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Association Between Arsenic Exposure in Drinking Water and Stillbirth: A Meta-Analysis

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ABSTRACT

There is controversial evidence from cross-sectional, ecological, cohort and case-control studies that arsenic exposure in drinking water is a risk factor for stillbirth. The objectives of this meta-analysis were to evaluate the association of stillbirth and arsenic exposure in drinking water and to improve the precision of estimates. A database search was conducted to identify relevant studies. The odds ratios (ORs) extracted from each study were pooled by using Mantel-Haenszel fixed effect model, while subgroup analysis was conducted by using random effect model. Heterogeneity of ORs in the included studies was analysed using I^2 statistics. Publication bias was tested by Begg's test. Eight studies involving 51,476 participants met the inclusion criteria. The pooled ORs of studies was 1.54 (95% CI: 1.32-1.79) with a small heterogeneity (I^2 = 25%, P =0.23) across studies and no publication bias was evident. This meta-analysis provided evidence that chronic arsenic exposure above 50 $\mu g.L^{-1}$ in drinking water is a significant risk factor for stillbirth.

INTRODUCTION

Inorganic arsenic is widely distributed throughout the earth's crust and is a common natural contaminant of drinking water all over the world (National Research Council 2001), which affects over 100 million people's drinking water safety, particularly in developing countries, including Bangladesh, Pakistan, India, Myanmar, Vietnam, China and Northern Chile (Ravenscroft et al. 2009). In developing countries, arsenic level in drinking water is often above 100 $\mu g.L^{-1}$ and can be over 1 $mg.L^{-1}$ in some cases (Rahman et al. 2005).

Chronic exposure to arsenic in drinking water causes several health problems including cancer, diabetes, cardiovascular disease, chronic cough and other diseases (Yoshida et al. 2004, Tapio & Grosche 2006, Brauner et al. 2014, Saint-Jacques et al. 2014, Tsuji et al. 2014a, Tsuji et al. 2014b). Emerging data now show that arsenic exposure also affects the developing fetus (Vahter 2009, Fei et al. 2013) and causes adverse pregnancy outcomes, including lower birth weight, smaller neonatal size, spontaneous abortion, stillbirth and neonatal deaths in pregnant women (Golub et al. 1998, Vahter 2009).

Stillbirth, a serious reproductive problem, was defined as birth of a dead fetus after 28 weeks of gestation (Dutta 1994). Some studies suggested that exposure of arsenic in drinking water posed a positive risk on stillbirth in pregnant women (Borzsonyi et al. 1992, Ahmad et al. 2001, Milton et al. 2005, von Ehrenstein et al. 2006, Cherry et al. 2008), while other studies suggested no significant association between arsenic exposure and stillbirth (Sen & Chaudhuri 2008, Myers et al. 2010, Rahman et al. 2010). Thus, the association between arsenic exposure in drinking water and stillbirth remains controversial.

In the current study, we conducted a meta-analysis that included all relevant cross-sectional studies, ecological studies, cohort studies and case-control studies of chronic arsenic exposure in drinking water and stillbirth, attempting to provide greater precision in estimating the association between arsenic exposure in drinking water and stillbirth risk, since meta-analyses can overcome the limitation of small sample sizes or rare outcomes by pooling results from a number of individual studies to generate a single best estimate (Nordmann et al. 2012).

MATERIALS AND METHODS

Selection criteria: In order to collect all of the literature relevant to arsenic exposure in drinking water and stillbirth, we searched sources in English and Chinese from PubMed, ScienceDirect, OVID LWW and China National Knowledge Infrastructure (CNKI). With the strict medical definition of stillbirth (birth of dead fetus after 28 weeks of gestation), we also limited the search terms strictly that are arsenic, inor-

ganic arsenic, stillbirth, late fetal loss and dead birth. Fig. 1 shows the flow diagram of literature survey.

