The American Journal of Clinical Nutrition 117 (2023) S160–S169

The American Journal of
CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Sponsored Supplement Publication

A modular systematic review of antenatal interventions targeting modifiable environmental exposures in improving low birth weight

Pieta K. Näsänen-Gilmore [1,2,*,†], Annariina M. Koivu [1,†], Patricia J. Hunter [3], Yvonne Muthiani [1], Pia Pörtfors [2], Otto Heimonen [1], Viivi Kajander [1], Per Ashorn [1,4], Ulla Ashorn [1]

[1] Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;
[2] Finnish Institute for Health and Welfare, FI-00271, Helsinki, Finland; [3] UCL Great Ormond Street Institute of Child Health, London, UK;
[4] Department of Paediatrics, Tampere University Hospital, Tampere, Finland

ABSTRACT

Background: Low birth weight (LBW) increases the risk of short- and long-term morbidity and mortality from early life to adulthood. Despite research effort to improve birth outcomes the progress has been slow.
Objective: This systematic search and review of English language scientific literature on clinical trials aimed to compare the efficacy antenatal interventions to reduce environmental exposures including a reduction of toxins exposure, and improving sanitation, hygiene, and health-seeking behaviors, which target pregnant women to improve birth outcomes.
Methods: We performed eight systematic searches in MEDLINE (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (Wiley Cochrane Library), Cochrane Central Register of Controlled Trials (Wiley Cochrane Library), CINAHL Complete (EbscoHOST) between 17 March 2020 and 26 May 2020.
Results: Four documents identified describe interventions to reduce indoor air pollution: two randomised controlled trials (RCTs), one systematic review and meta-analysis (SRMA) on preventative antihelminth treatment and one RCT on antenatal counselling against unnecessary caesarean section. Based on the published literature, interventions to reduce indoor air pollution (LBW: RR: 0.90 [0.56, 1.44], PTB: OR: 2.37 [1.11, 5.07]) or preventative antihelminth treatment (LBW: RR: 1.00 [0.79, 1.27], PTB: RR: 0.88 [0.43, 1.78]) are not likely to reduce the risk of LBW or Preterm birth (PTB). Data is insufficient on antenatal counselling against caesarian-sections. For other interventions, there is lack of published research data from RCTs.
Conclusions: We conclude that there is a paucity of evidence from RCT on interventions that modify environmental risk factors during pregnancy to potentially improve birth outcomes. Magic bullets approach might not work and that it would be important to study the effect of the broader interventions, particularly in LMIC settings. Global interdisciplinary action to reduce harmful environmental exposures, is likely to help to reach global targets for LBW reduction and sustainably improve long-term population health.

Keywords: Low birth weight, preterm birth, adverse birth outcomes, pregnancy intervention, low- and middle-income countries, environmental exposures, household fuel pollution, helminth infections

Introduction

Low birth weight (LBW) [1,2] has been linked to a risk of early life mortality [3] and life-course morbidity including growth faltering in infancy [4], poorer lung function [5,6] and fitness, as well as chronic non-communicable diseases [7,8]. LBW, i.e., birth weight of less than 2500g, can result from preterm birth (PTB, birth before 37 completed weeks of gestation), fetal growth restriction (FGR) that typically presents as the newborn being small for gestational age (SGA, weight below the 10th percentile for the gestational age and sex), or both [9]. Globally approximately 15-20% of all the infants are born with LBW with the highest prevalence in Sub-Saharan Africa and South Asia [10].

Abbreviations: ES, Effect size; EED, Environmental enteric dysfunction; CI, Confidence interval; CO, Carbon monoxide; GI, Gastrointestinal; HICs, High income countries; LBW, Low birth weight; LICs, Low-income countries; LMICs, Low- and middle- income countries; MA, Meta-analysis; PICO, Population, Intervention, Control, Outcome; $PM_{2.5\mu m}$, Particulate matter pollution; PTB, Preterm birth; UMIC, Upper middle-income country; RCT, Randomised controlled trial; SB, Stillbirth; SBF, Solid biomass fuels; SGA, Small for gestational age; SRMA, Systematic review and meta-analysis.

This article is published as part of a supplement sponsored by Tampere University, Faculty of Medicine and Health Technology with grant support from the Children's Investment Fund Foundation.

* Corresponding author. Faculty of Medicine and Health Technology, Tampere University, FIN-33014 Tampere, Finland. Tel +358 (0)50 4008682.
E-mail address: pieta.nasanen-gilmore@tuni.fi (P.K. Näsänen-Gilmore).
† These authors contributed equally

https://doi.org/10.1016/j.ajcnut.2022.11.029
Received 14 June 2022; Received in revised form 18 November 2022; Accepted 23 November 2022;

LBW prevalence is an important indicator of population health and improving birth outcomes should be considered as a key public health target globally [9].

Progress in preventing adverse birth outcomes has been slow and much of the existing research evidence has a high-income country focus albeit the LBW burden is the highest in low resource settings [10]. Currently, a great deal of primary research and recommendations on LBW prevention by antenatal interventions address maternal infections, dietary deficiencies, or undernutrition during pregnancy. Many modifiable environmental exposures are known to be risk factors of poor birth outcomes [11–17] including air and environmental pollutants from traffic and industrial activity [18], household cooking fumes [16], naturally occurring heavy metals from the living environment, [14] and fungal metabolites (aflatoxin) from food and vegetables [17]. Poor sanitation and hygiene can pose an environmental risk when unhygienic conditions expose pregnant women to environmental pathogens that can be hazardous for them [19,20]. Certain factors in social environment are determined by beliefs or common practices, including health behaviors e.g., choosing non-medically indicated caesarean section [21], can also be considered as risk factors. However, whilst there is plenty of evidence on the association between environmental risk factors and adverse birth outcomes, very little work appropriately synthesizes the effect of interventions targeting environmental risk factors. Designing interventions to reduce harmful environmental exposures is particularly relevant to low-and-middle-income countries (LMICs) where the burden is heaviest, and legislative and social measures to protect population from ambient and household air pollutants or unhealthy social behaviors are lagging behind. Hence, addressing environmental risk factors could provide a potential tool to improve birth outcomes.

