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Review Article

Association between Maternal Exposure to Arsenic during Pregnancy and Risk of Preterm Birth: A Systematic Review and Meta-Analysis

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Abstract

Background: Several observational studies have suggested that maternal exposure during pregnancy to arsenic is associated with the risk of preterm birth (PTB); however, available evidence is inconsistent. Therefore, we aimed to explore the relation of maternal exposure to arsenic to PTB risk.

Methods: A comprehensive systematic search was carried out from inception to April 2023 in PubMed and Scopus to retrieve all relevant studies. A pooled odds ratio (OR) with corresponding 95% confidence interval (CI) was employed using a random effects model to test the association.

Results: As a result, 14 eligible studies, with 12,619 participants, were included in the meta-analysis. Overall, the pooled OR of all analyzed studies indicated that higher maternal arsenic exposure is significantly related to the 1.12-fold increased odds of PTB (OR = 1.12, 95% CI = 1.04-1.21), with a remarkable heterogeneity across studies (P = <0.001, I^2 = 70.9%). This association was found in prospective cohort studies (OR = 1.15, 95% CI = 1.05-1.26), but not in non-cohort studies. In the stratified analysis, the majority of subgroups supported the association of arsenic with PTB.

Conclusion: Maternal exposure to arsenic during pregnancy is directly linked to the odds of PTB. Future studies are suggested to investigate the effectiveness of specific measures to decrease exposure to arsenic in high-risk communities, particularly in pregnant women.

Keywords: Arsenic; Preterm birth; Pregnancy; Meta-analysis

Introduction

Preterm birth (PTB), defined as birth at gestational age < 37 weeks, is a significant public health concern that affects up to 10% of all pregnancies and is responsible for a significant proportion of neonatal morbidity and mortality (1). Each year, over 15 million preterm babies are born in the world (2). Additionally, PTB contributes to 16% of mortalities in children under the

age of five and 35% of total neonatal deaths (3). Thus, identifying potential risk factors of PTB is essential to develop preventive approaches to decrease its health burdens.

Although the etiology of PTB is not well-recognized yet, smoking, a low education level, older maternal age, air pollution, unhealthy dietary patterns, a higher body mass index (BMI), and gestational diabetes has been identified as some risk factor for PTB (3, 4). Maternal exposure to certain environmental toxins can adversely affect pregnancy outcomes (2, 5).

In this line, arsenic exposure has been highlighted as a potential contributor to adverse pregnancy outcomes (6). Arsenic is a toxic metalloid that can cross the placental barrier and unfavorably affect fetal growth and development (7). Overall, increased arsenic exposure during pregnancy through various mechanisms, including oxidative stress, DNA damage, immune response, and epigenetic changes that can affect fetal development (8). Arsenic exposure may occur through ingestion of contaminated drinking water, dietary intake, and other environmental sources such as polluted air (9). The WHO has listed arsenic as one of the major toxic chemicals of public health concern (10). The prevalence of arsenic poisoning in pregnant women varies depending on the population and location. Studies conducted in Bangladesh have reported that 31.9% of pregnant women are affected by arsenic poisoning (11).

Accumulating investigations have examined the association between maternal exposure to arsenic during pregnancy and the risk of PTB, but the findings have been inconsistent (3, 12). While some studies reporting a significant direct relationship between higher concentrations of arsenic in serum (2), toenail (12), whole blood (1), and cord blood (13) and odds of PTB, other studies failed to find an association in urine (14), whole blood (15), and hair (3). Inconsistent results may be due to differences in type of exposure, time of sampling, study design, or limited power of individual studies to disclose relations because of small sample sizes. To date, no meta-analyses has investigated the relationship between arsenic and PBT.

Therefore, we aimed to evaluate the association between maternal exposure to arsenic during pregnancy in various biological samples and the risk of PTB by combining the results of available studies. The results of this meta-analysis may provide insights for future research and may have implications for public health interventions aimed at reducing the incidence of PTB in populations exposed to high levels of arsenic.

Methods

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to perform this study (16).

