Environment International 121 (2018) 981–989

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: The UGAAR randomized controlled trial

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A R T I C L E I N F O

Handling Editor: Olga-Ioanna Kalantzi

Keywords:
RCT
Intervention
HEPA
Fetal growth
Birth weight
Mongolia

A B S T R A C T

Background: Fine particulate matter ($PM_{2.5}$) exposure may impair fetal growth.
Aims/objectives: Our aim was to assess the effect of portable high efficiency particulate air (HEPA) filter air cleaner use during pregnancy on fetal growth.
Methods: The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind randomized controlled trial conducted in Ulaanbaatar, Mongolia. Non-smoking pregnant women recruited at ≤18 weeks gestation were randomized to an intervention (1–2 air cleaners in homes from early pregnancy until childbirth) or control (no air cleaners) group. Participants were not blinded to their intervention status. Demographic, health, and birth outcome data were obtained via questionnaires and clinic records. We used unadjusted linear and logistic regression and time-to-event analysis to evaluate the intervention. Our primary outcome was birth weight. Secondary outcomes were gestational age-adjusted birth weight, birth length, head circumference, gestational age at birth, and small for gestational age. The study is registered at ClinicalTrials.gov (NCT01741051).
Results: We recruited 540 participants (272 control and 268 intervention) from January 9, 2014 to May 1, 2015. There were 465 live births and 28 losses to follow up. We previously reported a 29% (95% CI: 21, 37%) reduction in indoor $PM_{2.5}$ concentrations with portable HEPA filter air cleaner use. The median (25th, 75th percentile) birth weights for control and intervention participants were 3450 g (3150, 3800 g) and 3550 g (3200, 3800 g), respectively ($p = 0.34$). The intervention was not associated with birth weight (18 g; 95% CI: −84, 120 g), but in a pre-specified subgroup analysis of 429 term births the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in mean birth weight.
Conclusions: HEPA filter air cleaner use in a high pollution setting was associated with greater birth weight only among babies born at term.

1. Introduction

Fine particulate ($PM_{2.5}$) air pollution is a leading contributor to the global burden of disease because exposure is ubiquitous and causes respiratory-, cardiovascular-, and cancer-related morbidity and mortality (GBD Risk Factors Collaborators, 2017). In 2016, 95% of the world's population lived in areas where $PM_{2.5}$ concentrations exceeded the World Health Organization annual average guideline of 10 μg/m^3 (Health Effects Institute, 2018). Although air pollution levels are decreasing in many high-income countries, concentrations in low and

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https://doi.org/10.1016/j.envint.2018.08.036
Received 30 May 2018; Received in revised form 19 July 2018; Accepted 15 August 2018
Available online 10 September 2018

middle-income (LMIC) countries remain unchanged or continue to increase (Brauer et al., 2016). Growing evidence from observational studies suggests that $PM_{2.5}$ exposures during pregnancy adversely affect fetal growth (Sun et al., 2016; Zhu et al., 2015). A recent meta-analysis of 32 studies presented pooled estimates of the effect of outdoor $PM_{2.5}$ on birth weight and/or low birth weight (LBW) (Sun et al., 2016). A 10 μg/m^3 increase in $PM_{2.5}$ over the full duration of pregnancy was associated with a 16 g (95% CI: 5, 27 g) reduction in birth weight and an increased risk of LBW (odds ratio (OR) = 1.09; 95% CI: 1.03, 1.15) (Sun et al., 2016). Nearly all of the studies focused on term births (≥37 weeks), and the majority were conducted in the US. The only randomized controlled trial (RCT) of air pollution and fetal growth reported a trend toward greater birth weight (89 g; 95% CI: −27, 204 g) among participants who used a chimney stove (n = 69) compared with those who used traditional open fires (n = 105) during pregnancy in rural Guatemala (Thompson et al., 2011).

Portable high efficiency particulate air (HEPA) filter air cleaners (henceforth "HEPA cleaners") are a promising intervention to lower $PM_{2.5}$ exposures at the household level. Their use has been shown to reduce indoor residential $PM_{2.5}$ concentrations by 29–62% (Allen et al., 2011; Barn et al., 2008, 2018; Brauner et al., 2008; Butz et al., 2011; Kajbafzadeh et al., 2015). These reductions in concentrations can have large impacts on exposure since individuals spend the majority of time indoors, and because HEPA cleaners target both outdoor pollution that infiltrates indoors and indoor-generated pollution from cigarettes, cooking, and other sources. The impact of portable air cleaners on fetal growth has not been previously studied, but their short-term use (days to weeks) may induce biological changes relevant to fetal growth (Kannan et al., 2006), including improvements in endothelial function (Brauner et al., 2008), inflammation (Allen et al., 2011), and blood pressure (Weichenthal et al., 2013). The objective of this randomized trial was to determine if HEPA cleaner use at home from early pregnancy until childbirth among pregnant women in Ulaanbaatar, Mongolia was associated with improvements in fetal growth, compared with no HEPA cleaner use. Our primary motivation for this work was to introduce an exposure gradient from which to investigate the causal role of $PM_{2.5}$ on fetal growth. Secondarily, we sought to evaluate HEPA cleaner use as a possible household level intervention in high pollution settings.

2. Methods

2.1. Study design

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind RCT designed to assess the effect of portable HEPA cleaner use during pregnancy on fetal growth and early childhood development in Ulaanbaatar, Mongolia (ClinicalTrials.gov: NCT01741051). This city is among the world's most polluted in wintertime, primarily due to coal combustion for heating in low income neighborhoods and emissions from three coal fired power plants (Hill et al., 2017). The population-weighted annual average $PM_{2.5}$ concentration in Ulaanbaatar is over seven times the World Health Organization (WHO) guideline concentration of 10 μg/m^3 (Hill et al., 2017). Household coal use occurs in gers, traditional felt-lined yurts, which house approximately 60% of the city's population (Guttikunda, 2007). Ulaanbaatar's other residents live in apartments that receive electricity and heat from the power plants. We previously reported that HEPA cleaners reduced indoor $PM_{2.5}$ by 29% (95% CI: 21, 37%) in this apartment-dwelling study population, with larger reductions in homes that received two air cleaners (33%, 95% CI: 25, 41%) than those that received one (20%, 95% CI: 6, 32%) (Barn et al., 2018).

