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Health risk assessment for exposure to nitrate and nitrite in drinking water in Iran: a systematic review and meta-analysis

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ABSTRACT

The aim of this study was to investigate the health risk assessment of nitrate and nitrite in drinking water resources in Iran by conducting a systematic review and meta-analysis. Electronic databases were searched before August 2017, and methodological quality was assessed by a modified Downs and Black checklist. Of 1,539 searched references, 49 studies were selected and included in the meta-analysis study. We used a random effects model to estimate the effect size with 95% confidence interval (CI) to summarize the results. The hazard index values for health risk assessment were calculated for accrued data. The pooled mean concentration of nitrate and nitrite in drinking water resources was 24.9 mg/L (95% CI 16.79–32.39) and 0.05 mg/L (95% CI 0.03–0.07), respectively. Using the random effects model, the pooled nitrite hazard index was found to be 0.40 (95% CI 0.30–0.48). The hazard index of 12.5% of drinking water resource was above 1. In central and northwestern parts of Iran, the concentration of nitrate and nitrite exceeded the drinking water standards (50 and 3 mg/L for nitrate and nitrite according to WHO guidelines and Iran standards) and could be associated with health risks in these regions. The main reasons for the elevating nitrate and nitrite concentration in Iran could be due to the usage animal and chemical fertilizers as well as lack of wastewater collection systems, which requires the necessary authorities to establish new laws.

Keywords: Drinking water; Health risk assessment; Meta-analysis; Nitrate; Nitrite

1. Introduction

The concentration of nitrate and nitrite in drinking waters in the whole world has increased over the past three decades [1]. Chemical fertilizers, organic wastes, and wastewater wells are responsible for the severe increase in nitrate concentration in both surface and groundwaters [2]. Soil bacteria oxidize ammonium to nitrite and subsequently, nitrate concentration increases in surface waters [3]. Although the denitrification process is naturally occurring, it contributes to significant nitrous oxide emissions, with a simultaneous reduction in nitrate/nitrite load from water bodies. However, these reactions in surface waters are minor compared with biological denitrification [4]. Nitrite is more dangerous in the form of nitrate which can also be reduced to nitrite [4]. Therefore, this reduction can increase the toxicity of these compounds. The enzymes present in human saliva as well as the secretions of the digestive system can reduce nitrate to nitrite [3]. Not only nitrite is being directly toxic, but it also aids the formation of carcinogenic compounds such as N-nitroso compounds in response to secondary and tertiary reactions with amines and amides [3]. High nitrate concentration in drinking water is accompanied by diseases, including methemoglobinemia, hypertension, diabetes, and spontaneous abortions [1,2].

Methemoglobinemia affects newborn babies and is acute and potentially fatal [3]. As a result, the WHO and Institute of Standards and Industrial Research of Iran have determined

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the maximum allowable concentration of nitrate and nitrite in drinking water to be 50 and 3 mg/L, respectively [5]. Nitrate concentration is an important factor in health risk assessment studies [6]. Water resources in some Iranian cities such as Semnan, Tehran, Mashhad, Rasht, Sari, Hamadan, Arak, and Isfahan have nitrate and nitrite problems [7–9]. A 5-year study of nitrate in drinking water by Jalali et al. [10,11] indicated that its concentration in agricultural communities increased from 24 to 43 mg/L over 5 years, and also increased by 8- to 10-fold in comparison with previous values. Ghadimi et al. [12] showed that climatic conditions and anthropological activities (especially agriculture) were responsible for short-term and long-term changes in nitrate concentration in drinking water. Other studies have shown that nitrate concentration in drinking water depends on seasonal runoffs and nitrogen fertilizer use in agricultural lands [12,13]. Nitrate concentration in Markazi Province increased from 0.05 to 40 mg/L over a 10-year period [14]. Considering the role played by nitrate and nitrite on health and their cumulative concentration in surface and groundwaters, a continual survey and analysis of these chemical parameters was strongly necessitated [15]. Various studies have been carried out about adverse health effects associated with nitrate and nitrite in various Iranian cities. However, there is no complete and comprehensive analysis of these data, which together with their integration should generate valuable conclusions. Hence, a systematic review and meta-analysis of these data were carried out. The objective of this review was to perform a systematic review of the literature to evaluate nitrate and nitrite concentrations and health risk assessment in drinking water resources in Iran.

2. Materials and methods

2.1. Search strategy

Two persons simultaneously searched PubMed, EMBASE, ISI Web of Science, Scopus, Ovid, Google Scholar Database, as well as Iranian databases including MagIran, IranMedex, and Scientific Information Databank for studies carried out on nitrate and nitrite concentrations before 15 August 2017. Additionally, all papers published in journals, as well as in national and international conferences related to nitrate and nitrite concentrations in water supplies from different parts of Iran were collected. The search keywords used included: "drinking water quality" or "water quality parameters" or "ground water resources" or "water quality index" or "pollution resource index" or "physical and chemical indicators" or "chemical analysis" or "groundwater hydrochemistry" linked with "nitrate" or "NO^-_3" or "nitrite" or "NO^-_2" or "nitrate intake".

The references of selected articles were explored to find the additional appropriate articles as well. Unpublished reports were received by sending an email and direct contact with the corresponding author. The inclusion criteria were all studies carried out in Iran which associated with nitrate and nitrite concentrations in drinking water using appropriate sampling and analytical methods. The selected papers contained sufficient information about the mean, 95% confidence interval (CI), and standard deviation (SD) of nitrate and nitrite concentrations (reported as mg/L NO_3^- and NO_2^-). The exclusion criteria were review papers, systematic review studies, letters to the editor, and studies with a small sample size (less than 20).

2.2. Data extraction

For each paper, information of the first author, year of publication, province, latitude, research design, type of water resource, nitrate and nitrite analysis method, sample size, and the major findings were extracted (Table 1). Search of references, quality control, study selection, and data extraction were performed by two investigators (B.K and S.S). The methodological quality of each paper was examined by Downs and Black checklist [16] (Table S1). The maximum score in this checklist was 16, where papers with 8 scores had a medium to high quality and could be included in the study [16,17]. The included studies were examined again using the Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) checklists, which classifies papers into high, medium, and low quality.

2.3. Health risk assessment

Non-carcinogens health risk model (U.S. EPA) for nitrate health risk assessment was calculated using Eq. (1):

$$\mathrm{HI} = \frac{\mathrm{CDI}}{\mathrm{RfD}} \tag{1}$$

where HI is non-carcinogens hazard risk, CDI is chronic daily intake (mg/kg.d), and RfD is reference dose (mg/kg.d) (Eq. (2)):

$$\mathrm{CDI} = \frac{\mathrm{CW} \times \mathrm{WI} \times F \times D}{W \times T} \tag{2}$$

where CW is chemicals content in water (mg/L), WI is water intake (L/d), F is exposure frequency (d/a), D is exposure duration (a/life time), W is weight (kg), and T is averaging time (a) [6].

For computing hazard index, water intake reference values were set at 2.3 and 1.5 L/d based on the EPA values, the average exposure time was the exposure duration (ED) × 365 d/a, the reference dose for nitrates was 1.6 mg/(kg·d) on the EPA's Integrated Risk Information System (IRIS), and a mean body weight of 70 kg were considered. Also, the nitrates reference value was set at 10 mg/L (measured as nitrogen) in drinking water [6].

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2.4. Data synthesis and statistical analysis

Statistical analyses were performed with STATA software version 12 (STATA Corporation, College Station, TX)

Table 1
Characteristics of all eligible studies

Author (publication year)	Year of sampling	Province	City	Type of water consumption	Sample size	Method	Type of study	Result	Reference
Nanbakhsh (2002)	2000	West Azerbaijan	Urmia	Wells	74	Titration	Cross sectional	Less than WHO standard	[18]
Fakhri et al. (2015)	2012	East Azerbaijan	Marand	Wells	48	Spectrophotometry	Cross sectional	12 Samples higher than WHO standard	[19]
Barzegar et al. (2017)	2014	East Azerbaijan	Marand	Wells	48	Spectrophotometry	Cross sectional	–	[20]
Osaloo et al. (2015)	2013	West Azerbaijan	Aras	River and dam	140	Spectrophotometry	Cross sectional	More than WHO standard	[21]
Nanbakhsh et al. (2010)	2010	West Azerbaijan	Urmia	Wells	120 Samples from 30 wells	Spectrophotometry	Cross sectional	Less than national standard of Iran (maximum permissible)	[22]
Solgi and Sheikhzadeh (2016)	2014	West Azerbaijan	Aras	River and dam	20	Spectrophotometry	Cross sectional	More than WHO standard	[23]
Abad et al. (2017)	2013	Ardabil	Ardabil	Wells	60	Spectrophotometry	Cross sectional	Some cases higher than the WHO standard	[24]
Aghazadeh et al. (2016)	2010	Ardabil	Ardabil	Wells	77	Spectrophotometry	Cross sectional	In most of the samples (88%), the nitrate concentration was below the permissible drinking limits set by the WHO (50 mg/L)	[25]
Durimandarik et al. (2017)	2013	Ardabil	Ardabil	Wells	63	Spectrophotometry	Cross sectional	The surrounding of agricultural lands are very polluted	[26]
Miranzadeh et al. (2010)	2007	Isfahan	Kashan	Tap water	57	Spectrophotometry	Cross sectional	Less than WHO standard	[27]
Gheisari et al. (2005)	2004–2008	Isfahan	Isfahan	Wells and tap water	513	Spectrophotometry		19 Samples (3.7%) exceeded the maximum contaminant level	[28]
Ebrahimi et al. (2014)	2006	Isfahan	Langan	Wells	25	Spectrophotometry	Cross sectional	Less than WHO standard	[29]
Heydari et al. (2013)	2006	Isfahan	Kashan	Wells	21	–	Cross sectional	Less than WHO standard	[30]
Heydari and Bidgoli (2012)	2006	Isfahan	Kashan	Wells	42	Spectrophotometry	Cross sectional	2% of samples showed higher concentration of NO	[31]
Amarlooei et al. (2014)	2010	Ilam	Ilam	Wells and tap water	60	Spectrophotometry	Cross sectional	1.67% of samples showed higher concentration of NO_3	[32]

(*continued*)

Table 1 (*continued*)

Author (publication year)	Year of sampling	Province	City	Type of water consumption	Sample size	Method	Type of study	Result	Reference
Shirani et al. (2013)	2011	Tehran	Tehran (14)	Wells	16	Ion chromatography	Cross sectional	More than WHO standard	[33]
Mahvi et al. (2004)	2002	Tehran	Tehran (17)	Wells	22	Titration	Cross sectional	Less than WHO standard	[34]
Mohammadi et al. (2011)	2010	Tehran	Tehran	Tap water	105	Spectrophotometry	Cross sectional	2% of samples are higher than standard	[35]
Sepehrnia et al. (2016)	2013	Tehran	Ray	Tap water	73	Spectrophotometry	Cross sectional	Some cases higher than the standard	[36]
Ostovari et al. (2015)	2010	Chaharmahal and Bakhtiari	Lordegan	Tap water	32	Spectrophotometry	Cross sectional	Less than WHO standard	[37]
Fadaei and Sadeghi (2014)	2014	Chaharmahal and Bakhtiari	Shahr-e Kord	Wells	230	Spectrophotometry	Cross sectional	The waters quality was high	[38]
Dowlati et al. (2016)	1956–2009	Razavi Khorasan	Mashhad	Wells	–	Titration	Cross sectional	Some points are higher than the standard	[39]
Fallahzadeh et al. (2016)	2015	South Khorasan	Birjand	Wells	57	–	Cross sectional	Nitrate concentration was more than the standard range (50 mg/L) according to the national standard of Iran (No. 1053) in one well	[40]
Emamgholizadeh et al. (2014)	2011	Khuzestan	Karun River	Tap water	200 Samples in 17 years	Spectrophotometry	Cross sectional	Less than national standard of Iran	[41]
Rahmati and Melesse (2016)	2013	Khuzestan	Khuzestan	Wells	75	Spectrophotometry	Cross sectional	Nitrate concentrations of 12 wells (12.9%) higher than the maximum threshold allowable for human consumption	[42]
Fazeli et al. (2011)	2007	Khuzestan	Behbahan	Tap water		Ion chromatography	Cross sectional	Some points are higher than standard	[43]
Fazli and Sadeghi (2003)	2008	Zanjan	Zanjan	Wells	280	Titration	Cross sectional	11% of cases higher than standard of Iran	[44]