Search strategy

A systematic search was carried out in PubMed and Scopus to find all pertinent publications from inception to April 2023. The following terms were applied for search: ("Arsenic"[Mesh] OR Arsenic[Title/Abstract] OR arsenicals[Title/Abstract] OR arsenicosis[Title/Abstract] OR arsenite[Title/Abstract] OR arsenate[Title/Abstract]) AND ("Pregnancy Outcome"[Majr] OR Pregnancy Outcome*[Title/Abstract] OR birth outcome*[Title/Abstract] OR fetal outcome*[Title/Abstract] OR fetus outcome*[Title/Abstract] OR perinatal outcome*[Title/Abstract] OR adverse outcome*[Title/Abstract] OR preterm[Title/Abstract] OR premature[Title/Abstract] OR "Premature Birth"[Majr]) AND ("Pregnancy"[Mesh] OR Pregnancy[Title/Abstract] OR pregnant[Title/Abstract] OR gestational[Title/Abstract] OR gestation[Title/Abstract] OR maternal[Title/Abstract] OR prenatal[Title/Abstract] OR mother*[Title/Abstract]). The search was restricted to English publications. Furthermore, the reference lists of included publications and reviews were screened manually to identify missing papers.

Eligibility criteria

Studies were included according to the following criteria: 1) studies with observational design (cohort, cross-sectional, or case-control); 2) investigated the relationship between maternal exposure to arsenic in different biological samples and risk of PTB (birth at <37 completed gestational weeks); 3) provided odds ratios (OR) or relative risk (RR) and their 95% confidence intervals (CI) or appropriate data to calculate the effect sizes; 4) the full-text of studies was available. Studies with insufficient data, studies with overlapped data, reviews, editorials, letters, animal studies, and studies on environmental exposures (air, soil, and water) were all excluded.

Data extraction and quality assessment

Data extraction was carried out independently by two researchers and any disagreement was resolved by discussion among all authors. The following items were obtained from eligible publications with the use of a data extraction form: first author's name and year of publication, region of study, trimester of sampling (first trimester: 0 to ≤3 months of pregnancy, second trimester: 3> to ≥6 months of pregnancy, third trimester: 6> to ≥9 months of pregnancy), age of participants, specimen type, effect sizes for associations (OR or RR and 95% CI), the laboratory method used to assess arsenic concentrations, sample size, study design, and adjustment variables. Using the Newcastle–Ottawa Scale (NOS) (17), the quality of studies was estimated by two reviewers. Bases on NOS, studies with a score of 0– 3, a score of 4–6, and a score of 7–9 were considering as low, moderate, and high quality, respectively.

Statistical analysis

The OR and RR with their 95% CI was used as the measure of effect size to test the association of arsenic exposure in various biological samples with PTB risk. The pooled effect size was reported as OR and 95% CI. The heterogeneity across the included publications was examined with the use of Cochran Q and I^2 and statistics; $p < 0.1$ or $I^2 < 50\%$ were considers as statistically significant heterogeneity (18). Because of the anticipated heterogeneity, data were pooled using a random effects model (19). In addition, subgroup analysis based on study design (prospective cohort vs. non-cohort), sample type (whole blood, serum, cord blood, toenail, hair, and urine), and time of sampling (first trimester, second trimester, third trimester, and postpartum) was conducted to reveal possible sources of heterogeneity. Publication bias was testes using the Egger's tests and reported in funnel plots (20, 21). Sensitivity analysis was also performed to evaluate the impact of each publication on the pooled effect sizes. Stata version 14 (Stata Corp, College Station, TX, USA) was applied to perform the analyses.

Results

Characteristics of the studies

The initial systematic search retrieved 599 publications. Of which, 136 publications were removed because of duplication and 409 articles were excluded after screening the titles/abstracts. After additional screening of the full-texts of potentially relevant studies (n = 54), a total of 14 papers (with 16 effect sizes) including a total of 12,619 participants (1-3, 6, 10, 12-15, 22-26), published during 2017 to 2023, finally met the inclusion criteria to be included in the present meta-analysis. Figure 1 presents the process of study selection.

