



Dose-response meta-analysis of arsenic exposure in drinking water and intelligence quotient

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Abstract

Objectives Exposure to inorganic arsenic through drinking water is a threat for public health. Using the arsenic-containing water in the long-term causes a variety of skin diseases, high blood pressure, and skin cancer. Arsenic also damages the nervous system. A wide range of studies have studied the effect of arsenic in drinking water on the level of intelligence in children.

Methods For the purpose of our research, we searched three electronic databases including Scopus, Web of Science, and Medline (PubMed) in English from 2000 to January 2018. We used the dose-response meta-analysis through applying random effect models in order to estimate the pooled association (with a 95% uncertainty) between water arsenic concentration and intelligence level.

Results Using a two-stage random effect model to investigate the dose-response association between arsenic concentration and Intelligence Quotient scale, we estimated a significant linear association as -0.08 (95% CI: $-0.14, -0.01$). Actually, for each unit increase in arsenic concentration (one microgram per liter), intelligence quotient scale decreases by 0.08%.

Conclusions Considering the significance of the relationship between arsenic concentration in drinking water and the level of intelligence quotient as an important factor in training, the level of arsenic and its associated risks should be decreased in water resources.

Keywords Arsenic · Dose-response · Intelligence quotient · Drinking water

Introduction

Arsenic is a natural element of earth's crust found in the soils, rocks, natural water, air and living organisms [28]. Arsenic

can be released into water and soils naturally via weathering reactions, microbiological activity, and volcanic eruptions. It can also be released from a wide range of anthropogenic activities, including mining activities, metal processing and using arsenical pesticides and fertilizers [3, 27]. Drinking water is the main source of human exposure to arsenic [4]. Arsenic in drinking water is a serious threat for human health and exposure to it can cause acute and chronic detrimental effects on human health. Acute arsenic poisoning is manifested by vomiting, severe diarrhea and abdominal pain. Diffuse skin rash, seizures, psychosis and toxic cardiomyopathy are of other symptoms of acute arsenic poisoning [20]. Epidemiological researches have suggested that chronic exposure to arsenic is associated with malignancies of lung [19], bladder [25], skin [18], kidney [6] and liver [2]. Other health effects caused by long-term exposure to arsenic include neurological effects, skin lesions, hypertension, cardiovascular disease, pulmonary disease, peripheral vascular disease, and diabetes mellitus [29].

One of the principal target for toxic effects of arsenic is the neurological system [21]. Many epidemiological studies have suggested that chronic exposure to arsenic can induce

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neurobehavioral disorders, cognitive dysfunction, and learning deficits in humans [10, 13, 30]. Children are especially vulnerable to the neurotoxic effects of arsenic [31]. Results of several published studies have shown that arsenic exposure is associated with alteration in cognitive function, such as intellectual performance and learning ability during childhood [11, 24, 36]. Grandjean et al. suggested that chronic exposure to arsenic is responsible for permanent decrease in intelligence quotient (IQ) and could lead to an increase in school failure [8]. In addition, Rocha-Amador et al. reported that increased levels of arsenic in drinking water and urine is related to a decrease in IQ in children aged 6–10 years [22]. The adverse effects of arsenic exposure on children's intelligence have also been previously reported from Mexico, Bangladesh, and the United States [1, 33, 36]. However, how strong the association is between arsenic and children's IQ is still a matter of debate. Thus, in this dose-response meta-analysis, we aimed to review the recently published epidemiological studies on the effect of chronic arsenic exposure in drinking water on intelligence quotient.

Materials and methods

Search strategy We applied a search strategy to identify all related studies. In this study, we searched for article titles and abstracts in order to access studies published in three electronic databases including Scopus, Web of Science, and Medline (PubMed) in English from 2000 to January 2018. We performed the searches using combinations of keywords and MeSH terms including “arsenic” OR “arsenate” OR “arsenate” OR “arsenicosis” OR “arsenic exposure” OR “arsenic poisoning” AND “intelligence” OR “intelligence quotient” OR “IQ” or “intellectual function” (Appendix 1). We reviewed the duplicate articles and then deleted them. In addition, if the full text of paper was unavailable, we requested the paper from the author via email.