Inclusion criteria: Studies meeting the following inclusion criteria were selected for meta-analysis: (1) Observational studies were based on populations including cross-sectional, cohort studies, case-control and ecological studies; (2) Concentration of arsenic in drinking water or measurable *in vivo* biomarkers of exposure; (3) The observed adverse pregnancy outcomes in stillbirth (birth of dead fetus after 28 weeks of gestation); (4) Results which are reported in relative risk (RR) or odds ratio (OR) with confidence intervals (CI value), or such parameters could be calculated from published data. All the relevant literature was carefully reviewed and identified according to the above inclusion criteria by two independent investigators to determine whether the individual studies were eligible for meta-analysis.

Data extraction: The following data were extracted from each source: (1) Basic information: the first author's name, year of publication and country where the research was performed; (2) Research design: study population, type of study, sample size and number of cases; (3) Data: arsenic exposure metric, number of events and total of exposed and control subjects.

The cut-point concentrations of arsenic in drinking water dividing exposed and control subjects were different in the various studies. In the current meta-analysis, arsenic concentration of control was set below 50 $\mu g.L^{-1}$, otherwise the lowest concentration would be regarded as control when there was no cut-point of 50 $\mu g.L^{-1}$.

Statistical analysis: Effect estimates were pooled by using Mantel-Haenszel fixed effect model. Heterogeneity across studies was evaluated using the I^2 statistic (Higgins & Thompson 2002), which measures the degree of heterogeneity among the plurality of results and describes the percentage caused by various studies, instead of sampling variation of the total variation. Subgroup analysis stratified by study design used random effect model (Jackson et al. 2010). Publication bias was tested by Begg's test (Begg & Mazumdar 1994). All the statistical analyses were performed using the Stata 12.0 software (Stata Corporation, College Station, Texas, USA). All reported probabilities (P value)

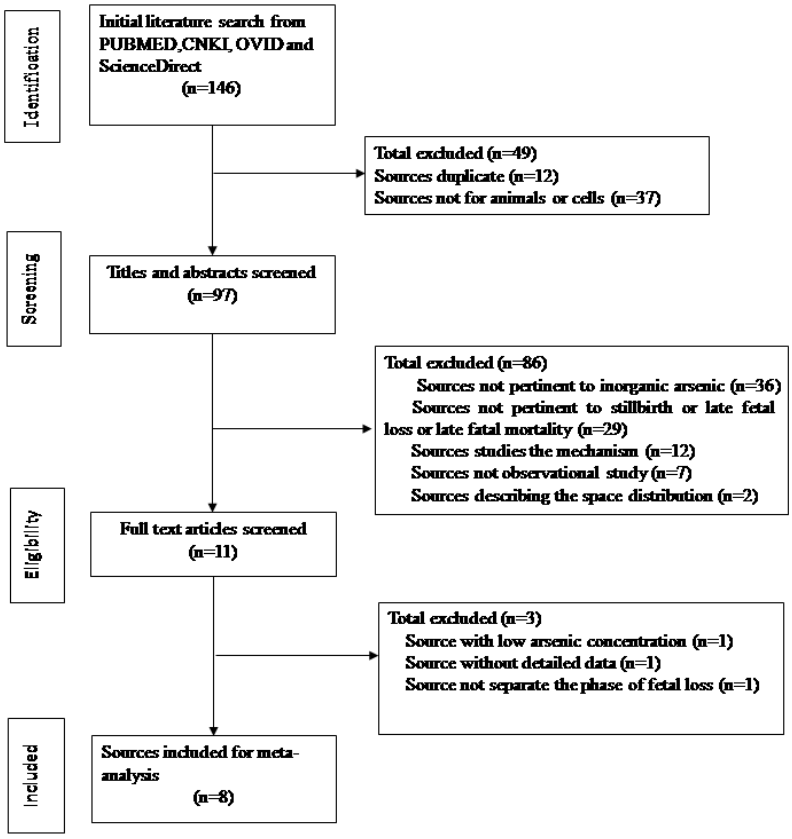

Fig. 1: Flow diagram of study selection.

