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Association between arsenic exposure and inflammatory cytokines and C-reaction protein

A systematic review and meta-analysis

Zheyu Zhang, MB[a], Ruozheng Pi, MB[a], Jieya Luo, MB[a], Ji Liu, MB[a], Aihua Zhang, MM[b], Baofei Sun, MD[a,b,*]

Abstract

Background: Previous studies have reported controversial results on levels of inflammatory cytokines in patients with arsenic exposure. This study aims to evaluate the associations between arsenic exposure and inflammatory cytokines and C-reaction protein (CRP).

Methods: We searched the databases including PubMed, Embase, Web of Science, and China national knowledge infrastructure (CNKI) for studies reporting levels of cytokines and CRP in patients with arsenic exposure compared to the controls. The retrieval time was from January 2000 to September 2022.

Results: 13 observational studies involving 1665 arsenic exposed and 1091 unexposed individuals were included. Among these studies, 6 from China, 4 from India, 2 from Bangladesh and 1 from Turkey. Our result showed that interleukin (IL)-6, IL-8, and IL-12 levels were significantly higher in arsenic-exposed individuals compared to the control group, IL-2 level was significantly lower, and Tumor necrosis factor-α, Interferon-γ, CRP, and IL-10 levels were not changed. After sensitivity analyses, tumor necrosis factor-α and Interferon-γ levels were significantly higher in arsenic-exposed individuals compared to the control group. High heterogeneity was detected in most studies.

Conclusion: Many cytokines (such as IL-6, IL-8, and IL-12) have altered in individuals with arsenic exposure, this indicates arsenic exposure could trigger the cell-mediated inflammatory response. Regular examining immune function (such as inflammatory cytokines) in individuals with the risk of arsenic exposure is important to human health.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, IFN-γ = interferon-γ, IL = interleukin, NOS = Newcastle-Ottawa quality assessment scale, SMD = standardized mean difference, TNF-α = tumor necrosis factor-α.

Keywords: arsenic, C-reactive protein (CRP), cytokines, immunotoxicity, inflammation

1. Introduction

Arsenic is a naturally existing toxic metal-like element which considered a common environmental pollutant.[1] Worldwide, arsenic exposure is a major public health challenge that affected more than 200 million individuals through drinking water which was considered the main source of arsenic exposure.[2,3] It is believed that chronic arsenic exposure could have serious harmful effects on human health, such as skin lesions, intestinal maladies, vascular diseases, neurological diseases, immunotoxicity, and various cancer.[4–7] However, the pathogenesis of arsenic exposure was still not clear enough.[8] Recently, researchers pay more attention to immunotoxicity and inflammation associated with chronic arsenic exposure.[9] Inflammation is a response considered to be caused by tissue injury or infection. In animal models, low chronic arsenic exposure could initiate inflammation and high exposure was believed to accentuate inflammation and trigger immunostimulatory.[10–12] Moreover, arsenic exposure could damage the functions of immune cells and alter the expression of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (interleukin [IL]-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-12 (IL-12).[12–14] C-reactive protein (CRP) is a protein considered an acute-phase reactant and the production of CRP is part of the nonspecific response to inflammation.[15] Many studies have reported altered levels of inflammatory cytokines in individuals with

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[a] College of Basic Medical, Guizhou Medical University, Guiyang city, Guizhou Province, China, [b] The Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang City, Guizhou Province, China.

** Correspondence: Baofei Sun, The Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, Guizhou 550000, China (e-mail: sunbaofei@sina.com).*

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arsenic exposure, the results of studies existed different, and some findings were even inconsistent with the results of animal experiments.[16–19]

Currently, the discussion of the association between arsenic exposure with inflammation in humans remains controversial. Therefore, we performed a systematic review and meta-analysis to evaluate the levels of inflammatory cytokines such as TNF-α and IL-2 among individuals with arsenic exposure compared to the controls. This study aims to investigate the association between arsenic exposure with inflammation according to published literature. Our results may provide more elucidation on the immunological effects of cytokines of chronic arsenic exposure.

2. Method

This study was designed and performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] The protocol of this meta-analysis was registered at PROSPERO (registration number: CRD42022359688 (https://www.crd.york.ac.uk/PROSPERO/)).