Study selection We used criteria of the PRISMA guidelines in our study [14]. Therefore, we included all English language studies in which the mineral arsenic was measured in drinking water using a standard laboratory method, and IQ value (Full scale) was assessed using the Raven's Standard Progressive Matrices and the Wechsler Intelligence Scale. To simplify faster screening, first, the titles were judged, where clearly irrelevant papers were scraped. Then, the abstracts of the related studies were read to ensure that the basic subject of the article was relevant to arsenic exposure and intelligence quotient. Final screening of the studies was based on the full texts. In this secondary study, letters to the editors, case reports, and previous systematic reviews and meta-analyses were not included. The selection process of the papers was not affected by the name of authors or title of journals.

Screening and data extraction All potentially relevant publications were inserted in EndNote X8 software and independently reviewed by two authors (MH and RM). Any discrepancies between the authors were resolved through a consensus with an expert (YM). All three authors extracted the data in order to identify eligible studies. After the final evaluation, the authors extracted and recorded the required data, including name of the first author, year of publication, country, sample size, exposure measurement (arsenic), outcome measurement (IQ), and standard deviation (SD) of the outcome. All the extracted data were then entered into the Excel software.

Quality assessment of the studies To assess the methodological quality of included studies, we used the Newcastle-Ottawa quality assessment adapted for cross-sectional studies [26]. We assessed the quality of all relevant studies in accordance with the type of study, sample size, participant's selection, setting, validity and reliability of measuring exposure and outcome, and appropriate statistical analysis. Finally, studies with high and medium quality were included in the analyses (three studies were excluded at this stage).

