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Pregnancy outcomes and ethanol cook stove intervention: A randomized-controlled trial in Ibadan, Nigeria[☆]

Donee A. Alexander[a], Amanda Northcross[b], Theodore Karrison[e], Oludare Morhasson-Bello[d], Nathaniel Wilson[c], Omolola M. Atalabi[f], Anindita Dutta[a], Damilola Adu[g], Tope Ibigbami[g], John Olamijulo[g], Dayo Adepoju[g], Oladosu Ojengbede[d], Christopher O. Olopade[a,*]

[a] *Department of Medicine and Center for Global Health, University of Chicago, Chicago, IL, United States*
[b] *Department of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University, Washington, DC, United States*
[c] *Pritzker School of Medicine, University of Chicago, Chicago, IL, United States*
[d] *Department of Obstetrics and Gynecology, University of Ibadan, Ibadan, Nigeria*
[e] *Department of Public Health Sciences, University of Chicago, United States*
[f] *Department of Radiology, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria*
[g] *Healthy Life for All Foundation, Ibadan, Nigeria*

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ABSTRACT

Background: Household air pollution (HAP) exposure has been linked to adverse pregnancy outcomes.
Objectives: A randomized controlled trial was undertaken in Ibadan, Nigeria to determine the impact of cooking with ethanol on pregnancy outcomes.
Methods: Three-hundred-twenty-four pregnant women were randomized to either the control (continued cooking using kerosene/firewood stove, n = 162) or intervention group (received ethanol stove, n = 162). Primary outcome variables were birthweight, preterm delivery, intrauterine growth restriction (IUGR), and occurrence of miscarriage/stillbirth.
Results: Mean birthweights for ethanol and controls were 3076 and 2988 g, respectively; the difference, 88 g, (95% confidence interval: − 18 g to 194 g), was not statistically significant (p = 0.10). After adjusting for covariates, the difference reached significance (p = 0.020). Rates of preterm delivery were 6.7% (ethanol) and 11.0% (control), (p = 0.22). Number of miscarriages was 1(ethanol) vs. 4 (control) and stillbirths was 3 (ethanol) vs. 7 (control) (both non-significant). Average gestational age at delivery was significantly (p = 0.015) higher in ethanol-users (39.2 weeks) compared to controls (38.2 weeks). Perinatal mortality (stillbirths and neonatal deaths) was twice as high in controls compared to ethanol-users (7.9% vs. 3.9%; p = 0.045, after adjustment for covariates). We did not detect significant differences in exposure levels between the two treatment arms, perhaps due to large seasonal effects and high ambient air pollution levels.
Conclusions: Transition from traditional biomass/kerosene fuel to ethanol reduced adverse pregnancy outcomes. However, the difference in birthweight was statistically significant only after covariate adjustment and the other significant differences were in tertiary endpoints. Our results are suggestive of a beneficial effect of ethanol use. Larger trials are required to validate these findings.

1. Introduction

Household air pollution (HAP) from the burning of biomass is the eighth leading contributor to overall global disease burden (Forouzanfar et al., 2016). As a major public health hazard that disproportionately affects nearly three billion people (predominantly women and children) living in developing countries, HAP poses a significant barrier to achieving health equity. In 2015, HAP was estimated to have caused approximately 2.9 million premature deaths and 85 million disability-adjusted life years (DALYs) globally (Forouzanfar et al., 2016).

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[*] Corresponding author at: The University of Chicago Medicine, 5841 S. Maryland Avenue, MC 6076, Chicago, IL 60637, United States.
E-mail address: solopade@bsd.uchicago.edu (C.O. Olopade).

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In Africa, biomass fuels are the primary energy source used for cooking in approximately 81% of households (Sander et al., 2011). Within Nigeria, an estimated 70% of the population uses solid fuels (Desalu et al., 2012; Ezeh et al., 2014), and up to 27% use kerosene (Ibitoye, 2013) for household energy needs. According to Nigeria Demographic and Health Survey records from 2013 (NDHS, 2013; Samuel et al., 2016), 26% of the Nigerian households (48% of urban households and 9% of rural households) use kerosene. Consequently, high levels of health-damaging pollutants such as particulate matter (PM), carbon monoxide (CO), and polycyclic aromatic hydrocarbons (PAH) emitted from incomplete combustion of these fuels threaten the health of vulnerable populations and worsen global environmental degradation (Ezeh et al., 2014; Lam et al., 2012; Naeher et al., 2007).

PM levels from incomplete combustion of cooking fuels can far exceed World Health Organization (WHO) indoor air quality guidelines (IAQGs) (WHO, 2014). The health impacts of HAP exposure for women and children include respiratory, cardiovascular, and ocular damage (Ezzati and Kammen, 2002). Nigeria, in particular, is one of the sub-Saharan countries where HAP is associated with high preventable mortality and DALYs (Forouzanfar et al., 2016).

Ambient air pollution (AAP) (Lacasana et al., 2005; Sapkota et al., 2012), HAP (Mishra et al., 2004; Thompson et al., 2011), active maternal smoking, and exposure to environmental tobacco smoke (Andres and Day, 2000) have been widely associated with adverse pregnancy outcomes such as first trimester miscarriages, low birthweight (LBW), preterm births, intrauterine growth restriction (IUGR), and decreased fetal head circumference. High levels of ambient $PM_{2.5}$ ($PM < 2.5\,\mu m$ in diameter) are significantly associated with lower infant birth weight (Morello-Frosch et al., 2010). Premature delivery risks have been shown to significantly increase with exposure to ambient PM, but reported levels of PM concentrations in previous research are substantially lower than in homes using biomass fuels (Ritz et al., 2007). Similar adverse health impacts have been seen with exposure to kerosene (Epstein et al., 2013; Lakshmi et al., 2013).

Similarly, HAP exposure from household cooking has been associated with adverse pregnancy outcomes (Amegah et al., 2014; Pope et al., 2010; Siddiqui et al., 2008), but much of the prior research on this topic has been cross-sectional and does not demonstrate clear causation. Currently, there are few groups conducting randomized controlled cookstove intervention studies to investigate birth outcomes, child survival and respiratory illness in children and blood pressure changes during pregnancy in women (Jack et al., 2015; Mortimer et al., 2017; Quinn et al., 2017; Tielsch et al., 2014). Yet, it is important to quantify the impacts of these exposures and evaluate practical solutions to reduce exposures to HAP. This randomized, controlled trial (RCT) was conducted in order to compare pregnancy outcomes in women exposed to HAP from wood and kerosene-fueled cookstoves in Ibadan, Nigeria to those in women who received ethanol CleanCook stoves (which meet tier 4 for indoor emissions performance standards based on the framework in the International Organization for Standardization's (ISO) Interim Workshop Agreement (IWA) Guidelines for evaluating cookstove performance (ISO, 2012). We hypothesized that this cookstove intervention would reduce exposure to $PM_{2.5}$ for pregnant women and improve pregnancy outcomes.

2. Methods

2.1. Study design

Between June 2013 and October 2015, a RCT was conducted with 324 pregnant women living in Ibadan, a Nigerian city of over three million; the population in this area is predominately Yoruba. Pregnant women were screened for eligibility at time of presentation at one of three primary health care centers (PHCs) within urban or peri-urban areas of Ibadan. These PHCs - Agbongbon, Oranyan, Ijaye, and Olorishaoko - are host to approximately 600, 750, 100, and 50 births per year, respectively. The study protocol was approved by ethical review boards at the University of Ibadan and the University of Chicago (UC) and is registered with ClinicalTrials.gov (NCT02394574). The primary outcomes of interest for this study were birthweight, preterm delivery, IUGR and occurrence of miscarriage or stillbirth. IUGR and other ultrasound assessments of fetal growth are the subject of a separate paper (in preparation). Exposure levels were secondary outcome variables. Tertiary endpoints included gestational age (GA), Apgar scores, placental weight, birth length, head circumference, respiratory rate, neonatal death, birth defects, and perinatal mortality (stillborn or neonatal death).

