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Isaac Luginaah, Edith Clarke, Kissinger Marfoh,
Samuel Jerry Cobbina, Edward Nketiah-Amponsah,
Proscovia Bazanya Namujju, Samuel Obiri,
and Mawuli Dzodzomenyo**

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Association of Arsenic with Adverse Pregnancy Outcomes–Infant Mortality: A Systematic Review and Meta-Analysis

Reginald Quansah,^{1,2} Frederick Ato Armah,³ David Kofi Essumang,⁴ Isaac Luginaah,⁵ Edith Clarke,^{6,2} Kissinger Marfoh,⁷ Samuel Jerry Cobbina,⁸ Edward Nketiah-Amponsah,⁹ Proscovia Bazanya Namujju,¹⁰ Samuel Obiri,¹¹ and Mawuli Dzodzomenyo²

¹Centre for Environmental and Respiratory Health Research, Faculty of Medicine, University Of Oulu, Finland; ²Department of Biological, Environmental & Occupational Health Sciences, School of Public Health, College of Health Sciences, University of Ghana, Legon, Accra, Ghana; ³Environmental Health and Hazards Lab, Department of Geography, Western University, Canada; ⁴Environmental Health Group, Department of Chemistry, University of Cape Coast, Cape Coast, Ghana; ⁵Department of Geography, Western University Canada, Canada; ⁶Ghana Health Service, Accra, Ghana; ⁷Public Health Unit (Biostatistics), Korle-bu Teaching Hospital, Accra, Ghana; ⁸School of the Environment, Jiangsu University, Jiangsu, China; ⁹Department of Economics, University of Ghana, Legon, Ghana; ¹⁰Department of Child, Adolescent and Adult Health, National Institute for Health and Welfare, Oulu, and School of Health Sciences, University of Tampere, Finland; ¹¹Council for Scientific and Industrial Research, Accra, Ghana

Address correspondence to Reginald Quansah, Centre for Environmental and Respiratory Health Research, P.O. Box 5000, 90014 University of Oulu, Finland. Telephone: +358 (0)406 724 292. E-mail: Reginald.quansah@oulu.fi. CERH website: <http://www.oulu.fi/cerh>

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Abstract

Background: Exposure to arsenic is one of the major global health problems affecting over 300 million people worldwide, but its effects on human reproduction are uncertain.

Objectives: We conducted a systematic review and meta-analysis to examine the association between arsenic and adverse pregnancy outcomes/infant mortality.

Methods: We searched PubMed, Ovid MEDLINE (from 1946 to July 2013) and EMBASE (from 1988 to July 2013) databases; and the reference lists of reviews and relevant articles. Studies satisfying our *a priori* eligibility criteria were evaluated independently by two authors.

Results: Our systematic search yielded 888 articles from which 23 were included in the systematic review. Sixteen provided sufficient data for our quantitative analysis. Arsenic in ground water ($\geq 50 \mu\text{g/l}$) was associated with increased risk of spontaneous abortion (six studies: OR 1.98; 95% CI: 1.27, 3.10), stillbirth (nine studies: OR 1.77; 95% CI: 1.32, 2.36), moderate risk of neonatal mortality (five studies: OR 1.51; 95% CI: 1.28, 1.78) and infant mortality (seven studies: OR 1.35; 95% CI: 1.12, 1.62). Exposure to environmental arsenic was associated with a significant reduction in birth weight (four studies: $\beta = -53.2$ grams; 95% CI: $-94.9, -11.4$). There was paucity of evidence for low-to-moderate arsenic dose.

Conclusions: Arsenic is associated with adverse pregnancy outcomes and infant mortality. The interpretation of the causal association is hampered by methodological challenges and limited studies on dose-response. Exposure to arsenic continues to be a major global health issue and we therefore advocate for high quality prospective studies that include individual level data to quantify the impact of arsenic on adverse pregnancy outcomes/infant mortality.

Introduction

Arsenic contamination of drinking water, air, food and beverages is one of the major global health problems (Essumang 2009; Essumang et al. 2007; Hughes 2006; Obiri et al. 2010; Navas-Acien and Nachman 2013) that affect over 300 million people worldwide. This includes an estimated 13 million people in the U.S.A. and about 70 million people in Bangladesh (Murcott 2012). At concentrations above 50µg/l, inorganic arsenic (iAs) has been associated with excess cancer risk (e.g. bladder, kidney, liver, lung, skin and prostate) (Ahamed et al. 2006a; McDonald et al. 2007; Mink et al. 2008; Steinmaus et al. 2000, 2003; Walvekar et al. 2007), cardiovascular diseases (Moon et al. 2013; Navas-Acien et al. 2005), high blood pressure (Abhyankar et al. 2012; Moon et al. 2013; Navas-Acien et al. 2005), anemia in pregnancy (Hopenhayn et al. 2006; Navas-Acien et al. 2006), mortality from respiratory diseases in both adults and children (Ahamed et al. 2006b; Ferreccio and Sancha 2006; Walvekar et al. 2007), diabetes in adults (Navas-Acien et al. 2006); and neurodevelopment problems (Hamadani et al. 2011). At concentrations around 10 µg/L which is considered safe by the World Health Organization's provisional guideline (WHO, 2011), iAs may still cause cancer in the order of 0.1-0.3% and increased systolic blood pressure in women six weeks postpartum (IARC 2004; Kwok 2007). Inorganic arsenic easily crosses human and animal placenta and has been demonstrated to increase the risk of impaired fetal growth and infant mortality in laboratory animal studies (Navarro et al. 2004; Smith and Steinmaus 2009; Vahter 2009). Several epidemiologic studies (e.g. Cherry et al. 2010; Myers et al. 2010; Rahman et al. 2010) have examined the relation between arsenic and adverse pregnancy outcomes/infant mortality, and the findings are equivocal. Our understanding of arsenic exposure and adverse pregnancy outcomes is limited and at best fragmented. To our knowledge, no systematic review and/or meta-analysis

has reported on the effect of arsenic on human pregnancy and infant health. Given the widespread low through moderate to high arsenic exposure in the general population, an understanding of the impact of iAs on maternal and fetal health is relevant for public health policy.

To fill this gap, we conducted a systematic review and meta-analysis of epidemiologic studies to examine the association between arsenic exposure and the risk of spontaneous abortion, stillbirth, preterm delivery, birth weight, and neonatal/infant mortality.

Methods

Search strategy and study selection

This study was conducted in accordance with the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) group (Moher et al. 2009). We searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Ovid MEDLINE (<http://ovidsp.tx.ovid.com>) (from 1946 to July 2013) and EMBASE (<http://www.embase.com/login>) (from 1988 to July 2013) databases (Fig. 1), using the terms “arsenic”, “arsenicals”, “arsenite”, “arsenate” and “abortion, spontaneous”, “fetal mortality”, “preterm delivery”, “low birthweight”, “birthweight”, “infant mortality”, “neonatal mortality” (See Supplemental Material, Search Strategy). In addition, we searched the reference lists of reviews (Bloom et al. 2010; Smith and Steinmaus 2009; Vahter 2009) and potentially relevant articles. Two authors (RQ and FAA) independently evaluated the articles. Studies that fulfilled the following *a priori* eligibility criteria were included: if the study (1) was an original study; (2) was a cross-sectional, or a case-control or a cohort design (3) reported on any one or more of the following outcomes: spontaneous abortion, stillbirth, preterm delivery, birth weight, and neonatal/infant mortality, (4) presented data on

arsenic exposure determined using environmental measures (arsenic in drinking water or airborne arsenic, or arsenic in soil), or biomarkers, or indirect measures (e.g. residing in arsenic endemic area). Our exclusion criteria were: (1) the study was an experimental or a case report or a case series or a letter, (2) a study of arsenic compounds for which human exposure was unlikely (e.g. arsenic in roots of plants: Landgren 1996), (3) a study using job title or living close to a smelter house as surrogate for arsenic exposure and (4) a study that did not include our relations of interest.