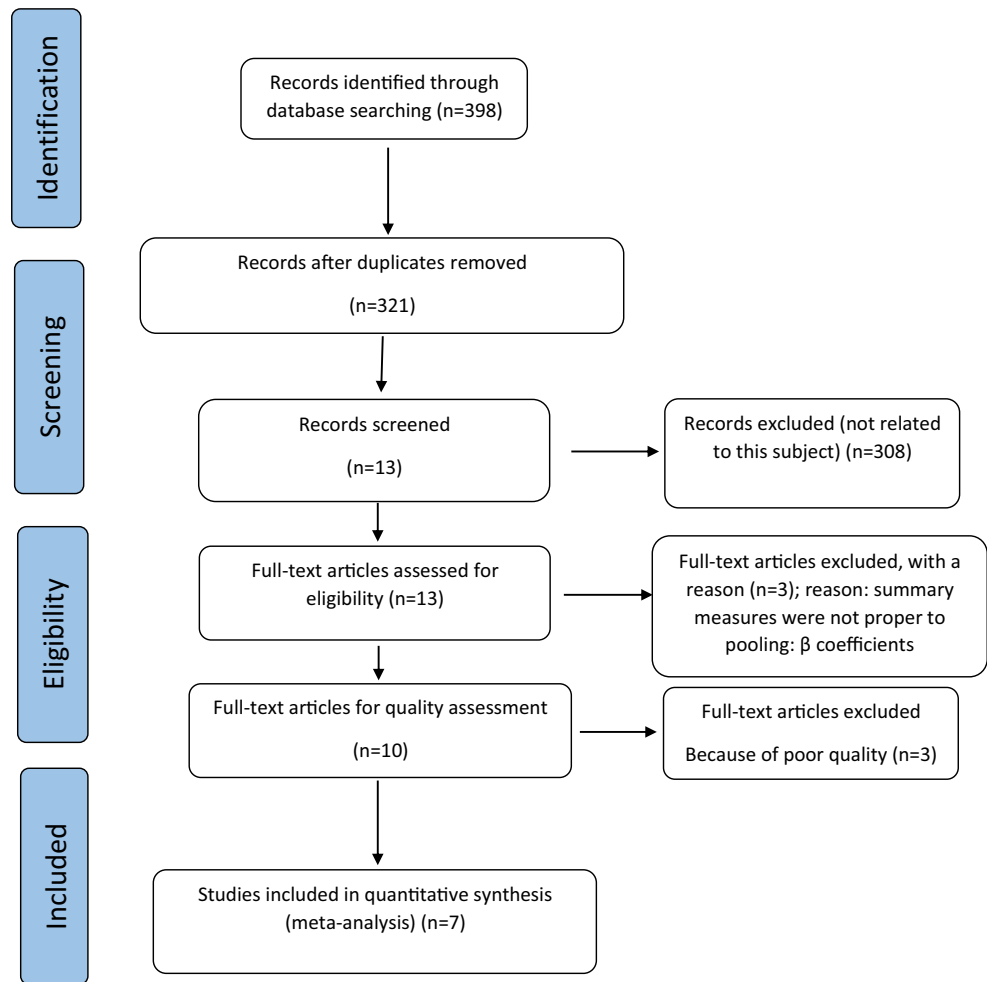
Statistical analysis I^2 statistics was applied to determine the degree of heterogeneity between the studies. Applying the random effect models, the pooled associations (with a 95% uncertainty) between arsenic concentration and IQ were presented as mean difference. R 3.6.0. with the “meta” package was used to perform the meta-analysis. In order to investigate the association between arsenic concentration in drinking water and IQ scale, we compared the high-dose arsenic concentration (ranged from 50 to 650 $\mu\text{g/L}$) versus control group (ranged from 2 to 60 $\mu\text{g/L}$) as well as the medium-dose arsenic concentration (ranged from 50 to 270 $\mu\text{g/L}$) versus control group. It should be noted that those defined levels of arsenic concentration have to some extent a degree of overlap in different studies. Because of these overlapped levels of exposure, we conducted a dose-response meta-analysis. Therefore, using the “mvmeta” and “dosresmeta” packages, we tried to perform dose-response meta-analysis to evaluate the relationship between arsenic ($\mu\text{g/L}$) and IQ scale. This way, two-stage random effects models (linear and cubic spline) were performed and the best model was chosen according to the AIC and BIC.

Finally, publication bias was checked through applying Egger's test. (Funnel plot was not applied due to low number of studies = 7).

Results

Up to 2018, seven observational studies (Fig. 1) with a total of 2126 men and women were included in the present study.

Fig. 1 Flow diagram of the study selection process and included publication for dose-response meta-analysis of arsenic in drinking water and IQ scale



High dose arsenic concentration versus control dose

Figure 2 depicts the pooled estimate of IQ mean difference between high-dose arsenic concentrations (ranged from 50 to 650 µg/L) versus control group (ranged from 2 to 60 µg/L). We estimated the mean difference as -11.73 (95% CI: -16.01, -7.44), that is statistically significant. Actually, exposure to high-dose arsenic concentration compared to control dose resulted in lower IQ scale. The I^2 statistics was estimated as 78%.

Medium dose arsenic concentration versus control dose

Figure 3 depicts the pooled estimate of IQ mean difference between medium-dose arsenic concentrations (ranged from 50 to 650 µg/L) versus control group (ranged from 2 to 60 µg/L). We estimated the mean difference as -8.25 (95% CI: -12.49, -4.01), that is statistically significant. The I^2 statistics was estimated as 61%.

Dose-response association between arsenic concentration and IQ scale

Using the two-stage random effects model to investigate the dose-response association between arsenic concentration and IQ scale, we estimated a significant linear association as -0.08 (95% CI: -0.14, -0.01). Actually, for each unit increase in arsenic concentration (one microgram per liter), IQ scale decreases by 0.08% (Fig. 4).