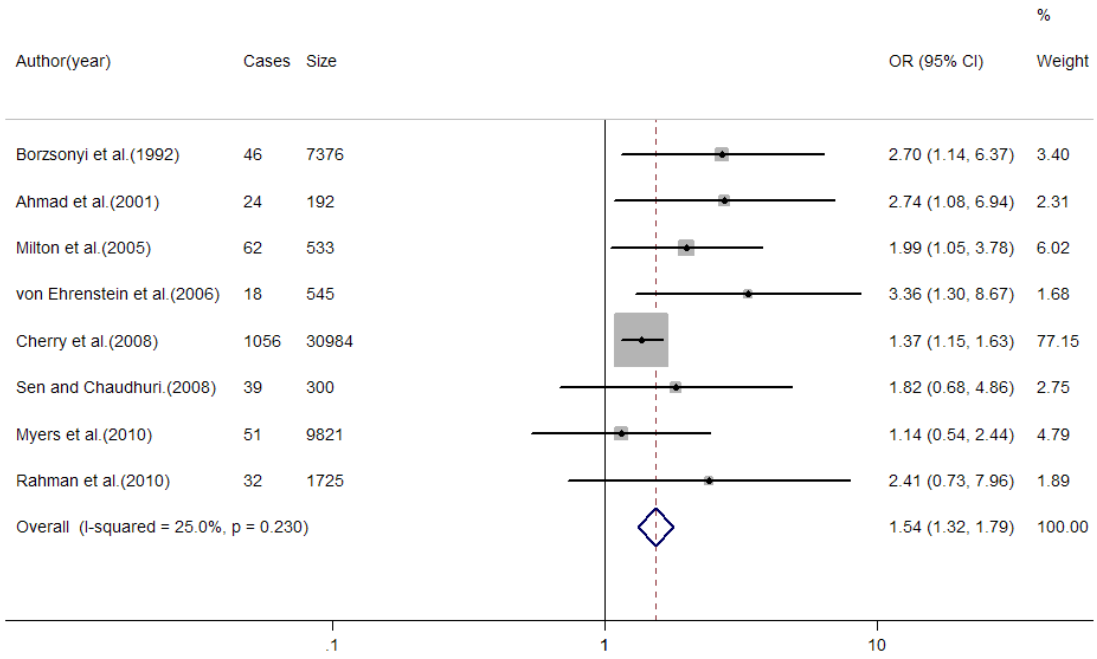

Fig. 2: Forest plot of the odds ratios (ORs) with corresponding 95% CIs of eight studies on arsenic in drinking water and stillbirth. The size of grey box is positively proportional to the weight assigned to each study and horizontal lines represent the 95% CIs.

were two sided, with P≤0.05 considered statistically significant.

RESULTS

Characteristics of studies: According to inclusion criteria, we identified five cross-sectional studies, two ecological studies and one cohort study with total 51,476 participants eligible for meta-analysis to explore the association between arsenic exposure in drinking water and stillbirth risk. The detailed characteristics of sources are given in **Table 1.**

Quantitative synthesis: The meta-analysis results are presented with forest plots in Fig. 2. All of the 8 studies indicated a positive association between arsenic in drinking water and stillbirth, with 5 of them being statistically significant. The pooled OR of studies is 1.54 (95% CI: 1.32-1.79; I^2=25%, $P_{heterogeneity}$ =0.23), indicating significantly positive association between chronic arsenic exposure in drinking water and stillbirth risk (OR>1.0) with a small heterogeneity across the studies.

Subgroup analysis: For further investigating the sensitivity of sources included in meta-analysis, a subgroup analysis stratified by study design was conducted using M-H heterogeneity random effect model. Group 1 included two ecologic studies, while group 2 consisted of five cross-sectional studies and one cohort study. The pooled OR of group 1 was 1.68 (95% CI: 0.91-3.11; I^2= 57.2%, $P_{heterogeneity}$ =0.126), while that of group 2 was 2.0 (95% CI:1.41-2.83; I^2 = 0.0%, $P_{heterogeneity}$=0.579) (Fig. 4). The overall OR of subgroup analysis was 1.75 (95% CI: 1.34-2.29). Both ORs of subgroups and the overall OR showed a significant positive association between arsenic exposure in drinking water and stillbirth risk.

Influence analysis: The results of the influence analysis showed that, one study (Cherry et al. 2008) exerted a disproportionate influence on the pooled estimate for arsenic in drinking water and stillbirth (Fig. 3).