The study was conducted at two branches of the Sukhbaatar district Health Center of Ulaanbaatar. The study protocol was approved by the Simon Fraser University Office of Research Ethics (2013s0016) and the Mongolian Ministry of Health Medical Ethics Approval Committee (Decree No.7).

2.2. Participants

We recruited women who met the following criteria: ≥18 years of age, ≤18 weeks of a single-gestation pregnancy, non-smoker, living in an apartment, planning to give birth in a medical facility in the city, and not using a residential portable air cleaner at enrollment. We excluded women who lived in ger households because electricity is unreliable in ger neighborhoods and gers may have higher indoor-outdoor air exchange rates, which reduces HEPA cleaner effectiveness. Moreover, gers generally have higher indoor pollution emissions, and we were primarily interested in the effects of community air pollution. We recruited participants at one of two reproductive health clinics in the centrally-located Sukhbaatar district. This district was targeted due to its large population living in apartments, its relatively high pollution concentrations, and our relationships with clinic staff. All participants provided written informed consent prior to data collection. Participants were compensated with 65,000 tugriks (approximately $30 USD) upon completion of data collection; a pro-rated amount was provided to participants who withdrew before completion of the study.

2.3. Randomization and blinding

We used simple randomization to assign participants to the intervention or control group using sealed opaque envelopes containing randomly generated "filter" or "control" allocations and labeled with participant identification numbers from one to 580 by a principal investigator (RWA). Allocation was done on a 1:1 ratio. Once an individual was deemed eligible and provided written consent, a sealed envelope was drawn in sequential order and opened by a study coordinator who informed the participant of their allocation. Only one envelope was opened per participant; if a participant did not agree to her allocation she was not enrolled in the study. The envelope was then discarded and a new one was opened when the next participant was enrolled. Participants were not blinded to their intervention status.

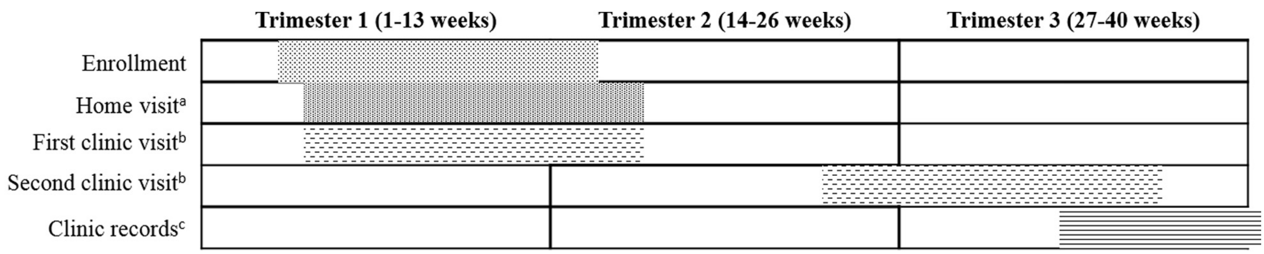
2.4. Intervention

The intervention group received one or two HEPA cleaners (Coway AP-1009CH), based on the size of their home, to use from enrollment to the end of pregnancy. The control group received no air cleaners.

2.5. Procedures

We installed one HEPA cleaner in the main living area of apartments with areas < 40 m^2; in larger apartments a second HEPA cleaner was installed in the participant's bedroom. We installed air cleaners at the first home visit, which occurred shortly after enrollment, and participants were encouraged to use the air cleaners continuously. The HEPA cleaners have a clean air delivery rate for tobacco smoke (particles sized 0.09–1.0 μm) of 149 cubic feet per minute, which is appropriate for rooms up to approximately 22 m^2. Two features, an internal PM sensor and light that changes colour based on PM concentration, were disabled to avoid biasing participants' behavior. The units were set to operate only on the second-highest fan setting due to noise at the highest fan setting.

Data were collected at clinic visits that occurred shortly after enrollment (5–19 weeks gestation) and later in pregnancy (24–37 weeks gestation; Fig. 1). At these visits staff collected data on housing, lifestyle, and maternal health via questionnaires. During the second clinic visit we asked participants to estimate the percentage of time HEPA cleaners were used. After birth, we obtained birth weight, length, head circumference, gestational age, sex, and mode of delivery from clinic records. Participants self-reported the occurrence and timing of spontaneous abortions, and information on stillbirths was obtained from



[a]Air cleaners were deployed in homes of intervention participants.
[b]Questionnaires on lifestyle and health were administered.
[c]Post delivery, the following data were extracted from clinic records: birth weight, length, head circumference, gestational age, sex, type of delivery, and health of participant during pregnancy (e.g. presence of infections, gestational diabetes and hypertension, preeclampsia).

Fig. 1. Data collection.

clinic records. We also collected information from clinic records on pregnancy complications and co-morbidities, including pre-existing and gestational diabetes and hypertension, anemia, and TORCH (Toxoplasmosis, Others [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, Herpes) infections. A full summary of UGAAR data collection activities is provided in the supplemental material (Fig. A1).

