)	245 (60.9)	272 (69.0)	292 (72.3)
Missing	0	0	**0**	**0**	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)
Vitamin Intake[5], N (%)								
Multiple micronutrient tablets	129 (32.3)	142 (35.5)	0	0	21 (5.3)	26 (6.5)	31 (7.9)	30 (7.4)
Iron	185 (46.3)	211 (52.8)	374 (93.5)	376 (94.2)	180 (45.5)	169 (42.0)	208 (52.9)	218 (54.1)
Vitamin A	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.3)	4 (1.0)	3 (0.8)	4 (1.0)	6 (1.5)

	Guatemala		India		Peru		Rwanda	
	I* N=400	C N=400	I N=400	C N=399	I N=396	C N=402	I N=394	C N=404
Folate	187 (46.8)	213 (53.3)	384 (96.0)	392 (98.3)	179 (45.2)	169 (42.0)	127 (32.3)	137 (34.0)
Other	3 (0.8)	5 (1.3)	36 (9.0)	37 (9.3)	3 (0.8)	2 (0.5)	2 (0.5)	2 (0.5)
None	**138 (34.5)**	**110 (27.5)**	9 (2.25)	6 (1.5)	115 (24.0)	131 (32.6)	80 (20.3)	67 (16.6)
Maternal hemoglobin, mean (SD); N missing	12.7 (1.0); 1	12.9 (1.1); 2	10.3 (1.2); 0	10.4 (1.3); 0	14.3 (1.3); 9	14.3 (1.2); 10	12.4 (1.6); 3	12.4 (1.5); 5
Number of people sleeping in house, mean (SD)	5.3 (2.7)	5.1 (2.6)	3.8 (1.5)	3.7 (1.6)	4.5 (1.7)	4.7 (1.8)	3.5 (1.5)	3.5 (1.5)
Owns household assets, N (%)								
Color Television	169 (42.3)	188 (47.0)	291 (72.8)	301 (75.4)	247 (62.4)	260 (64.7)	**67 (17.0)**	**34 (8.4)**
Radio	153 (38.3)	151 (37.8)	57 (14.3)	52 (13.0)	289 (73.0)	304 (75.6)	235 (59.6)	214 (53.0)
Mobile phone	361 (90.3)	370 (92.5)	328 (82.0)	327 (82.0)	378 (95.5)	388 (96.5)	321 (81.5)	310 (76.7)
Bicycle	45 (11.3)	53 (13.3)	60 (15.0)	61 (15.3)	147 (37.1)	162 (40.3)	113 (28.7)	133 (32.9)
Bank account	99 (24.8)	98 (24.5)	357 (89.3)	359 (90.0)	94 (23.7)	86 (21.4)	**147 (37.3)**	**85 (21.0)**
Someone in household smokes[6], N (%)	22 (5.5)	22 (5.5)	119 (29.8)	134 (33.6)	4 (1.0)	3 (0.7)	**8 (2.0)**	**22 (5.4)**

$p<0.05$ in bold; SD, standard deviation, *I-intervention, C-control
[1]N=3,200 women were randomized; 5 women were deemed ineligible after randomization
[2]Adapted from Food and Agriculture Organization of the United Nations Minimum Diet Diversity for Women (FAO 2016b)
[3]The Food Insecurity Experience Scale, developed by the Food and Agriculture Organization of the United Nations, http://www.fao.org/3/as583e/as583e.pdf
[4]Nulliparous defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond; miscarriages can have occurred in a woman who is nulliparous.
[5] Vitamins taken in the past 12 months
[6]Someone in the household other than the pregnant woman smokes; pregnant women were all non-smokers based on eligibility criteria

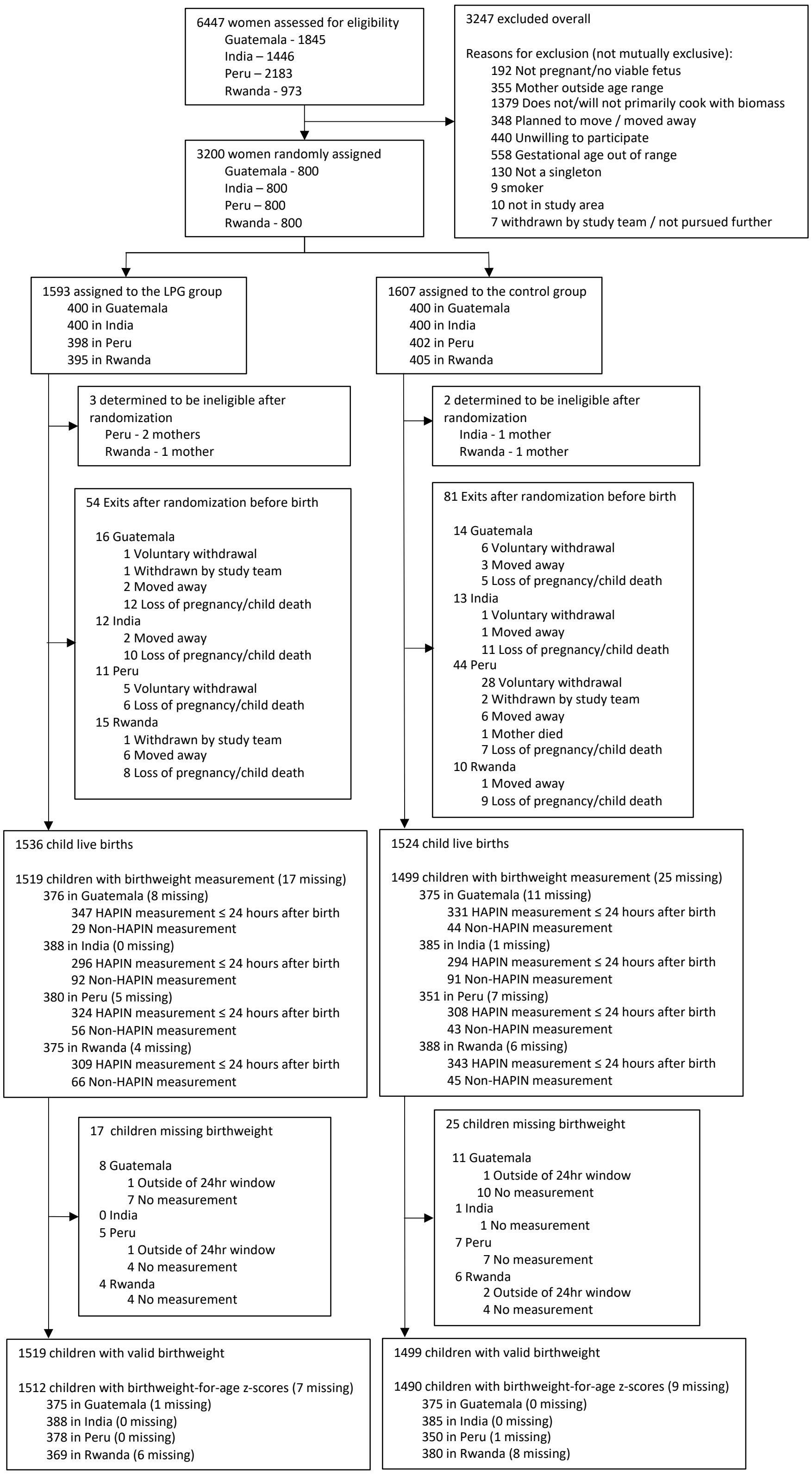

Figure 2.1: *CONSORT Flow Diagram*

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Chapter 3: Effects of a LPG stove and fuel intervention on adverse maternal outcomes: a multi-country randomized controlled trial conducted by the Household Air Pollution Intervention Network (HAPIN)