Currently, the understanding the effectiveness of the antenatal interventions tackling environmental exposures is limited, as interventions are of varying designs and often location specific [22]. This does not allow for global comparison of the effectiveness of interventions to reduce the LBW prevalence. The aim of this article is to present a synthesis of published literature on eight interventions addressing environmental exposures and unfavorable living environment and health-seeking behaviors in pregnancy to reduce LBW and related adverse birth outcomes.

Methods

This article reports a part of an evidence synthesis on a range of antenatal interventions that could be used to reduce the incidence of LBW, PTB, SGA and stillbirth (SB) globally. Out of the 46 antenatal interventions, the current review focuses on eight antenatal interventions that aim to address toxin exposure and sanitation, hygiene, and health-seeking behaviors in pregnancy:

1) Reduction of indoor air pollution;
2) Reduction of outdoor air pollution;
3) Antenatal counselling about avoidance of aflatoxins or heavy metals;
4) Water, sanitation and hygiene (WASH) interventions;
5) Preventative anthelmintic treatment;
6) Screening and treatment of maternal environmental enteric dysfunction (EED);
7) Antenatal counselling about living in high altitude and related hypoxia;
8) Antenatal counselling against non-medically indicated caesarian-section

We have provided a list of search terms [Supplementary data 1-8]. We defined environmental interventions as those that work through reduction of known environmental risk factors of adverse birth outcomes. The evidence on interventions related to maternal nutrition, infection control and sociopsychological exposures are be reported elsewhere [23–25].

For the search, study selection, and evidence synthesis, we used a recently described novel systematic search and review method, the modular review, that allows concomitant review of multiple interventions [26]. The modular review consists of a streamlined process to evaluate, synthesize, summaries and categorize evidence optimized to inform decision-making, policy and program planning [26]. While the design of the method, particularly its ability to review multiple interventions simultaneously, precluded the registration of the study in prospective registers of systematic reviews of single interventions, an a priori protocol was used and the method was published in detail [26].

Following the Modular Review method we carried out the initial screen with title and abstract by a single reviewer, followed by screening of full-text articles by two independent reviewers. Full details of the modular review are provided in Supplementary methods. In brief, we performed eight systematic searches in MEDLINE (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (Wiley Cochrane Library), Cochrane Central Register of Controlled Trials (Wiley Cochrane Library), CINAHL Complete (EbscoHOST) between 17 March 2020 and 26 May 2020. Search strategies were developed as a teamwork, in collaboration with two information specialists. Search terms were identified through test searches, database-specific thesauri, benchmarking search results against known relevant studies, and through the research groups' subject expertise.

We included English-language studies that were relevant to population, intervention, study design and outcomes.

Population

The population of interest was pregnant females and studies including females at any stage of pregnancy prior to the initiation of labor were included. We excluded non-pregnant females of childbearing age.

Intervention

The selected environmental interventions were chosen because they are particularly relevant to LMICs Also, many LMICs lag in legislative and social measures to protect population from ambient and household air pollutants or unhealthy social behaviors. For instance, the prevalence of air pollutants from household cooking and heating is higher in LMICs than in HICs [27] and play a more important role in health determinants of women than tobacco smoking in low resource settings but remains much unaddressed. In LMICs, people often live in environments where poor or absent sanitary and hygiene measures play a crucial role as health determinants and where a high infection load from poor sanitary conditions during pregnancy can cause fetal malnutrition and poor intrauterine growth [19,20]. Similarly, high altitude residences are more commonly of limited resource settings exposing vulnerable populations to risk of adverse birth outcomes [28]. The implementation of the interventions reviewed in this paper is not currently explicitly recommended by the World Health Organization (WHO) although screening of the risk factor may be so. However, the international research community has considered these interventions as potential tools to reduce the burden of LBW, because they address potentially modifiable environmental risk factors for LBW, PTB, or SGA that are prevalent in (LMICs) [Table 1].

Overall, searches for the environmental interventions were built on risk factors. For some interventions, we applied an additional modified

Table 1
List of interventions to tackle environmental and related risk factors

Intervention	Addressed risk factor	Prevalence of the risk factor	Assumed mode of action
Antenatal interventions to reduce toxin exposure in pregnant women			
Reduction of ambient/outdoor air pollution	Exposure to ambient/outdoor air pollution	Over 90% of the world's population is exposed to poor quality air. Whilst in HIC countries air quality has improved through intervening, but the problem persists in LMIC countries [27].	Reduced inhalation of particulate matter and carbon monoxide from traffic and industrial fumes through improved combustion of fuels, use of cleaners and filters to trap harmful pollution. Reduced exposure reduces airway irritation and symptoms of asthma and airway diseases as well as subclinical inflammation. Systemic inflammation has been linked to poor birth outcomes [41]. Reduction of systemic inflammation caused by pollution exposure may improve birth outcomes.
Reduction of indoor air pollution exposure	Exposure to household fuel pollution or the use of low quality SBF	Globally 36% of world's population cooked using low quality solid biomass fuels (SBF) in 2020. Despite a drastic decline from over 50% prevalence in 1990s the use of poor quality SBF continues in rural areas and particularly in LMIC [27]	Reduced inhalation of particulate matter and carbon monoxide from fumes resulting from household cooking/heating. Use of higher quality fuels to improve combustion of fuels, use of chimneys, air filters to reduce pollution levels. Systemic inflammation has been linked to poor birth outcomes [41]. Reduced exposure may reduce chronic airway irritation and subclinical systemic inflammation resulting from particulate matter irritation in the lungs.
Antenatal counselling about avoidance of aflatoxins or heavy metals	Exposure to aflatoxins and heavy metals	Details of prevalences globally or in LIC are not available. For aflatoxins the highest occurrences are in hot and humid regions which is optimal for fungal growth [17] .	Exposure to heavy metal and aflatoxins have been linked to poorer birth outcomes [14,17] Education and counselling in pregnancy of health dangers of heavy metal and aflatoxin exposure eradicate behaviors which lead to unnecessary exposure. and improve birth outcomes.
Antenatal interventions to improve sanitation, hygiene, and health-seeking behaviors in pregnant women			
Preventative anthelmintic treatment during pregnancy	High infectious load, poor gut absorption, micronutrient deficiencies and anemia	24% of global populations are infected with helminths. The prevalence is highest in tropical areas in Sub-Saharan Africa, China, and East Asia [42]	Inflammatory state and poorer gastrointestinal function and reduced nutrition absorption [43]. Medical treatment targeting anthelminthic infectious agents, e.g., helminthic worms will clear the worm infestation in the gastrointestinal track (GI), reducing inflammatory state which give a rise to improved GI immune defense and better absorption of nutrients through the GI track which leads to a better nutritional status and improve birth outcomes.
Water, sanitation, and hygiene (WASH) interventions in pregnancy to improve sanitation	Poor hygiene and sanitation	46% of the world population have no access to improved sanitation facilities, representing 82% in LIC. Of global population 26% do not have an access to clean drinking water, compared with 71% in LIC [44]	Inflammatory state and poorer gastrointestinal function and reduced nutrition absorption [43]. Improved hygiene and sanitation through hand washing, use of soap and proper sewage disposal, use of latrines, hygiene in food preparation These actions reduce infection load, lower infections burden, improve immunity and nutritional status to improve GI immune defenses and improve birth outcomes.
Screening and treatment for maternal EED during pregnancy	Poor hygiene and sanitation, certain gut infections, and micronutrient deficiencies	The global prevalence of maternal EED is impossible to estimate as much goes asymptomatic, particularly in low resource settings where other health burdens are high.	Inflammatory state and poorer gastrointestinal function and reduced nutrition absorption [43]. Reduced infection load may lower infection burden, improved immunity, and improve nutritional status and potentially improve birth outcomes.
Antenatal counselling against unnecessary c-sections	Shortened gestation due to elected, non- medically indicated caesarian sections	Global prevalence of performance of unnecessary c-sections have increased from 6.7% to 19.1%, with an average annual increase rate of 4.4%: region-specific increases are Europe 11.2 to 25%,in Asia 4.4 to19.5%, in Africa 2.9% to 7.4% [45]	Education and antenatal counselling on benefits of natural birthing. Education on short-term and long-term harmful impact of reduced gestation. Promotion of appropriate medical care and promotion of freedom of choice in birthing practices and may improve birth outcomes.
Counselling to temporarily move from high to low altitude during pregnancy	Altitude-related hypoxia during pregnancy	23% of the world's population live in above 500 m from the sea level. Of which approximately 12% at altitude of 500-2500m. Much of these areas are in East Africa, China, Nepal, Chile, Peru. [46]	Hypoxia from altitude residence during pregnancy may influence birth outcomes [28]. Education and antenatal counselling will improve the understanding of adversities of altitude-induced hypoxia during pregnancy and the importance of temporary relocation to low altitude settings in order to avoid avoidable harm from hypoxia related to altitude may improve birth outcomes.