2.6. Outcomes

Our primary outcome was birth weight. We also analyzed secondary outcomes, including gestational age-adjusted birth weight, birth length, head circumference, and small for gestational age (SGA) at birth, as additional measures of intrauterine growth restriction, as well as gestational age at birth. Birth weight was available to the nearest 10 g, and birth length and head circumference were available to the nearest 1 cm. Gestational age was available either as a completed week or as a one-week interval (e.g. 37–38 weeks); for the latter, the mid-point of the interval was used (e.g. 37.5 weeks). SGA was defined as a birth weight < 10th percentile for sex and gestational age of the WHO fetal growth chart (Kiserud et al., 2017). We also explored additional outcomes that were not pre-specified: ponderal index, LBW, and preterm birth (PTB). Ponderal index was calculated as 100 multiplied by birth weight (g) divided by crown-heel length cubed (cm^3). Low birth weight was defined as < 2500 g, and PTB was defined as birth at < 37 weeks gestation. Adverse events were spontaneous abortion, stillbirth, and neonatal death. Spontaneous abortion and stillbirth were defined as pregnancy loss at < 20 weeks and ≥20 weeks, respectively. Neonatal death was defined as a death occurring within 28 days of a live birth. Stillbirth weight was not included in the analysis of birth weight since these data were not available.

2.7. Statistical analysis

Sample size calculations were based on term birth weight. We expected infants in the intervention group to weigh 120 g more at birth, on average, than infants in the control group (from a mean ± standard deviation of 3490 g ± 520 g). This value was based on previous estimates of outdoor $PM_{2.5}$ effects on term birth weight (Bell et al., 2007; Morello-Frosch et al., 2010) as well as assumptions on indoor and outdoor $PM_{2.5}$ concentrations (Allen et al., 2013), infiltration of outdoor $PM_{2.5}$ (Chen and Zhao, 2011), the effect of HEPA cleaners on indoor $PM_{2.5}$ (Allen et al., 2011; Barn et al., 2008), and time spent in different microenvironments during pregnancy (Nethery et al., 2009). To detect a 120 g difference in mean birth weight with a type I error rate of 0.05 (2-sided) and a type II error rate of 0.20, we estimated that 460 participants, in equal numbers in both treatment groups, were needed. We assumed 18% attrition due to dropout and pregnancy loss, so we targeted a population of 540 participants.

We used unadjusted linear and logistic regression to assess the effect of the intervention on all continuous and categorical outcomes, respectively, except for gestational age. Since gestational age had a non-normal distribution, we used time-to-event analysis to calculate hazard ratios for time to a live birth comparing intervention with control participants; we censored lost to follow up participants and treated pregnancy loss from spontaneous abortion or stillbirth as a competing risk. Models of gestational age-adjusted birth weight were adjusted for gestational age using linear and quadratic terms to account for the non-linear relationship between fetal growth and gestational age. We conducted a complete case analysis among all live births, excluding those involving a chromosomal abnormality, as well as participants who were lost to follow up or who had a pregnancy loss. Participants were analyzed according to their original intervention assignments, regardless of which treatment they were given or used.

Because nearly all of the existing observational evidence (Sun et al., 2016), including the studies used in our sample size calculations, is based on term births we stratified the analyses by gestational age (all births and term births, defined as ≥37 weeks) in a priori planned analyses. We also tested effect modification using stratified analyses and interaction terms in the models for variables identified a priori: gestational age at birth, exposure to second hand smoke, average time spent indoors at home during pregnancy, sex of the baby, season of birth, and self-reported air cleaner use. We additionally investigated income, as a proxy for socioeconomic status, as a potential effect modifier post hoc. Finally, we repeated all analyses to also estimate the effect of one and two air cleaners on our outcomes.

We assessed the sensitivity of the intervention effect estimates for birth weight to different factors. First, as an alternative to our intention-to-treat analysis, we estimated the effect of the intervention based on the treatment that participants received (i.e. "per protocol"). We also estimated intervention effects on birth weight after excluding (i) neonatal deaths, (ii) participants who reported smoking at any time in pregnancy, and (iii) potential errors in gestational age or birth weight (identified as observations that exceeded the WHO fetal growth chart 95th percentiles of birth weight for gestational age and sex by ≥20%). Finally, we estimated effects while adjusting for anemia status and PTB in the regression models.

2.8. Role of funding source

This study was funded by the Canadian Institutes of Health Research. Woongjin-Coway provided modified and discounted air cleaners. The funder and the company had no role in study design, data collection, data analysis, interpretation of study findings, or manuscript preparation.

3. Results

We recruited 540 participants from January 9, 2014 to May 1, 2015. Participants were enrolled in the study at a median (25th, 75th percentile) gestation of 10 weeks (8, 12 weeks). Two hundred and seventy-