(*continued*)

Table 1 (*continued*)

Author (publication year)	Year of sampling	Province	City	Type of water consumption	Sample size	Method	Type of study	Result	Reference
Mirzaei et al. (2015)	2009	Semnan	Shahrud and Damghan	Wells	154	Spectrophotometry	Cross sectional	5.4% of cases higher than national Standard of Iran	[45]
Barani and Yazdanpanah (2011)	2011	Zahedan	Zabol	River and dam	324	Spectrophotometry	Cross sectional	Less than WHO standard	[46]
Badeenezhad et al. (2012)	2011	Fars	Shiraz	Wells and tap water	220	Spectrophotometry	Cross sectional	16% of cases higher than standard	[47]
Kochi and Kochi (2011)	2006	Fars	Fasa	Wells	288	Titration	Cross sectional	Nitrate concentration was increased	[48]
Nezhad et al. (2014)	2010	Fars	Shiraz	Wells	110	Titration	Cross sectional	Less than WHO standard	[49]
Ali and Karyab (2016)	2015	Qazvin	Qazvin	Wells	19	Spectrophotometry	Cross sectional	90% of cases higher than WHO standard	[50]
Sharifi and Sinegani (2012)	2012	Kurdistan	Qorveh plain	Wells	25	Spectrophotometry	Cross sectional	The quality of the groundwater is not suitable for drinking purpose	[51]
Zahiri et al. (2014)	2013	Kurdistan	Damghan	Wells	20	Spectrophotometry	Cross sectional	Very polluted	[52]
Rahmati et al. (2015)	2008–2013	Kurdistan	Ghorve-Dehgolan	Wells	72	Spectrophotometry	Cross sectional	12 Wells (12.9%) exceeded WHO acceptable threshold (50 mg/L) in 2013	[53]
Malakootian and Momeni (2012)	2009	Kerman	Bardsir	Wells	134	Spectrophotometry	Cross sectional	Less than standard of Iran	[54]
Setreh et al. (2014)	2010	Kermanshah	Sangar	Wells	73	Spectrophotometry	Cross sectional	Some points are more than WHO standard	[55]
Semnani et al. (2009)	2004	Golestan	Golestan	Tap water	–	Spectrophotometry	Cross sectional	Less than WHO standard	[56]

(*continued*)

Table 1 (*continued*)

Author (publication year)	Year of sampling	Province	City	Type of water consumption	Sample size	Method	Type of study	Result	Reference
Moeinian et al. (2014)	2011	Gilan	Talysh	Tap water	15	Spectrophotometry	Cross sectional	Slightly contaminated	[57]
Zare et al. (2011)	2010	Markazi	Arak	Tap water	–	Spectrophotometry	Cross sectional	Some points are more than WHO standard	[58]
Rajaei et al. (2013)	2013	Markazi	Arak	Wells	114	Spectrophotometry	Cross sectional	Some points are more than WHO standard	[59]
Arabgol et al. (2015)	2016	Markazi	Arak	Wells	160	Spectrophotometry	Cross sectional	Some points are more than WHO standard	[60]
Darabi et al. (2014)	2013	Lorestan	Borujerd	Tap water	70	Titration	Cross sectional	Less than WHO standard	[61]
Rahimi et al. (2017)	2006–2013	Qom	Qom	Tap water	600	Spectrophotometry	Cross sectional	70% of samples showed nitrate contamination	[62]
Nezhad et al. (2017)	2010–2014	Fars	Shiraz	Wells	344	Spectrophotometry	Cross sectional	38 (11%) of the samples had nitrate concentrations above the standard level	[63]
Fallahzadeh et al. (2016)	2015	Yazd	Yazd	Wells	24	Spectrophotometry	Cross sectional	Nitrate and nitrite rate was in WHO standard range	[64]

and R version 3.3.2 (R Core Team 2015). Q test was used to evaluate heterogeneity between the studies. Further, the extent of heterogeneity was calculated by measuring I^2 statistic. Random effects model (REM) and fixed effect model (FEM) were used for measuring effect size of studies based on Mantel–Haenszel and DerSimonian methods, respectively [17]. When $I^2 > 50\%$ and $p < 0.10$, REM was employed. The sources of heterogeneity were studied using meta-regression for geographical latitudes, year of study, and sample size [17]. The type of water samples (well water, river and dam, and tap water), nitrate analysis methods (titration, spectrophotometry, and ion chromatography), and study quality were used for subgroup analysis. The potential of publication bias was considered by funnel plots, where the effect sizes are against standard error. Begg's test was used for evaluation of asymmetry ($p < 0.10$). Trim-and-fill method was used for determination of non-diagnostic studies. Sensitivity analysis was performed to determine the effect of removing each study on the changes in total concentration of nitrate [17].

3. Results and discussion

After the initial search of databases, 1,539 papers were identified. Of them, 765 papers were excluded following evaluation of the titles and abstracts. After qualitative investigation using the two checklists and eliminating repetitive papers and those with unsuitable information from the study, 101 papers were included in the study. In addition, 52 papers were excluded due to lack of sufficient statistical information. Finally, 49 articles fulfilled the quality assessment criteria and were included in the meta-analysis (Fig. 1).

All of the included studies were cross sectional, except the one which was an ecological study [56]. Based on the quality assessment of the papers using the STROBE Checklist, 23 (46.9%) of the investigated studies were of high quality, 15 (30.6%) were of medium quality, while the 11 (22.45%) were of low quality. The mean nitrate concentration and population density across Iranian cities are presented in Fig. 2. Northern and western cities with large populations also had high nitrate concentration. As shown in Fig. 2, the maximum population density and nitrate concentration were

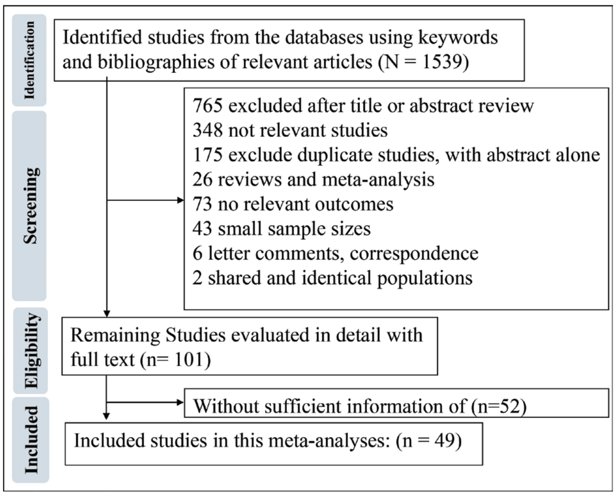

Fig. 1. Flowchart of literature selection and study identification.

associated with Tehran Province; concentration was higher than WHO guidelines (50 mg/L). Using nitrate analysis methods, the mean nitrate concentration was compared with the type of water consumption (Fig. 3). Other related studies that report high concentrations of nitrate are given in Fig. 4.

The pooled mean concentration of nitrate from all selected studies using REM and FEM (presented in the supplementary material) was 24.59 mg/L (95% CI 16.79–32.39) and 14.29 mg/L (95% CI 14.22–14.36), respectively (Figs. S1 and S2). The pooled hazard index of nitrite by the REM was 0.40 (95% CI 0.306–0.480) (Fig. S3). The results showed that 12.5% of the water consumed in Iran had hazard index values of above 1. Hazard index <1 indicated the relatively safe condition. The pooled nitrite concentration in Iran using the REM was 0.05 mg/L (95% CI 0.03–0.07) (Fig. S4). To investigate the source of heterogeneity, meta-regression model for sample size and year of study were significant. However, the effect of other parameters including latitude cannot affect heterogeneity (Table 2).

The results obtained from subgroup analyses based on sampling point (well, dam, and tap water), nitrate analysis methods (titration, spectrophotometry, and ion chromatography), geographical region, and related hazard index are shown in Table 3. The Forest plot indicating sampling point, nitrate analysis methods, and geographical region are provided with a supplementary material (Figs. S5–S7).

The funnel plot was asymmetrical and Egger's test was not significant ($p = 0.039$). Trim-and-fill method suggested 61 studies for complete symmetry of funnel plot ($Q = 8.1 \times 10^4$ and $p = 0.00$). Sensitivity analysis was performed by removing each study randomly. Except for Osaloo et al.'s [21] study, no significant change was observed in nitrate concentrations (Fig. S7). The funnel plot, Begg's funnel plot, and sensitivity analysis are given in supplementary material (Figs. S8 and S9).

Water supply contamination by nitrate and nitrite has been reported as major environmental and health problems in all countries of the world, including Iran [77]. Therefore, IARC is classified as probably carcinogenic to humans [78]. The pooled mean concentrations of nitrate and nitrite in Iran were 24.59 mg/L (95% CI 16.79–32.39) and 0.05 mg/L (95% CI 0.03–0.07), which was higher than some regions of the world including Iowa in the United States [79,80]. However, it was lower than other regions, including Saudi Arabia [81], India [82], UK [83], North America [84], Australia [85], and Changshu in China [86].

Subgroup analysis indicated that the pooled mean concentration of nitrate in wells, rivers, and dams as well as tap water were 21.9, 32.46, and 12.8 mg/L, respectively. The results of this meta-analysis indicate that nitrate concentration in surface water (rivers and dams) was greater than groundwater. Groundwater contamination by nitrate has been commonly reported in other studies [18,19]. Although, nitrate consumption in surface waters by algae and aquatic plants has been reported by Barani and Yazdanpanah [46]. However, studies have also shown that surface waters are very polluted by chemical and animal fertilizers, organic wastes, and wastewater wells [21,23]. In most of the included studies, groundwater samples were used, which reveals the importance of groundwater resources as drinking water supply in Iran. The main sources of nitrate and nitrite pollution in surface waters of Iran were due to the application

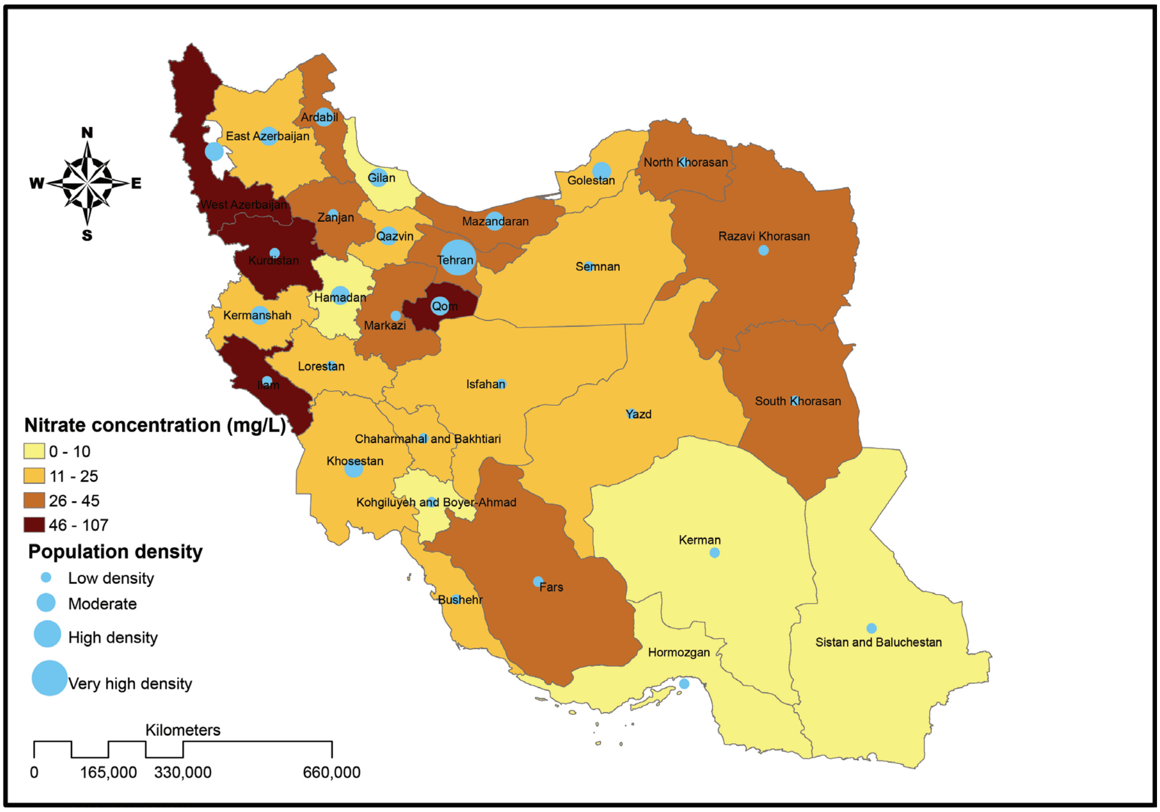

Fig. 2. Mean concentration of nitrate and population density in Iran.

