

Supplementary Appendix

Supplement to: Clasen TF, Chang HH, Thompson LM, et al. Liquefied petroleum gas or biomass for cooking and effects on birth weight. *N Engl J Med* 2022;387:1735-46. DOI: 10.1056/NEJMoa2206734

This appendix has been provided by the authors to give readers additional information about the work.

NEJM Submission – Supplemental Appendix

Liquefied Petroleum Gas or Biomass for Cooking and Effects on Birth Weight (Clasen et al.)

Contents:

1. Investigators	2
2. Acknowledgements	3
3. Figure S1. Secondary Outcomes: Risk Ratio for Low Birth Weight and Change in Z-Score.	4
4. Table S1. Characteristics of the Participants at Baseline, by Research Center	5
5. Table S2. Representativeness of the Study Population	7
6. Table S3. Primary and Secondary Outcomes by Study Group, Overall and by Research Center	8
7. Table S4. Numerical Results for Selected Primary and Secondary Outcomes.....	9

HAPIN Investigators: Gloriose Bankundiye, Vanessa Burrowes, Alejandra Bussalleu, Devan Campbell, Eduardo Canuz, Rachel Craik, Mary Crocker, Victor G. Davila-Roman, Lisa de las Fuentes, Oscar De León, Ephrem Dusabimana, Lisa Elon, Juan Gabriel Espinoza, Irma Sayury Pineda Fuentes, Ahana Ghosh, Dina Goodman, Savannah Gupton, Sarah Hamid, Steven A. Harvey, Mayari Hengstermann, Ian Hennessee, Phabiola Herrera, Shakir Hossen, Marjorie Howard, Penelope P. Howards, Lindsay Jaacks, Katherine Kearns, Jacob Kremer, Margaret A. Laws, Pattie Lenzen, Jiawen Liao, Jane Mbabazi, Julia N. McPeek, Rachel Meyers, J. Jaime Miranda, Erick Mollinedo, Bernard Mutariyani, Abidan Nambajimana, Durairaj Natesan, Laura Nicolaou, Azhar Nizam, Jean de Dieu Ntivuguruzwa, Elisa Puzzolo, Karthikeyan Dharmapuri Rajamani, Sarah Rajkumar, Rengaraj Ramasami, Alexander Ramirez, P. Barry Ryan, Sudhakar Saidam, Zoe Sakas, Jeremy A. Sarnat, Suzanne Simkovich, Kirk R. Smith, Damien Swearing, Ashley Toenjes, Jean Damascene Uwizeyimana, Viviane Valdes, Amit Verma, Megan Warnock, Wenlu Ye, Bonnie N. Young.