1. Introduction

Approximately 1.8 million deaths and 60.9 million disability-adjusted life years (DALYs) were attributed to household air pollution (HAP) globally in 2017 (Lee et al., 2020). HAP has been associated with asthma, acute respiratory infection, chronic obstructive pulmonary disease, lung cancer, cerebrovascular and ischemic heart disease, low birthweight, stillbirth, under-5 mortality, as well as respiratory and cardiovascular mortality (Lee et al., 2020). The burden of adverse health effects attributed to HAP mainly occurs in low- and middle-income countries (LMICs) where unclean fuel is used for cooking. The incomplete combustion of solid cooking fuels releases pollutants such as carbon monoxide (CO) and particulate matter (PM) (Smith et al., 2014). Particulate matter can penetrate the lungs and cross into the blood stream increasing the risk for a wide range of diseases and in 2013 the World Health Organization (WHO) the International Agency for Research on Cancer (IARC) classified PM as carcinogenic to humans (WHO, 2013). In an effort to reduce the risk of acute and chronic health conditions from air pollution, the WHO updated their Global Air Quality Guidelines in 2021 to 15 μg/m^3 24-hour mean for fine particulate matter ($PM_{2.5}$) from 25 μg/m^3 in the 2005 guidelines (WHO, 2021).

The placenta functions to regulate fetal growth and acts as the interface between fetal and maternal circulation. Oxidative stress, DNA methylation and mitochondrial DNA alteration, and endocrine disruption have been identified as mechanisms for $PM_{2.5}$ inducing adverse health effects (Li et al., 2018). Pollutants released from the cooking of solid fuels such as $PM_{2.5}$ and CO absorb into the maternal blood stream increasing risk of adverse health effects and can affect fetal growth by directly crossing the placenta (Amegah et al., 2014, Dutta et al., 2017).

Hypoperfusion of the placenta due to chronic hypoxia restricts nutrient supply. The Ghana Randomized Air Pollution and Health Study (GRAPHS) randomized 1414 pregnant women into 3 groups: LPG cookstove, improved biomass cookstove or control traditional 3-stone fire. Participants were monitored for 72-hr personal CO exposure and cord blood was collected immediately following delivery. The study demonstrated an increased biomarker of mitochondrial function that reflects cumulative oxidative stress markers in cord blood of children in the control group compared to the clean cookstove intervention groups (Kaali et al., 2018). CO also has the ability to cross the placental barrier and oxygen delivery to fetal circulation is further compromised since fetal hemoglobin has a higher affinity to CO than adult hemoglobin (Amegah et al., 2014; Longo 1977; Di Cera et al., 1989).

While several studies have linked HAP exposure with adverse birth outcomes like low birth weight, stillbirth, and neonatal death, evidence on maternal health outcomes has been mixed with many relying on ambient pollution data (Alexander et al., 2018; Amegah et al., 2014; Epstein et al., 2013; Patel et al., 2015; Pope et al., 2010). Alexander et al. 2018 conducted a randomized stove intervention trial by investigating the impact of cooking with ethanol fuel on adverse birth outcomes that included spontaneous abortion (SAB). SAB is defined as a loss of fetus before 20 weeks of pregnancy. The trial randomized 324 pregnant women in Ibadan, Nigeria to enter continue cooking with kerosene/firewood stove (control) versus a received ethanol stove (intervention). There were only 4 reported SABs and while fewer occurred in the ethanol group (1 ethanol, 3 control) the numbers were too small to uncover significant differences between groups.

Agrawal & Yamamoto (2015) investigated the associated between exposure to HAP from biomass and solid fuel combustion and preeclampsia/eclampsia symptoms in India women using the National Family Health Survey (NFHS-3, 2005-2006). Results demonstrated that women living in households using biomass/solid fuels have a higher likelihood of reporting preeclampsia/eclampsia compared to women living in households cooking with cleaner fuels (OR=2.21, 95% CI: 1.26, 3.87). Two studies examined the association between ambient air pollution and maternal mortality but none have been conducted on HAP from cooking fuel (Lien et al., 2019; Owili et al., 2017). Similarly there is limited evidence associating HAP with post-partum hemorrhage (Weber et al., 2021).

The quality of the evidence from prior research between unclean fuel use during pregnancy on pregnancy outcomes is limited by variability in exposure assessment, residual and unmeasured confounding, and inconsistency in assessing birth outcomes (Younger et al., 2021). The Household Air Pollution Intervention Network (HAPIN) Trial is a randomized controlled trial (RCT) of a LPG stove intervention with continuous, free fuel distribution and behavioral reinforcement to encourage LPG use in intervention homes across four countries: India, Guatemala, Peru and Rwanda. The overall objective of the HAPIN Trial is to investigate the effect of a randomized LPG stove and fuel intervention on health outcomes in four diverse LMIC populations, determine the exposure-response relationships as well as measure targeted and exploratory biomarkers of exposure on health effects.

The objective of this paper is to investigate if adverse maternal outcomes (spontaneous abortion, hypertensive disorders of pregnancy, postpartum hemorrhage and maternal mortality) differ based on stove type across four country sites within the HAPIN Trial. We hypothesized that the relationship between the LPG intervention would reduce personal exposures to HAP during pregnancy and would thus reduce the incidence of adverse maternal outcomes, compared to women in the control arm who continued to cook over traditional fires.