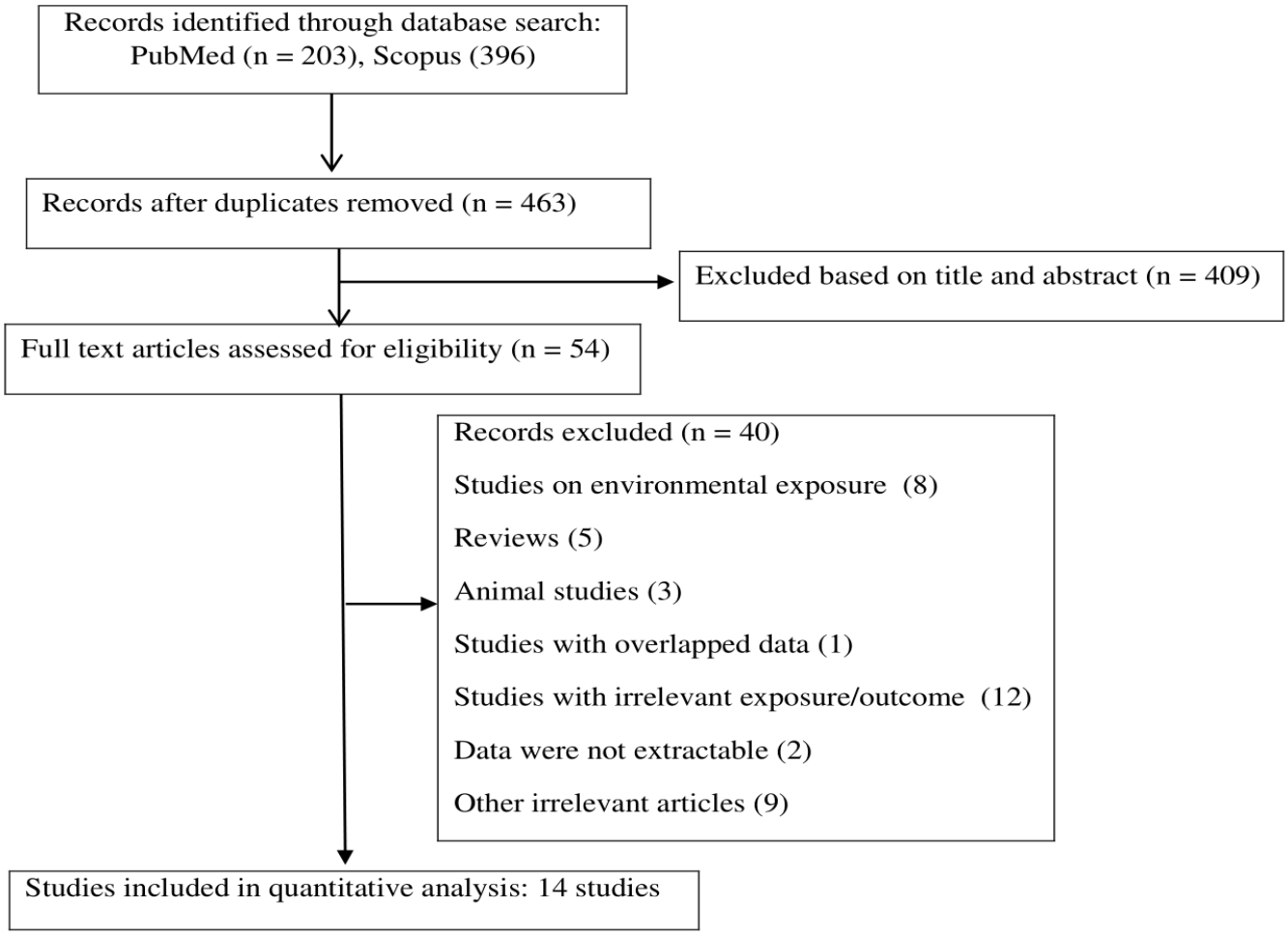

Fig. 1: Flow chart for studies selection

The majority of the analyzed publications were performed in Asia (n=7) (2, 3, 6, 12, 13, 24, 26), followed by the north/south America (n=6) (1, 14, 15, 22, 23, 25), and Africa (n=1) (10). Most of the included articles applied a prospective cohort design (n=9) (1, 2, 6, 10, 12, 13, 22-24), while 3 studies were cross-sectional (14, 15, 25) and 2 studies were case-control (3, 26) in design. Regarding the sampling type of arsenic, there were 3 studies, with 5 effect sizes, on serum (2, 6, 26), 4 studies on whole blood (1, 15, 22, 25), 4 studies on urine (10, 14, 23, 24), 1 study on toenail (12), 1 study on hair (3), and 1 study on cord blood (13). Among the included studies, 4 (2, 3, 15, 26), 5 (2, 10, 14, 22, 26), 2 (23, 24), 1 (6), 1 (1), and 3 (12, 13, 25) studies investigated the association of arsenic exposure to PTB in the first, second, third, first/second, and second/third trimesters and in postpartum, respectively. The results for all included studied had been adjusted for potential covariates. The quality of the studies, measured by the NOS, was high, with the scores ranging between 7 and 9 (Table 1).The descriptive characteristics of included articles are presented in Table 2.