search strategy to capture all relevant articles of interest (screening and treatment of maternal EED and antenatal counselling about moving from high altitude to low, and WASH).

Controlled studies

For each intervention, we sought the best estimate of effect size (ES) from the included studies. ES documents consisted of the most recent quantitative evidence, with reviews of reviews (umbrella reviews, meta-reviews, reviews of (systematic) reviews) constituting the highest level of evidence. The Next level consisted of reviews from the Cochrane collaboration, followed by high quality systematic reviews with or without meta-analyses. If there were no reviews available, we used peer reviewed published RCTs to estimate the combined effect size. In addition to identifying the latest reviews as ES documents, we also identified RCTs published after the review as ES documents. In such case, results from the more recent RCTs were reported separately. In reporting of effect size, we used relative risk (RR) or odds ratio with 95% or 90% confidence intervals (CI), stating the number of randomized participants.

Outcome

Outcomes of interest were LBW, PTB, SGA or SB. As study designs, we included RCTs and reviews of RCTs. The included studies had to report at least one of the listed outcomes. While LBW was the starting point of our project, PTB and SGA indicate the two main pathways that lead to it and SB is an extreme outcome that often results from the same processes that limit fetal growth or shorten the duration of pregnancy. Thus, all four outcomes can be partially attributed to the same antecedents [29].

Quality

In assessing the quality of evidence, we primarily accepted the assessment given in the Summary of Findings tables of the utilized ES documents that were reviewed. Typically, the tables are produced according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process and they provide the quality of evidence rating for each outcome [30]. In the older ES documents, the assessment was typically described to indicate the "quality" of evidence, whereas in the newer documents it was marked as the "certainty" of evidence. For RCTs used as ES documents, we used an applied version of the GRADE system to assess the risk of bias for individual studies. This was converted into an assessment of quality of evidence (detailed in Supplementary methods).

To interpret the impact of the interventions on each outcome, we sorted our findings into 5 categories based on the calculated effect size, the 95% or 90% CI, the number of studies and the quality of evidence. Each intervention was given standardized statement in relation to its effect on each outcome, accompanied by a color code [Table 2].

For reporting the results, we applied a modified preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist [31]. For each intervention, we report quantitative estimates on the size of effect of the intervention on LBW, PTB, SGA and SB with an assessment of the quality of evidence.

Results

We found 4995 records across seven searches. After electronic removal of duplicate records, we screened 3013 records for eligibility and reviewed 542 full texts. Eleven randomized controlled trials and systematic reviews and meta-analyses fulfilled the inclusion criteria.

Table 2
Summary of categorization of the evidence.

Color	Interpretation	Criteria
Green	The intervention likely reduces the risk of the adverse outcome.	• At least two moderate-to-high quality RCTs in a meta-analysis / IPD analysis, with 95% CI of the point estimate of the RR entirely below 1.
Yellow	The intervention may reduce the risk of the adverse outcome.	• At least two RCTs in a meta-analysis / IPD analysis, where either the 95% CI of the point estimate of the RR is entirely below 1 but the quality of the evidence is low, or the quality is moderate-to-high and the 90% CI of the point estimate of the RR entirely below 1. • One moderate-to-high quality RCT, with 95% CI of the point estimate of the RR entirely below 1.
Red	The intervention is not likely to reduce the risk of the adverse outcome.	• Situations that do not be meet the requirements for other categories, including meta-analysis results suggestive of harm. In other words, there is sufficient evidence to conclude that the intervention is unlikely to have a positive effect on the outcome.
Grey	Inconclusive published research on the intervention's effect on the outcome.	• At least two RCTs, 95% CI of the point estimate of the RR ranges from < 0.5 to > 2.
White	Insufficient published research on the intervention's effect on the outcome.	• No RCTs or one low quality RCT (any result) • One moderate-to-high quality RCT where 95% CI of the RR includes 1. • Narrative reporting

Seven studies were excluded from the effect size estimate as they only reported birth weight/length but no prespecified birth outcomes (LBW, PTB, SGA or SB) or the focus of analysis did not allow clear conclusions on the effect of the intervention on birth outcomes. The remaining four records qualified as effect size (ES) documents [Figure 1].