If more than one report was published from the same study, the most recent study or the study using the best assessment of arsenic and/or outcome was included. For studies that reported estimates for more than one biomarker the estimate for the most appropriate biomarker was preferred. The order of preference was as follows: nail>hair>urine. If a study provided estimates for water and a biomarker, the estimate from the latter was used.

Data extraction and quality assessment

Most relevant characteristics of eligible studies including study design, study size, location and country of study, method of arsenic assessment, exposure marker for arsenic, exposure contrast, exposure dose, type of adverse pregnancy/infant mortality and their definitions, year of publication, year of data collection, adjustment for adequate confounders, and study results (i.e. measures of association) were recorded in a standard data extraction form (Quansah and Jaakkola 2010) independently by two authors (RQ and FAA). Any discrepancies were resolved by consensus. RQ and FAA applied the Newcastle-Ottawa Scale (NOS) (Wells et al. 2009) for observational studies to assess quality of eligible studies with the maximum score of 9. Studies

scoring 7 or more were categorized as high quality (See Supplemental Material, Tables S1 and S2).

Statistical methods

First, odds ratio (OR) or relative risk (RR) and their 95% confidence intervals (CIs) were derived or abstracted from eligible studies. Almost all the studies presented ORs and their 95% CIs and therefore we used ORs in our analysis. One study (Ahmad et al. 2001) presented adjusted odds ratios and exact p-values but not the 95 % CI, we calculated the 95 % CI from the p-values following Borenstein et al. (2009). Two studies (Guan et al. 2012; Rahman et al. 2007) presented RRs and these were converted to ORs (Zhang and Yu 1998). Some relevant studies presented ORs for more than 2 exposure levels for the outcomes and therefore in the meta-analysis we calculated summary ORs comparing our outcomes of interest (adverse pregnancy outcomes/infant mortality) in the highest (exposed group) and lowest (reference group) arsenic exposure categories presented in the studies. The exposed groups were heterogeneous and consisted of populations exposed to arsenic dose above the WHO guideline (i.e. $>10\mu\text{g/l}$) (WHO 2011). We separated the groups into high dose (exposed to $\geq 50\mu\text{g/l}$) and low-to-moderate dose (exposed to $<50\mu\text{g/l}$) for further analysis (explained below).

We applied the random-effects model (Borenstein et al. 2009), because we anticipated heterogeneity in the study-specific estimates. In the forest plots we presented summary ORs of the random-effects model. Heterogeneity was computed using the Q ($p < 0.1$ considered significant) - and I^2 - statistics (I^2 - statistics $> 50\%$ indicates high, 25-50% moderate, and $< 25\%$ low heterogeneity). We examined the influence of various characteristics on the study-specific effect estimates by first, stratifying the analysis by (i) arsenic dose (i.e. high arsenic dose: $>$

50µg/L versus low-to-moderate arsenic dose: <50µg/l) and (ii) arsenic measured using individual data versus group data. We also performed a series of sensitivity analyses. First, we investigated the relative influence of each study on the summary OR by omitting each study one at a time. None of the studies had substantial influence on the summary ORs for our relations of interest and this finding was not reported. Second, we restricted the analysis to high quality studies, prospective cohort studies and studies adjusting for potential adequate confounders (see Supplemental Material, Table S3) documented in the literature (e.g. Di Mario et al. 2007; George 2006; Ghosh 2012; Kramer 1987, 2003; McClure et al. 2006; Moss et al. 2002; Shah et al. 2011). We also presented dose-response for studies with at least 3 exposure levels graphically. Publication bias was explored with funnel plots. The *trim* and *fill* method was used to assess the potential impact of missing studies in the funnel plot. Statistical analysis was performed using STATA software version 9 (STATA Corp, College Station, TX, USA).

Results

Study characteristics

Our systematic literature search strategy is shown in Figure 1. A total of 888 studies were retrieved from which 56 studies were reviewed in-depth. Twenty-three studies fulfilled our a priori inclusion criteria (Table 1) for this systematic review. Data from sixteen studies were included in our quantitative analysis (see Supplemental Material, Table S4 and Table S5). Thirty-three studies were excluded for various reasons (see Supplemental Material, Table S6). We had no data from the authors of two studies on birthweight (Fei et al. 2013; Guan et al. 2012) to calculate 95% CI, so we only included the studies in our qualitative analysis. Five studies (Ahamed et al. 2006a; Chakraborti et al. 2003; Mukherjee et al. 2005; Sen and Chaudhuri 2008; Rahman et al. 2005) did not control for potential confounders and they were also included in our

qualitative analysis. Five studies (Cherry et al. 2008, 2010; Hopenhayn-Rich et al. 2000; Milton et al. 2005; Myers et al. 2010) were ecological retrospective cohort designs. Two studies were ecological case-control designs (Aschengrau et al. 1989; Ihrig et al. 1998). Only one (Rahman et al. 2007) of the five prospective cohort designs was an ecological study. Seven of the ten cross-sectional designs were ecological studies. Nine studies were conducted in Bangladesh, five in India, three in China, two in Chile, one in Taiwan and three in the U.S.A. Twenty-two studies were conducted in populations exposed to arsenic in drinking water. Of these, six applied biomarkers including urine, maternal/cord/placenta blood, hair and nail; and the remaining studies measured arsenic dose at the region/village/household level. Ihrig et al. (1998) measured arsenic dose in airborne emissions. Huyck et al. (2007) measured maternal hair arsenic dose at first prenatal visit, maternal hair arsenic dose at birth, and maternal nail arsenic dose at first prenatal visit, but the estimates of the latter biomarker was considered suitable and included in the meta-analysis. There were ten reports on spontaneous abortion, fourteen on stillbirth, three on preterm delivery, six on birth weight, five on neonatal mortality, and seven on infant mortality. Eligible studies applied either questionnaire/interview or hospital/medical records or national registers to ascertain information on the outcomes of interest. Most of the studies (Table 1) scored low on the Newcastle-Ottawa Scale due to several reasons including bias associated with selection of study population, measurement of arsenic exposure, lack of individual arsenic data, inappropriate definition of cases/controls, inappropriate comparable reference, and a lack of adequate adjustment for potential confounders (Table 1).

Arsenic exposure in the general population

Spontaneous abortion

In all 10 studies that examined the association with spontaneous abortion, 4 were excluded from our quantitative analysis because the authors did not control for potential confounders. Sen and Chaudhuri (2008) studied outcome of pregnancy in 240 married women. In women with the highest concentrations of arsenic in drinking water (501-1200 µg/l), there was an increase in spontaneous abortion. A similar observation was noted in Ahamed et al. (2006b), Mukherjee et al. (2005), and Rahman et al. (2005). Six studies provided data for our quantitative analysis (see Supplemental Material, Table S4). All the studies reported ORs. Summary OR in populations exposed to high arsenic dose (>50µg/l) in ground water showed increased association (OR 1.98; 95% CI: 1.27, 3.10; Figure 2a). Our finding in populations exposed to low-to-moderate arsenic in ground water (Guo et al. 2003) or in public tap water (Aschengrau et al. 1989) was inconclusive (Figure 2b). Overall, the summary OR was 2.02 (95% CI: 1.40, 2.91). The direction and magnitude of the association persisted in studies applying biomarkers/individual arsenic data, prospective studies, studies adjusting for adequate potential confounders and high quality studies (Table 2). Figure 3a shows the dose-response relation of arsenic in drinking water and spontaneous abortion. The risk trend was not consistent across the studies. A funnel plot suggested influence of publication bias (see Supplemental Material, Figure S1 (a)), and an adjustment with the *trim* and *fill* method did not change the strength of the overall summary OR (Table 2).