2. Methods

2.1 Trial design and study settings

The HAPIN trial is a randomized controlled trial of LPG stoves and free fuel distribution conducted in nearly 3200 households across four low-and middle-income countries: India (2 study sites), Guatemala, Peru (6 study sites) and Rwanda from September 2016 to June 2021. Participating households were followed for an average of 18 months. Stove and fuel delivery records, questionnaires, visual observations and temperature-logging stove use monitors (SUMs) that continuously monitored traditional stoves in intervention homes throughout the trial were used to evaluate fidelity and adherence to LPG stove use. Results showed 96% of participants in the LPG intervention arm reported cooking exclusively with LPG at the two follow-up visits during the prenatal period. For those who retained the traditional stove (68.6%), the majority (59.5%) did not use them as detected via SUMs (Quinn et al., 2021). The study protocol is available at ClinicalTrials.gov Identifier: NCT02944682 and study methods are detailed in study design paper (Clasen et al., 2020).

2.2 Participant recruitment and enrollment

Eligible pregnant women were identified at antenatal clinics in cooperation with local ministries of health (MoH). 800 pregnant women were recruited from each research site (aged 18 to <35 years, 9 to <20 weeks gestation confirmed by ultrasound) who used traditional biomass stoves for cooking (Clasen et al., 2020). Half of the participating households in each site were randomly assigned to the intervention arm to receive an LPG cookstove and a 18-month supply of free fuel delivered to their home. The other half of enrolled pregnant women were anticipated to continue cooking with solid biomass fuels as the control arm. Figure 1 presents the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Moher et al., 2010).

Informed consent was obtained from all study participants that met eligibility requirements and participants were able to withdraw from the study at any time. The consent forms and study protocol were reviewed and approved by institutional review boards (IRBs) or ethics committees at Emory University (00089799), Johns Hopkins University (00007403), Sri Ramachandra Institute of Higher Education and Research (IEC- N1/16/JUL/54/49) and the Indian Council of Medical Research– Health Ministry Screening Committee [5/8/4-30/(Env)/Indo-US/ 2016-NCD-I], Universidad del Valle de Guatemala (146-08-2016/ 11-2016) and Guatemalan Ministry of Health National Ethics Committee (11-2016), Asociacion Benefica PRISMA (CE2981.17), London School of Hygiene and Tropical Medicine (11664-5), Rwandan National Ethics Committee (No. 357/RNEC/2018), and Washington University in St. Louis (201611159).

2.3 Randomization and intervention

Randomization lists were assembled by the Emory University data management core and sent the assignments to the participating international research centers in sealed tamper-proof envelopes where they were further stratified into two sites in India and six sites in Peru. Eligible participants were randomized into intervention and control arms after participants selected one of six envelopes provided to them by trained study field staff visiting their homes. The intervention households received a high-quality, locally available LPG stove as well as continuous supply of free LPG fuel for 18 months during the study. Exclusive stove use during fuel deliveries was encouraged by field staff and details of the behavior change program have been published (Williams et al., 2020). Control households received compensations specific to the international research center (IRC) and also had the option to receive an LPG stove at the end of the study when the child reached 12 months of age.

2.4 Data collection and outcome measures

A total of 3195 pregnant women were enrolled and randomized to the intervention (1590) or control arm (1605) as detailed in Figure 1. A baseline survey administered by a trained, local field worker or nurse following recruitment and informed consent included questions about cooking behaviors, household characteristics, socioeconomic and demographic info, medical and obstetric history, physical activity, dietary diversity, and household food insecurity. The resting blood pressure of enrolled pregnant women was measured in triplicate, and height and weight in duplicate (Clasen et al., 2020). Additional follow-up home study visits occurred two additional times before birth, at 24-28 weeks and 32-36 weeks gestation where trained local fieldworkers repeated many of the same procedures that occurred at the baseline visit.

Adverse events (AEs) and serious adverse events (SAEs) were defined according to standard definitions used in clinical trials (OHRP, 2007). Participants were monitored for adverse events (AEs) and serious adverse events (SAEs) throughout the 18-month trial. Whenever an event occurred, the fieldworker collected detailed information was collected by the fieldworker on the appropriate case report form and uploaded in REDCap™. In the event of pregnancy loss or hospitalization between interval visits, participants were encouraged to contact fieldworkers. Referrals were made to the nearest health center for ongoing health conditions requiring medical attention. SAEs were then sent to the research project manager at Emory (AL) via a secure REDCap™ server hosted by Emory University, who reviewed the reports and requested follow-up information as needed. SAEs were reported to IRB and ethics committees per institutional guidelines and sent to the HAPIN data safety monitoring board (DSMB) periodically for review. Within 24 hours of birth, fieldworkers met the participants at the clinic or hospital to collect birth information.

We define spontaneous abortion (SAB) as a loss of fetus before 20 weeks of pregnancy; maternal mortality defined as the death of a woman while pregnant or within 42 days of termination of pregnancy irrespective of the duration and site of the pregnancy and post-partum hemorrhage as loss of more than 500 ml to 1,000 ml of blood within the first 24 hours following childbirth. The outcome of hypertensive disorders of pregnancy included preeclampsia defined as a new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or postpartum in a previously normotensive woman. hypertensive disorders of pregnancy also included cases of gestational hypertension defined as the new onset of hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation.

2.5 Statistical analysis

First, baseline data was summarized by frequencies and percentages for categorical variables and by means and standard deviation (SD) for continuous variables; missing data were reported separately. Second, we compared outcomes using two sample t-tests for continuous variables and chi-square tests for categorical variables. Third, we conducted intention-to-treat (ITT) analyses according to the randomized allocation. Binary outcomes of SAB, postpartum hemorrhage, hypertensive disorders of pregnancy, and maternal mortality were compared between the intervention and control arms using log binomial regression models. We performed two-tailed hypothesis tests at an α-level of 0.05, and calculated risk ratios for all binary outcomes. We also created a composite score by summing reported SAB, hypertensive disorders of pregnancy, postpartum hemorrhage and maternal mortality into one binary adverse neonatal and fetal outcome. The composite score accounted for the potential for multiple outcomes in the same participant. In combining strata-specific differences using inverse-variance weighting, analyses also accounted for the randomization stratum (two randomization strata in India and six strata in Peru based on number of sites). Analyses for the relationship between stove type and each maternal outcome were conducted with unadjusted and adjusted models

3. Results

3.1 Baseline characteristics

Table 3.1 details baseline characteristics by intervention versus control arm. The mean gestational age of enrollment was 15.4 (SD 3.1) weeks overall and was similar across the 4 country sites (Supplemental Table 3.4). Most of the included women were in either the 20-24 (37.4%) and 25-29 (31.8%) age groups. Enrolled women were evenly distributed across educational categories into each category of education levels that were divided into no formal education (32.5%), primary completed (34.2%) to secondary completed (33.3%). Over half of the participants (56.2%) fell into the low category in the minimum dietary diversity score and only 11.5% were in the high dietary diversity category. Over half reported being food secure in the Household food insecurity categories (56.1%) and the smallest percentage in the severe food insecurity category (15.4%). The mean body mass index (BMI) for pregnant women at enrollment was 23.2 (SD 4.1) and 38.4% were nulliparous.