2.2. Subject recruitment

Women who presented at any of the PHCs for antenatal care and were less than or equal to 18 weeks pregnant, determined by ultrasound biometry, were eligible to participate. Additionally, they had to already be using either wood burning or kerosene stoves as their primary cooking fuel. Individuals were excluded if they were HIV positive, smokers, lived with a smoker, cooked for a living, or had a high-risk pregnancy (defined as pregnancy with multiple gestations, uncontrolled maternal hypertension, maternal age > 35 for first delivery, three or more prior miscarriages, or prior Cesarean-section).

2.3. Enrollment and randomization

When first presenting to an eligible PHC, interested women were given a detailed description of the study and participation requirements and a summary of associated risks. Consenting women were then evaluated against the inclusion and exclusion criteria listed above.

Those that met all criteria were individually randomized to the ethanol or control arm using the web-based randomization module in REDCap (Harris et al., 2009). Randomization was stratified by parity ($< =4$ vs. > 4 children) and the presence or absence of diabetes. Treatment assignments were prepared in advance by the study biostatistician using the method of permuted blocks (Matts and Lachin, 1988) Of the 324 women enrolled, 162 were assigned to the ethanol-stove group. Women in this group were given a CleanCook ethanol stove (CLEANCOOK Sweden AB) and an initial supply of fuel at the first home visit, which occurred between 16–18 weeks GA. During this visit, comprehensive training regarding the dangers of smoke exposure and the proper use of the stove was provided. Additionally, field workers observed each woman refill, light, and use the stove for the first time. Women randomized to the control group ($n = 162$) continued to use their original firewood or kerosene stoves. Each woman in this group was also given training and a poster that had information on the dangers of smoke exposure and how to reduce their exposure to smoke while cooking. The ethanol used in the study was imported and secured through support from Shell Exploratory Company. Shell had no input or contribution to the study design and implementation beyond the contribution of about 50,000 l of ethanol.

2.4. Data collection

A detailed breakdown of the study flow and the timing of data collection are depicted in Fig. 1. Data collection began at the PHCs after interested, eligible women gave informed consent. At this first visit, interview with a trained study staff member using a structured questionnaire in Yoruba was administered to gather information on socioeconomic status, prior education, obstetrics history, current health status, pertinent past medical history, and family history. The questionnaires were then back-translated and checked for accuracy. Participants also received routine antenatal care and blood draws for complete blood count, serum biomarker levels, and malaria parasites once during their second and third trimesters, as well as spirometry tests. All women underwent ultrasound scans at least six times during pregnancy

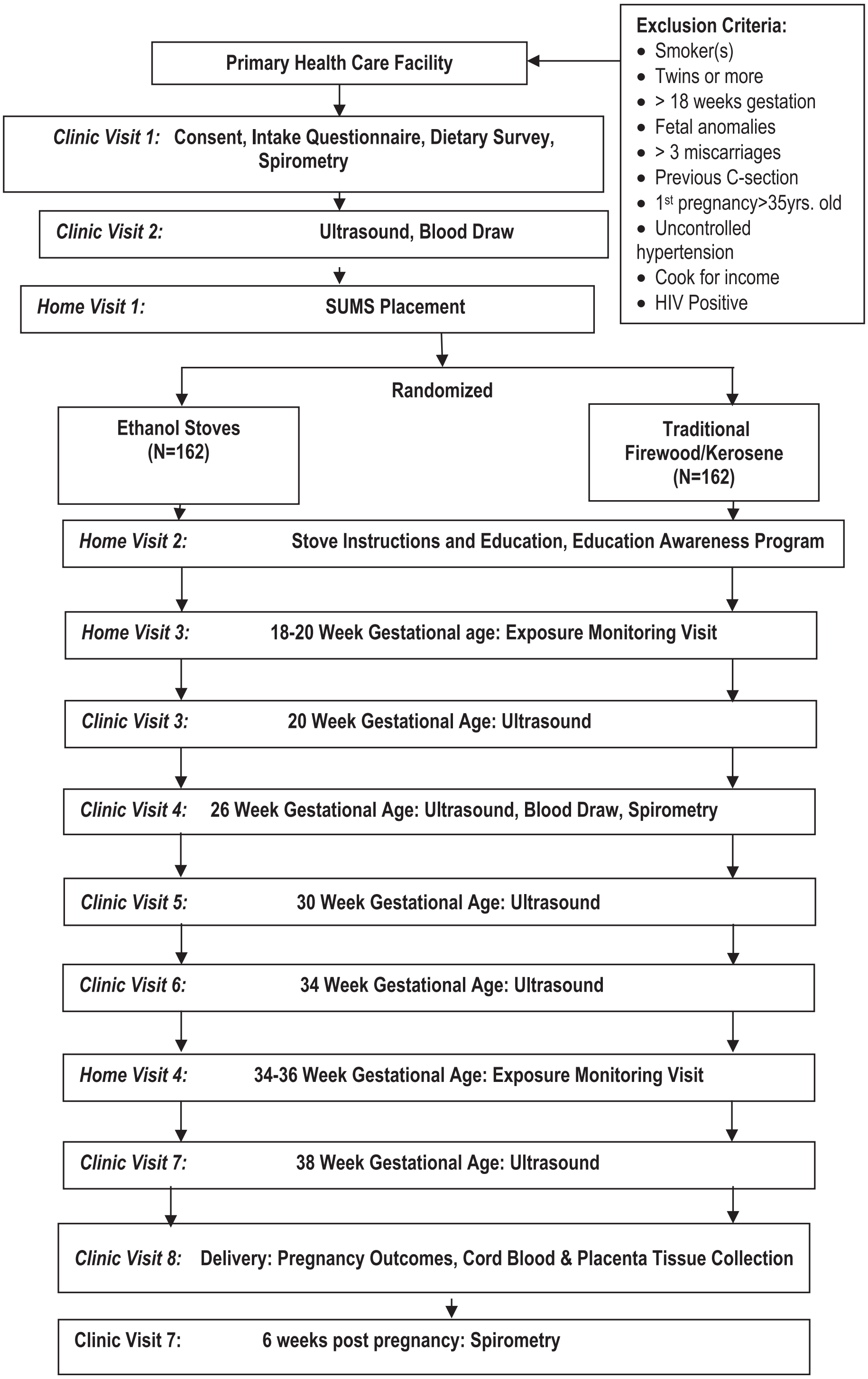


Fig. 1. Trial schema and visit schedule.

under the supervision of a dedicated and trained radiologist using Sonosite Micromaxx ultrasound system (Bothell, WA). For all women enrolled into the study, ultrasound was used to determine gestational age at entry and to monitor intrauterine growth during pregnancy. All measurements were taken three times and the mean values were recorded. Fetal weight (U-EDD) was estimated using the Hadlock method (Salomon et al., 2007). In addition to the day after initial clinic presentation, ultrasounds were performed at 20, 26, 30, 34, 36, and 38 weeks gestation. Health symptom questionnaires were administered at each visit to the PHC.

Following delivery, birthweight, GA, placental weight, Apgar scores, birth length, head circumference, respiratory rate, and the occurrence of preterm delivery, miscarriage, stillbirth, birth defects, and neonatal death were recorded. Birthweight was determined immediately after delivery using Delecto Digital baby scale (Webb city, MO). If the infant weight was < 2500 g, it was considered as low birth weight (LBW); delivery before 37 weeks was considered as preterm delivery. Stillbirths were defined as fetal deaths that occurred after 24 weeks of pregnancy. Miscarriages were characterized as fetal loss before 24 weeks of pregnancy (NHS, 2015). Since Apgar scores and placental weights were missing in over half the cases, these measures were excluded from analysis. A final clinic visit was scheduled six weeks post-delivery.

