

Randomized controlled ethanol cookstove intervention and blood pressure in pregnant Nigerian women

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Include an “At a Glance Commentary” which addresses the following two issues:

Hypertensive disease during pregnancy is a major cause of mortality and morbidity in pregnant women and their developing fetus. Exposure to household air pollution has been demonstrated to increase the risk of adverse pregnancy outcomes, but there are no

randomized, controlled interventions that have investigated the efficacy of clean fuels in mitigating challenges related to hypertension in pregnant women.

Scientific Knowledge on the Subject, and What This Study Adds to the Field. The entire "At a Glance" section should not exceed 200 words. Please note that this same text should be included at the end of your Manuscript

In the first randomized, controlled intervention study to investigate the role of improved cooking fuel on BP changes during pregnancy, we show that ethanol fuel for cooking led to significant reductions in diastolic BP and prevalence of systemic hypertension. In this study, pregnant women who cooked initially with kerosene or firewood were randomized into either an intervention group that cooked with a CleanCook ethanol stove or a control arm that continued to cook with kerosene or firewood. We demonstrate the ability of a clean-burning ethanol cookstove to reduce diastolic BP and hypertension during pregnancy and the potential for clean cooking fuels to reduce adverse health impacts associated with HAP.

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Abstract

Rationale: Hypertension during pregnancy is a leading cause of maternal mortality. Exposure to household air pollution (HAP) elevates blood pressure (BP).

Objectives: Investigate ability of clean cookstove intervention to lower BP during pregnancy.

Methods: A randomized, controlled trial (RCT) was conducted in Nigeria. Pregnant women cooking with kerosene or firewood were randomly assigned to ethanol (n = 162) or control arms (n = 162). BP measurements were taken during 6 antenatal visits. Primary analysis compared ethanol users with controls. Subgroup analyses compared baseline kerosene users assigned to intervention with kerosene controls and baseline firewood users assigned to ethanol with firewood controls.

Measurements and Main Results: The change in diastolic BP (DBP) over time was significantly different between ethanol users and controls (p = 0.040); systolic BP (SBP) did not differ (p = 0.86). In subgroup analyses, there was no significant intervention effect for SBP; a significant difference for DBP (p = 0.031) existed among pre-intervention kerosene users. At last visit, mean DBP was 2.8 mmHg higher in controls vs. ethanol users (3.6 mmHg greater in controls vs. ethanol users among pre-intervention kerosene users); 6.4% of controls were hypertensive (SBP \geq 140 and/or DBP \geq 90) vs. 1.9% of ethanol users (p=0.051). Among pre-intervention kerosene users, 8.8% of controls were hypertensive compared to 1.8% of ethanol users (p=0.029).

Conclusions: This is the first cookstove RCT examining prenatal BP. Ethanol cookstoves have potential to reduce DBP and hypertension during pregnancy. Accordingly, clean cooking fuels may reduce adverse health impacts associated with HAP.

Word count (Abstract) = 250

Key terms (3-5 keywords only): ethanol cookstove intervention, hypertension, pregnancy, household air pollution, blood pressure

Introduction

Approximately 40% of the global population uses solid fuels (wood, crop wastes, charcoal, coal, dung) for daily energy needs.(1) In sub-Saharan Africa, 75% of households use solid fuels for cooking and heating. Burning solid fuels in traditional stoves results in incomplete combustion, which produces high levels of household air pollution (HAP) and levels of fine particulate matter (PM) that far exceeds the World Health Organization's (WHO) indoor air quality guidelines.(2) Exposure to HAP is the eighth leading risk factor for global disease burden, contributing to 2.9 million deaths in 2015.(3) The majority of HAP-associated morbidity and mortality occurs in low- to middle-income countries (LMICs) disproportionately impacting women and children.(4) An estimated 60% of HAP-related deaths are due to cardiovascular disease.(5)

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Additionally, over 500 million households worldwide use kerosene,(6) another important contributor to HAP. Known health impacts of kerosene smoke exposure include small-for-gestational-age babies and increased risk of tuberculosis.(7, 8) Accordingly, WHO has discouraged using kerosene for household energy needs.(9)

PM exposure is associated with elevated BP.(10-12) Studies of ambient PM have shown that variances in long-term exposures as small as $2 \mu\text{g}/\text{m}^3$ can result in differences in BP as high as 3.1 mmHg.(10, 13, 14) Exposure to ambient air pollution has been associated with adverse pregnancy outcomes (15-18); HAP exposure is also a risk factor for increased BP.(19-21) Interventions aimed at reducing HAP exposures through use of advanced biomass stoves

(stoves that are cleaner burning or more efficient than traditional stoves) have resulted in reductions in BP.(22-24) The exact mechanism of PM-induced BP changes is unclear; it likely involves oxidative stress, endothelial injury, systemic inflammation, and thrombosis, eventually resulting in atherosclerosis and increased peripheral vascular resistance. (25, 26)

BP changes have important implications for hypertensive disorders in pregnancy. Gestational hypertension is a leading cause of maternal mortality complicating about 7% of pregnancies.(27) In LMICs, pregnancy-induced hypertension accounts for 10-15% of maternal deaths.(28) Preeclampsia, defined by gestational hypertension and end-organ dysfunction, is the most severe gestational hypertensive disorder. It is responsible for 15% of preterm births and is associated with a fivefold increase in perinatal mortality.(27) Severe gestational hypertension is associated with prematurity and small-for-gestational-age babies.

(27)

Pregnant women and their fetuses are vulnerable to impacts of HAP exposure because the women do most household cooking. Maternal exposure to PM_{2.5} (PM less than 2.5µm in diameter) from biomass and kerosene smoke can cause elevated BP, which may explain associations between HAP and increased risk of low birthweight and stillbirth in meta-analysis. (29) Evidence of effects of prenatal HAP exposure on changes in BP and cardiovascular health in women from LMICs is essential for protecting the health of mothers and their fetuses.(30)

Optimal BP control during pregnancy is critical for maternal-fetal health. The impact of using dirty fuels is currently unquantified. Though some studies have studied the impact of advanced biomass stoves on respiratory health (31), no studies have evaluated the effects of

using clean fuels on BP changes during pregnancy. Clean-burning fuels may reduce HAP exposure and achieve WHO Indoor Air Quality Guidelines for household fuel combustion.(32) Therefore, evaluation of the effects of reducing HAP exposure on BP during pregnancy is crucial.

In Nigeria, over 90 million households cook with solid fuels and approximately 23% use kerosene for household energy.(33) This randomized, controlled trial (RCT) investigated the impact of clean-burning ethanol cookstoves on BP in pregnant women who cooked predominantly with kerosene or firewood prior to enrollment in Ibadan, Nigeria. Some of the results of these studies were previously reported as an abstract.(34)

Methods

Institutional review boards at the University of Ibadan (Ibadan, Nigeria) and the University of Chicago (Chicago, USA) approved this study.

Study population. This RCT was conducted between June 2013 and October 2015 with 324 pregnant women (predominantly Yoruba descent) living in Ibadan, Nigeria, a city of over 3 million. Pregnant women were screened for eligibility when visiting one of four primary health care centers (PHCs) in Ibadan or adjoining peri-urban areas. Reported numbers of births at these PHCs from 2013 to 2015 ranged from 555- 796 (Agbongbon), 721-867 (Oranyan), 38-88 (Ijaye), and 44-62 (Olorishaoko).

Eligible women had to be their household's primary cook, <18 weeks pregnant (determined by self-reported first day of last known menstrual period and ultrasound biometry), and use wood and/or kerosene as their primary cooking fuel. Randomization was not stratified by type of primary cooking fuel because when the study began only women using wood-burning

stoves were intended to be included. Due to the lower-than-expected number of such families, the study was expanded to include kerosene controls. The secondary analyses stratify (post-hoc) by pre-intervention stove type. Women were excluded if they were HIV positive, smoked, lived with a smoker, cooked for a living, or had a high-risk pregnancy (multiple gestations, uncontrolled maternal hypertension, >35 for first delivery, three or more miscarriages, or Caesarean-section).

Enrollment. Upon presentation at an eligible PHC, women were given a detailed study description, participation requirements, and associated benefits and risks. Consenting women were evaluated against inclusion and exclusion criteria, asked to give written consent, and indicate their primary cooking fuel.

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Consented women were stratified by parity (≤ 4 vs. > 4 children) and presence of diabetes, then randomized using the method of permuted blocks and the MT64 random number generator in STATA (College Station, TX). (35) REDCap's web-based randomization module conveyed the assigned treatment. Of 324 women, 50% were assigned to the ethanol stove group (111 used kerosene; 51 used firewood pre-intervention). These women were given a two-burner, aluminum CleanCook ethanol stove (CLEANCOOK Sweden AB) and an initial supply of fuel during a home visit between 16-18 weeks gestational age (GA); comprehensive training regarding dangers of smoke exposure and proper use of the ethanol stove were provided simultaneously. Additionally, staff observed each woman use the stove for the first time and hung the stove manual in their kitchen. The control group continued to use their kerosene (n=104) or firewood stove (n=58). They were given education on dangers of smoke exposure and were encouraged to reduce smoke exposure through behavioral and environmental modification.

Data Collection. Data collection began the day of study enrollment. An interview with structured questionnaire was administered in the local language (Yoruba) to gather information on socio-economic status, education, obstetrics history, current health status, past medical history, and family history. Afterwards, when participants had been seated for at least 10 minutes, a trained nurse took BP measurements. An automatic BP monitor (Microlife BP 3BM1-3, Switzerland) measured systolic BP (SBP) and diastolic BP (DBP) in the supported left arm of the seated participant. The monitor automatically takes 3 consecutive readings and calculates an averaged result. BP measurements were taken during the first PHC visit (before randomization) and at each subsequent visit (approximately 20, 26, 30, 34, and 38 weeks GA), totaling 6 serial BP measurements. Figure 1 depicts a detailed breakdown of the study flow and data collection.

All data were collected on paper case report forms by staff and entered into Dell tablets (Venue 8 pro) on the same day. Two additional data technicians verified the data entered into the tablet with the paper copies. All data were synced to a secure server at Healthy Life for All Foundation (Ibadan, Nigeria) and sent to a secure site at the University of Chicago weekly, where a biostatistician checked again for completeness and anomalies. The field team corrected flagged erroneous values.