Enrolled pregnant women reported iron (69.1%) and folate (56%) supplementation and the overall mean hemoglobin was 12.5 (SD 1.9). Stratification by IRC revealed Peru's mean hemoglobin levels from the intervention (14.3, SD 1.3) and control arms (14.3, SD 1.2) were higher than the overall. Conversely, India's mean hemoglobin in both the intervention (10.3, SD 1.2) and control arms (10.4, SD 1.3) are classified as anemia in pregnancy (WHO, 2011). The mean number of people sleeping in a household was 4.3 (SD 2.0). In terms of household assets, 87.1% of participant households owned a mobile phone, 41.5% had a bank account, 48.7% had a color television and 45.5% had a radio. To meet inclusion criteria enrolled women were non-smokers but 10.5% reported a smoker in their household. Randomization resulted in balanced arms except for the categories of maternal education, household food insecurity and bank account. Adjusting for these three variables were performed in addition to unadjusted analyses. Baseline characteristics were compared within each country site by arms and imbalances were found in Guatemala (no vitamin intake), India (nulliparity), Peru (BMI), Rwanda (maternal education, dietary diversity, household food insecurity, color tv, bank account, household smoking).

3.2 Maternal Outcomes

Maternal outcomes by study arm are presented in Table 3.2. Among the 3195 pregnant women in the study, there were 11 SAB (8 intervention, 3 control), 59 hypertensive disorders of pregnancy (39 intervention, 44 control), 11 post postpartum hemorrhage (5 intervention, 6 control), and 5 maternal deaths (3 intervention, 2 control). Table 3.3 displays results of maternal outcomes by study arm stratified by international research center. Among the 800 pregnant women enrolled in Guatemala, 3 SAB (3 intervention, 0 control), 32 hypertensive disorders of pregnancy (16 intervention, 16 control), 3 post postpartum hemorrhage (0 intervention, 3 control), and no maternal deaths were reported. The India IRC included 799 pregnant women and 2 SABs (0 intervention, 2 control), 17 hypertensive disorders of pregnancy (8 intervention, 9 control), 2 post postpartum hemorrhage (2 intervention, 0 control), and 2 maternal deaths (2 intervention, 0 control) were reported. Within the Peru IRC 798 pregnant women participated and reported 5 SABs (4 intervention, 1 control), 21 hypertensive disorders of pregnancy (10 intervention, 11 control), 6 post postpartum hemorrhage (3 intervention, 3 control), and 3 maternal deaths (1 intervention, 2 control). Among the 798 pregnant women from the Rwanda

IRC there were 1 SAB (1 intervention, 0 control), 16 hypertensive disorders of pregnancy (5 intervention, 8 control), no post postpartum hemorrhage or maternal deaths. Across IRCs Peru reported highest number of SABs (5), postpartum hemorrhage (6), and maternal deaths (3). Guatemala recorded the most cases of hypertensive disorders of pregnancy (32).

The overall incidence of SAB was 0.50% in the intervention arm (8/1590) and 0.19% in the control arm (3/1605). Compared to the control arm, the unadjusted relative risk of SAB among women in the intervention arm was 2.69 (95% CI: 0.71, 10.12) (Table 3.2). After adjusting for maternal education, household food insecurity and bank account it was 2.52 (95% CI: 0.67, 9.51). The analysis showed a higher risk for the intervention arm, although the association was not significant. The highest incidence of SAB occurred in Peru with 1.01% in the intervention arm.

The overall incidence of hypertensive disorders of pregnancy was 2.45% in the intervention arm (39/1590) and 2.74% in the control arm (44/1605). Compared with the control arm, the unadjusted relative risk of hypertensive disorders of pregnancy among women in the intervention arm was 0.89 (95% CI: 0.58, 1.37). After adjusting for control variables, the relative risk decreased slightly to 0.88 (95% CI: 0.57, 1.36). Both models were not statistically significant. Guatemala reported the highest incidence of hypertensive disorders of pregnancy in the intervention arm at 4.00% and controls. Peru reported a hypertensive disorders of pregnancy incidence of 2.53% for the intervention arm compared to 2.74% in the control arm. Rwanda reported a hypertensive disorders of pregnancy incidence of 1.27% for the intervention arm compared to 1.98% in the control arm.

The overall incidence of postpartum hemorrhage was 0.31% in the intervention arm (5/1590) and 0.37% in the control arm (6/1605). Compared with the control arm, the unadjusted relative risk of postpartum hemorrhage among women in the intervention arm was 0.84 (95% CI: 0.26, 2.74) and 0.85 (95% CI: 0.26, 2.80) after adjusting for control variables. The analysis showed a slightly lower risk for the intervention arm, although the association was not significant. The incidence of postpartum hemorrhage was highest in the intervention arm in Peru with 0.76% compared to 0.75% in the control arm. Rwanda reported no postpartum hemorrhage events

The overall incidence of maternal mortality was 0.19% in the intervention arm (3/1590) and 0.12% in the control arm (2/1605). Compared with the control arm, the unadjusted relative risk of maternal mortality among women in the intervention arm was 1.51 (95% CI: 0.25, 9.03) and 0.1.66 (95% CI: 0.28, 9.94) after adjusting for control variables. Both models did not show a significant association. The incidence of maternal mortality was highest in the control arm in Peru (0.50%) and the intervention arm in India (0.50%). Guatemala and Rwanda reported no maternal deaths.

Finally, the proportion of overall adverse maternal composite outcome (SAB, postpartum hemorrhage, hypertensive disorders of pregnancy, and maternal mortality) was 3.33% in the intervention arm (53/1590) and 3.30% in the control arm (53/1605). Compared with the control arm, the unadjusted relative risk of a composite adverse maternal outcome among women randomized to the intervention was 1.01 (95% CI: 0.69, 1.46). The adjusted model slightly decreased the relative risk to 0.99 (95% CI: 0.68, 1.46) but remained statistically insignificant. The country site with the highest incidence of combined adverse maternal outcomes was reported in Guatemala among the intervention and control arms with 4.75%. The lowest incidence was occurred among the intervention arm in Rwanda at 1.52%.

4. Discussion

The HAPIN Trial is the first multi-country RCT collecting high-quality data on personal air pollution and health outcomes on pregnant women, their infants and older adult women living in almost 3200 households. We found that adverse maternal outcomes (SAB, hypertensive disorders of pregnancy, postpartum hemorrhage and maternal mortality) did not differ based on stove type across four country research sites. In intention-to-treat analyses women assigned to the LPG intervention arm had a higher risk of SAB (RR 2.69, 95% CI: 0.71, 10.12) and maternal mortality (RR 1.51, 95% CI: 0.25, 9.03) compared to women in the control arm. These results were not statistically significant even after adjusting for maternal education, household food insecurity and bank account. In regards to hypertensive disorders of pregnancy and postpartum hemorrhage, women assigned to the LPG intervention arm had a lower risk of hypertensive disorders of pregnancy (RR 0.89, 95% CI: 0.58, 1.37) and postpartum hemorrhage (RR 0.84, 95% CI: 0.26, 2.74) but were not statistically significant.