2.5. Personal exposure monitoring

Each woman in the study carried small CO and PM exposure monitors for three consecutive days (once during the second trimester and then again during the third trimester). Monitors were placed in culturally appropriate bags on the hips. $PM_{2.5}$ was measured using RTI MicroPEM monitors. The MicroPEM simultaneously collects aerodynamically sized $PM_{2.5}$ real-time light scattering concentrations as well as an integrated filter (15 mm PTFE, MTLcorp) for gravimetric and additional post analyses. The MicroPEMS were set at the flow rate of 0.4 lpm with sampling time of 10 s and system on time of 60 s and off time of 120 s. The filters were pre-weighed in batches at George Washington University, Washington, DC (GWU) prior to use in the field. We maintained 1 lab blank filter for every 10 deployed filter, which were handled by field staff in the same manner as sample filters. The field blank filters were used to pick up any potential contamination during shipping and handling in the field and were not used to help determine LOD. The filter concentration (calculated from the gravimetric mass and total sample volume) was used to correct the real-time data. Theoretically, the average real-time concentration should be equal to the filter mass. However, this rarely happens due to differences in particle size distributions, particle optical properties, and how efficiently a device may measure particles. Because of this, we used the gravimetric data to correct the real-time data. After sample collection, the filters were stored at 4 °C until they were returned to GWU for post sample analysis.

CO was monitored using Gasbadge Pro data-logging electrochemical monitors. These sensors are able to measure CO at 1 ppm resolution between 0 and 1000 ppm continuously at 1-minute time intervals. To ensure accuracy, the monitors were exposed in a small chamber to two concentrations of span gas CO of a known concentration at study onset. However, since local procurement of calibration gas was not possible, there was uncertainty regarding the validity of the CO data and the data were excluded from analysis. Third trimester $PM_{2.5}$ values were not collected in 39 of the women due to scheduling problems and relocation, 15 due to miscarriage and stillbirth; 50 filters were damaged during transportation to Chicago for post-exposure weight correction for $PM_{2.5}$ levels. The filters were first shipped to the University of Chicago and then shipped to GWU for post weighing and data correction since the filters were pre-weighed in the same lab before being deployed to the field.

2.6. Data storage

Data were collected on paper case report forms (CRFs). Each CRF was entered into a Dell tablet (Venue 8 Pro) by the administrator on the day of data collection. Data entered into the tablets were cross-checked by two independent data technicians, synced to a server, and sent to UC periodically. These data were then checked for completeness, outliers, and anomalies by the biostatistician; the data technicians corrected erroneous values and sent updated files to UC.

2.7. Statistical analysis

Baseline categorical data are summarized by frequency distributions; continuous variables are summarized by mean, standard deviation (SD), and range. Of 324 individuals enrolled in the trial, 215 were baseline kerosene users randomized to ethanol (E_K: n = 111) or kerosene (K_K: n = 104) and 109 were baseline firewood users randomized to ethanol (E_F: n = 51) or firewood (F_F: n = 58). The higher kerosene use at entry may reflect the more urban nature of the study population. Two sets of analyses were performed. The first (primary) set of analyses compared the ethanol (Ethanol = $E_K + E_F$: n = 162) and control (Control = $K_K + F_F$: n = 162) groups. The second set compared ethanol vs. kerosene among the subgroup of kerosene users at baseline (i.e., E_K vs. K_K), and the third ethanol vs. firewood among the subgroup of firewood users at baseline (E_F vs. F_F). These subgroup analyses were conducted to explore whether the intervention effects differed by control stove type while preserving the randomization.

All analyses, with the exception of those evaluating exposure-outcome relationships, were by intent-to-treat (ITT); participants were included in the group to which they were randomized regardless of stove use compliance. Pregnancy outcomes were compared using two-sample *t*-tests for continuous variables and chi-square or Fisher's exact test for categorical data. In addition to unadjusted comparisons, comparisons adjusted for marital status and BMI, two factors on which the groups differed at baseline, were performed using multiple linear regression for continuous outcome variables and generalized linear models (binomial family with a logarithmic link function) for binary outcomes, from which risk ratios were derived. Models adjusting for maternal age, the number of prior miscarriages, prior stillbirths, and a positive malaria test were also fitted, but none of these factors was found to be associated with birth outcomes (data not shown).

Exposure levels were compared between treatment arms using mixed-effects regression modeling (Gibbons and Hedeker, 2000) with season (rainy or dry) and intervention arm as fixed effects and subjects as a random effect to account for correlation between the multiple measurements (up to two) for each subject. Three summary measures derived for each participant over the three-day measurement period were utilized: the average exposure level adjusted for filter concentration (72 h mean concentration), the number of minutes that the $PM_{2.5}$ concentration was above a threshold (chosen arbitrarily because it was almost four times above WHO standards [i.e. 100 μg/m^3 during that 72-hour period]), and the 95th percentile of the exposure distribution over the 72-hour monitoring period.

The relationships between birth outcomes and personal exposure levels were examined using multiple linear regression models for continuous variables and generalized linear models for binary outcomes. The analyses were stratified by season of measurement to allow for possible differential effects by season. Due to small numbers of events, in the generalized linear models, exposure levels were categorized into just two groups according to whether the reading was below or above the median. In models for the continuous outcome variables, exposure levels were divided into quartiles (see Supplementary Table S3) in order to allow for non-linear relations, and the overall test for significance was based on the F-statistic with 3 and n-4 degrees of freedom. All statistical analyses were performed using SAS version 9.4 (Cary, NC) or STATA version 14 (College Station, TX).

2.8. Power calculations

Power calculations were performed for the primary outcomes. Among records obtained from the Adeoyo Maternity Hospital in Ibadan, Nigeria over the period Jan-Dec. 2010, there were 4775 deliveries with 300 (6.3%) being stillbirths and 14% LBW. Using these data, we assumed a mean weight in the control group of 3300 g with a standard deviation (SD) of 750 g (slightly greater than a quarter of the range). A sample size of 300 participants (n = 150 per group) was chosen, which provided 80% power (two-sided alpha = 0.05) to detect a 250 g difference between groups. For preterm delivery, we calculated that the study would have 80% power to detect a reduction from 20% in the control arm to approximately 9% in the ethanol group. Miscarriage, IUGR, and stillbirth rates were expected to be relatively low, so we anticipated that only non-significant trends would emerge for those outcomes.

3. Results

3.1. Baseline characteristics

Table 1 shows baseline clinical and demographic characteristics of the study participants by intervention arm. Nearly half of the women

Table 1
Baseline demographic and clinical characteristics by intervention arm.