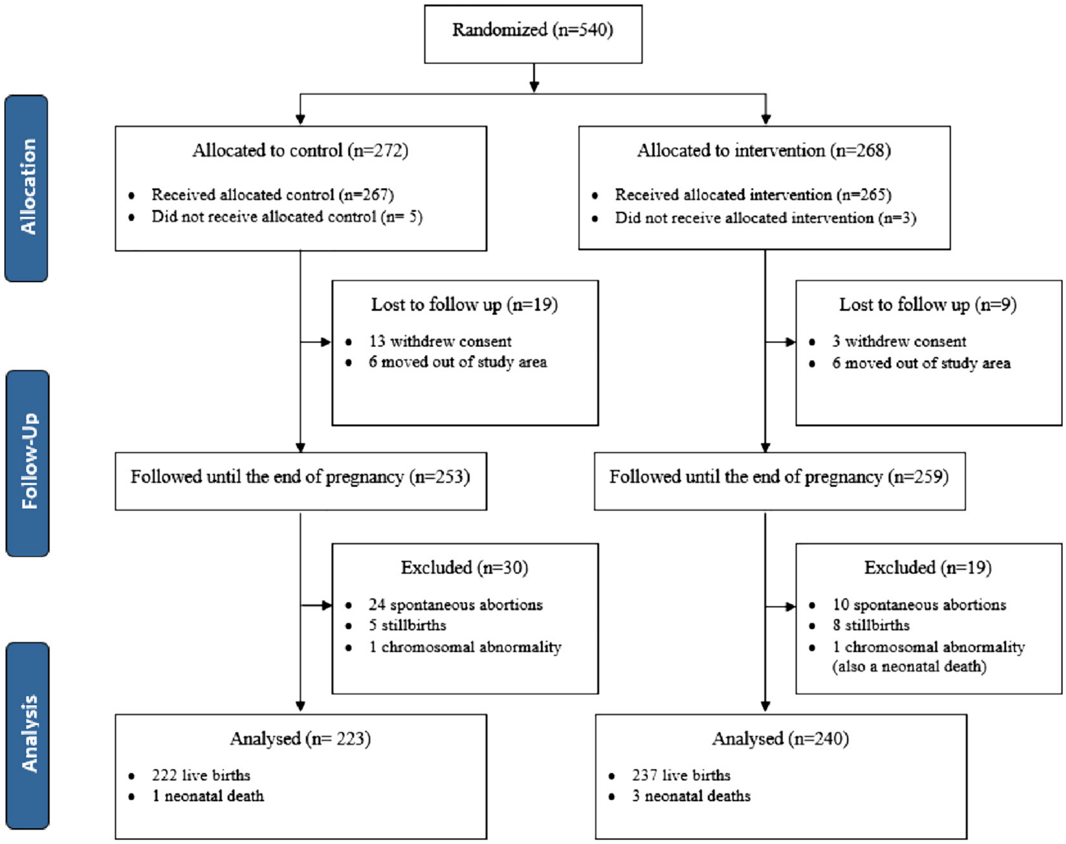


Fig. 2. Trial profile.

two participants were randomized to the control group and 268 were randomized to the intervention group (Fig. 2). Five participants that were allocated to the control group mistakenly received the intervention, while three participants allocated to the intervention group did not receive HEPA cleaners; data from these participants were analyzed according to their original treatment assignments. Twenty-eight (5%) participants were lost to follow up, and there were 34 (6%) spontaneous abortions and 13 stillbirths (2%). In total, 465 participants (86%) had a known live birth, five of which resulted in neonatal deaths (1%) due to heart defects (n = 2), respiratory failure (n = 2), and brain injury (n = 1). Two children were excluded due to chromosomal abnormalities (trisomy 18 and 21), leaving 463 live births in our complete case analysis.

Participants lost to follow up and those who remained in the study had similar demographics and lifestyles, including age at enrollment, household income, maternal education, marital status, parity, and pre-pregnancy BMI (Table A1). Some participants withdrew consent before our first questionnaire was administered resulting in more missing observations for these variables. More control participants were lost to follow up (19 vs. 9; p = 0.06).

Baseline characteristics were similar among control and intervention participants (Table 1). The median (25th, 75th percentile) age at enrollment was 29 years (25, 33 years). Control and intervention participants were enrolled at median (25th, 75th percentile) gestational ages of 11 (9, 12) and 11 (9, 13) weeks, respectively. The seasonal pattern of enrollment was also similar between the groups, with the most participants enrolled in winter (32%) and the fewest participants enrolled in summer (12%). Over half of the participants in both groups reported a monthly household income at or above the city's average of 800,000 Tugriks (approximately $360 US) (Mongolian Statistical Information Service, 2017). Most participants (≥80%) completed university or college and reported being married/common-law. Although all participants identified as non-smokers at enrollment, 8% of participants in both groups reported smoking in early pregnancy. Parity was similar between groups. Control participants had a shorter interval from the last pregnancy (24 vs 31 months), although the response rate to this question was poor with over 40% of observations missing. The intervention was implemented at a median (25th, 75th percentile) of 11 weeks gestation (9, 13 weeks). Sixty-eight households received one HEPA cleaner and 173 households received two HEPA cleaners. The ratio of air cleaners to apartment area was similar for participants who received one (median: 3.0 air cleaners/100 m^2; 25th, 75th percentile: 2.3, 3.7 air cleaners/100 m^2) and two (median: 3.4 air cleaners/100 m^2; 25th, 75th percentile: 2.4, 3.9 air cleaners/100 m^2) HEPA cleaners. Participants reported using HEPA cleaners for a median of 70% of the time; reported use did not differ by the number of air cleaners received. We previously reported that outdoor $PM_{2.5}$ concentrations measured at centrally-located government monitoring stations during the study period were similar for control and intervention participants (Barn et al., 2018).

Maternal weight gain, second hand smoke exposure, and health complications during pregnancy were similar between groups (Table 2). Roughly half of control and intervention participants reported living with a smoker. A higher frequency of intervention participants reported anemia during pregnancy (22% vs 15%; p = 0.07). No control or intervention participants had diabetes or gestational diabetes. Similarly, few participants had hypertension, gestational hypertension, or TORCH infections.

The birth weight distributions were skewed by PTBs (Fig. 3). The median (25th, 75th percentile) birth weights for control and intervention participants were 3450 g (3150, 3800 g) and 3550 g (3200, 3800 g), respectively (p = 0.34; Table 3). Regression results indicated no significant intervention effect on mean birth weight (18 g; 95% CI: −84, 120 g), but after adjusting for PTB the intervention was associated with an 84 g (95% CI: −1, 170 g) increase in birth weight (Table A2). The effect estimates from our other sensitivity analyses were generally

Table 1
Summary of baseline characteristics for control and intervention participants.