2.1. Search strategy

Two researchers (Z.Y.Z and R.Z.P) independently conducted a literature review of the search for this study. We searched the databases including PubMed, Embase, Web of Science, and China national knowledge infrastructure (CNKI). The retrieval time was from January 2000 to September 2022. The language was limited to English and Chinese. The following was the search strategy: (arsenic OR Arsenicum OR Arsenium OR arsenic exposure) AND (Inflammation OR inflammatory OR cytokines OR chemokine OR IL-1β OR IL-2 OR IL-4 OR IL-5 OR IL-6 OR IL-8 OR IL-10 OR IL-12 OR "Tumor Necrosis Factor-alpha" OR TNF-α OR CRP OR "C-reactive protein" OR IFN-γ OR "Interferons" OR interferon gamma). The literature retrieval process of PubMed database was shown in Supplementary material 1, Supplemental Digital Content, http://links.lww.com/MD/I163.

2.2. Inclusion and exclusion criteria

Inclusion criteria: The study participants must be patients with a history of arsenic exposure (e.g., occupational arsenic exposure, Arsenic-endemic study areas, etc.), the participants in the control group were healthy controls without a history of arsenic exposure; Study reported arsenic levels in the drinking water or in the participants (e.g., hair, nail, or plasma); The outcomes of the study included at least 1 of serum level of cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, TGF-β, IFN-γ, and CRP)

Exclusion criteria: Case reports, literature reviews, editorials, animal studies, or republished studies; Single arm study; Raw data cannot be extracted or the full text was not available; study did not report any outcome; Participants < 18 years old, having diseases that affect immune function and recent infections.

2.3. Data extraction

Two researchers (Z.Y.Z and J.Y.L) independently extracted the raw data from included studies. The following data were extracted in each study: Title, journal of publication, the 1st author, years of publication, country, details of arsenic exposure (source, duration, and arsenic levels), patient characteristics, and level of cytokines (Mean ± standard deviation).

2.4. Assessment of the risk of bias

Two researchers (Z.Y.Z and R.Z.P) independently assessed the risk of bias in each included study. The Newcastle-Ottawa quality assessment scale (NOS) was used for assessing the risk of bias in case-control studies in meta-analysis.[21] NOS has 3 domains: selection of study, comparability, and evaluation of outcomes, with a total score of 9 points. Scores ≥ 7 are considered a high-quality study.

2.5. Statistical analysis

Meta-analyses were performed by using RevMan5.3 software according to the Cochrane Manual for Systematic Evaluation of Interventions. Meta-analysis would be performed when more than 2 studies (≥2) have reported levels of a kind of cytokine. Mean difference and 95% confidence intervals (CI) were used to assess the pooled effect size when the concentration units of included studies are the same. Otherwise, standardized mean difference (SMD) and 95% CI were used. For studies with multiple arsenic exposure groups according to different levels of exposure, subgroup data were combined for meta-analysis.[22] The Cochran's Q test combined I^2 statistics were used to evaluate the statistical heterogeneity in this meta-analysis. The fixed-effects model (Mantel-Haenszel method) was selected when no significant heterogeneity was detected (I^2 < 50% or *P*-value for heterogeneity > .1). The random-effects model (Der Simonian-Laird method) was selected when significant heterogeneity was detected (I^2 ≥ 50% or *P* value for heterogeneity ≤ .1). Subgroup analyses are performed when significant heterogeneity was found. If subgroup analyses could not find the source of heterogeneity, sensitivity analyses would be performed to find difference between studies. For meta-analysis with the number of included studies > 5, the publication bias was assessing both through Funnel plots and Egger's tests. Egger's test was performing using Stata15 Software. A *P* value of > .05 was considered statistically significant.

3. Results

3.1. Literature search

The literature search yielded 4927 studies. After duplication removal, a total of 1943 studies were removed. Following screening the titles and abstracts, 2753 studies were excluded. 131 articles met our eligibility criteria and a full-text evaluation was performed in these studies. Finally, a total of 13 studies[16–19,23–31] were included in this meta-analysis. Among included studies, 4 were in Chinese,[24–27] and 9 were in Engl ish.[16–19,23,28–31] Besides, all studies were conducted in developing countries, 6 from China,[24–27,30,31] 4 from India,[16,17,23,28] 2 from Bangladesh[19,29] and 1 from Turkey.[18] Most exposure sources of included studies were from environment exposure[16,17,19,23–29,31] except 2 studies[18,30] from occupational exposure. The flow diagram of study selection and exclusion was shown in Figure 1.

3.2. Characteristics of included studies

13 studies with 1665 arsenic exposed and 1091 unexposed individuals were included in the final analysis and 8 cytokines were assessed for association with arsenic exposure. The main characteristics of included studies were presented in Table 1. The risk of bias in included studies was assessed by NOS. All included studies were assessed as high-quality studies for scoring ≥ 7. NOS scoring details were presented in Table 2.

