Published in final edited form as:
N Engl J Med. 2022 November 10; 387(19): 1735–1746. doi:10.1056/NEJMoa2206734.

Liquefied Petroleum Gas or Biomass for Cooking and Effects on Birth Weight

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Abstract

Background—Exposure during pregnancy to household air pollution caused by the burning of solid biomass fuel is associated with adverse health outcomes, including low birth weight. Whether the replacement of a biomass cookstove with a liquefied petroleum gas (LPG) cookstove would result in an increase in birth weight is unclear.

Methods—We performed a randomized, controlled trial involving pregnant women (18 to <35 years of age and at 9 to <20 weeks' gestation as confirmed on ultrasonography) in Guatemala, India, Peru, and Rwanda. The women were assigned in a 1:1 ratio to use a free LPG cookstove and fuel (intervention group) or to continue using a biomass cookstove (control group). Birth weight, one of four prespecified primary outcomes, was the primary outcome for this report; data for the other three outcomes are not yet available. Birth weight was measured within 24 hours after birth. In addition, 24-hour personal exposures to fine particulate matter (particles with a diameter of ≤2.5 μm [$PM_{2.5}$]), black carbon, and carbon monoxide were measured at baseline and twice during pregnancy.

Results—A total of 3200 women underwent randomization; 1593 were assigned to the intervention group, and 1607 to the control group. Uptake of the intervention was nearly complete, with traditional biomass cookstoves being used at a median rate of less than 1 day per month. After randomization, the median 24-hour personal exposure to fine particulate matter was 23.9 μg per cubic meter in the intervention group and 70.7 μg per cubic meter in the control group. Among 3061 live births, a valid birth weight was available for 94.9% of the infants born to women in the intervention group and for 92.7% of infants born to those in the control group. The mean (±SD) birth weight was 2921±474.3 g in the intervention group and 2898±467.9 g in the control group, for an adjusted mean difference of 19.6 g (95% confidence interval, −10.1 to 49.2).

Conclusions—The birth weight of infants did not differ significantly between those born to women who used LPG cookstoves and those born to women who used biomass cookstoves. (Funded by the National Institutes of Health and the Bill and Melinda Gates Foundation; HAPIN ClinicalTrials.gov number, NCT02944682.)

MORE THAN 3 BILLION PEOPLE COOK on open fires and traditional stoves using solid biomass fuels (biomass) such as wood, dung, charcoal, and agricultural waste — a number that has not changed substantially in the past three decades.[1] Exposure to the resulting household air pollution is a leading health risk in populations in low-income and middle-income countries and accounts for an estimated 2.3 million premature deaths annually and 91.5 million disability-adjusted life years.[2] Exposure to household air pollution is associated with pneumonia, tuberculosis, chronic lung disease, cardiovascular disease, lung cancer, and other health disorders.[3]

Low birth weight (<2500 g) remains a major public health challenge, particularly in low-income and middle-income countries.[4,5] One study showed that more than 80% of neonatal deaths occurred in newborns with a low birth weight, of whom two thirds were born preterm and a third were born at term but were small for gestational age.[6] Low birth weight is associated with impaired physical and cognitive development, as well as longer-term medical conditions such as cardiovascular disease.[6] Risk factors for low birth weight include maternal age (particularly among women <16 years or >40 years of age), smoking, multiple births, obstetric complications, hypertension and other conditions related to maternity, infections, poor nutritional status, and household air pollution.[7] A systematic review of 19 studies concluded that the use of solid fuel for cooking or heating resulted in a mean reduction in birth weight of 86 g (95% confidence interval [CI], 55 to 117) and a 35% increased risk of low birth weight (summary effect estimate, 1.35; 95% CI, 1.23 to 1.48).[8] However, in a more recent review of 23 studies (including 3 randomized clinical trials), questions were raised about the methodologic quality of the included studies, and the authors concluded that more research was necessary to infer a causal relationship between household air pollution and birth outcomes, including birth weight.[9]

Other trials of alternatives to traditional cooking with biomass have not shown clear protective effects on birth weight. In a trial of the use of ethanol cookstoves that involved 324 households in Nigeria, the mean birth weight was higher by 88 g in households that received an ethanol cookstove than in those that continued to use biomass cookstoves, but the difference was not significant, with a 95% confidence interval of −18 to 194 g.[10] Separate trials in Nepal and Ghana, each of which compared the use of improved biomass cookstoves or liquefied petroleum gas (LPG) cookstoves with the use of traditional biomass cookstoves, also showed no beneficial effect on birth weight.[11,12] In these trials, however, the intervention stoves were not used exclusively, and use of the stoves and fuel did not reduce measured exposures to household air pollution substantially or meet the World Health Organization Annual Interim Target 1 (WHO-IT1) for a level of fine particulate matter (particles with a diameter of ≤2.5 μm [$PM_{2.5}$]) of 35 μg per cubic meter, an important benchmark.