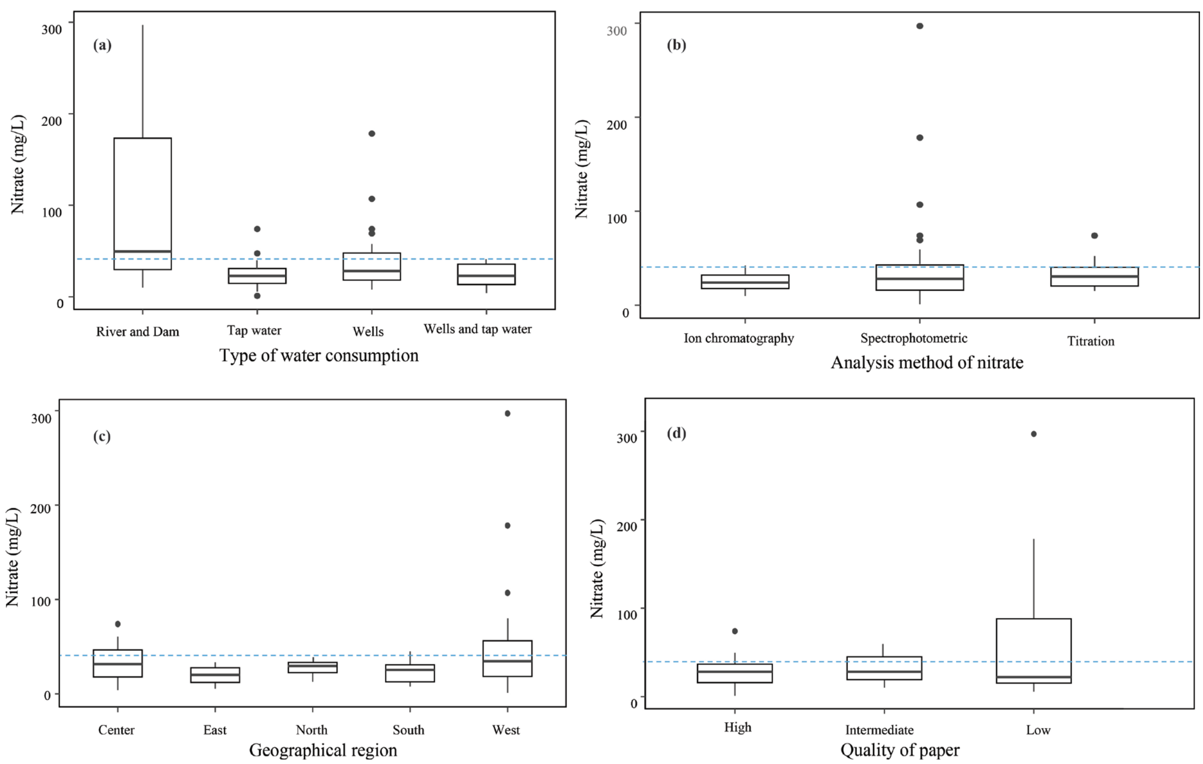

Fig. 3. The association between nitrate concentration and (a) type of water consumption, (b) analysis method of nitrate, (c) geographical region, and (d) quality of the paper.

of livestock waste and untreated wastewater used in agricultural areas [87,88].

According to Panahi and Moghaddam [89], the baseline concentration of nitrate in Iranian cities was 4–9 mg/L in groundwater. They proposed that higher concentrations of nitrate from 9 mg/L indicate water contamination [89]. Five studies included in this meta-analysis reported considerably high nitrate concentrations based on WHO guidelines (50 mg/L) [21,23,33,36,51,52]. In a study by Sharifi and Sinegani [51] in the Qorveh, Kurdistan region, nitrate concentration was determined as 178.3 mg/L (SD = 234.4). Similarly, in two studies by Solgi and Sheikhzadeh [23] and Osaloo et al. [21] in Aras River water, West Azerbaijan, a remarkably high concentration of nitrate was reported (respectively, 297 ± 195.8 mg/L and 51 ± 45.5 mg/L). Thereafter, in the water wells of Ilam Province, a 106.96 mg/L (SD = 86.5) concentration was reported [33]. Similarly, two studies by Zahiri et al. [52] in Kurdistan and Sepehrnia et al. [36] in Tehran reported nitrate concentrations of 69.2 ± 8.82 mg/L and 47.43 ± 22.6 mg/L, respectively. These high nitrate concentrations are associated with Tehran, West Azerbaijan, Kurdistan, Zanjan, Ardabil, and Razavi Khorasan provinces. The HI results indicated that in these megacities, serious and health risks exist. As a

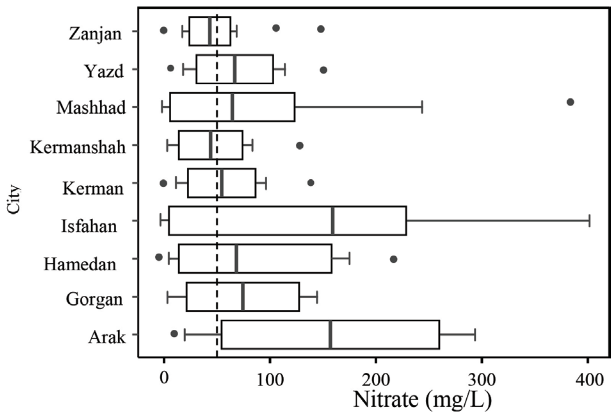

Fig. 4. Box plots of nitrate concentration in some cities of Iran: (box plots illustrate the 25th, 50th, and 75th percentiles; the circles represent outliers; and the whiskers indicate the 10th and 90th percentiles) Arak [65], Mashhad [66–68] Zanjan [69], Kermanshah [70], Hamedan [71], Isfahan [72,73] Kerman [74] Gorgan [75], and Yazd [76].

result, the findings of these studies resulted in increasing the pooled mean concentrations of nitrate in this meta-analysis.

Other studies that reported considerably high concentrations of nitrate in drinking water were excluded from this meta-analysis [65–76,90,91]. For example, in Hamadan plain, which is a centre of potato production in Iran, the high use of urea-based fertilizers is the main cause of nitrate level elevation [90]. Moreover, in certain cities of Iran, including Mashhad, Rasht, Sari, Hamadan, Arak, and Isfahan, nitrate concentration was elevated from the standard level. For example, nitrate concentration in Mashhad and Arak cities was six- to eightfold higher than the EPA's drinking water standard (46 mg/L) (Fig. 4).

The main cause of nitrate pollution in drinking water reported in studies includes overuse of animal and chemical fertilizers, nitrate leachate from agricultural lands, lack of wastewater collection systems, household wastewater wells, unhealthy discharge of solid wastes, and herbicide usage on farms [92,93]. In addition, Malekabadi et al. [72] reported that the use of poultry and livestock fertilizers is the main cause of nitrate water pollution in Isfahan Province. In this regard, the leaching of nitrate from the soil surface by acid rain or irrigation has been reported to increase nitrate concentration in surface and groundwaters [94].

To reduce water pollution by nitrate, it is recommended that nitrogen fertilizer use be reduced in central and western regions of Iran and non-nitrogen fertilizers should be used instead. In addition, irrigation methods should be changed from traditional methods to modern and higher effective methods including compressed and drip irrigation. Furthermore, the construction of the wastewater collection system and other suitable methods should be considered for long-term reduction of nitrate concentration in water. In some southern and southeastern parts of Iran, the concentration of nitrate and other minerals increased due to water evaporation. In these regions, adsorption, mixing with high-quality freshwater and water treatment can be used [95]. The reverse osmosis, ion exchange, and electrodialysis can be used for water treatment [96–98]. Other alternative water treatment processes, including chemical reduction, biological denitrification, and autotrophic–heterotrophic denitrification along with zerovalent iron, can also be used in in-situ treatment [95]. Finally, water resource management should be undertaken to preserve surface and groundwater quality.

Table 2
Meta-regression analysis of nitrate concentrations in Iran

Parameter	Coefficient	Standard error	*P* > *t*	95% Confidence interval	
Nitrate					
Sample size	–0.00755	0.026942	0.0481	–0.00623	–0.0472
Publication years	0.414391	0.0865602	0.0535	0.34472	2.173506
Constant	–809.83	1,739.843	0.645	–4,345.62	2,725.957
Nitrite					
Years	0.042	4.221179	0.099	–8.9553	9.0392
Sample size	0.0000955	0.340457	0.54	–0.72576	0.7256
Constant	–84.23	8,493.46	0.099	–18,187.6	18,019.16

Table 3
The pooled nitrate concentrations (mg/L) and HI in Iran based on type of water consumptions, nitrate measurement method, geographical region, and quality of studies

Type of water consumptions	Nitrate	95% Confidence interval		HI	95% Confidence interval		% Weight	Heterogeneity statistic	df	P	I^2	Tau-squared
Wells	25.4	19.9	30.9	0.45	0.36	0.55	59.8	174.72	30	0	82.80%	91.5
River and dam	32.5	–6.2	71.1	0.58	–0.11	1.27	5.9	2,218.51	2	0	99.90%	783.9
Tap water	12.8	6.2	19.4	0.23	0.11	0.35	26.3	45.18	11	0	75.70%	51.1
Wells and tap water	18.2	–1.6	38.0	0.33	–0.03	0.68	8.0	13.03	2	0.001	84.60%	251.3
Nitrate measurement method												
Titration	25.6	22.7	28.5	0.46	0.41	0.51	15.2	2.19	6	0.902	0.00%	0.0
Spectrophotometry	24.8	16.1	33.4	0.44	0.29	0.60	81.3	38,136.31	39	0	99.90%	543.4
Ion chromatography	19.7	–4.4	43.9	0.35	–0.08	0.78	3.5	0.03	1	0.865	0.00%	0.0
Geographical region												
West	28.5	9.8	47.2	0.51	0.18	0.84	31.7	11,208.77	18	0	99.80%	1,200.0
Centre	20.5	13.4	27.6	0.37	0.24	0.49	33.1	56.13	15	0	73.30%	86.1
South	22.2	13.2	31.2	0.40	0.24	0.56	19.4	102.77	6	0	94.20%	116.1
East	21.8	8.8	34.7	0.39	0.16	0.62	7.9	0.51	3	0.918	0.00%	0.0
North	11.5	3.9	19.0	0.21	0.07	0.34	8.0	6.35	2	0.042	68.50%	26.5
Quality of studies												
Intermediate	23.4	15.3	31.5	0.42	0.27	0.56	32.3	39.0	14.0	0.0	0.6	112.8
High	22.1	13.1	31.0	0.39	0.23	0.55	20.0	53.4	10.0	0.0	0.8	99.0
Low	25.9	11.5	40.4	0.46	0.21	0.72	47.7	12,986.2	22.0	0.0	1.0	987.6

4. Conclusions

Groundwater contamination by nitrate and nitrite in Iranian cities has increased over the past decades; however, the risks are not clear. The nitrate and nitrite concentrations of drinking water in some central and northwestern parts of Iran were higher than the recommended standard and can be related to adverse health effects. The nitrate and nitrite concentrations in surface water resources such as rivers and dams were high in the northwestern area. Some modifications, as well as studies on solutions, should be undertaken to improve the water quality in these regions. To achieve this, it is suggested that the use of nitrogen fertilizers be reduced through legislation. The treatment of contaminated water and wastewater reuse should also be considered.