Publication bias: We assessed the potential publication bias with funnel plots of the effect sizes versus the standard errors and identified the significant asymmetry by the Begg's test. The results showed that there was no significant (P>0.05) publication bias in sources included in this meta-analysis (Fig. 5).

DISCUSSION

Reproductive toxicity of arsenic has been a concern in recent decades. Population-based researches performed to assess the association between arsenic exposure in drinking water and pregnancy outcome risk have presented conflicting results. Single studies suffer from relatively small samples with weak power for detecting an effect. However, meta-analysis is an appropriate method to obtain a more reliable conclusion by quantitative synthesis of the relevant data

Table 1: Characteristics of sources included in the meta-analysis (concentration unit: μg.L^{-1}).

Sources (year)	Country	Study design	Sample size (cases)	Cut-points for arsenic exposure	Concentration, event, total (c)※ Concentration, event, total (e)	Adjustment for covariates
Borzsonyi et al. (1992)	Hungary	Ecologic	7376(46)	Not given	Low 6 2118 High 40 5258	unknown
Ahmad et al. (2001)	Bangladesh	Cross-sectional	192(24)	Drinking water arsenic concentration <20,>50	<20 7 96 >50 17 96	age, socioeconomic status, education, and age at marriage
Milton et al. (2005)	Bangladesh	Cross-sectional	533(62)	Tube-well water arsenic concentration ≤50,50-100,>100	≤50 13 176 >50 49 357	height, history of hypertension and diabetes
Von Ehrenstein et al. (2006)	India	Cross-sectional	545(18)	Drinking water arsenic concentration 0-49,50-199,≥200	0-49 8 392 >50 10 153	age, BMI, education and housing material
Cherry et al. (2008)	Bangladesh	Ecologic	30984(1056)	Drinking water arsenic concentration <10,10-50,≥50	<50 903 27529 ≥50 153 3455	unknown
Sen and Chaudhuri (2008)	India	Cross-sectional	300(39)	Tube-well water arsenic concentration <10,10-600	<10 5 60 10-600 34 240	age, socioeconomic status, education, and age at marriage
Rahman et al. (2010)	Bangladesh	Cohort	1725(32)	Urine arsenic concentration <38,39-67,68-133,134-267,268-2019	<38 3 341 39-2019 29 1384	asset index and gestational age
Myers et al. (2010)	China	Cross-sectional	9821(51)	Well-water arsenic concentration BLD-50,>50 ※	BLD-50 43 8447 >50 8 1374	adequacy of prenatal care

※ e:exposure; c:control; BLD: below the limit of detection

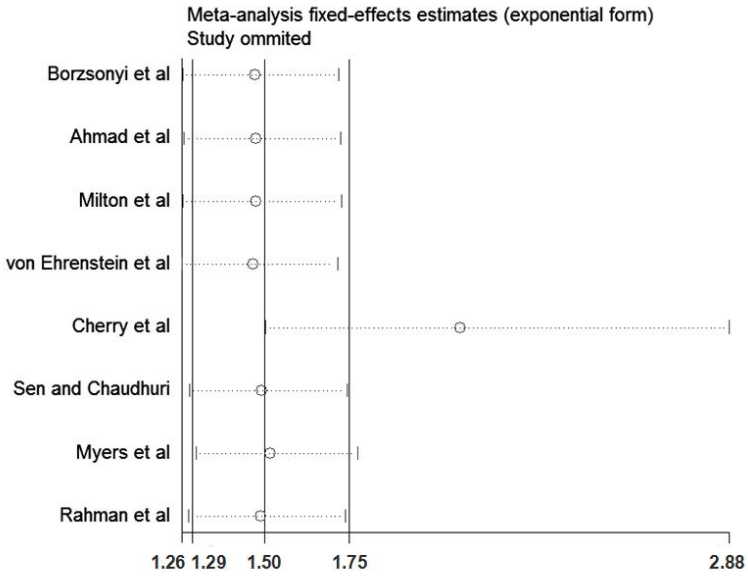

Fig. 3: Sensitivity analysis of the pooled ORs and 95% CI for the overall analysis, omitting each dataset in the meta-analysis. Fixed-effects model was used.