	Control (n = 223)	Intervention (n = 240)
	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)
Mother's age at enrollment, years	28 (25, 33)	30 (25, 33)
Gestational age at enrollment, weeks	11 (9, 12)	11 (9, 13)
Season of enrollment		
Winter (December, January, February)	77 (34)	71 (30)
Spring (March, April, May)	66 (30)	63 (26)
Summer (June, July, August)	23 (10)	33 (14)
Fall (September, October, November)	57 (26)	73 (30)
Monthly household income		
< 800,000 Tugriks[a]	69 (31)	83 (34)
≥800, 000 Tugriks	150 (67)	155 (65)
Not reported, N (%)	4 (2)	2 (1)
Mother's education		
Completed university	179 (80)	191 (80)
Did not complete university	29 (13)	28 (11)
Not reported, N (%)	15 (7)	21 (9)
Marital status		
Married/common-law	184 (83)	207 (86)
Not married/common-law	39 (17)	33 (14)
Not reported, N (%)	0 (0)	0 (0)
Worked/volunteered outside the home		
No	69 (31)	78 (32)
Yes	151 (68)	160 (67)
Not reported, N (%)	3 (1)	2 (1)
Parity		
0	21 (9)	24 (10)
1	88 (40)	86 (36)
≥2	44 (20)	59 (24)
Not reported, N (%)	70 (31)	71 (30)
Time since last pregnancy, months[b]	24 (10, 51)	31 (15, 61)
Not reported, N (%)	99 (44)	105 (44)
Previous poor pregnancy outcome[c]		
No	42 (19)	54 (23)
Yes	50 (22)	54 (23)
Not reported, N (%)	131 (59)	132 (54)
Pre-pregnancy BMI, kg/m^2	21.7 (19.6, 23.9)	21.4 (19.8, 24.0)
Not reported, N (%)	21 (9)	8 (3)
Time spent indoors at home in early pregnancy, h/day	16.0 (14.0,18.7)	16.1 (14.0, 19.0)
Not reported, N (%)	46 (21)	63 (26)

[a] Approximate average monthly income in Ulaanbaatar in 2014 (Mongolian Statistical Information Service, 2017). At the time of data collection, 800,000 Tugriks was the equivalent of approximately $360 US.
[b] Defined as the period between the end of the last pregnancy, including live births and pregnancy losses, and start of current pregnancy.
[c] Previous poor outcome included spontaneous abortion, still birth, low birth weight, macrosomia, ectopic pregnancy, birth defect, and intrauterine growth restriction.

Table 2
Summary of variables assessed during pregnancy.

	Control (n = 223)	Intervention (n = 240)	p-value[a]
	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)	
Weight gain during pregnancy (kg)[b]	12 (8, 15)	11 (8, 15)	0.93
Not reported	43 (19)	31 (14)	
Smoked at any time in pregnancy			
No	203 (91)	217 (91)	0.99
Yes	19 (9)	20 (8)	
Not reported, N (%)	1 (0)	3 (1)	
Lived with a smoker at any time in pregnancy			
No	106 (48)	121 (51)	0.64
Yes	112 (50)	115 (48)	
Not reported, N (%)	5 (2)	4 (1)	
Health during pregnancy			
Anemia	34 (15)	53 (22)	0.07
Not reported, N (%)	0 (0)	0 (0)	
Hypertension	11 (5)	13 (5)	0.84
Not reported, N (%)	0 (0)	0 (0)	
Gestational hypertension	16 (7)	16 (7)	0.85
Not reported, N (%)	23 (10)	15 (6)	
TORCH infections[c]	3 (1)	5 (2)	0.72
Not reported, N (%)	10 (4)	4 (2)	
Type of delivery			
Caesarean delivery	88 (39)	86 (36)	0.50
Vaginal delivery	135 (61)	154 (63)	
Sex of child			
Female	108 (48)	109 (45)	0.58
Male	115 (52)	131 (55)	
Season of birth			
Winter (Dec, Jan, Feb)	26 (12)	35 (15)	0.56
Spring (Mar, Apr, May)	52 (23)	59 (24)	
Summer (Jun, Jul, Aug)	70 (31)	78 (33)	
Fall (Sep, Oct, Nov)	75 (34)	68 (28)	

[a] p-values were generated using Fisher's exact tests, 2-sample *t*-tests, and Mann-Whitney tests as appropriate.
[b] From approximately week 11 to week 31.
[c] Toxoplasmosis, Others [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, Herpes infections.

similar to those from the main analysis (Table A2). Gestational age, birth length, head circumference, ponderal index, and frequency of LBW and SGA were similar for control and intervention participants (Table 3). The intervention was associated with a significantly elevated risk of PTB (10% vs. 4%; OR = 2.37; 1.11, 5.07). When stratified by late (34–36 weeks) versus early (< 34 weeks) cases, a significantly elevated risk remained for late PTB (OR = 3.55; 95% CI: 1.29, 9.73) but not early PTB (OR = 1.18; 95% CI: 0.36, 3.94).

Among term births, the median (25th, 75th percentile) birth weights for control and intervention participants were 3500 g (3200, 3800 g) and 3600 g (3300, 3850 g), respectively. The intervention was associated with greater term birth weight (85 g; 95% CI: 3, 167 g; Fig. 4) and gestational age-adjusted term birth weight (81 g; 95% CI: 2, 159 g), as well as a trend toward decreased risk of SGA (OR = 0.44; 95% CI: 0.19, 1.05). No variables modified the intervention effects for all births or term births (Fig. 4).

We also estimated the effects of using one or two air cleaners on birth outcomes separately because we previously reported greater $PM_{2.5}$ reductions among participants who received two air cleaners (Barn et al., 2018). Use of one HEPA cleaner was not associated with significant differences in birth weight (26 g; 95% CI: −100, 151 g) or gestational age-adjusted birth weight (17 g; 95% CI: −104, 138 g) among term births. For participants who received two HEPA cleaners, the intervention was associated with non-significant trends toward greater birth weight (85 g; 95% CI: −7, 177 g) and gestational age-adjusted birth weight (82 g; 95% CI: −5, 168 g) among term births.

