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Claire Castellano Date

Assessing the Effect of Liquefied Petroleum Gas (LPG) stoves on Child Mortality through the Household Air Pollution Intervention Network (HAPIN) Trial

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Master of Public Health

Global Epidemiology

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Bachelor of Arts

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2016

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Abstract

Assessing the Effect of Liquefied Petroleum Gas (LPG) stoves on Child Mortality through the Household Air Pollution Intervention Network (HAPIN) Trial

By Claire Castellano

Background: Household air pollution (HAP) has been cited as a leading environmental cause of global disease burden. The use of solid fuels for cooking and heating is an important and prevalent contributor to HAP, with nearly 3 billion people using solid fuels around the world, especially in Low- to Middle- Income Countries (LMICs). Young children are especially affected by HAP, being vulnerable to the toxic effects both in utero and as a developing infant. Liquified petroleum gas (LPG) stoves are a promising scalable clean alternative to solid fuels. This study aims to investigate the effect of a possible alternative to solid fuel HAP and its effect on child health, in particular child mortality.

Methods: The Household Air Pollution Intervention Network (HAPIN) trial is a multi-center randomized control trial that assigned pregnant women in Guatemala, India, Peru, and Rwanda to receive a free LPG stove and fuel (intervention) or to continue using a traditional stove (control). Women and their children were followed through pregnancy and until the child was 24-months. Cox proportional hazards models were used to assess the effect of the intervention on child mortality.

Results: 3200 pregnant women were randomized to the treatment groups, resulting in 3061 live births. 64 children died over a 24-month follow-up period, with 40 deaths in the neonatal period (less than 28 days of life). The hazard rate of death among children in the intervention group was 0.772 (0.471, 1.266) times the hazard rate of death among children in the control group.

Conclusions: There was no statistically significant difference in child mortality through 24-months when comparing the intervention group (LPG cookstoves) to the control group (traditional stoves).

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Introduction

Household Air Pollution (HAP)

The relationship between air quality and human health has been discussed from as early as 400 BCE. From Hippocrates' book, "Airs, waters and places," commenting on the connection between air quality and human disease, to the "1273 Smoke Abatement Act" in England acknowledging the use of coal as detrimental to health, to "The Clean Air Act" of 1970 in the United States, there have been countless data collection tools, queries, laws, and amendments over the centuries surrounding the notion of air pollution and health (EPA , Fowler, Brimblecombe et al. 2020). Yet, despite the recognition of the harm of pollutants from centuries ago, air pollution remains a major public health concern today.

The World Health Organization (WHO) defines air pollution as a chemical, physical, or biologic agent that contaminates the atmospheric environment (WHO 2023). In 2019, air pollution became the fourth leading cause of death globally, only behind high blood pressure, tobacco, and poor diet (HEI 2020). According to the most recent WHO data and global air quality guidelines, 99% of the world's population is breathing air with levels of particulate matter ($PM_{2.5}$ or particulate matter less than 2.5 microns in width), ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide that are higher than recommended (World Health 2021). The Global Burden of Disease (GBD) project utilizes data from over 160 countries and territories to calculate the health loss from various exposures and diseases, and found that household air pollution is associated with the loss of 5.9 million disability-adjusted life years (DALYs) globally and 1.6 million premature deaths (2018). In addition, a study looking specifically at the global burden of disease from major air pollution sources found that if fossil fuel combustion were eliminated, 1.05 million deaths could be prevented (McDuffie, Martin et al. 2021). Among

the many causes of air pollution, fine particulate matter, or $PM_{2.5}$, is a leading bad actor, responsible for over 60% of global deaths and 55% of DALYs attributable to air pollution (HEI 2020).

Air pollution can broadly be grouped into two categories: household air pollution and ambient particulate matter. Household air pollution, or HAP, is commonly caused by the burning of solid fuels for cooking or heating. Solid fuels, also known as biomass, are materials such as wood, coal, charcoal, agricultural crop residues, or dung that get heated over an indoor open fire or a poorly ventilated stove. The burning of solid fuels exposes household members to air pollution somewhere between the level of actively smoking and being exposed to second-hand smoke (Bonjour, Adair-Rohani et al. 2013). However, the impacts of air pollution, in particular HAP, are disproportionate.

From 1980 to 2010, the proportion of households in the world that used solid fuels for heating and cooking decreased. However, the actual number of people in households relying on solid fuels has stayed constant around 2.8 billion (Bonjour, Adair-Rohani et al. 2013). This is because the majority of households that use solid fuels are in Africa and Southeast Asia, where demographic shifts over the past few decades have led to population growth. More recent data from the GBD project shows that exposure to HAP decreases as economic development increases (2018). So even though proportion of the world exposed to the deleterious effects of HAP is decreasing, we continue to see a stable contingent of the world's population relying on solid fuel and thus exposed to HAP, and this population is disproportionately concentrated in poor communities in Low- to Middle-Income Countries (LMICs) (2018, Clasen, Checkley et al. 2020).

The negative association between HAP and health is well documented, with many studies citing increased risk of chronic lung diseases, tuberculosis, malignancy, pneumonia and other lower respiratory infections, preterm birth, and low birth weight (Clasen, Checkley et al. 2020). However, these risks are also not equally distributed among the population. Women and children are often exposed to higher levels of HAP (Lee, Bing et al. 2020) (2018). This is likely due to the division of labor and cultural norms surrounding household chores and cooking. One study found that women spend between three to seven hours a day near a solid fuel stove (Po, FitzGerald et al. 2011). In addition, children often stay with their mothers, or are held on their mothers' backs, as these women carry out their chores near the stove, making HAP exposure levels for children similar to that of their mothers (Po, FitzGerald et al. 2011).

Child Health Disparities

The United Nations (UN) outlined its goals for the health of the planet and its people through a call to action in seventeen Sustainable Development Goals (SDG) of 2015. Included in these goals is a focus on reducing child mortality. In particular, reducing mortality for children under five years old to at most 25 deaths per 1000 live births and to reduce mortality for neonates in the first 28 days of life to at most 12 deaths per 1000 live births (UN). However, as of 2021, global child mortality rates remain much higher with an average 38 deaths per 1000 live births for children under five (IGME)). The numbers are staggering with 5 million children dying before age five, and around 2.3 million neonates dying within the first 28 days of life (IGME)). Even more staggering, is the disparity between child mortality rates across countries: the average mortality rate for children under five is 5 deaths per 1000 live births in high-income countries but 67 deaths per 1000 live births in low-income countries (IGME)).

There are a multitude of factors to explain the inequity in child mortality rates across countries, ranging from differences in socioeconomic status to sanitation (Rana, Islam et al. 2021). And most likely, the explanation is multifactorial with multiple risk factors working in tandem. However, many of the top causes of childhood mortality are preventable with better infection control, water sanitation, adequate nutrition, access to vaccinations, and access to routine health care (WHO 2022). Another possible preventable risk factor to explain the disparity in child mortality rates is the unequal access to clean fuels and thus unequal exposure to air pollution.

HAP and Child Health and Mortality

Various studies have investigated the association between HAP and child mortality. A systematic review by Bruce and Dherani et al. utilizing data from multiple data sources, including Demographic Health Surveys and World Health Surveys, collated information on fuel type from 150 countries to assess the relationship between child health and HAP. They found evidence suggesting a relationship between HAP exposure and multiple health outcomes, including pre-term birth, acute lower respiratory infections, and all-cause mortality (Bruce, Dherani et al. 2013). However, most of the studies they analyzed were observational with much heterogeneity among groups, limiting the conclusions they could draw and generalizability of their findings.

A recent study assessed the neonatal, infant, and under-five child mortality rates in Myanmar based on exposure to solid fuels for cooking as proxies for HAP, described by the 2016 Demographic and Health Survey (Rana, Islam et al. 2021). They found that the risk of mortality for infants and children under-five were statistically significantly higher in the

households with solid fuel exposure, compared to those that used clean cookstoves (for infants: adjusted risk ratio (aRR) 2.02, confidence interval (CI) 1.01 – 4.05, p-value = 0.048; for children under-five: aRR 2.16, CI 1.07 – 4.36, p-value = 0.031) (Rana, Islam et al. 2021). Although the results of this study are striking, this was a cross-sectional study where 79% of the population used solid fuels, which limits the ability to fully explore the multiple variables possibly confounding the effect of HAP on mortality.

Another study analyzed in the impact of using solid fuels as an energy source and the effect on infant mortality across countries, each at differing levels of development (Asghar, Amjad et al. 2022). Regardless of economic developmental status of the country, they saw a positive relationship between use of solid fuels and infant mortality. The findings of these studies highlight the need to improve access to clean fuels to improve overall health. However, many barriers persist to actual scale up such a needed change, especially in LMICs. (Bruce, Dherani et al. 2013).

As previously mentioned, nearly 3 billion people still use solid fuels for heating and cooking (Clasen, Checkley et al. 2020). There are many options for cleaner energy sources, including natural gas, electricity, and liquified petroleum gas (IEA 2017). Although such alternative methods of energy and fuel to heat homes and aid in cooking exist, these methods are often cost-prohibitive and inaccessible to households in LMICs (Po, FitzGerald et al. 2011). Liquified petroleum gas, or LPG, is a fuel made up of a mixture of hydrocarbons, including propane and butane. Deliverable to even remote locations in portable cylinders, it is one of the most utilized and available options for cleaner energy in LMICs (Clasen, Checkley et al. 2020, Floess, Grieshop et al. 2023). However, much of the current understanding around the health benefits of cleaner alternatives to biomass cooking fuels is based on observational studies,

including exposure-response relationships. Until recently, no randomized control trials have been conducted to assess the health benefits of utilizing an LPG cookstove compared to solid fuels in a rigorous manner (Clasen, Checkley et al. 2020). This changed with the creation of the Household Air Pollution Intervention Network (HAPIN) trial.