The Household Air Pollution Intervention Network (HAPIN) trial was designed to assess health effects after the replacement of biomass cookstoves with LPG cookstoves, with the goal of reducing household air pollution in low-income and middle-income countries.[13] In previous reports, the trial was shown to have high fidelity (i.e., delivery of the intervention as intended) and adherence to the intervention[14] and to have led to a substantial reduction in personal exposure to fine particulate matter and black carbon during pregnancy.[15] Here, we report the effects of the intervention on infant birth weight, one of four primary outcomes and the first for which we have reached the designated number of outcome measurements for analysis.

METHODS

TRIAL DESIGN AND SETTING

The trial design and methods have been described previously.[13,16,17] The HAPIN trial was a multicenter, parallel-group, individually randomized, controlled trial with four primary outcomes: infant birth weight, growth stunting in infants, severe pneumonia in infants, and systolic blood pressure in women living in the same household as the pregnant women. We aimed to recruit 800 eligible women from areas in each of four low-income and middle-income countries (Jalapa, Guatemala; Tamil Nadu, India; Puno, Peru; and Eastern Province, Rwanda) in which large portions of the population use solid biomass as the primary fuel for cooking. The trial settings were selected on the basis of logistic considerations and the potential to recruit eligible participants.

The trial protocol, available with the full text of this article at NEJM.org, was reviewed and approved by the institutional review boards or ethics committees of Emory University, Johns Hopkins University, the Sri Ramachandra Institute of Higher Education and Research, Universidad del Valle de Guatemala, Asociación Benéfica PRISMA, the London School of Hygiene and Tropical Medicine, and Washington University in St. Louis and by the Indian Council of Medical Research–Health Ministry Screening Committee, the Guatemalan Ministry of Health National Ethics Committee, and the Rwandan National Ethics Committee. The first and last two authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANT ELIGIBILITY

Potentially eligible trial participants were identified in clinic registries and at prenatal clinics and were referred by community health workers. Women were eligible if they had a confirmed pregnancy (blood or urine test positive for human chorionic gonadotropin), were 18 to less than 35 years of age (confirmed by government-issued identification document, whenever possible), cooked primarily with biomass stoves, lived in a trial area, were at 9 to less than 20 weeks' gestation with a viable singleton pregnancy (confirmed by ultrasonography), had continued pregnancy (confirmed by participant report) at the time of randomization, and provided written informed consent. Pregnant women were excluded if they currently smoked tobacco products, planned to move permanently outside the trial area within 12 months, or currently used a clean-fuel cookstove or were likely to acquire and predominantly use one in the near future.

RANDOMIZATION

After informed consent was obtained and baseline assessments were completed, eligible pregnant women were randomly assigned in a 1:1 ratio to use a free LPG cookstove and fuel (intervention group) or to continue using a biomass cookstove (control group). Sealed envelopes containing the trial-group assignments, which were prepared by the trial data management center at Emory University, were selected by the participants. Randomization was stratified according to trial site in each of the four countries (two sites in India, six sites in Peru, one site in Guatemala, and one site in Rwanda) to achieve balance among discrete geographic regions within the trial areas. Although blinding at the participant and field-staff levels was not possible, other investigators (i.e., anyone working on the trial who was not involved in collecting data directly from the participants) were unaware of the trial-group assignments, except for two designated persons (the lead of the data management core and an epidemiologist) for the purpose of sharing unblinded information required by the data and safety monitoring board.

TRIAL-GROUP ASSIGNMENTS

The intervention consisted of a free LPG cookstove; a continuous supply of free LPG fuel that was delivered to the homes of the women during pregnancy and until the infant was 1 year of age; and education and behavior-based messaging to promote safe, exclusive use of the LPG cookstove.[13] LPG cookstove types varied according to local availability and cooking practices, but all met applicable safety requirements and had at least two burners. To minimize the use of multiple stoves or fuels, we monitored for continued use of biomass fuel after delivery of an LPG cookstove through a combination of observation and reports during follow-up visits and stove-mounted temperature sensors.[18,19] Women in the control group received no intervention after enrollment and were expected to follow their customary cooking practices, although they received compensation designed to minimize loss to follow-up and offset the economic advantage accorded to intervention households receiving free stoves and fuel.[20]

OUTCOMES

In accordance with the trial protocol, birth weight (primary outcome) was measured within 24 hours after birth by a trained nurse or field worker using a mobile digital infant scale (Seca). Newborns were weighed while they were unclothed or wearing preweighed clothing. Duplicate measurements were recorded to the nearest 10 g; if the two measurements differed by more than 10 g, a third measurement was obtained, and the two closest measurements were averaged. Infants were typically assessed at the health facilities where they were born. For infants for whom we could not measure birth weight during the prescribed 24-hour window (mainly because of restrictions related to coronavirus disease 2019 or because the infant was critically ill and thus admitted to a newborn intensive care unit or referral hospital), we used measurements provided by the facility, if available. Low birth weight was defined as a body weight of less than 2500 g, and very low birth weight was defined as a body weight of less than 1500 g.[21]