The mechanisms behind pregnancy loss are multifactorial and can include genetics demographics, history of miscarriage but many cases have unknown causes (Ha et al., 2018). In a US-based prospective cohort study among couples trying to conceive, Ha et al., 2018 reported an increase in the hazard ratio per interquartile increase of ambient $PM_{2.5}$ across the entire pregnancy and faster time to pregnancy loss (HR 1.13, 95% CI: 1.03, 1.24). The authors concluded that chronic exposure may be more detrimental than acute exposure during specific gestational windows. A case control study in Sri Lanka reported women who experienced SAB were more likely (OR 3.83, 95% CI: 1.50, 9.90) to be exposed to cooking smoke from firewood (Samaraweera et al., 2010). However, the study defined SAB as pregnancy loss up to 28 weeks gestation and results for CO exposure and SAB were inconclusive (Grippo et al., 2018). Since approximately 80% of early pregnancy loss occurs in the first trimester, SAB outcomes in our study may have been under reported considering the mean gestational age of enrollment occurred at 15.4 (SD 3.1) weeks (Dugas & Slane, 2021). Also, introducing the LPG intervention in the second trimester may not have been enough protection to counter chronic particulate matter exposure.

Lien et al. 2019 utilized annual mean ambient biomass $PM_{2.5}$ distribution concentrations for 16 years across 45 countries to analyze the relationship with maternal mortality. The study found biomass $PM_{2.5}$ concentrations were associated with an increased incidence rate ratio (IRR) of maternal deaths in Asia (IRR=1.09, 95% CI: 1.08, 1.10). A second study also used 16 years of annual mean ambient biomass $PM_{2.5}$ data included 54 countries in Africa but defined maternal death as a death during pregnancy from any cause (Owili et al., 2017). The results linked ambient biomass burning $PM_{2.5}$ increase the rate of maternal mortality in Central Africa (IRR=1.19, 95% CI: 1.15, 1.23). In their analysis of HAP from biomass and solid fuel combustion and preeclampsia/eclampsia symptoms, Agrawal & Yamamoto (2015) relied on self-report to ascertain cases women which may have been subject to recall bias. Hypertensive disorders of pregnancy and postpartum hemorrhage have complex etiologies and may be influenced by many factors including parity and obstetric history. Unfortunately we could not use these covariates in our analysis due missing data.

The main strength of this study centered around the HAPIN trial being one of the largest and first multi-country RCT using a standardized protocol to assess the effect of a LPG stove intervention on exposure to HAP and adverse birth outcomes. Multiple exposure measurements of $PM_{2.5}$ and CO coupled with stove use monitoring to assess stove stacking enabled comprehensive assessments of HAP. Throughout the Covid-19 pandemic, field workers, participants and researchers continued to conduct the trial resulting in low loss to follow-up and high fidelity and adherence to the intervention. This study addressed many of the gaps in the literature and was the first study to explore HAP exposure on multiple maternal outcomes in LMICs.

There are several limitations to this study. The mechanisms behind pregnancy loss and adverse events during pregnancy are multifactorial and intertwined with conditions of poverty. The trend of a LPG protective effect seen in postpartum hemorrhage and hypertensive disorders of pregnancy may have been overshadowed by the impact of nutrition and poverty on maternal health. Missing from the data collection were potential confounders such as number of prenatal visits, history of adverse outcomes (too many missing responses), household density, user/compliance to new/unmonitored biomass stoves in LPG homes, or acquisition of LPG stoves in control homes. Since enrollment occurred during the second trimester our study may have missed important windows of gestational development more sensitive to HAP exposure. Second trimester enrollment also limits our estimate of SAB outcomes that more frequently occur in the first trimester. Additionally, recruitment occurred at prenatal clinics and may have missed pregnant women who do not have access to or do not seek antenatal care. The calculated power for primary outcomes in the HAPIN Trial may not have been enough to detect differences in more rare outcomes presented in this study. Finally, this study was limited to ITT analysis and an exposure-response analysis may show more detailed trends between HAP exposure and maternal outcomes.

5. Conclusion

The HAPIN trial was the first multi-country RCT of LPG stove and fuel distribution in nearly 3200 households and forthcoming papers will examine effects on child stunting and pneumonia during infancy, and a range of secondary outcomes including early child development. We did not find a significant reduction in incidence of adverse maternal outcomes with the LPG intervention arm compared to women in the control arm. These results were statistically not significant despite evidence that the LPG intervention reduced HAP exposure and demonstrated high fidelity and adherence by the trial participants (Johnson et al., 2021; Quinn et al., 2021). While this reduction in HAP exposure was significant it may have been not sufficient to impact risk reduction in maternal outcomes. Combining clean fuel initiatives with other global efforts for poverty reduction and access to quality healthcare may result in a more significant impact on health outcomes.

Table 3.1: *Demographic characteristics at baseline by control and intervention arm*

	Control N = 1,605	**Intervention** N= 1,590	**Overall** N= 3,195[1]
Gestational week at enrollment, mean (SD)	15.3 (3.2)	15.5 (3.1)	15.4 (3.1)
Maternal age in years, N (%)			
<20	209 (13.0)	189 (11.9)	398 (12.5)
20-24	579 (36.1)	616 (38.7)	1,195 (37.4)
25-29	517 (32.2)	500 (31.5)	1,017 (31.8)
30-35	300 (18.7)	285 (17.9)	585 (18.3)
Highest level of education Completed, N (%)*			
No formal education	558 (34.8)	481 (30.3)	1,039 (32.5)
Primary completed	533 (33.2)	558 (35.1)	1,091 (34.2)
Secondary completed	514 (32.0)	550 (34.6)	1,064 (33.3)
Minimum dietary diversity, Category (score)[2], N (%)			
Low (<4)	906 (56.4)	890 (56.0)	1,796 (56.2)
Medium (4-5)	533 (33.2)	496 (31.2)	1,029 (32.2)
High (>5)	165 (10.3)	203 (12.8)	368 (11.5)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
Household food insecurity Category (score)[3]*, N (%)			
Food secure	863 (53.8)	930 (58.5)	1,793 (56.1)
Mild (1, 2, 3)	448 (27.9)	416 (26.2)	864 (27.0)
Moderate (4, 5, 6) / Severe (7, 8)	272 (16.9)	220 (13.8)	492 (15.4)
Missing	22 (1.4)	24 (1.5)	46 (1.4)
Height in cm, mean (SD); N missing	152.1 (6.0); 4	152.3 (6.2); 8	152.2 (6.1); 12
Body mass index (kg/m^2), mean (SD); N missing	23.1 (4.0); 7	23.3 (4.1); 12	23.2 (4.1); 19
Nulliparous[4], N (%)			
Yes	589 (36.7)	639(40.2)	1,228 (38.4)
No	1,014 (63.2)	947(59.6)	1,961 (61.4)
Missing	2 (0.1)	4 (0.3)	6 (0.2)