Data Analysis. Baseline categorical data are summarized by frequency distributions, while continuous variables are summarized by mean, standard deviation (SD), and range. Analysis of longitudinal BP measurements was performed using mixed-effects regression models.⁽³⁶⁾ Two different models were fitted. The first grouped the post-randomization data by visit and used the pre-intervention BP as a covariate. Subjects were treated as a random effect

(allowing for correlation within subject). Fixed effects were a group indicator variable (ethanol vs. control), visit, and group-by visit interaction terms. Letting y_{ij} denote the measurement for subject i at post-intervention visit j ($j = 2, 3, \dots, 6$), the model is

$$y_{ij} = \beta_1 y_{i1} + (\beta_2 + \beta_{2T}\delta)v_{ij2} + (\beta_3 + \beta_{3T}\delta)v_{ij3} + \dots + (\beta_6 + \beta_{6T}\delta)v_{ij6} + a_i + \epsilon_{ij} \quad (1)$$

where y_{i1} is the baseline BP obtained at pre-intervention visit 1, δ is an indicator variable for treatment group, $v_{ij2}, v_{ij3}, \dots, v_{ij6}$ are indicator variables specifying the visit number at which the measurement was obtained, a_i is the random subject effect, and ϵ_{ij} is residual error. Under this parameterization, $\beta_{2T}, \beta_{3T}, \beta_{4T}, \beta_{5T}$, and β_{6T} are the treatment group differences at visits 2, 3, 4, 5, and 6, respectively. A joint test of the null hypothesis $\beta_{2T} = \beta_{3T} = \beta_{4T} = \beta_{5T} = \beta_{6T} = 0$, based on five degrees-of-freedom (df), was performed to determine the statistical significance of the effect of the intervention.

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Because BP is known to decrease, then rise during pregnancy (37, 38), we also fit a mixed effects model quadratic in time, using the exact date of each visit relative to the date of randomization. This model, which included both random subject intercept and slope terms, is given by

$$y_{ij} = \beta_0 + \beta_1 y_{i1} + \beta_2 \delta + (\beta_3 + \beta_4 \delta)t_{ij} + (\beta_5 + \beta_6 \delta)t_{ij}^2 + a_i + b_i t_{ij} + \epsilon_{ij}, \quad (2)$$

where y_{i1} is the baseline BP treated as a covariate, a_i and b_i are the random intercept and slope for subject i , and ϵ_{ij} is the residual error. This model is less robust than model (1), but provides a potentially more powerful, three degrees-of-freedom test of the overall treatment effect ($\beta_2 = \beta_4 = \beta_6 = 0$). We assessed whether the quadratic model provided a good fit to the data by examining the trend in BPs over time using a locally weighted smoother (LOWESS) (44) and by examining residual diagnostic plots from the fitted regression curves. Models (1) and (2) were compared using the Akaike information criterion (AIC).

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The primary analyses compared the ethanol (E) and control (C) arms. However, the firewood and kerosene groups were recruited from different areas within Ibadan. Kerosene users were primarily urban, while firewood users mostly lived in peri-urban areas. To investigate the impact of possible differences in ambient exposures, lifestyle differences, and different traditional cooking fuels, subgroup analyses are presented in addition to the main comparison. Baseline kerosene users randomized to ethanol are denoted as group K→E (switched from kerosene to ethanol), and baseline kerosene users randomized to control (continued kerosene use) as K→K. Similarly, baseline firewood users randomized to ethanol or control, are denoted F→E and F→F, respectively. Subgroup analyses compared ethanol to kerosene among the subgroup of kerosene users at baseline (K→E vs. K→K), and ethanol to firewood among the subgroup of firewood users at baseline (F→E vs. F→F).

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In addition to longitudinal analysis of BP measurements, patients were categorized as normal (SBP <120 and DBP <80 mmHg), pre-hypertensive (SBP 120-139 or DBP 80-89 mmHg), or hypertensive (SBP ≥ 140 and/or DBP ≥ 90 mmHg) at their final prenatal visit. Fisher's exact test was performed to compare frequencies across the three classes in the two treatment arms (3x2 table) as well as the number of frankly hypertensive women in each group (i.e., hypertensive vs. pre-hypertensive/normal).

Results

Study Population. In total, 324 women were randomized into the trial, 162 to ethanol and 162 to control. This study population consisted of 215 baseline kerosene users randomized to ethanol (K→E: n=111) or kerosene (K→K: n=104), and 109 baseline firewood users randomized to ethanol (F→E: n=51) or firewood (F→F: n=58).

Table 1 shows baseline clinical and demographic variables by intervention arm. Overall, few participants had diabetes and most had two or fewer children at enrollment. Mean age was approximately 28 years (range 14-42). Mean body mass index (BMI) was approximately 24 kg/m² (range 14-45). Education varied from none to beyond high school. Mean GA at entry was 13 weeks. Over 25% of the women had prior miscarriage, and 8% had prior stillbirth. Randomization resulted in similar baseline distributions in the ethanol and control arms. Of note, baseline firewood users tended to reside in peri-urban regions (69% vs. 13%), had more children (8.2% with >4 children vs. 2.8%), and received less education (56% none vs. 22%) than baseline kerosene users.

Table 2 provides descriptive statistics on BP levels over time. Supplemental Table S1 provides the same statistics stratified by type of stove use at entry. Mean BP values decreased and then rose to baseline levels or higher over the course of the pregnancy. Figures 2A and 2B show plots of individual BP values vs. time since randomization for SBP and DBP, respectively. The solid lines are LOWESS curves depicting the overall trend in BP over time in the two treatment groups. The curves confirm the expected pattern of decline in BP during early-to-mid pregnancy followed by a rise during the third trimester. Mean values (\pm SE) grouped by visit number are shown in Figures 3A and 3B. From the mixed effects model (1), the post-randomization differences in SBP between the ethanol and control groups are not statistically significant adjusting for the baseline (pre-intervention) values ($\chi^2_5 = 1.93, p=0.86$). The DBP profiles, however, differed significantly between the two groups ($\chi^2_5 = 11.66, p=0.040$). Results obtained from fitting the quadratic model (2) were similar (SBP: $\chi^2_3 = 1.57, p=0.67$; DBP: $\chi^2_3 = 10.19, p=0.017$). Based on the AIC criterion, in both instances the quadratic model provided the better fit, but the basic findings are the same.

Analysis of mean BPs at the final time point (visit 6) also yielded similar results. SBPs were not significantly different (mean \pm SEM, E: 111.5 ± 0.99 mmHg vs. C: 112.8 ± 1.20 mmHg, $p=0.40$ by two-sample t test), whereas mean DBPs differed significantly (E: 70.1 ± 0.70 mmHg vs. C: 72.9 ± 0.87 mmHg, $p=0.014$).

Results of analyses of the subgroup of participants who were kerosene users at baseline are summarized in Figures 4A and 4B for SBP and DBP, respectively. (Scatter and LOWESS plots are available as Supplemental Figures 1A and 1B.) There was no statistically significant intervention effect on SBP (model 1 $\chi^2_5 = 2.75$, $p=0.74$; model 2 $\chi^2_3 = 0.91$, $p=0.82$) but there was a significant effect for DBP (model 1 $\chi^2_5 = 12.29$, $p=0.031$; model 2 $\chi^2_3 = 10.40$, $p=0.016$). The mean difference in DBP between the ethanol and control arms at the final visit was 3.6 mmHg among baseline kerosene users (mean \pm SEM, E: 70.9 ± 0.85 vs. C: 74.5 ± 1.16 , $p=0.011$). Figures 5A and 5B (and supplemental Figures 2A and 2B) show results for the subgroup of firewood users at baseline. No statistically significant differences emerged for either SBP (model 1 $\chi^2_5 = 4.69$, $p=0.45$; model 2 $\chi^2_3 = 3.44$, $p=0.33$) or DBP (model 1 $\chi^2_5 = 5.24$, $p=0.39$; model 2 $\chi^2_3 = 2.09$, $p=0.55$).

Table 3 shows the number of participants with normal BP, pre-hypertension, or hypertension at their last prenatal visit. Hypertensives were further subdivided according to systolic hypertension, diastolic hypertension, or both. The percentage of participants with hypertension in the different intervention groups was compared using Fisher's exact test. The results parallel those above from the longitudinal analyses. In the overall ethanol and control comparison, there was a borderline significant difference in the proportion of patients with hypertension, with fewer in the ethanol group than in the control arm (1.9% vs. 6.4%,

$p=0.051$). This difference reached statistical significance in the subgroup of baseline kerosene users ($p=0.029$). Results from the 3x2 table analyses (normal, pre-hypertensive, or hypertensive by treatment group) were slightly weaker but still favored the ethanol group. Only one woman in each intervention arm was hypertensive at the last prenatal visit within the subgroup of baseline firewood users.

Discussion

There have been several epidemiologic studies on HAP and BP, including a recent paper by Quinn et al. (39) highlighting the positive association between exposure to carbon monoxide and DBP in pregnant women.(21-24, 39, 40) However, this study is the first cookstove RCT to examine serial BP levels of pregnant women. Study results reveal statistically significant differences in DBP profiles when comparing pregnant women in intervention and control arms ($p=0.0051$). Lower BP during late pregnancy was observed among the ethanol users compared to control subjects. Subgroup analyses indicate that this difference is driven by BP differences between kerosene users randomized to ethanol versus kerosene users in the control group.

For uncomplicated pregnancies, SBP and DBP decrease in early and mid-pregnancy, but sustained increases in both SBP and DBP occur during the 3rd trimester through the post-partum period.(37, 38) Rebelo and colleagues (38) found that excessive weight gain early in pregnancy was associated with greater increases in both SBP and DBP. In our cohort, similar physiologic changes in both SBP and DBP were observed in the ethanol and control arms during pregnancy. However, the women in the intervention group who were younger than women in the Brazilian study conducted by Rebelo et al. and had normal BMI had significantly lower DBP at the end of pregnancy relative to controls.(38) A higher percentage

of women in the control group also developed systolic and diastolic hypertension near delivery.(38)

Compared to other studies of HAP and BP, our finding of a difference of approximately 3 mmHg in DBP is similar to that previously reported in McCracken et al.'s RCT.(23)

However, their study (23) focused on elderly women with low BP over an 18-month period, where SBP was also reduced. A reduction in BP, beginning at about 100-120 days post-randomization (30-34 weeks gestation) and rising to approximately 3 mmHg toward the end of pregnancy, is clinically significant, as it has the potential to reduce the risks of cardiovascular complications such as preeclampsia and eclampsia that can lead to adverse pregnancy outcomes. The reduction of BP to this degree has not been previously observed in a cookstove RCT that involved a young cohort such as this one.