Assessment of publication bias

We conducted the Egger’s test to check the probability of the publication bias. The results showed that there was no publication bias in the present study (P value = 0.811).

Discussion

We identified seven epidemiological studies that had investigated the association between arsenic in drinking water and IQ

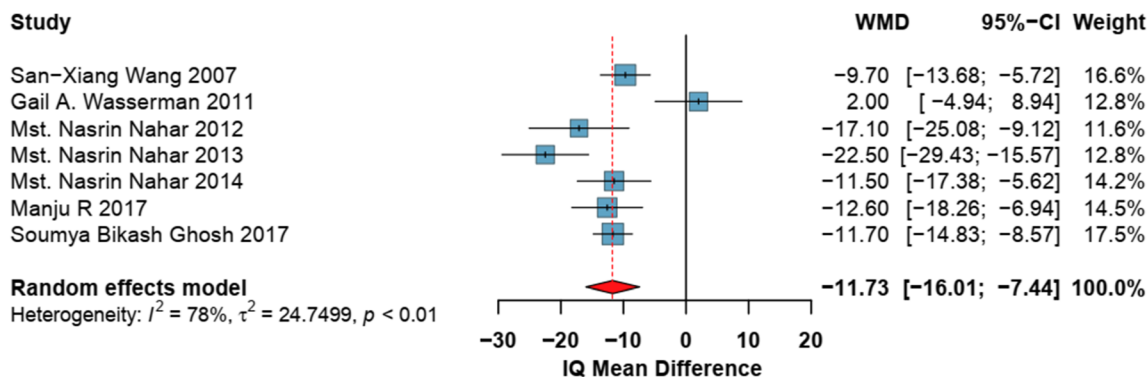


Fig. 2 Pooled estimate of IQ mean difference of high-dose and control-dose (low) arsenic concentration

scale. We excluded insufficient studies and estimated the dose-response association. There was a negative and statistically significant association between arsenic and IQ scale. In fact, according to the results, higher arsenic concentration could lead to lower IQ scale. Wasserman et al. [34], using a linear regression model, estimated the association between arsenic concentration in drinking water and IQ scale with a beta coefficient of -0.03 . According to their findings, each unit increase in arsenic concentration could lead to a decrease in IQ scale by 0.3 score [34]. Previous systematic review and meta-analysis by Dong and Su [5] indicated that living in an arsenicosis area compared to non-arsenicosis area could reduce IQ scale of children [5]. Another systematic review and meta-analysis by Rodriguez-Barranco et al. [23] showed a negative association between arsenic and IQ scale. They estimated that a 50% increase in arsenic level in urine, could lower the IQ of children by 0.4 (Rodríguez-Barranco, Lacasaña et al. [23]). None of those two meta-analyses used a dose-response method. In essence, our study is an update on them to examine the dose-response relationship of arsenic of drinking water and IQ scale. Furthermore, a research by Wasserman et al. [37] revealed that decreasing creatinine-adjusted urinary arsenic and blood arsenic as exposure biomarkers was associated with improvement in working memory score; however, it was not significantly associated with full scale IQ. Nonetheless, they believed that the period of the study was short (a 2-year follow-up study) [37].

It seems that sex of children could be an effect modifier when investigating the association between arsenic in

drinking water and IQ scale. A study by Hamadani et al. [9], using a multivariable-adjusted regression analysis and controlling for potential confounders, i.e. social-demographic variables, showed that arsenic exposure might have adverse effects on IQ scale in girls but not boys [9]. In our study, all seven studies were conducted on both genders.

To our knowledge, the present study is the first effort to perform the dose-response analysis of the relationship between arsenic in drinking water and IQ scale. One of the main limitations of this study is unmeasured confounding. Actually, individual studies have better focus on this methodological point and try to consider the confounding.