References

[1] D.M. Manassaram, L.C. Backer, D.M. Moll, A review of nitrates in drinking water: maternal exposure and adverse reproductive and developmental outcomes, Ciencia Saude Coletiva, 12 (2007) 153–163.
[2] M.H. Ward, Workgroup report: drinking-water nitrate and health—recent findings and research needs, Environ. Health Perspect., 113 (2005) 1607.
[3] L. Fewtrell, Drinking-water nitrate, methemoglobinemia, and global burden of disease: a discussion, Environ. Health Perspect., 112 (2004) 1371.
[4] M.O. Rivett, S.R. Buss, P. Morgan, J.W. Smith, C.D. Bemment, Nitrate attenuation in groundwater: a review of biogeochemical controlling processes, Water Res., 42 (2008) 4215–4232.
[5] WHO (World Health Organization), Guidelines for Drinking-water Quality, 4th ed., WHO, Geneva, Switzerland, 2011. Available at: http://www.who.int/water_sanitation_health/publications/2011/9789241548151_toc.pdf (Accessed 18 September 2018).
[6] X. Su, H. Wang, Y. Zhang, Health risk assessment of nitrate contamination in groundwater: a case study of an agricultural area in Northeast China, Water Resour. Manage., 27 (2013) 3025–3034.
[7] M. Jalali, Nitrate pollution of groundwater in Toyserkan, western Iran, Environ. Earth Sci., 62 (2011) 907–913.
[8] A. Neshat, B. Pradhan, Risk assessment of groundwater pollution with a new methodological framework: application of Dempster–Shafer theory and GIS, Nat. Hazards, 78 (2015) 1565–1585.
[9] A.A. Masoud, K. Koike, H.A. Mashaly, F. Gergis, Spatio-temporal trends and change factors of groundwater quality in an arid area with peat rich aquifers: emergence of water environmental problems in Tanta District, Egypt, J. Arid. Environ., 124 (2016) 360–376.
[10] M. Jalali, Nitrates leaching from agricultural land in Hamadan, western Iran, Agric. Ecosyst. Environ., 110 (2005) 210–218.
[11] M. Jalali, Major ion chemistry of groundwaters in the Bahar area, Hamadan, western Iran, Environ. Geol., 47 (2005) 763–772.
[12] F. Ghadimi, M. Ghomi, R. Azimi, Sources of nitrate and bromide contaminants of groundwater of the alluvial aquifer of Arak, Iran, J. Water Sci. Res., 4 (2016) 100–115.
[13] M. Rezaei, N. Shariatifar, G.J. Khaniki, M. Javadzadeh, Nitrite in hamburgers in Arak, Iran, Food Addit. Contam., 6 (2013) 285–288.
[14] K. Fukushi, F. Kurisu, K. Oguma, H. Furumai, P. Fontanos, Southeast Asian Water Environment 4, IWA Publishing, U.K., 2010.
[15] W. Bedale, J.J. Sindelar, A.L. Milkowski, Dietary nitrate and nitrite: benefits, risks, and evolving perceptions, Meat Sci., 120 (2016) 85–92.
[16] S.H. Downs, N. Black, The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions, J. Epidemiol. Commun. Health, 52 (1998) 377–384.
[17] B. Karimi, M. Yunesian, R. Nabizadeh, P. Mehdipour, A. Aghaie, Is leukocyte telomere length related with lung cancer risk? A meta-analysis, Iran, Biomed. J., 21 (2017) 142–148.
[18] H. Nanbakhsh, Study of chemical and bacterial quality of potable ground water sources in Urmia in 2000, J. Urmia Univ. Med. Sci., 2 (2002) 127–134.
[19] M. Fakhri, A.A. Moghaddam, N. Morteza, R. Barzegar, Investigation of nitrate concentration in groundwater resources of Marand plain and evaluation of groundwater vulnerability by AVI and GODS, J. Environ. Stud., 41 (2015) 49–66.
[20] R. Barzegar, A.A. Moghaddam, E. Tziritis, M.S. Fakhri, S. Soltani, Identification of hydrogeochemical processes and pollution sources of groundwater resources in the Marand plain, northwest of Iran, Environ. Earth Sci., 76 (2017) 297.
[21] J.A. Osaloo, A.M. Pour Azari, F.A. Nekoie, M. Sydgar, M.Y. Zadeh, S. Shiry, M.A. Kalshani, Cross-sectional study of the lake water quality changes behind the Aras dam, J. Wetlands Ecol., 1 (2015) 5–14.
[22] H. Nanbakhsh, A. Mohammadi, A. Ebrahimi, Investigating of nitrate and nitrite concentration of drinking water wells in villages around of the industrial park, in Urmia city, J. Health Syst. Res., 6 (2010) 881–888.
[23] E. Solgi, H. Sheikhzadeh, Study of water quality of Aras river using physico-chemical variables, Iran, Water Resour. Res., 12 (2016) 207–213.
[24] Z.S.A. Abad, F. Asadzadeh, P. Hussein, Application of DWQI index for comprehensive assessment of water quality in Ardabil aquifer, Iran. J. Ecohydrol., 4 (2017) 421–436.
[25] N. Aghazadeh, M. Chitsazan, Y. Golestan, Hydrochemistry and quality assessment of groundwater in the Ardabil area, Iran, Appl. Water Sci., 5 (2016) 1–18.
[26] S.M. Durimandarik, P. Hussein, F. Asadzadeh, A. Arianfar, Evaluation of nitrate pollution in groundwater resources of Ardabil aquifer using geographic information system, Iran. J. Ecohydrology, 4 (2017) 215–224.
[27] M.B. Miranzadeh, A.R. Mesdaghinia, M. Heidari, M. Younesian, K. Nadafi, A.H. Mahvi, Investigating the chemical quality and chlorination status of drinking water in Kashan's villages, Health Syst. Res., 6 (2010) 889–897.
[28] M.M. Gheisari, M. Messripour, M. Hoodaji, M. Noroozi, A. Abdollahi, Nitrate intake from drinking water in Isfahan in 2004, J. Sci. Iran, 16 (2005) 113–116.
[29] A. Ebrahimi, M.M. Amin, M. Hajian, B. Bina, Evaluation of vulnerability of groundwater in the province of Lanjan in terms of total organic carbon, nitrate, and some cations and anions on a pilot scale using geographic information system (GIS), J. Environ. Sci. Technol., 16 (2014) 189–203.
[30] M.M. Heydari, A. Abbasi, S.M. Rohani, S.M.A. Hosseini, Correlation study and regression analysis of drinking water quality in Kashan City, Iran, Walailak J. Sci. Technol., 10 (2013) 315–324.
[31] M.M. Heydari, H.N. Bidgoli, Chemical analysis of drinking water of Kashan District, Central Iran, World Appl. Sci. J., 16 (2012) 799–805.
[32] A. Amarlooei, M. Nazeri, H. Nourmoradi, K. Sayehmiri, F. Khodarahmi, Investigation on the concentration of nitrate and nitrite in Ilam ground waters, J. Ilam Univ. Med. Sci., 22 (2014) 34–41.
[33] Z. Shirani, M. Abbaspour, A.H. Javid, L. Taghavi, Assessment of groundwater pollution sources in the urban environment (Case Study: Tehran Municipality of District 14), J. Manage. Syst., 11 (2013) 1–16.
[34] A.H. Mahvi, S.E. Hashemi, M. Younessian, Health aspects of drinking water in district 17 of Tehran, Payesh J., 1 (2005) 7–9.
[35] H. Mohammadi, A. Yazdanbakhsh, A.S. Mohammadi, G. Bonyadinejad, A. Alinejad, G. Ghanbari, Investigation of nitrite and nitrate in drinking water of regions under surveillance of Shahid Beheshti University of Medical Sciences in Tehran Province, Iran, Health Syst. Res., 7 (2011) 782–789.

[36] B. Sepehrnia, R. Nabizadeh, A. Mahvi, S. Naseri, Water quality analysis of drinking water distribution systems of Rey township using IWQIS software, Iran, J. Health Environ., 9 (2016) 103–114.
[37] Y. Ostovari, H.B. Harchegany, S. Heshmati, Assessment of groundwater quality of Lordegan aquifer with GWQI index in GIS environment, Iranian Remote Sensing GIS, 7 (2015) 107–120.
[38] A. Fadaei, M. Sadeghi, Evaluation and assessment of drinking water quality in Shahrekord, Iran, Resour. Environ., 4 (2014) 168–172.
[39] J. Dowlati, G.L. Por, N. Hafezi, Environmental Impact of City Development on Aquifer and Water Resources: Case Study of Mashhad, Kurdistan University, Ed., The 6th Iranian National Conference on Water Resources Management, Kurdistan University, Kurdistan, Iran, 2016.
[40] R.A. Fallahzadeh, H.R. Azimzadeh, R. Khosravi, S.A. Almodaresi, M. Khodadadi, H. Eslami, Z. Derakhshan, S. Sadeghi, R. Peirovi-Minaee, Using geographic information system (GIS) and remote sensing (RS) in zoning nitrate concentration in the groundwater of Birjand, Iran, J. Adv. Environ. Health Res., 4 (2016) 129–134.
[41] S. Emamgholizadeh, H. Kashi, I. Marofpoor, E. Zalaghi, Prediction of water quality parameters of Karoon River (Iran) by artificial intelligence-based models, Int. J. Environ. Sci. Technol., 11 (2014) 645–656.
[42] O. Rahmati, A.M. Melesse, Application of Dempster–Shafer theory, spatial analysis and remote sensing for groundwater potentiality and nitrate pollution analysis in the semi-arid region of Khuzestan, Iran, Sci. Total Environ., 568 (2016) 1110–1123.
[43] M. Fazeli, N. Kalantari, M.H. Rahimi, K. Ali, Study of temporal and spatial distribution of nitrate contamination of groundwater resources in Zydaron to nitrate, J. Water Resour. Eng., 4 (2011) 45–51.
[44] M.M. Fazli, G.R. Sadeghi, Investigation of drinking water supply contamination in Zanjan city during 1980–79, J. Zanjan Univ. Med. Sci., 11 (2003) 49–54.
[45] R. Mirzaei, M. Sakizadeh, H. Ghorbani, Nitrate contamination of drinking and agricultural groundwater resources in Shahrood and Damghan, Iran, J. Mazandaran Univ. Med. Sci., 25 (2015) 117–127.
[46] M.K. Barani, N. Yazdanpanah, Study on physical, chemical and biological qualities of Chah-Nimeh water reservoirs in Zabol for year 2011, J. Zabol Univ. Med. Sci. Health Serv., 5 (2011) 15–24.
[47] A. Badeenezhad, M. Gholami, A.J. Jafari, A. Ameri, Factors affecting nitrate concentrations in Shiraz groundwater using geographical information system(GIS), TolooeBehdasht, 11 (2012) 47–56.
[48] E.H. Kochi, E.H. Kochi, Verification of changes in the nitrate with amount of raining in drinking water of Fars villages during years of 2007–2008, J. Fasa Univ. Med. Sci., 1 (2011) 43–48.
[49] A.B. Nezhad, M. Farzadkia, M. Gholami, A.J. Jafari, Chemical quality assessment of Shiraz plain's groundwater as a drinking water resource using geographical information system (GIS), Iran South Med. J., 17 (2014) 358–367.
[50] R.H. Ali, H. Karyab, Predicting nitrate concentration in groundwater resources using lumped-parameter model: case study in Qazvin Plain, Iran. J. Health Environ., 8 (2016) 459–470.
[51] Z. Sharifi, A.A.S. Sinegani, Assessment of arsenic, nitrate and phosphorus pollutions in shallow groundwater of the rural area in Kurdistan Province (Iran), Curr. World Environ., 7 (2012) 233–241.
[52] F.M. Zahiri, B. Safari, Z. Bagheri, S.S. Ardakani, Investigation of pollution of nitrate and nitrite in groundwater resources of Dehgolan City, Man Environ., 12 (2014) 1–11.
[53] O. Rahmati, A.N. Samani, N. Mahmoodi, M. Mahdavi, Assessment of the contribution of N-fertilizers to nitrate pollution of groundwater in western Iran (Case Study: Ghorveh–Dehgelan Aquifer), Water Qual. Exposure Health, 7 (2015) 143–151.
[54] M. Malakootian, J. Momeni, Quality survey of drinking water in Bardsir, Iran 2009–2010, J. Rafsanjan Univ. Med. Sci., 11 (2012) 403–410.
[55] P. Setreh, M. Rezaei, A.H. Hassani, A.A. Zaynatizadeh, Dispersion of groundwater pollution to nitrate in GIS Environment: a case study of Sangar Plain, J. Kermanshah Univ. Med. Sci., 3 (2014) 157–164.
[56] S. Semnani, A. Keshtkar, N. Behnampour, S. Besharat, G. Roshandel, Nitrate and nitrite level of drinking water and the risk of upper gastrointestinal cancers in urban areas of Golestan Province, Northeast of Iran, J. Kerman Univ. Med. Sci., 16 (2009) 281–290.
[57] K. Moeinian, H. Hosseinnejad, T. Rastgoo, Concentration of nitrate, nitrite and some other parameters in drinking water wells, Talesh (Northern IRAN), 2011, J. Guilan Univ. Med. Sci., 22 (2014) 26–33.
[58] A. Zare, V. Bayat, A. Daneshkare, Forecasting nitrate concentration in groundwater using artificial neural network and linear regression models, Int. Agrophys., 25 (2011) 187–192.
[59] M. Rajaei, Z. Salemi, B. Karimi, M. Ghanadzadeh, M. Mashayekhi, Effect of household water treatment systems on the physical and chemical quality of water in 2011–2012, Arak Med. Univ. J., 16 (2013) 26–36.
[60] R. Arabgol, M. Sartaj, K. Asghari, Predicting nitrate concentration and its spatial distribution in groundwater resources using support vector machines (SVMs) model, Environ. Model. Assess., 21 (2016) 71–82.
[61] M. Darabi, S.J. Zadeh, M. Chegeny, Chemical and physical indicators in drinking water and water sources of Borujerd using principal components analysis, Med. Lab. J., 8 (2014) 76–82.
[62] M.H. Rahimi, N. Kalantari, Z. Aliyari, R.M. Ahmadabadi, Evaluation of nitrate contamination of drinking water wells in the City of Qom, Water Wastewater, 28 (2017) 21–33.
[63] A.B. Nezhad, M.M. Emamjomeh, M. Farzadkia, A.J. Jafari, M. Sayadi, A.H.D. Talab, Nitrite and nitrate concentrations in the drinking groundwater of Shiraz City, south-central Iran by statistical models, Iran. J. Public Health, 46 (2017) 1275.
[64] R.A. Fallahzadeh, S.A. Almodaresi, M.M. Dashti, A. Fattahi, M. Sadeghnia, H. Eslami, R. Khosravi, R.P. Minaee, M. Taghavi, Zoning of nitrite and nitrate concentration in groundwater using geografic information system (GIS), case study: drinking water wells in Yazd city, J. Geosci. Environ. Prot., 4 (2016) 91.
[65] M.S. Rajaee, Arak Groundwater Survey, Environmental Health Engineering, Tehran University of Medical Sciences, Tehran, Iran, 1996.
[66] G. Lashkaripour, M. Ghafouri, Investigation of nitrate level in groundwater of Mashhad, J. Water Wasewater, 41 (2001) 2–7.
[67] S.F. Latife, S. Mousavi, M. Afyuni, S. Velayati, Investigation of nitrate pollution and sources in groundwater in Mashhad plain, J. Agric. Sci. Nat. Resour., 12 (2005) 21–32.
[68] P. Asadi, B. Ataie-Ashtiani, A. Beheshti, Vulnerability assessment of urban groundwater resources to nitrate: the case study of Mashhad, Iran, Environ. Earth Sci., 76 (2017) 41–56.
[69] G.R. Sadeghi, M.M. Fazli, E. Shams, Study of Nitrate and Nitrite Ions in Zanjan Distribution Network, 8th National Conference on Environmental Health, Tehran University of Medical Sciences, Tehran, Iran, 2005.
[70] A. Karami, Investigation of Nitrate Ion in Groundwater Resources of Kermanshah, 8th National Conference on Environmental Health, 2005.
[71] H. Noorozi, S. Ali, R. Mohammad, H.M. Safdari, Study of Nitrate and Nitrite Ions in Groundwater of Hamadan Province, 8th National Conference on Environmental Health, Tehran University of Medical Sciences, Tehran, Iran, 2005.
[72] A.J. Malekabadi, M. Afyuni, S. Mousavi, A. Khosravi, Nitrate concentration in groundwater in Isfahan Province, J. Water Soil Sci., 8 (2004) 69–83.
[73] A. Esmaeili, F. Moore, B. Keshavarzi, Nitrate contamination in irrigation groundwater, Isfahan, Iran, Environ. Earth Sci., 72 (2014) 2511–2522.
[74] M. Dehghani, A.A. Nejad, Cadmium, arsenic, lead and nitrate pollution in the groundwater of Anar Plain, J. Environ. Stud., 36 (2011) 28–32.
[75] M. Raghimi, M.R. Mojaveri, S.M.S. Khademi, Investigation of the source of nitrate contamination in ground waters of Gorgan, Iran (2005), J. Gorgan Univ. Med. Sci., 10 (2009) 34–39.