Antenatal interventions to reduce toxin exposure in pregnant women

Two ES documents (both RCTs) covered interventions addressing toxin exposure among pregnant women. The documents were published between 2011-2018 and data was collected in upper or lower middle-income countries from (UMIC or LMIC) [Table 3].

Both of the identified ES documents contributed to the estimate on the size of effect on the *Reduction of indoor air pollution exposure*. These documents reported results from RCTs that were conducted in Guatemala and Mongolia. The target group included all healthy pregnant women from households or communities cooking on poor quality solid biomass stoves. Both studies reported an outcome data for LBW (number of participants=637) and one (N=463) for PTB and SGA. Among women receiving the intervention, the relative risk (95% CI) of LBW was 0.90 (0.56, 1.44), whilst the odds ratio (95% CI) for PTB was 2.37 (1.11, 5.07) and that for SGA was 0.81 (0.40, 1.64). No data was available for SB. The quality of evidence was moderate. A detailed summary of the impact of environmental interventions to reduce indoor air pollution exposure is shown in [Supplementary data 1].

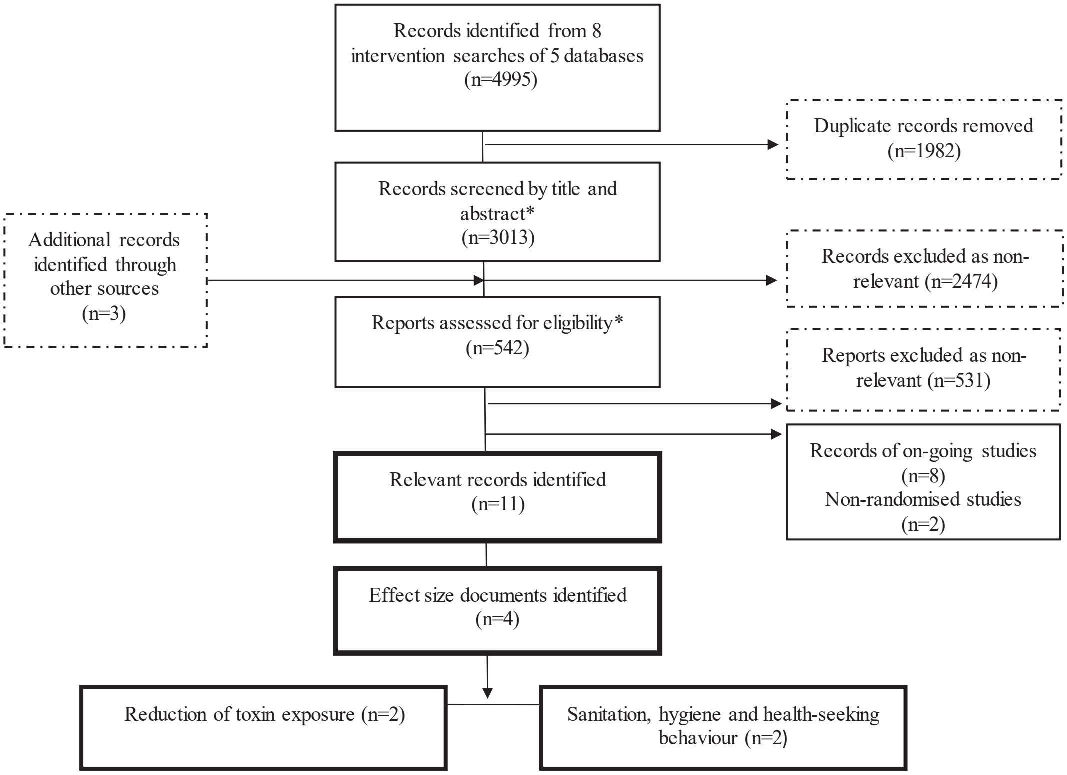

Figure 1. Summary flow diagram. Selection of publications for the analysis of interventions targeting modifiable environmental factors to reduce adverse birth in pregnancy. Adapted from Prisma 2020. [31] Some records occur more than once due to being relevant to more than one intervention.

No ES documents reported the impact of interventions to *reduce outdoor or ambient air pollution exposure,* or the *reduction of heavy metal or aflatoxin exposure* on birth outcomes [Supplementary data 2-3].

In summary, for the interventions to reduce environmental toxin exposure there was very little data or data was insufficient to draw conclusions of their effect on birth outcomes, more specifically on the intervention to reduce outdoor air pollution exposure or heavy metal or aflatoxin exposure. Moderate quality evidence from LMIC and UMIC suggested that interventions to reduce indoor air pollution were not likely to reduce the prevalence of LBW, PTB or SGA [Table 4].

Antenatal interventions to improve sanitation, hygiene, and health-seeking behaviors in pregnant women

Two ES documents, one Cochrane SRMA from 2015 and one RCT from 2013 covered interventions on sanitation, hygiene, and health-seeking behaviors. The two documents described results from a total of four studies, conducted both in high-, middle- and low-income countries [Table 5].

One SRMA contributed to the effect size estimate on the *Preventative anthelminthic treatment during pregnancy*. This review consisted of three RCTs published between 2006 and 2010, from Uganda (two) and Peru (one). The target group included pregnant women at risk of poor hygiene and sanitation, which may result in higher risk of helminth infection. The intervention included a single dose of albendazole or mebendazole, or a respective placebo, given after the 1st trimester of pregnancy with or without concomitant iron supplementation. The number of studies (participants) reporting specific outcome data was three (N=3255) for LBW and two (N=1318) for PTB. No study reported SGA or SB as an outcome. Compared to control women, the relative risk (95%CI) of LBW among women who received anti-helminth treatment was 1.00 (0.79, 1.27). The corresponding risk of