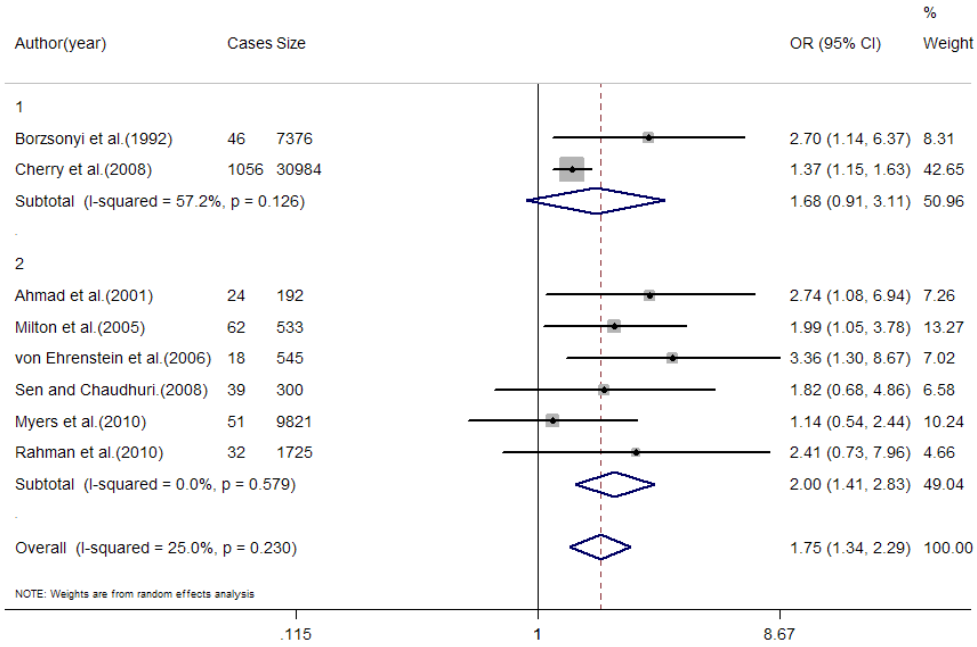

Fig. 4: Forest plot of subgroup analysis stratified by the type of study on arsenic in drinking water and stillbirth. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

extracted from the literature. The current meta-analysis, containing a total of 51,476 participants, strongly identified the statistically significant association between exposure to arsenic in drinking water and stillbirth risk (OR=1.54; 95% CI: 1.32-1.79; I^2=25%, $H_{eterogeneity}$ =0.23). It seems that the conclusion is reasonable as arsenic is a toxic substance that can easily cross the placenta and influence fetal growth and development (Concha et al. 1998). Experimental animal studies showed that arsenic could cause abnormalities, growth retardation, death and other reproductive and developmental toxicity in mammals (Golub et al. 1998, Singh & Rana 2007). However, knowledge of how arsenic causes

stillbirth is still extremely scarce. It is important to explore the mechanism of stillbirth caused by exposure to arsenic in drinking water.

In the current meta-analysis, 7 of 8 included studies provided the concentrations of arsenic in drinking water, while one study (Rahman et al. 2010) provided urinary arsenic concentrations. In this study, participants were from an area with highly-elevated concentrations of arsenic in tube wells in Matlab, Bangladesh; while the control population drank water with lower concentration (<50 μL^{-1}) (Vahter et al. 2006, Rahman et al. 2010). Previous study suggested that total arsenic excreted in urine was linearly correlated with total arsenic in drinking water (Ahmed et al. 2014). More importantly, this difference in determination of arsenic exposure does not influence the meta-analysis results greatly, because when the study was excluded, the meta-analysis results still showed a statistically significant association between arsenic exposure in drinking water and stillbirth risk (OR=1.52; 95%CI:1.30-1.77; I^2=31.0%; $P_{heterogeneity}$ =0.191) (Fig. 6).