[76] T. Farhadinejad, A. Khakzad, M. Jafari, Z. Shoaee, K. Khosrotehrani, R. Nobari, V. Shahrokhi, The study of environmental effects of chemical fertilizers and domestic sewage on water quality of Taft region, Central Iran, Arab. J. Geosci., 7 (2014) 221–229.
[77] R. Sadler, B. Maetam, B. Edokpolo, D. Connell, J. Yu, D. Stewart, M.-J. Park, D. Gray, B. Laksono, Health risk assessment for exposure to nitrate in drinking water from village wells in Semarang, Indonesia, Environ. Pollut., 216 (2016) 738–745.
[78] International Agency for Research on Cancer, Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. WHO Press, Lyon, France, 2010.
[79] D. Perrot, N.P. Molotch, M.W. Williams, S.M. Jepsen, J.O. Sickman, Relationships between stream nitrate concentration and spatially distributed snowmelt in high-elevation catchments of the western US, Water Resour. Res., 50 (2014) 8694–8713.
[80] R.R. Jones, P.J. Weyer, C.T. DellaValle, M. Inoue-Choi, K.E. Anderson, K.P. Cantor, S. Krasner, K. Robien, L.E.B. Freeman, D.T. Silverman, Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa, Environ. Health Perspect., 124 (2016) 1751–1762.
[81] J.M. Alqahtani, A.M. Asaad, E.M. Ahmed, M.A. Qureshi, Drinking water quality and public health in Southwestern Saudi Arabia: the need for a national monitoring program, J. Family Commun. Med., 22 (2015) 19–28.
[82] K. Rina, P. Datta, C.K. Singh, S. Mukherjee, Determining the genetic origin of nitrate contamination in aquifers of Northern Gujarat, India, Environ. Earth Sci., 71 (2014) 1711–1719.
[83] C. Neal, H.P. Jarvie, M. Neal, L. Hill, H. Wickham, Nitrate concentrations in river waters of the upper Thames and its tributaries, Sci. Total Environ., 365 (2006) 15–32.
[84] J. Power, J. Schepers, Nitrate contamination of groundwater in North America, Agric. Ecosyst. Environ., 26 (1989) 165–187.
[85] V. Rasiah, J. Armour, P. Nelson, Nitrate in shallow fluctuating groundwater under sugarcane: quantifying the lateral export quantities to surface waters, Agric. Ecosyst. Environ., 180 (2013) 103–110.
[86] X. Ying-Xin, Z.-Q. Xiong, X. Guang-Xi, S. Guo-Qing, Z. Zhao-Liang, Assessment of nitrogen pollutant sources in surface waters of Taihu Lake region, Pedosphere, 17 (2007) 200–208.
[87] J. Burkholder, B. Libra, P. Weyer, S. Heathcote, D. Kolpin, P.S. Thorne, M. Wichman, Impacts of waste from concentrated animal feeding operations on water quality, Environ. Health Perspect., 115 (2007) 308–318.
[88] P. Hooda, A. Edwards, H. Anderson, A. Miller, A review of water quality concerns in livestock farming areas, Sci. Total Environ., 250 (2000) 143–167.
[89] S. Panahi, M.A. Moghaddam, Evaluation of nitrate concentration in groundwater and drinking water distribution network of Robat-Karim City, Tehran Province, Iran, Water Pract. Technol., 7 (2012) 201–212.
[90] S. Akhavan, J. Abedi-Koupai, S.-F. Mousavi, M. Afyuni, S.-S. Eslamian, K.C. Abbaspour, Application of SWAT model to investigate nitrate leaching in Hamadan–Bahar Watershed, Iran, Agric. Ecosyst. Environ., 139 (2010) 675–688.
[91] M. Jalali, Z. Kolahchi, Nitrate concentration in groundwater of Bahar area, Hamadan, Environ. Geol., 47 (2005) 763–772.
[92] J.G.R. Khaniki, M. Dehghani, A. Mahvi, L. Rafati, F. Tavanafar, Concentrations of nitrate and nitrite in groundwater resources of Hamadan Province, Iran, Res. J. Chem. Environ., 12 (2008) 56–58.
[93] M.R. Mohebbi, R. Saeedi, A. Montazeri, K.A. Vaghefi, S. Labbafi, S. Oktaie, M. Abtahi, A. Mohagheghian, Assessment of water quality in groundwater resources of Iran using a modified drinking water quality index (DWQI), Ecol. Indic., 30 (2013) 28–34.
[94] T. Nasrabadi, P.A. Maedeh, Groundwater quality assessment in southern parts of Tehran plain, Iran, Environ. Earth Sci., 71 (2014) 2077–2086.
[95] B. Karimi, M.-S. Rajaei, A. Koulivand, R.D.C. Soltani, Performance evaluation of advanced $Fe^{\circ}/Fe^{+2}/Fe^{+3}/H_2O_2$ process in the reduction of nitrate and organic matter from aqueous solution, Desal. Water Treat., 52 (2014) 6240–6248.
[96] B. Karimi, M. Rajaei, M. Habibi, M. Esvand, M. Abdollahy, Effect of UV/H_2O_2 advanced oxidation processes for the removal of naphthalene from the water solution, Arak Med. Univ. J. (AMUJ), 16 (2013) 50–64.
[97] M.H. Dehghani, B. Karimi, M.S. Rajaei, The effect of aeration on advanced coagulation, flotation and advanced oxidation processes for color removal from wastewater, J. Mol. Liq., 223 (2016) 75–80.
[98] B. Karimi, M. Rajaee, Performance evaluation of nanoscale zero-valent iron adsorbed on calcium alginate in nitrate reduction in aqueous systems, Water Wastwater, 5 (2015) 67–75.

Supplementary material

Table S1
Modified Downs and Black checklist for the quality assessment of epidemiological studies

Factor	Score
External validity	
1. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
2. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? Participation rate for cases and controls of at least 70%	1
Subtotal	2
Internal validity-bias	
3. Was an attempt made to blind those measuring the main outcomes of the exposure?	1
4. If any of the results of the study were based on "data dredging", was this made clear?	1
5. Were the statistical tests used to assess the main outcomes appropriate?	1
6. Was compliance with the intervention/s reliable?	1
7. Were the main outcome measures used accurate valid and reliable?	1
Subtotal	5
Internal validity-exposure measurement	
8. Were measures of exposure robust? Exposure status was either documented or determined via biomarker 2; used small area ecological measures, job titles, or was self-reported 1; was based on large area ecological measures 0.	2
9. Was there a sufficient exposure gradient? The degree of variability between categories of exposure level was certain or not.	1
10. Were measures of exposure specific? Exposure measures were specific 2; based on broader, chemically related groups 1; based on broad groupings of diverse chemical and toxicological properties 0.	2
Subtotal	5
Internal validity—confounding	
11. Were the cases and controls recruited from the same population?	1
12. Were the cases and controls recruited over the same period of time?	1
13. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? The study collected data on all major 2, some including basic demographic only 1, or no 0 potential confounders and assessed their effect in analysis.	2
Subtotal	4
Total	16