HAPIN Trial

The Household Air Pollution Intervention Network, or HAPIN, trial is a multi-center randomized control trial (RCT) investigating the impacts of HAP on health in LMICs. To goal of this trial was to implement an intervention that is scalable and practical in other LMICs, and to collect data on a variety of health outcomes to provide policy makers the evidence needed to support a similar intervention on a wider scale (Clasen, Checkley et al. 2020). The HAPIN trial focused on maternal, child, and adult health outcomes when comparing use of LPG stoves to use of solid fuels (traditional stoves) across four LMICs: India, Guatemala, Peru, and Rwanda. Broadly, the RCT recruited and enrolled 800 pregnant women from each country and enrolled half in the intervention arm, to receive a free LPG stove and fuel, while half remained in the control group, continuing to use traditional stoves cook and heat. They followed these women throughout their pregnancy and until their child was one-year old, for approximately 18 months, collecting data on maternal health, adult health from other household members, and child health once the child was born. Additional funding has allowed continued follow-up for an additional year, or until the child reaches 24-months (Clasen, Checkley et al. 2020). (See Methods section for more.)

Two critical components along the theory of change that are inextricably tied to the intervention's ability to decrease HAP are fidelity (i.e. was the intervention was delivered as

intended?) and adherence (i.e. was the intervention used as intended?) (Quinn, Williams et al. 2021). Fidelity was measured by assessing: 1) time between randomization and delivery of the intervention, to ensure that the intervnetion began during the woman's pregnancy, with a goal of starting the intervention within 14 days from randomization; 2) consistent and timely LPG fuel delivery, with a goal of less than seven days between fuel request and delivery; 3) adequate maintenance and timely repair of the stoves to ensure functionality of the stove; and 4) training and support for participants, to ensure participants understood how to use the LPG stove and were being encouraged to exclusively use it (Quinn, Williams et al. 2021). Adherence was measured by assessing both use of the LPG stove and no use of the traditional stove. Data was collected through 1) questionnaires on self-reported stove use, 2) stove use monitors (SUMs) to quantitatively capture how often a traditional stove was used (utilizing algorithms that detected temperature changes to predict stove use events, divided over the total SUM days), and 3) visual observations by study staff at site visits.

Next, it is essential to confirm that good fidelity and adherence actually led to decreased HAP exposure. Exposure to carbon monoxide (CO), black carbon (BC), and fine particulate matter ($PM_{2.5}$) was measured for all participants at three time points: once before randomization and twice after randomization. Exposure levels were measured over a 24-hour period using lightweight monitors that were secured on a vest or apron each woman was asked to wear(Johnson, Steenland et al. 2020). Ambient air was also sampled, to provide a baseline and comparison point when looking at how $PM_{2.5}$ changed with different stove use. Child exposure data was captured indirectly: children wore a smaller, coin-sized monitor to track their location, while larger, air-sampling monitors were set in the child's sleeping area and the household's cooking area. Viewed together, this data could help predict the child's exposure based on how

much time he or she spent in each area (Johnson, Steenland et al. 2020). The change in exposure after randomization between the control and intervention groups were calculated directly and indirectly with linear mixed-effect models (Johnson, Pillarisetti et al. 2022). Results indicate considerable reduction in exposure of all three polluants, and were similar for all four study sites. In particular, polluants were lower in the intervention arm by 66% for $PM_{2.5}$, 70% for BC, and 82% for CO when compared to the control group (Johnson, Pillarisetti et al. 2022).

Overall, despite the challenges of COVID, the HAPIN trial was successful in securing nearly exclusive use of the intervention stove and fuel among intervention group participants, both during pregnancy (Quinn, Williams et al. 2021) and through the child's first birthday (Williams, in progress). This resulted in substantial reductions in exposure to measured air pollutants.

Study Aims

Here, we use data from the HAPIN trial to investigate if there is a difference in child mortality between the LPG intervention group and control group through 24-months of follow-up. Mortality is a secondary outcome of the trial, and accordingly, the study was not powered around the mortality as an end point. However, we believe this is a crucial outcome to study even given the inequities in child mortality, unfortunately similar to the patterns seen around inequities in access to clean energy and detrimental effects of air pollution. This is an exploratory study investigating the effect of the intervention on child mortality. We acknowledge that our numbers are small and underpowered to detect an effect, and also know that HAP causes a great deal of morbidity, from asthma and allergic rhinitis to respiratory infections, chronic lung disease, and respiratory tract cancers, without mortality (Gordon, Bruce et al. 2014, Eguiluz-

Gracia, Mathioudakis et al. 2020). Regardless, analysis of this outcome is key to thoroughly understanding the spectrum of how and when HAP impacts child health.

Methods

Study Design

The HAPIN study is a multi-center randomized controlled trial seeking to investigate the relationship between use of LPG stoves (intervention) and various health outcomes in both adults and children. The primary HAPIN trial outcomes were focused on: 1) low birthweight in infants, 2) growth stunting in infants, 3) severe pneumonia in infants, and 4) systolic blood pressure in older adult women (Clasen, Checkley et al. 2020). The goal was to enroll 800 women from each site, beginning in May 2018 and continuing through February 2020. Four LMICs were selected for enrollment based on logistical considerations, ability to recruit and enroll participants, and the fact that solid fuels were the primary indoor fuel used at each location (Clasen, Chang et al. 2022). The sites were: Jalapa, Guatemala; Tamil Nadu, India; Puno, Peru; and Eastern Province, Rwanda (Clasen, Chang et al. 2022). The study protocol was 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), A.B. PRISMA, the London School of Hygiene and Tropical Medicine (11664-5) and the Rwandan National Ethics Committee (No.357/RNEC/2018), and Washington University in St. Louis (201611159). The study has been registered with ClinicalTrials.gov

(Identifier NCT029446282). The study was funded by the U.S. National Institutes of Health (cooperative agreement 1UM1HL134590) in collaboration with the Bill & Melinda Gates Foundation (OPP1131279).

Participants

Eligible participants were defined as women who were between 18 to 35 years old, primarily used a solid fuels stove for indoor cooking, lived within the pre-identified trial sites, were pregnant (confirmed with a urine or blood human chorionic gonadotropin (hCG) positive test) with one baby between 9 to 20 weeks gestation (confirmed at enrollment via ultrasound), and with a continued pregnancy at randomization (confirmed via self-report). Exclusion criteria included women who currently used (or were likely to begin using) a clean fuel stove for cooking, women who smoked tobacco, and women who were planning to move away from the pre-identified trial site area. Eligible women who provided an informed written consent were enrolled in the study and began baseline assessments (Clasen, Chang et al. 2022). Baseline assessments included surveys on demographic and socioeconomic data, cooking behavior, physical activity, diversity of diet, and household food insecurity among other variables. Baseline health data (such as blood pressure) and biomarkers (such as atherosclerosis measured by common carotid artery US) were collected (Clasen, Checkley et al. 2020). (See Results for more on baseline assessments.) In addition, baseline data were collected to measure exposure levels of the following pollutants: CO, BC, and $PM_{2.5}$ (Johnson, Pillarisetti et al. 2022).

Intervention

The intervention was to provide a free LPG stove with at least two burners and a free, continuous supply of LPG fuel to homes for a total of 18 months, approximately six months while the woman was pregnant and 12 months after the child was born. Fuel was delivered via fuel cylinders, by the study staff, in Guatemala, Rwanda, and Peru, and by public sector oil companies in India. In both cases, the intervention homes were supplied with stove installation and repair and fuel delivery and refill. At each fuel delivery, LPG fuel cylinder weights were measured to calculate the amount of fuel used, on average, each day by the household. These calculations aided in both tracking LPG fuel use and anticipating the next refill (Clasen, Checkley et al. 2020). In addition to the stoves and fuel, the intervention group received education and behavioral messaging surrounding use of the stove, including encouraging LPG stove use and discouraging traditional stove use. Behavioral and educational initiatives were grounded in formative research, which identified factors that families prioritized in deciding what cookstove to use or not use. In-depth interviews, focus group discussions, and observations were conducted to better understand the landscape in each community around LPG stoves, and identified nine key domains that could impact the interventions' success, from family preferences around cooking practices to awareness of LPG stoves. For example, national efforts by the government in India and Peru were promoting LPG cookstoves; thus, individuals in India and Peru were more aware of the benefits of LPG cookstoves than individuals in Guatemala and Rwanda. Important nuances and insights from the formative research helped structure the educational and behavioral efforts to promote the intervention, specifically to encourage exclusive LPG use and abandonment of traditional cookstoves, given that "stove stacking" or

concurrent use of LPG stoves and traditional stoves was common and could dilute and muddle to effects of the intervention (Johnson, Steenland et al. 2020) (Williams, Thompson et al. 2020).

The intervention continued for 18 months or until the child reached 12 months of age (Clasen, Checkley et al. 2020). Women in the control group received compensation to avoid loss to follow-up, provide economic assistance given they were not getting a free cookstove and fuel, and ensure ethical fairness given the burden of not potentially benefitting from the intervention (Clasen, Checkley et al. 2020). Specifics of the compensation were determined given the cultural context, community input, and each country's specific ethic requirements. In Guatemala, control participants received coupons equal in value to that of the intervention LPG stove, which could be redeemed for any household item (including an LPG stove). In Peru, control participants received the intervention LPG stove at the end of the trial period (18 months) plus free fuel for one month. In Rwanda, control participants could choose between an LPG stove with four refills of fuel, a solar kit, or equivalent value in cash at the end of the trial. And in India, control participants all received the intervention LPG stove plus 18 months of free fuel at the end of the trial, in effect getting the exact intervention just at a later time. In addition, control participants in Peru, Rwanda, and India received small compensation during the trial itself (Quinn, Williams et al. 2019).

Randomization

Stratified randomization was utilized to divide participants within geographic regions at each country site. Eligible pregnant women participants were randomly divided into the intervention and control groups in a 1:1 ratio. This study was single blinded: with unblinded

participants and blinded research investigators (as was feasible, excluding two lead investigators to communicate with the data and safety monitoring board).

Outcomes

This study is focused on all-cause child mortality. As previously stated, child mortality is a secondary outcome of this trial. The HAPIN trial was initially designed and powered for the primary outcomes of interest (infant birth weight, infant growth stunting, infant severe pneumonia, and older adult women blood pressure), with an 80% power and type I error rate with an alpha level of 0.0125, accounting for a suspected 10% loss to follow-up. However, it was not adequately powered to detect a difference in secondary outcomes, such as child mortality. Although underpowered, we still investigated the difference in child mortality between the intervention (LPG stove) and control (traditional stove) groups.