3.3. TNF-α

Seven studies[16–19,23,26,31] reported the TNF-α level in the As-exposed (n = 985) and control (n = 551) groups. Significant

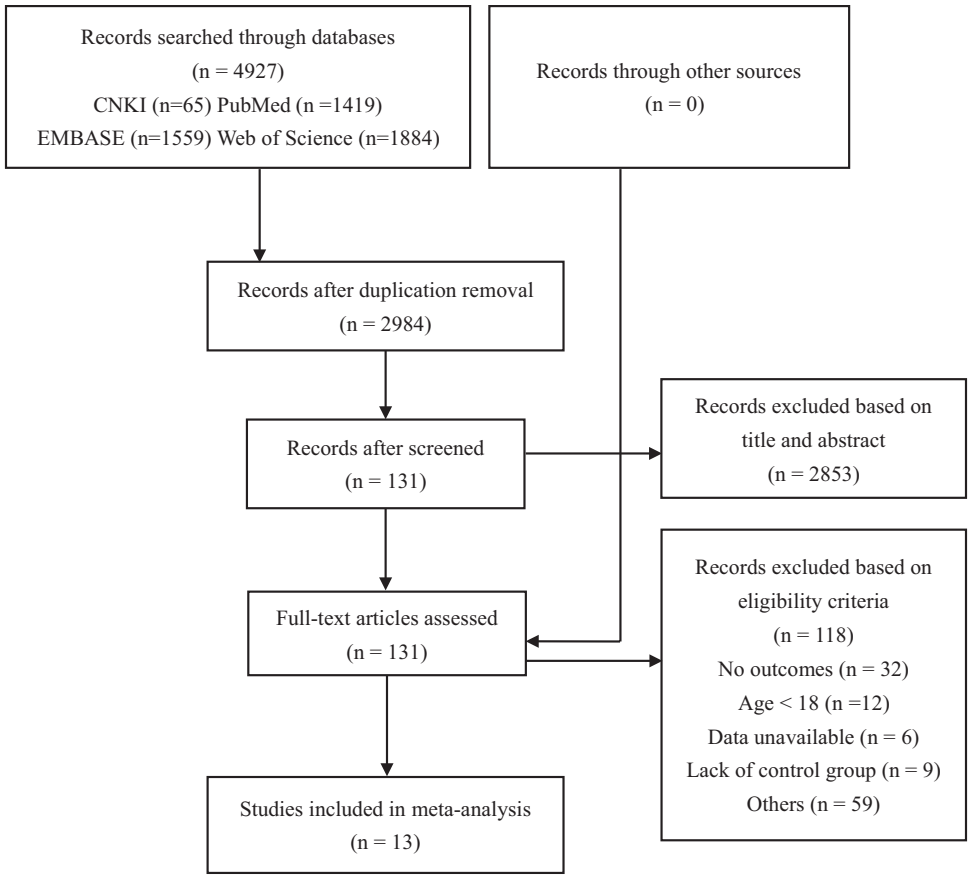

Figure 1. The flow diagram of study selection and exclusion.

heterogeneity was detected between studies (I^2 = 94%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the TNF-α level was not significantly changed in As-exposed patients compared to the controls (SMD = 0.32, 95%CI (-0.18, 0.82), P = .21) (Fig. 2).

3.4. IFN-γ

Two studies[16,19] reported the IFN-γ level in the As-exposed (n = 429) and control (n = 161) groups. Significant heterogeneity was detected between studies (I^2 = 98%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the IFN-γ level was not significantly changed in As-exposed patients compared to the controls (SMD = -1.19, 95%CI (-4.13, 1.75), P = .43) (Fig. 3).

3.5. CRP

Five studies[17,18,24,29,30] reported the CRP level in the As-exposed (n = 564) and control (n = 601) groups. Significant heterogeneity was detected between studies (I^2 = 95%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the CRP level was not significantly changed in As-exposed patients compared to the controls (SMD = 0.43, 95%CI (-0.13, 0.99), P = .14) (Fig. 4).

3.6. IL-2

Four studies[16,25,27,31] reported the IL-2 level in the As-exposed (n = 490) and control (n = 152) groups. Significant heterogeneity was detected between studies (I^2 = 98%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the IL-2 level was significantly decreased in As-exposed patients compared to the controls (SMD = -1.58, 95%CI (-3.12, -0.04), P = .04) (Fig. 5).

3.7. IL-6

Five studies[17,18,23,28,31] reported the IL-6 level in the As-exposed (n = 560) and control (n = 392) groups. Significant heterogeneity was detected between studies (I^2 = 85%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the IL-6 level was significantly increased in As-exposed patients compared to the controls (SMD = 1.00, 95%CI (0.61, 1.38), P < .00001) (Fig. 6).