Table S2
Quality assessment of the included epidemiological studies

Author/year of sampling	Reference	External validity		Internal validity											Total score
				Bias					Exposure measurement			Confounding			
		Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	16
Nanbakhsh (2000)	[18]	1	0	0	1	1	1	0	2	1	1	1	1	1	11
Fakhri et al. (2012)	[19]	1	1	0	1	1	1	1	2	1	2	1	1	2	15
Barzegar et al. (2014)	[20]	0	1	1	1	1	0	2	1	2	1	1	2	1	14
Osaloo et al. (2013)	[21]	1	0	0	1	1	1	0	2	1	1	1	1	2	12
Nanbakhsh et al. (2010)	[22]	0	1	1	1	1	1	2	1	2	1	1	1	1	14
Solgi and Sheikhzadeh (2014)	[23]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Abad et al. (2013)	[24]	0	0	0	1	1	0	2	1	1	1	1	2	1	11
Aghazadeh et al. (2010)	[25]	0	0	0	1	1	0	1	1	1	1	1	2	1	10
Durimandarik et al. (2013)	[26]	0	0	0	1	1	1	2	1	2	1	1	2	1	13
Miranzadeh et al. (2007)	[27]	0	0	1	1	1	1	2	1	2	1	1	2	2	15
Gheisari et al. (2004–2008)	[28]	0	1	1	1	1	1	2	1	2	1	1	1	2	15
Ebrahimi et al. (2006)	[29]	0	0	1	1	1	1	2	1	2	1	1	2	2	15
Heydari et al. (2006)	[30]	0	0	1	1	1	1	2	1	2	1	1	2	1	14
Heydari and Bidgoli (2006)	[31]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Amarlooei et al. (2010)	[32]	0	0	0	1	1	0	1	2	1	1	1	2	1	11
Shirani et al. (2011)	[33]	0	0	0	1	1	0	2	1	1	1	1	2	2	12
Mahvi et al. (2002)	[34]	0	0	0	1	1	0	2	1	1	1	1	2	2	12
Mohammadi et al. (2010)	[35]	0	0	0	1	1	1	2	1	2	1	1	2	2	14
Sepehrnia et al. (2013)	[36]	0	0	1	1	0	1	2	1	1	1	1	1	1	11
Ostovari et al. (2010)	[37]	0	0	0	1	1	0	2	1	1	1	1	2	1	11
Fadaei and Sadeghi (2014)	[38]	0	1	1	1	1	1	2	1	2	1	1	2	1	15
Dowlati et al. (1956–2009)	[39]	0	0	0	1	1	1	2	1	2	1	1	2	1	13
Fallahzadeh et al. (2015)	[40]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Emamgholizadeh et al. (2011)	[41]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Rahmati and Melesse (2013)	[42]	0	0	1	1	1	0	2	1	1	1	1	1	1	11
Fazeli et al. (2007)	[43]	0	0	1	0	1	0	2	1	1	1	1	1	1	10
Fazli and Sadeghi (2008)	[44]	0	0	1	1	1	0	2	1	1	1	1	1	1	11

(continued)

Table S2 (*continued*)

Author/year of sampling	Reference	External validity		Internal validity											Total score
				Bias					Exposure measurement			Confounding			
		Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	16
Mirzaei et al. (2009)	[45]	0	0	1	1	1	0	2	1	1	1	1	2	2	13
Barani and Yazdanpanah (2011)	[46]	0	0	1	0	1	0	2	1	1	1	1	2	1	11
Badeenezhad et al. (2011)	[47]	0	0	1	0	1	0	2	1	1	1	1	1	1	10
Kochi and Kochi (2006)	[48]	0	0	0	1	1	0	1	2	1	1	1	2	2	12
Nezhad et al. (2010)	[49]	0	0	1	1	1	0	2	1	2	1	1	2	2	14
Ali and Karyab (2015)	[50]	0	0	1	0	1	0	2	1	1	1	1	1	1	10
Sharifi and Sinegani (2012)	[51]	0	1	1	1	1	0	2	1	2	1	1	2	1	14
Zahiri et al. (2013)	[52]	0	0	0	1	1	0	2	1	1	1	1	2	1	11
Rahmati et al. (2008–2013)	[53]	0	0	0	1	1	1	2	1	2	1	1	2	1	13
Malakootian and Momeni (2009)	[54]	0	1	1	1	1	0	2	1	2	1	1	2	1	14
Setreh et al. (2010)	[55]	0	0	1	1	1	1	2	1	2	1	1	2	1	14
Semnani et al. (2004)	[56]	0	0	1	1	1	0	2	1	1	1	1	1	1	11
Moeinian et al. (2011)	[57]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Zare et al. (2010)	[58]	0	0	1	1	1	0	2	1	1	1	1	2	1	12
Rajaei et al. (2013)	[59]	0	0	0	1	1	1	2	0	2	1	1	2	2	13
Arabgol et al. (2015)	[60]	1	0	0	1	1	1	0	2	1	1	1	1	1	11
Darabi et al. (2013)	[61]	1	1	0	1	1	1	1	2	1	2	1	1	2	15
Rahimi et al (2006–2013)	[62]	0	1	1	1	1	0	2	1	2	1	1	2	1	14
Nezhad et al. (2010–2014)	[63]	1	0	0	1	1	1	0	2	1	1	1	1	2	12
Fallahzadeh et al. (2015)	[64]	0	1	1	1	1	1	2	1	2	1	1	1	1	14

Table S3
STROBE Checklist for quality control of systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	

(*continued*)

Table S3 (*continued*)

Section/topic	#	Checklist item	Reported on page
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

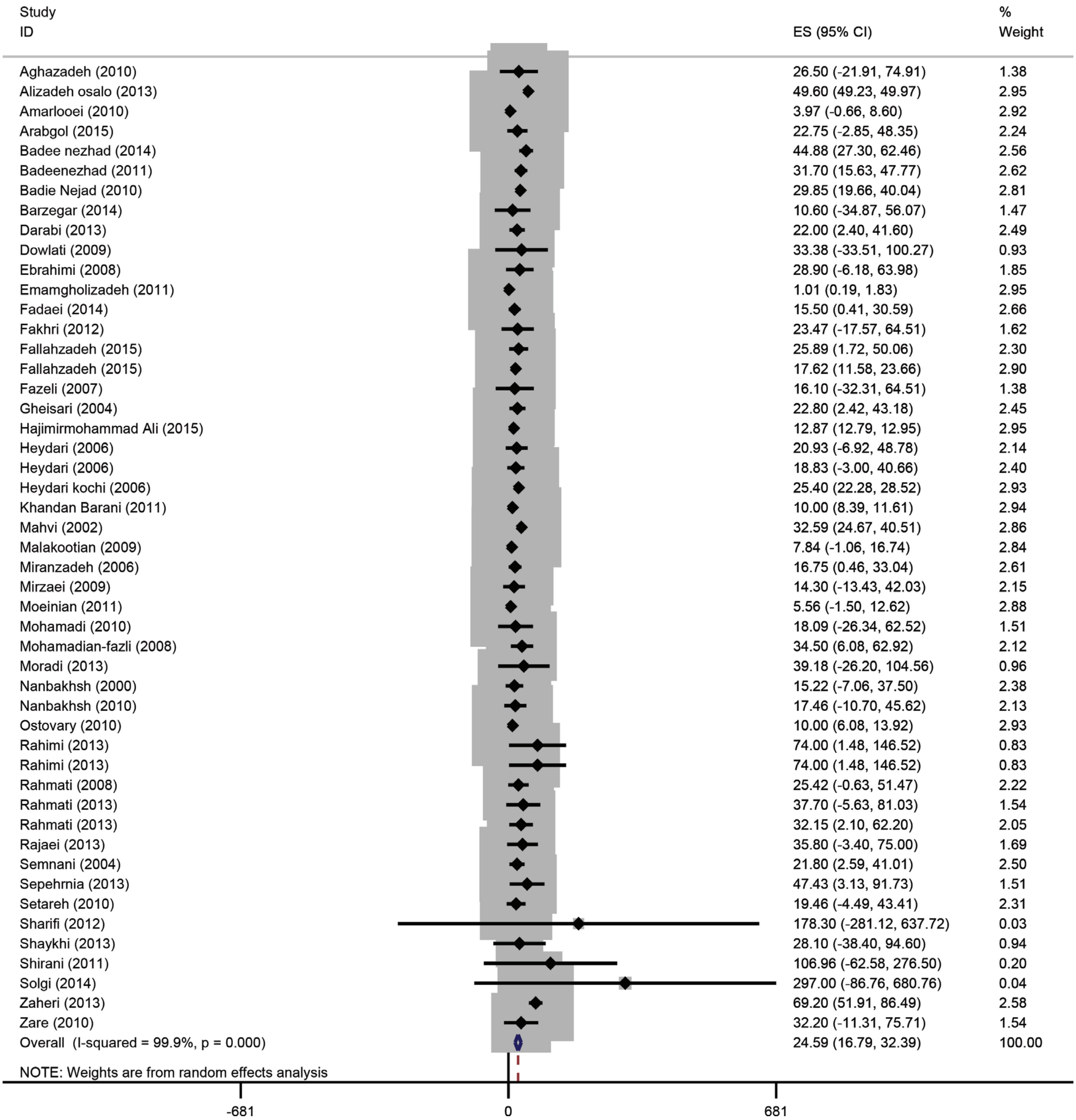

Fig. S1. Forest plots and pooled concentration of nitrate in drinking water resource of Iran by random effect model.

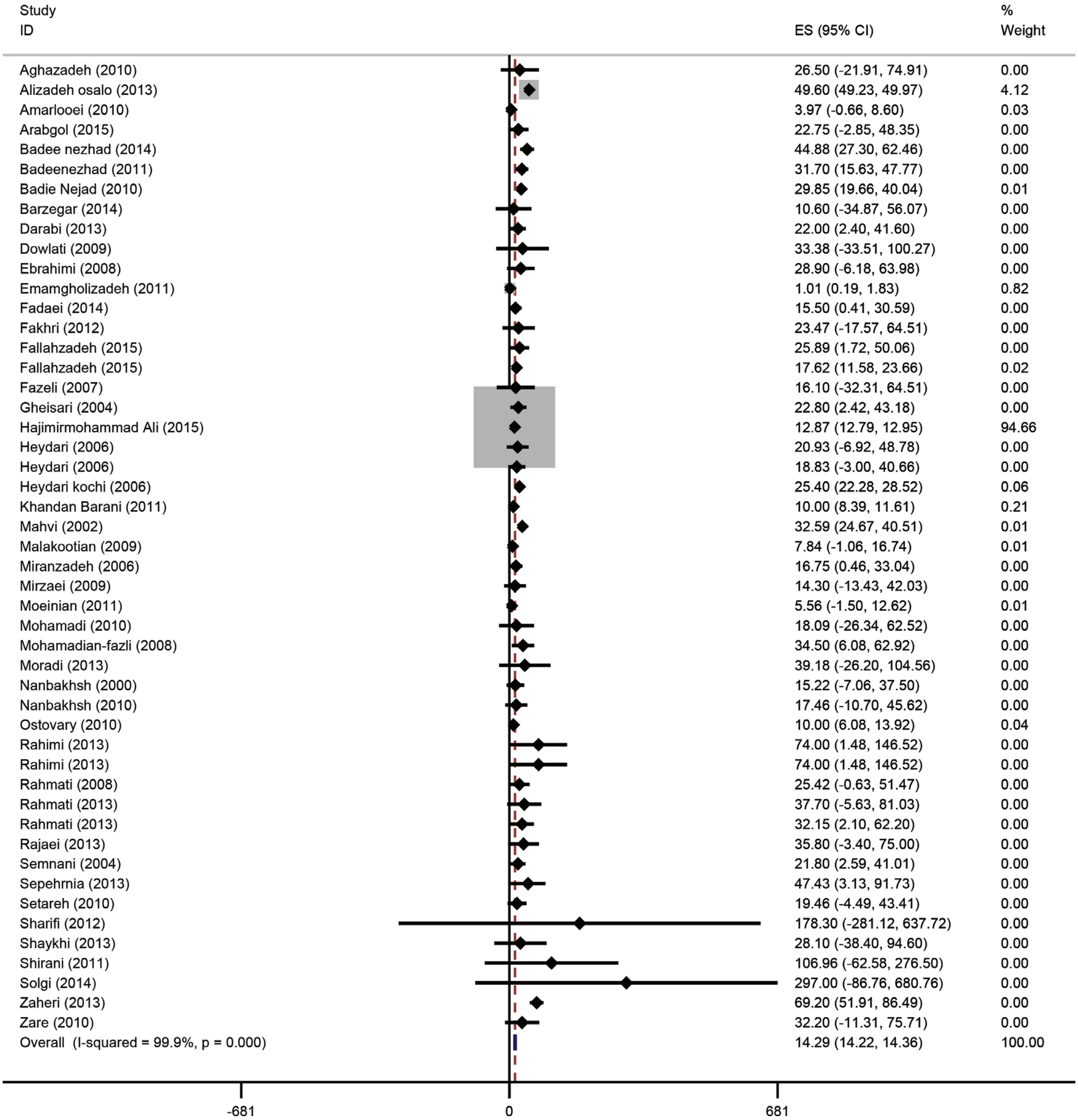

Fig. S2. Forest plots and pooled concentration of nitrate in drinking water resource of Iran by fixed effect model.