Table 1: Quality assessment of studies included in this systematic review and meta-analysis[1]

Prospective studies (reference)	***Representativeness of the exposed cohort***	***Selection of the non-exposed cohort***	***Ascertainment of exposure***	***Demonstration that outcome of interest was not present at start of study***	***Study controls for maternal age***	***Study controls for any additional factor***	***Assessment of outcome***	***Was follow-up long enough for outcomes to occur ≥ 6 month)***	***Adequacy of follow up of cohorts (loss-to-follow up <20%)***	***Total score***
Rahman et al. 2018 (12)	*	*	*	*	*	*	*	NA	*	8
Huang et al. 2021 (2)	*	*	*	*	*	*	*	*	NA	8
Kim et al. 2018 (23)	*	*	*	*	*	*	*	NA	NA	7
Wai et al. 2017 (24)	*	*	*	*	*	*	*	NA	*	8
Fisher et al. 2023 (1)	*	*	*	*	*	*	*	NA	NA	7
Huang et al. 2021 (13)	*	*	*	*	*	*	*	NA	NA	7
Nyanza et al. 2020 (10)	*	*	*	*	*	*	*	NA	*	8
Ashrap et al. 2020 (22)	*	*	*	*	*	*	*	NA	*	8
Wang et al. 2018 (6)	*	*	*	*	*	*	*	*	NA	8

Cross-sectional studies

	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Study controls for maternal age	Study controls for any additional factor	Ascertainment of outcome	Statistical test	Total score
Xu et al. 2022 (25)	*	*	NA	*	*	*	**	*	8
Fano-Sizgorich et al. 2021 (14)	*	NA	NA	*	*	*	**	*	7
Bank-Nielsen et al. 2019 (15)	*	*	NA	*	*	*	**	*	8
Ren et al. 2022 (3)	*	*	NA	*	*	*	**	*	8
Yu et al. 2019 (26)	*	*	NA	*	*	*	**	*	8

[1]According to the Newcastle-Ottawa Scale (NOS) criteria
NA: Not Applicable

Table 2: Characteristics of included studies

Reference	*Year*	*Location*	*Arsenic assessment Age of mother, years (mean ± sd)*	*Sample type*		*Sampling time*	*Adjustment*
Rahman et al(12)	2018	Bangladesh	22·97 ± 3·94	Toenail	ICP-MS	Postpartum	Maternal age, education, enrollment BMI, number of past pregnancies, secondhand smoking, child marriage and pregnancy weight gain
Xu et al.(25)	2022	Argentina	28.8 ± 6.6	Whole blood	ICP-MS	Postpartum	Maternal age, parity, pre-pregnancy BMI, smoking, and education
Huang et al. (2)	2021	Bangladesh	22.72±4.01	Serum	ICP-MS	First trimester Second trimester	BMI, parents' education level, income levels, and marriage age, maternal baseline age, secondhand smoking status and number of previous pregnancies
Fano-Sizgorich et al.(14)	2021	Peru	28.16 ± 6.08	Urinary	ICP-MS	Second trimester	Mother's age, pre-gestational BMI, newborn's sex, parity, and education.
Bank-Nielsen et al.(15)	2019	Greenland	27.5 ± 5.0	Whole blood	ICP-MS	First trimester	Age, BMI, alcohol during pregnancy, cotinine, parity, n-3/n-6 ratio and region
Kim et al.(23)	2018	USA	32.2 ± 1.6	Urinary	ICP-MS	Third trimester	specific gravity, maternal age, race, education, pre-pregnancy BMI, gestational age at time of sample collection
Wai et al.(24)	2017	Myanmar	27.9 ± 6.6	Urinary	ICP-MS	Third trimester	Maternal age, maternal education, the baby's sex, smoking status, the gestational age, being primigravida and antenatal visits
Fisher et al.(1)	2023	Canada	≥18	Whole blood	ICP-MS	Second/third trimester	Maternal age, pre-pregnancy BMI, season, fish consumption, self-reported walking and smoking.
Ren et al.(3)	2022	China	NR	Hair	ICP-MS	First trimester	Age, BMI, education level, parity, aquatic food intake, decavitamin supplement and anemia status
Huang et al.(13)	2021	Bangladesh	22.83 ±4.10	Cord blood	ICP-MS	Postpartum	Maternal age, marriage age, maternal BMI, maternal education level, paternal education level, second-hand smoking, and family income
Nyanza et al.(10)	2020	Tanzania	25.5±6.3	Urinary	ICP-MS	Second trimester	Folic acid uptake, gravidity, maternal age, marital status, maternal education, maternal occupa-

Table 2: Continued...