Table 3
Source documents for effect size (ES) estimate

Antenatal intervention	Authors	Year	Study design	Country of data collection	Population	Sample size	Description of Intervention	Description of Control
Reduction of indoor air pollution exposure	Thompson [47]	2011	RCT -single-blinded	Guatemala (1)	Healthy pregnant women	N=174	Wood-burning stoves with chimneys	Open fires without chimneys
Reduction of indoor air pollution exposure	Barn [40]	2018	RCT -single-blinded	Mongolia (1)	Women were less than 18 weeks of GA, with singleton pregnancy, had no air filter in their house and were planning to give birth at a medical facility	N=463	HEPA air filter fitted in the house to clean the household air, one filter per 40m^2, if larger accommodation a second filter was provided.	No HEPA filter

Table 4
Effect size estimates per intervention type: Reduction of toxin exposure.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Reduction of indoor air pollution	No	**No**	Insufficient data	Insufficient data
	RR: 0.90 [0.56 to 1.44]. (N=636)	OR: 2.37 [1.11 to 5.07] (N=463)	OR: 0.81 [0.40 to 1.64] (N=463)	N/A
	MODERATE	MODERATE	Moderate	N/A
Reduction of outdoor air pollution	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
Antenatal counselling about avoidance of aflatoxins or heavy metals	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

PTB was 0.88 (0.43 to 1.78). The authors of the review considered the evidence of moderate quality [Supplementary data 4].

One unblinded RCT, including 871 participants from Australia and published in 2013 contributed to the effect size estimate for *antenatal counselling against unnecessary c-sections.* The target group was pregnant women with no risk or no medical indication for a caesarean section delivery. Compared to control women, the odds ratio (95% CI) of PTB among women in the intervention group was 0.76 (0.49, 1.16); the prevalence of LBW, SGA, and SB was not reported. The quality of evidence was considered low [Supplementary data 5].

No ES documents reported the impact of *WASH interventions*, *screening and treatment of maternal environmental enteric dysfunction (EED)*, or *counselling to pregnant women to temporarily move from high to lower altitude during pregnancy* on any of the selected birth outcomes [Supplementary data 6-8].

In summary, there was very little data or data was mostly insufficient to draw conclusions on the impact of interventions to improve sanitation, hygiene, and health-seeking behaviors on birth outcomes. There was moderate quality evidence from LMIC settings indicating that preventative antihelminth treatment during pregnancy is not likely to reduce the prevalence of LBW or PTB [Table 6].

Discussion

The aim of this paper was to review and summarize English-language literature on RCT evidence about the impact of eight

Table 5
Source documents for effect size (ES) estimate. Sanitation, hygiene, and health-seeking behaviors

Antenatal intervention	Authors	Year	Study design	Country of data collection	Population	Sample size	Description of intervention	Description of control
Preventative anthelminthic treatment	Salam [48]	2015	SRMA	Uganda (2), Peru (1)	Pregnant women in the second or third trimester.	LBW 3 studies (N=3255) PTB: 2 studies (N=1318)	Albendazole or mebendazole with or without iron	Placebo
Antenatal counselling against non-medically indicated caesarian sections.	Tracy [49]	2013	Unblinded RCT, parallel-group trial	Australia (1)	Pregnant women >18 years of age and <24 weeks of gestation at the 1st booking. Excluded: Women who had planned caesarian, with multiple fetus, planning to use GP, private obstetrician or participate in the MANGO study.	PTB: 1 studies (N=871)	The M@NGO study: Caseload midwifes work on annual salary and regular shifts. Each midwife cares for 40 women/year and shadows another 40. Women have a designated midwife from early pregnancy to postnatal care. Women can attend antenatal/postnatal groups. Women are advised by their midwife throughout and are encouraged to go home early where midwife visits regularly for 6 weeks to provide support.	Standard midwifery care: midwives employed to provide rostered care min 38 hours a week, to match the workload requirements. Women can have several carers, attend routine antenatal clinics and during labor. Routine birthing care and are discharged early if appropriate as according to the Australian national midwifery guidelines.

Table 6
Effect size estimates per intervention type: Improving Hygiene and Sanitation and health-seeking behaviors.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Preventive antihelminth treatment in pregnancy	No	No	Insufficient data	Insufficient data
	RR: 1.00 [0.79 to 1.27] (N=3255)	RR: 0.88 [0.43 to 1.78] (N=1318)	N/A	N/A
	MODERATE	MODERATE	N/A	N/A
Antenatal counselling against medically non-indicated C-sections	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	OR: 0.76 [0.49 to 1.16] (N=871)	N/A	N/A
	N/A	LOW	N/A	N/A
WASH[1] interventions in pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
Screening and treatment for maternal EED[2] environmental enteric dysfunction during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
Counselling to temporarily move from high to lower altitude during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

[1]WASH: Water, hygiene, and sanitation
[2]EED: environmental enteric dysfunction during

antenatal interventions to reduce the risk of LBW and related adverse outcomes, focusing on environmental risk factors during pregnancy. Synthesizing data from five databases, we established a scarcity of evidence on interventions addressing environmental risk factors on birth outcomes. Particularly, RCT evidence was missing on interventions addressing outdoor air pollution, aflatoxin exposures, antenatal high-altitude exposure, poor sanitation, and hygiene, and maternal EED. Of eight antenatal interventions aiming to reduce environmental exposures, indoor air pollution reduction intervention and preventative antihelminth treatment were summarized as likely not to reduce the prevalence of adverse birth outcomes. For antenatal counselling against non-medically indicated caesarian section, the effect of the intervention was uncertain and limited to HIC.

The validity of our sample findings may be compromised by our search method in cases where birth outcomes of interest were not included in the title and abstract, or they were reported as secondary outcomes. Moreover, a single risk-factor based search method for some of the interventions may potentially have led to exclusions of some relevant work. However, we verified systematically the comprehensiveness of identified literature, through random checks and the use of multiple search engines [26]. Thus, the identified scientific literature is likely to be representative of the existing evidence on pregnancy interventions to improve birth outcomes. Of the eight reviewed antenatal interventions targeting environmental exposures, none is therefore likely to improve birth outcomes, or the evidence is insufficient to make conclusions.

Modifiable environmental toxin exposures represent a disproportionally high adverse health burden in low-income context. In 2005, WHO declared household fuel pollution as a silent killer of women in low resource settings where poor quality solid biomass fuels and chimneyless stoves are commonly used for cooking and heating [32, 33]. Women and small children are the most vulnerable to adversities from fuel pollution exposure as they spend much time at home and are chronically exposed to pollutants from cooking and heating. This predisposes women in reproductive age and their unborn babies and small children to early life and long-term health problems [34].

