



Increased allergic and asthmatic risks in children residing in industrial areas by surveying the pre-inflammatory (IgE, IL-4 and IL-13) biomarkers

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Abstract

Toxic metal(loid)s can lead to high damages on human. This work was conducted to investigate the levels of metal(loid)s in PM_{2.5} and a total of 123 male children's (aged 6–9 years) blood chosen from different areas in Ahvaz and their association with the *pre-inflammatory (Immunoglobulin E and cytokines: IgE, IL-4 and IL-13)* responses in serum cells. Six metal(loid)s (arsenic, cadmium, chromium, mercury, nickel and lead) in three regions including industrial (Padad), vehicle traffic (Golestan) and reference (Kianpars) areas were studied. Results showed the concentrations of As, Cr, Cd, Ni and Hg in the ambient air of industrial area (Padad) ($P < 0.001$), and Pb in vehicle traffic area (Golestan) were higher ($p < 0.001$). Moreover, the mean levels of IgE (mean = 146.44 pg/200landa, $P < 0.003$), IL-4 (mean = 548.23 pg/200landa, $P < 0.001$) and IL-13 (mean = 53.21 pg/200landa, $P < 0.001$) in Padad were higher than Golestan and Kianpars. Our results suggest that living in industrial areas leads to accelerated synthesis of IgE, IL-4 and IL-13 in blood. The spatial distribution of children's serum IgE, IL-4 and IL-13 concentrations showed an abnormal increase of 240 to 400 pg/200landa for IgE, 950 to 1400 pg/200landa for IL-4 and 90 to 128 pg/200landa for IL-13. Our results indicate children in the industrial area are prone to asthma, allergy, miRNA mutation, and other chronic diseases.

Keywords Industrial area · Children · Pro-inflammatory factors (IgE IL-4 and IL-13) · Spatial distribution. Allergy and asthma

Introduction

Factories and industrial areas emit large amounts of pollutants into the environment and reduce the quality of environmental health. Residing in industrial cities with poor environmental circumstances leads to human health concerns. Metals and metalloids enter the human body through drinking water, ingestion of food and supplements, inhalation, dermal absorption, and incidental ingestion [1, 2]. Several studies indicate that in the industrial cities, metalloids inhalation bound to the PM_{2.5} is increasing [3, 4]. Also, increase in exposure to inhalation of heavy metals had a significant relationship with lung function decrease in adults [3]. Allergic, atopic and other chronic diseases such as asthma are global illnesses that affect about 150 million children and adults worldwide [5]. Chronic diseases or syndromes are associated with an increase in pro-inflammatory biomarkers in humans. Children For some reasons are more sensitive than adults to the harmful health effects of air pollution [6]. Physiological and biological

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responses to the chemical in children are differing significantly from adults [7]. Children spend more time in outdoor and have more daily activities; such as soccer and other games, this group is breathing 20 to 50% more air and air pollutions than adults [8]. They don't show similar symptoms even when exposed to higher concentrations of air pollution. It is not known clearly if they ignore or don't feel the symptoms because of being preoccupied with physical activities. Human's immune system is being developed in childhood; it is less poly-functional and produces fewer cytokines in comparison to maturity [9]. In a cohort study carried out in New York City from 1998 to 2006 through 24 Months age children, it was reported that an increase in ambient air heavy metals (AAHM) was associated with increase in the probability of wheezing and coughing. However, there was no significant relation between total atmospheric PM_{2.5} and wheezing or coughing [10]. In a study conducted by Dunea et al. about the effect of heavy metals on Immunoglobulin-E (IgE), eosinophil's, and wheezing in children diagnosed with respiratory diseases, showed that raising in the IgE production and lung disease is related to increasing atmospheric PM_{2.5} [11]. IgE is an antibody produced by the immune system, which causes allergic reactions in the nose, lungs, throat, or on the skin. There are some relationships between asthma and IgE that appear to be independent of allergen sensitization [12]. In addition, IL-4 and IL-13 secreted into plasma by Th2 lymphocytes and mast cells have some similar properties. These cytokines are overproduced in atopic, asthma and allergic reactions and play important roles by inducing IgE synthesis in naive B-lymphocytes [13]. Up to now, no study has been done about the effect of PM_{2.5}-bound metal(loid)s in industrial area on the synthesis of pro-inflammatory IgE, IL-4 and IL-13. This work was conducted for the first time in Ahvaz as a highly industrialized city, to fulfill this gap. Present study aimed to investigate the relation of ambient air PM_{2.5}-bound metal(loid)s concentration in industrial, vehicle traffic and reference areas and synthesis of IgE, IL-4 and IL-13 in the blood serum of children.