3.8. IL-8

Three studies[17,23,28] reported the IL-8 level in the As-exposed (n = 297) and control (n = 274) groups. Significant heterogeneity was detected between studies (I^2 = 95%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the IL-8 level was significantly increased in As-exposed patients compared to the controls (SMD = 12.14, 95%CI (8.13, 16.14), P < .00001) (Fig. 7).

3.9. IL-10

Three studies[16,18,23] reported the IL-10 level in the As-exposed (n = 224) and control (n = 222) groups. Significant heterogeneity was detected between studies (I^2 = 96%, heterogeneity P < .00001), and the random-effects model was used. Our study showed that the IL-10 level was not significantly changed in As-exposed patients compared to the controls (SMD = -2.34, 95%CI (22.26, 17.58), P = .82) (Fig. 8).

Table 1

The main characteristics of included studies.

Study	Country	Exposure sources	Exposure variables	Age, yr (exposed/unexposed)		Sample size (exposed/unexposed)	Outcomes	Detection method
Biswas 2008[16]	India	Environment exposure	Drinking water, urine, nail, hair	41.05	46.05	38 (20/18)	①②④⑦	CBA
Ji 2011[23]	China	Environment exposure	Drinking water	49.92 ± 9.06	53.33 ± 8.28	90 (58/32)	③	Nephelometry
Das 2012[27]	India	Environment exposure	Drinking water, urine	40.13 ± 13.36	40.03 ± 13.01	65 (32/33)	⑤⑥	ELISA
Karim 2013[28]	Bangladesh	Environment exposure	Drinking water, nail, hair	37.55 ± 11.71	35.04 ± 10.93	313 (207/106)	③	ELISA
Ning 2014[25]	China	Environment exposure	Not mentioned	55.7 ± 6.2	53.8 ± 4.9	58 (28/30)	①	ELISA
Dutta 2015[29]	India	Environment exposure	Drinking water	38 ± 6	39 ± 4	273 (142/131)	①⑤⑥⑦⑧	ELISA
Wang 2016[26]	China	Environment exposure	Drinking water, urine	28.92 ± 3.86	28.28 ± 5.05	168 (120/48)	④	ELISA
Prasad 2017[17]	India	Environment exposure	Drinking water	38 ± 7	39 ± 5	233 (123/110)	①③⑤⑥⑧	ELISA
Gao 2018[30]	China	Occupational exposure	Urine	26.43 ± 5.76	25.76 ± 6.57	394 (114/280)	③	Not mentioned
Xu 2020[31]	China	Environment exposure	Urine	49.07 ± 10.04	50.52 ± 9.97	246 (201/45)	①④⑤	ELISA
Fang 2019[24]	China	Environment exposure	Urine	50.69 ± 6.14	45.76 ± 7.88	190 (149/41)	④	ELISA
Tutkun 2019[18]	Turkey	Occupational exposure	Serum	Not mentioned (>18)		135 (62/73)	①③⑤⑦	ELISA
Rahman 2021[19]	Bangladesh	Environment exposure	Drinking water	37.5 ± 11.3	35.9 ± 11.2	553 (409/144)	①②	ELISA

CBA = cytometric bead array, ELISA = enzyme linked immunosorbent assay.
①: TNF-α ②: IFN-γ ③: CRP ④: IL-2 ⑤: IL-6 ⑥: IL-8 ⑦: IL-10 ⑧: IL-12.

3.10. IL-12

Two studies[17,23] reported the IL-12 level in the As-exposed (n = 265) and control (n = 241) groups. No significant heterogeneity was detected between studies (I^2 = 0%, heterogeneity P = .60), and the fixed-effects model was used. Our study showed that the IL-12 level was significantly increased in As-exposed patients compared to the controls (SMD = 9.64, 95%CI (8.70, 10.59), P < .00001) (Figure 9.).

Table 2

Risk of bias assessment of included studies.