Stillbirth

Of the fourteen studies reporting association with stillbirth, 5 (Ahamed et al. 2006b; Chakroborti et al. 2003; Mukherjee et al. 2005; Rahman et al. 2005; Sen and Chaudhuri 2008) were excluded

from our quantitative analysis because the authors did not control for potential confounders. All the 5 studies observed an increase in stillbirth in women with the highest concentrations of arsenic in their drinking water. Nine studies examining the association between environmental arsenic and stillbirth provided data for our quantitative analysis (see Supplemental Material, Table S4). Two studies (Hopenhayn-Rich et al. 2000; Rahman et al. 2007) reported RRs. Arsenic was measured in ground water in eight studies and in air in one study. Summary OR in populations exposed to high arsenic dose ($>50\mu\text{g/l}$) in ground water was increased (OR = 1.77; 95% CI: 1.32, 2.36; Figure 4a). Only one study (Ihrig et al. 1998) was conducted in a population exposed to low-to-moderate arsenic dose (Figure 4b). The overall summary OR for environmental arsenic was 1.84 (95% CI: 1.38, 2.45). In subgroup/sensitivity analyses the risk of stillbirth was increased in studies applying biomarkers/individual arsenic data, studies using group data on arsenic, studies adjusting for adequate potential confounders, prospective studies and high quality studies (Table 2). Five studies reported dose-response relation between environmental arsenic and stillbirth (Figure 3b). Risk trend was consistent in two studies in high arsenic dose area (Milton et al. 2005; Rahman et al. 2010), but this trend was not obvious in the other studies. A funnel plot suggested influence of small positive studies (see Supplemental Material, Figure S1(b)). The *trim* and *fill* method for adjustment of publication bias imputed four studies and as expected, the strength of the summary OR was attenuated but remained statistically significant (Table 2).

Preterm delivery

In all, three studies (Ahmad et al. 2001; Myers et al. 2010; Yang et al. 2003) investigated the relation between arsenic exposure and preterm delivery (see Supplemental Material, Table S4). They all reported ORs and were conducted in populations exposed to high arsenic dose in ground

water. The finding of the summary OR was inconclusive (OR 1.41; 95% CI: 0.83, 2.41; Figure 5a).

Birth weight

The association between arsenic and birth weight was examined in six studies. Two studies did not provide sufficient quantitative data for the meta-analysis. Fei et al. (2013) measured arsenic dose in maternal urine (U-As) and observed an inverse dose-relation (coefficient: $\beta = -1.3$) between U-As and birth weight. Guan et al. (2012) also observed that newborns of mother whose U-As was more than 5.30 $\mu\text{g/L}$ weighed on average 0.22kg less than mothers whose U-As was less than 5.30 $\mu\text{g/L}$. Four studies (Hopenhayn et al. 2003; Huyck et al. 2007; Rahman et al. 2009; Yang et al. 2003) provided regression coefficient and standard errors for our quantitative analysis (see Supplemental Material, Table S4). Environmental arsenic shows a significant reduction in birth weight [-53.2 grams; 95% CI: -94.9, -11.4; Figure 5b].

Neonatal mortality

Five studies examined neonatal mortality (see Supplemental Material, Table S5), of which two reported (Hopenhayn-Rich et al. 2000; Rahman et al. 2007) RRs. All the studies were conducted in populations exposed to high arsenic dose in ground water. The overall summary OR was 1.51 (95% CI: 1.28, 1.78; Figure 5c). The direction of association did not change in studies applying biomarkers/individual arsenic data and in studies adjusting for adequate potential confounders (Table 2). Rahman et al. (2007) reported on this relation. Dose-response relation was examined in three studies (Figure 3c.) A consistent dose-response trend was observed in von Ehrenstein et al. (2006) but the risk trend was inconsistent in Milton et al. (2005) and Rahman et al. (2007). Evidence of publication bias was observed in the funnel plot (see Supplemental Material, Figure

S1(c)). The *trim* and *fill* method imputed 2 studies and the strength of association was reduced marginally (Table 2).

Infant mortality

Arsenic and infant mortality was investigated in seven studies (see Supplemental Material, Table S5) with two (Hopenhayn-Rich et al. 2000; Rahman et al. 2007) reporting RRs. The studies were conducted in populations exposed to high arsenic dose in ground water. Summary OR was 1.35 (95% CI: 1.12, 1.62; Figure 5d). Compared to the overall summary OR, the association was slightly elevated in studies applying biomarkers/individual arsenic data, studies adjusting for adequate potential confounders and high quality studies but marginally reduced in studies using group data on arsenic (Table 2). Our findings from 2 prospective studies were inconclusive. Among three studies examining dose-response relations (Figure 3d), a consistent risk trend was observed in Rahman et al. (2010), but the risk trend was not consistent in Rahman et al. (2007) and von Ehrenstein et al. (2006). A funnel plot showed evidence of asymmetry suggesting influence of small positive studies (see Supplemental Material, Figure S1(d)). As expected, the strength of association was attenuated with the *trim* and *fill* method and 3 missing studies were imputed (Table 2).

Discussion

This is the first systematic review and meta-analysis on the association between inorganic arsenic exposure and adverse pregnancy outcomes/infant mortality. We found positive associations of arsenic with spontaneous abortion, stillbirth, birth weight and neonatal and infant mortality. These findings are important to many countries around the globe where pregnant

women and infants continue to be exposed to low through moderate to high arsenic dose in different media (e.g. drinking water, air, food and beverages).

Validity issues

Our study has a number of strengths. We searched several databases including reference lists of reviews and relevant studies. Two authors independently checked the eligibility of the studies according to a predefined set of criteria. We followed systematically, the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Since the upper limits of arsenic exposure differed among studies, we studied the effect in populations in low-to-moderate arsenic areas (i.e. $<50\mu\text{g/l}$) separately from the effect in populations in high arsenic areas (i.e. $\geq 50\mu\text{g/l}$). In studies of spontaneous abortion and stillbirth the findings were inconclusive.

We excluded from our quantitative analysis small ecological studies that did not adjust for potential confounders (Altman 1994; Turner et al. 2013). Also, in considering our core and additional confounders various studies should have adjusted for, we followed recommendations in the literature (e.g. Di Mario et al. 2007; Kumar 2011; Ghosh 2012; Kramer 1987, 2003; McClure et al. 2006; Moss et al. 2002; Shah et al. 2011).

While acknowledging the importance of our findings, there are a number of limitations worth noting. First, the use of summary scores to identify high quality studies in NOS is a bit problematic. A Risk of bias tool that applies a domain-based evaluation may allow one to explore the influence of each domain on the overall summary effect estimate (Higgins and Green, 2009; NAS, 2014). Secondly, a well-designed study may be categorized as low quality because the authors failed to provide detail information in the publication. Finally, some items of

the NOS such as representativeness of study cohort with respect to community and duration of follow-up do not belong to the risk of bias tools (Deeks et al. 2003; NAS, 2004; Sanderson et al. 2007). Thus, the interpretation of how well a study does on the NOS in our study should be done with caution. Inclusion of ecological studies in our review may possibly lead to underestimation of our observed associations. Also the studies incorporated in this meta-analysis were different with regards to exposure levels in the reference groups. However, in computing the overall summary OR from the different studies we made an implicit assumption that any differences in exposure levels in the reference groups will not have much influence on our summary OR.