Secondary outcomes were gestational age at birth (calculated from the gestational age estimated at the time of recruitment and corroborated by means of ultrasonography), preterm birth (live birth at <37 weeks' gestation), early preterm birth (live birth at <34 weeks' gestation), preterm delivery (delivery at <37 weeks' gestation among live births and stillbirths), and stillbirth (birth at ≥20 weeks' gestation with no signs of life). Serious adverse events, including burns, were reported within 48 hours.

STATISTICAL ANALYSIS

Assuming a residual standard deviation in birth weight of 437 g on the basis of previous reports[22,23] and a 10% loss to follow-up, we estimated that a sample of 3200 participants would provide the trial with 80% power to detect a difference in mean birth weight of 54 g at an alpha level of 0.0125, which reflects a Bonferroni correction for multiple testing of the four primary outcomes. All analyses of birth weight were restricted to the use of records in which the birth weight was measured as described above, and z scores for weight at birth, standardized for gestational age and sex, were calculated with the use of INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) tables.[24] Because the INTERGROWTH-21st standard applies to infants born at 33 to 42 weeks' gestation, analyses were limited to the use of birth weights that were measured during this period of gestation. Birth weight was analyzed in the intention-to-treat population (all infants with a valid birth weight born to women who had undergone randomization) by means of linear regression, adjusted for randomization strata (the trial sites within each country).

Continuous secondary and other outcomes were analyzed with the use of the same methods used for birth weight; for the dichotomous secondary outcomes, we estimated relative risks using log-binomial regression. The continuous secondary outcomes were analyzed in the intention-to-treat population by means of linear regression, adjusted for randomization strata. The dichotomous secondary outcomes were also analyzed in the intention-to-treat population by means of log-binomial regression for estimating relative risks.

We performed subgroup analyses according to country, infant sex, and the timing of stove installation. Early introduction of the intervention was defined as installation of an LPG cookstove either before the median gestational age or during the first trimester. In these analyses, the early- and late-intervention groups were each compared with the entire control group.

Because our intention-to-treat analyses were adjusted for randomization strata and our subgroup analyses included covariates, missing data were handled by assuming that the data were missing at random within the distinct levels of the randomization strata and covariates. Multiple imputation for missing outcomes was not conducted. In the secondary and subgroup analyses, the 95% confidence intervals were not adjusted for multiple comparisons; thus, they should not be used in place of hypothesis testing.

RESULTS

TRIAL PARTICIPANTS

Between May 7, 2018, and February 29, 2020, a total of 3200 pregnant women across four country-based research centers underwent randomization; 1593 were assigned to the intervention group, and 1607 to the control group (Fig. 1). A total of 5 women were found to be ineligible after randomization (3 in the intervention group and 2 in the control group) and were withdrawn from the trial. The characteristics of the women at baseline were similar in the two groups, both trialwide (Table 1) and within each research center (Table S1 in the Supplementary Appendix, available at NEJM.org). The participants were thought to be representative, according to race, ethnic group, age, and sex, of the broader population affected by indoor air pollution from burning biomass fuel (Table S2). The mean gestational age at baseline was 15.5 weeks in the intervention group and 15.3 weeks in the control group. The 3195 pregnancies yielded 3061 live births to women still enrolled in the trial (95.8%) — 1536 (96.4%) in the intervention group and 1525 (94.9%) in the control group (Fig. 1).

INTERVENTION COVERAGE AND ADHERENCE

Intervention coverage was nearly complete, and in the households, the LPG cookstoves were used almost exclusively. The control households continued to rely on their traditional cookstoves and fuel.[14] Intervention households received the intervention at a median of 8 days (interquartile range, 5 to 15) after randomization and at a median gestational age of 17.9 weeks (interquartile range, 15.4 to 20.6).[14] Early introduction of the intervention before the median gestational age or during the first trimester occurred in 186 intervention households (12.4%). Traditional cookstoves were either not used or used less than 1 day per month of follow-up in more than 86% of intervention households. Given the high levels of coverage and use, we did not undertake a separate per-protocol analysis. By contrast, less than 2% of the households in the control group used LPG cookstoves, except in Peru, where approximately one fifth of the control households adopted use of an LPG cookstove by the first follow-up visit, as compared with 96% of the intervention households.[14]