							tion, place of delivery, history of preterm birth and socioeconomic status, and sex of the infants
Ashrap et al.(22)	2020	Puerto Rico	26.7 ± 5.7	Whole blood	ICP-MS	Second trimester	Maternal age, maternal education, pre-pregnancy BMI, and exposure to secondhand smoking.
Yu et al.(26)	2019	China	25.84 ± 4.77	Serum	ICP-MS	First trimester Second trimester	Maternal age, BMI, education, occupation, residence, gravidity, parity, spontaneous abortion history, folic acid use, drug use, passive smoking, and child gender
Wang et al.(6)	2018	China	27.5 ± 3.2	Serum	Hydride generation-atomic fluorescence spectrometry	First/second trimester	Maternal serum cadmium level, maternal pre-pregnancy BMI, maternal age, parity, gravidity, and monthly income

ICP-MS: Inductively coupled plasma mass spectrometry; BMI: body mass index

Overall and subgroup analysis of pooled data

Overall, when all effect sizes were pooled using a random effects model, arsenic exposure during pregnancy was significantly associated with a 12% increased risk of PTB (OR = 1.12, 95% CI = 1.04-1.21) (Fig. 2), and a remarkable heterogeneity was detected across the studies (P = <0.001, I^2 = 70.9%). This association was supported by prospective cohort studies (OR = 1.15, 95% CI = 1.05-1.26) (Table 3). The subgroup analysis by sample type revealed that higher maternal arsenic level in serum (OR = 1.35, 95% CI = 1.37-1.70), toenail (OR = 1.13, 95% CI = 1.03-1.24), and cord blood (OR = 1.34, 95% CI = 1.04-1.73) was positively related to PTB, while no such relationship was observed for whole blood and urinary exposure (Table 3). Moreover, the significant relationship between arsenic exposure and PTB was found for studies with sampling time during first/second trimester (OR = 1.50, 95% CI = 1.08-2.09), second/third trimester (OR = 1.10, 95% CI = 1.02-1.19), and postpartum (OR = 1.15, 95% CI = 1.06-1.26) (Table 3).

Sensitivity analysis and publication bias

In the sensitivity analysis the pooled OR and 95% CI ranged from OR = 1.09 (95% CI = 1.01-1.17) to OR = 1.15 (95% CI = 1.05 -1.26) by removing single studies, indicating that the pooled effect size was not significantly modified by individual studies (Fig. 3). A significant evidence for publication bias was observed (P-value for Egger's test = 0.01) (Fig. 4). The trim-and-fill analysis suggested 4 additional unpublished studies. Correction for potential publication bias using the trim-and-fill method was performed with 20 imputed studies, which altered the significant positive association between arsenic and PTB (OR = 1.05, 95% CI = 0.97-1.14).