We observed substantial heterogeneity in the study-specific estimates for studies on spontaneous abortion, stillbirth; and moderate heterogeneity for studies on neonatal and infant mortality. In stratified analysis, heterogeneity persisted in studies applying biomarkers for the association with spontaneous abortion, stillbirth and infant mortality. In sensitivity analyses, heterogeneity persisted in prospective studies on infant mortality, studies on stillbirth and infant mortality that have controlled for adequate potential confounders, and high quality studies on neonatal and infant mortality. The original studies also applied different exposure assessment methods and incorporated different exposure contrasts and thus, making it difficult to relate any exposure increase to change in birth weight. Differences in responses to arsenic exposure may also exist across study populations (Concha et al. 2002; Hopenhayn-Rich et al. 1998; Abhyankar et al. 2012) and these could be potential sources of the observed heterogeneity. We lacked data on these factors and we also did not have sufficient data from the original studies to elaborate further, the reasons for the heterogeneity. We applied *trim* and *fill* method to examine the impact of publication bias on our overall summary OR and the summary OR was slightly reduced for stillbirth, neonatal mortality and infant mortality suggesting that publication bias is not an

explanation of our observed associations. Nonetheless, it should be noted that the *trim and fill* method performs poorly in the presence of substantial heterogeneity and therefore the influence of publication bias on the observed associations cannot be ruled out.

Our findings, however, should be interpreted in the light of limitations inherent in the original studies. Some studies failed to adjust for appropriate potential confounders of adverse pregnancy outcomes/infant mortality and could not establish the independent role of arsenic. Although few studies adjusted for proxies of socio-economic status, only one study considered access and utilization of prenatal care. This is an important socio-economic factor to be considered in the studies of stillbirth and neonatal/infant mortality (Kiely et al. 1985; Ronsmans et al. 2005; Shah et al. 2011). Exposure assessment was also a major challenge in the studies. Three studies measured arsenic contents in urine (Fei et al. 2013; Rahman et al. 2007, 2010). One study measured arsenic content in blood (Guan et al. 2012) and Huyck et al. (2007) measured arsenic content in hair. Arsenic content in urine/blood is a marker of current exposure whereas information on chronic exposure can be obtained from arsenic content in hair or finger/toe nails. The remaining studies applied ecological measures. Questionnaires were administered in most studies but data on water consumption pattern (i.e. the frequency and quantity of water intake) were not reported. Lack of individual data may result in measurement error with under-estimation of the true effect. Many of the studies were cross-sectional in design precluding temporality. Although few studies have collected data on our outcomes of interest from medical records/established registers, most studies have relied on maternal recall. Methods applied in collecting data on spontaneous abortion were not sensitive to detect events occurring in early pregnancy. Thus, the fetal and infant health effect of arsenic observed in our study may have been substantially under-estimated.

Comparison with previous studies

Only two qualitative reviews were available on this subject. In the first study, Smith and Steinmaus (2009) examined the effects of arsenic and chromium in drinking water on low birthweight and infant mortality. The authors identified ten studies and failed to reach any conclusion. In the second study, Bloom et al. (2010) examined the relation of spontaneous abortion and arsenic in drinking water. The authors also identified nine studies and concluded that chronic exposure to arsenic was associated with spontaneous abortion. In the present study, we observed excess risk of 102% for spontaneous abortion, 84% for stillbirth, 51% for neonatal mortality, 35% for infant mortality and 53 grams reduction in birth weight. The magnitude of association persisted in studies applying biomarkers, studies using aggregate data on arsenic exposure, studies adjusting for adequate potential confounders, and high quality studies. From the global public health point of view, the observed association is relevant considering the magnitude of the estimated effect and the extent of exposure to arsenic globally.

The precise biologic window of susceptibility of arsenic for adverse pregnancy outcomes is unknown (Vahter 2007, 2009). But arsenic exposure at different periods before or during pregnancy could cause a wide range of adverse pregnancy outcomes (Selevan et al. 2000). In laboratory animals, prenatal arsenic exposure causes spontaneous abortion by defective implantation, zygote development and aneuploidy or through aberrant placental vasculogenesis and placental insufficiency (He et al. 2007; Navarro et al. 2004). Epidemiologic studies have also shown that arsenic causes oxidative stress, lipid peroxidation, interference of hormonal activities, and perturbation of DNA methylation which may be associated with a wide range of adverse pregnancy outcomes through defective placentation and pre-eclampsia (Concha et al. 1998; Hood et al. 1988; Hu et al. 1998; Hughes 2002; Vahter 2007, 2009).

Our findings suggest that the effect of arsenic is strongest for spontaneous abortion. Although methylation is expected to have improved dramatically in the second trimester (Concha et al. 1998; Vahter 2007), at high arsenic dose ($\geq 50 \mu\text{g/l}$) observed in the populations included in our study, methylation is inhibited and the fetus blood plasma may essentially contain un-methylated arsenic and MMA which could threatened fetal survival and growth (Hall et al. 2013; Vahter, 2007). Exposure to arsenic in *utero* and in early life may also pose a threat to infant survival (Hughes 2002; Vahter 2007). This observation has been noted in series of cohort studies conducted in the developing countries (Milton et al. 2005; Myers et al. 2010; Rahman et al. 2009, 2010).

Studies with the greatest weight in the meta-analyses did not provide data for the evaluation of dose-response trend. However, in the few studies that provided data, we observed inconsistent dose-response trend at high arsenic dose. The evidence was scarce for low-to-moderate arsenic dose and for studies evaluating preterm delivery.

Conclusions

Our systematic review and meta-analysis found positive associations of arsenic exposure with spontaneous abortion, stillbirth, birth weight and neonatal and infant mortality. However, the interpretation of causal association of high arsenic dose in drinking water is limited by methodological problems in the original studies and limited studies on dose-response.

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Table 1. Characteristics of studies included in the systematic review and meta-analysis.

Sources (Study design)	Location	Study population	Arsenic concentration			Outcome studied	Confounders adjusted for	Total score on NOS
			Marker for exposure	Exposure contrast	Range/median/mean			
Fei et al. 2013 ^{a,b} (PCO)	New Hampshire in the U.S.A.	133 pregnant women	Arsenic levels in urine	NA	Not reported	Birth weight	Infant gender, maternal age, gestational age	7/9
Guan et al. 2012 ^{b,c} (CS)	Dalian in China	125 mother-infant pairs	Arsenic levels in maternal and cord blood	Arsenic affected area (590 µg/L) vs. arsenic free area	Not reported	Birth weight	Maternal age, body mass index, parity, gestational age at delivery, maternal education, maternal second smoke, infant gender	5/9
Cherry et al. 2010 ^{c,d} (RCO)	Gonoshasthaya Kendra villages in Bangladesh	934 infant mortality occurring in designated area between 2001 and 2003	Arsenic levels in tube-well water	≥ 50 µg/L vs. < 10 µg/L	0.05-166 µg/L	infant mortality	First pregnancies, others with no formal education, mothers designated as destitutes	7/9
Myers et al. 2010 ^{c,d} (RCO)	Bayingnormen in Mongolia China	9890 singleton deliveries of mothers	arsenic levels in tube well water	>50 µg/L vs. ≤50 µg/L	UD-1200 µg/L	birth weight, preterm delivery, stillbirth and neonatal mortality	maternal age, gravidity, infant sex for the analysis of birth weight and maternal age, gravidity, infant sex adequacy for the analysis of preterm delivery, stillbirth and neonatal mortality	7/9
Rahman et al. 2010 ^{b,c} (PCO)	Matlab district in Bangladesh	2924 pregnant women	Arsenic levels in urine	249-1253 µg/L vs. <33 µg/L (spontaneous abortion) 268-2019 µg/L vs. <38 µg/L (stillbirth) 268-2019 vs. <38 µg/L (infant mortality)	UD-1253 µg/L	spontaneous abortion, stillbirth, infant mortality	No significant confounder was found	7/9
Rahman et al. 2009 ^{b,c} (PCO)	Matlab in Bangladesh	1578 women with single births.	Arsenic concentration in urine	≥100 µg/L vs. <100 µg/L	6-978 µg/L	birth weight	Asset score, BMI, height, age, education, season, gestational age at birth, sex of infant	8/9
Cherry et al. 2008 ^{c,d} (RCO)	Villages in 13 sub- districts in Bangladesh	30, 984 pregnancies and outcomes	Average arsenic concentrations in hand pump well water	≥50 µg/L vs. <0.10 µg/L	UD-81 µg/L	stillbirth	Age, gender, previous pregnancy, previous stillbirth, low socio- economic status, maternal education, parental education, maternal smoking, mother high BP, mother oedema, gestational age, birth weight, home delivery	8/9