Variable	Ethanol (E) (n = 162)	Control (C) (n = 162)	p-Value
Clinic			0.67
Agbongbon	76 (47.2%)	68 (42.2%)	
Oranyan	42 (26.1%)	46 (28.6%)	
Ijaye/Olorishaoko	43 (26.7%)	47 (29.2%)	
Missing	1	1	
Diabetic			1.0
Yes	2 (1.2%)	3 (1.9%)	
No	159 (98.8%)	158 (98.1%)	
Missing	1	1	
Number of children			0.25
None	41 (25.5%)	42 (25.9%)	
1–2	72 (44.7%)	71 (43.8%)	
3–4	37 (23.0%)	45 (27.8%)	
> 4	11 (6.8%)	4 (2.5%)	
Missing	1	0	
Marital status			0.060
Single	17 (10.6%)	7 (4.3%)	
Married	143 (88.8%)	155 (95.7%)	
Separated	1 (0.6%)	0 (0.0%)	
Missing	1	0	
Mother's age, yrs.			
Mean, SD	28.0, 6.1	27.9, 5.4	0.90
Range	15–44	14–42	
Missing	10	12	
Mother's BMI (kg/m^2)			0.0054
Mean, SD	23.2, 4.2	24.7, 5.3	
Range	14.2–35.2	17.1–45.0	
Missing	10	12	
Education level			0.57
None	51 (31.7%)	58 (35.8%)	
Primary School	16 (9.9%)	17 (10.5%)	
Junior Secondary	9 (5.6%)	13 (8.0%)	
Senior Secondary	68 (42.2%)	60 (37.0%)	
High School	10 (6.2%)	6 (3.7%)	
Polytechnic	7 (4.4%)	6 (3.7%)	
University	0 (0.0%)	2 (1.2%)	
Missing	1	0	
Read/write			
Yes	100 (62.1%)	92 (56.8%)	0.39
No	61 (37.9%)	70 (43.2%)	
Missing	1	0	
Gestational age at entry (weeks)			0.73
Mean, SD	12.9, 3.0	13.1, 3.0	
Range	6.7–18.0	7.1–18.0	
Missing	3	5	
Prior miscarriage			0.64
Yes	43 (26.7%)	47 (29.0%)	
No	118 (73.3%)	115 (71.0%)	
Missing	1	0	
# of miscarriages			0.72
None	118 (73.3%)	115 (71.0%)	
1	30 (18.6%)	36(22.2%)	
2	10 (6.2%)	7 (4.3%)	
3	3 (1.9%)	2 (1.9%)	
> 3	0 (0.0%)	1 (0.6%)	
Missing	1	0	
Prior stillbirth			0.84
Yes	12 (7.4%)	14 (8.6%)	
No	149 (92.6%)	148 (91.4%)	
Missing	1	0	
Season at randomization			0.46
Rainy[a]	111 (68.5%)	118 (72.8%)	
Dry[b]	51 (31.5%)	44 (27.2%)	
Missing	0	0	

[a] March–October.
[b] November–February.

were recruited from the Agbongbon PHC. Overall, very few participants had diabetes and the majority had two or fewer children at enrollment. The mean age of the mothers was 28 years (range 14–44) and mean BMI was 24 kg/m^2 (range 14.2–45.0). Education levels varied from none to beyond high school; many participants were illiterate. Mean GA at entry was 13 weeks, ranging from 6.7–18 weeks. Over 25% of the women had a prior miscarriage and 8% a prior stillbirth. Randomization produced comparable groups, although chance differences in BMI and marital status existed (mean BMI in the ethanol group was 23.2 vs. 24.7 in the control group; 10.6% of women in the ethanol group were single compared to 4.3% in controls). Since these two variables, in particular BMI, could impact pregnancy outcomes, statistical analyses adjusting for these two factors were performed in addition to unadjusted analyses.

3.2. Birth outcomes (ethanol vs. control)

Of the 324 enrolled participants, 306 completed the study; 18 participants dropped out between randomization and delivery (8 ethanol, 10 control). Table 2 presents outcomes by intervention arm. A total of 26 patients had missing birthweight data (11 ethanol, 15 control) because they delivered outside the primary health centers (at home, church or mosque). There were 4 miscarriages (1 ethanol, 3 control), 11 stillbirths (4 ethanol, 7 control), and 7 neonatal deaths (2 ethanol, 5 control); these cases also had missing birthweights. GA near delivery was not recorded for the seven neonatal deaths and was missing for one miscarriage (ethanol arm). The total number of subjects with missing data is included in the table for each variable.

Mean birthweights were 3076 g and 2988 g in the ethanol and control groups, respectively (p = 0.10). The observed difference was 88 g with a 95% confidence interval ranging from − 18 g to 194 g. After adjusting for marital status and BMI, the difference reached statistical significance (p = 0.020). The adjusted difference, 128 g (95% CI: 20 g to 236 g), was greater than the unadjusted difference because BMI was positively associated with birthweight ($p < 0.0001$) and mean BMI was higher in the control group compared to the ethanol arm. Histograms of the birthweights by treatment arm are shown in Fig. 2A; the distribution in the ethanol group is modestly shifted to the right relative to the controls. A sensitivity analysis was conducted to determine whether the difference between the unadjusted and adjusted results was due to the fact that the two analytic populations were different because of missing covariate data. There was no indication that this was the case, as unadjusted comparison of birthweights between the ethanol and control groups among patients with non-missing BMI and marital status yielded results similar to those reported above (mean birthweights of 3074 and. 2997, respectively, p = 0.16).

With regard to the other primary endpoints, there were fewer preterm infants (< 37 weeks) in the ethanol group compared to controls, but this difference was not statistically significant (p = 0.22). There were also fewer stillbirths and miscarriages, but the numbers were small and neither was statistically significant.

Among the tertiary endpoints, average GA at delivery was significantly higher in the ethanol group (39.2 weeks) compared to the controls (38.2 weeks; p = 0.015). As shown in Fig. 2B, this was primarily due to more deliveries occurring before 35 weeks in the control arm (10 vs. 1). Among 10 births in the control arm < 35 weeks, three were miscarriages and five were stillborn. Adjustment for covariates did not alter this finding (p = 0.011). If miscarriages and stillbirths are deleted, the difference in GA is no longer significant (p = 0.59). Birth length, head circumference, and respiratory rate distributions were similar in the two arms and none of the differences, unadjusted or adjusted, was statistically significant. There were more neonatal deaths in the control arm but again the difference was not significant. There were no recorded birth defects in either intervention group.

The rate of perinatal mortality was twice as high in controls compared to the ethanol group (7.9% vs. 3.9%; p = 0.15). Adjusting for marital status and BMI yielded a statistically significant difference in favor of ethanol (p = 0.045) with an adjusted risk ratio (RR) of 0.4 (95% CI: 0.1 to 0.98). The adjusted RR was lower than the unadjusted RR because single status was a risk factor for this endpoint (RR = 3.5,

Table 2
Pregnancy outcomes by intervention arm.

Variable	Ethanol (E) (n = 162)	Control (C) (n = 162)	Estimated effect[a]	95% CI	p-Value
Primary endpoints					
Birthweight (gm)					
Mean, SD	3076, 448	2988, 415	88	(− 18, 194)	0.10
Range	2000–4300	1860–4000			
Missing	26	40			
Preterm (< 37 wks.)					
Yes	10 (6.7%)	16 (11.0%)	0.6	(0.3, 1.3)	0.22
No	140 (93.3%)	130 (89.0%)			
Missing	12	16			
Stillborn					
Yes	4 (2.6%)	7 (4.6%)	0.6	(0.2, 1.9)	0.38
No	150 (97.4%)	145 (95.4%)			
Missing	8	10			
Miscarriage					
Yes	1 (0.6%)	3 (2.0%)	0.4	(0.04, 3.1)	0.37
No	153 (99.4%)	149 (98.0%)			
Missing	8	10			
Tertiary endpoints[b]					
Gestational age (weeks)					
Mean, SD	39.2, 1.6	38.2, 4.8	1.0	(0.2, 1.9)	0.015*
Range	33–42	36–44			
Missing	14	16			
Birth length (cm)					
Mean, SD	46.1, 5.0	45.9, 4.9	0.2	(− 1.0, 1.4)	0.77
Range	33–65	32–58			
Missing	26	41			
Head circumference (cm)					
Mean, SD	34.5, 2.9	34.4, 2.5	0.1	(− 0.7, 0.7)	0.98
Range	23–44	24–44			
Missing	27	40			
Respiratory rate (breaths/min)					
Mean, SD	123.9, 13.8	122.8, 10.5	1.1	(− 2.0, 4.2)	0.48
(Range)	(35–143)	(70–144)			
Missing	29	44			
Neonatal death					
Yes	2 (1.3%)	5 (3.3%)	0.4	(0.1, 1.4)	0.28
No	152 (98.7%)	147 (96.7%)			
Missing	8	10			
Birth defect					
Yes	0 (0%)	0 (0%)	–	–	1.0
No	139 (100%)	128 (100%)			
Missing	23	34			
Perinatal mortality[c]					
Yes	6 (3.9%)	12 (7.9%)	0.5	(0.2, 1.3)	0.15
No	148 (96.1%)	140 (92.1%)			
Missing	8	10			

[a] Mean difference or risk ratio.
[b] Secondary endpoints appear in Table 4.
[c] Stillbirth or neonatal death.

p = 0.034) and there were more single women in the ethanol group (10.6% vs. 4.3%).