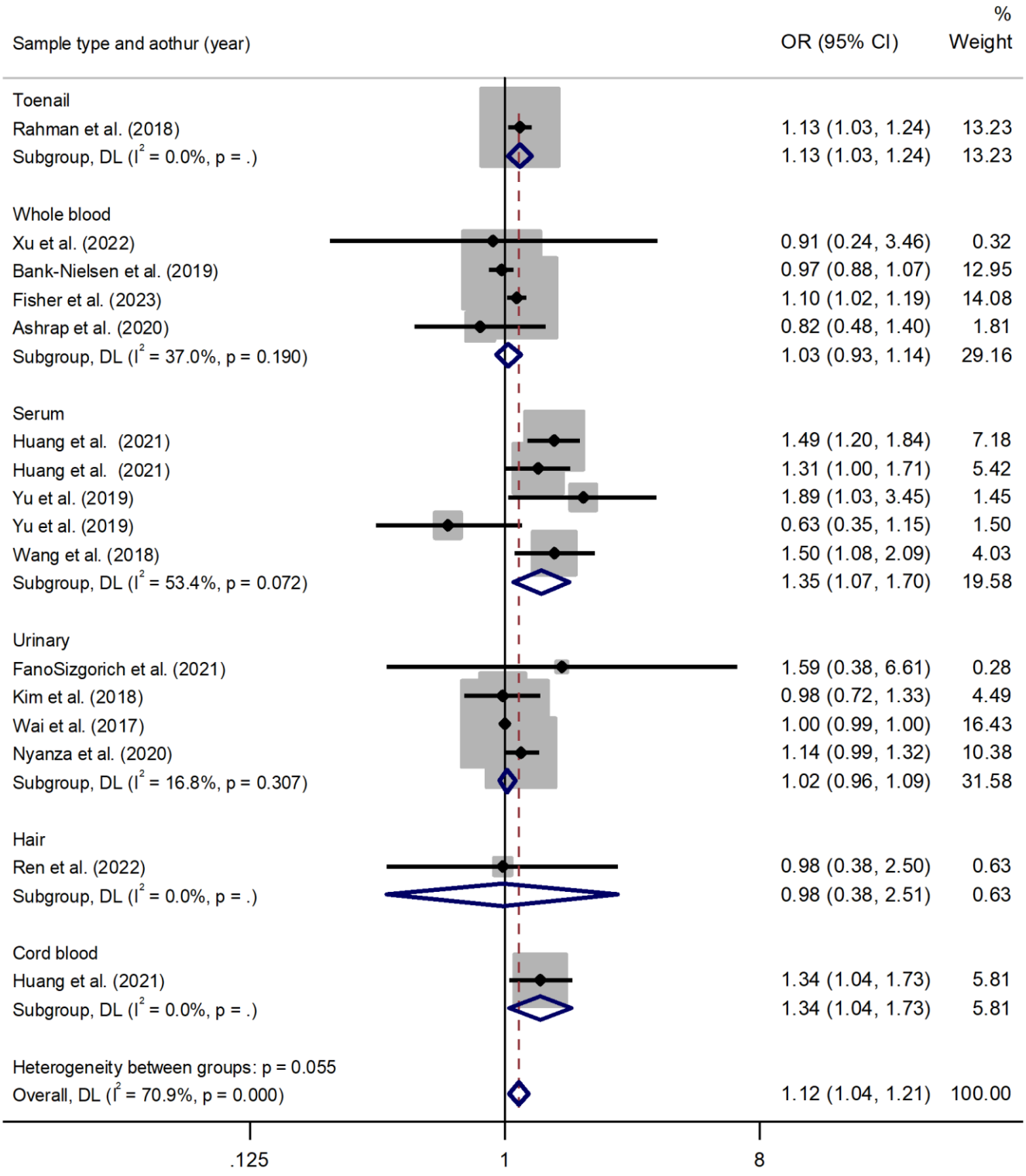

Fig. 2: Forest plot of the pooled data for the association between maternal arsenic and risk of PTB by type of sample

Table 3: Subgroup analysis for the association between arsenic exposure during pregnancy and risk of preterm birth stratified by study design, sample type, and sampling time

Variable			*Test of association*		*Test of heterogeneity*	
Subgroup by	Subgroups	Effect sizes	Odd ratio	95%CI	I^2 (%)	P
	Overall	16	1.12	1.04 to 1.21	70.9	<0.001
Study design	Prospective cohort	10	1.15	1.05 to 1.26	79.6	<0.001
	Non-cohort	6	1.02	0.77 to 1.36	30.0	0.21
Sample type	Serum exposure	5	1.35	1.37 to 1.70	53.4	0.07
	Whole blood exposure	4	1.03	0.93 to 1.14	37.0	0.19
	Urinary exposure	4	1.02	0.96 to 1.09	16.8	0.30
	Toenail exposure	1	1.13	1.03 to 1.24	-	-
	Hair exposure	1	0.98	0.38 to 2.51	-	-
	Cord blood	1	1.34	1.04 to 1.73	-	-
Sampling time	First trimester	4	1.27	0.89 to 1.80	81.8	<0.001
	Second trimester	5	1.08	0.88 to 1.34	38.3	0.16
	Third trimester	2	1.00	0.99 to 1.01	0.0	0.89
	First/second trimester	1	1.50	1.08 to 2.09	0.0	0.38
	Second/third trimester	1	1.10	1.02 to 1.19	-	-
	Postpartum	3	1.15	1.06 to 1.26	0.0	0.44