EXPOSURE TO AIR POLLUTION

Full details of the effects of the intervention on personal exposure to air pollution are reported elsewhere.[15] The levels of exposure to measured air pollution at baseline were similar in the two trial groups. After randomization, the median 24-hour personal exposure to fine particulate matter was 66% lower in the intervention group than in the control group (23.9 vs. 70.7 μg per cubic meter). The median 24-hour exposure to fine particulate matter was below the WHO-IT1 limit in 69% of the intervention households and in 23% of control households, as compared with approximately 17% of the households in both groups at baseline. The median 24-hour exposure to black carbon was 71% lower in the intervention households than in the control households after randomization (2.8 vs. 9.6 μg per cubic meter), and the median 24-hour exposure to carbon monoxide was 83% lower in the intervention households (0.2 vs. 1.1 parts per million). The reductions in exposure were consistent over time and similar across research locations.[15]

PRIMARY ANALYSIS

Among the 3200 women who had undergone randomization, 3061 remained in the trial and had live births. Of these, valid birth weights were collected for 3018 children; thus, data on birth weight represented 98.6% of the live births and 94.3% of the randomly assigned women (Fig. 1). This number included 2552 birth weights measured by HAPIN field workers and 466 birth weights obtained from medical records (223 in the intervention group and 243 in the control group). A total of 16 infants were excluded from the analysis because their gestational ages at birth were greater than the INTERGROWTH-21st gestation limit of 300 days. The mean (±SD) birth weight was 2921±474.3 g in the intervention group and 2898±467.9 in the control group (Tables 2 and S3), for a difference of 19.6 g (95% CI, −10.1 to 49.2). The results of a sensitivity analysis in which the birth weights were restricted to those measured by HAPIN field workers were similar to those of the primary analysis.

SECONDARY AND SUBGROUP ANALYSES AND SECONDARY OUTCOMES

In the secondary analyses of the primary outcome, the prevalence of low birth weight varied according to research center, with nearly 40% of infants born in India, as compared with 5% of those born in Peru, having a birth weight of less than 2500 g, a finding that corresponds with differences in body-mass index according to research center at enrollment. We observed no substantial between-group differences in the prevalences of low or very low birth weight at any research center (Table 2).

Subgroup analyses according to infant sex did not show a meaningful difference in the intervention effect on the mean birth weight, the mean z score for birth weight standardized for gestational age and sex, or the prevalence of low birth weight, although there was some potential heterogeneity across research centers with respect to the mean birth weight and z scores (Figs. 2 and S1 and Table S4). Findings from the households where the intervention was introduced earlier during pregnancy were suggestive of the possibility that earlier intervention may be more beneficial than one implemented later in the gestation period. The between-group difference in birth weight appeared to be slightly greater among infants born to women who received the intervention at less than 18 weeks' gestation (33.8 g [95% CI, −2.6 to 70.2]) than among infants born to women who received the intervention at a later time (5.3 g [95% CI, −31.0 to 41.7]). The mean z score for birth weight, standardized for gestational age and sex, among infants born to women who received the intervention during the first trimester was estimated to be 0.15 standard deviations (95% CI, 0.01 to 0.28) higher than that among infants born to women in the control group.

For all the secondary outcomes, there were no substantial differences between the intervention group and the control group with respect to gestational age at birth, preterm birth, early preterm birth, preterm delivery, or stillbirth (Table 2). In regard to adverse events, burns were reported by 18 women (1.1%) in the intervention group and by 12 women (0.7%) in the control group; none were categorized as serious adverse events.

DISCUSSION

In this randomized trial conducted across areas in each of four low-income and middle-income countries, an LPG cookstove and fuel intervention did not result in a higher birth weight than the use of biomass cookstoves. This result was inconsistent with our expectations that were based on previous observational studies suggesting that exposure to household air pollution during pregnancy is associated with lower birth weight.[8,9] Intention-to-treat analyses of three previous randomized, controlled trials likewise showed no significant effect on birth weight from clean-cooking interventions, but null findings were ascribed to failure of the intervention to achieve meaningful reductions in household air pollution, owing to stoves with poor performance, partial or inconsistent use of the stove intervention, or other sources of indoor air pollution.[10-12] In contrast, our intervention substantially reduced exposure to fine particulate matter and black carbon, and intervention fidelity and adherence were high in our trial.[16]

There are several possible reasons for our findings. First, the reduction in air pollution exposure associated with the intervention, although substantial, may have been insufficient. Although the intervention brought most of the households within the WHO-IT1 limit, that standard is seven times as high as the recently revised annual WHO guideline value of 5 μg per cubic meter.[27] Concentration–response curves suggest that the interim guideline value, which was adopted to encourage incremental progress, may still be associated with adverse health outcomes.[28] Second, the intervention was implemented mainly during the second trimester of pregnancy, which may not have been early enough to have a meaningful effect on birth weight. Risk factors present during the first trimester can adversely affect a range of birth outcomes, including birth weight.[29] The results of our secondary analyses were suggestive of the possibility that earlier intervention may be more beneficial than one implemented later in the gestation period. Third, the intervention may not have reduced other harmful pollutants, such as nitrogen dioxide, to WHO guideline levels[30]; data are not yet available on these levels or on the levels of volatile organic compounds. Although LPG has been categorized as a "clean fuel" according to the WHO[31] and has been promoted widely as a scalable alternative to solid biomass fuel, pollutant emissions from leaking connections or poor-quality stoves may reduce the potential health gains.[32] Moreover, because we did not have information on the locations of the biomass cookstoves, it is possible that in some cases indoor LPG cookstoves replaced outdoor biomass cooking, thereby limiting the benefits of the intervention with respect to indoor air pollution. Finally, other mediators of low birth weight, such as poor maternal nutrition, may outweigh the benefit of reduced exposure to air pollution.