Most investigations of the health effects of HAP have focused on biomass fuels, but recently, there has been a surge in evidence pointing toward the toxicity of kerosene. In a cross-sectional study conducted in Bangalore, India, Choi et al. (41) found an increased risk of respiratory illness associated with kerosene fuel use among urban-dwelling women relative to those cooking with liquid petroleum gas (LPG).(41) Bates and colleagues (42) investigated the association between household cooking fuel type and acute lower respiratory infections (ALRI) in young children in Nepal.(42) Their case-control study showed a positive association between 3 fuel types (LPG, kerosene, and biomass) and ALRI relative to use of electricity for cooking. Notably, the odds ratio (OR) for kerosene stove use compared to electricity was similar to the OR for biomass stove use compared to electricity (2.33; 95% CI: 1.40, 3.86 and 2.13; 95% CI: 1.34, 3.41, respectively). Additionally, a study conducted in Nepal by Pokhrel and colleagues (7) on the risk factors for pulmonary tuberculosis reported

stronger associations with kerosene cooking (OR = 3.36; 95% CI: 1.01, 11.22) than cooking with biomass (OR = 1.21; 95% CI: 0.48, 3.05).(7)

These studies, and others, have led WHO to discourage the use of kerosene for household cooking until further research is conducted.(1) This RCT provides further evidence on kerosene's detrimental health effects. Specifically, this is the first study to demonstrate elevated BP levels in pregnant women using kerosene for cooking compared to cooking with an ethanol stove that meets ISO IWA tier 4 cookstove performance standards for indoor emissions.(43)

This study demonstrates that clean cookstove interventions have the potential to impact the health of pregnant women, though intervention is both a challenging task and a complex process.(44) This is true even in urban settings where ambient concentrations of PM can be high enough to potentially reduce the impact of a clean-burning cookstove on personal exposures.

A limitation of the study is the smaller number of firewood users enrolled into the trial. As a consequence, the lack of any statistically significant difference in favor of ethanol in this subgroup may be due to insufficient power. Additionally, as part of the education program, both groups were informed about potential harmful effects of smoke exposure, and the control group was encouraged to cook in ventilated rooms or outside to reduce their exposure. The training given to the control group may have artificially lowered their exposure throughout the duration of the study; however, this cannot be verified, as everyone in the control group received this education. Although not shown here, more stacking (combining usage of the intervention stoves with the traditional ones) was observed in firewood users

randomized to ethanol than kerosene users randomized to ethanol, potentially decreasing the impact of the intervention on firewood users. This is likely due to the differences in cooking styles of firewood users compared to kerosene users.

Another limitation is that, over time, the number of patients with blood pressure readings available declined from $n=320$ at baseline to $n=286$ at visit 6 (approximately 11%). The mixed effects regression model assumes that these values are "missing at random (MAR)," which means that the missingness is unrelated to the true (but unobserved) value, although it can depend on previous observed values and therefore with longitudinal data MAR is not considered a restrictive assumption. MAR would be violated if, for example, patients with high (low) blood pressure dropped out of the study before their elevated (reduced) pressures were observed.

A strength of these findings is that the differences in longitudinal profiles in DBP were followed by borderline significant (primary comparison) or significant (kerosene subgroup) differences in the rates of evident hypertension. These differences occurred after only 6 months of cookstove use in a relatively young cohort, which shows the potential for the CleanCook stove to impact health in a relatively short timeframe. A weakness is the lack of a concomitant significant difference in SBP, although SBP levels were consistently higher in the control arm.

Hypertension during pregnancy is a risk factor for numerous health effects including preterm delivery and small-for-gestational-age babies and is a leading cause of maternal and perinatal mortality. The statistically significant difference in rates of hypertension between control and intervention groups illustrate the damaging impact of prenatal HAP exposure and may

explain why HAP has been associated with an increased risk of low birthweight and stillbirth in meta-analysis.(29, 45, 46)

This paper provides evidence that cooking with an ethanol-burning cookstove can positively impact BP. This reduction not only reduces pregnancy risks, but also the wider burden of disease for those exposed to HAP.

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REFERENCES

1. WHO. Household air pollution and health. World Health Organization Fact Sheet; 2014.
2. Bonjour S, Adair-Rohani H, Wolf J, Bruce NG, Mehta S, Pruss-Ustun A, Lahiff M, Rehfuess EA, Mishra V, Smith KR. Solid fuel use for household cooking: country and regional estimates for 1980-2010. *Environ Health Perspect* 2013; 121: 784-790.
3. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, al. e. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1659-1724.
4. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, al e. A comparative risk assessment of burden of disease and injury attributable to 67 risk factor and risk factor clusters in 21 regions, 1990-2010: systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224-2260.
5. WHO | Global Burden of Disease (GBD) 2010. Available from: http://www.who.int/healthinfo/global_burden_disease/gbd/en/.
6. Lam NL, Smith KR, Gauthier A, Bates MN. KEROSENE: A REVIEW OF HOUSEHOLD USES AND THEIR HAZARDS IN LOW- AND MIDDLE-INCOME COUNTRIES.

- Journal of toxicology and environmental health Part B, Critical reviews* 2012; 15: 396-432.
7. Pokhrel AK, Bates MN, Verma SC, Joshi HS, Sreeramareddy CT, Smith KR. Tuberculosis and indoor biomass and kerosene use in Nepal: a case-control study. *Environ Health Perspect* 2010; 118: 558-564.
 8. Aimakhu CO, Olayemi O. Maternal haematocrit and pregnancy outcome in Nigerian women. *West Afr J Med* 2003; 22: 18-21.
 9. WHO. Frequently Asked Questions WHO guidelines for indoor air quality: household fuel combustion November 2014. 2014 [cited 2016 06/07]. Available from: http://www.who.int/indoorair/guidelines/hhfc/FAQs_Nov2014.pdf.
 10. Chuang K-J, Yan Y-H, Cheng T-J. Effect of air pollution on blood pressure, blood lipids, and blood sugar: a population-based approach. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine* 2010; 52: 258-262.
 11. Auchincloss AH, Diez Roux AV, Dvorchak JT, Brown PL, Barr RG, Daviglus ML, Goff DC, Kaufman JD, O'Neill MS. Associations between Recent Exposure to Ambient Fine Particulate Matter and Blood Pressure in the Multi-Ethnic Study of Atherosclerosis (MESA). *Environmental Health Perspectives* 2008; 116: 486-491.
 12. Kateryna F, Sabine H, Anja V, Michael N, Susanne M, Hermann J, Christoph K, Raimund E, Karl-Heinz J, Barbara H. Long-term Urban Background Particulate Air Pollution Increases Arterial Blood Pressure. A48 AIR POLLUTION AND CARDIOVASCULAR DISEASE, UPDATE ON MECHANISMS AND EPIDEMIOLOGY: American Thoracic Society, 2010, p. A1712-A1712.
 13. Fuks K, Moebus S, Hertel S, Viehmann A, Nonnemacher M, Dragano N, Möhlenkamp S, Jakobs H, Kessler C, Erbel R. Long-term urban particulate air pollution, traffic noise, and arterial blood pressure. *Environmental Health Perspectives* 2011; 119: 1706.
 14. Schwartz J, Alexeeff SE, Mordukhovich I, Gryparis A, Vokonas P, Suh H, Coull BA. Association between long-term exposure to traffic particles and blood pressure in the Veterans Administration Normative Aging Study. *Occupational and environmental medicine* 2012; 69: 422-427.
 15. Davdand P, Ostro B, Figueras F, Foraster M, Basagaña X, Valentín A, Martínez D, Beelen R, Cirach M, Hoek G. Residential proximity to major roads and term low birth weight: the roles of air pollution, heat, noise, and road-adjacent trees. *Epidemiology* 2014; 25: 518-525.
 16. Brook RD, Rajagopalan S, Pope CAI, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010; 121: 224-230.
 17. Schultz ES, Hallberg J, Bellander T, Bergström A, Bottai M, Chiesa F, Gustafsson PM, Gruziova O, Thunqvist P, Pershagen G, Melén E. Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence. *American Journal of Respiratory and Critical Care Medicine* 2015; 193: 171-177.
 18. Chuang K-J, Chan C-C, Su T-C, Lee C-T, Tang C-S. The Effect of Urban Air Pollution on Inflammation, Oxidative Stress, Coagulation, and Autonomic Dysfunction in Young Adults. *American Journal of Respiratory and Critical Care Medicine* 2007; 176: 370-376.
 19. Lee M-S, Hang J, Zhang F, Dai H, Su L, Christiani DC. In-home solid fuel use and cardiovascular disease: a cross-sectional analysis of the Shanghai Putuo study. *Environ Health* 2012; 11: 1-8.
 20. Dutta A, Ray MR. Hypertension and respiratory health in biomass smoke-exposed premenopausal Indian women. *Air Qual Atmos Health* 2014; 7: 229-238.

21. Baumgartner J, Schauer JJ, Ezzati M, Lu L, Cheng C, Patz JA, Bautista LE. Indoor air pollution and blood pressure in adult women living in rural china. *Environ Health Perspect* 2011; 119: 1390-1395.
22. Alexander D, Larson T, Bolton S, Vedal S. Systolic blood pressure changes in indigenous Bolivian women associated with an improved cookstove intervention. *Air Quality, Atmosphere & Health* 2014; 8: 47-53.
23. McCracken JP, Smith KR, Diaz A, Mittleman MA, Schwartz J. Chimney stove intervention to reduce long-term wood smoke exposure lowers blood pressure among Guatemalan women. *Environ Health Perspect* 2007; 115: 996-1001.
24. Clark ML, Bachand AM, Heiderscheidt JM, Yoder SA, Luna B, Volckens J, Koehler KA, Conway S, Reynolds SJ, Peel JL. Impact of a cleaner-burning cookstove intervention on blood pressure in Nicaraguan women. *Indoor Air* 2013; 23: 105-114.
25. Mutlu GM, Green D, Bellmeyer A, Baker CM, Burgess Z, Rajamannan N, Christman JW, Foiles N, Kamp DW, Ghio AJ, Chandel NS, Dean DA, Sznajder JI, Budinger GR. Ambient particulate matter accelerates coagulation via an IL-6-dependent pathway. *The Journal of clinical investigation* 2007; 117: 2952-2961.
26. Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, Lee LM, Okabe K, Verrier RL, Godleski JJ. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. *Environmental Health Perspectives* 2009; 117: 361-366.
27. Buchbinder A, Sibai BM, Caritis S, Macpherson C, Hauth J, Lindheimer MD, Klebanoff M, Vandorsten P, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G, Units NJoCHaHDNoM-FM. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. *American Journal of Obstetrics and Gynecology* 2002; 186: 66-71.
28. van Middendorp D, ten Asbroek A, Bio FY, Edusei A, Meijjer L, Newton S, Agyemang C. Rural and urban differences in blood pressure and pregnancy-induced hypertension among pregnant women in Ghana. *Globalization and Health* 2013; 9: 59.
29. Pope DP, Mishra V, Thompson L, Siddiqui AR, Rehfuess EA, Weber M, Bruce N. Risk of low birth weight and stillbirth associated with indoor air pollution from solid fuel use in developing countries. *Epidemiol Rev* 2010; 32: 70-81.
30. Gall ET, Carter EM, Earnest CM, Stephens B. Indoor air pollution in developing countries: research and implementation needs for improvements in global public health. *American Journal of Public Health* 2013; 103: e67-72.
31. Romieu I, Riojas-Rodriguez H, Marron-Mares AT, Schilman A, Perez-Padilla R, Masera O. Improved biomass stove intervention in rural Mexico: impact on the respiratory health of women. *Am J Respir Crit Care Med* 2009; 180: 649-656.
32. Organization WH. Indoor Air Quality Guidelines: Household Fuel Combustion. 2014.
33. Brauer M, Bartlett K, Regalado-Pineda J, Perez-Padilla R. Assessment of Particulate Concentrations from Domestic Biomass Combustion in Rural Mexico. *ENVIRONMENTAL SCIENCE & TECHNOLOGY* 1996; 30: 104-109.
34. Alexander D, Northcross A, Pandya R, Adu D, Ibigbami T, Olajumilo J, Karrison T, Ojengbede O, Olopade C. RANdomized controlled study of bioethanol stove intervention on blood pressure changes during pregnancy in nigerian women. *Chest* 2015; 148: 763A-763A.
35. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Controlled Clinical Trials* 1988; 9: 327-344.
36. Diggle P, Heagerty P, Liang K-Y, Zeger S. Analysis of longitudinal data. OUP Oxford; 2013.