Data was collected from pregnant women, older adult women, and children at multiple time points: during pregnancy, at child birth, and post-child birth. Figure 1 outlines the various points of pre-determined data collection from recruitment through 24-monhts. As illustrated in the figure, the timepoints can be viewed as time post-randomization or post-child birth. Here, we analyze child mortality through 24-months. For the purpose of this study focused on child outcomes, we will refer to time as post-child birth and use data collected at the following five time points: when the child was born, was around 3-months old, was around 6-months old, was around 9-months old, and was around 12-months old. (The two additional time points with data collection were focused on maternal and older adult women data before the child was born: at < 20 weeks gestation (or baseline) and between 24-28 weeks gestation). During the second 12 months (12-24 months) of the study, data was collected only once, at the 24-month time point

(Clasen, Checkley et al. 2020) Throughout the study, adverse and serious adverse events were recorded and reported to the study's Data Safety Monitoring Board (DSMB). Of note, Peru was not included in the study after the first 12 months of child life. Thus, for the second year, we only have data from India, Guatemala, and Rwanda.

Within the first year of life, a data entry of a child death was distinguished as a neonatal death, a death within the first 28 days, or a child death, a death any time after 28 days. In the second year of life, there was no distinction among any child death recorded. For the entire 24-month period, deaths were also captured by a variable documenting a serious adverse event. Data from such moments were recorded on the "as needed" basis, not a pre-determined time for data collection.

Statistical Analysis

Data was analyzed in SAS. Child mortality was analyzed using a cox proportional hazards model (Johnson and Shih 2007) on an intention-to-treat (ITT) basis, with child data divided based on the treatment arm (intervention or control) into which the mother was randomized. The cox proportional hazards model was used to present time to an event, in this case time to death, between both groups. Cause of death was not distinguished. Children were censored if they exited the study for any reason (including participant voluntary withdrawal, withdrawal by the study team, moving away from the study area, loss to follow-up, or other unspecified reasons) or completed the study (i.e. remained living at the 24-month time point).

Hazard ratios for child mortality were analyzed for all children through 24 months, including children from Peru through 12 months and children from India, Guatemala, and Rwanda through 24 months all together. Adjusted hazard ratios were again calculated,

controlling for the intervention research center (IRC) or country the child was from. Given that Peru left the study after 12 months, sensitivity analyses were performed to assess the potential impact of this loss. These survival analyses focused on two sub-populations: 1) Peru alone through 12 months and 2) India, Guatemala, and Rwanda alone through 24-months. Given that this was a randomized control trial analyzed with ITT analysis, it was assumed that any missing data was missing at random, and thus no imputation was conducted (Clasen, Chang et al. 2022).

Results

Maternal and Child Baseline Characteristics

Over 6000 women were assessed for eligibility to be enrolled in the HAPIN trial. Of them, 3200 women were randomized, 800 from each Intervention Research Center (IRC): Guatemala, India, Peru, and Rwanda. The women were randomized in a 1:1 ratio to either the intervention or control arm; 1593 were randomized to the intervention group to receive an LPG stove and 1607 were randomized to the control group to continue to use their traditional stove. After randomization but prior to delivery, five women were found to be ineligible, reducing the number of pregnant women to 3195. Another 134 were lost to follow up, either from withdrawing, being removed by the study team, moving away from the study site, or losing the pregnancy before delivery, resulting in 3061 live births. Of these, 1536 live births were from women in the intervention group and 1525 live births were from women in the control group. The cohort of women who had live births were then continued to be followed up, when their baby was 3 months, 6 months, 9 moths, 12 months, and 24 months old. Of note, women and children in Peru were only followed-up until 12 months. There was variable loss to follow-up for mothers and children over the 12-24 month period. 1914 children were documented as being

consented and enrolled still in the study at 24-months: 947 in the intervention arm and 967 in the control arm. The CONSORT (Consolidated Standards of Reporting Trials) diagram in Figure 2 outlines in detail the screening, randomization, and loss to follow-up for participants in the HAPIN trial, from screening through 24-months.

Baseline characteristics for women at the start of the study, within one week of recruitment, are summarized in Tables 1a and 1b. Table 1a compares baseline characteristics of women in the intervention and control groups and illustrates that the two groups are very similar across multiple baseline assessment domains, as would be expected from randomization. Of note, the mean gestational age of women at baseline was 15.5 weeks in the intervention group and 15.3 weeks in the control group. Given that we analyzed Guatemala, India, and Rwanda as a separate sub-cohort in our sensitivity analysis, Table 1b compares baseline characteristics between the intervention and control groups for this sub-cohort. The two groups again have similar baseline characteristics. Of note, the mean gestational age of women at baseline was 15.4 weeks in the intervention group and 15.2 weeks in the control group, very similar to the trend seen in all four IRCs in Table 1a. Further analysis comparing the intervention and control group for each trial site also revealed similar baseline characteristics (Clasen, Chang et al. 2022).

Baseline characteristics for children at birth are summarized in Tables 1c and 1d. Children were indirectly randomized into the intervention and control groups based on their mother's randomization status. Thus, it is reasonable to assume that baseline characteristics among children should be similar as well. Table 1c compares baseline characteristics of infants at birth across all four IRCs. Of note, 47.9% of infants were born female in the intervention group and 48.4% of infants were born female in the control group. Table 1d compares baseline characteristics of infants at birth looking specifically at Guatemala, India, and Rwanda, the three

study sites that remained in the study until 24-months. Of note, 47.4% of infants were born female in the intervention group and 47.6% of infants were born female in the control group, again, very similar to the percentages seen in all four IRCs in Table 1c.

Overall, the data highlighted in each Table 1 underscore that randomization was successful in creating two relatively equal groups for the intervention and control, and the similarity in groups persisted in the children born.

Environmental Health Theory of Change: Fidelity, Adherence, and Exposure

Previous work has shown that the intervention was accepted and adhered to quite well. The median time it took for households to receive the intervention after randomization was eight days, and the median gestational age of the pregnant woman was 17.9 weeks. Of note, this is into the second trimester, and very few households (around 12%) started the intervention during the woman's first trimester. Over 86% of the intervention households almost exclusively used the LPG stove, using their traditional stove no more than 1 day per month. In addition, in Guatemala, India, and Rwanda, the control group almost exclusively used the traditional stove, with less than 2% of households utilizing an LPG stove during the trial period. However, in Peru, around 20% of the control households utilized an LPG cookstove (Quinn, Williams et al. 2021).

Previous work has also illustrated the change in exposure levels prior to and after trial initiation. At baseline, both groups had similar levels of HAP exposure, with around 17% in both groups experiencing exposure to fine particulate matter that was below the WHO's limit. After randomization, 69% of households in the intervention group experienced fine particulate matter below the WHO interim target limit of 35 micrograms per cubic meter, while only 23% of

households in the control group experienced levels below the limit. (Johnson, Pillarisetti et al. 2022). Further details on the analysis are out of scope of this paper.

Child Mortality: Summary

Of 3061 live births, 1914 children were still enrolled in the study at the 24-month timepoint. The difference in numbers is due to child deaths, study exits (including participant voluntary withdrawal, loss to follow-up, etc.), and the drop out of Peru from the study after 12-months. During the 24-month period, a total of 64 children died. Of the 64 deaths, 40 deaths were during the neonatal period or within the first 28 days. The remaining 24 deaths were during the infant period, or after the first 28 days but before the 12-month mark. There were no deaths in the second year of life, from 12-months through 24-months. The deaths were distributed across study sites and study arms, with a total of 36 deaths in the control arm and 28 deaths in the intervention arm. Table 2 summarizes the findings in child death over time and across IRCs and treatment groups.

Child death only accounts for a portion of the difference in children enrolled from birth (3061 children) through 24-months (1914 children). The largest component of the difference from birth until 24-months is from Peru's drop out, with 743 children initially born in Peru. When a child exited the study, their reason for why was recorded: participant voluntary withdrawal, withdrawal by the study team, moving away from the study area, loss to follow-up, or other unspecified reasons. Table 3 shows how many children exited the study due to a specific reason from each study arm. Of note, the majority of participants completed the study. Children from Peru who left the study at 12-months all were considered to have completed the study. In

addition, households who did not participate in the 24-month visit were reached out to in order to complete a study exit form, but not all of these households were reached.

Child Mortality: Survival Analysis

A Kaplan-Meier survival curve graphically illustrates the proportion of individuals surviving over time. Survival probability is calculated as one minus the quotient from the number of events divided by number at risk. In this case, the number of events is the number of deaths, and the number at risk is the remaining number of children at risk of dying in the study. At time zero, the survival probability is one, and over time will decrease as events (or deaths) occur. Figure 3 illustrates the survival curve for both children in the intervention arm (red line) and children in the control arm (blue line). The lines stop at the point when the last death or event occurred. In this case, the last death occurred in the control group earlier than in the intervention group. Although the survival probabilities are similar in both groups, the survival probability in the intervention group is slightly higher than that in the control group. However, statistical tests are needed to assess if the difference in survival between groups is meaningfully different.

Cox Proportional Hazards Model

We used a cox proportional hazards model to assess the effect of the intervention on child mortality. The cox proportional hazard model allows us to determine the instantaneous rate of hazard of death over time, while including other covariates in the model. The hazard ratio (HR) compares the hazard rate, or the instantaneous risk, of death among children in the intervention group against the hazard rate of death among children in the control group. An unadjusted HR

represents the influence of the intervention, LPG stoves, on the outcome, mortality. An adjusted HR represents the influence of the intervention on the outcome, while controlling for other covariates. Given that this was an RCT, none of the covariates are confounders, as we have nearly equal distribution in both treatment arms (See Tables 1). Therefore, the only covariate we will adjust for is the IRC or country. As a reminder, we are using an ITT analysis, which adjusts for randomization strata, similar to IRCs. Here, we choose to adjust for IRCs instead of strata.