Although this analysis provided no evidence of the effectiveness of the intervention for increasing birth weight, a prespecified exposure–response analysis showed associations between birth weight and exposure to fine particulate matter or black carbon but not between birth weight and carbon monoxide exposure.[33] An increase in average prenatal exposure to fine particulate matter equal to the interquartile range (74.5 μg per cubic meter) was associated with a reduction in birth weight of 14.8 g (95% CI, −28.7 to −0.8); with regard to black carbon, an increase in average prenatal exposure equal to the interquartile range (7.3 μg per cubic meter) was associated with a reduction in birth weight of 21.9 g (95% CI, −37.3 to −6.1).

Despite a high uptake of the intervention and substantial reductions in exposure to air pollution, birth weight (one of four primary outcomes in the current trial) was not higher with an LPG cookstove and fuel intervention at 9 to less than 20 weeks' gestation than with the use of biomass cookstoves. In regard to the other three primary outcomes, continued follow-up of our trial population is under way to investigate whether this intervention can reduce the risks of other adverse effects associated with burning biomass fuels — namely, stunting in infants, severe pneumonia in infants, and high systolic blood pressure in women.[13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by the National Institutes of Health (cooperative agreement 1UM1HL134590) and the Bill and Melinda Gates Foundation (OPP1131279).

We thank the members of the advisory committee (Patrick Brysse, Donna Spiegelman, and Joel Kaufman) for their insight and guidance throughout the implementation of the trial and the research staff and trial participants for their dedication to and participation in this trial.

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REFERENCES

1. The state of global air 2020: a special report on global exposure to air pollution and its health impacts. Boston: Health Effects Institute, 2020.
2. Bennitt FB, Wozniak SS, Causey K, Burkart K, Brauer M. Estimating disease burden attributable to household air pollution: new methods within the Global Burden of Disease Study. Lancet Glob Health 2021;9:S18. abstract. (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00126-1/fulltext).
3. Lee KK, Bing R, Kiang J, et al. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. Lancet Glob Health 2020;8(11):e1427–e1434. [PubMed: 33069303]
4. Ghosh R, Causey K, Burkart K, Wozniak S, Cohen A, Brauer M. Ambient and household PM2.5 pollution and adverse perinatal outcomes: a meta-regression and analysis of attributable global burden for 204 countries and territories. PLoS Med 2021;18(9):e1003718. [PubMed: 34582444]
5. Bachwenkizi J, Liu C, Meng X, et al. Maternal exposure to fine particulate matter and preterm birth and low birth weight in Africa. Environ Int 2022;160:107053. [PubMed: 34942408]
6. Weichenthal S, Kulka R, Lavigne E, et al. Biomass burning as a source of ambient fine particulate air pollution and acute myocardial infarction. Epidemiology 2017;28:329–37. [PubMed: 28177951]
7. Blencowe H, Krasevec J, de Onis M, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2019;7(7):e849–e860. [PubMed: 31103470]
8. Amegah AK, Quansah R, Jaakkola JJK. Household air pollution from solid fuel use and risk of adverse pregnancy outcomes: a systematic review and meta-analysis of the empirical evidence. PLoS One 2014;9(12):e113920. [PubMed: 25463771]
9. Younger A, Alkon A, Harknett K, Jean Louis R, Thompson LM. Adverse birth outcomes associated with household air pollution from unclean cooking fuels in low- and middle-income countries: a systematic review. Environ Res 2022;204:112274. [PubMed: 34710435]
10. Alexander DA, Northcross A, Karrison T, et al. Pregnancy outcomes and ethanol cook stove intervention: a randomized-controlled trial in Ibadan, Nigeria. Environ Int 2018;111:152–63. [PubMed: 29216559]