Differences of gender, age of participants, study design, research quality, arsenic level in drinking water and heterogeneity across the studies are common in meta-analysis (Munafo & Flint 2004). Thus, it is essential to identify the potential sources of the heterogeneity across studies. In the present meta-analysis, the heterogeneity was not significant (I^2=25%, $P_{heterogeneity}$ =0.23) (Fig. 2). Sensitivity analyses (leave one-out) indicated that the heterogeneity came of the ecologic study conducted by Cherry et al. (2008) (Fig. 3). Ecologic studies have several methodological problems that severely limit causal inference, including ecologic and cross-level bias, problems of confounder control, within-group mis-classification, lack of adequate data, temporal ambiguity, and migration across groups (Morgenstern 2005). When separating the ecologic studies from the other observational studies for sub-group analysis using random effect model, the results showed that the heterogeneity indicator descended to 0% (p=0.579) (Fig. 4).

CONCLUSION

This meta-analysis provided notable evidence that exposure to arsenic in drinking water over 50 $\mu g.L^{-1}$ is a significant risk factor for stillbirth. The observed association between arsenic exposure and stillbirth is of clinical and public health importance.

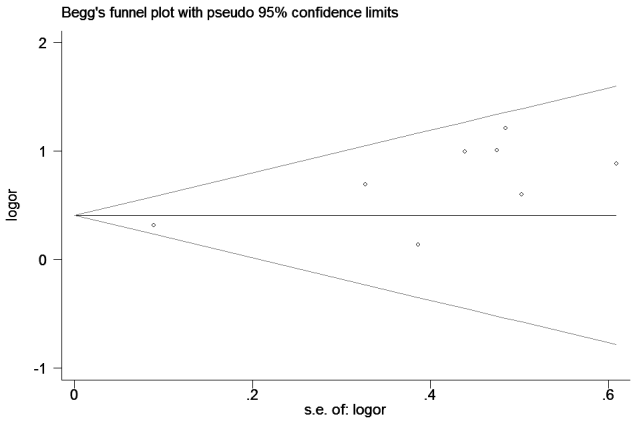

Fig. 5: Begg's funnel plot for publication bias on arsenic in drinking water and stillbirth. Each dot represents a different study.

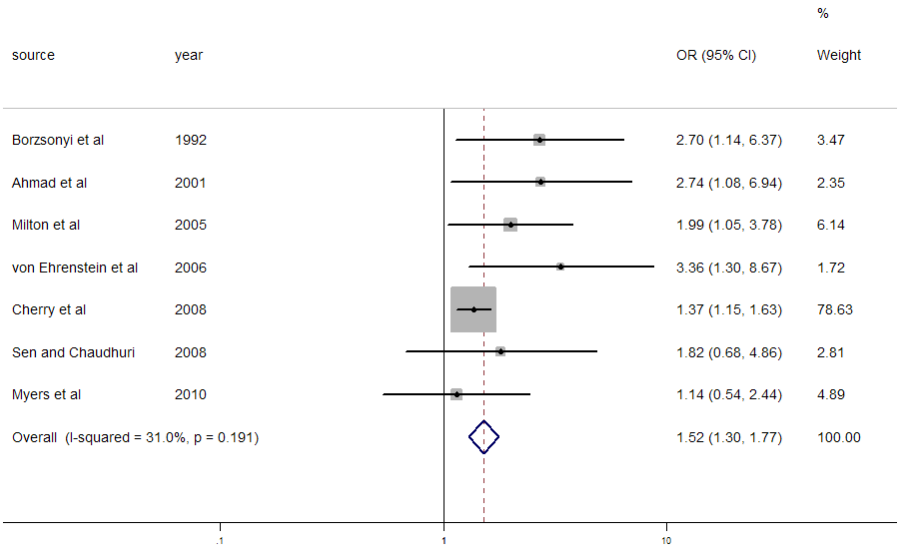

Fig. 6: Forest plot of seven studies excluding one study detecting arsenic in urine. The size of grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

ABBREVIATIONS

CI: Confidence Intervals Value
CNKI: China National Knowledge Infrastructure
RR: Relative Risk
OR: Odds Ratio

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