	Selection				Comparability	Outcome			
Study	1	2	3	4	5	6	7	8	Score
Biswas 2008[16]	*	*	*	*	**	*	*	*	9
Ji 2011[23]	*	*	*	*	**	*	*	*	9
Das 2012[27]	*	*	*	*	**	*	*	*	9
Karim 2013[28]	*	*	*	*	**	*	*		8
Ning 2014[25]	*	*	*	*	*		*	*	7
Dutta 2015[29]	*	*	*	*	**		*	*	8
Wang 2016[26]	*	*	*	*	*		*	*	7
Prasad 2017[17]	*	*	*	*	*	*	*	*	8
Gao 2018[30]	*	*	*	*	**	*	*	*	9
Xu 2020[31]	*	*	*	*	**	*	*	*	9
Fang 2019[24]	*	*	*	*	**		*	*	8
Tutkun 2019[18]	*	*	*	*	*		*	*	7
Rahman 2021[19]	*	*	*	*	**	*	*	*	9

(1) Sufficient definition of the cases (2) Representativeness of the cases (3) Selection of the controls (4) Definition of the controls (5) Comparability of cases and controls based on the design or analysis (6) Assessment of exposure (7) Same method of ascertainment for cases and controls (8) non-response rate.

3.11. Subgroup analyses and Sensitivity analyses

Subgroup analyses could not explain the heterogeneity in this meta-analysis. Sensitivity analyses showed significantly higher levels of TNF-α (SMD = 0.59, 95%CI (0.14, 1.04), P = .01) (Fig. 10) and IFN-γ (SMD = 0.28, 95%CI (0.09, 0.47), P = .004) (Fig. 11) in Arsenic exposed group compared to the control group when Biswas's study[16] was excluded.

3.12. Publication bias

Only the number of included studies of meta-analysis of TNF-α were more than 5. The Funnel plot (Fig. 12) and Egger's test (P = .994) both suggested no publication bias was found in this meta-analysis.

4. Discussion

To the best of our knowledge, this is the 1st meta-analysis to evaluate the effect of arsenic exposure on human immunity by conducting a systemic review and meta-analysis. Studies reporting inflammatory cytokines levels in arsenic-exposed and unexposed individuals were identified by literature search. Our results showed that IL-6, IL-8, and IL-12 levels were significantly higher in arsenic-exposed individuals compared to the control group, IL-2 level was significantly lower, and TNF-α, IFN-γ, CRP, and IL-10 levels were not changed. When Biswas's study was excluded, TNF-α and IFN-γ levels were significantly higher in arsenic-exposed individuals compared to the control group. Biswas's study showed that all the 6 cytokines significantly decreased in the arsenic-exposed individuals compared to the control group, which was different from other included studies. This may be attributed to the severity of the arsenic exposure group because all individuals

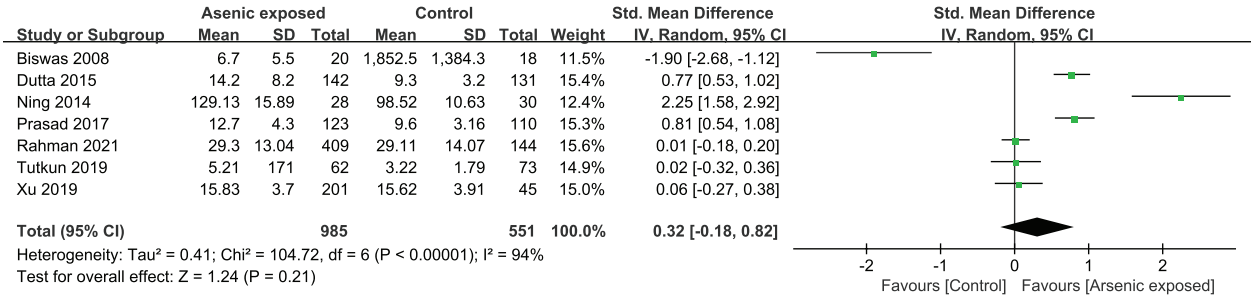

Figure 2. Forest plot for TNF-α. TNF-α = tumor necrosis factor-α.

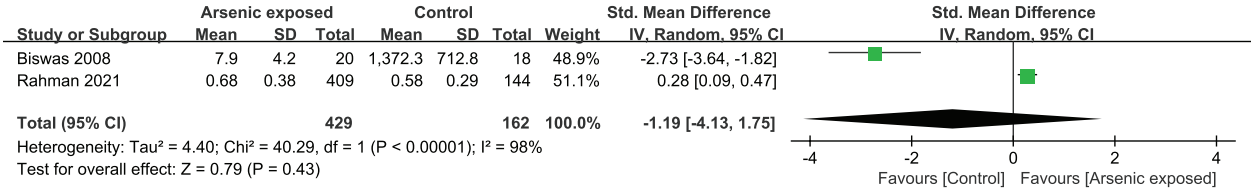

Figure 3. Forest plot for IFN-γ. IFN-γ = interferon-γ.