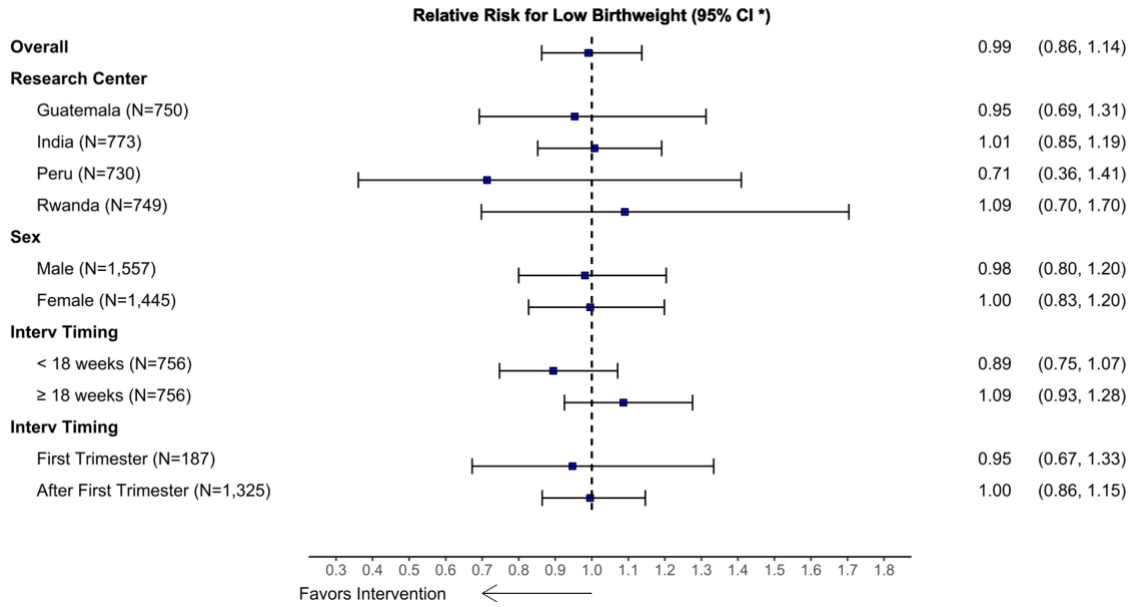
ACKNOWLEDGEMENTS

The HAPIN trial is funded by the U.S. National Institutes of Health (cooperative agreement 1UM1HL134590) in collaboration with the Bill & Melinda Gates Foundation [OPP1131279].

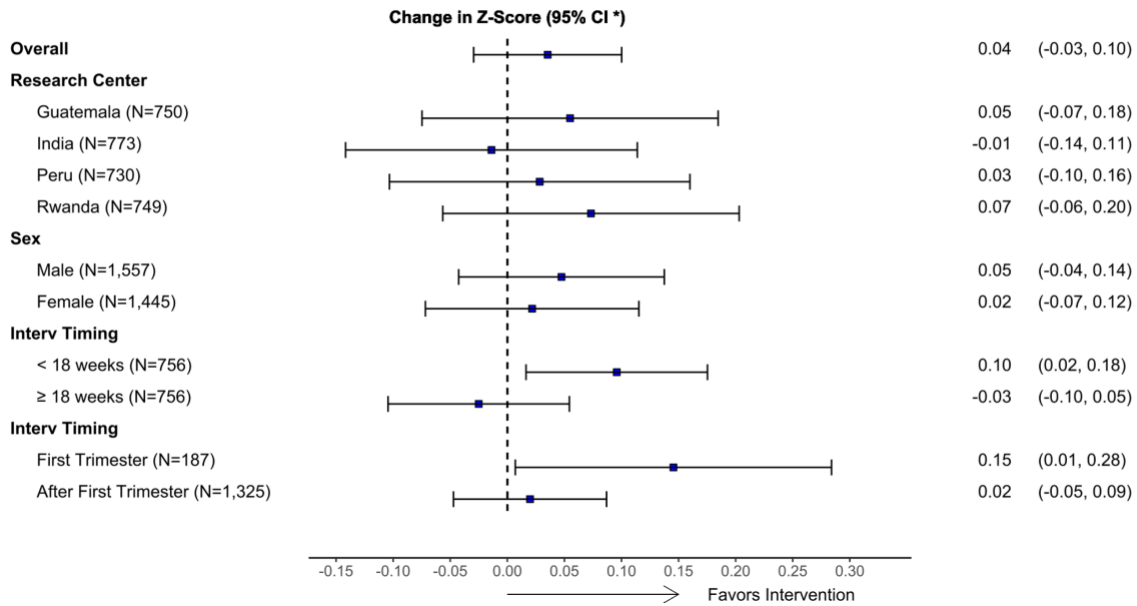
A multidisciplinary, independent Data and Safety Monitoring Board (DSMB) appointed by the National Heart, Lung, and Blood Institute (NHLBI) monitors the quality of the data and protects the safety of patients enrolled in the HAPIN trial. NHLBI DSMB: Catherine Karr (Chair), Nancy R. Cook, Stephen Hecht, Joseph Millum, Nalini Sathiakumar, Paul K. Whelton, Gail Weinmann and Thomas Croxton (Executive Secretaries). Program Coordination: Gail Rodgers, Bill & Melinda Gates Foundation; Claudia L. Thompson, National Institute of Environmental Health Science; Mark J. Parascandola, National Cancer Institute; Marion Koso-Thomas, Eunice Kennedy Shriver National Institute of Child Health and Human Development; Joshua P. Rosenthal, Fogarty International Center; Conception R. Nierras, NIH Office of Strategic Coordination Common Fund; Katherine Kavounis, Dong-Yun Kim, Antonello Punturieri, and Barry S. Schmetter, NHLBI.