	Control N = 1,605	**Intervention** N= 1,590	**Overall** N= 3,195[1]
Vitamin Intake[5], N(%)			
Multiple micronutrient tablets	198 (12.3)	181 (11.4)	379 (11.9)
Iron	974 (60.7)	947 (59.6)	1,921 (60.1)
Vitamin A	15 (0.9)	10 (0.6)	25 (0.8)
Folate	911 (56.8)	877 (55.2)	1,788 (56.0)
Other	46 (2.9)	44 (2.8)	90 (2.8)
None	314 (19.6)	342 (21.5)	656 (20.5)
Maternal hemoglobin, mean (SD); N missing	12.5 (1.9); 13	12.4 (1.9); 17	12.5 (1.9); 30
Number of people sleeping in house, mean (SD); N missing	4.3 (2.0); 0	4.3 (2.0); 1	4.3 (2.0); 1
Owns household assets, N (%)			
Color television	783 (48.8)	774 (48.7)	1,557 (48.7)
Radio	721 (44.9)	734 (46.2)	1,455 (45.5)
Mobile phone	1,395 (86.9)	1,388 (87.3)	2, 783 (87.1)
Bicycle	409 (25.5)	365 (23.0)	774 (24.2)
Bank account*	628 (39.1)	697 (43.8)	1,325 (41.5)
Someone in household Smokes[6], N (%)	181 (11.3)	153 (9.6)	335 (10.5)

*p<0.05; SD, standard deviation

[1]N=3,200 women were randomized; 5 women were deemed ineligible after randomization

[2]Adapted from Food and Agriculture Organization of the United Nations Minimum Diet Diversity for Women (FAO 2016b)

[3]The Food Insecurity Experience Scale, developed by the Food and Agriculture Organization of the United Nations, http://www.fao.org/3/as583e/as583e.pdf

[4]Nulliparous defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond; miscarriages can have occurred in a woman who is nulliparous.

[5] Vitamins taken in the past 12 months

[6]Someone in the household other than the pregnant woman smokes; pregnant women were all non-smokers based on eligibility criteria

Table 3.2: *Effects of the intervention on maternal outcomes* (N=3195)*

Outcome	Intervention (n=1590)	Control (n=1605)	Relative Risk	95% CI	Adjusted Relative Risk	95% CI
Spontaneous abortion						
Yes	8 (0.50%)	3 (0.19%)	2.69	(0.71, 10.12)	2.52	(0.67, 9.51)
No	1582 (99.50%)	1602 (99.81%)				
Hypertensive disorders of pregnancy						
Yes	39 (2.45%)	44 (2.74%)	0.89	(0.58, 1.37)	0.88	(0.57, 1.36)
No	1551(97.55%)	1561 (97.26%)				
Postpartum hemorrhage						
Yes	5 (0.31%)	6 (0.37%)	0.84	(0.26, 2.74)	0.85	(0.26, 2.80)
No	1585 (99.69%)	1599 (99.63%)				
Maternal mortality						
Yes	3 (0.19%)	2 (0.12%)	1.51	(0.25, 9.03)	1.66	(0.28, 9.94)
No	1587 (99.81%)	1603 (99.88%)				
Composite outcome						
Yes	53 (3.33%)	53 (3.30%)	1.01	(0.69, 1.46)	0.99	(0.68, 1.46)
No	1537 (96.67%)	1552 (96.70%)				

*Overall model adjusted for maternal education, household food insecurity and bank account

Table 3.3: *Effects of the intervention on maternal outcomes by country site, N(%)*

Outcome	Guatemala Intervention (n=400)	Guatemala Control (n=400)	India Intervention (n=400)	India Control (n=399)	Peru Intervention (n=396)	Peru Control (n=402)	Rwanda Intervention (n=394)	Rwanda Control (n=404)
Spontaneous abortion								
Yes	3 (0.75)	0 (0.00)	0 (0.00)	2 (0.50)	4 (1.01)	1 (0.25)	1 (0.25)	0 (0.00)
No	397 (99.25)	400 (100.00)	400 (100.00)	397 (99.50)	392 (98.99)	401 (99.75)	393 (99.75)	404 (100.00)
Hypertensive disorders of pregnancy								
Yes	16 (4.00)	16 (4.00)	8 (2.00)	9 (2.26)	10 (2.53)	11 (2.74)	5 (1.27)	8 (1.98)
No	384 (96.00)	384 (96.00)	392 (98.00)	390 (97.74)	386 (97.47)	391 (97.26)	389 (98.73)	396 (98.02)
Postpartum hemorrhage								
Yes	0 (0.00)	3 (0.75)	2 (0.50)	0 (0.00)	3 (0.76)	3 (0.75)	0 (0.00)	0 (0.00)
No	400 (100.00)	397 (99.25)	398 (99.50)	399 (100.00)	393 (99.24)	399 (99.25)	394 (100.00)	404 (100.00)
Maternal mortality								
Yes	0 (0.00)	0 (0.00)	2 (0.50)	0 (0.00)	1 (0.50)	2 (0.25)	0 (0.00)	0 (0.00)
No	400 (100.00)	400 (100.00)	398 (99.50)	399 (100.00)	395 (99.75)	400 (99.50)	394 (100.00)	404 (100.00)
Composite outcome								
Yes	19 (4.75)	19 (4.75)	10 (2.50)	11 (2.76)	18 (4.55)	15 (3.73)	6 (1.52)	8 (1.98)
No	381 (95.25)	381 (95.25)	390 (97.50)	388 (97.24)	378 (95.45)	387 (96.27)	388 (98.48)	396 (98.02)

Supplemental Table 3.4: *Demographic characteristics at baseline by intervention and control arm for each IRC (N=3,195)*[1]