37. Hermida RC, Ayala DE, Mojon A, Fernandez JR, Alonso I, Silva I, Uceda R, Iglesias M. Blood pressure patterns in normal pregnancy, gestational hypertension, and preeclampsia. *Hypertension (Dallas, Tex : 1979)* 2000; 36: 149-158.
38. Rebelo F, Farias DR, Mendes RH, Schlüssel MM, Kac G. Blood Pressure Variation Throughout Pregnancy According to Early Gestational BMI: A Brazilian Cohort. *Arquivos Brasileiros de Cardiologia* 2015; 104: 284-291.
39. Quinn AK, Ae-Ngibise KA, Jack DW, Boamah EA, Enuameh Y, Mujtaba MN, Chillrud SN, Wylie BJ, Owusu-Agyei S, Kinney PL, Asante KP. Association of Carbon Monoxide exposure with blood pressure among pregnant women in rural Ghana: Evidence from GRAPHs. *International journal of hygiene and environmental health* 2016; 219: 176-183.
40. Norris C, Goldberg MS, Marshall JD, Valois M-F, Pradeep T, Narayanswamy M, Jain G, Sethuraman K, Baumgartner J. A panel study of the acute effects of personal exposure to household air pollution on ambulatory blood pressure in rural Indian women. *Environmental Research* 2016; 147: 331-342.
41. Choi J-Y, Baumgartner J, Harnden S, Alexander BH, Town RJ, D'Souza G, Ramachandran G. Increased risk of respiratory illness associated with kerosene fuel use among women and children in urban Bangalore, India. *Occupational and Environmental Medicine* 2014; oemed-2014-102472.
42. Bates MN, Chandyo RK, Valentiner-Branth P, Pokhrel AK, Mathisen M, Basnet S, Shrestha PS, Strand TA, Smith KR. Acute lower respiratory infection in childhood and household fuel use in Bhaktapur, Nepal. *Environ Health Perspect* 2013; 121: 637-642.
43. IWA. Guidelines for evaluating cookstove performance. 2012 [cited 2016 May 2]. Available from: http://www.iso.org/iso/catalogue_detail?csnumber=61975.
44. Naeher LP. Biomass-fueled intervention stoves in the developing world: potential and challenges. *Am J Respir Crit Care Med* 2009; 180: 586-587.
45. Lee P-C, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. *Maternal and child health journal* 2013; 17: 545-555.
46. van den Hooven EH, de Kluizenaar Y, Pierik FH, Hofman A, van Ratingen SW, Zandveld PY, Mackenbach JP, Steegers EA, Miedema HM, Jaddoe VW. Air pollution, blood pressure, and the risk of hypertensive complications during pregnancy the generation R study. *Hypertension (Dallas, Tex : 1979)* 2011; 57: 406-412.

Tables

Table 1. Baseline Demographic and Clinical Distributions by Intervention Arm

| Variable | Ethanol (n = 162) | Control (n = 162) |
|-------------------------------|------------------------------|------------------------------|
| Clinic | | |
| Agbongbon | 76 (47.2%) | 68 (42.2%) |
| Olorisaoko | 43 (26.7%) | 47 (29.2%) |
| Oranyan | 42 (26.1%) | 46 (28.6%) |
| Missing | 1 | 1 |
| Diabetic | | |
| Yes | 2 (1.2%) | 3 (1.9%) |
| No | 159 (98.8%) | 158 (98.1%) |
| Missing | 1 | 1 |
| Number of Children | | |
| 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 | | |
| Single | 17 (10.6%) | 7 (4.3%) |
| Married | 143 (88.8%) | 155 (95.7%) |

| | | |
|-------------------------------|-------------|---------------|
| Separated | 1 (0.6%) | 0 (0.0%) |
| Missing | 1 | 0 |
| Age (years) | | |
| Mean, SD | 28.0, 6.1 | 27.9, 5.4 |
| (range) | (15 – 44) | (14 – 42) |
| Missing | 10 | 12 |
| BMI (kg/m²) | | |
| Mean, SD | 23.2, 4.2 | 24.7, 5.3 |
| (range) | (14.2-36.2) | (17.1 – 45.0) |
| Missing | 10 | 12 |
| Education Level | | |
| None | 51 (31.7%) | 58 (35.8%) |
| Primary | 16 (9.9%) | 17 (10.5%) |
| School | | |
| Junior | 9 (5.6%) | 13 (8.0%) |
| Secondary | | |
| Senior | 68 (42.2%) | 60 (37.0%) |
| Secondary | | |
| 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 |
| Literate | | |
| Yes | 100 (62.1%) | 92 (56.8%) |

| | | |
|---|--------------|--------------|
| No | 61 (37.9%) | 70 (43.2%) |
| Missing | 1 | 0 |
| Gestational Age at Entry (weeks) | | |
| Mean, SD | 12.9, 3.0 | 13.1, 3.0 |
| (range) | (6.7 – 18.0) | (7.1 – 18.0) |
| Missing | 3 | 5 |
| Prior Miscarriage | | |
| Yes | 43 (26.7%) | 47 (29.0%) |
| No | 118 (73.3%) | 115 (71.0%) |
| Missing | 1 | 0 |
| # of Miscarriages | | |
| None | 118 (73.3%) | 115 (71.0%) |
| 1 | 30 (18.6%) | 36 (22.2%) |
| 2 | 10(6.2%) | 7 (1.8%) |
| => 3 | 3 (1.9%) | 4 (2.5%) |
| Missing | 1 | 0 |
| Prior Stillbirth | | |
| Yes | 12 (7.4%) | 14 (8.6%) |
| No | 149 (92.6%) | 148 (91.4%) |
| Missing | 1 | 0 |

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Table 2. Mean Systolic and Diastolic Blood Pressure at Each Prenatal Visit

| | | Ethanol | | | Control | | |
|---------|-----|---------|-------|------|---------|-------|------|
| | | N | Mean | SD | N | Mean | SD |
| | | mm Hg | | | mm Hg | | |
| Visit 1 | SBP | 161 | 110.4 | 11.9 | 159 | 111.3 | 10.8 |
| | DBP | 161 | 69.2 | 9.5 | 159 | 70.0 | 10.3 |
| Visit 2 | SBP | 150 | 107.2 | 11.4 | 153 | 109.0 | 10.5 |
| | DBP | 150 | 66.7 | 8.3 | 153 | 66.3 | 8.6 |
| Visit 3 | SBP | 148 | 107.6 | 11.0 | 144 | 108.7 | 10.5 |
| | DBP | 148 | 67.1 | 7.9 | 144 | 67.3 | 8.0 |
| Visit 4 | SBP | 150 | 108.3 | 10.3 | 146 | 109.9 | 11.1 |
| | DBP | 151 | 66.5 | 9.1 | 146 | 68.2 | 8.2 |
| Visit 5 | SBP | 149 | 109.5 | 12.2 | 135 | 111.0 | 11.1 |
| | DBP | 148 | 68.9 | 8.3 | 135 | 70.0 | 9.0 |
| Visit 6 | SBP | 148 | 111.5 | 12.1 | 138 | 112.8 | 14.1 |
| | DBP | 148 | 70.1 | 8.6 | 137 | 72.9 | 10.2 |

SD: standard deviation; Visit 1: baseline, Visits 2-6: post randomization

Table 3. Prevalence of hypertension at last visit prior to delivery**A. Ethanol vs. Control**

| Arterial blood pressure | Ethanol (E) (n=158) ^a | Control (C) (n= 155) ^a | P value |
|---|--|---|--------------------|
| Normal (SBP <120 and DBP <80 mmHg) | 118 (74.7%) | 106 (68.0%) | |
| Pre-hypertension (SBP 120-139 and DBP 80-89 mmHg) | 37 (23.4%) | 39(25.2%) | |
| Hypertension (SBP ≥ 140 and/or DBP ≥ 90 mmHg) | 3 (1.9%) | 10 (6.4%) | 0.051 ^b |

Fisher's exact test, 3x2 table: p= 0.106

B. K→E vs. K→K

| Arterial blood pressure | (K→E) (n=110) ^a | (K→K) (n= 102) ^a | P value |
|---|--------------------------------------|---------------------------------------|--------------------|
| Normal (SBP <120 and DBP <80 mmHg) | 79 (71.8%) | 66 (64.7%) | |
| Pre-hypertension (SBP 120-139 and DBP 80-89 mmHg) | 29 (26.4%) | 27 (26.5%) | |
| Hypertension (SBP ≥ 140 and/or DBP ≥ 90 mmHg) | 2 (1.8%) | 9 (8.8%) | 0.029 ^b |

Fisher's exact test, 3x2 table: p=0.065

C. F→E vs. F→F

| Arterial blood pressure | (F→E) (n=48) ^a | (F→F) (n= 53) ^a | P value |
|---|---------------------------|-------------------------------|------------------|
| Normal (SBP <120 and DBP <80 mmHg) | 39 (81.2%) | 40 (75.5%) | |
| Pre-hypertension (SBP 120-139 and DBP 80-89 mmHg) | 8 (16.7%) | 12 (22.6%) | |
| Hypertension (SBP ≥ 140 and/or DBP ≥ 90 mmHg) | 1 (2.1%) | 1 (1.9%) | 1.0 ^b |

Fisher’s exact test, 3x2 table: p=0.81

^aNumbers differ from total enrolled due to missing data; ^bFisher’s exact test: Hypertensive vs.

non-hypertensive

Figure legends

Figure 1. Visual representation of study flow and data collection. The number randomized per treatment group and the number of subjects with blood pressure data available at each clinic visit are also shown.

Figure 2A. SBP by Time Since Randomization and LOWESS curves– All Participants (Red: Ethanol, Blue: Control).