The investigators would like to thank the members of the advisory committee - Patrick Brysse, Donna Spiegelman, and Joel Kaufman - for their valuable insight and guidance throughout the implementation of the trial. We also wish to acknowledge all of the research staff and study participants for their dedication to and participation in this important trial.

Statistical analyses were conducted by Howard Chang, Kyle Steenland, Dong-Yun Kim and Larry Moulton.



*95% Confidence Intervals are not adjusted for multiple comparisons and should not be used as hypothesis test.



*95% Confidence Intervals are not adjusted for multiple comparisons and should not be used as hypothesis test.

Figure S1. Secondary Outcomes: Risk Ratio for Low Birth Weight and Change in Z-Score.

Table S1. Characteristics of the Participants at Baseline, by Research Center.

	All		Guatemala		India		Peru		Rwanda	
	Intervention N=1,590	Control N=1,605	Intervention N=400	Control N=400	Intervention N=400	Control N=399	Intervention N=396	Control N=402	Intervention N=394	Control N=404
Age (years), N (%)										
<20	189 (11.9)	209 (13.0)	64 (16.0)	58 (14.5)	62 (15.5)	66 (16.5)	40 (10.1)	59 (14.7)	23 (5.8)	26 (6.4)
20-24	616 (38.7)	579 (36.%)	168 (42.0)	156 (39.0)	192 (48.0)	190 (47.6)	151 (38.1)	135 (33.6)	105 (26.6)	98 (24.3)
25-29	500 (31.4)	517 (32.2)	110 (27.5)	121 (30.3)	117 (29.3)	113 (28.3)	130 (32.8)	127 (31.6)	143 (36.3)	156 (38.6)
30-35	285 (17.9)	300 (18.7)	58 (14.5)	65 (16.3)	29 (7.3)	30 (7.5)	75 (18.9)	81 (20.1)	123 (31.2)	124 (30.7)
Gestational age (weeks), mean (SD)	15.5 (3.1)	15.3 (3.2)	14.4 (3.0)	14.2 (3.1)	16.1 (3.0)	66 (16.5)	15.8 (3.3)	15.6 (3.4)	15.6 (2.8)	15.4 (2.7)
Nulliparous, N (%)										
Yes	639 (40.2)	589 (36.7)	119 (29.8)	108 (27.0)	245 (61.3)	214 (53.6)	154 (38.9)	156 (38.8)	121 (30.7)	111 (27.5)
No	947 (59.6)	1,014 (63.2)	281 (70.3)	292 (73.0)	155 (38.8)	185 (46.4)	239 (60.4)	245 (60.9)	272 (69.0)	292 (72.3)
Missing	4 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.2)	1 (0.3)	1 (0.2)
Highest level of education completed, N (%)										
No formal education or primary school incomplete	481 (30.3)	558 (34.8)	189 (47.3)	192 (48.0)	130 (32.5)	155 (38.8)	15 (3.8)	20 (5.0)	147 (37.3)	191 (47.3)
Primary school complete or secondary school incomplete	558 (35.1)	533 (33.2)	160 (40.0)	152 (38.0)	116 (29.0)	111 (27.8)	131 (33.1)	103 (25.6)	151 (38.3)	167 (41.3)
Secondary school complete or Vocational or some college or university	550 (34.6)	514 (32.0)	51 (12.8)	56 (14.0)	154 (38)	133 (33.3)	249 (62.9)	279 (69.4)	96 (24.4)	46 (11.4)
Missing	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm), mean (SD); N missing	152.3 (6.2); 8	152.1 (6.0); 4	148.6 (5.0); 1	148.2 (5.7); 0	151.0 (5.9); 0	151.2 (5.3); 0	152.7 (4.6); 6	152.6 (4.5); 4	156.9 (6.0); 1	156.2 (5.7); 0
Body mass index (kg/m²)* on enrollment, mean (SD); N missing	23.3 (4.1); 12	23.1 (4.0); 7	23.9 (3.4); 3	23.7 (3.3); 2	19.8 (3.3); 0	19.6 (3.1); 0	26.3 (3.6); 6	25.8 (3.6); 4	23.3 (3.5); 3	23.5 (3.3); 1
Hemoglobin (gm/dl), mean (SD); N missing	12.4 (1.9); 13	12.5 (1.9); 17	12.7 (1.0); 1	12.9 (1.1); 2	10.3 (1.2); 0	10.4 (1.3); 0	14.3 (1.3); 9	14.3 (1.2); 10	12.4 (1.6); 3	12.4 (1.5); 5