There were 47 adverse events not prespecified as secondary outcomes, including 34 spontaneous abortions (24 control, 10 intervention) and 13 stillbirths (5 control, 8 intervention). Participants who had a spontaneous abortion were enrolled at a median (25th, 75th

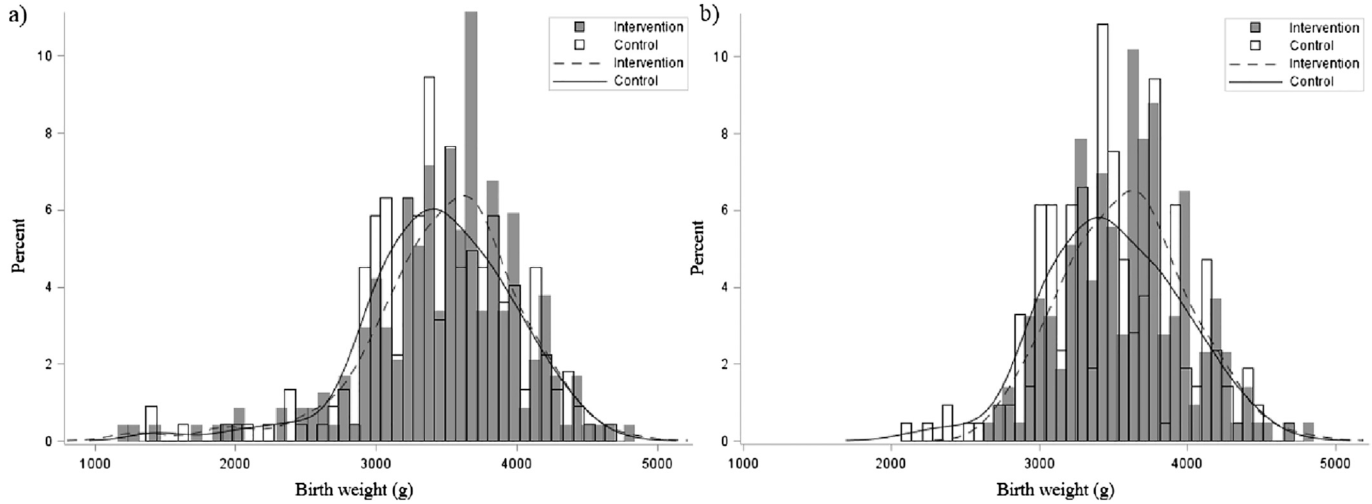


Fig. 3. Distribution of birth weight by treatment assignment for all births (a) and term births (b).

percentile) of 8.0 weeks (7.0, 9.0 weeks), and participants who had a stillbirth were enrolled at a median (25th, 75th percentile) of 10.0 weeks (5.0, 12.0 weeks). Spontaneous abortions occurred at a median (25th, 75th percentile) of 12.0 weeks (9.5, 14.0 weeks) and stillbirths occurred at a median (25th, 75th percentile) of 30.0 weeks (20.5, 36.0 weeks). There were no significant differences in the timing of spontaneous abortions or stillbirths between groups. The intervention was associated with a decreased risk of spontaneous abortion (OR = 0.38; 95% CI: 0.18, 0.82), but there was no association with stillbirth (OR = 1.58; 95% CI: 0.51, 4.90).

4. Discussion

In this single-blind RCT in a community exposed to very high air pollution concentrations, portable HEPA cleaner use during pregnancy was not associated with improvements in fetal growth among all births. However, the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in term birth weight. Unexpectedly, we also saw an increased risk of PTB (OR = 2.37; 95% CI: 1.11, 5.07) and a decreased risk of spontaneous abortion (OR = 0.38; 95% CI: 0.18, 0.82).

Fetal growth restriction and shorter duration of gestation can both cause reductions in birth weight. To reduce the influence of gestational age and evaluate the effect of air pollution on "normal" fetal growth, others have restricted their investigations to term births (Savitz et al., 2014; Sun et al., 2016; Wilcox, 2001). We observed a 100 g greater median birth weight among the intervention group in our full study population, but this difference was not statistically significant based on a non-parametric test of medians or our linear regression model that tested for differences in means. However, adjusting for PTB resulted in a nearly identical intervention effect estimate (84 g; 95% CI: −1, 170 g) as that of our subgroup analysis of term births (85 g; 95% CI: 3, 167 g). This suggests that the intervention improved fetal growth in the full study population, but that improvement was offset by a higher frequency of PTB in the intervention group.

The effects of air pollution on fetal growth may be most detrimental in later pregnancy. For example, in their recent meta-analysis, Sun et al. (2016) suggested that the second and third trimesters might be a critical exposure window for $PM_{2.5}$ (Sun et al., 2016). Similarly, Rich et al. (2015) reported that infants born to women in Beijing who had their eighth month of pregnancy during the 2008 Olympics, when outdoor pollution levels were substantially reduced, had a 23 g (95% CI; 5, 40 g) greater mean term birth weight compared with infants whose eighth

Table 3
Effect of the intervention on fetal growth and birth outcomes.

Outcome	Median (25th, 75th percentile) or N (%)			Effect of intervention		
	Control n = 223	Intervention n = 240	p-Value[a]	Measure of association	All births n = 463	Term births[b] n = 429
Birth weight, g	3450 (3150, 3800)	3550 (3200, 3800)	0.34	Mean difference (95% CI)	18 (−84, 120)	85 (3, 167)
Gestational age-adjusted birth weight, g[c]	–	–	–	Mean difference (95% CI)	48 (−31, 126)	81 (2, 159)
Birth length, cm	50 (50, 52)	51 (50, 52)	0.63	Mean difference (95% CI)	−0.01 (−0.53, 0.51)	0.32 (−0.04, 0.68)
Head circumference, cm	35 (34, 36)	35 (34, 36)	0.23	Mean difference (95% CI)	−0.07 (−0.4, 0.26)	0.14 (−0.13, 0.4)
Ponderal index, g/cm^3	2.6 (2.5, 2.8)	2.6 (2.5, 2.8)	0.92	Mean difference (95% CI)	0.01 (−0.04, 0.07)	0.02 (−0.02, 0.06)
Gestational age	39.5 (38.5, 40.0)	39.5 (38.5, 40.0)	0.87	Hazard ratio for time to a live birth (95% CI)	1.12 (0.96, 1.32)	1.06 (0.90, 1.25)
Small for gestational age	18 (8)	16 (7)	0.67	Odds ratio (95% CI)	0.81 (0.4, 1.64)	0.44 (0.19, 1.05)
Low birth weight[d]	10 (4)	13 (5)	0.60	Odds ratio (95% CI)	1.22 (0.52, 2.84)	–
Preterm birth	10 (4)	24 (10)	0.03	Odds ratio (95% CI)	2.37 (1.11, 5.07)	–