In calculating cox proportional hazard ratios, an important assumption is that hazards in both groups are proportional over time. In other words, the hazard ratio is assumed to be constant over time. There are multiple ways assess this assumption, both graphically and through statistically calculations. We chose to assess the assumption by determining if an interaction term between survival time and the intervention in the model is significant. The p-value for the interaction term is 0.399, which is not statistically significant ($p > 0.05$ is not significant). Without significant interaction between time and the intervention, we can conclude that the proportional hazards assumption is met.

Child Mortality Analysis: Cox Proportional Hazards Model

We first analyzed the effect of the intervention on survival where survival time was calculated from the child's date of birth until when 1) the child died or 2) the child was censored, or exited the study in some way. The child may have been censored for any of the following reasons: exiting the study early (including participant voluntary withdrawal, withdrawal by the study team, moving away from the study area, loss to follow-up, or other unspecified reasons) or completing the study (or remaining alive through 24-months for children in Guatemala, India, and Rwanda, and through 12-months for children in Peru). In other words, the child is censored

from any outcome other than death. The survival time is the time from birth until either event: dying or being censored. Survival analysis allows each participant to contribute different amounts of time to the analysis based on the time each was at risk of the outcome of interest, death.

The hazard rate of death among children in the intervention group was 0.772 (0.471, 1.266) times the hazard rate of death among children in the control group (Table 4). When controlling for the IRC, the HR was very similar: hazard rate of death among children in the intervention group was 0.964 (0.476, 1.950) times the hazard rate of death among children in the control group (Table 4).

Child Mortality: Sensitivity Analysis

The proportional hazards assumption is met, implying that there is no time-dependent interaction between our exposure, the intervention, and outcome, mortality. However, we know that there was a large drop off in study participants from year one (12 months) to year two (24 months). We also know that Peru dropped out of the study after the end of the intervention, when the child was one-year (12-months) old. It is reasonable to be concerned Peru could be disrupting the survival analysis results, given the discrepancy in study enrollment when comparing children from Peru to children form the three other IRCs. Here, we will repeat the cox proportional hazards model without Peru, the sub-population of children who were enrolled throughout the 24-month period.

First, we will assess how the presence or absence of Peru from the analysis changes the survival time. Table 5 compares measures of central tendency and spread for child survival time when looking at a dataset with all four IRCs and a dataset with only Guatemala, India and

Rwanda (excluding Peru). The variable, survival time, looks similar between both treatment arms.

The Kaplan-Meier survival plot without Peru (Figure 4) visually depicts the change in survival probability over time and shows very similar probabilities for both the intervention and control group. However, to rigorously assess the intervention's effect on survival when analyzing data from children only from Guatemala, India, and Rwanda, we will use a cox proportional hazard model to calculate the adjusted and unadjusted hazard ratio, as done previously with all four IRCs.

The hazard rate of death among children in the intervention group was 0.973 (0.556, 1.704) times the hazard rate of death among children in the control group (Table 6). When controlling for the IRC, the HR is again very similar: hazard rate of death among children in the intervention group was 1.052 (0.480, 2.303) times the hazard rate of death among children in the control group (Table 6).

Next, we will look at the effect of the intervention on mortality in Peru alone. The Kaplan-Meier survival Plot (Figure 5) visually depicts deaths in the intervention group are consolidated to the first 100 days, while deaths in the control group are spread out throughout the first year. Unlike the other Kaplan-Meier survival plots, when looking at Peru alone, there is a more noticeable difference in survival between the two treatment arms. However, the unadjusted HR is still not statistically significant (Table 7): the hazard rate of death among children in the intervention group was 0.339 (0.108, 1.064) times the hazard rate of death among children in the control group. Of note, there is no adjusted HR because the analysis is specific to one country so there is no need to control for country.

Discussion

Summary of Results

The HAPIN trial investigated the impact of LPG cookstove on health, with a focus on child mortality in this analysis. There was no significant difference in child mortality through 24-months in the intervention group when compared to the control group. This finding was held when assessing the effect of the intervention alone (unadjusted HR) and when adjusting for the IRC (adjusted HR). In addition, there was no significant difference in child mortality when assessing: 1) children in Peru alone through 12-months, 2) children in Guatemala, India, and Rwanda alone through 24-months, and 3) children from all four countries combined through 24-months (although children in Peru dropped out after 12 months). Mortality was an exploratory outcome of the HAPIN trial only; the study was not powered to detect an effect and the data on mortality was accumulated primarily to meet ethical requirements to monitor and report serious adverse events. Accordingly, a finding of no intervention effects was not unanticipated.

Other findings are also worth noting. First, all deaths were within the first 12 months of life, and of those, most deaths were within the neonatal period. This is not surprising given that the neonatal period is the most vulnerable period in a child's life with the highest rates of child mortality globally (WHO 2022). Second, there was a substantial drop-off in study participants from the 12-month mark to the 24-month mark. This may be attributable to several factors, including the fact that the original study extended for only the child's first birthday, the absence of quarterly follow-up study visits during the second year, and normal attrition from longer-prospective cohorts. Lastly, although Peru had a unique role in the trial, it did not translate to a meaningful effect on mortality: the HRs for both Peru alone and Guatemala, India, and Rwanda alone were not statistically significant. As a reminder, participants in Peru were only enrolled in

the study until the child reached one year of age and a considerable number of control households in Peru (20%) used an LPG gas stove by the first follow-up visit.

Only one previous cross-sectional study in Myanmar reported an association between cooking with solid fuels and mortality, in particular in infants and children under-five (Rana, Islam et al. 2021). They hypothesized this may be due to the underlying physiology of younger children: infants and young children have both higher respiratory rates and narrower airways, which make them able to breathe up to 50% more polluted air than older children and adults (Rana, Islam et al. 2021). Furthermore, infants are susceptible to infections causing more detrimental effects due to a weaker immune system (Rana, Islam et al. 2021). Rana and Islam (2021) propose many reasonable explanations to support their findings from children in Myanmar, which could also offer a mechanism to understand how HAP impacts child mortality. However, we did not find any change in mortality in our analysis.

Reflection on Results

Apart from the analysis being under-powered, there are multiple possible mechanisms that may explain the null findings. First, the effect of the intervention may not be fully realized in the child by 24-months. The results from the cross-sectional study in Myanmar support this hypothesis, in that there was no significant difference in mortality in neonates, but there was in older children up until 5 years of age (Rana, Islam et al. 2021). Neonates may be immune to the effects of solid fuel cookstoves if mothers doing house chores do not carrying neonates on their backs because they are too young, and only begin this practice when the babies become a bit older (Rana, Islam et al. 2021). In the HAPIN trial, HAP exposure was measured through pregnancy and showed a difference in exposure in both treatment arms (Quinn, Williams et al.

2021), but results on difference in exposure through the child's first birthday are still in progress (Williams, in progress). Once this data is finalized, it will elucidate an important piece of this possible hypothesis. However, as shown in Table 2a, the majority of deaths were within the neonatal period and no deaths were after the 12-months through 24-months, suggesting that the effect of the intervention may indeed be fully realized by 24-months. Further work following the children until five years of age will be important to see if the effect of the intervention on child health will become more pronounced with time.

Another possibility is that the effect of the intervention may be strongest in utero and show its "fully realized" impact during pregnancy alone. Under this hypothesis, it would be better to assess the difference in miscarriages in both treatment arms rather than assessing child mortality after birth. If a fetus made it through pregnancy with HAP exposure, then one could propose the individual possesses strength and vitality to continue to withstand HAP as a small child. Previous work by Clasen et al. found that there was no significant difference in birth weight in the intervention versus control group (Clasen, Chang et al. 2022). This may also suggest that the intervention's effect was strongest during pregnancy, and once a pregnancy made it to a live birth, the sub-population of live children did not have substantially different birth weights (Clasen, Chang et al. 2022) or susceptibility to illnesses that may lead to death.

Third, although we know the intervention is reducing particulate matter exposure, the reduction may not be enough to cause a measurable change in outcomes. The intervention reduced $PM_{2.5}$ levels to within an acceptable range per the WHO Interim Target-1 (IT1) guidelines in 2005, which set the yearly exposure cut off of $PM_{2.5}$ to 35 micrograms per cubic meter (World Health 2005). However, the WHO recently updated their guidelines in 2021 for $PM_{2.5}$ exposure to 5 micrograms per cubic meter each year, one-seventh of what it used to be

(World Health 2021). The intervention did not reduce particulate matter enough to be in the clear of this updated standard, and perhaps did not reduce HAP exposure enough to translate to differences in outcome (Clasen, Chang et al. 2022).

Fourth, although LPG stoves are an improvement to stoves using solid biomass fuels, they do not eliminate exposure to all air pollutants. A recent study done in U.S. homes with natural gas stoves found that stoves emit methane and nitrogen oxides, both during use and when appliances are not in use (Lebel, Finnegan et al. 2022). This study highlights how gas stoves are contributing to HAP in insidious ways through small, but persistent, release of pollutants when the stove is not in use, completely reframing how we approach thinking about HAP and what makes an appliance safe. LPG stoves used in the intervention may also be contributing to HAP in ways that we have not yet understood and that our current measurements are unable to capture. In addition, it is important to think creatively about what a solution is: although an appliance may be beneficial in isolation, in context it may not have the desired effect. For example, even if LPG stoves do reduce HAP when used, if they increase HAP when not in use in a way that biomass stoves did not, and the overall effect of the stove on HAP may be negligible.

Lastly, all-cause mortality is an outcome that encompasses many possible root causes. There are also many other factors that may be protective against mortality, including diet, activity level, and stress level, in both moms and babies. By only looking at all-cause mortality, we may be grouping many different factors together and diluting the overall effect. For example, there may be a difference in mortality due to respiratory causes, such as pneumonia or severe respiratory infections, seen in the intervention versus control group, but no difference in mortality from other factors, such as cancer or congenital abnormalities. By grouping all

potential causes of mortality together, the signal of significant differences may be diluted out by the noise of non-significant differences, and thus we measure no overall difference in mortality.