Figure 2B. DBP by Time Since Randomization and LOWESS curves– All Participants (Red: Ethanol, Blue: Control).

Figure 3A. Mean SBP by Visit – All Participants (Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.

Figure 3B. Mean DBP by Visit – All Participants (Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.

Figure 4A. Mean SBP by Visit – Baseline Kerosene Users (Red: Ethanol, Blue: Control), Error bars indicate one standard error. BL: Baseline.

Figure 4B. Mean DBP by Visit – Baseline Kerosene Users (Red: Ethanol, Blue: Control), Error bars indicate one standard error. BL: Baseline.

Figure 5A. Mean SBP by Visit – Baseline Firewood Users (Red: Ethanol, Blue: Control), Error bars indicate one standard error. BL: Baseline.

Figure 5B. Mean DBP by Visit – Baseline Firewood Users (Red: Ethanol, Blue: Control), Error bars indicate one standard error. BL: Baseline.

Figure 1. Visual representation of study flow and data collection

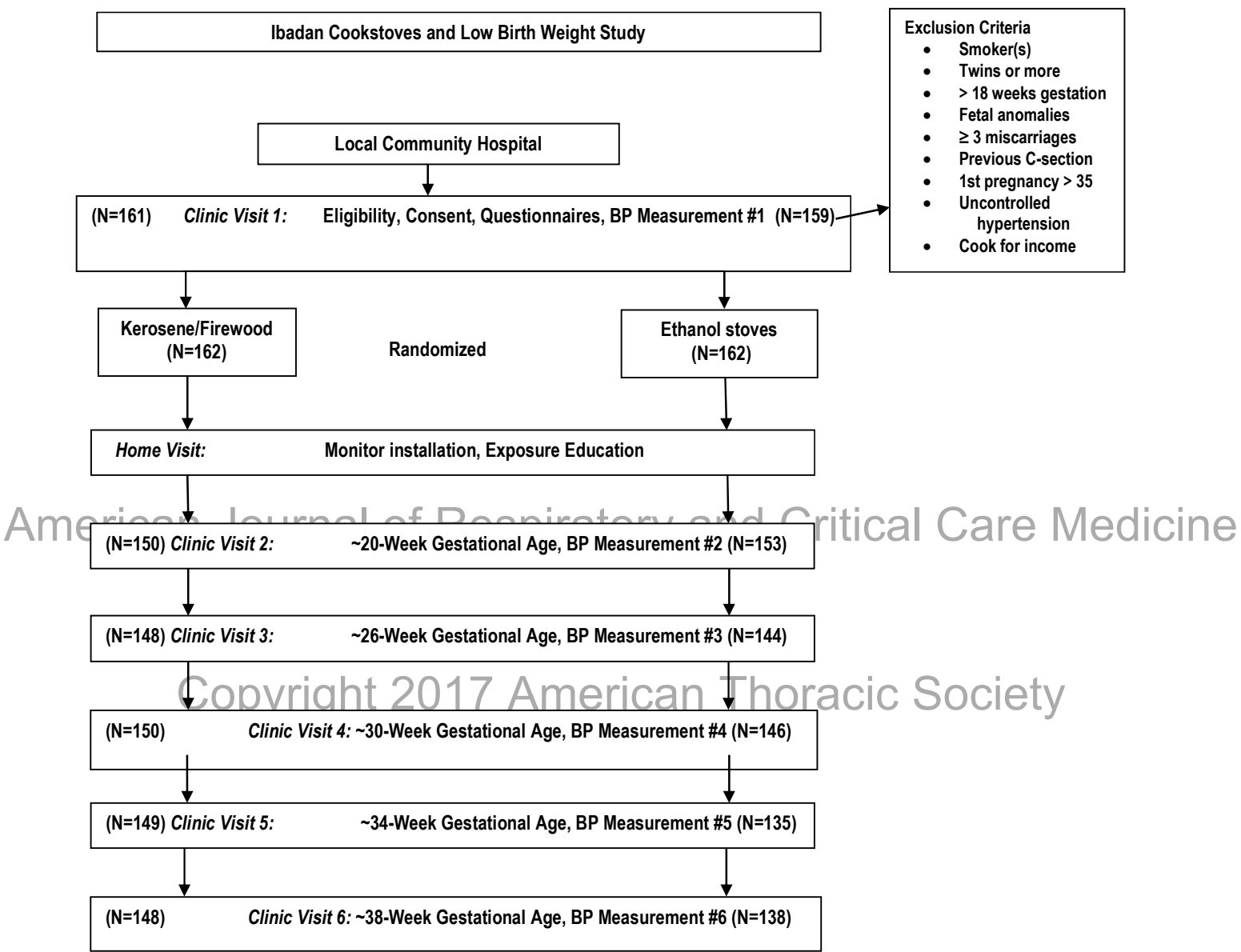
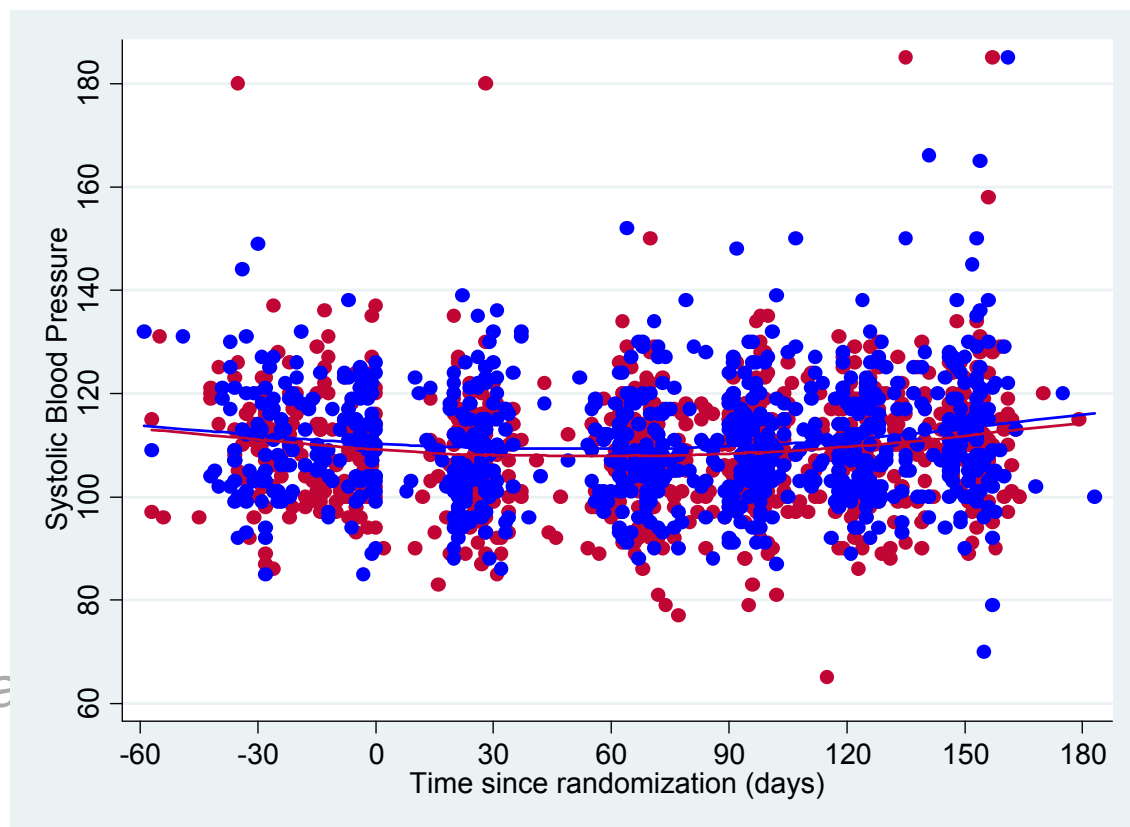
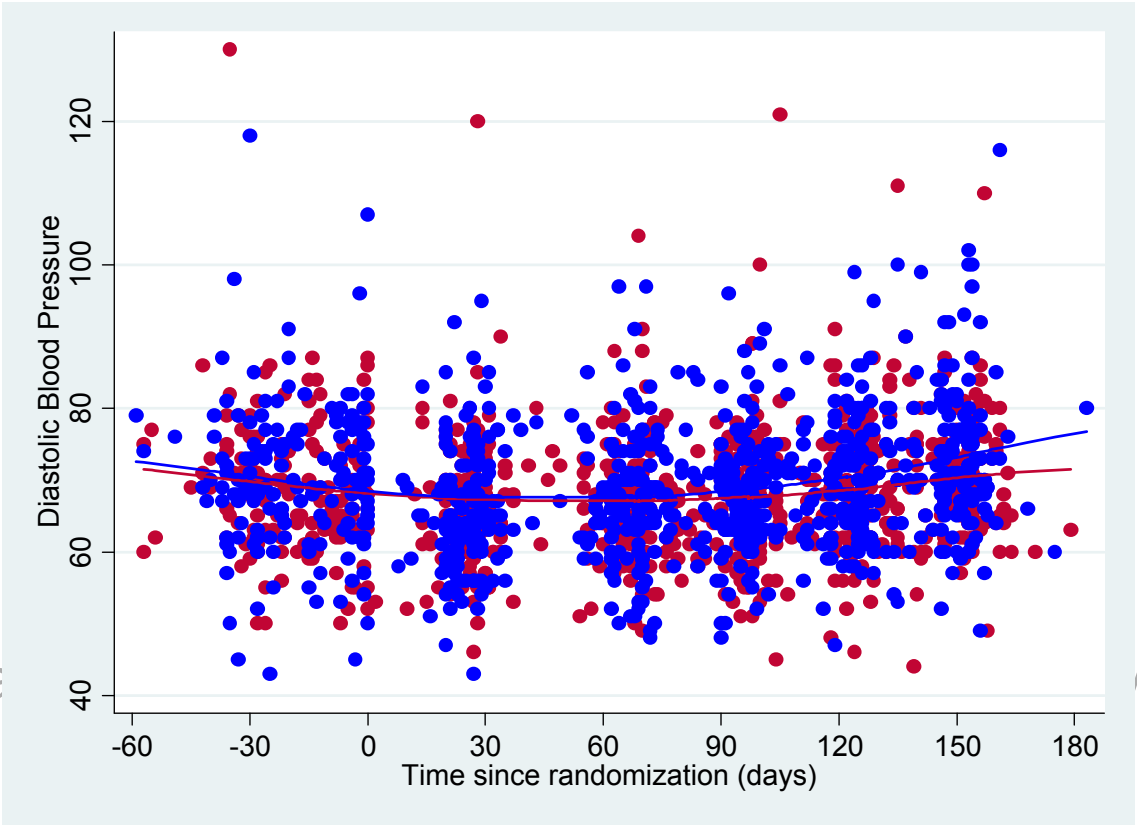


Figure 2A. SBP by Time Since Randomization and LOWESS Curves– All Participants (Red: Ethanol, Blue: Control).