Methodology

Description of the study area

Ahvaz city is located in the south-west of Iran and has a tropical climate with a limited downfall period, high humidity and temperature during the year. Ahvaz has a surface area of about 220 km² and a total population of about 1.3 million with an about density of 4815.73 people per square kilometer [14, 15]. Three locations in Ahvaz selected to ambient air metal(loid)s sampling were as follows: 1) Health center No. 18 in Padad region (industrial area) (31°17'32.49"N, 48°42'18.01"E) which is located in the east of Ahvaz and adjacent to steel,

carbon black, pipeline manufacturing industries and Karun industrial area, 2) Department of Environmental Protection of Khuzestan in Golestan region (vehicle traffic area) (31°18'30.80"N, 48°38'37.00"E) located in southwest of Ahvaz, 3) Rajaei dormitory located in Kianpars region (reference area) (31°20'36.45"N, 48°41'5.00"E). Figure 1 shows the location of areas where the study was conducted.

Study participants description

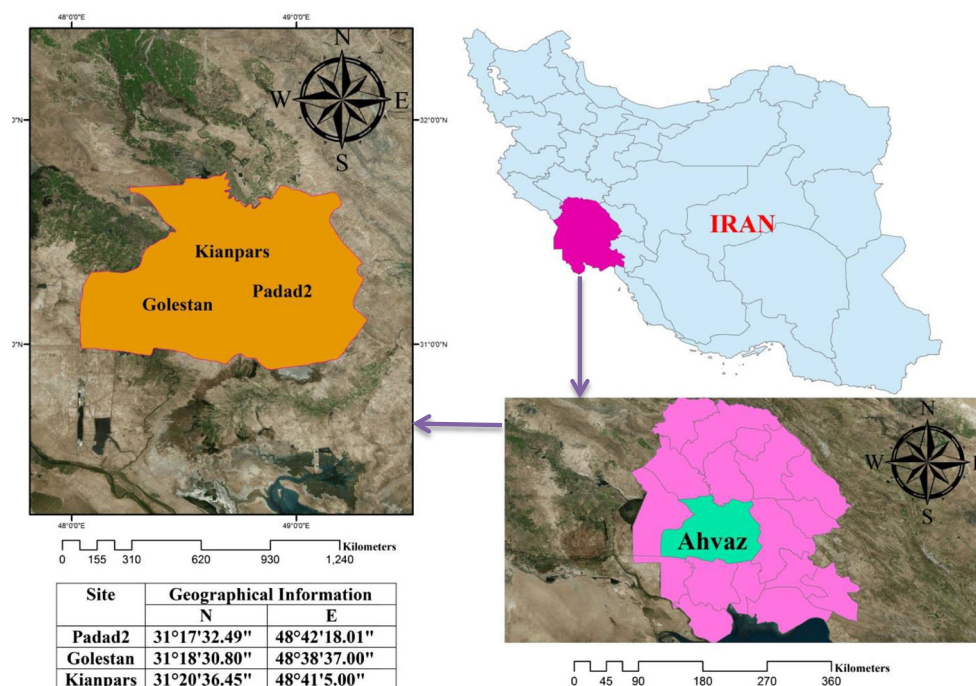
A total of 123 children aged 6 to 9 years old were blood sampled. All of the participants based on income level belonged to the middle-class family and within 1000-m radius areas where the study was conducted. Students were selected from schools (49 male students from Padad, 49 male students from Golestan and 25 male students from Kianpars). The most important inclusion criteria for children to be included in the study were: 1) No history of allergies, respiratory and other chronic illnesses; 2) No cold during one month to sampling; 3) No history of respiratory and other chronic illnesses in parents; 4) Lack of parental smoking; 5) A history of five years of living in the chosen sampling area; 6) School and home located inside the sampling region; 6) To belong to a same socio-economic group and have a similar dietary intake [16].

Blood sampling and preparation procedure

On an appointed day, all of the participants were taken the blood samples. Firstly, written informed consent was obtained from the parents. 3 ml of venous blood obtained from every child by two skillful nurses in order to measure the level of IgE, IL-4 and IL-13. A total of 123 blood samples were taken by vacutainer needles. Previous studies have shown these needles do not add pollutions to the blood [17]. Blood sample tubes with a volume of 3 ml were centrifuged at room temperature for 10 min at 3000 RPM [18], aliquoted (200 µL serum supernatant was taken and discharged into microtube), and separated serum stored at -80 °C until the IgE, IL-4 and IL-13 analyses [19].