11. Jack DW, Ae-Ngibise KA, Gould CF, et al. A cluster randomised trial of cookstove interventions to improve infant health in Ghana. BMJ Glob Health 2021;6(8):e005599.
12. Katz J, Tielsch JM, Khatry SK, et al. Impact of improved biomass and liquid petroleum gas stoves on birth outcomes in rural Nepal: results of 2 randomized trials. Glob Health Sci Pract 2020;8:372–82. [PubMed: 32680912]
13. Clasen T, Checkley W, Peel JL, et al. Design and rationale of the HAPIN study: a multicountry randomized controlled trial to assess the effect of liquefied petroleum gas stove and continuous fuel distribution. Environ Health Perspect 2020;128:47008. [PubMed: 32347766]
14. Quinn AK, Williams KN, Thompson LM, et al. Fidelity and adherence to a liquefied petroleum gas stove and fuel intervention during gestation: the multi-country Household Air Pollution Intervention Network (HAPIN) randomized controlled trial. Int J Environ Res Public Health 2021;18:12592. [PubMed: 34886324]
15. Johnson M, Pillarisetti A, Piedrahita R, et al. Exposure contrasts of pregnant women during the Household Air Pollution Intervention Network randomized controlled trial. Environ Health Perspect 2022;130:97005. [PubMed: 36112539]
16. Barr DB, Puttaswamy N, Jaacks LM, et al. Design and rationale of the biomarker center of the Household Air Pollution Intervention Network (HAPIN) trial. Environ Health Perspect 2020;128:47010. [PubMed: 32347765]
17. Johnson MA, Steenland K, Piedrahita R, et al. Air pollutant exposure and stove use assessment methods for the Household Air Pollution Intervention Network (HAPIN) trial. Environ Health Perspect 2020;128:47009. [PubMed: 32347764]
18. Williams KN, Thompson LM, Sakas Z, et al. Designing a comprehensive behaviour change intervention to promote and monitor exclusive use of liquefied petroleum gas stoves for the Household Air Pollution Intervention Network (HAPIN) trial. BMJ Open 2020;10(9):e037761.
19. Wilson DL, Williams KN, Pillarisetti A. An integrated sensor data logging, survey, and analytics platform for field research and its application in HAPIN, a multi-center household energy intervention trial. Sustainability 2020;12:1805 (https://www.mdpi.com/2071-1050/12/5/1805).
20. Quinn AK, Williams K, Thompson LM, et al. Compensating control participants when the intervention is of significant value: experience in Guatemala, India, Peru and Rwanda. BMJ Glob Health 2019;4(4):e001567.
21. World Health Organization. ICD-10: international statistical classification of diseases and related health problems: tenth revision, 2nd ed. 2004 (https://apps.who.int/iris/handle/10665/42980).
22. Thompson LM, Bruce N, Eskenazi B, Diaz A, Pope D, Smith KR. Impact of reduced maternal exposures to wood smoke from an introduced chimney stove on newborn birth weight in rural Guatemala. Environ Health Perspect 2011;119:1489–94. [PubMed: 21652290]
23. Steenland K, Pillarisetti A, Kirby M, et al. Modeling the potential health benefits of lower household air pollution after a hypothetical liquified petroleum gas (LPG) cookstove intervention. Environ Int 2018;111:71–9. [PubMed: 29182949]
24. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTER-GROWTH-21st Project. Lancet 2014;384:857–68. [PubMed: 25209487]
25. FAO and FHI 360. Minimum dietary diversity for women: a guide for measurement. Rome: FAO, 2016 (https://www.fao.org/3/i5486e/i5486e.pdf).
26. Ballard TJ, Kepple AW, Cafiero C. The food insecurity experience scale: development of a global standard for monitoring hunger worldwide: technical paper. Rome: FAO, 2013 (https://www.fao.org/fileadmin/templates/ess/voh/FIES_Technical_Paper_v1.1.pdf).
27. World Health Organization. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. 2021 (https://apps.who.int/iris/handle/10665/345329).
28. World Health Organization. WHO guidelines for indoor air quality: household fuel combustion. January 21, 2014 (https://www.who.int/publications-detail-redirect/9789241548885).
29. Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA 2010;303:527–34. [PubMed: 20145229]

30. Kephart JL, Fandiño-Del-Rio M, Williams KN, et al. Nitrogen dioxide exposures from LPG stoves in a cleaner-cooking intervention trial. Environ Int 2021;146:106196. [PubMed: 33160161]

31. World Health Organization. Defining clean fuels and technologies. 2022 (https://www.who.int/tools/clean-household-energy-solutions-toolkit/module-7-defining-clean).

32. Lebel ED, Finnegan CJ, Ouyang Z, Jackson RB. Methane and NOx emissions from natural gas stoves, cooktops, and ovens in residential homes. Environ Sci Technol 2022;56:2529–39. [PubMed: 35081712]

33. Balakrishnan K, Steenland K, Clasen T, et al. Exposure–response relationships for personal exposure to fine particulate matter ($PM_{2.5}$), carbon monoxide, and black carbon and birthweight: results from the multi-country Household Air Pollution Intervention Network (HAPIN) trial. August 8, 2022 (https://medrxiv.org/lookup/doi/10.1101/2022.08.06.22278373). preprint.