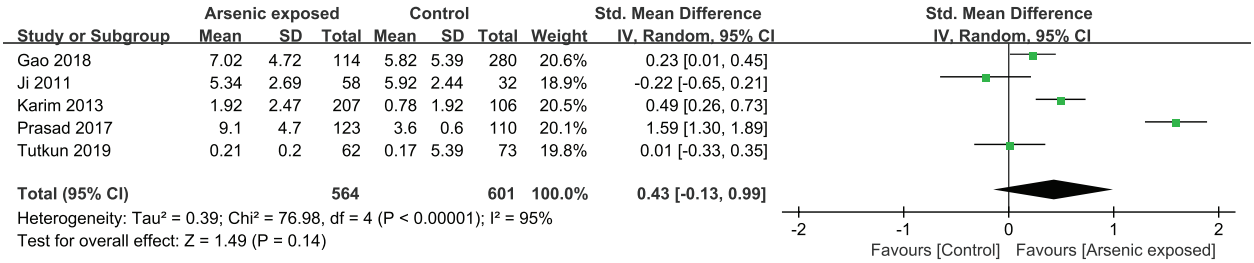

Figure 4. Forest plot for CRP. CRP = C-reactive protein.

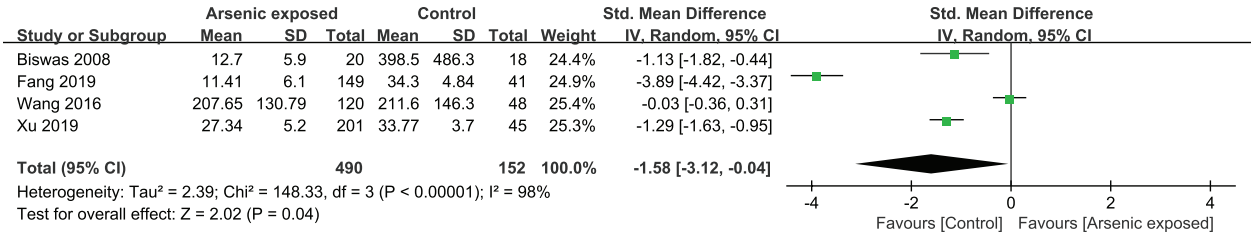

Figure 5. Forest plot for IL-2. IL = interleukin.

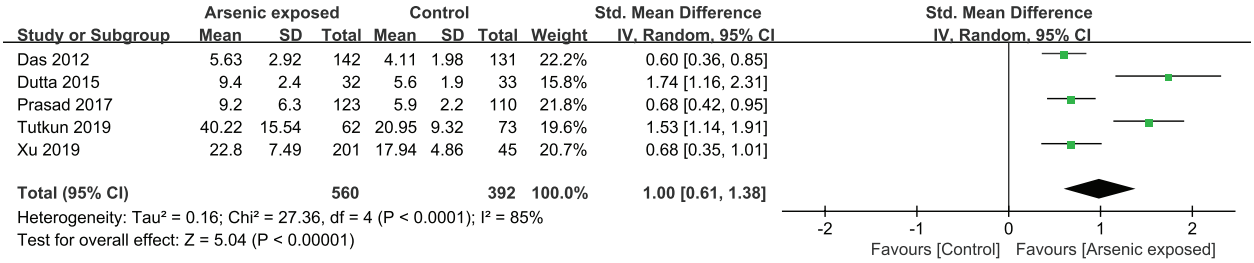

Figure 6. Forest plot for IL-6. IL = interleukin.

with arsenic exposure suffered skin lesions. Prolonged and high-dose arsenic exposure may trigger immunosuppression in humans. Due to the limited number of included studies, the dose-response analysis could not be performed for finding the association between the severity of arsenic exposure and levels of cytokines in humans.

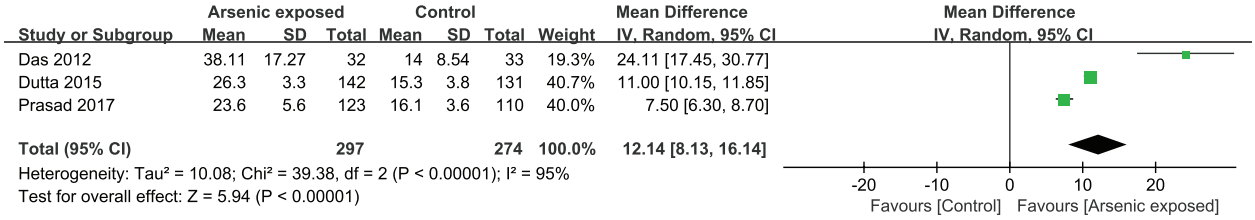

Figure 7. Forest plot for IL-8. IL = interleukin.