Heavy metals analysis

The digested PM_{2.5}-bound metal(loid)s were injected into the ICP-OES (Spectro Arcos) instrument to identify and quantify 6 elements of Arsenic (As), Cadmium (Cd), Chrome (Cr), Mercury (Hg), Nickel (Ni) and Lead (Pb). Limit of detection (LOD) and limit of quantitation (LOQ) were calculated based on the Center for Disease Control and prevention (CDC) guideline [20]. LOD, LOQ, blank samples (BS) and the de-ionized water (DW) specification for all elements are indicated in (Table 1).

Fig. 1 Map of location study areas

Cytokines (IL-4 and IL-13) and immunoglobulin E (IgE) measurements

IgE, IL-4 and IL-13 factors were measured by enzyme-linked immune sorbent assay (ELISA). Serum samples were taken from the freezer (-80°C) and kept at room temperature for 30 min to become liquid. For uniformity of cell supernatants, micro tubes were shaken several times. Preparation of IgE, IL-4 and IL-13 were fulfilled using eBioscience sandwich ELISA Kits - Germany (product code base Kit: 15501647; IgE: 15521757; IL-4: 15511777; IL-13) according to the manufacturer's protocol. Lastly, an ELISA Reader (BioTek; USA; ELx808) was used for sample determination at 450 nm as a Measurement and 620 nm as Reference [21].

Statistical analysis

The Excel and SPSS v.21 software were applied to data analysis. Firstly, the mean and standard deviation were calculated

for all data. Shapiro Wilks test, Kruskal-Wallis (nonparametric test) and spearman correlation were used to evaluate the normality of the data and significance ($P < 0.001$) among sampling areas and IgE, IL-4 and IL-13 factors. The ANOVA test was used to study the relation between $\text{PM}_{2.5}$ -bound metal(loid)s and pre-inflammatory biomarkers (IgE, IL-4 and IL-13) ($P < 0.001$) in study areas.

Results and discussion

$\text{PM}_{2.5}$ concentrations in study areas

Present study was conducted for the first time on evaluation and association among ambient air heavy metals and asthma and allergy pre-inflammatory factors (IgE, IL-4 and IL-13) in children in Ahvaz as a highly industrialized city in Iran. $\text{PM}_{2.5}$ sampling was done in three sites. Table 2 shows that mean concentration of $\text{PM}_{2.5}$ at each site exceeded the WHO daily

Table 1 The LOD, LOQ, DW and BS of ICP-OES for heavy metals analysis

Element	LOD (ng mL ⁻¹)	LOQ (ng mL ⁻¹)	DW (ng mL ⁻¹)	BS (ng mL ⁻¹)
As	0.358	1.074	<0.358	<0.358
Cd	0.49	1.47	<0.49	1.4
Cr	0.96	2.88	<0.96	3.78
Hg	0.351	1.053	<0.351	<0.351
Ni	0.286	0.858	0.356	2.93
Pb	2.2	6.6	<2.2	4.3

LOD limit of detection, LOQ limit of quantitation, DW deionized water, BS blank sample

Table 2 The significant relation of IgE and IL-4 levels of children and PM_{2.5}-bound metal(loid)s from Padad, Golestan and Kianpars

Parameter	Regions									P value
	Padad			Golestan			Kianpars			
	N=24			N=24			N=24			
pollutants	CI5%	Mean	CI95%	CI5%	Mean	CI95%	CI5%	Mean	CI95%	
PM _{2.5} (µg/m ³)	61.56	68.56	75.57	59.27	67.06	74.84	45.94	55.31	64.67	0.031
As (ng/m ³)	70.89	94.51	118.12	33.07	38.99	44.91	13.05	19.79	26.54	<0.001
Cd (ng/m ³)	7.52	8.06	8.59	6.64	7.24	7.84	4.23	4.44	4.67	<0.001
Cr (ng/m ³)	14.22	15.06	15.91	13.61	14.45	15.3	10.63	11.01	11.4	<0.001
Hg (ng/m ³)	6.51	7.11	7.72	6.24	6.42	6.59	4.15	4.21	4.28	<0.001
Ni (ng/m ³)	11.86	12.63	13.41	10.88	11.48	12.07	7.49	8.15	8.81	<0.001
Pb (ng/m ³)	200.68	298.38	396.1	385.88	443.77	501.66	165.81	209.3	252.7	<0.001
Blood	N=49			N=49			N=25			p value
IgE and IL-4										
IgE	104.88	141.63	178.38	60.1	86.99	113.89	36.33	58.96	81.58	0.003
(pg/200landa)										
IL-4 (pg/200landa)	372.31	505.5	638.67	131.23	198.92	266.6	80.02	127.27	174.52	<0.001
IL-13 (pg/200landa)	39.24	53.21	67.19	17.95	27.77	37.59	9.02	13.91	18.8	<0.001