[a] p-Values were generated using non-parametric Wilcoxon rank tests for continuous outcomes and Fisher's exact tests for categorical outcomes.
[b] Births occurring ≥37 weeks gestation.
[c] Models were adjusted for gestational week and gestational week squared.
[d] There were no cases of low birth weight among term births in the intervention group.

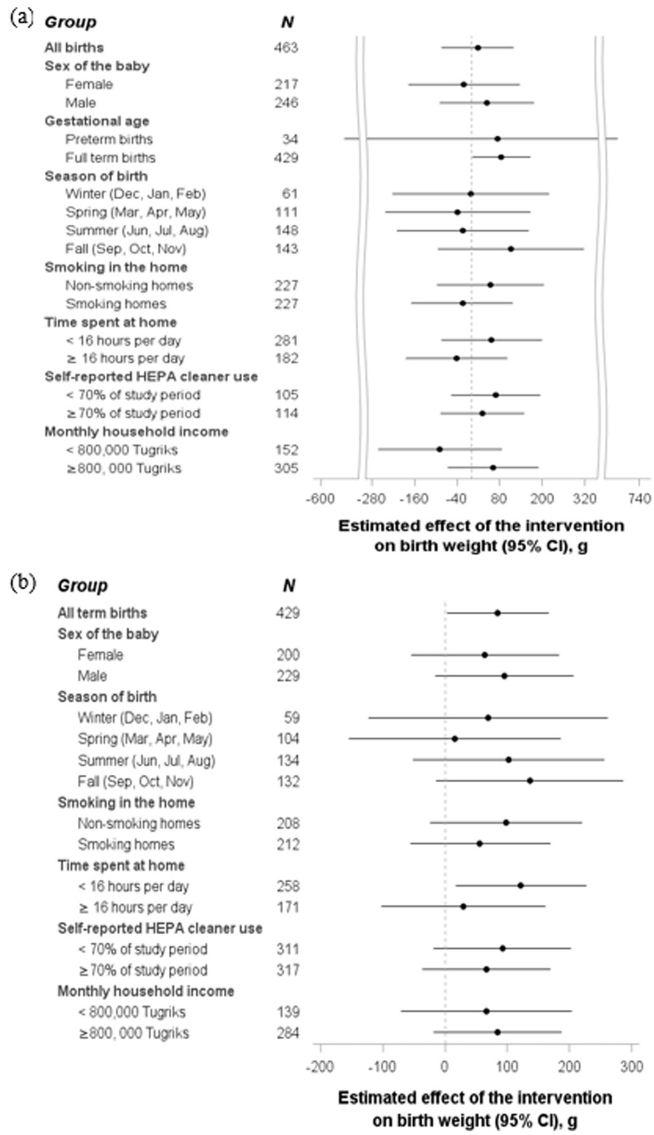


Fig. 4. Effect of the intervention on birth weight in stratified analyses for (a) all births and (b) term births.
Note: 16 h per day was the median time spent at home and 70% was the median self-reported use of the HEPA air cleaners. Numbers (Ns) reported for self-reported HEPA cleaner use reflect the number of intervention homes and effect estimates are relative to control homes. Monthly household income, as a proxy for socioeconomic status, was investigated as a potential effect modifier post hoc.

month fell in the same time period in the year before or after the Olympics (Rich et al., 2015). Studies using repeated ultrasound measurements also suggest that air pollution may not alter growth trajectories until late in the second trimester (Clemens et al., 2017; van den Hooven et al., 2012).

The observed relationship between the intervention and birth weight is biologically plausible. Air pollution has been linked with changes relevant to fetal growth, such as systemic oxidative stress, inflammation, endothelial dysfunction, blood coagulation, and blood pressure (Brook et al., 2010). During pregnancy, these mechanisms are thought to decrease utero-placental blood flow from improper placental vascularization and increase blood flow resistance, among other effects (Kannan et al., 2006). The pathophysiology of growth restriction is thought to be rooted in the inability of the fetus to receive adequate nutrients and oxygen due to placental dysfunction brought upon by these mechanisms (Mayer and Joseph, 2013). Constituents adsorbed onto particles may act through additional pathways. For example, heavy metals such as cadmium may deregulate processes such as calcium transport and placental release of progesterone (Hutcheon et al., 2008). Randomized trials of portable air cleaner use over 4–14 days have demonstrated improved endothelial function, and reduced systemic inflammation and blood pressure, in healthy adults (20 to 75 years of age) (Allen et al., 2011; Brauner et al., 2008; Weichenthal et al., 2013). A recent RCT also reported lower diastolic blood pressure among 162 pregnant women using cleaner burning ethanol stoves compared with 162 pregnant women using more polluting kerosene or firewood stoves in Ibadan, Nigeria ($p = 0.04$) (Alexander et al., 2017).