	Guatemala		India		Peru		Rwanda	
	I* N=400	**C N=400**	**I N=400**	**C N=399**	**I N=396**	**C N=402**	**I N=394**	**C N=404**
Gestational week at enrollment, mean (SD)	14.4 (3.0)	14.2 (3.1)	16.1 (3.0)	16.0 (3.1)	15.8 (3.3)	15.6 (3.4)	15.6 (2.8)	15.4 (2.7)
Maternal age, years, N (%)								
<20	64 (16.0)	58 (14.5)	62 (15.5)	66 (16.5)	40 (10.1)	59 (14.7)	23 (5.8)	26 (6.4)
20-24	168 (42.0)	156 (39.0)	192 (48.0)	190 (47.6)	151 (38.1)	135 (33.6)	105 (26.6)	98 (24.3)
25-29	110 (27.5)	121 (30.3)	117 (29.3)	113 (28.3)	130 (32.8)	127 (31.6)	143 (36.3)	156 (38.6)
30-35	58 (14.5)	65 (16.3)	29 (7.3)	30 (7.5)	75 (18.9)	81 (20.1)	123 (31.2)	124 (30.7)
Highest level of education achieved, N (%)								
No formal education	189 (47.3)	192 (48.0)	130 (32.5)	155 (38.9)	15 (3.8)	20 (5.0)	**147 (37.3)**	**191 (47.3)**
Primary completed	160 (40.0)	152 (38.0)	116 (29.0)	111 (27.8)	131 (33.2)	103 (25.6)	**151 (38.3)**	**167 (41.3)**
Secondary completed	51 (12.8)	56 (14.0)	154 (38.5)	133 (33.3)	249 (63.0)	279 (69.4)	**96 (24.4)**	**46 (11.4)**
Minimum dietary diversity, Category (score)[2], N (%)								
Low (<4)	279 (69.9)	268 (67.0)	315 (78.8)	306 (76.7)	46 (11.6)	41 (10.2)	**250 (63.5)**	**291 (72.2)**
Medium (4-5)	104 (26.1)	115 (28.8)	73 (18.3)	81 (20.3)	203 (51.3)	234 (58.2)	**116 (29.4)**	**103 (25.6)**
High (>5)	16 (4.0)	17 (4.3)	12 (3.0)	12 (3.0)	147 (37.1)	127 (31.6)	**28 (7.1)**	**9 (2.2)**

	Guatemala		India		Peru		Rwanda	
	I* **N=400**	**C** **N=400**	**I** **N=400**	**C** **N=399**	**I** **N=396**	**C** **N=402**	**I** **N=394**	**C** **N=404**
Household food insecurity Category (score)[3], N (%)								
Food secure	225 (56.3)	215 (53.8)	324 (81.0)	321 (80.5)	210 (53.0)	202 (50.3)	**171 (43.4)**	**125 (30.9)**
Mild (1, 2, 3)	126 (31.5)	129 (32.3)	54 (13.5)	60 (15.0)	128 (32.3)	146 (36.3)	**108 (27.4)**	**113 (28.0)**
Moderate (4, 5, 6) / Severe (7, 8)	43 (10.8)	52 (13.0)	19 (4.8)	17 (4.3)	53 (13.4)	47 (11.7)	**105 (26.7)**	**156 (38.6)**
Missing	6 (1.5)	4 (1.0)	3 (0.8)	1 (0.3)	5 (1.3)	7 (1.7)	**10 (2.5)**	**10 (2.5)**
Height in cm, mean (SD); missing	148.6 (5.0); 1	148.2 (5.7); 0	151.0 (5.9); 0	151.2 (5.3); 0	152.7 (4.6); 6	152.6 (4.5); 4	156.9 (6.0); 1	156.2 (5.7); 0
Body mass index (kg/m^2), mean (SD); N missing	23.9 (3.4); 3	23.7 (3.3); 2	19.8 (3.3); 0	19.6 (3.1); 0	**26.3 (3.6); 6**	**25.8 (3.6); 4**	23.3 (3.5); 3	23.5 (3.3); 1
Nulliparous[4], N (%)								
Yes	119 (29.8)	108 (27.0)	**245 (61.3)**	**214 (53.6)**	154 (38.9)	156 (38.8)	121 (30.7)	111 (27.5)
No	281 (70.3)	292 (73.0)	**155 (38.8)**	**185 (46.4)**	239 (60.3)	245 (60.9)	272 (69.0)	292 (72.3)
Missing	0	0	**0**	**0**	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)
Vitamin Intake[5], N (%)								
Multiple micronutrient tablets	129 (32.3)	142 (35.5)	0	0	21 (5.3)	26 (6.5)	31 (7.9)	30 (7.4)
Iron	185 (46.3)	211 (52.8)	374 (93.5)	376 (94.2)	180 (45.5)	169 (42.0)	208 (52.9)	218 (54.1)
Vitamin A	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.3)	4 (1.0)	3 (0.8)	4 (1.0)	6 (1.5)

	Guatemala		India		Peru		Rwanda	
	I* N=400	C N=400	I N=400	C N=399	I N=396	C N=402	I N=394	C N=404
Folate	187 (46.8)	213 (53.3)	384 (96.0)	392 (98.3)	179 (45.2)	169 (42.0)	127 (32.3)	137 (34.0)
Other	3 (0.8)	5 (1.3)	36 (9.0)	37 (9.3)	3 (0.8)	2 (0.5)	2 (0.5)	2 (0.5)
None	**138 (34.5)**	**110 (27.5)**	9 (2.25)	6 (1.5)	115 (24.0)	131 (32.6)	80 (20.3)	67 (16.6)
Maternal hemoglobin, mean (SD); N missing	12.7 (1.0); 1	12.9 (1.1); 2	10.3 (1.2); 0	10.4 (1.3); 0	14.3 (1.3); 9	14.3 (1.2); 10	12.4 (1.6); 3	12.4 (1.5); 5
Number of people sleeping in house, mean (SD)	5.3 (2.7)	5.1 (2.6)	3.8 (1.5)	3.7 (1.6)	4.5 (1.7)	4.7 (1.8)	3.5 (1.5)	3.5 (1.5)
Owns household assets, N (%)								
Color Television	169 (42.3)	188 (47.0)	291 (72.8)	301 (75.4)	247 (62.4)	260 (64.7)	**67 (17.0)**	**34 (8.4)**
Radio	153 (38.3)	151 (37.8)	57 (14.3)	52 (13.0)	289 (73.0)	304 (75.6)	235 (59.6)	214 (53.0)
Mobile phone	361 (90.3)	370 (92.5)	328 (82.0)	327 (82.0)	378 (95.5)	388 (96.5)	321 (81.5)	310 (76.7)
Bicycle	45 (11.3)	53 (13.3)	60 (15.0)	61 (15.3)	147 (37.1)	162 (40.3)	113 (28.7)	133 (32.9)
Bank account	99 (24.8)	98 (24.5)	357 (89.3)	359 (90.0)	94 (23.7)	86 (21.4)	**147 (37.3)**	**85 (21.0)**
Someone in household smokes[6], N (%)	22 (5.5)	22 (5.5)	119 (29.8)	134 (33.6)	4 (1.0)	3 (0.7)	**8 (2.0)**	**22 (5.4)**