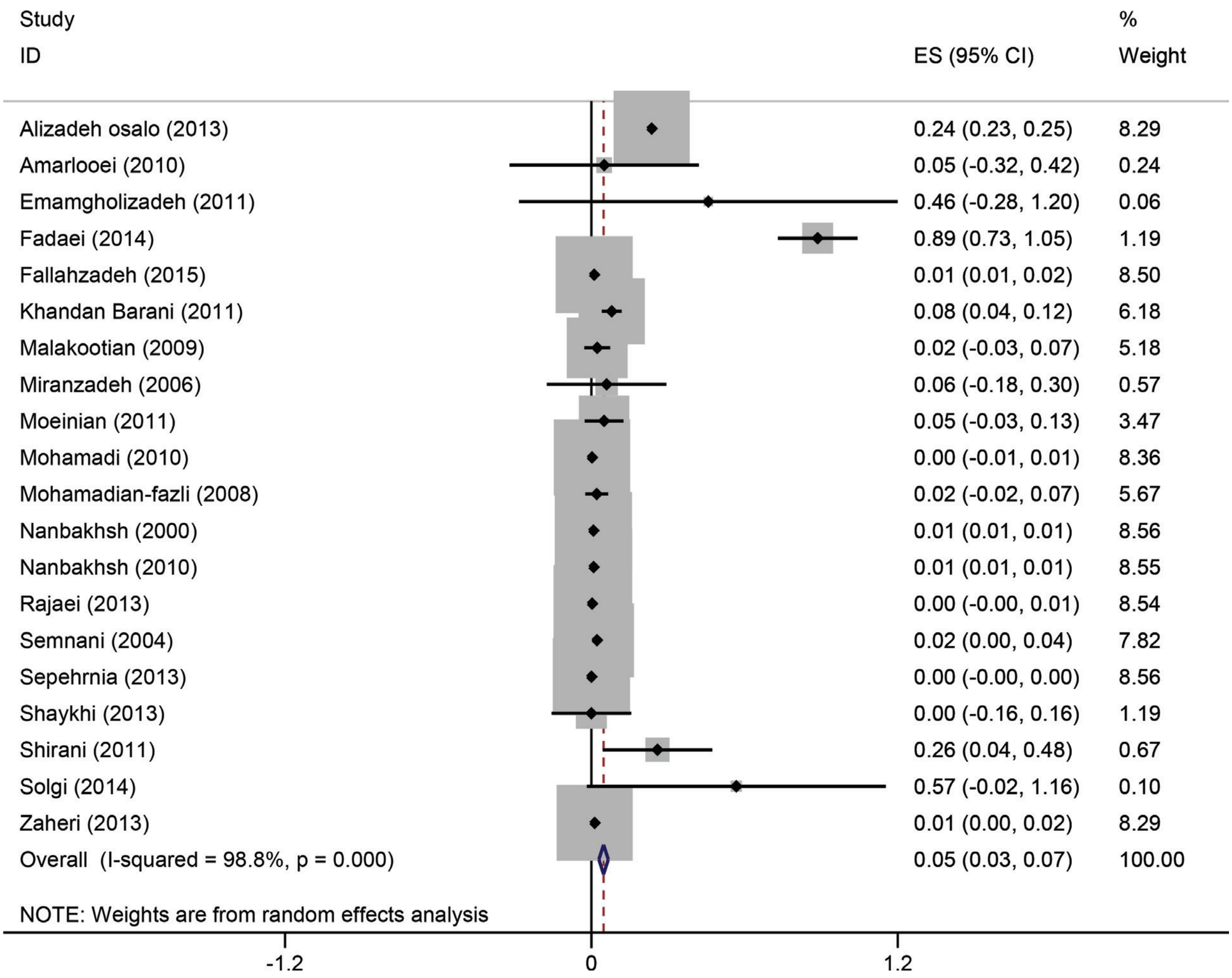

Fig. S3. Forest plots and pooled concentration of nitrite by the random effect model in drinking water resource of Iran.

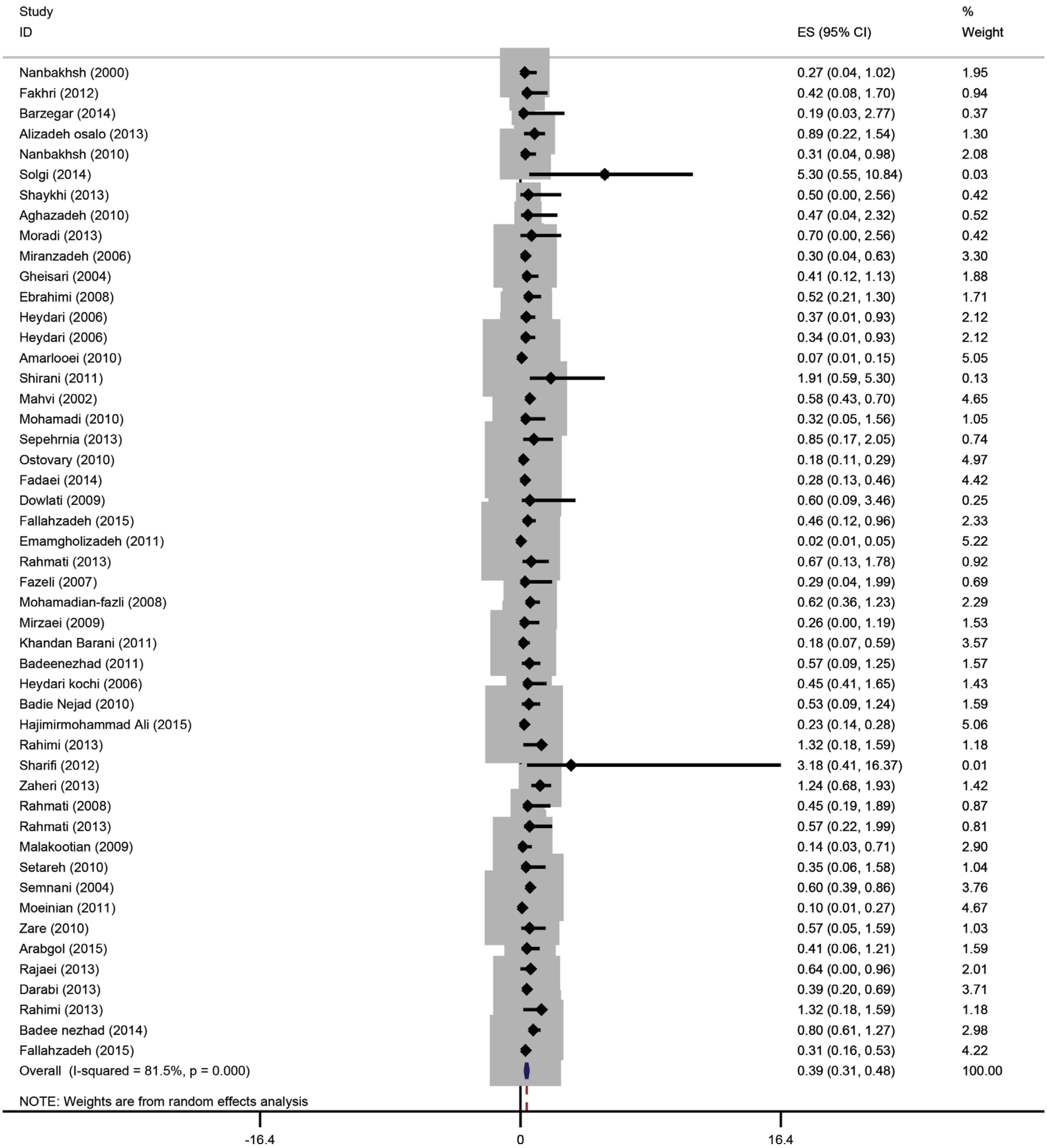

Fig. S4. Forest plots and pooled hazard index of nitrite by the random effect model in drinking water resource of Iran.

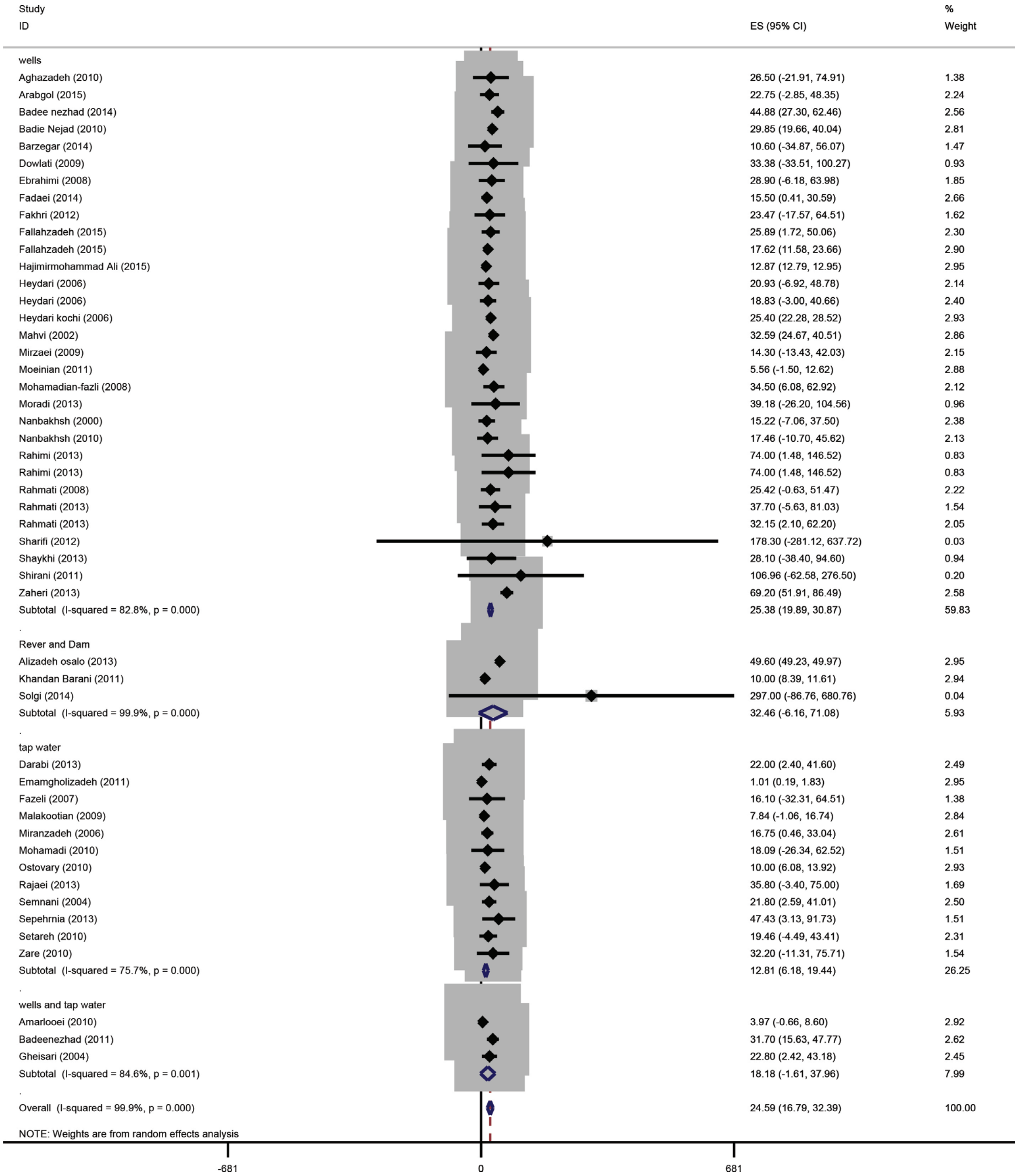

Fig. S5. Forest plots and subgroup analyses based on sampling point (well, dam, and tap water) in drinking water resource of Iran.