Based on the adverse health effects related to arsenic contamination in surface and ground water resources, US Environmental Protection Agency (USEPA) and World Health Organization (WHO) set arsenic as a class-A carcinogen(1,2) Accordingly, the WHO lowered the arsenic guideline level for drinking water from 50 to 10 $\mu\text{g/L}$ in 1993. In many regions of the world, the recommended level of 10 $\mu\text{g/L}$ has been accepted as an enforceable standard (3) Arsenic in water should be removed or lowered to the standard level. However, lowering the arsenic level or its removal from water resources requires financial sources and proper technologies. In many parts of the world especially developing countries, there are problems with arsenic removal. Although many efficient methods of water treatment has been studied and recommended, mainly coagulation methods (3), adsorption (4), membrane technologies (5) and adsorption process (6) but in practice, some challenges exist. Adsorption via low cost material

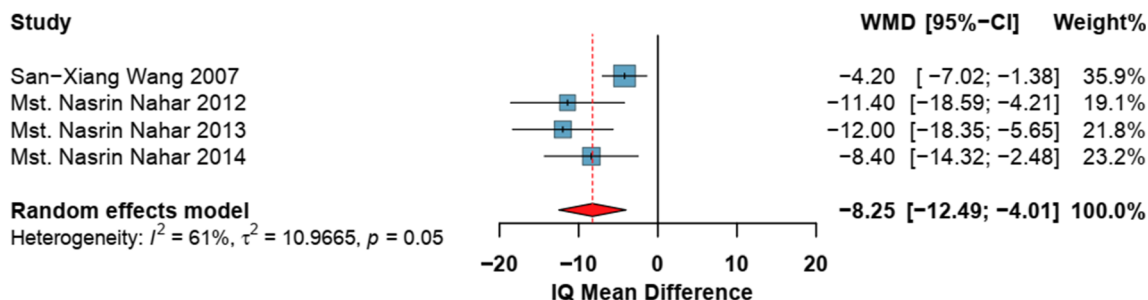
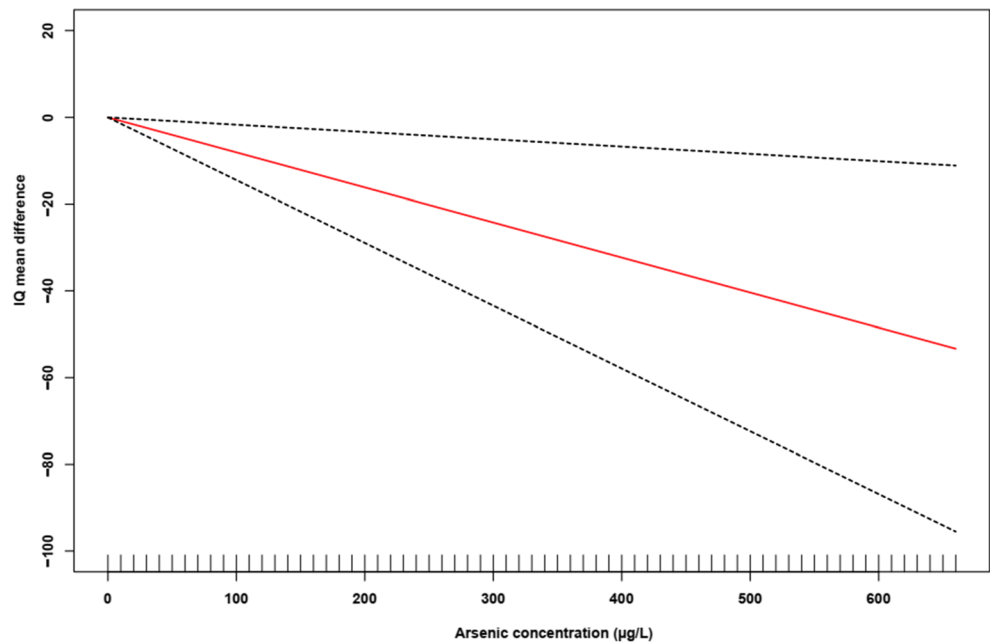


Fig. 3 Pooled estimate of IQ mean difference of medium-dose and control-dose (low) arsenic concentration

Fig. 4 Dose-response association between arsenic concentration and IQ scale based on the linear model; the solid line represents the fitted linear trend, and dash line represents the 95% confidence interval



(activated carbon) has been more applicable for arsenic removal from water in low income and developing countries.