Strengths, Limitations, and Further Research

As previously mentioned, the HAPIN trial is one of a very small sub-set of randomized control trials to assess the impact of an environmental exposure. This trial is unique in its breadth, being carried out in four countries, and its effectiveness, with evidence to show very good adherence and fidelity to the intervention and thus a reduction of exposure in the intervention arm (Quinn, Williams et al. 2021, Johnson, Pillarisetti et al. 2022). However, as with any study, there are also limitations. Although a positive in many other regards, the low number of child deaths relative to the study population is an important limitation, underpowering the study to detect a difference in child mortality.

Further research is needed to more thoroughly explore the possible impact on child mortality. First, analysis of cause-specific mortality would help illuminate if all-cause mortality is diluting the effect of certain specific causes. Pneumonia is the leading cause of child mortality globally for children under five (McAllister, Liu et al. 2019). Is there a difference in mortality from pneumonia across the treatment groups? This trial was carried out during the COVID-19 pandemic, which almost undeniably had an impact. Preliminary analysis suggests there may be differences in pneumonia incidence in the pre-COVID, COVID, and post-COVID eras (in progress). Is there a difference in mortality looking at each era (Pre-COVID, COVID, and post-COVID) and when looking at pneumonia rates within each era? Similarly, analyzing mortality across a 24-month period all together may be diluting the effect of time-specific mortality, as suggested by the clustering of many deaths in the neonatal period. Further work can repeat the

cox proportional hazards model while looking specifically at certain time points: one month, two months, one year, etc. Lastly, continued follow-up of children through five years of age would add to this analysis by extending the time where children may "fully realize" the effects of the intervention. As seen with the SDGs, which specifically focus on reducing both neonatal mortality and children under-five mortality, children are vulnerable beyond 24-months, and thus tracking them until five years of age will add to the generalizability and thoroughness of this study (UN).

Relatability and Generalizability

The HAPIN trial is an important, novel example of environmental health research in that it successfully employed a large scale, multi-center, randomized intervention, with very good uptake, adherence, and fidelity (Clasen, Checkley et al. 2020). However, the compensation and resources associated with a well-funded study are very different than real life. Although the HAPIN trial specifically chose one of the most utilized, available, and scalable options to deliver cleaner energy to LMICs with LPG stoves, there are still many barriers to converting the efforts of this study into a sustainable reality for the millions of people living without access to clean energy. Another important one of the seventeen SDGs focuses on improving access to "affordable, reliable, sustainable, and modern energy for all." Unfortunately, progress on this goal has slowed and there still is a long way to go (UN). Many, if not all, of the SDGs are inextricably linked. In order to make progress on all seventeen SDGs, considerable thought, creativity, and energy must be spent on implementation science to move an idea to something that can be accessed, used, and sustained.

Finally, although this study focuses on a global scale on four specific LMICs, it would be remiss to think the disparities in child mortality are only seen in certain places. A recent New York Times article, "Childbirth Is Deadlier for Black Families Even When They're Rich, Expansive Study Finds," eloquently visualized and conveyed the disturbing reality of child mortality for women in the United States based race and income status (Claire Cain Miller 2023). The article summarizes findings from a study done in California with first-time moms, specifically looking at dichotomous groups of the moms and babies by race (Black or White) and income status (top 10% of family income as the "richest" and bottom 10% of family income as the "poorest"). They found that the women from lower income have higher rates of child mortality with the first year than women from higher income, but not enough to compensate the difference seen due to race: the poorest white moms still have lower rates of child mortality than the richest Black moms (Claire Cain Miller 2023). The causes of child mortality are multifactorial, but the influence of systemic racism, and epigenetic changes from generations of toxic stress of structural and systemic racism, is an undeniable component.

As we think about the potential impact of the HAPIN study, is it important to remember that an individual's exposure to particulate matter is an important droplet, but just one in a larger bucket. It is essential to remember the rest of the bucket, from inequities in housing to education, and how all factors come together as we try to use science to influence human health, with a goal of make meaningful, sustainable, and lasting change.

Figures and Tables

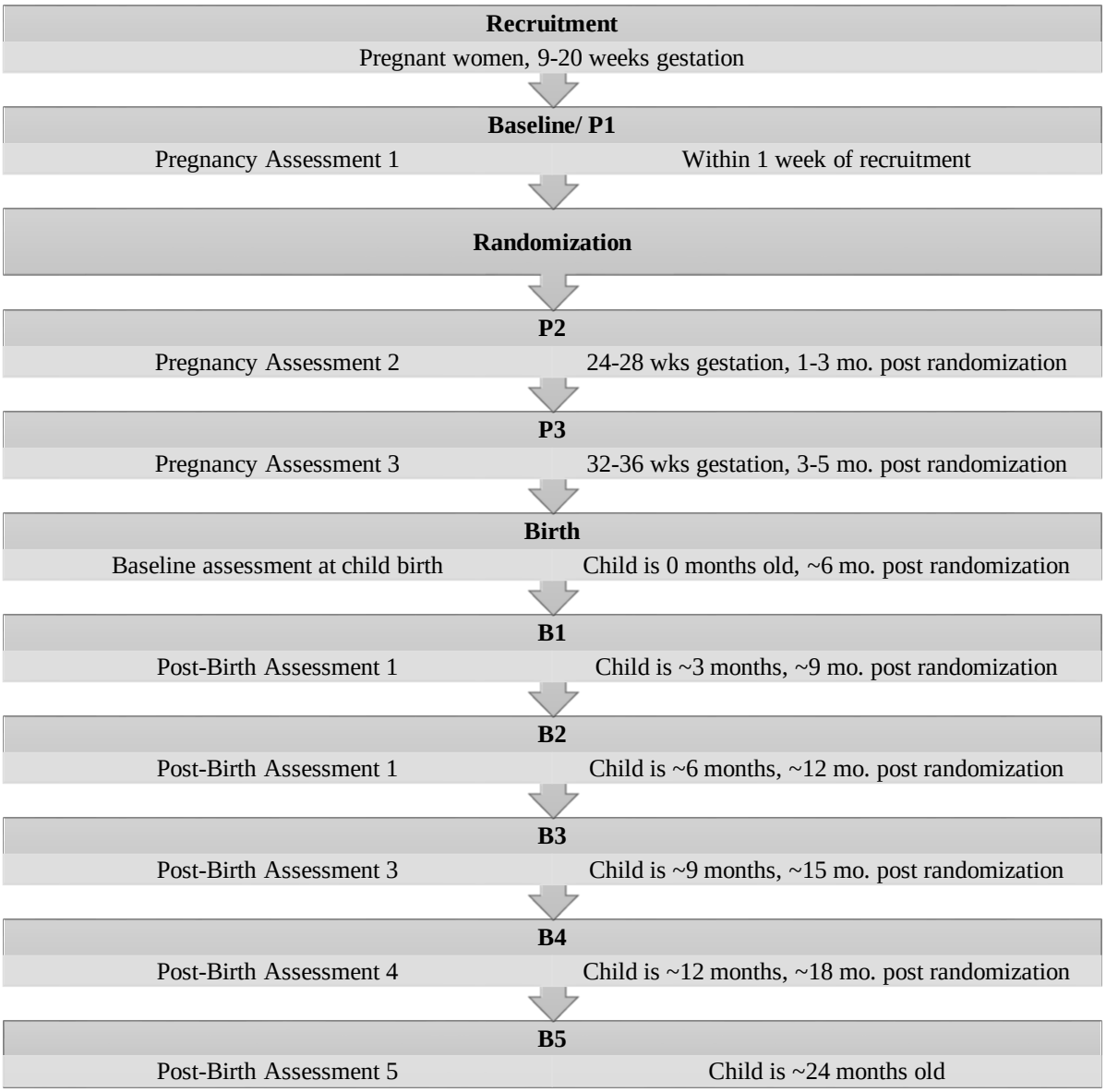
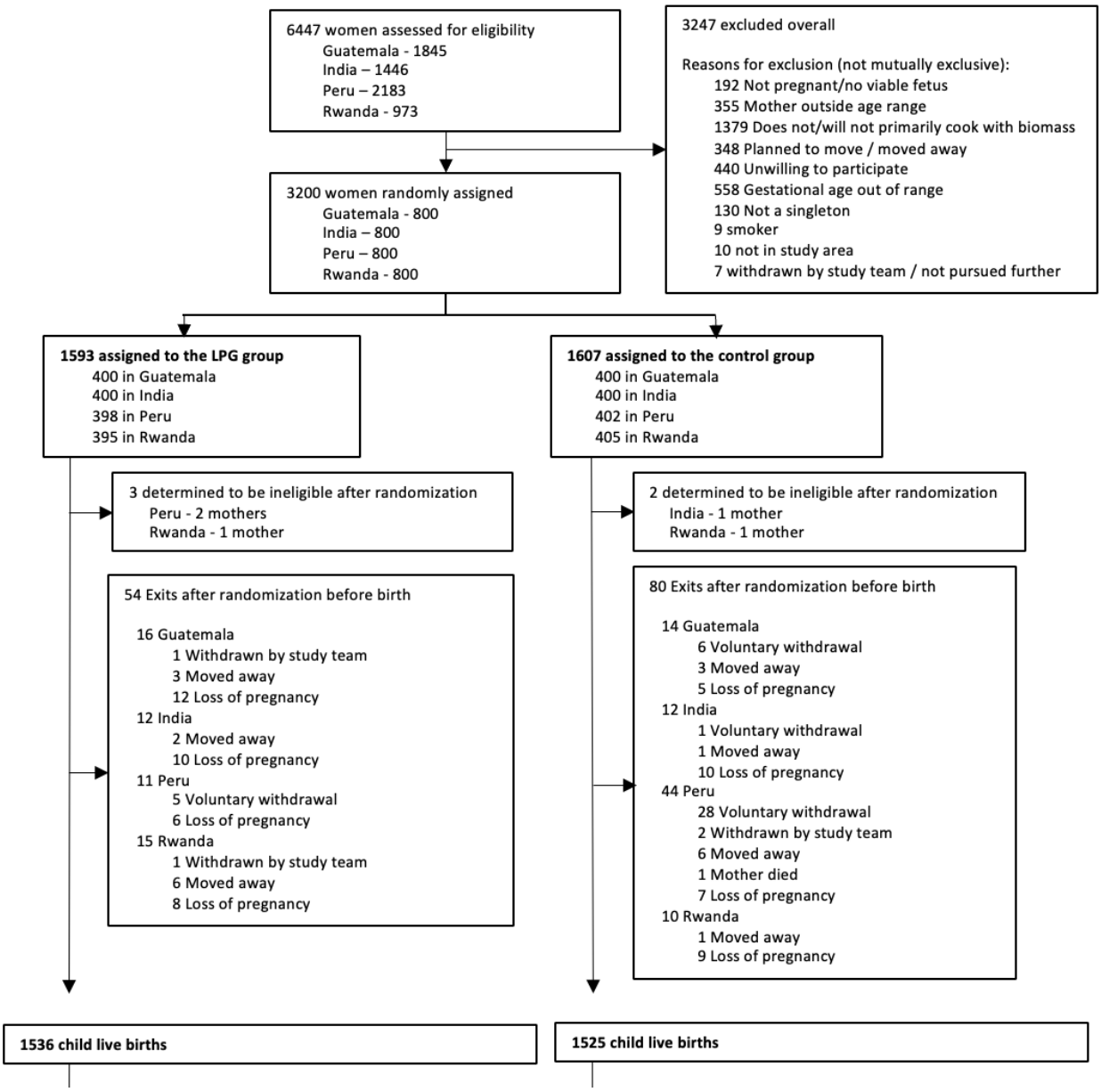