Sources (Study design)	Location	Study population	Arsenic concentration			Outcome studied	Confounders adjusted for	Total score on NOS
			Marker for exposure	Exposure contrast	Range/median/mean			
Sen and Chaudhuri, 2008 ^{c,d,e} (CS)	Villages located in North 24 Parganas district of the states of West Bengal	Pregnancy outcomes of 240 married women	Arsenic levels in tube-well water	600 µg/L vs. <10 µg/L	10-600 µg/L	spontaneous abortion and stillbirth	none	2/9
Huyck et al. 2007 ^{b,c} (PCO)	42 villages in Sirajdikhan Upakila of Munshigan district of Bangladesh	49 women who were 18 years or older	Arsenic levels in maternal hair at first visit	≥2.70 µg/g vs. <0.28 µg/g	0.14-3.28 µg/g	Birth weight	gestational age at first prenatal visit, maternal weight gain, birth gestational age, and activity level during pregnancy	7/9
Rahman et al. 2007 ^{c,d} (PCO)	Matlab in Bangladesh	29, 134 pregnancies identified by the HDS in 1991-2000	Arsenic levels in tube-well water	≥409 µg/L vs. <10 µg/L	224 µg/L	Fetal loss, infant mortality, neonatal	Age, parity, education and socio-economic status	7/9
Ahamed et al. 2006 ^{c,d,e} (CS)	Eruani village in Bangladesh	56 pregnancy outcomes of women of reproductive age	Arsenic levels in tube-well water	Exposed area (501-1200 µg/L) vs. control area	501-1200 µg/L	Spontaneous abortion and stillbirth,	None	1/9
von Ehrenstein et al. 2006 ^{c,d} (CS)	21 villages in West Bengali (south 24-Parganas district) in India	202 married women age between 20-40 years	Arsenic levels in tube-well water	≥200 µg/L vs. <50 µg/L	Mean=101.7 µg/L	Spontaneous abortion, stillbirth, neonatal mortality, infant mortality	mother's age at child's birth, BMI, maternal education, education of the head of the household and type of housing material	3/9
Milton et al. 2005 ^{c,d} (CS)	29 villages in Comilla district, 2 villages in the Chandpur district, 43 villages in the Chaudanga district in Bangladesh	533 ever-married women age 15-49 years	Arsenic levels in tube-well water	>50 µg/L vs. ≤50 µg/L	UD-1710 µg/L	Spontaneous abortion, stillbirth and neonatal mortality	Height, history of hypertension and diabetes and age at first pregnancy for neonatal mortality	3/9
Mukherjee et al. 2005 ^{c,d,e} (CS)	Murshidabad in West Bengal, India	17 married women in the reproductive age group of 18-40 years with least 1 pregnancy	Arsenic levels in drinking water	Exposed area (401-1474 µg/L) vs. non-exposed area (<3 µg/L)	401-1474 µg/L	Spontaneous abortion and stillbirth	None	1/9
Rahman et al. 2005 ^{c,d,e} (CS)	Jalangi block in India	13 married women in their reproductive age (18-40)	Arsenic levels in drinking water	Women in exposed areas (501-1474 µg/L) vs. women in control area (<10 µg/L)	not reported	Spontaneous abortion, and stillbirth	None	1/9
Chakraborti et al. 2003 ^{c,d,e} (CS)	Semria Ojha Patti village of Ara in Bhoipur, India	16 adult females	Arsenic levels in tubes-well water	(463-1025 µg/L) vs. (7-39 µg/L)	7-1025 µg/L	stillbirth	None	1/9
Guo et al. 2003 ^{a,d} (CS)	Villages in Wuyan county in Inner Mongolia, China	224 women	Arsenic levels in well water	Exposed area (43 µg/L) vs. non-exposed area (9.6 µg/L)	Not reported	Spontaneous abortion	Sex, age, smoking and alcohol consumption	3/9

Sources (Study design)	Location	Study population	Arsenic concentration			Outcome studied	Confounders adjusted for	Total score on NOS
			Marker for exposure	Exposure contrast	Range/median/mean			
Hopenhayn et al. 2003 ^{a,d} (PCO)	Antofagasta and Valparaiso cities in Chile	844 singleton mothers age between 18 to 45 years	Arsenic levels in water	40 µg/L vs. <1 µg/L	32.9-52.7 µg/L	Birth weight	Location, calendar time, arsenic exposure	6/9
Yang et al. 2003 ^{a,d} (RCO)	18 villages in 4 township in Lanyang Basin IN Taiwan	18,259 singleton births	High exposed community used as a surrogate	Exposed area (undetectable -3590 µg/L) vs. non-exposed area	UD-3.59 ppm	preterm delivery, birth weight	Maternal age, marital status, maternal education, sex of baby	6/9
Ahmad et al. 2001 ^{c,d} (CS)	village of Samta in thana Sharsha, Jessore district; village of Katiarchar in Sadar thana, Kishorgonj district in Bangladesh	192 married women of reproductive age(15-49 yrs)	Arsenic levels in tube-well water	>50 µg/L vs. ≤0.2 µg/L	200-450 µg/L	spontaneous abortion, stillbirth and preterm birth	Socioeconomic status, education, and age at marriage	3/9
Hopenhayn-Rich et al. 2000 ^{c,d} (RCO)	Antofagasta and Valparaiso cities in Chile	Mortality of infant of the period between 1950 to 1996	Arsenic levels in public water	>50 vs. 5 µg/L	40-860 µg/L	fetal mortality, neonatal mortality,	Location, calendar time, arsenic exposure	6/9
Ihrig et al. 1998 ^{c,d} (C-C)	Bryan a small city in Texas in the USA	119 case babies and 267 control babies	Arsenic levels estimate from airborne emissions	>100 vs. 0 ng/m ³	not reported	stillbirths	Maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction	7/9
Aschengrau et al. 1989 (C-C) ^{a,d}	Boston in the USA	286 cases 1391 controls	arsenic levels in Public drinking water	(1.4-1.9) µg/L vs. UD	UD-19 µg/L	spontaneous abortion	Water source, maternal age, educational level, history of prior spontaneous abortion	7/9

Abbreviations: C-C, case-control study; CS, cross-sectional study; NA, not applicable; NOS, Newcastle-Ottawa Scale; PCO, prospective cohort study; RCO, retrospective cohort study; UD, Undetected.