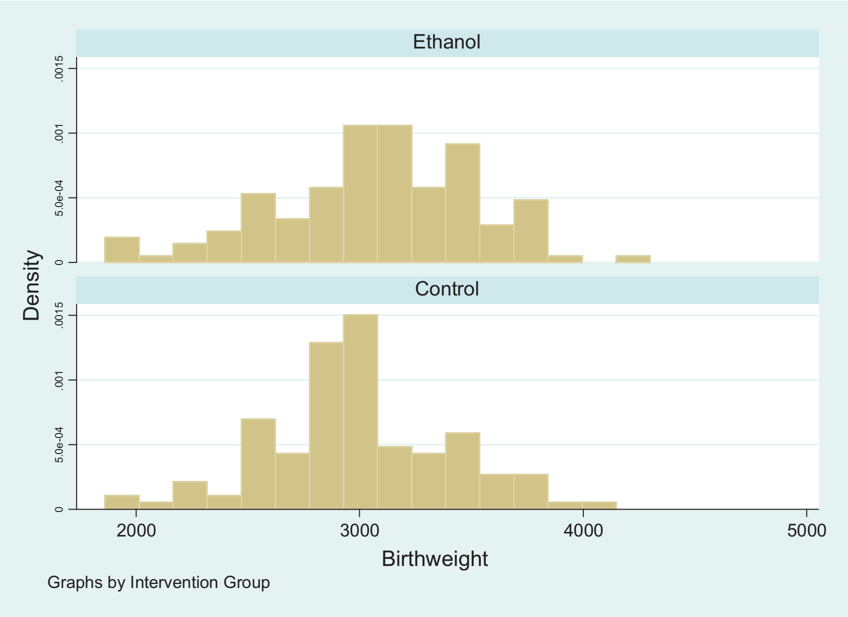
3.3. Birth outcomes stratified by stove use at entry

Table 3 displays results stratified by stove use at study enrollment. The second, third, and sixth columns summarize the comparisons of the ethanol vs. kerosene groups among baseline kerosene users (E_K vs. K_K), and the fourth, fifth, and seventh columns summarize results for ethanol vs. firewood comparisons among baseline firewood users (E_F vs. F_F). There were no statistically significant differences among the unadjusted comparisons. The comparison of birthweights was significant in the adjusted analysis of E_F vs. F_F (p = 0.025) with an adjusted difference of 197 g (95% CI: 25 g to 368 g). Again, the disparity between the unadjusted and adjusted results was not due to differing numbers of patients contributing to the two analyses. Among patients with non-missing BMI and marital status, the unadjusted difference was similar to that reported in Table 3 and not statistically significant (mean birthweights of 3091 and 2959, respectively, p = 0.14).

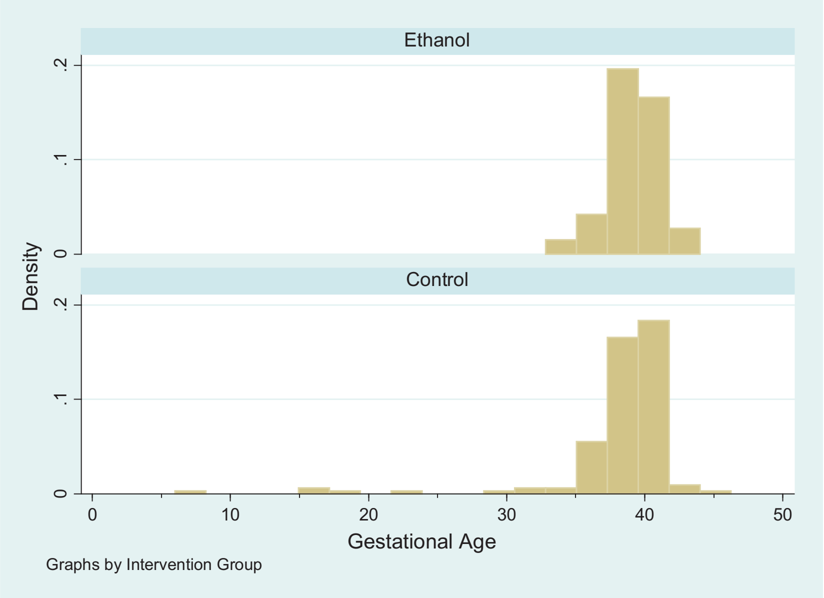
The difference in mean gestational age was not significant in the E_F vs. F_F comparison (p = 0.058) but this difference reached statistical significance after adjusting for marital status and BMI (adjusted difference = 1.6 weeks, 95% CI: 0.04 to 3.2 weeks; p = 0.045). This was again primarily due to the higher rate of stillbirths and miscarriages in the F_F arm; if these are excluded, the difference in GA is not significant (p = 0.23). The reduced sample sizes for these subgroup comparisons should be noted when interpreting the results.

3.4. Personal exposure levels

HAP exposure levels were designated as a secondary endpoint of the study. Analysis of the effect of the intervention on exposure levels was complicated by the fact that the levels differed markedly between the dry and rainy seasons (noticeably higher during the dry season). As mentioned above, exposure levels were to be assessed twice for each individual, once during the second and once during the third trimester, but in 107 participants only the second trimester measurement was obtained. Descriptive statistics are shown in Table 4 by season and



A. Birthweight



B. Gestational age

Fig. 2. Birth outcomes by intervention arm. (A) birthweight. (B) gestational age.

intervention arm. If a participant had two measurements during the same season, the third trimester value was used in these calculations. The data exhibit high variability between subjects with the SD exceeding the mean in every instance. Correlation among the three metrics was fairly high: $r = 0.83$ between mean 72-hour $PM_{2.5}$ and minutes above 100 $\mu g/m^3$, $r = 0.81$ between mean 72-hour $PM_{2.5}$ and 95th percentile, and $r = 0.51$ between minutes above 100 $\mu g/m^3$ and 95th percentile (all $p < 0.001$). Mixed-effects regression modeling revealed statistically significant ($p < 0.001$) seasonal effects for all three exposure indices, but there were no statistically significant intervention effects.