The magnitude of our PTB-adjusted birth weight result and our term birth weight result is comparable with the only previous randomized trial of air pollution and fetal growth. Thompson et al. (2011) randomized 69 pregnant women in rural Guatemala to receive a chimney stove, and 105 pregnant women to a control group that continued to use open fires for cooking (Thompson et al., 2011). The intervention was associated with a 39% reduction in carbon monoxide exposure and an 89 g (95% CI: −27, 204 g) increase in mean birth weight (Thompson et al., 2011). Our estimated intervention effects on fetal growth are also comparable to those from maternal nutrition interventions aimed at increasing birth weight. A pooled analyses of 19 randomized trials conducted in countries such as Taiwan, India, Iran, England, and the US reported 74 g (95% CI: 30, 117 g) greater mean birth weights among women receiving protein energy supplementation compared with control participants consuming routine diets (Imdad and Bhutta, 2012). Another pooled analyses reported that dietary interventions were associated with greater mean birth weights of 94 g, starting from a weight of 3086 g, in low-income countries and 49 g, from a starting weight of 3406 g, in high-income countries (Gresham et al., 2014). Maternal malnutrition is a key contributor to poor fetal growth, and like air pollution, it disproportionately affects populations in LMICs (Landrigan et al., 2018; Vaivada et al., 2017). However, unlike air pollution-related interventions, considerable emphasis has been placed on maternal nutrition intervention programs in LMICs to improve pregnancy and birth outcomes (Bhutta et al., 2013).

We unexpectedly found the intervention was associated with a decreased risk of spontaneous abortion. There was no difference in timing of enrollment or spontaneous abortion between intervention and control participants. Active smoking and second hand smoke exposures during pregnancy have been linked to spontaneous abortion (Pineles et al., 2014), but the evidence for air pollution is conflicting. Enkhmaa et al. (2014) reported strong positive correlations between monthly outdoor air pollution concentrations and monthly hospital admissions for spontaneous abortion in Ulaanbaatar ($r > 0.80$) (Enkhmaa et al., 2014). Monthly rates of spontaneous abortion were approximately 2.5 times greater in winter than in summer. The investigators did not consider other seasonally varying factors such as vitamin D or influenza exposure. In contrast, other studies conducted in Brazil (Pereira et al., 1998) and China (Hou et al., 2014) reported no associations between outdoor PM and spontaneous abortion.

Although we also found an increased risk of PTB among intervention participants, the intervention did not significantly impact the risk of early (< 34 weeks) PTBs (OR = 1.18; 95% CI: 0.36, 3.94), which are less likely to reflect iatrogenic intervention. The risk of late (34–36 weeks) PTBs was significantly elevated among intervention participants. The reason for the surprising increase in PTB in the intervention group may be found, in part, in the higher frequency of spontaneous abortions in the control group; the presence of the intervention may have enabled fetuses to survive long enough to be born preterm. The downstream effects of $PM_{2.5}$-induced oxidative stress and inflammation on fetal growth may be seen in early pregnancy, resulting in pregnancy loss, or in later pregnancy, resulting in PTB and/or SGA (Burton and Jauniaux, 2011; El-Mohandes et al., 2010; Khong and Brosens, 2011; Mifsud and Sebire, 2014). Although unlikely, an increased risk caused by noise from the HEPA cleaners cannot be ruled out. No studies have investigated the potential effects of air cleaner-related noise, but limited research suggests that exposure to noise from aircraft and road traffic during pregnancy may increase the risk of PTB, possibly by increasing the release of stress hormones that interfere with production and release of progesterone (Nieuwenhuijsen et al., 2017). Our findings of an adverse effect on PTB and a decreased risk of spontaneous abortion merit further investigation.

Some important limitations of this study should be noted. Participants were not blinded to their intervention status, which likely contributed to the greater loss to follow-up among control participants. Although the treatment groups were similar in age, marital status, household income, pre-pregnancy BMI, and parity, it is possible that the groups differed in unmeasured ways despite randomization. Participants received air cleaners at a median of 11 weeks gestation so the HEPA cleaners did not influence exposure during much of the first trimester. Spontaneous abortions were based on participant report, and we were not able to distinguish between spontaneous and medically indicated cases of PTB. Gestational age at birth was assessed from clinic records and was based on a combination of first trimester ultrasound, last menstrual period, and clinical assessment (symphyseal-fundal height measurements and/or Dubowitz or Ballard score). Participants reported using the HEPA cleaners for a median 70% of the study period but we were unable to assess how/if use changed throughout the study period. Anecdotal reports from participants indicated that HEPA cleaner use may have been reduced due to concerns about noise and electricity costs, and this may have reduced the benefits of the intervention.

5. Conclusions

Our motivations for studying the impact of HEPA cleaners on fetal growth were to investigate the causal role of $PM_{2.5}$ on fetal growth and to assess this household level intervention. We previously reported that HEPA filter air cleaner use was associated with significant reductions in indoor residential $PM_{2.5}$ concentrations (Barn et al., 2018). In the present study, HEPA cleaner use was associated with greater birth weight, but the effect was offset by a higher frequency of PTB in the intervention group. We speculate that the apparent increase in risk of PTB was due, at least in part, to selection bias resulting from a reduction in spontaneous abortions. Our findings provide additional evidence for the health benefits of reducing air pollution. While HEPA cleaners can reduce exposures at the household level, this intervention is not accessible to or appropriate for everyone. Portable air cleaners require a constant supply of electricity, have costs related to initial purchase, operation, and maintenance that may be prohibitive to some, and are generally less effective in dwellings with high air exchange rates such as temporary or poorly constructed structures or in warm climates where windows are frequently opened. Thus, in any community, relying solely on such household level interventions to address air pollution exposures will not protect everyone, particularly those most vulnerable. In the long-term, strategies to reduce community-wide air pollution concentrations are needed to ensure that the benefits of exposure reduction are available to all.

Acknowledgements

We are extremely grateful to the UGAAR study participants, and to all study staff. This study was funded by the Canadian Institutes of Health Research (MOP 142380).

Declaration of interests

The air cleaners used in this study were purchased at a discounted rate from the manufacturer, who also made minor modifications to the air cleaners at our request (described in the paper). The authors have no other conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.08.036.

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