$p<0.05$ in bold; SD, standard deviation, *I-intervention, C-control
[1]N=3,200 women were randomized; 5 women were deemed ineligible after randomization
[2]Adapted from Food and Agriculture Organization of the United Nations Minimum Diet Diversity for Women (FAO 2016b)
[3]The Food Insecurity Experience Scale, developed by the Food and Agriculture Organization of the United Nations, http://www.fao.org/3/as583e/as583e.pdf
[4]Nulliparous defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond; miscarriages can have occurred in a woman who is nulliparous.
[5] Vitamins taken in the past 12 months
[6]Someone in the household other than the pregnant woman smokes; pregnant women were all non-smokers based on eligibility criteria

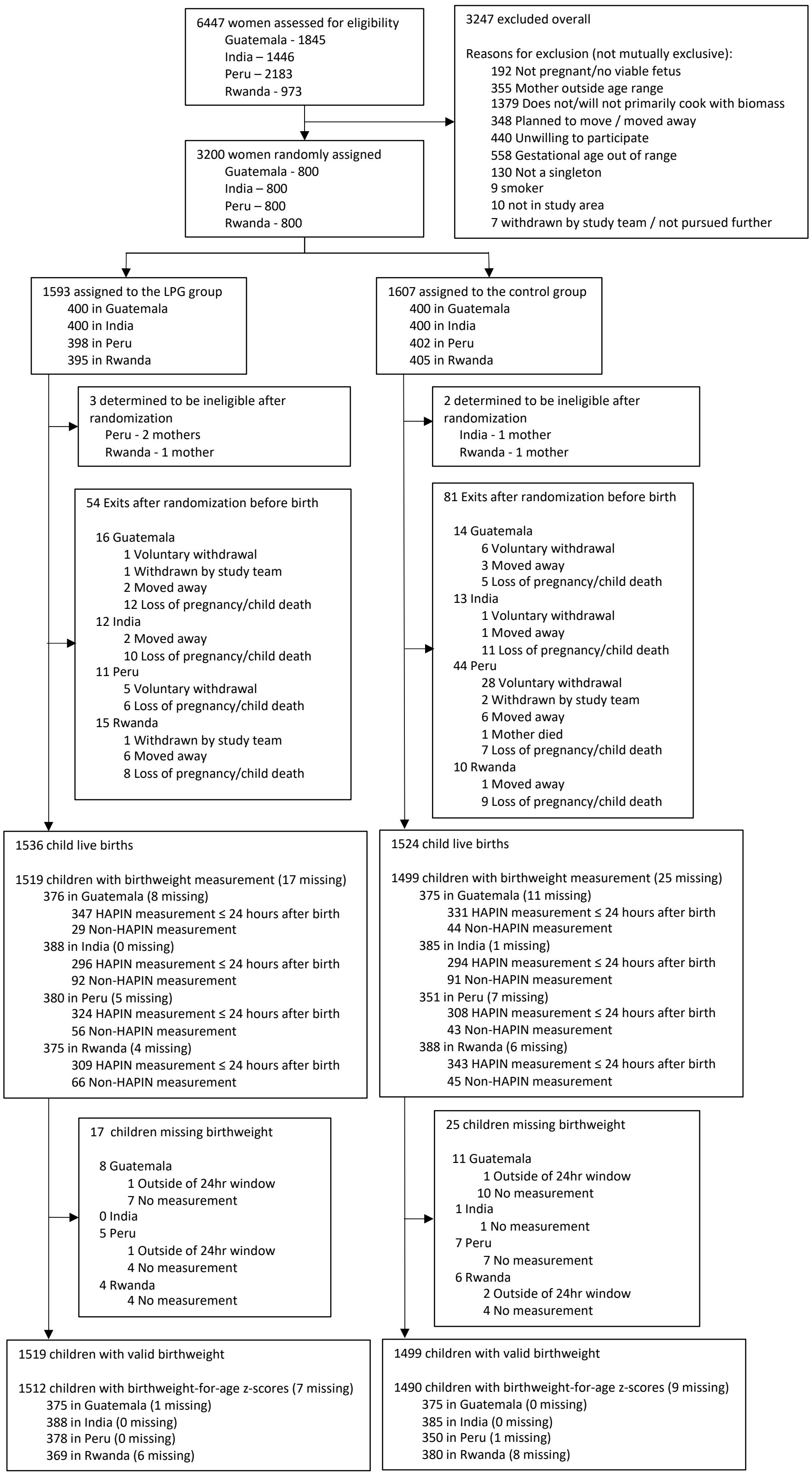

Figure 3.1: *CONSORT Flow Diagram*

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Conclusion

Across the globe, approximately 3 billion people cook with unclean fuels and the use remains widespread despite evidence of an association of household air pollution and harmful health effects. This dissertation aimed to appraise the evidence of an association between household air pollution from unclean cooking fuel and adverse birth outcomes, and evaluate the impact of an LPG stove intervention on adverse fetal, neonatal and maternal outcomes in low- and middle-income countries. The systematic review presented evidence for an increased risk of low birth weight, preterm birth, small for gestational age, stillbirth, neonatal mortality and reduction in birthweight with solid fuel and kerosene use compared to cleaner fuels like gas and LPG. The HAPIN trial was the first multi-country RCT collecting data on household air pollution and health outcomes on pregnant women across four countries. While the LPG stove intervention did not significantly reduce the relative risk of adverse birth outcomes, women assigned to the LPG intervention group had a slightly lower risk of congenital anomaly, neonatal mortality, hypertensive disorders of pregnancy and postpartum hemorrhage compared to women in the control arm.

A primary strength of this dissertation work is the vast amount of information and data gathered on pregnant women and household air pollution across nearly 3200 households. This was made possible by the herculean effort made by the HAPIN Trial field workers and women who participated.

Primary limitations of this study include maintaining reliability in data collection across four country sites. While the study design is a randomized control trial there may be confounding variables that were not included in the original data collection. The variability of culture and field workers teams across the four country may result in discrepancies in the reporting adverse outcomes. Also, the low incidence of adverse outcomes limited the detectable effect sizes between the intervention and control arms. Other factors related to poverty and access to adequate prenatal care may play a more critical role in improving health outcomes.

The results of this dissertation research contributes to the evidence on the relationship of HAP from cooking fuel on adverse fetal, neonatal and maternal outcomes. The UN Sustainable Development Goals support evidence-based policy and their progress over the next ten years may influence political will in low- and middle-income countries to improve access to clean household energy solutions. Access to sustainable and affordable energy should remain a priority for the global community.

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