3.5. Birth outcomes and personal exposure levels

Table 5 presents estimates of risk ratios for the binary birth outcomes comparing groups above and below the median $PM_{2.5}$ level (average over 72 h). Miscarriages and neonatal deaths among women measured in the dry season are excluded because there were too few events for meaningful analysis. None of the risk ratios is statistically significant. Very similar results were obtained for the other two exposure variables (Supplemental Tables S1 and S2). The results of analysis of the continuous birth outcomes are depicted in Fig. 3. Shown are mean levels of the outcome (± SE) for each quartile of exposure (mean 72-hour $PM_{2.5}$), stratified by whether the exposure was measured during the rainy or dry season. Birthweights declined with increasing exposure derived from the rainy season measurements, but the effect was not statistically significant ($p = 0.16$). The relationship based on the dry season measurements was in the opposite direction. The only statistically significant effect detected was for head circumference based on the rainy season measurements, where there was a consistent decrease in circumference per each quartile increase in the level of $PM_{2.5}$ exposure ($p = 0.016$). Analyses based on the other two exposure

Table 3
Pregnancy outcomes by intervention arm stratified by baseline stove type.

	Baseline kerosene users		Baseline firewood users			
Variable	Ethanol (E_K) (n = 111)	Kerosene (K_K) (n = 104)	Ethanol (E_F) (n = 51)	Firewood (F_F) (n = 58)	p-Value E_K vs. K_K	p-Value E_F vs. F_F
Primary endpoints						
Birthweight (gm)						
Mean, SD	3073, 438	3017, 423	3081 470	2942, 403	0.41	0.12
Range	2000–4300	1950–4000	2000–3860	1860–3800		
Missing	25	30	1	10		
Preterm (< 37 wks.)						
Yes	5 (5.0%)	11 (12.0%)	5 (9.8%)	5 (9.3%)	0.12	1.0
No	94 (95.0%)	81 (88.0%)	46 (90.2%)	49 (90.7%)		
Missing	12	12	0	4		
Stillborn						
Yes	4 (3.9%)	5 (5.1%)	0 (0%)	2 (3.7%)	0.74	0.50
No	99 (96.1%)	93 (94.9%)	51 (100%)	52 (96.3%)		
Missing	8	6	0	4		
Miscarriage						
Yes	1 (1.0%)	2 (2.0%)	0 (0%)	1 (1.8%)	0.61	1.0
No	102 (99%)	96 (98%)	51 (100%)	53 (98.2%)		
Missing	8	6	0	4	0.12	0.058
Missing	23	27	1	8		
Tertiary endpoints						
Gestational age (weeks)						
Mean, SD	39.1, 1.6	38.3, 4.4	39.4, 1.6	37.9, 5.5		
Range	33–42	15–44	35–42	6–41		
Missing	14	12	0	4		
Birth length (cm)						
Mean, SD	45.8, 4.9	45.5, 4.5	46.6, 5.3	46.4, 5.4	0.74	0.92
Range	33–61	32–55	35–65	32–58		
Missing	25	30	1	11		
Head circumference (cm)						
Mean, SD	34.8, 2.9	34.5, 2.7	33.8, 2.9	34.3, 2.1	0.47	0.30
Range	28–44	24–44	23–39	30–42		
Missing	26	30	1	10		
Respiratory rate (breaths/min)						
Mean, SD	123.2, 8.3	122.7, 10.4	125.0, 20.1	123.0, 10.7	0.71	0.53
Range	100–142	70–144	35–143	78–138		
Missing	27	32	2	12		
Neonatal death						
Yes	2 (1.9%)	5 (5.1%)	0 (0%)	0 (0%)	0.27	1.0
No	101 (98.1%)	93 (94.9%)	51 (100%)	54 (100%)		
Missing	8	6	0	4		
Birth defect						
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0	1.0
No	89 (100%)	78 (100.0%)	50 (100%)	50 (100%)		
Missing	22	26	1	8		
Perinatal mortality[a]						
Yes	6 (5.8%)	10 (10.2%)	0 (0.0%)	2 (3.7%)	0.30	0.50
No	97 (94.2%)	88 (89.8%)	51 (100.0%)	52 (96.3%)		
Missing	8	6	0	4		

[a] Stillbirth or neonatal death.

Table 4
Exposure levels by season and intervention arm.

Season	Variable	Arm	n	Mean	SD
Rainy[a]	Mean 72-hr $PM_{2.5}$ (μg/m^3)	Ethanol	114	61	74
		Control	116	66	82
	Minutes above 100 μg/m^3	Ethanol	114	198	392
		Control	116	183	312
	95th percentile (μg/m^3)	Ethanol	114	166	249
		Control	116	190	281
Dry[b]	Mean 72-hr $PM_{2.5}$ (μg/m^3)	Ethanol	99	118	166
		Control	98	102	102
	Minutes above 100 μg/m^3	Ethanol	99	352	490
		Control	98	364	446
	95th percentile (μg/m^3)	Ethanol	99	250	368
		Control	98	265	302

[a] March–October.
[b] November–February.

Table 5
Birth outcomes in women with $PM_{2.5}$ concentration (72-hour average) above and below the median.

Variable	Risk ratio[a]	95% CI	p-Value
Preterm delivery			
Rainy season[b]	1.5	(0.4, 5.2)	0.49
Dry season[c]	1.8	(0.6, 5.9)	0.32
Stillborn			
Rainy season	0.5	(0.1, 5.5)	0.58
Dry season	1.0	(0.2, 4.7)	0.98
Neonatal death			
Rainy season	1.5	(0.3, 8.8)	0.64
Dry season	–	–	–
Perinatal mortality			
Rainy season	1.0	(0.3, 3.9)	0.99
Dry season	1.3	(0.3, 5.6)	0.71

[a] Above median/below median.
[b] Exposure measured during rainy season.
[c] Exposure measured during dry season.

indices (minutes above 100 μg/m^3 and 95th percentile) were similar and are displayed in Supplemental Figs. S1 and S2.

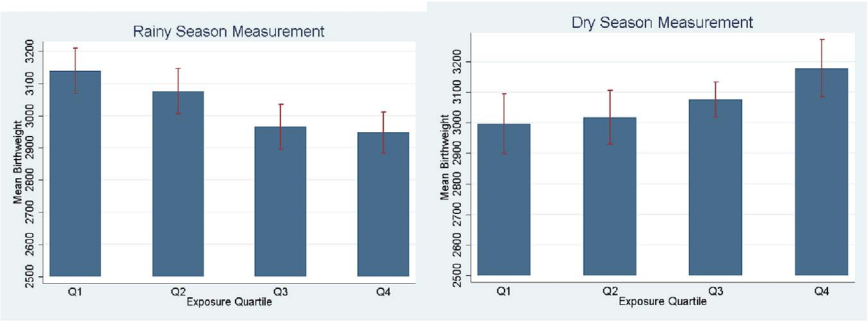
4. Discussion

To date, most studies evaluating the impact of solid fuel use on pregnancy outcomes have been cross-sectional, case-control, or cohort (Amegah et al., 2014; Epstein et al., 2013; Lakshmi et al., 2013). This is the first RCT to use ethanol as the alternative clean fuel to kerosene and firewood in an intervention study investigating the impact of HAP exposure on pregnancy outcomes. Moreover, this RCT measured personal exposure to $PM_{2.5}$ on pregnant women in both the second and third trimesters of pregnancy.