^aStudies examining low-to-moderate arsenic dose in the general population. ^bStudies examining high arsenic dose in the general population.

^cStudies applying biomarkers/individual level data. ^dStudies applying group/ecological data. ^eStudies that did not control for potential confounders.

Table 2. Summary OR for the relation between arsenic and the risk of adverse pregnancy/infant mortality and stratified/sensitivity analysis according to the study characteristics.

Analysis	Spontaneous abortion		Stillbirth		Neonatal mortality		Infant mortality	
	Random-effects model OR (95%CI)	Heterogeneity Statistics Q (n)-statistics I ² -index (%) p-value	Random-effects model OR (95%CI)	Heterogeneity Statistics Q (n)-statistics I ² -index (%) p-value	Random-effects model OR (95%CI)	Heterogeneity Statistics Q (n)-statistics I ² -index (%) p-value	Random-effects model OR (95%CI)	Heterogeneity Statistics Q (n)-statistics I ² -index (%) p-value
Summary OR	2.02 (1.40, 2.91)	11.2 (6) 55.3 0.048	1.84 (1.38, 2.45)	38.40 (9) 79.2 0.000	1.51 (1.28, 1.78)	5.34 (5) 25.1 0.254	1.35 (1.12, 1.62)	8.31 (7) 30.4 0.216
Stratified analysis								
<i>Assessment of arsenic exposure</i>								
Individual data/biomarker	2.20 (1.04, 3.46)	7.96 (3) 74.9 0.019	1.96 (1.17, 3.29)	19.91 (5) 79.9 0.001	1.30 (1.00, 1.67)	4.78 (2) 16.4 0.274	1.74 (0.92, 3.28)	6.02 (3) 66.8 0.049
Group data	1.51 (0.79, 2.87)	1.59 (3) 0.0 0.951	1.79 (1.29, 2.48)	5.46 (4) 45.1 0.141	1.59 (1.43, 1.77)	1.75 (3) 0.0 0.416	1.32 (1.08, 1.60)	2.44 (4) 0.0 0.486
Sensitivity analysis								
Prospective cohort studies ^a	1.45 (0.99, 2.12)	0.66 (2) 0.0 0.951	1.13 (0.98, 1.30)	0.67 (2) 0.0 0.412	1.21 (0.98, 1.50) ^a		2.12 (0.53, 8.42)	4.84 (2) 79.3 0.028
Studies adjusting for potential confounders	1.72 (1.25, 2.37)	4.43 (5) 9.7 0.351	1.85 (1.22, 2.82)	18.06 (7) 66.8 0.005	1.53 (1.11, 2.10)	4.63 (4) 35.2 0.201	1.65 (1.01, 2.47)	8.39 (5) 52.3 0.078
High quality studies (>7 on NOS)	1.45 (0.99, 1.12)	1.65 (3) 0.0 0.438	1.28 (0.98, 1.67)	4.27 (4) 29.7 0.234	1.49 (0.92, 2.31)	2.57 (2) 61.1 0.109	1.41 (1.04, 1.92)	7.55 (4) 60.2 0.056
Impact of missing studies on overall summary OR								
By trim and fill method	2.02 (1.20, 2.91)	55.3 (6) 55.3 0.048	1.43 (1.11, 1.85)	58.06 (13) 79.33 0.000	1.47 (1.27, 1.71)	7.15 (7) 2.15 0.307	1.22 (0.98, 1.53)	8.62 (10) 30.0 0.017

^aOne prospective study reported on neonatal mortality. Q(n), n: number of studies.

Figure Legends

Figure 1. Study Selection Flow Diagram

Figure 2. Forest plot for the relation between arsenic exposure and the risk of spontaneous abortion Assessed by (a) high arsenic dose and (b) low-to-moderate arsenic dose. D+L, Random effect summary OR from the DerSimonian-Laird method, I-V, fixed effects model summary OR from the generic inverse variance method.

Figure 3. Plots of dose-response relations for arsenic and (a) spontaneous abortion (b) stillbirth (c) neonatal mortality and (d) infant mortality in the general population

Figure 4. Forest plot for the relation between arsenic exposure and the risk of stillbirth. Assessed by (a) high arsenic dose and (b) low-to-moderate arsenic dose. D+L, Random effect summary OR from the DerSimonian-Laird method, IV, fixed effects model summary OR from the generic inverse variance method

Figure 5. Forest plot for the relation between arsenic exposure and (a) preterm delivery, (b) birth weight, (c) neonatal mortality and (d) infant mortality. D+L, Random effect pool estimates from the DerSimonian-Laird method, I-V, fixed effects model pool estimates from the generic inverse variance method.

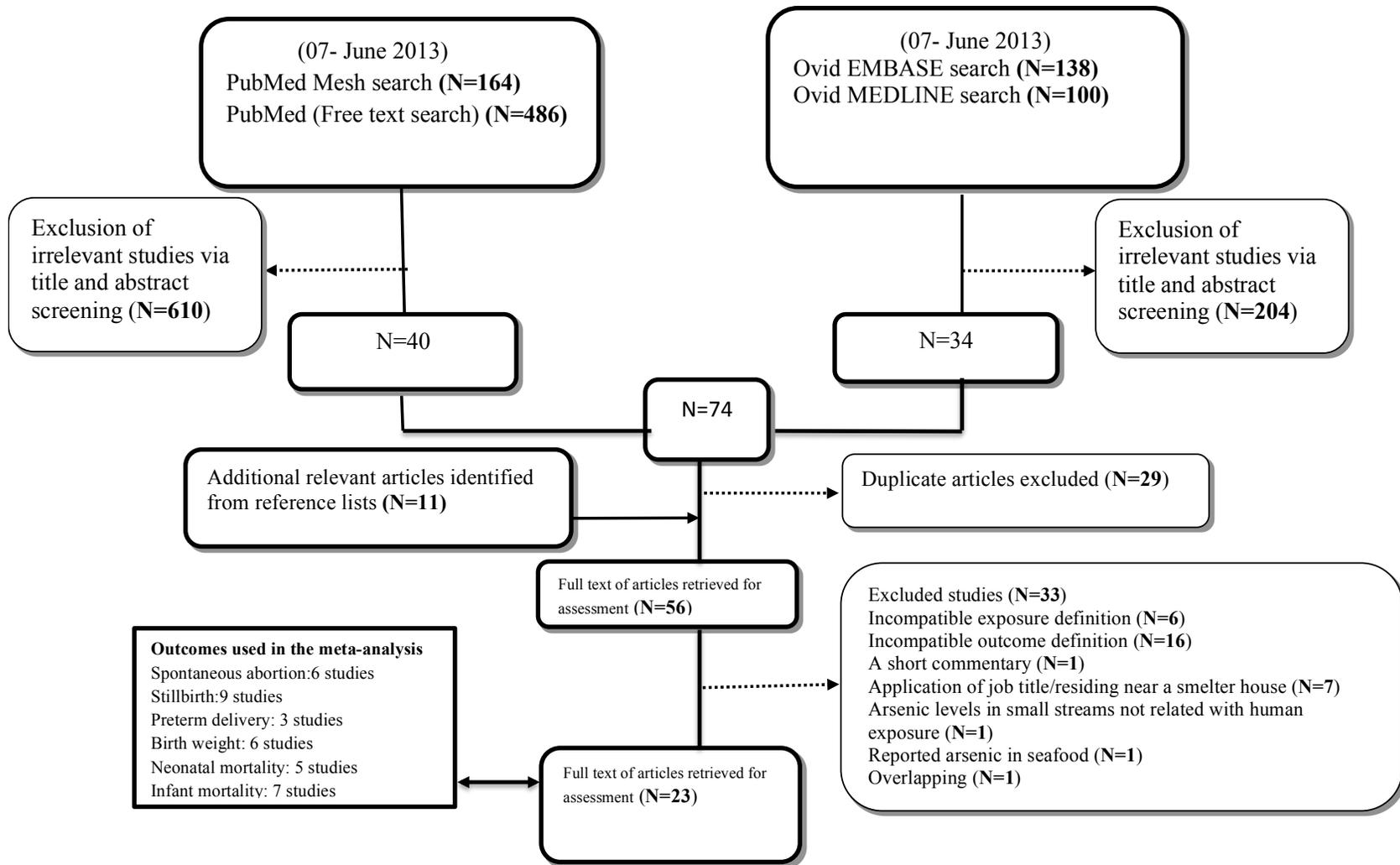


Figure 1.