Conclusion

Identifying the dose-response association between arsenic and IQ scale could pave the way for policy makers in order to plan for control of decreasing IQ scale. Minimizing (or at least decreasing) arsenic removal from drinking water could be an important health strategy.

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Authors' contributions Mahsa Hasanvand: Methodology – Writing – original draft.

Nahid Khoshnamvand: Conceptualization – search & Methodology, Rasool Mohammadi: Data Analysis-Writing – original draft.

Ali Jafari: Search & Methodology – Critical revision and editing of the manuscript.

Hossein Safari Palangi: Review & editing – Formal analysis.

Yaser Mokhayeri: Data Analysis – Writing – review & editing.

Compliance with ethical standards

Conflict of interest The writers remark, that they have no special financial interests or personal relationships that could have appeared to affect the work reported in this study.

Appendix 1

Search Strategy in Pub Med:

(arsenic[Title/Abstract] OR arsenate[Title/Abstract] OR arsenite[Title/Abstract] OR arsenicosis[Title/Abstract] OR

“arsenic exposure”[Title/Abstract] OR “arsenic poisoning”[Title/Abstract]) AND (Intelligence[Title/Abstract] OR IQ[Title/Abstract] OR “intelligence quotient”[Title/Abstract])

Search Strategy in Scopus:

(TITLE-ABS-KEY (arsenic OR arsenate OR arsenite OR arsenicosis OR “arsenic exposure” OR “arsenic poisoning”) AND TITLE-ABS-KEY (intelligence OR “children intelligence” OR iq OR “intelligence quotient”)) AND (LIMIT-TO (DOCTYPE, “cp”) OR LIMIT-TO (DOCTYPE, “ar”))

Search Strategy in Web of Science:

#2 AND #1

Refined by: DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR MEETING ABSTRACT)

Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#2 AND #1

Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

TS=(Intelligence or “children intelligence” or IQ or “intelligence quotient”)

Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

TS=(arsenic or arsenate or arsenite or arsenicosis or “arsenic exposure” or “arsenic poisoning”)

Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

Appendix 2

SD_control	14.7	21.4	29.5	6.98	11.34	20.3	28.5
SD_medium	15.6	22.6	28.2			17.3	
SD_high	16.6	22.3	19.3	9.6	6.17	15.4	33
IQ_control	104.8	52.2	50	108.7	30.55	56.5	107
IQ_medium	100.6	43.8	38			45.1	
IQ_high	95.1	40.7	27.5	97	17.95	39.4	109
Dose_control	2	9	60	6	2	59	2.37
Dose_medium	142	50	270			221	
Dose_high	190	120	650	50.6	90	653	82
Sample size (control)	196	120	255	28	20	58	151
Sample size (medium)	253	96	112			47	
Sample size (high)	91	96	41	114	20	25	152
Sample size	540	312	404	142	40	130	303
Sex	Both	Both	Both	Both	Both	Both	Both
YOP	2007	2014	2013	2017	2017	2012	2011
Country	Bangladesh	Bangladesh	Bangladesh	India	India	Bangladesh	Bangladesh
First author	San-Xiang Wang et al. [32]	Mst. Nasrin Nahar et al. [17]	Mst. Nasrin Nahar et al. [16]	Soumya Bikash Ghosh et al. [7]	Manju et al. [12]	Mst. Nasrin Nahar [15]	Gail A. Wasserman et al. [35]
ID	1	2	3	4	5	6	7

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