Dietary diversity score,** Category (score) N (%)²⁵										
Low (<4)	890 (56.0)	906 (56.4)	279 (69.8)	268 (67.0)	315 (78.8)	306 (76.7)	46 (11.6)	41 (10.2)	250 (63.5)	291 (72.0)
Medium (4-5)	496 (31.2)	533 (33.2)	104 (26.0)	115 (28.8)	73 (18.3)	81 (20.3)	203 (51.3)	234 (58.2)	116 (29.4)	103 (25.5)
High (>5)	203 (12.8)	165 (10.3)	16 (4.0)	17 (4.3)	12 (3.0)	12 (3.0)	147 (37.1)	127 (31.6)	28 (7.1)	9 (2.2)
Missing	1 (0.1)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Household food insecurity score,*** Category (score), N (%)²⁶										
Food secure	930 (58.5)	863 (53.8)	225 (56.3)	215 (53.8)	324 (81.0)	321 (80.5)	210 (53.0)	202 (50.2)	171 (43.4)	125 (30.9)
Mild (1,2,3)	416 (26.2)	448 (27.9)	126 (31.5)	129 (32.3)	54 (13.5)	60 (15.0)	128 (32.3)	146 (36.3)	108 (27.4)	113 (28.0)
Moderate (4,5,6) / Severe (7,8)	220 (13.8)	272 (16.9)	43 (10.8)	52 (13.0)	19 (4.8)	17 (4.3)	53 (13.4)	47 (11.7)	105 (26.6)	156 (38.6)
Missing	24 (1.5)	22 (1.4)	6 (1.5)	4 (1.0)	3 (0.8)	1 (0.3)	5 (1.3)	7 (1.7)	10 (2.5)	10 (2.5)
Number of people sleeping in house, mean (SD); N missing	4.3 (2.0); 1	4.3 (2.0); 0	5.3 (2.7); 0	5.1 (2.6); 0	3.7 (1.6); 0	3.8 (1.5); 0	4.5 (1.7); 1	4.7 (1.8); 0	3.5 (1.5); 0	3.5 (1.5); 0
Someone in the household smokes, N (%)										
Yes	153 (9.6)	181 (11.3)	22 (5.5)	22 (5.5)	119 (29.8)	134 (33.6)	4 (1.0)	3 (0.7)	8 (2.0)	22 (5.4)
No	1,436 (90.3)	1,421 (88.5)	378 (94.5)	378 (94.5)	281 (70.3)	265 (66.4)	392 (99.0)	397 (98.8)	385 (97.7)	381 (94.3)
Missing	1 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)	1 (0.2)
Owns household assets, N (%)										
Color television	774 (48.7)	783 (48.8)	169 (42.3)	188 (47.0)	291 (72.8)	301 (75.4)	247 (62.4)	260 (64.7)	67 (17.0)	34 (8.4)
Radio	734 (46.2)	721 (44.9)	153 (38.3)	151 (37.8)	57 (14.3)	52 (13.0)	289 (73.0)	304 (75.6)	235 (59.6)	214 (53.0)
Mobile phone	1,388 (87.3)	1,395 (86.9)	361 (90.3)	370 (92.5)	328 (82.0)	327 (82.0)	378 (95.5)	388 (96.5)	321 (81.5)	310 (76.7)
Bicycle	365 (23.0)	409 (25.5)	45 (11.3)	53 (13.3)	60 (15.0)	61 (15.3)	147 (37.1)	162 (40.3)	113 (28.7)	133 (32.9)
Bank account	697 (43.8)	628 (39.1)	99 (24.8)	98 (24.5)	357 (89.3)	359 (90.0)	94 (23.7)	86 (21.4)	147 (37.3)	85 (21.0)