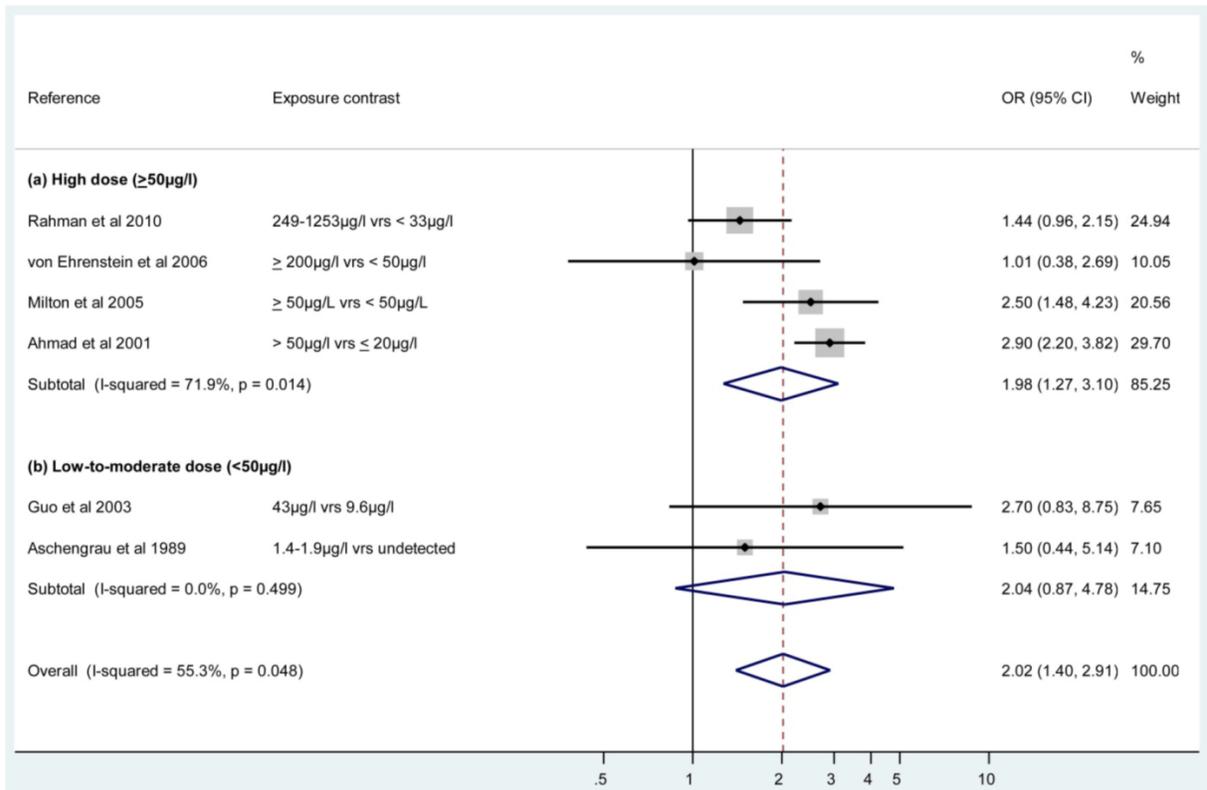


Figure 2.

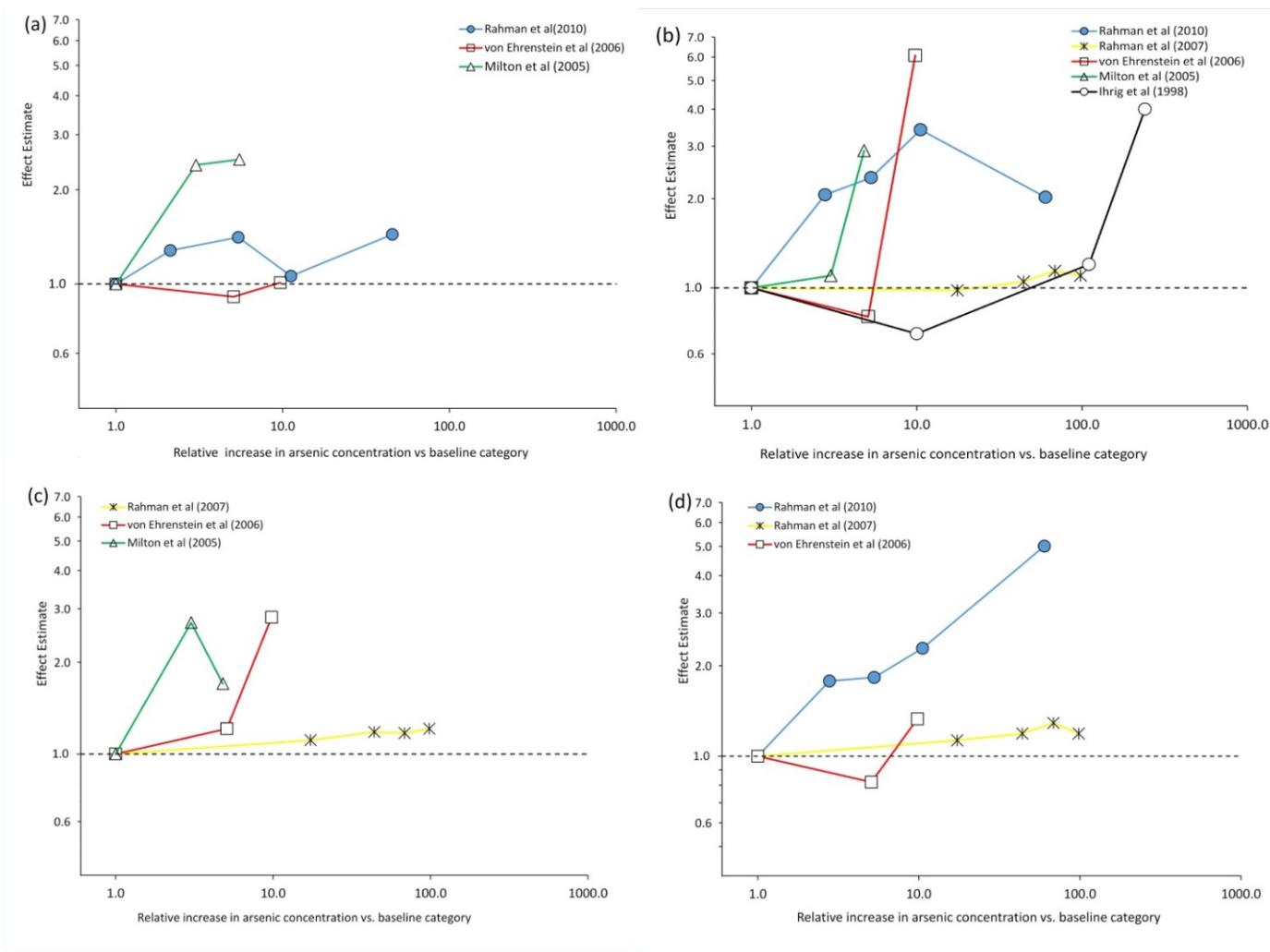


Figure 3.