Our findings on interventions reducing indoor air pollution are consistent with more recent evidence from Nepal, where households were provided liquid petroleum gas stoves to reduce pollution exposure and reported no effect on birth outcomes as a result of intervention [35]. This work, however, suggested that despite lower pollutant levels, the measured values were still far beyond the recommended safe exposure levels recommended by WHO [35]. It may be that interventions to reduce indoor air pollution are not actually efficient enough to reduce pollutant levels, hence it is not surprising that there are no impacts on birth outcomes. Furthermore this work speculated on high ambient air pollution as the contributor of persistently high indoor air pollution levels [35]. Given that the 2021 WHO air quality guidelines estimate that 90% of global population is at risk of harmful air pollution exposure [36], it is clear that a reduction of environmental pollution exposures is paramount, but also the complexity of factors which may influence intervention success requires recognition [37].

Currently, WHO recommends a periodic antihelminth treatment to all children and women at reproductive age in endemic areas where helminth infestation affects approximately 44 million pregnancies [38]. Even though our search found no data to support deworming during pregnancy to improve birth outcomes, it may reduce neonatal mortality [15]. This recent multicountry study also suggested a risk reduction in LBW in LMIC [15]. In any case, deworming is considered safe and provides health benefits when given to pregnant women when there is a population level deworming campaign [39].

Our review highlighted the scarcity of clinical trial evidence on environmental interventions targeting pregnant women, which systematically measure the effect on birth outcomes. However, lack of evidence does not necessarily signal lack of effect. The effect of interventions reducing environmental risk factors may be harder to quantify or separate from other socio-behavioral factors, which may influence the success of the intervention [37]. This could at least partially explain the absence of evidence on WASH interventions or intervention targeting maternal environmental enteric dysfunction during pregnancy. A potential direction for future research could be moving the focus from risk factor analysis to designing more multifaceted interventions to reduce modifiable environmental exposures among women in reproductive age. Whilst single-pronged antenatal interventions have not been effective in improving pregnancy outcomes, It may be that broader investigation of social determinants of health including housing and availability of adequate health care would reveal more effective solutions to reduce harm from environmental exposures. It may be that broader investigation of social determinants of health including housing and availability of adequate health care would reveal more effective solutions to reduce harm from environmental exposures. It is important to also recognize that what may work in HIC settings, might not work in low resource settings. Furthermore, a contextual understanding of local settings is highly relevant, but equally important is the learning from multicountry studies alongside. Learning from these approaches may help to contribute to the progress flagged by the World Health Assembly on the reduction of global LBW prevalence [9].

Our work focused on RCT designs and excluded other study designs, such as non-randomized designs, cohorts, and cross-sectional studies. However, environmental exposures are often part of an integrated living environment and therefore very complex to tackle. Research on interventions addressing environmental risk factors is commonly carried out as community-wide interventions, which are often of non-RCT design, and could have contributed relevant data on the effectiveness of interventions on birth outcomes. We also did not include studies where the intervention started in preconception time or after the start of labor, which may have limited the effect of the intervention in this review. There is an inbuilt problem with interventions focusing on pregnancy. By design an intervention can start from the confirmation of pregnancy in late first trimester, which may actually be too late in terms of fetal development [40]. Furthermore, we did not specifically review the work which focused on PTB before 34 weeks of gestation.

Our work has highlighted a scarcity of scientific evidence of RCT interventions on the impact of antenatal interventions to reduce harmful environmental exposures to improve birth outcomes. Harmful environmental exposures are highly prevalent across the globe but particularly problematic in resource poor settings where the infrastructure to mitigate the problem is lacking. Changing viewpoint from RCTs to broader intervention designs and focusing resources into the reduction of environmental risk factors at local level with multicountry comparisons is likely to be effective and the way forward to improve birth outcomes and long-term health in LMIC settings. Global interdisciplinary action towards reducing harmful environmental exposures can contribute to the progress global LBW prevalence reduction and improve long-term population health sustainably.

Acknowledgements

The authors gratefully acknowledge Jaana Isojärvi, Taina Peltonen, Päivi Lukin and Heather Chesters for support in information retrieval. We thank all members of the TAU Center for Child, Adolescent and Maternal Health for their advice and feedback, in particular, Juho Luoma for statistical support and Maryam Hadji, Meeri Salenius, Kalpana Bastola, and Raija Vimpeli for research assistance.

Author contribution

PA, UA, PNG, AK, PH and YM designed research, including project conception and development of overall research plan. PA and UA provided study oversight. PNG, AK, PH and YM conducted research. PNG, AK, PH, YM, PP, VK collected or analyzed data. OH performed statistical analysis. PNG and AK drafted the manuscript. PNG had primary responsibility for final content. All authors have read and approved the final manuscript.

Data described in the manuscript will be made available upon reasonable request.

Sources of support for the work:

The study was funded by the Children's Investment Fund Foundation (CIFF), Grant Reference Number 1808-02973. The funder had no role in the design, implementation, analysis and interpretation of the data.

Conflicts of interest

Pieta Näsänen-Gilmore – No conflict of interest
Annariina Koivu – No conflict of interest
Patricia J Hunter – No conflict of interest
Yvonne Muthiani – No conflict of interest
Pia Pörtfors – No conflict of interest
Otto Heimonen – No conflict of interest
Viivi Kajander – No conflict of interest
Per Ashorn – No conflict of interest
Ulla Ashorn – No conflict of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.11.029.