Figure 1. Overview of data collection time points during the study period. Note that time points can be referred to as time post-randomization or time pre- and post-child birth (with pre-child birth given in weeks gestation and post-child birth given in child age).


6447 women assessed for eligibility
Guatemala - 1845
India – 1446
Peru – 2183
Rwanda - 973
3247 excluded overall
Reasons for exclusion (not mutually exclusive):
192 Not pregnant/no viable fetus
355 Mother outside age range
1379 Does not/will not primarily cook with biomass
348 Planned to move / moved away
440 Unwilling to participate
558 Gestational age out of range
130 Not a singleton
9 smoker
10 not in study area
7 withdrawn by study team / not pursued further
3200 women randomly assigned
Guatemala - 800
India – 800
Peru – 800
Rwanda - 800
1593 assigned to the LPG group
400 in Guatemala
400 in India
398 in Peru
395 in Rwanda
1607 assigned to the control group
400 in Guatemala
400 in India
402 in Peru
405 in Rwanda
3 determined to be ineligible after randomization
Peru - 2 mothers
Rwanda - 1 mother
2 determined to be ineligible after randomization
India - 1 mother
Rwanda - 1 mother
54 Exits after randomization before birth
16 Guatemala
1 Withdrawn by study team
3 Moved away
12 Loss of pregnancy
12 India
2 Moved away
10 Loss of pregnancy
11 Peru
5 Voluntary withdrawal
6 Loss of pregnancy
15 Rwanda
1 Withdrawn by study team
6 Moved away
8 Loss of pregnancy
80 Exits after randomization before birth
14 Guatemala
6 Voluntary withdrawal
3 Moved away
5 Loss of pregnancy
12 India
1 Voluntary withdrawal
1 Moved away
10 Loss of pregnancy
44 Peru
28 Voluntary withdrawal
2 Withdrawn by study team
6 Moved away
1 Mother died
7 Loss of pregnancy
10 Rwanda
1 Moved away
9 Loss of pregnancy
1536 child live births
1525 child live births

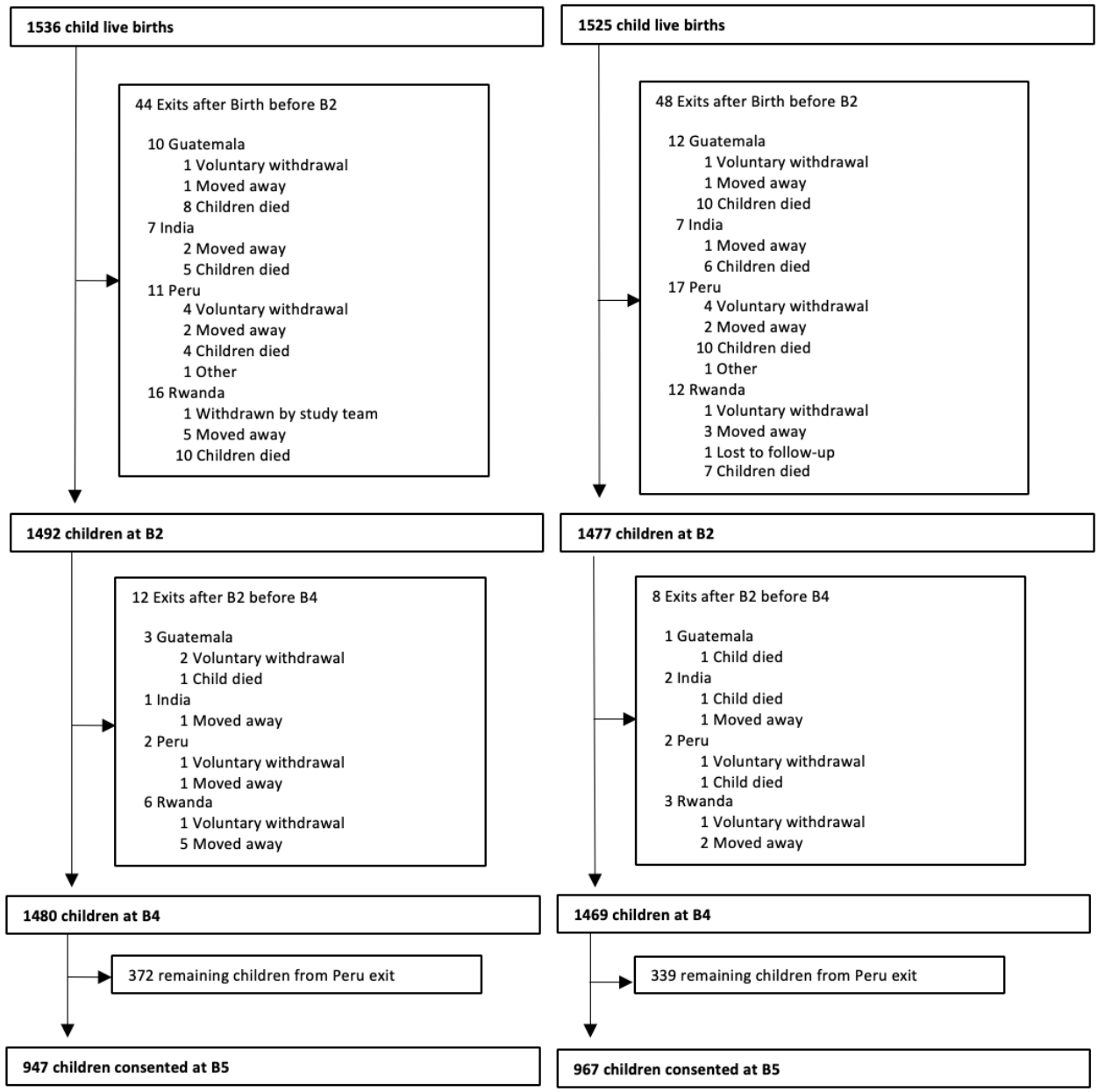


Figure 2. CONSORT Diagram summarizing the screening, randomization, and loss to follow-up for trial participants. Note that the diagram begins with the pregnant women initially screened, enrolled, and randomized in the trial. After birth, the participant of interest shifts to the child.

Table 1a: Baseline Maternal Characteristics from all 4 IRCs (n = 3195)

Characteristic		**Intervention (n= 1590)**	**Control (n= 1605)**
Age: no. (%)			
	<20 yr	189 (11.9)	209 (13.0)
	20-24 yr	616 (38.7)	579 (36.1)
	25-29 yr	500 (31.5)	517 (32.2)
	30-35 yr	285 (17.9)	300 (18.7)
Gestational age (weeks)		15.5 +/- 3.1	15.3 +/- 3.2
Nulliparous: no. (%)			
	Yes	639 (40.2)	589 (36.7)
	No	947 (59.6)	1014 (63.2)
	Missing data	4 (0.2)	2 (0.1)
Body-Mass Index (at enrollment)			
	Mean	23.3 +/- 4.1	23.1 +/- 4.0
	Missing data (no.)	12	7
Highest Level of Education: no. (%)			
	No formal education or primary school incomplete	481 (30.3)	558 (34.8)
	Primary school complete or secondary school incomplete	558 (35.1)	533 (33.2)
	Secondary school complete or vocational or some college or university	550 (34.6)	514 (32.0)
	Missing data	1 (< 0.1)	0 (0.0)
Dietary Diversity Score: no. (%)			
	<4: low diversity	890 (56.0)	906 (56.5)
	4 – 5: medium diversity	496 (31.2)	533 (33.2)
	>5: high diversity	203 (12.8)	165 (10.3)
	Missing data	1 (< 0.1)	1 (< 0.1)
Household food insecurity score: no. (%)			
	0: None	930 (58.5)	863 (53.8)
	1 – 3: Mild	416 (26.2)	448 (27.9)
	4 – 8: Moderate/ Severe	220 (13.8)	272 (16.9)
	Missing data	24 (1.5)	22 (1.4)
Number of persons sleeping in household			
	Mean	4.3 +/- 2.0	4.3 +/- 2.0
	Missing data (no. of households)	1	0
Household assets owned: no. (%)			
	Color Television	774 (48.7)	783 (48.8)
	Radio	734 (46.2)	721 (44.9)
	Mobile Telephone	1388 (87.3)	1395 (86.9)
	Bicycle	365 (23.0)	409 (25.5)
	Bank Account	697 (43.8)	628 (39.1)

Table 1b: Baseline Maternal Characteristics from Guatemala, India, and Rwanda (n = 2397)