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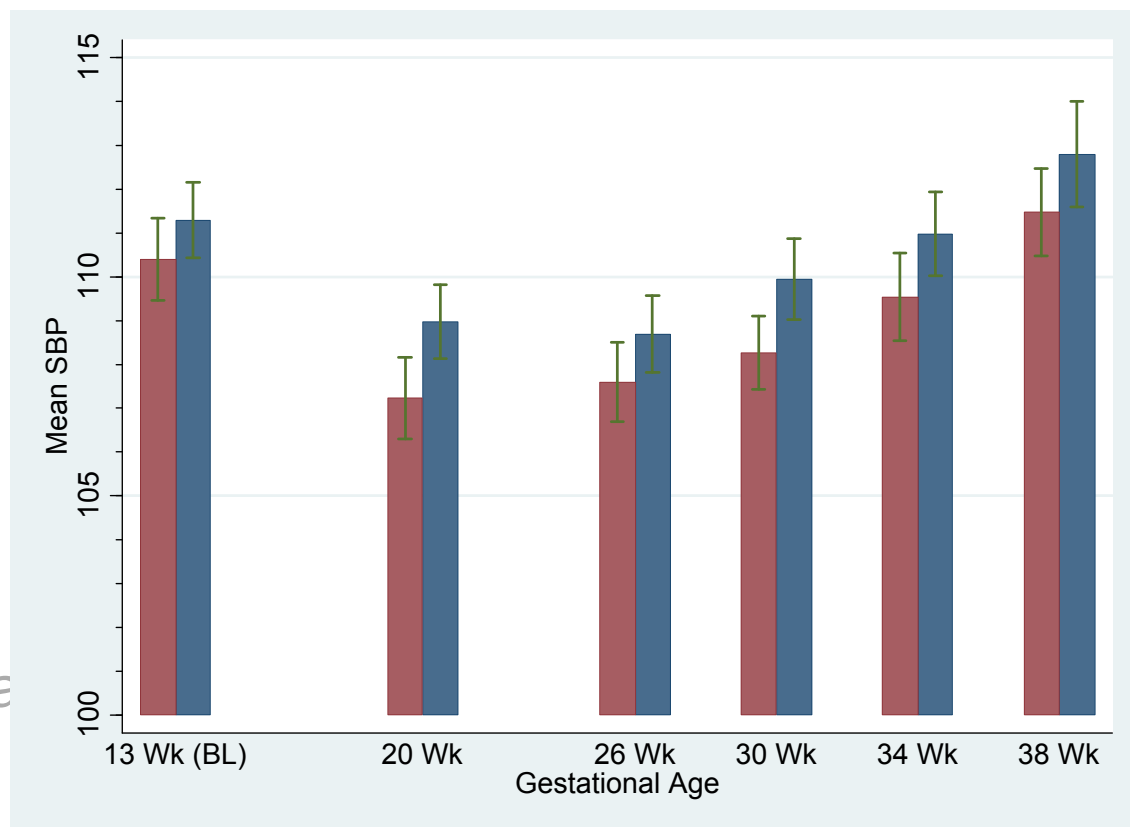
Figure 2B. DBP by Time Since Randomization and LOWESS Curves– All Participants (Red: Ethanol, Blue: Control).



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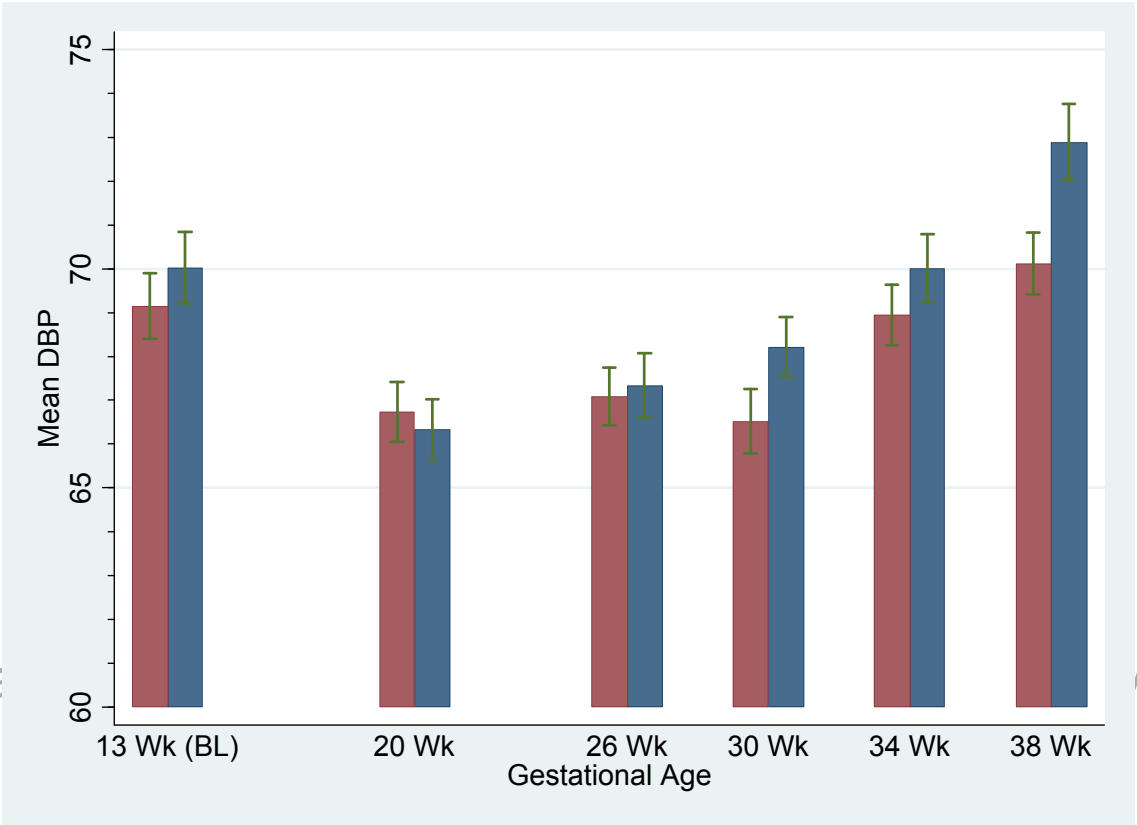
Figure 3A. Mean SBP by Visit – All Participants

(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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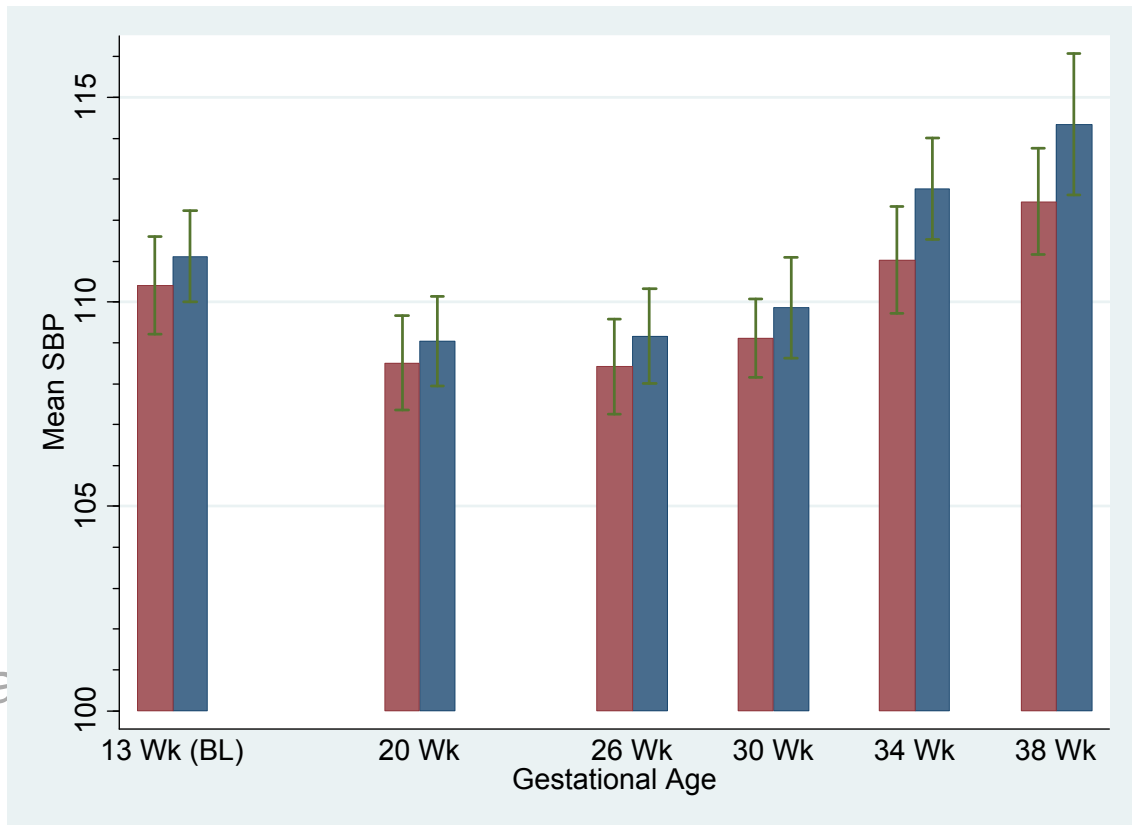
Figure 3B. Mean DBP by Visit – All Participants
(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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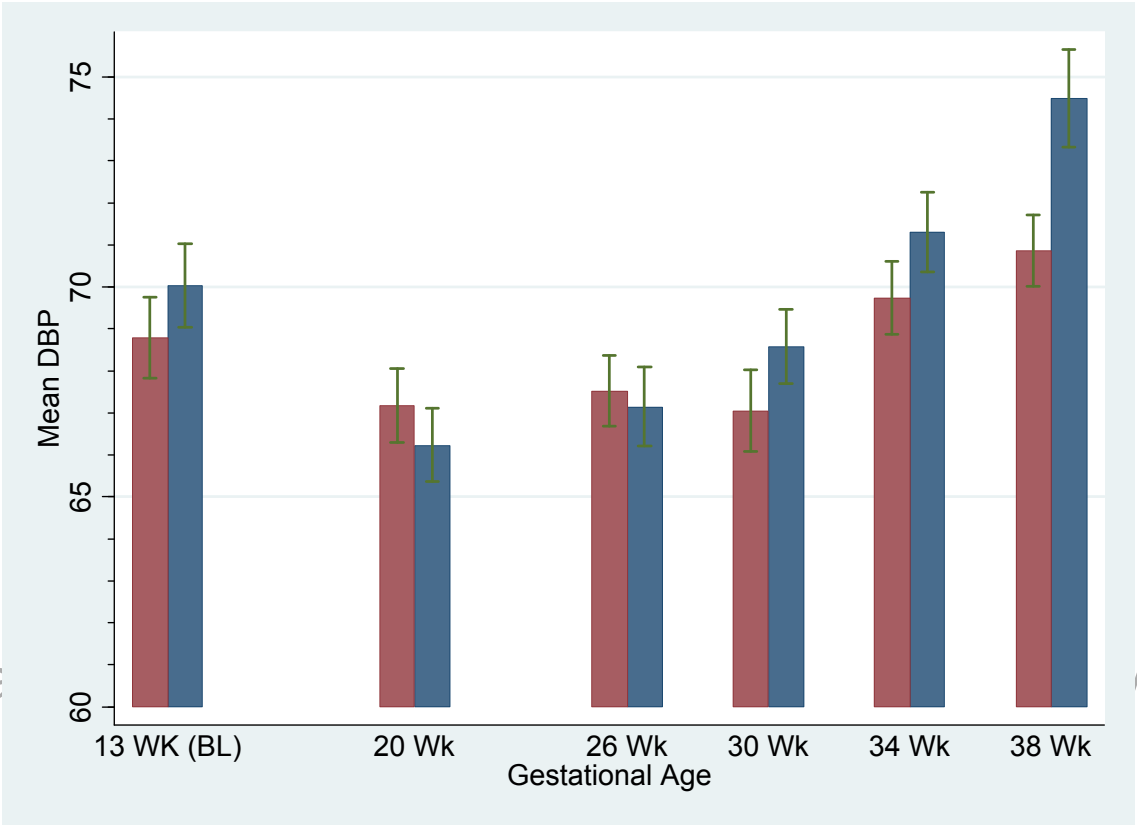
Figure 4A. Mean SBP by Visit – Baseline Kerosene Users