References

[1] M.M. Hughes, R.E. Black, J. Katz, 2500-g Low Birth Weight Cutoff: History and Implications for Future Research and Policy, Matern Child Health J 21 (2) (2017 Feb) 283–289.
[2] M.C. McCormick, The Contribution of Low Birth Weight to Infant Mortality and Childhood Morbidity, N Engl J Med 312 (2) (1985 Jan 10) 82–90.
[3] J. Katz, A.C. Lee, N. Kozuki, J.E. Lawn, S. Cousens, H. Blencowe, M. Ezzati, Z.A. Bhutta, T. Machant, B.A. Willey, et al., Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis, The Lancet 382 (9890) (2013 Aug) 417–425.
[4] C.G. Victora, M. de Onis, P.C. Hallal, M. Blossner, R. Shrimpton, Worldwide Timing of Growth Faltering: Revisiting Implications for Interventions, Pediatrics 125 (3) (2010 Mar 1) e473–e480.
[5] L.W. Doyle, S. Andersson, A. Bush, J.L.Y. Cheong, H. Clemm, K.A.I. Evensen, A. Cough, T. Halvorsen, P. Hovi, E. Kajantie, et al., Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data, Lancet Respir Med 7 (8) (2019 Aug) 677–686.
[6] P. Näsänen-Gilmore, M. Sipola-Leppänen, M. Tikanmäki, H.M. Matinolli, J.G. Eriksson, M.R. Järvelin, M. Vääräsmäki, P. Hovi, E. Kajantie, Lung function in adults born preterm, in: K.K. Ryckman (Ed.), PLOS ONE 13 (10) (2018 Oct 19), e0205979.
[7] C. Osmond, D.J.P. Barker, Fetal, Infant, and Childhood Growth Are Predictors of Coronary Heart Disease, Diabetes, and Hypertension in Adult Men and Women, Environ Health Perspect 108 (2000) 9.

[8] K.R. Risnes, L.J. Vatten, J.L. Baker, K. Jameson, U. Sovio, E. Kajantie, M. Osler, R. Morley, M. Jokela, R.C. Painter, et al., Birthweight and mortality in adulthood: a systematic review and meta-analysis, Int J Epidemiol 40 (3) (2011 Jun) 647–661.

[9] H. Blencowe, J. Krasevec, M. de Onis, R.E. Black, X. An, G.A. Stevens, E. Borghi, C. Hayshi, D. Estevez, L. Cegolon, et al., National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis, Lancet Glob Health 7 (7) (2019 Jul) e849–e860.

[10] J.E. Lawn, H. Blencowe, S. Oza, D. You, A.C. Lee, P. Waiswa, M. Lalli, Z. Bhutta, A.J.D. Barros, P. Christian, et al., Every Newborn: progress, priorities, and potential beyond survival, The Lancet 384 (9938) (2014 Jul) 189–205.

[11] A.K. Amegah, R. Quansah, J.J.K. Jaakkola, Household Air Pollution from Solid Fuel Use and Risk of Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis of the Empirical Evidence, PLoS ONE 9 (12) (2014 Dec 2), e113920.

[12] S.P.K. Nasanen-Gilmore, S. Saha, I. Rasul, E.K. Rousham, Household environment and behavioral determinants of respiratory tract infection in infants and young children in northern Bangladesh, Am J Hum Biol 27 (6) (2015 Nov) 851–858.

[13] D.P. Pope, V. Mishra, L. Thompson, A.R. Siddiqui, E.A. Rehfuess, M. Weber, N. Bruce, Risk of Low Birth Weight and Stillbirth Associated With Indoor Air Pollution From Solid Fuel Use in Developing Countries, Epidemiol Rev 32 (1) (2010 Apr 1) 70–81.

[14] A. Rahman, M. Vahter, A.H. Smith, B. Nermell, M. Yunus, S. El Arifeen, L.Å. Persson, E.L. Ekström, Arsenic Exposure During Pregnancy and Size at Birth: A Prospective Cohort Study in Bangladesh, Am J Epidemiol 169 (3) (2008 Nov 25) 304–312.

[15] B. Walia, B.L. Kmush, S.D. Lane, T. Endy, A. Montresor, D.A. Larsen, Routine deworming during antenatal care decreases risk of neonatal mortality and low birthweight: A retrospective cohort of survey data. Chai jong Y, editor, PLoS Negl Trop Dis 15 (4) (2021 Apr 29), e0009282.

[16] B.J. Wylie, Y. Kishashu, E. Matechi, Z. Zhou, B. Coull, A.I. Abioye, K.L. Dionisio, F. Mugusi, Z. Premji, et al., Maternal exposure to carbon monoxide and fine particulate matter during pregnancy in an urban Tanzanian cohort, Indoor Air 27 (1) (2017 Jan) 136–146.

[17] S. Passarelli, S. Bromage, A.M. Darling, J. Wang, S. Aboud, F. Mugusi, J.K. Griffiths, W. Fawzi, Aflatoxin exposure in utero and birth and growth outcomes in Tanzania, Matern Child Nutr [Internet] 16 (2) (2020 Apr).

[18] V. Moghaddam-Hosseini, A. Dowlatabadi, M.L. Najafi, M. Ghalenovi, N.S. Pajohanfar, S. Ghezi, S. Mehrabadi, E.H. Estiri, M. Miri, Association of traffic-related air pollution with Newborn's anthropometric indexes at birth, Environ Res 204 (2022 Mar 1), 112000.

[19] L. Cameron, C. Chase, D. Contreras Suarez, Relationship between water and sanitation and maternal health: Evidence from Indonesia, World Dev 147 (2021 Nov 1), 105637.

[20] A. Prüss-Ustün, J. Wolf, J. Bartram, T. Clasen, O. Cumming, M.C. Freeman, B. Gordon, P.R. Hunter, K. Medlicot, R. Johnston, Burden of disease from inadequate water, sanitation and hygiene for selected adverse health outcomes: An updated analysis with a focus on low- and middle-income countries, Int J Hyg Environ Health 222 (5) (2019 Jun 1) 765–777.

[21] C. Yuill, C. McCourt, H. Cheyne, N. Leister, Women's experiences of decision-making and informed choice about pregnancy and birth care: a systematic review and meta-synthesis of qualitative research, BMC Pregnancy Childbirth 20 (1) (2020 Jun 10) 343.

[22] A. Symon, J. Pringle, S. Downe, V. Hundley, E. Lee, F. Lynn, A. McFadden, J. McNeil, M.J. Renfrew, M. Ross-Davie, Antenatal care trial interventions: a systematic scoping review and taxonomy development of care models, BMC Pregnancy Childbirth 17 (1) (2017 Dec) 8.

[23] P.J. Hunter, Y. Muthiani, P.K. Nasanen-Gilmore, A.M. Koivu, P. Portfors, K. Bastola, R. Vimpeli, J. Luoma, U. Ashorn, P. Ashorn, A modular systematic review of antenatal interventions to address undernutrition during pregnancy in the prevention of low birth weight, Am J Clin Nutr 117 (2023) S134–S147.