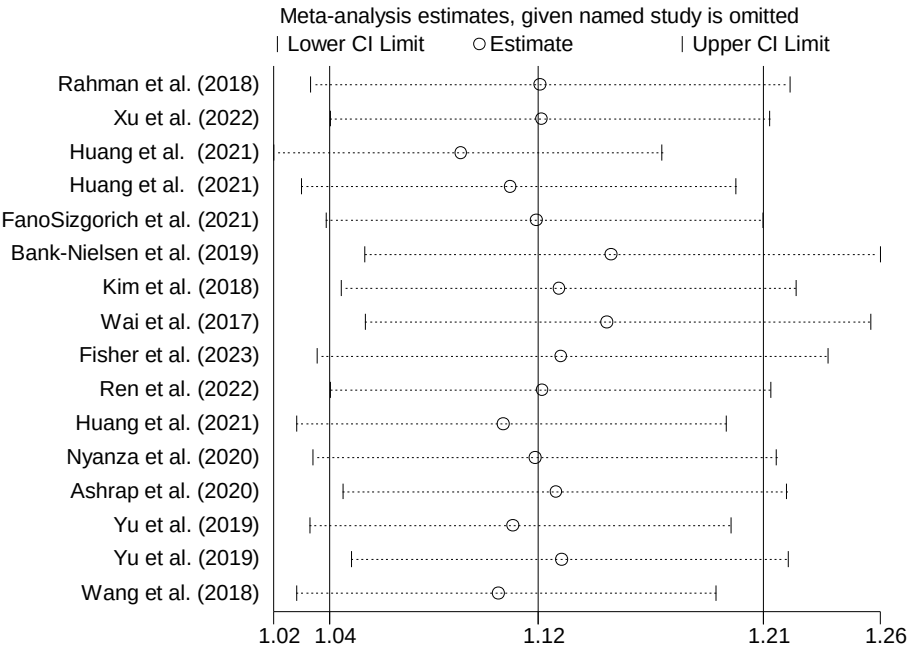

Fig. 3: Sensitivity analysis graph for included studies

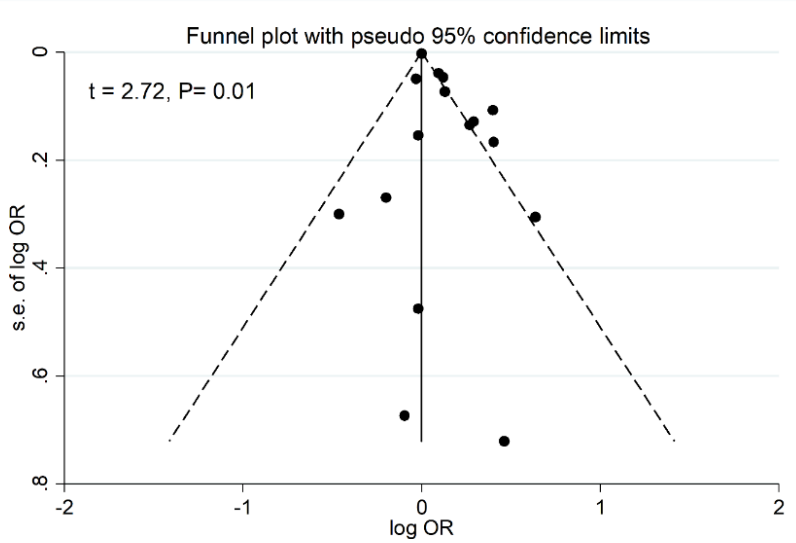

Fig. 4: Funnel plot for publication bias

Discussion

In the present meta-analysis, we systematically explored the association of maternal arsenic exposure during pregnancy with the odds of PTB. In general, the analyses revealed a significant direct association between arsenic exposures of pregnant women with the risk of PTB.

In the present meta-analysis, the increased risk of PTB due to arsenic exposure was supported by cohort studies, but not non-cohort studies. We included 10 effect sizes from cohort studies but 6 effect sizes for non-cohort studies. The significant association observed in cohort studies may be due to the higher statistical power to detect the true association. Moreover, cohort studies are generally considered more reliable than non-cohort studies because they follow participants over time, may have better exposure assessment methods, and may better control for potential confounding factors, which can affect the association between arsenic exposure and PTB. Non-cohort studies, on the other hand, may be more prone to bias and confounding. The heterogeneous results detected in the exploratory subgroup analyses by sample type and sampling time should be interpreted with caution as small number of studies were included in each subgroup. Future studies using various sample types and sampling times could improve our understanding of the effect of the differences in sample type and sampling time on the association between arsenic exposure and PTB.

It is well recognized that PTB is a main cause of neonatal mortality (6). The association between gestational arsenic exposure in biological samples and PTB among previous studies has been inconclusive with positive (1, 2) or null (22) results; these inconsistencies could be due to differences in type of sampling or sampling time (different trimesters). The findings of the present meta-analysis are in agreement with previous studies that has identified higher odds of PTB in regions with higher environmental arsenic pollution as compared with regions with lower exposures (27, 28). Evidence from populations in Bangladesh (27) and USA (29) also found that exposure to arsenic during pregnancy through drinking water remarkably elevated PTB incidence. Moreover, confirming our results, Rahman et al. (12) showed that decreasing arsenic exposure could significantly diminish the odds of PTB. Our results have significant implications for maternal-neonatal health in arsenic contaminated regions to optimize fertility (30). Accordingly, specific measures should be implemented to decrease ex-

posure to arsenic in high-risk communities, particularly in pregnant women. Since contaminated drinking water has been the leading source of arsenic exposure during the recent decades (31), safe water programs and remediation activities could be among required actions to reduce the burden of arsenic exposure (32). Nevertheless, the rate of arsenic exposure remains high at the populations levels and has reduced slowly only in recent years (33).