(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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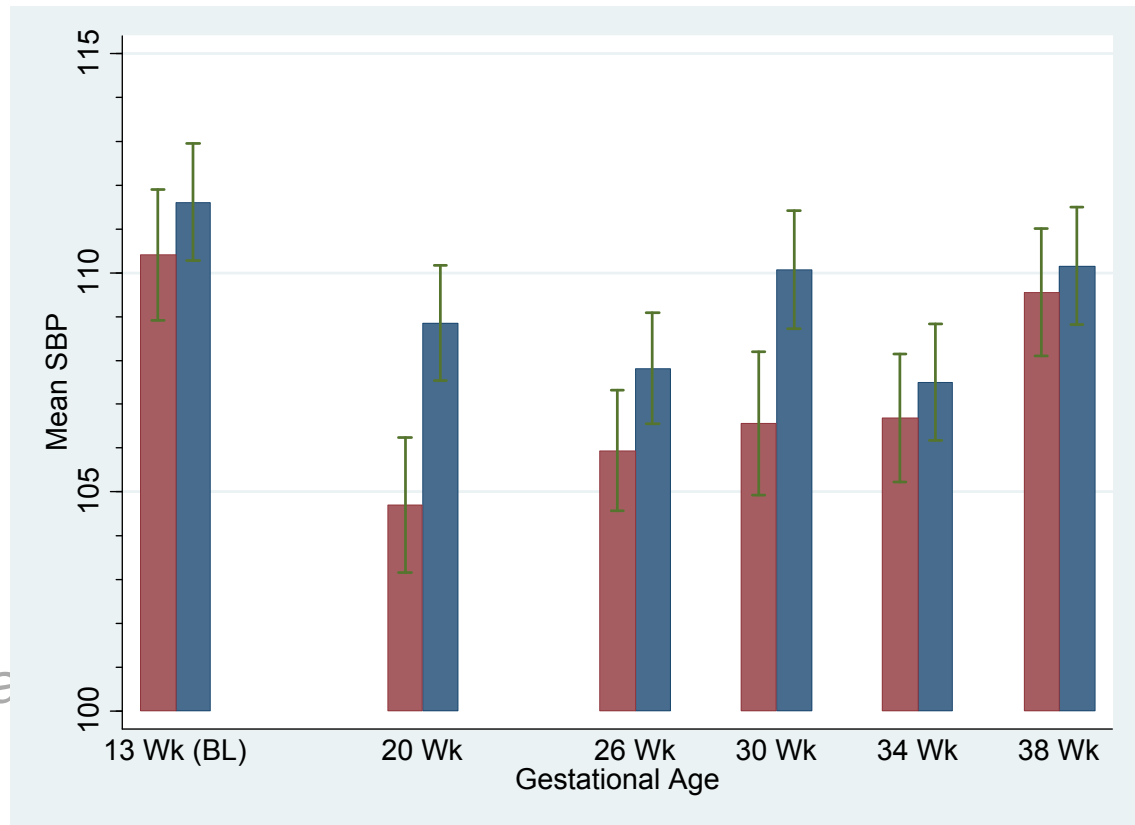
Figure 4B. Mean DBP by Visit – Baseline Kerosene Users
(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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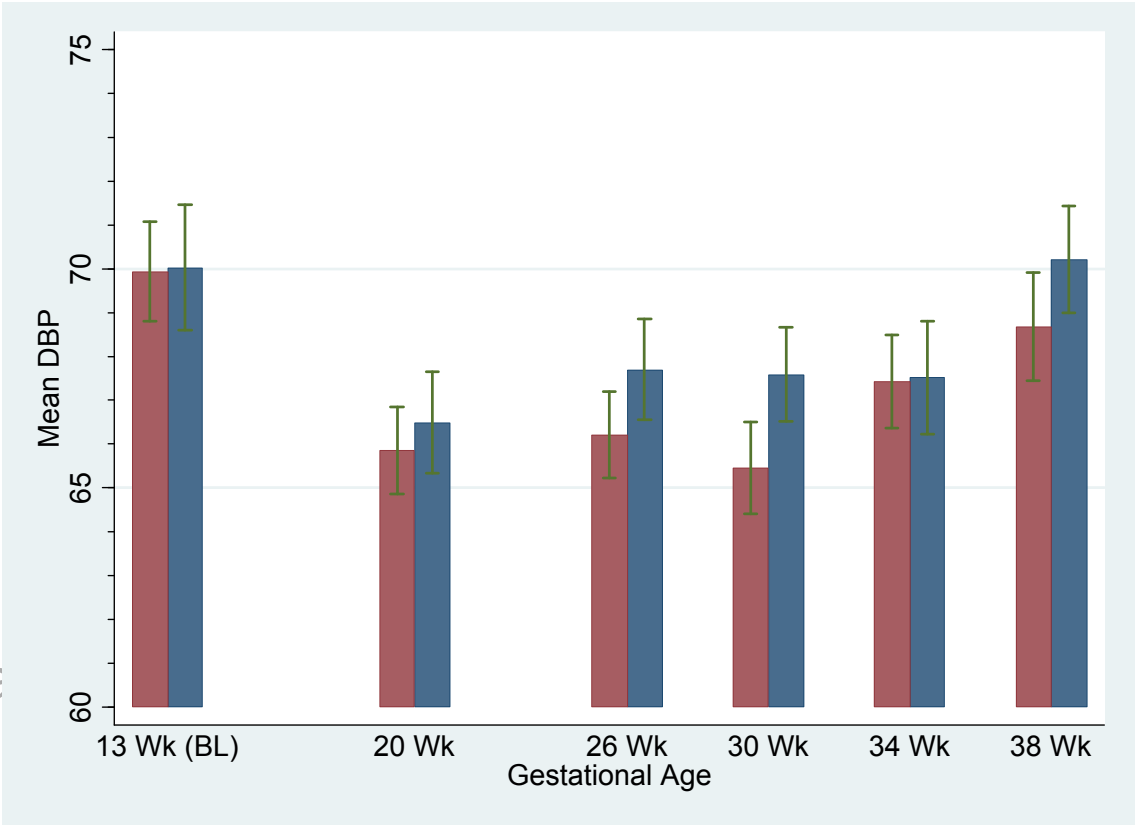
Figure 5A. Mean SBP by Visit – Baseline Firewood Users

(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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Figure 5B. Mean DBP by Visit – Baseline Firewood Users
(Red: Ethanol, Blue: Control). Error bars indicate one standard error. BL: Baseline.



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Supplemental Table S1. Mean Systolic and Diastolic Blood Pressure at Each Prenatal Visit by Stove Type at Entry.

| | | Baseline Kerosene Users | | | | | | Baseline Firewood Users | | | | | |
|---------|-----|-------------------------|-------|------|-------|-------|------|-------------------------|-------|------|-------|-------|------|
| | | K→E | | | K→K | | | F→E | | | F→F | | |
| | | N | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| | | mm Hg | | | mm Hg | | | mm Hg | | | mm Hg | | |
| Visit 1 | SBP | 110 | 110.4 | 12.5 | 102 | 111.0 | 11.2 | 51 | 110.4 | 10.6 | 57 | 111.6 | 10.1 |
| | DBP | 110 | 68.8 | 10.1 | 102 | 70.0 | 10.0 | 51 | 69.9 | 8.1 | 57 | 70.0 | 10.8 |
| Visit 2 | SBP | 100 | 108.5 | 11.5 | 98 | 109.0 | 10.9 | 50 | 104.7 | 10.9 | 55 | 108.9 | 9.8 |
| | DBP | 100 | 67.2 | 8.8 | 98 | 66.2 | 8.7 | 50 | 65.9 | 7.0 | 55 | 66.5 | 8.6 |
| Visit 3 | SBP | 99 | 108.4 | 11.6 | 94 | 109.2 | 11.2 | 49 | 105.9 | 9.6 | 50 | 107.8 | 9.0 |
| | DBP | 99 | 67.5 | 8.4 | 94 | 67.1 | 9.1 | 49 | 66.2 | 6.9 | 50 | 67.7 | 8.1 |
| Visit 4 | SBP | 100 | 109.1 | 9.6 | 92 | 109.9 | 11.8 | 50 | 106.6 | 11.5 | 54 | 110.1 | 9.9 |
| | DBP | 101 | 67.0 | 9.8 | 92 | 68.6 | 8.5 | 50 | 65.5 | 7.4 | 54 | 67.6 | 7.8 |
| Visit 5 | SBP | 98 | 111.0 | 12.9 | 89 | 112.8 | 11.7 | 51 | 106.7 | 10.4 | 46 | 107.5 | 9.0 |
| | DBP | 97 | 69.7 | 8.6 | 89 | 71.3 | 8.9 | 51 | 67.4 | 7.6 | 46 | 67.5 | 8.8 |
| Visit 6 | SBP | 98 | 112.5 | 12.9 | 87 | 114.3 | 16.0 | 50 | 109.6 | 10.3 | 51 | 110.2 | 9.5 |
| | DBP | 98 | 70.9 | 8.4 | 86 | 74.5 | 10.7 | 50 | 68.7 | 8.7 | 51 | 70.2 | 8.8 |

SD: standard deviation; Visit 1: baseline, Visits 2-6: post randomization

Figure legends

Supplemental Figure S1A. SBP by Time Since Randomization and LOWESS Curves-Baseline Kerosene Users (Red: $K \rightarrow E$, Blue: $K \rightarrow K$).