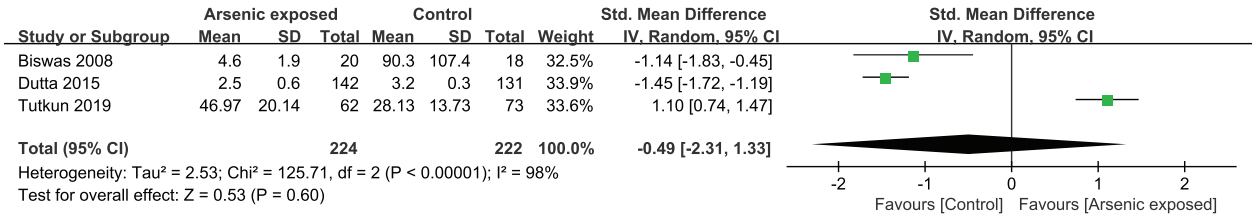

Figure 8. Forest plot for IL-10. IL = interleukin.

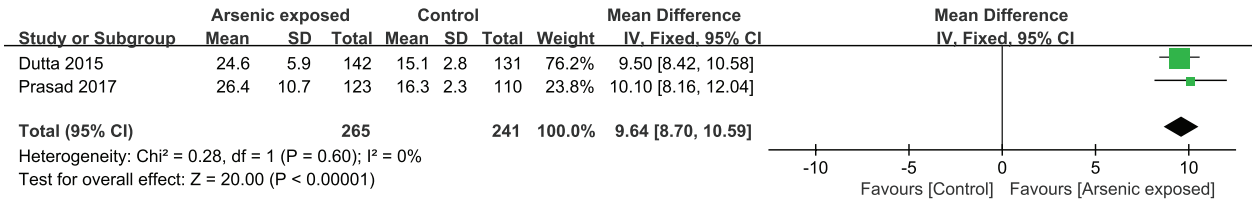

Figure 9. Forest plot for IL-12. IL = interleukin.

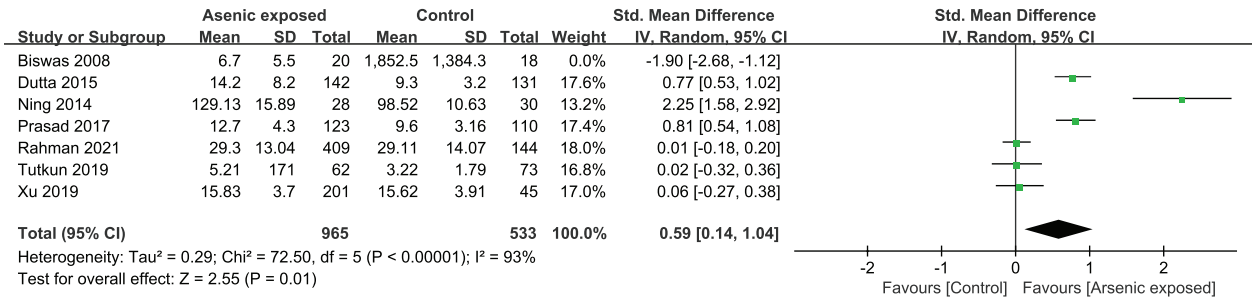

Figure 10. Forest plot of sensitivity for TNF-α. TNF-α = tumor necrosis factor-α.

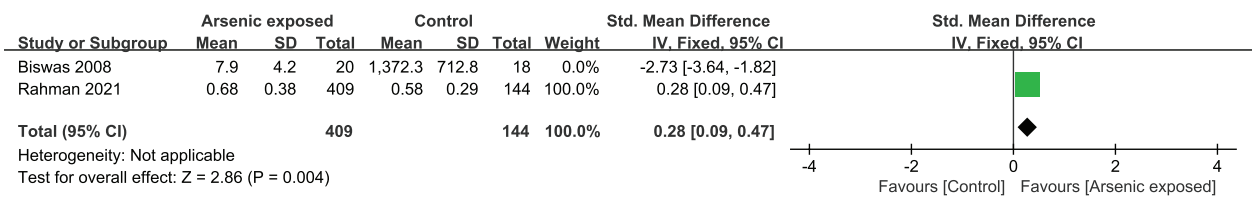

Figure 11. Forest plot of sensitivity for IFN-γ. IFN-γ = interferon-γ.