* 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

*** The household food insecurity score 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 S2. Representativeness of the Study Population.

Problem	Exposure to household air pollution (chiefly from biomass cooking)
<i>Special considerations related to:</i>	
Sex and gender	Women and children are most impacted by exposure to household air pollution. ¹
Age	Women of all ages and children are the most impacted by exposure to household air pollution. ¹
Race and ethnic group	Areas of Africa and Southeast Asia, and Latin America are the most impacted by exposure to household air pollution. Within region and without countries, populations most impacted often include Indigenous populations and lower-income populations. ¹⁻³
Geography	Areas of Africa and Southeast Asia are the most heavily impacted by exposure to household air pollution. ¹⁻³
Overall representativeness of this trial	The participants in this trial, here pregnant women ≥ 18 years and < 35 years, along with the infants born from their pregnancies, represented populations around the world who are most impacted by exposure to household air pollution. The countries included represent the regions most impacted by exposure to household air pollution.

References:

1. WEO-2017 Special Report: Energy Access Outlook, International Energy Agency, 2017 (<https://webstore.iea.org/weo-2017-special-report-energy-access-outlook>)
2. Health Effects Institute. 2020. State of Global Air 2020. Available: www.stateofglobalair.org [accessed July 22, 2022].
3. Stoner, O., Lewis, J., Martínez, I.L. *et al.* Household cooking fuel estimates at global and country level for 1990 to 2030. *Nat Commun* **12**, 5793 (2021). <https://doi.org/10.1038/s41467-021-26036-x>

Table S3. Primary and Secondary Outcomes by Study Group, Overall and by Research Center.

	Overall		Guatemala		India		Peru		Rwanda	
	Intervention N=1,512	Control N=1,490	Intervention N=375	Control N=375	Intervention N=388	Control N=385	Intervention N=380	Control N=350	Intervention N=369	Control N=380
Mean birth weight in grams (SD) (primary outcome)	2,921 (474.3)	2,898 (467.9)	2,876.6 (406.0)	2,846.0 (449.2)	2,590.1 (395.6)	2,592.8 (392.6)	3,194.3 (420.6)	3,164.6 (397.0)	3,032.9 (449.7)	3,011.7 (428.9)
Mean z score of birth weight by gestational age and sex (SD)	-0.8 0 (1.04)	-0.80 (1.01)	-0.81 (0.94)	-0.86 (0.98)	-1.43 (0.86)	-1.42 (0.84)	-0.10 (0.89)	-0.13 (0.87)	-0.65 (1.00)	-0.73 (0.92)
LBW* N (%)	263 (17.4)	268 (18.0)	61 (16.3)	64 (17.1)	152 (39.2)	152 (39.5)	14 (3.7)	18 (5.1)	36 (9.8)	34 (8.9)
VLBW,** N (%)	8 (0.5)	6 (0.4)	1 (0.3)	2 (0.5)	5 (1.3)	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
	Intervention N=1536	Control N=1525	Intervention N=384	Control N=386	Intervention N=388	Control N=387	Intervention N=385	Control N=358	Intervention N=379	Control N=394
Mean gestational age at birth in weeks (SD)	39.3 (1.6)	39.3 (1.7)	39.2 (1.6)	39.1 (1.7)	38.9 (1.5)	38.8 (1.6)	39.4 (1.4)	39.3 (1.4)	39.8 (1.9)	39.9 (1.8)
Preterm live birth <37 weeks, N (%)	90 (5.9)	83 (5.4)	25 (6.5)	25 (6.5)	27 (7.0)	24 (6.2)	21 (5.5)	15 (4.2)	17 (4.5)	19 (4.8)
Early preterm live birth <34 weeks, N (%)	19 (1.2)	14 (0.9)	5 (1.3)	5 (1.3)	4 (1.0)	4 (1.0)	3 (0.8)	2 (0.6)	7 (1.8)	3 (0.8)
	Intervention N=1565	Control N=1554	Intervention N=394	Control N=391	Intervention N=398	Control N=395	Intervention N=387	Control N=365	Intervention N=386	Control N=403
Preterm delivery <37 weeks among live births and stillbirths, N (%)	112 (7.2)	101 (6.5)	31 (7.9)	29 (7.4)	36 (9.0)	27 (6.8)	23 (5.9)	22 (6.0)	22 (5.7)	23 (5.7)
Stillbirth, N (%)	29 (1.9)	29 (1.9)	10 (2.5)	5 (1.3)	10 (2.5)	8 (2.0)	2 (0.5)	7 (1.9)	7 (1.8)	9 (2.2)