The underlying mechanisms by which arsenic may increase the risk of PTB are complex and not yet fully understood. Arsenic can cross the placenta and accumulate in fetal tissues. Arsenic exposure during pregnancy can induce premature birth by several interrelated mechanisms related to inflammation, oxidative stress, hormonal imbalance, vasoconstriction, impaired placenta formation, and DNA damage (9). Arsenic induces the activation of immune cells, predominantly macrophages and neutrophils, and the subsequent release of inflammatory cytokines, such as IL(interleukin)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) (34). These cytokines can cause premature rupture of the fetal membranes or trigger contractions of the uterus leading to preterm labor (35). The increased production of prostaglandins, which are powerful uterine stimulants, further drives the onset of labor and premature delivery (36). Arsenic also promotes the generation of reactive oxygen species (ROS), leading to oxidative stress both in the maternal and fetal tissues (37). ROS-induced damage to cellular structures, including proteins, lipids, and DNA, in the fetal membranes and the placenta can disturb the balance of enzymes and hormones responsible for maintaining pregnancy, leading to PTB (38-40). Arsenic can disrupt hormonal balance, leading to abnormal levels of stress hormones such as cortisol, catecholamines, and corticotropin-releasing hormone (CRH) (41). An excess of these hormones can stimulate the onset of early labor and lead to the premature delivery of the fetus (42). Moreover, arsenic exposure can cause vasoconstriction, resulting in restricted blood flow to the developing fetus, further increasing the likelihood of PTB (43). Impaired placenta formation and function are also associated with arsenic exposure during pregnancy resulting in increased risk of PTB (10). Arsenic exposure has been shown to interfere with the differentiation and invasion of trophoblast cells, which are essential for the development of placental blood vessels; this can lead to placental insufficiency, which decreases nutrient and oxygen delivery to the fetus, causing fetal distress and eventual PTB (44). Lastly, arsenic can induce DNA damage in fetal cells, which may trigger the death of fetal cells, leading to premature delivery (45). Understanding these mechanisms is crucial to promote effective preventive strategies to reduce exposure to environmental toxins, thereby protecting maternal and fetal health.

To the best of our knowledge, this is the first meta-analysis on the relationship between gestational exposure to arsenic and the risk of PTB. The study has some strengths. First, the majority of the analyzed publications were prospective birth cohorts, which are less prone to bias compared to non-cohort studies, improving the reliability of the findings. Second, the results of all studies were adjusted for potential covariate. However, several limitations of the current meta-analysis should be highlighted. First, there was a remarkable heterogeneity across the analyzed publications; subgroup analysis identified that the observed heterogeneity is partly due to differences in sample type, sampling time, and study design. Second, the number of studies in subgroups was relatively low, which may lead to false negative results because of low statistical power. Accordingly, the findings obtained from the stratified analyses should be interpreted cautiously. Third, the test of publication bias was significant; the present meta-analysis included English publications, which may has resulted in missing of studies. Correction for potential publication bias using the trim-and-fill method yielded a non- significant association between arsenic and PTB, indicating that the pooled analysis should be interpreted with caution due to the risk of bias. Lastly, we limited our search to PubMed, Scopus as

main databases related to our study, and other databases were not searched, which may result in publication bias.

Conclusion

This meta-analysis identified gestational exposure to arsenic as a significant risk factor for developing PTB. These results improve our knowledge of the unfavorable impacts of arsenic exposure during pregnancy on fetal outcomes and highlight the importance of diminishing prenatal exposure to arsenic by reducing the environmental arsenic pollution to improve fetal health. Additional investigations are required to explain the underling mechanisms linking arsenic to PTB. We suggest that future studies investigate the effectiveness of specific measures to decrease exposure to arsenic in high-risk communities, particularly in pregnant women. Safe water programs and remediation activities could be among required actions to reduce the burden of arsenic exposure.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Competing interest

The authors of this work have nothing to disclose

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