Characteristic		**Intervention (n= 1194)**	**Control (n = 1203)**
Age: no. (%)			
	<20 yr	149 (12.5)	150 (12.5)
	20-24 yr	465 (38.9)	444 (36.9)
	25-29 yr	370 (31.0)	390 (32.4)
	30-35 yr	210 (17.6)	219 (18.2)
Gestational age (weeks)		15.4 +/- 3.0	15.2 +/- 3.1
Nulliparous: no. (%)			
	Yes	485 (40.6)	433 (36.0)
	No	708 (59.3)	769 (63.9)
	Missing data	1 (0.1)	1 (0.1)
Body-Mass Index (at enrollment)			
	Mean	22.3 +/- 3.8	22.3 +/- 3.7
	Missing data (no.)	6	3
Highest Level of Education: no. (%)			
	No formal education or primary school incomplete	466 (39.0)	538 (44.7)
	Primary school complete or secondary school incomplete	427 (35.8)	430 (35.7)
	Secondary school complete or vocational or some college or university	301 (25.2)	235 (19.5)
	Missing data	0	0
Dietary Diversity Score: no. (%)			
	<4: low diversity	844 (70.7)	865 (71.9)
	4 – 5: medium diversity	293 (24.5)	299 (24.9)
	>5: high diversity	56 (4.7)	38 (3.1)
	Missing data	1 (0.1)	1 (0.1)
Household food insecurity score: no. (%)			
	0: None	720 (60.3)	661 (55.0)
	1 – 3: Mild	288 (24.1)	302 (25.1)
	4 – 8: Moderate/ Severe	167 (14.0)	225 (18.7)
	Missing data	19 (1.6)	15 (1.2)
Number of persons sleeping in household			
	Mean	4.2 +/- 2.1	4.1 +/- 2.1
	Missing data (no. of households)	0	0
Household assets owned: no. (%)			
	Color Television	527 (44.1)	523 (43.5)
	Radio	445 (37.3)	417 (34.7)
	Mobile Telephone	1010 (84.6)	1007 (83.7)
	Bicycle	218 (18.3)	247 (20.5)
	Bank Account	603 (50.5)	542 (45.1)

Table 1c: Baseline Characteristics of Children at Birth from all 4 IRCs (n = 3061)

Characteristic		**Intervention (n = 1536)**	**Control (n = 1525)**
Sex: no. (%)			
	Female	736 (47.9)	738 (48.4)
	Male	800 (52.1)	787 (51.6)
Delivery Location: no. (%)			
	Public Hospital	1005 (65.4)	993 (65.1)
	Private Hospital	33 (2.2)	26 (1.7)
	Own House	53 (3.5)	61 (4.0)
	Community health worker's house	0 (0.0)	3 (0.2)
	Other family member's house	3 (0.2)	3 (0.2)
	Public health center/ post	414 (26.9)	419 (27.5)
	Private Clinic	11 (0.7)	8 (0.5)
	Other	15 (1.0)	10 (0.7)
	Missing	2 (0.1)	2 (0.1)
Delivery Kind: no. (%)			
	Normal spontaneous vaginal birth	1188 (77.4)	1196 (78.4)
	Caesarean	342 (22.3)	320 (21.0)
	Vaginal, with forceps/ vacuum	2 (0.1)	5 (0.3)
	Breech vaginal birth	2 (0.1)	3 (0.2)
	Missing	2 (0.1)	1 (0.1)
Caesarean Type: no. (%)			
	Emergency	185 (12.0)	174 (11.4)
	Elective	60 (3.9)	53 (3.5)
	Missing/ Unknown	1291 (84.1)	1298 (85.1)
Labor Time (in hours) : no. (%)			
	< 12 hours	1017 (66.2)	1017 (66.7)
	12 – 24 hours	271 (17.6)	270 (17.7)
	> 24 hours	100 (6.5)	102 (6.7)
	No labor	145 (9.5)	133 (8.7)
	Missing	3 (0.2)	3 (0.2)

Table 1d: Baseline Characteristic of Children at Birth from Guatemala, India, and Rwanda (n = 2318)

Characteristic		**Intervention (n=1151)**	**Control (n = 1167)**
Sex: no. (%)			
	Female	546 (47.4)	555 (47.6)
	Male	605 (52.6)	612 (52.4)
Delivery Location: no. (%)			
	Public Hospital	755 (65.6)	752 (64.4)
	Private Hospital	30 (2.6)	22 (1.9)
	Own House	43 (3.7)	52 (4.4)
	Community health worker's house	0 (0.0)	2 (0.2)
	Other family member's house	2 (0.2)	2 (0.2)
	Public health center/ post	304 (26.4)	326 (27.9)
	Private Clinic	2 (0.2)	1 (0.1)
	Other	13 (1.1)	8 (0.7)
	Missing	2 (0.2)	2 (0.2)
Delivery Kind: no. (%)			
	Normal spontaneous vaginal birth	859 (74.6)	906 (77.6)
	Caesarean	287 (24.9)	255 (21.8)
	Vaginal, with forceps/ vacuum	2 (0.2)	3 (0.3)
	Breech vaginal birth	1 (0.1)	2 (0.2)
	Missing	2 (0.2)	1 (0.1)
Caesarean Type: no. (%)			
	Emergency	175 (15.2)	163 (14.0)
	Elective	58 (5.0)	50 (4.3)
	Missing/ Unknown	918 (79.8)	954 (81.7)
Labor Time (in hours) : no. (%)			
	< 12 hours	788 (68.5)	831 (71.2)
	12 – 24 hours	165 (14.3)	171 (14.6)
	> 24 hours	73 (6.3)	65 (5.6)
	No labor	123 (10.7)	98 (8.4)
	Missing	2 (0.2)	2 (0.2)

	Time Period			
	Neonatal (< 28 days)	**Infant, year 1** (28 days – 12 months)	**Child, year 2** (12 – 24 months)	**Total**
Number of Deaths	40	24	0	64

Table 2a. Distribution of child mortality over time. Note that all child deaths occur within the first year of life, with the majority occurring within the neonatal period.

	Study Arm		
Research Site	**Control**	**Intervention**	**Total**
Guatemala	11	9	20
India	7	5	12
Peru	11	4	15
Rwanda	7	10	17
Total	36	28	**64**

Table 2b. Distribution of child mortality across research sites and study groups. Note that slightly more children died in the control group when compared to the intervention group (36 vs. 28, respectively) and slightly more children died in Guatemala compared to the other IRCs.

Study Exit Reason	**Intervention: n (%)**	**Control: n (%)**	**Total**
Death	28 (1.82)	36 (2.36)	64 (2.09)
Study Completion	1477 (96.16)	1467 (97.20)	2944 (96.18)
Participant voluntary withdrawal	9 (0.59)	8 (0.52)	17 (0.56)
Withdrawal by study team	3 (0.20)	0 (0)	3 (0.10)
Moved away from study area	17 (1.11)	11 (0.72)	28 (0.91)
Loss to follow-up	1 (0.07)	2 (0.13)	3 (0.10)
Other	1 (0.07)	1 (0.07)	2 (0.06)
Total	1536	1525	3061

Table 3. Reasons for study exit in children in both the intervention and control groups. Note that the majority of children are categorized as completing the study.

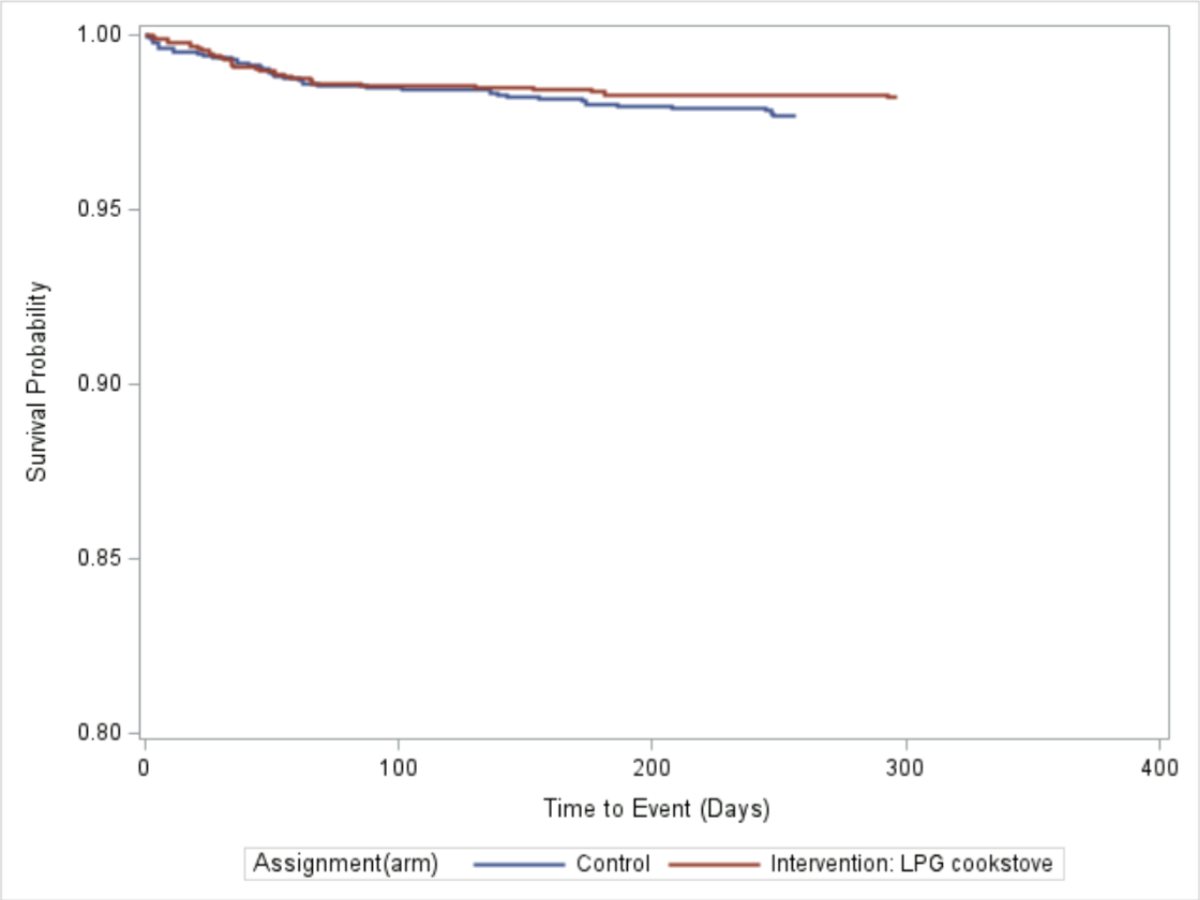


Figure 3. Kaplan Meier Survival Curve. Note that only the last point plotted for each line is the last death that has occurred. The intervention group's survival probability is higher than the control and the last death in the intervention group is later than in the control group.