Cytokines can mediate inflammatory responses. The interaction between proinflammatory cytokines (IL-2, IL-6, IL-8, IL-12, TNF-α, IFN-γ, and et. al.) and anti-inflammatory (IL-4, IL-10, and et. al.) cytokine regulates the immune response in human.[32] Current findings included the tendency of elevated IL-6, IL-8, IL-12, TNF-α, and IFN-γ, while a reduction in IL-2 levels in individuals with arsenic exposure as compared to the control group, which were in line with the results of animal experiments basically.[12,13,33,34] Arsenic-induced pro-inflammatory response may lead to various diseases, such as autoimmune disorders, allergic diseases, and cardiovascular events.[19,28,29] Moreover, Polymorphisms of inflammatory genes could increase the risk of disorders of body function and diseases in arsenic-exposure populations.[35–38] These results indicated that the expression of cytokines may be a potential and useful biomarker of arsenic exposure and arsenic-induced damage to tissues and organs.

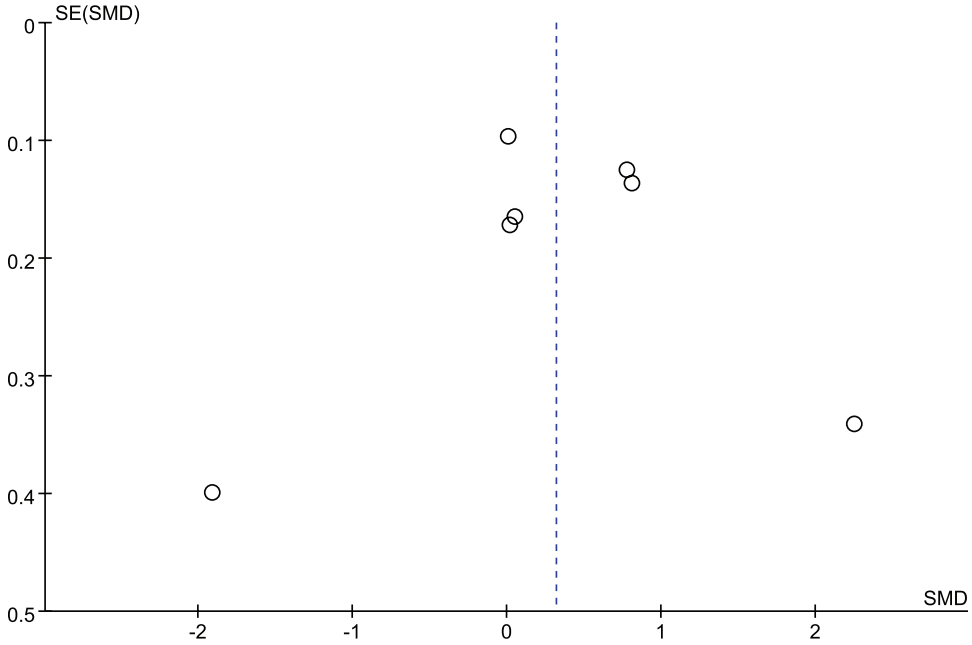

Figure 12. The funnel plot.

Several limitations existed in this present study. First, high heterogeneity between studies was detected and cannot be explained by subgroup analysis or sensitivity analysis. Second, the number of included studies was relatively small and the types of cytokines were different, resulting in a small sample size for meta-analysis of each cytokine. Third, this present study failed to compare the differential effects of low versus high arsenic exposure on levels of cytokines in humans.

5. Conclusions

In summary, arsenic exposure is a public health problem that affected hundreds of millions of people. Exposure to arsenic demonstrated altered inflammatory cytokines, which indicated that arsenic exposure could trigger inflammatory responses. The immunotoxicity of arsenic exposure may be related to cell-mediated responses. This present study has the limitations of a small sample size and large heterogeneity. Large sample sizes and high-quality case-control studies on the association between inflammatory cytokines and arsenic exposure are still necessary in the future. Important tissues and organ damage due to arsenic exposure may be mediated by inflammatory responses. Thus, regular examining immune function (such as inflammatory cytokines) in individuals with the risk of arsenic exposure is important to human body health.

Author contributions

Conceptualization: Baofei Sun.
Data curation: Zheyu Zhang, Ruozheng Pi, Jieya Luo.
Formal analysis: Zheyu Zhang, Ruozheng Pi.
Methodology: Zheyu Zhang, Ji Liu.
Software: Zheyu Zhang, Jieya Luo.
Supervision: Baofei Sun, Aihua Zhang.
Writing – original draft: Zheyu Zhang, Ruozheng Pi.
Writing – review & editing: Zheyu Zhang, Baofei Sun.

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