Supplemental Figure S1B. DBP by Time Since Randomization and LOWESS Curves-Baseline Kerosene Users (Red: $K \rightarrow E$, Blue: $K \rightarrow K$).

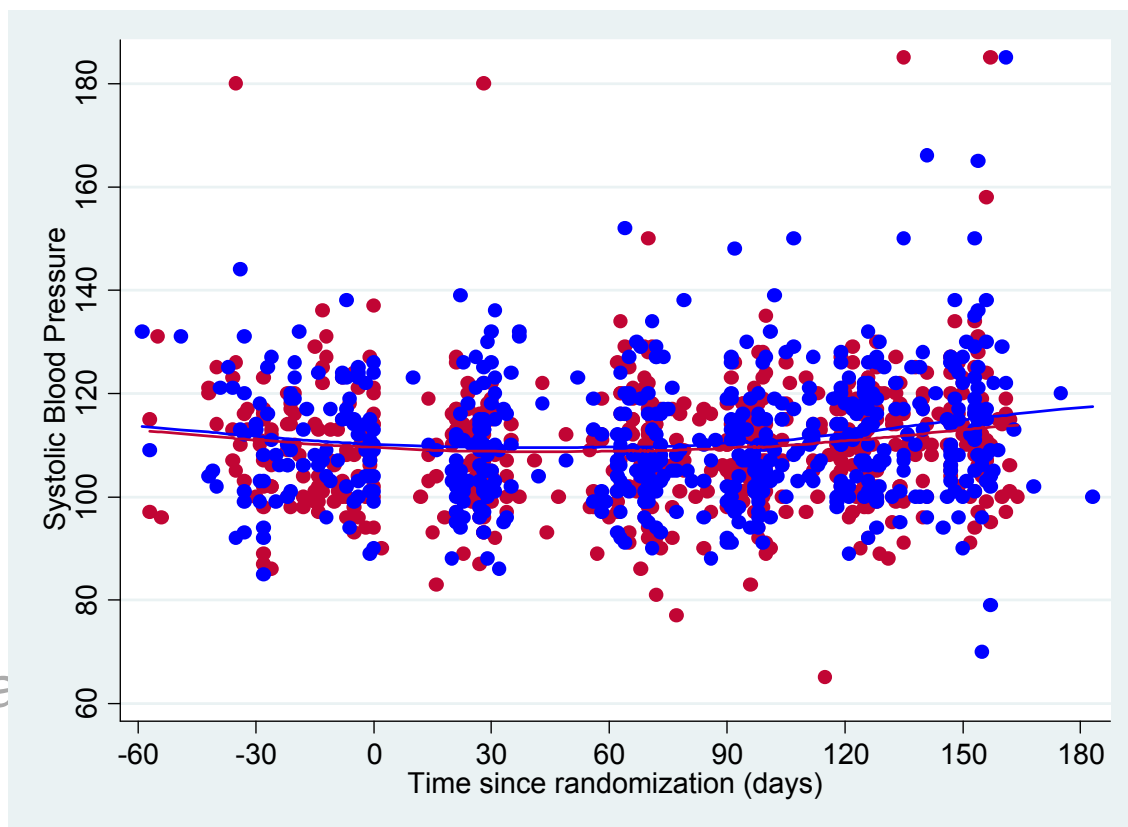
Supplemental Figure S2A. SBP by Time Since Randomization and LOWESS Curves-Baseline Firewood Users (Red: $F \rightarrow E$, Blue: $F \rightarrow F$).

Supplemental Figure S2B. DBP by Time Since Randomization and LOWESS Curves-Baseline Firewood Users (Red: $F \rightarrow E$, Blue: $F \rightarrow F$).

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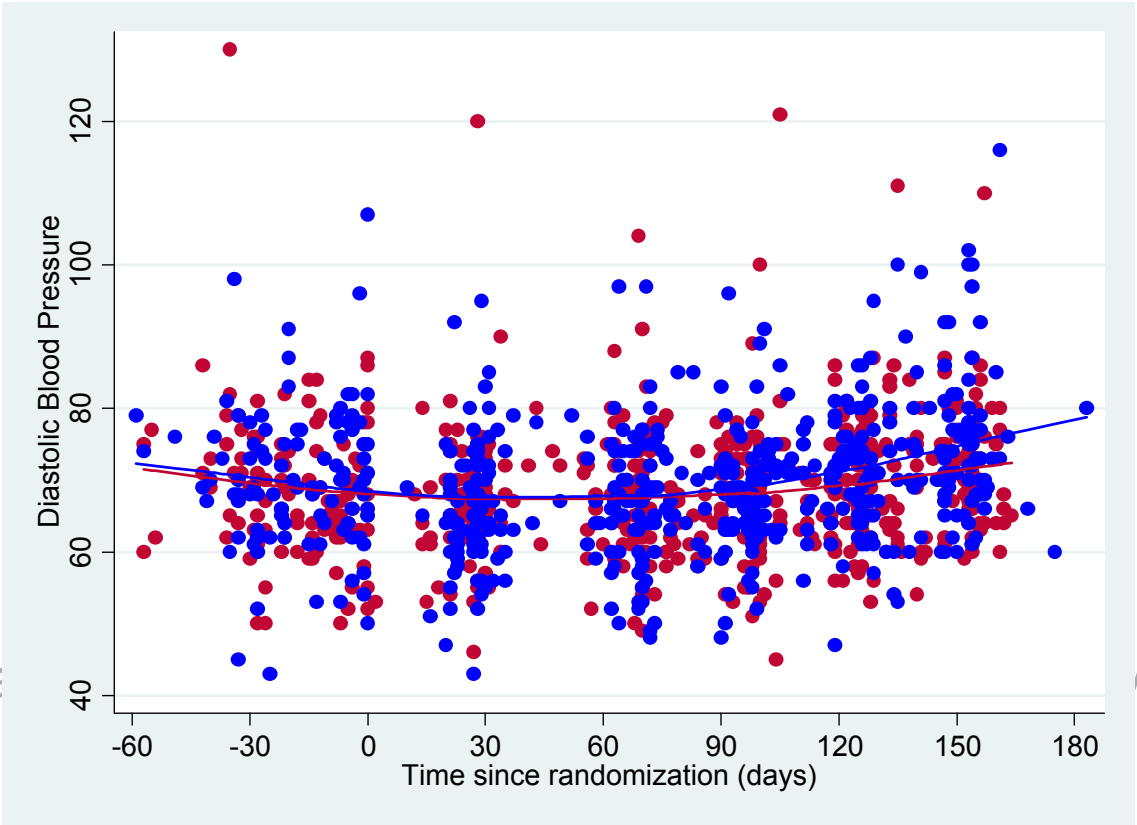
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Supplemental Figure S1A. SBP by Time Since Randomization and LOWESS Curves - Baseline Kerosene Users (Red: K→E; Blue: K→K).



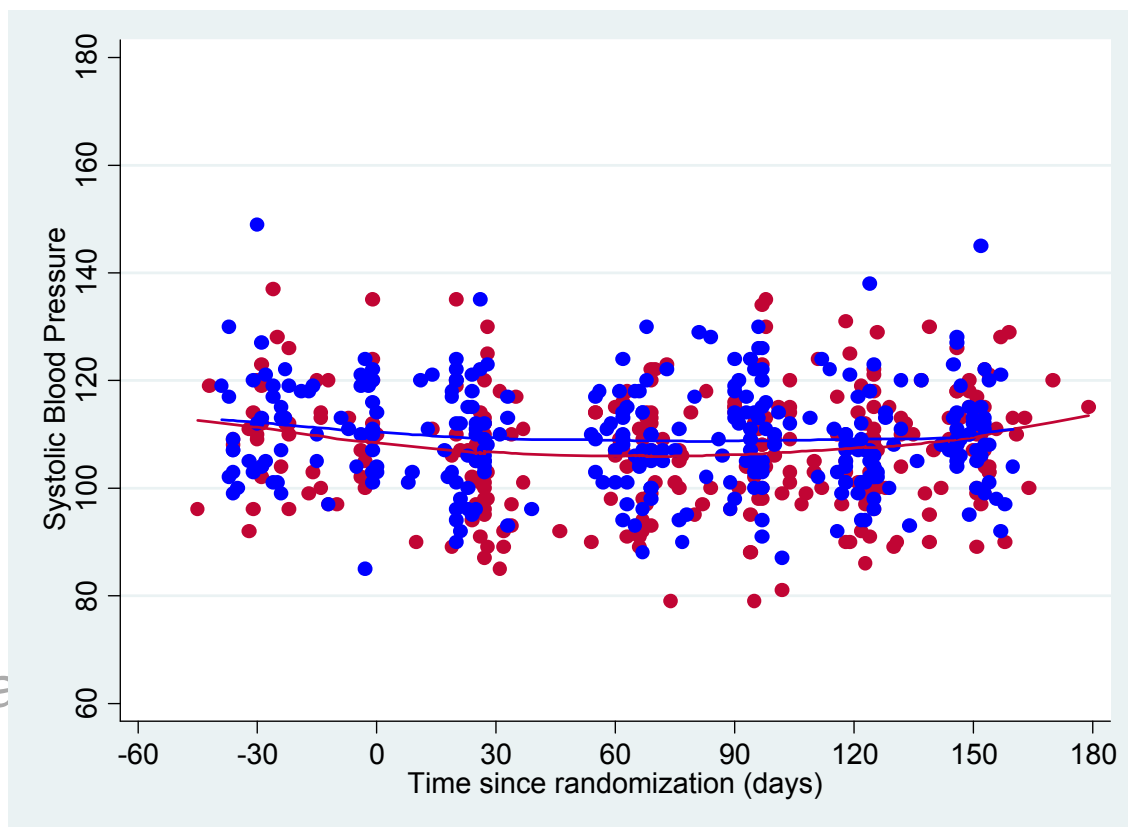
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Supplemental Figure S1B. DBP by Time Since Randomization and LOWESS Curves - Baseline Kerosene Users (Red: K→E, Blue: K→K).



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Supplemental Figure S2A. SBP by Time Since Randomization and LOWESS Curves - Baseline Firewood Users (Red: F→E, Blue: F→F).



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Supplemental Figure S2B. DBP by Time Since Randomization and LOWESS Curves - Baseline Firewood Users (Red: F→E, Blue: F→F).