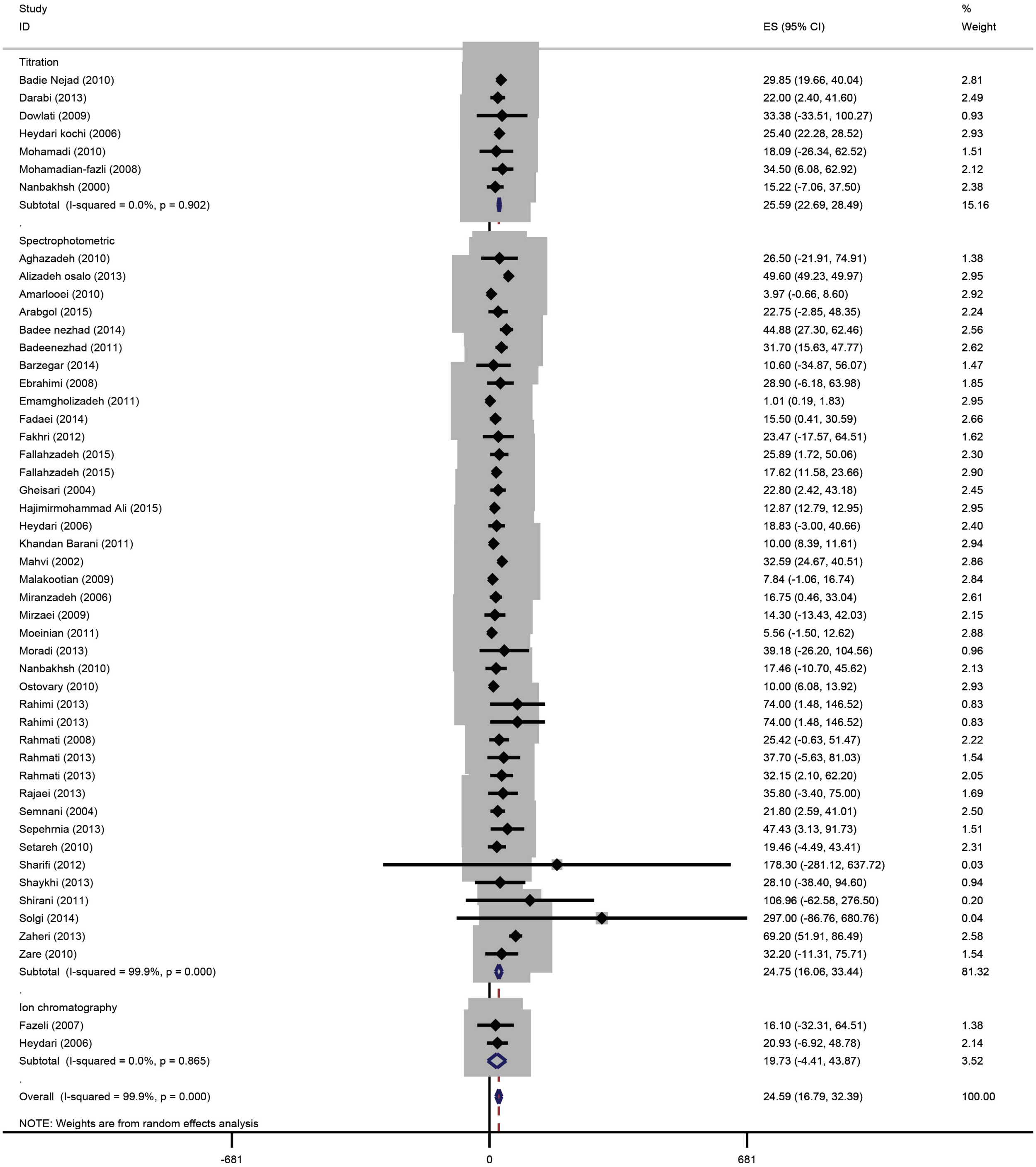

Fig. S6. Forest plots and subgroup analyses based on nitrate analysis methods (titration, spectrophotometer ion-chromatography) in drinking water resource of Iran.

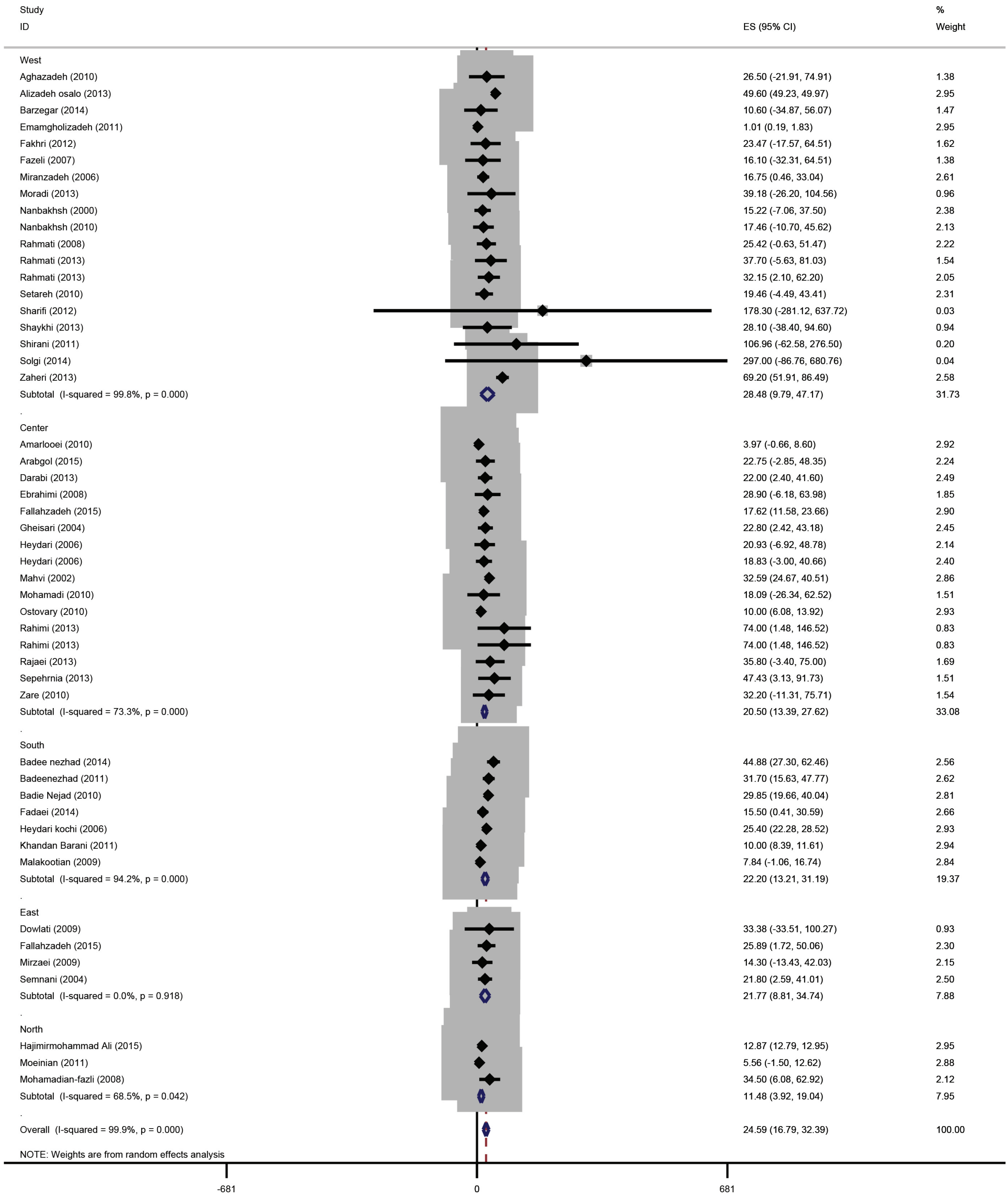

Fig. S7. Forest plots and subgroup analyses based on geographical region in drinking water resource of Iran.

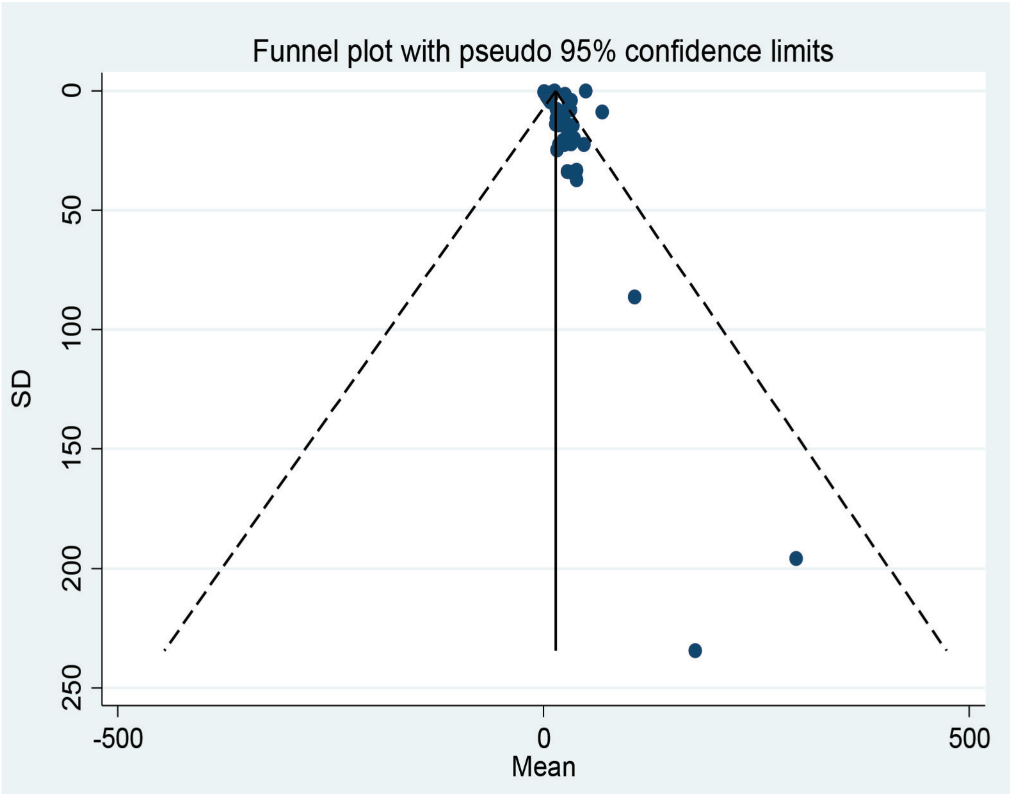

Fig. S8. The potential of publication bias by Funnel plot with pseudo 95% confidence limits.

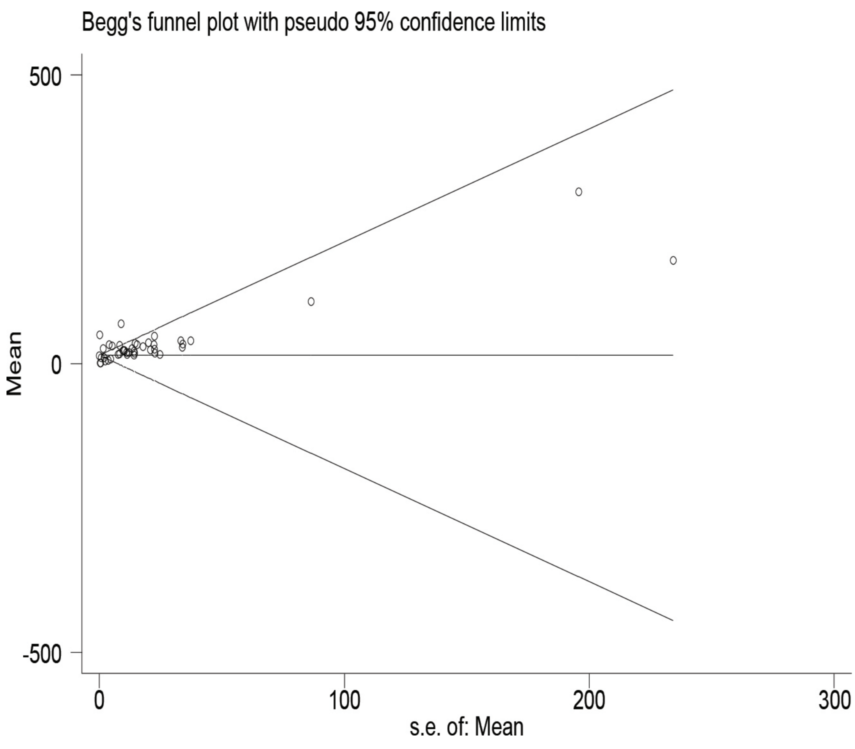

Fig. S9. Begg's-test with pseudo 95% confidence limits for evaluation of asymmetry.