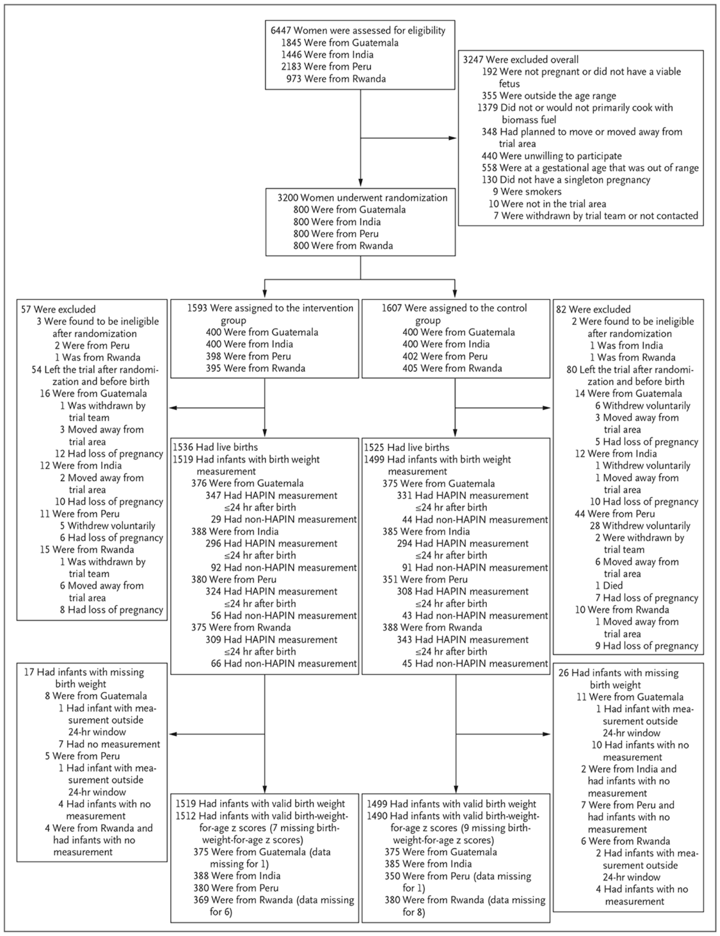
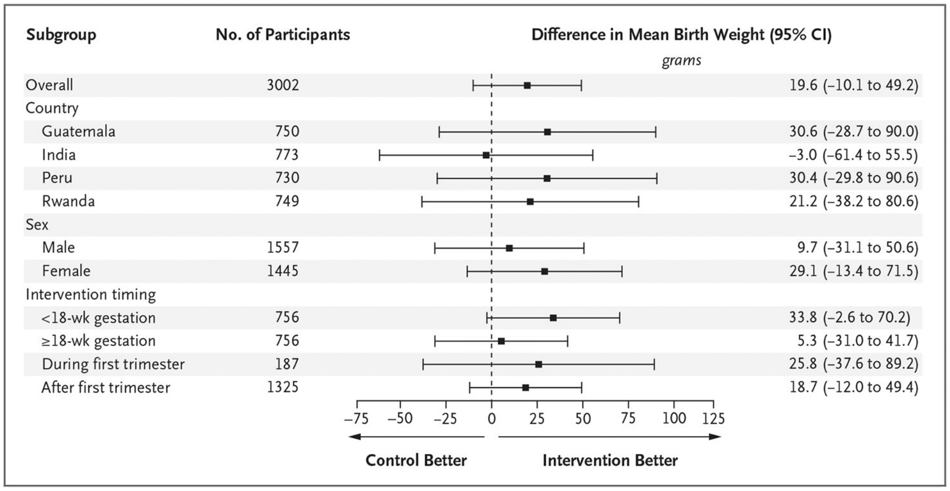


Figure 1. Screening, Randomization, and Follow-up.

The women were randomly assigned in a 1:1 ratio to use a free liquefied petroleum gas (LPG) cookstove and fuel (intervention group) or to continue using a biomass cookstove (control group). The reasons for exclusion from the trial before randomization were not mutually exclusive. HAPIN denotes Household Air Pollution Intervention Network.



Subgroup	No. of Participants	Difference in Mean Birth Weight (95% CI)
		grams
Overall	3002	19.6 (–10.1 to 49.2)
Country		
Guatemala	750	30.6 (–28.7 to 90.0)
India	773	–3.0 (–61.4 to 55.5)
Peru	730	30.4 (–29.8 to 90.6)
Rwanda	749	21.2 (–38.2 to 80.6)
Sex		
Male	1557	9.7 (–31.1 to 50.6)
Female	1445	29.1 (–13.4 to 71.5)
Intervention timing		
<18-wk gestation	756	33.8 (–2.6 to 70.2)
≥18-wk gestation	756	5.3 (–31.0 to 41.7)
During first trimester	187	25.8 (–37.6 to 89.2)
After first trimester	1325	18.7 (–12.0 to 49.4)

Figure 2. Overall and Subgroup Analyses of the Difference in Birth Weight between the Intervention Group and Control Group.