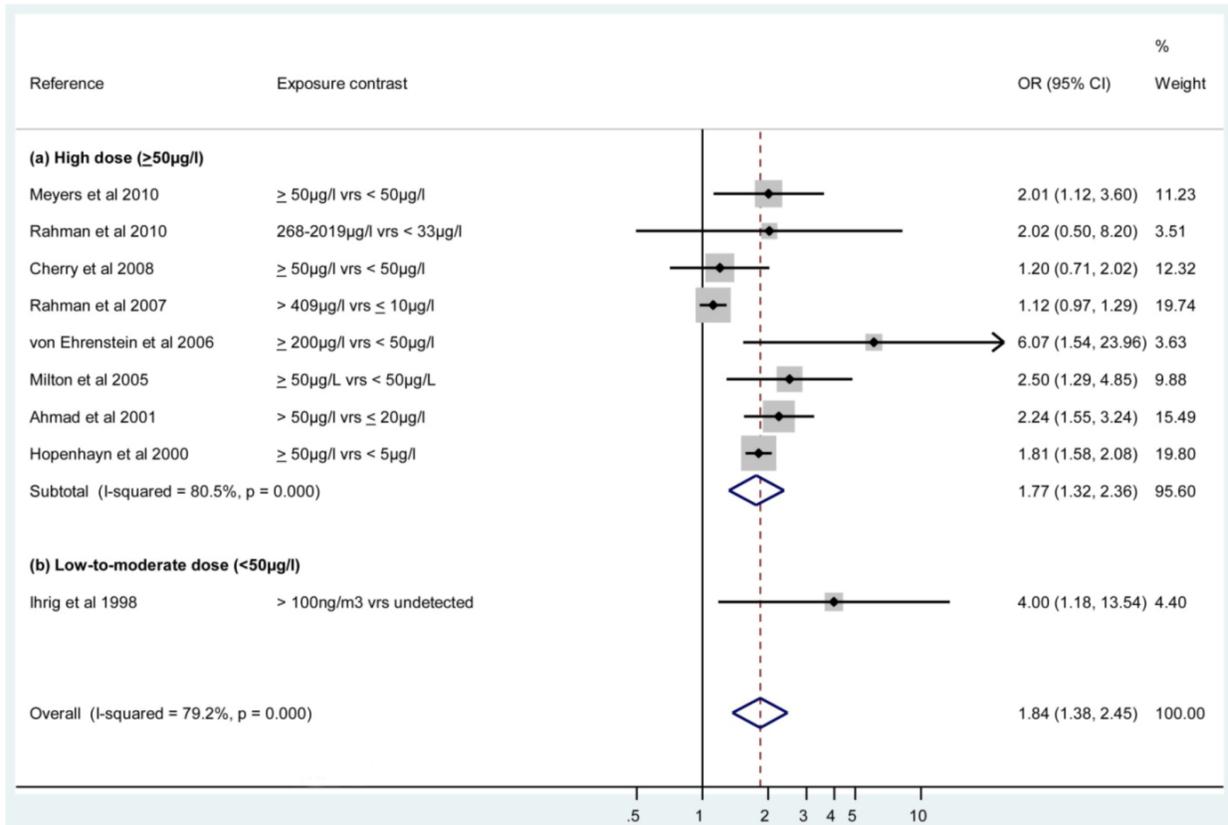


Figure 4.

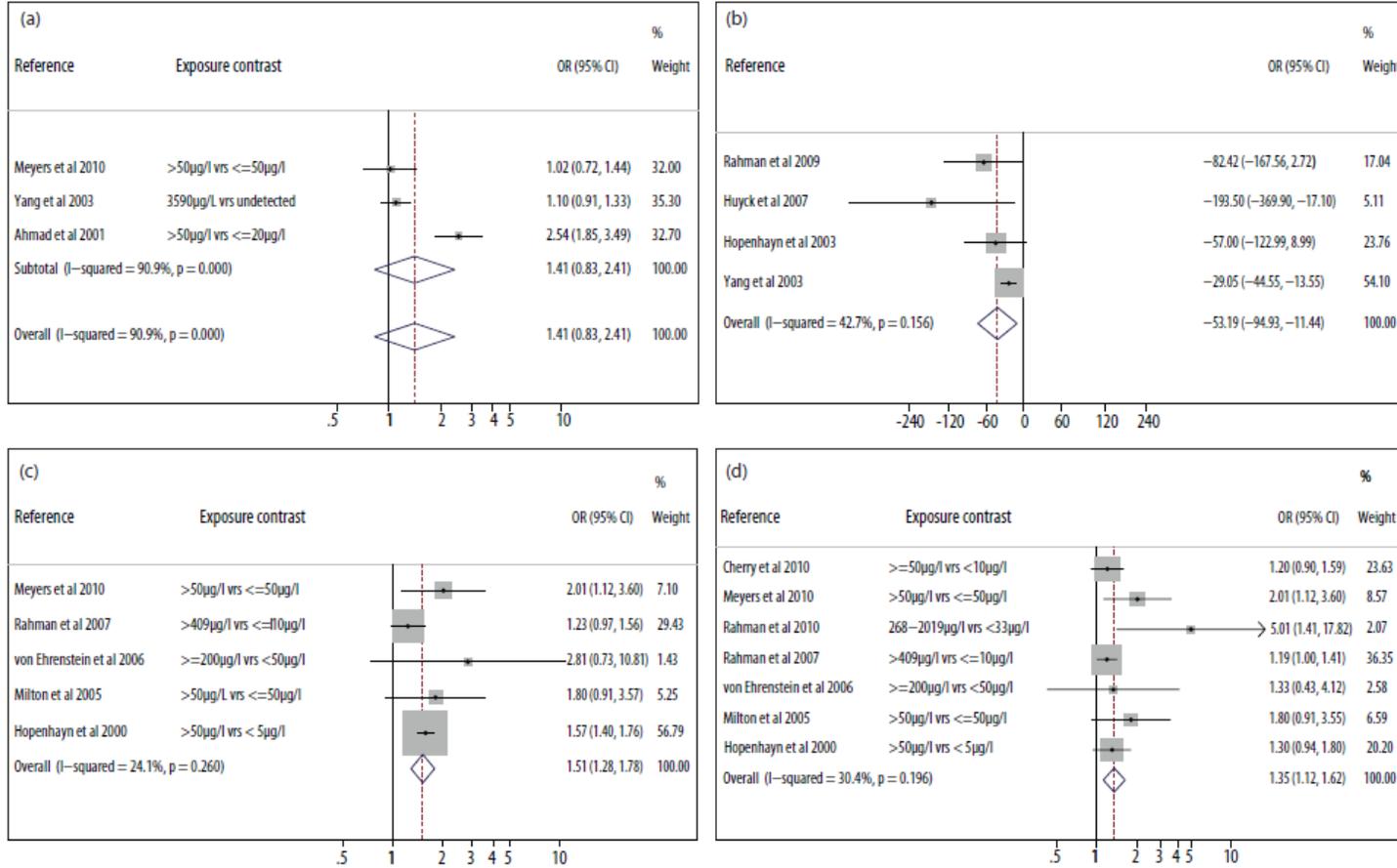


Figure 5.