* 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.

Table S4. Numerical Results for Selected Primary and Secondary Outcomes.

Outcome	Type	Estimate	SE	95% CI*
Change in mean birth weight (Grams)	Overall	19.56	15.13	(-10.10, 49.21)
	Guatemala	30.63	30.27	(-28.70, 89.96)
	India	-2.98	29.82	(-61.42, 55.46)
	Peru	30.39	30.71	(-29.81, 90.58)
	Rwanda	21.18	30.29	(-38.19, 80.56)
	Male	9.75	20.85	(-331.11, 50.61)
	Female	29.06	21.65	(-13.37, 71.49)
	Intervention <18 weeks	33.82	18.56	(-2.55, 70.19)
	Intervention ≥18 weeks	5.31	18.55	(-31.04, 41.67)
	Intervention first trimester	25.8	32.33	(-2.55, 70.19)
	Intervention after first trimester	18.7	15.6	(-12.00, 49.36)
Change in mean Z-score	Overall	0.04	0.03	(-0.03, 0.10)
	Guatemala	0.05	0.07	(-0.07, 0.18)
	India	-0.01	0.07	(-0.14, 0.11)
	Peru	0.03	0.07	(-0.10, 0.16)
	Rwanda	0.07	0.07	(-0.06, 0.20)
	Male	0.05	0.05	(-0.04, 0.14)
	Female	0.02	0.05	(-0.07, 0.12)
	Intervention <18 weeks	0.10	0.04	(0.020, 0.18)
	Intervention ≥18 weeks	-0.03	0.04	(-0.10, 0.05)
	Intervention first trimester	0.15	0.07	(0.01, 0.28)
	Intervention after first trimester	0.02	0.03	(-0.05, 0.09)
Log rate ratio for low birth weight (LBW)	Overall	-0.01	0.07	(-0.15, 0.13)
	Guatemala	-0.05	0.16	(-0.37, 0.27)
	India	0.01	0.09	(-0.16, 0.17)
	Peru	-0.34	0.35	(-1.02, 0.34)
	Rwanda	0.09	0.23	(-0.36, 0.53)
	Male	-0.02	0.10	(-0.22, 0.19)
	Female	0.00	0.09	(-0.19, 0.18)
	Intervention <18 weeks	-0.11	0.09	(-0.29, 0.07)
	Intervention ≥18 weeks	0.08	0.08	(-0.08, 0.24)
	Intervention first trimester	-0.05	0.17	(-0.40, 0.29)
	Intervention after first trimester	0.00	0.07	(-0.15, 0.14)

*95% CIs noting that these are not adjusted for multiplicity and should not be used as hypothesis test.