Shown is a forest plot of the between-group differences in birth weight. All analyses were adjusted for the randomization strata (the trial sites within each country). The actual birth weights are provided in Table S3.

Table 1.

Characteristics of the Participants at Baseline.[*]

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 (31.4)	517 (32.2)
30–35 yr	285 (17.9)	300 (18.7)
Gestational age — wk	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 (0.3)	2 (0.1)
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
Height		
Mean — cm	152.3±6.2	152.1±6.0
Missing data — no.	8	4
Body-mass index at enrollment[†]		
Mean	23.3±4.1	23.1±4.0
Missing data — no.	12	7
Hemoglobin level		
Mean — g/dl	12.4±1.9	12.5±1.9
Missing data — no.	13	17
Dietary diversity score — no. (%)[‡]		
<4: low diversity	890 (56.0)	906 (56.4)
4 or 5: medium diversity	496 (31.2)	533 (33.2)
>5: high diversity	203 (12.8)	165 (10.3)

Characteristic	**Intervention (N = 1590)**	**Control (N = 1605)**
Missing data	1 (<0.1)	1 (<0.1)
Household food insecurity score — no. (%)[§]		
0: food secure	930 (58.5)	863 (53.8)
1–3: mild insecurity	416 (26.2)	448 (27.9)
4–8: moderate or severe insecurity	220 (13.8)	272 (16.9)
Missing data	24 (1.5)	22 (1.4)
No. of persons sleeping in household		
Mean	4.3±2.0	4.3±2.0
Missing data — no. of households	1	0
Someone in the household smokes — no. (%)		
Yes	153 (9.6)	181 (11.3)
No	1436 (90.3)	1421 (88.5)
Missing data	1 (<0.1)	3 (0.2)
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)

[*] Plus–minus values are means ±SD.

[†] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] The dietary diversity score is derived from the Minimum Dietary Diversity for Women (MDD-W) questionnaire, which we adapted to cover a 30-day reference period. In the MDD-W, minimum dietary diversity is defined as consuming at least 5 of 10 food groups in the previous day.[25]

[§] Household food insecurity is measured by the Food Insecurity Experience Scale (FIES), which was applied with a 30-day reference period. In the FIES, higher scores represent increasingly severe food insecurity.[26]

Table 2.

Primary and Secondary Outcomes.[*]

Outcome	Intervention	Control	Intervention Effect (95% CI)[†]
Primary outcome			
Birth weight — g[‡]	2921±474.3	2898±467.9	19.6 (−10.1 to 49.2)
Secondary analyses			
z Score for birth weight, standardized for gestational age and sex[§]	−0.80±1.04	−0.80±1.01	0.04 (−0.03 to 0.10)
Low birth weight — no./total no. (%)[¶]	263/1512 (17.4)	268/1490 (18.0)	0.99 (0.86 to 1.14)
Very low birth weight — no./total no. (%)[‖]	8/1512 (0.5)	6/1490 (0.4)	1.33 (0.46 to 3.80)
Secondary outcomes			
Gestational age at birth — wk[**]	39.3±1.6	39.3±1.7	0.0 (−0.1 to 0.2)
Preterm live birth at <37 wk — no./total no. (%)	90/1536 (5.9)	83/1525 (5.4)	1.08 (0.81 to 1.44)
Early preterm live birth at <34 wk — no./total no. (%)	19/1536 (1.2)	14/1525 (0.9)	1.36 (0.68 to 2.70)
Preterm delivery at <37 wk among live births and stillbirths — no./total no. (%)	112/1565 (7.2)	101/1554 (6.5)	1.10 (0.85 to 1.43)
Stillbirth — no./total no. (%)	29/1565 (1.9)	29/1554 (1.9)	1.00 (0.60 to 1.66)

[*] Plus–minus values are means ±SD.

[†] Adjusted mean differences are shown for the continuous outcomes, and relative risks are shown for the dichotomous outcomes. The 95% confidence intervals for the secondary outcomes and other measurements were not adjusted for multiplicity and should not be used in place of hypothesis testing.

[‡] Data on birth weight were available for 1512 infants in the intervention group and for 1490 infants in the control group.

[§] Data on z score for birth weight, standardized for gestational age and sex, were available for 1512 infants in the intervention group and for 1490 infants in the control group.

[¶] Low birth weight (not a prespecified outcome) was defined as a body weight of less than 2500 g.

[‖] Very low birth weight (not a prespecified outcome) was defined as a body weight of less than 1500 g.

[**] Data on gestational age at birth were available for 1525 infants in the intervention group and for 1536 infants in the control group.