Study Arm	**Hazard Ratio (95% CI)**	**Adjusted HR (95% CI)[a]**
Intervention (LPG)	0.772 (0.471, 1.266)	0.964 (0.476, 1.950)
Control	REF (reference)	REF

a = IRC

Table 4. Unadjusted and Adjusted Hazard Ratio (HR) for death in all four IRCs. Note that neither the adjusted nor unadjusted HR are significant.

Variable: Survival Time (in days)	**Dataset with all four IRCs (n = 3061)**	**Dataset with three IRCs, excluding Peru (n = 2318)**
Mean	391.59	395.68
Median	382.0	380.0
Mode	370.0	370.0
Standard deviation	76.15	78.67
Minimum	0	0
Q1	370	369
Q3	405	416
Interquartile Range	35	47
Maximum	773	773

Table 5. Compare measures of central tendency and spread for the variable, survival time (in days). Note that the values for each metric assessed is very similar between the group of children from all four IRCs and the group of children from only Guatemala, India, and Rwanda.

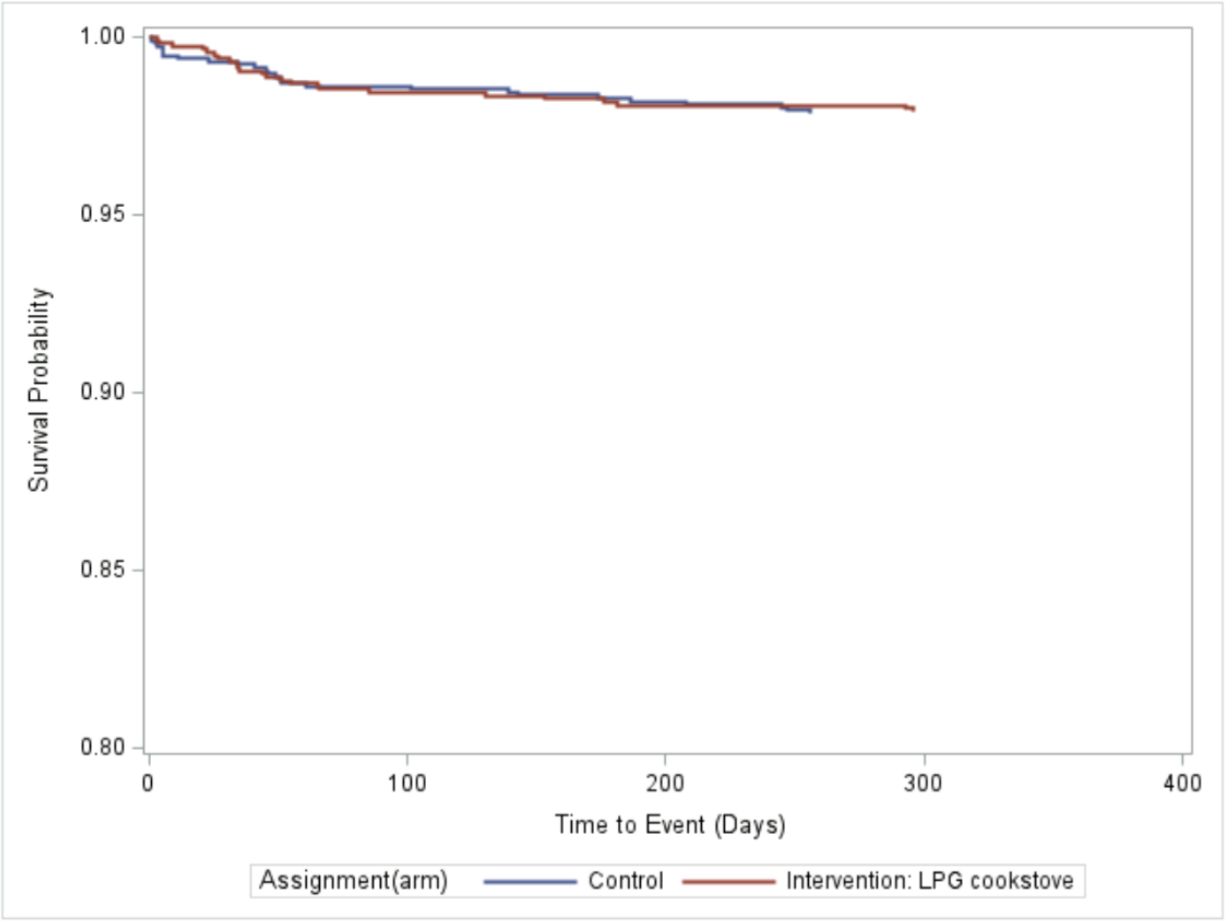


Figure 4. Kaplan Meier Survival Curve for Guatemala, India, and Rwanda. Note that the intervention group (red line) and control group (blue line) have very similar survival probabilities over the course of the study. Again, the lines stop when the last death, event of interest, has occurred.

Study Arm	**Hazard Ratio (95% CI)**	**Adjusted HR (95% CI)[a]**
Intervention (LPG)	0.973 (0.556, 1.704)	1.052 (0.480, 2.303)
Control	REF	REF

a = IRC

Table 6. Unadjusted and Adjusted Hazard Ratio (HR) for death in Guatemala, India, and Rwanda only. Note that neither the adjusted nor unadjusted HR are significant.

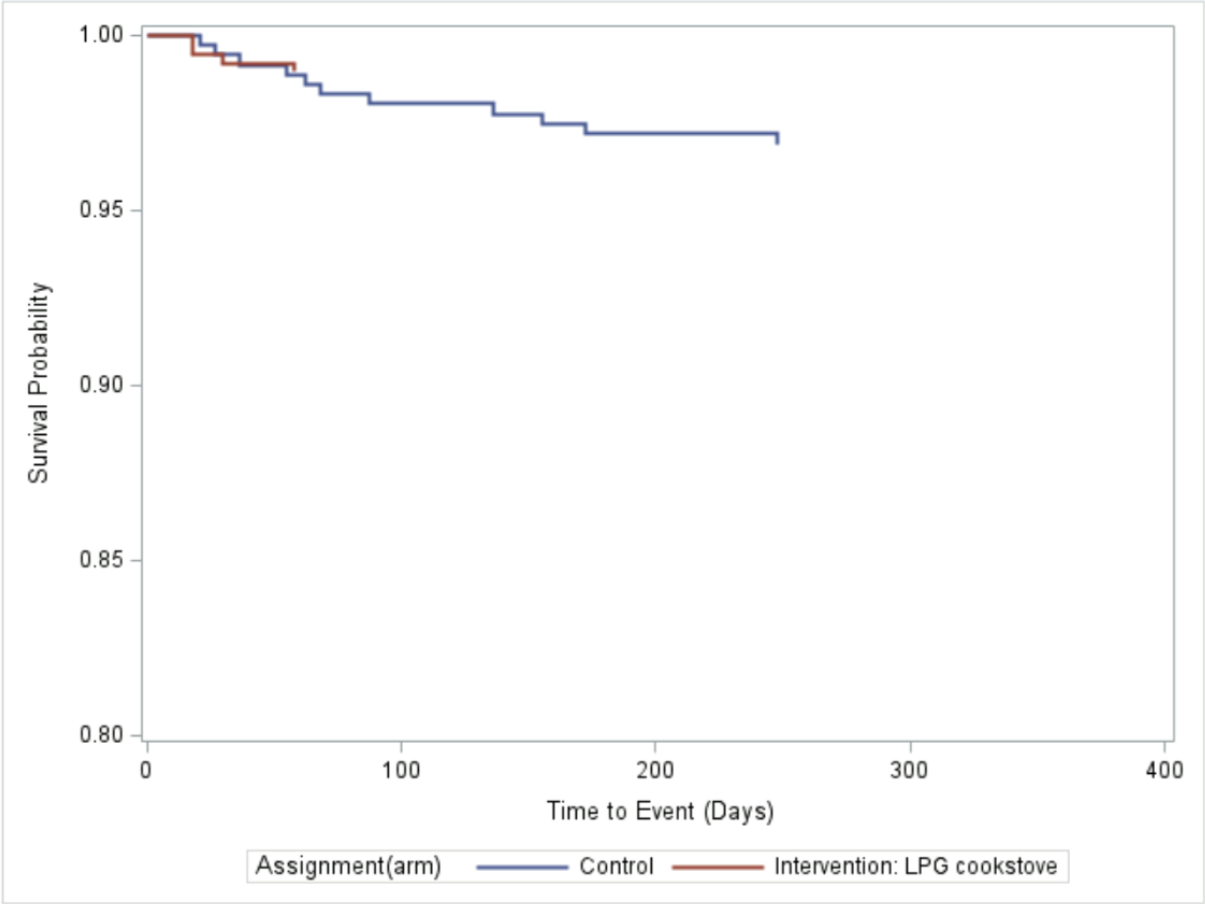


Figure 5. Kaplan Meier Survival Curve for Peru. Note that the deaths in the intervention group (red line) are consolidated within the first 100 days, while the deaths in the control group (blue line) are spread throughout the first year.

Study Arm	**Hazard Ratio (95% CI)**
Intervention (LPG)	0.339 (0.108, 1.064)
Control	REF

Table 7. Unadjusted Hazard Ratio (HR) for death in Peru only. Note that the unadjusted HR is not statistically significant. Given that there was only one IRC in this analysis, there is no adjusted HR.

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