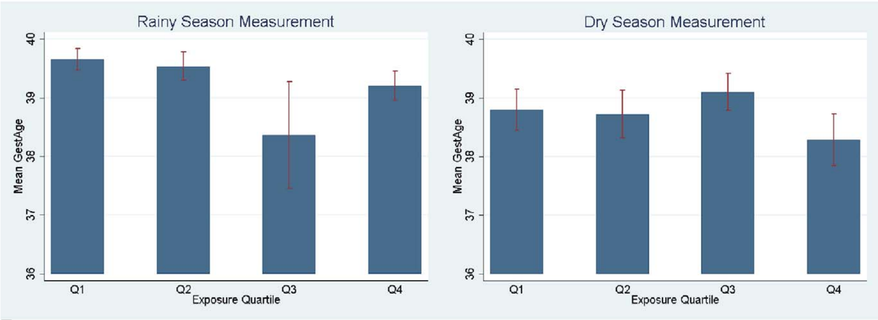
According to a meta-analysis by Amegah et al. (2014), HAP from solid fuel use is associated with increased risk of LBW and stillbirth (Amegah et al., 2014). This meta-analysis of 19 studies, which was done in comparison to cleaner fuel users, found that household combustion of solid fuels results in a reduction in birth weight by almost 87 g and an increased risk of LBW and stillbirth. Similarly, for liquid fuel like kerosene, Lakshmi and colleagues (Lakshmi et al., 2013) reported an adjusted OR for stillbirth of 1.36 (95% CI: 1.10, 1.67; $p = 0.004$) for cooking with kerosene compared with liquefied petroleum gas (LPG) or electricity. In another analysis of the Indian National Family Health Survey data, authors found adjusted effects of kerosene use on mean birthweight of − 103 g (95% CI: − 153.5 to, − 59.4; $p < 0.001$), and ORs for LBW and neonatal deaths of 1.51 (95% CI: 1.08 to 2.12; $p < 0.05$) and 2.88 (95% CI: 1.18 to 7.02; $p < 0.05$), respectively, compared to LPG and biogas (Epstein et al., 2013).

There is circumstantial evidence that a low-emission or clean cookstoves could significantly impact the rate of LBW births and adverse pregnancy outcomes (Bruce et al., 2013), but, to date, there are no RCTs demonstrating the efficacy of switching to clean fuels to improve pregnancy outcomes. In the only published RCT evaluating pregnancy outcomes, researchers found that, after adjusting for covariates, infants born to mothers who used biomass chimney stoves weighed 89 g more on average than infants randomized to an open fire stove, although this difference did not reach statistical significance (Thompson et al., 2011).

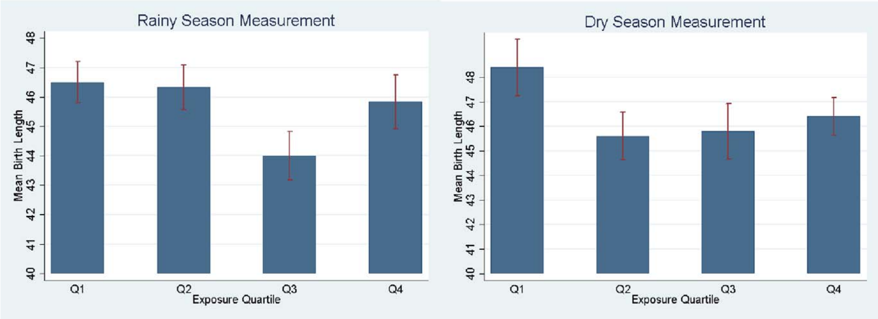
Babies born weighing < 2500 g have lifelong health complications (Temple et al., 2010) and require extra resources, which can be very burdensome in resource-limited settings (Emmelin and Wall, 2007).



A. Birthweight (p=0.16 and p=0.44 for rainy and dry season measurements, respectively)

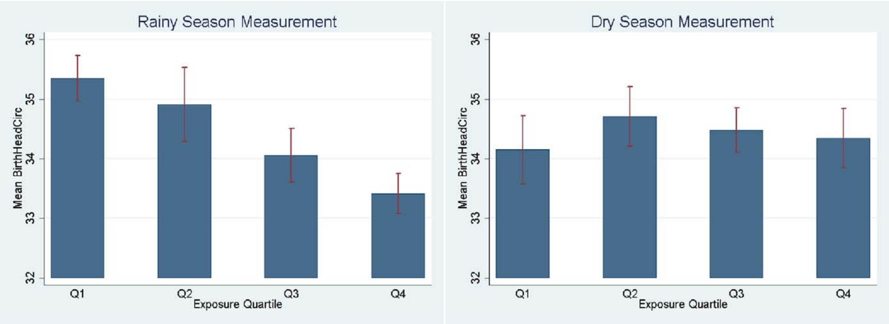


B. Gestational age (p=0.24 and p=0.51 for rainy and dry season measurements, respectively)

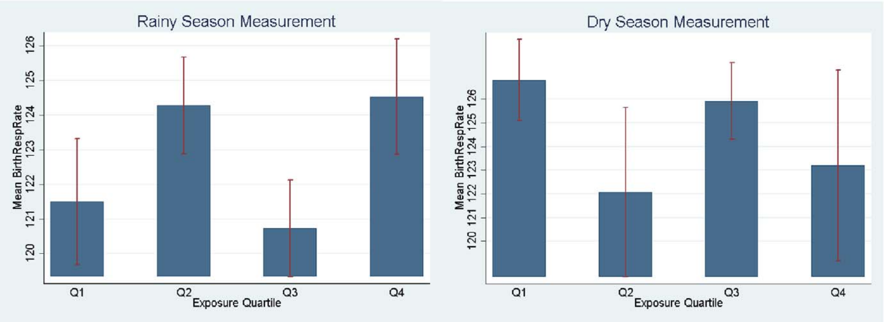


C. Birth length (p=0.12 and p=0.20 for rainy and dry season measurements, respectively)

Fig. 3. Birth outcomes vs. quartile of $PM_{2.5}$ exposure (72-hour average) for rainy season ($n = 162$) and dry season ($n = 125$) measurements: (A) birthweight (B) gestational age, (C) birth length, (D) head circumference, and (E) respiratory rate.



D. Birth head circumference (p=0.016 and p=0.88 for rainy and dry season measurements, respectively)



E. Respiratory rate (p=0.22 and p=0.63 for rainy and dry season measurements, respectively)

Fig. 3. (*continued*)

Reducing the number of babies born with LBW will improve long-term health outcomes for mother and child (Witt et al., 2012). This RCT study shows that after adjusting for BMI and marital status, mean birthweights were significantly ($p = 0.020$) higher in the ethanol group than the controls (3076 g and 2988 g, respectively). Average GA at delivery was also significantly ($p = 0.015$) higher in ethanol users (39.2 weeks) compared to controls (38.2 weeks). As discussed in the literature, GA plays an important role in stillbirth or miscarriage and the causes differ with varying GA (Akolekar et al., 2011; Da Silva et al., 2016; Qu et al., 2017; Rashid et al., 2017; Stormdal Bring et al., 2014). Hence, the findings might have been influenced by the significant difference in GA between the two groups. Though not statistically significant, there were fewer preterm infants (< 37 weeks) in the ethanol group. Perinatal mortality was over twice as high in controls compared to the ethanol group (7.9% vs. 3.9%); and the difference was statistically significant ($p = 0.045$) after adjusting for marital status and BMI. Our study showed higher birthweights compared to those from the Guatemala RCT (mean birthweight of 2728 g and 2797 g for babies born to open fire users and chimney stove users, respectively). Although birthweights in the Guatemalan study were smaller, on average, than the birthweights in this study, the 89 g increase in babies born to women who used a chimney stove compared to women who cooked over an open fire is very similar to our findings, where babies born to mothers using kerosene/firewood fuel weighed 88 g less than those born to ethanol-using mothers. Collectively, these findings suggest evidence to prioritize the need for access to safer household cooking methods for expecting mothers.

When comparing subgroups stratified according to stove type use at entry, firewood users randomized to receive ethanol cookstoves exhibited better birth outcomes than those randomized to continue using firewood. The difference in birthweights was statistically significant in the adjusted analysis of E_F vs. F_F ($p = 0.025$) with an adjusted difference of 197 g (95% CI: 25 g to 368 g). The difference in mean GA in the E_F vs. F_F comparison was also statistically significant after adjusting for marital status and BMI (adjusted difference = 1.6 weeks, 95% CI: 0.04 to 3.2 weeks, $p = 0.045$). Among baseline kerosene users, observed differences generally favored those randomized to ethanol, but none was statistically significant.