[24] Y. Muthiani, P.J. Hunter, P.K. Nasanen-Gilmore, A.M. Koivu, J. Isojarvi, J. Luoma, M. Salenius, M. Hadji, U. Ashorn, P. Ashorn, Antenatal interventions to reduce risk of low birth weight related to maternal infections during pregnancy, Am J Clin Nutr 117 (2023) S118–S133.

[25] A.M. Koivu, T. Haapaniemi, S. Askari, N. Bhandari, R.E. Black, R. Matthew Chico, K.G. Dewey, C.P. Duggan, N. Klein, S. Kumar, J.E. Lawn, K. Manji, P.K. Nasanen-Gilmore, M. Salasibew, K.E.A. Semrau, U. Ashorn, P. Ashorn, The LBW prevention prioritization working group. What more can be done? Prioritizing the most promising antenatal interventions to improve birth weight, Am J Clin Nutr 117 (2023) S107–S117.

[26] A.M. Koivu, P.J. Hunter, P. Näsänen-Gilmore, Y. Muthiani, J. Isojärvi, P. Pörtfors, U. Ashorn, P. Ashorn, Modular literature review: a novel systematic search and review method to support priority setting in health policy and practice, BMC Med Res Methodol 21 (1) (2021 Dec) 268.

[27] Ritchie, Hannah, Roser, Max. Air Pollution [Internet]. Published online at OurWorldInData.org.; Available from: 'https://ourworldindata.org/air-pollution' [Online Resource].

[28] S. Hartinger, V. Tapia, C. Carrillo, L. Bejarano, G.F. Gonzales, Birth weight at high altitudes in Peru, Int J Gynecol Obstet 93 (3) (2006 Jun) 275–281.

[29] E. Malacova, A. Regan, N. Nassar, C. Raynes-Greenow, H. Leonard, R. Srinivasjois, A.W. Shand, T. Lavin, G. Pereira, Risk of stillbirth, preterm delivery, and fetal growth restriction following exposure in a previous birth: systematic review and meta-analysis, BJOG Int J Obstet Gynaecol 125 (2018) 183–192.

[30] H. Schünemann, J. Brożek, G. Guyatt, A. Oxman, GRADE handbook for grading quality of evidence and strength of recommendations [Internet], The GRADE Working Group, 2013. Available from: Available Guidel Orghandbook. 2013.

[31] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ (2021 Mar 29) n71.

[32] World Health Organization Regional Office for Europe, Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide, World Health Organization. Regional Office for Europe, 2006.

[33] K.F. Austin, M.T. Mejia, Household air pollution as a silent killer: women's status and solid fuel use in developing nations, Popul Environ 39 (1) (2017 Sep 1) 1–25.

[34] A. Vanker, W. Barnett, L. Workman, P.M. Nduru, P.D. Sly, R.P. Gie, H.J. Zar, Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study, Lancet Planet Health 1 (8) (2017 Nov 1) e328–e336.

[35] J. Katz, J.M. Tielsch, S.K. Khatry, L. Shrestha, P. Breysse, S.L. Zeger, N. Kozuki, W. Checkley, S.C. LeClerg, L.C. Mullary, Impact of Improved Biomass and Liquid Petroleum Gas Stoves on Birth Outcomes in Rural Nepal: Results of 2 Randomized Trials, Glob Health Sci Pract 8 (3) (2020 Sep 30) 372–382.

[36] World Health Organization, WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide, World Health Organization, 2021.

[37] R.W. Allen, P.K. Barn, B.P. Lanphear, Randomized controlled trials in environmental health research: unethical or underutilized? PLoS Med 12 (1) (2015 Jan 6) e1001775, e1001775.

[38] World Health Organization, Guideline: preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups [Internet], World Health Organization, Geneva, 2017 [cited 2022 Jun 9]. Available from: https://apps.who.int/iris/handle/10665/260297.

[39] B. Imhoff-Kunsch, V. Briggs, Antihelminthics in Pregnancy and Maternal, Newborn and Child Health, Paediatr Perinat Epidemiol 26 (s1) (2012) 223–238.

[40] P. Barn, E. Gombojav, C. Ochir, B. Boldbaatar, B. Beejin, G. Naidan, J. Gallsuren, B. Legtseg, T. Byambaa, J.A. Hutcheon, C. Janes, et al., The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: The UGAAR randomized controlled trial, Environ Int 121 (2018 Dec) 981–989.

[41] S. Kannan, D.P. Misra, J.T. Dvonch, A. Krishnakumar, Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition, Environ Health Perspect 114 (11) (2006 Nov) 1636–1642.

[42] World Health Organisation. Soil-transmitted helminth infections, fact-sheet [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections.

[43] K.G. Dewey, D.R. Mayers, Early child growth: how do nutrition and infection interact?. Maternal & Child Nutrition, Matern Child Nutr 7 (2011) 129–142.

[44] The WHO/UNICEF Joint Monitoring Programme (JMP), 2020. Available from: https://washdata.org/data.

[45] I. Chen, N. Opiyo, E. Tavender, S. Mortazhejri, T. Rader, J. Petkovic, S. Yogosingam, M. Taljaard, S. Agarwal, M. Laopaiboon, et al., Non-clinical interventions for reducing unnecessary caesarean section. Cochrane Effective

Practice and Organisation of Care Group, Cochrane Database Syst Rev [Internet] (2018 Sep 28) [cited 2022 Jan 11];2018(9).

[46] J.C. Tremblay, P.N. Ainslie, Global and country-level estimates of human population at high altitude, Proc Natl Acad Sci 118 (18) (2021 May 4), e2102463118.

[47] L.M. Thompson, N. Bruce, B. Eskenazi, A. Diaz, D. Pope, K.R. Smith, Impact of Reduced Maternal Exposures to Wood Smoke from an Introduced Chimney Stove on Newborn Birth Weight in Rural Guatemala, Environ Health Perspect 119 (10) (2011 Oct) 1489–1494.

[48] R.A. Salam, B.A. Haider, Q. Humayun, Z.A. Bhutta, Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy. Cochrane Pregnancy and Childbirth Group, Cochrane Database Syst Rev [Internet, 2015 Jun 18 [cited 2021 Sep 6].

[49] S.K. Tracy, D.L. Hartz, M.B. Tracy, J. Allen, A. Forti, B. Hall, J. White, A. Lainchbury, H. Stapleton, M. Beckmann, et al., Caseload midwifery care versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial, The Lancet 382 (9906) (2013 Nov) 1723–1732.