Personal exposure monitoring of $PM_{2.5}$ for all participants provided the unique opportunity to assess individual HAP exposure and its relationship to pregnancy outcomes. Of note, the most pronounced differences in measured HAP exposure levels were between the rainy and dry seasons when levels were predictably lower during the rainy season, and there were no significant differences between the ethanol and control arms controlling for season. Analysis of exposure-response relationships were generally negative, though, with the exception of rainy season exposure and head circumference ($p = 0.016$). This is important for long-term health, as Lohaugen and colleagues demonstrated that smaller head circumference increased the likelihood of developmental delay or cognitive impairment in childhood (Lohaugen et al., 2013). The CleanCook stove used in this RCT meets tier 4 for indoor emissions performance standards based on the framework in the ISO IWA Guidelines on evaluating cookstove performance that are matched only by LPG stoves, biogas, and solar energy (ISO, 2012).

As described in our earlier publication (Northcross et al., 2016), all stoves in each household were equipped with a stove use monitoring system (SUMS) to monitor stove usage. We found consistent use of the ethanol stove for kerosene users randomized to ethanol in our trial, with very little stacking (combining usage of the ethanol stoves with the traditional ones) occurring (Northcross et al., 2016). The same trend did not hold true for firewood users randomized to ethanol, where stacking was still observed. Furthermore, follow-up one year after the conclusion of the study showed that 83% of women in the ethanol group continued to purchase ethanol with personal funds (data not presented here), which is a strong measure of adoption of the CleanCook stove. Similar to the ethanol users, controls in the RCT who were given the CleanCook stove a year after the conclusion of the study, have been using personal funds to purchase ethanol. We did not observe any burn injury in this study, a finding that we attribute to the education on safe stove handling at study onset for all participants and the safety of the CleanCook stove. Given the importance of the increase in premature mortality from HAP exposure (Abtahi et al., 2017; Balakrishnan et al., 2014; WHO, 2016) and the dismal projection of further significant increases in cardiovascular mortality over the next 20 years (Couser et al., 2011; Kones, 2011), we believe that the timing of our RCT is both appropriate and important. This study demonstrates the willingness of women, who bear the major brunt of HAP exposure, to utilize clean-burning fuels.

Our study has several important limitations. Although the sample size provided sufficient power to detect a 250 g difference in mean birthweight and a 50% reduction in the rate of preterm delivery, the trial was not powered to detect smaller effects. In addition, we observed lower rates of preterm births than assumed in our power calculations. Perhaps this was due to the educational information about the harmful effects of HAP that was provided to families in both arms. Future trial investigators may wish to increase sample sizes to allow for lower-than-expected event rates. Reliable exposure assessments were limited to $PM_{2.5}$ and we did not consistently achieve our goal of two measurements per household, which meant that in a sizable fraction of the participants (51%), we did not have an exposure measurement during both the rainy and dry seasons. It is also possible that ambient air pollution levels over the 72-hr monitoring period masked household differences since our GPS monitoring data on the mothers revealed that 70% of the exposures occurred indoors while the remaining 30% occurred outdoors (data not shown). There were 8 dropouts in the ethanol arm and 10 in the control group, and while we sought to minimize other missing data, missing data could not be avoided. For example, after excluding miscarriages and stillbirths, birthweights were missing in 6.2% of the ethanol users and 8.6% of the controls. We examined whether the findings with respect to birthweight and gestational age could have resulted from bias due to missing data. We compared baseline characteristics between those with and without missing birthweights and gestational ages to assess whether study participants with missing data were different from those without missing data. The two groups were comparable with two exceptions: subjects with missing birthweights were more likely to have been randomized during the rainy season (83% vs. 67%, $p = 0.017$) and those with missing gestational ages were more likely to be single (20% vs. 6%, $p = 0.038$). However, season of enrollment was not associated with birth outcomes and although marital status did have an effect on gestational age at birth (single women had a 1.9-week lower mean than married women, $p = 0.029$), the effect of intervention on gestational age remained statistically significant after adjusting for marital status. Furthermore, in the case of gestational age, the number missing in the two treatment arms was similar. We therefore do not find any indication that missingness accounts for the group differences we observed. Finally, the control arm was a mixture of 64% kerosene and 36% firewood users, and subgroup analyses by type of stove in use at entry into the trial were limited by the reduced sample sizes. Nevertheless, we believe this study provides informative results and the basis for undertaking a larger-scale RCT in the future.

Several million disadvantaged women are chronically exposed to HAP in low- and middle-income countries of Asia, sub-Saharan Africa, and Latin America. In many sub-Saharan countries, HAP appears to be a greater menace than ambient air pollution (Forouzanfar et al., 2016). Noubiap et al. (2015) rightly suggest that there is compelling need to implement efficient strategies to educate populations about health issues associated with HAP and to gather high quality evidence to facilitate efficient policy-making in this region. Nigeria, as an implementing national partner of the Global Alliance for Clean Cookstoves, launched the Nigerian Alliance for Clean Cookstoves, which is aimed at reducing adverse health effects caused by exposure to smoke from HAP. This policy change and commitment by the government provided a unique opportunity to investigate the health benefits of using cleaner fuel for cooking. The results of this study may be used to support ongoing stove intervention programs in the most populous country in Africa, which contains many at-risk women and children.

5. Conclusions

In summary, switching to ethanol-burning stoves has the potential to provide needed protection for women and their developing fetus, especially during pregnancy. We believe our findings are indicative of beneficial effects of ethanol stoves on pregnancy outcomes, but there are several caveats that temper our conclusions. The difference in average birthweight was statistically significant only after adjusting for covariates. None of the differences in the other primary endpoints (preterm delivery, stillbirths, and miscarriages), although all favoring the ethanol arm, were statistically significant. There was a nominally significant difference in mean gestational age between the two groups, but this was one of several tertiary endpoints analyzed. There was high variability in measured exposure levels and a strong seasonal effect that complicated HAP exposure assessments. Nonetheless, this study, if validated, has the potential to influence health policy and to make significant contributions to reductions in health-damaging effects of biomass fuel use for energy needs in Nigeria and other developing countries. The adoption of clean cookstoves and fuels is essential in mitigating the effects of HAP exposure. It could also lead to health policy changes in Nigeria and other low to middle income countries (LMIC), which could promote increased awareness of adverse effects of biomass and kerosene fuels, modification of housing codes for new home construction to promote better ventilation, introduction and distribution of more environmentally-friendly and cleaner cooking stoves, and expansion of the production of cleaner fuels from farm produce. We feel strongly that a larger RCT is needed.

Contributors

Donee Alexander: study design, study implementation, data collection and manuscript writing and editing; Amanda Northcross: study design, exposure assessment, data analysis and manuscript editing; Nathaniel Wilson: study design, data collection and manuscript editing; Anindita Dutta: data review, literature search and writing first draft of manuscript; Tope Ibigbami: study implementation, data collection and manuscript editing; Damilola Adu: study implementation, data collection and manuscript editing; John Olamijulo: data collection and manuscript editing; Dayo Adepoju: study implementation, data stewardship and manuscript editing; Oludare Morhasson-Bello: study design and manuscript editing; Theodore Karrison; study design, randomization schedule creation, statistical analysis and manuscript editing; Mojisola Atalabi; ultrasound evaluations for gestational age, manuscript editing; Oladosu Ojengbede: project design, leadership and manuscript editing: Christopher O Olopade: project concept and study design, project leadership, data review, manuscript review and finalization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2017.11.021.

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