(50 µg/m³) and annually (10 µg/m³) guideline reference values [22]. According to the Table 2 PM_{2.5} exposure levels from Padad region (68.56 µg/m³), were higher than those from Golestan (67.06 µg/m³) and Kianpars (55.31 µg/m³) regions, although no significant correlation ($P = 0.031$) was observed. High concentrations of PM_{2.5} in Ahvaz are related to vehicular traffics, vicinity to many industrial factories and Proximity to local and external dust sources [23]. In 2012 high level concentrations of PM have been reported in Ahvaz [14], which shows that Iran should develop a strategic plan to improve air quality in Ahvaz.

PM_{2.5}-bound metal(loid)s in study areas

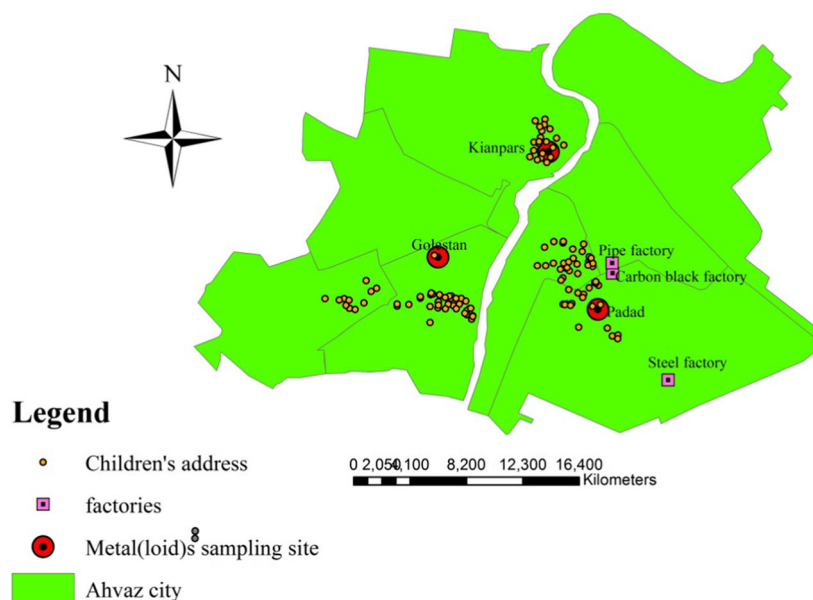
We found that the As, Cd, Cr, Ni and Hg levels in ambient air from Padad with significant difference ($p < 0.001$) were higher than those of Golestan and Kianpars areas. These might be due to the proximity of large number of industries (steel, carbon black, pipe production, oil refinery, reactor production, etc.) to this region. Pastuzka reported that As, Cd, Cr, Hg, Ni and Pb concentrations were higher in industrial sites [24]. Results of a study in Singapore showed that metallurgical industries, diesel vehicles and industrial sources with fossil fuel combustion emit Cd, Cr, Co and Ni into atmosphere [25]. In a study, road dust sample analyses in Ahvaz city showed that the heavy metal ranges across different sites were from 4.35–3577.06 mg kg⁻¹ for Pb, 32.40–1220.40 mg kg⁻¹ for Ni, 4.40–36.10 mg kg⁻¹ for Co, 22.40–312.40 mg kg⁻¹ for Cr, < 0.01–721.29 mg kg⁻¹ for Cu, 1.80–51.60 mg kg⁻¹ for As, 0.15–78 mg kg⁻¹ for Cd. The results of this study have shown that in industrial road dust of Ahvaz, the concentration of heavy metals were higher

than those levels of the reference area [23]. In addition, the average levels of Hg, Cr, V, Sb, Co, Mn, Ni, Zn, Pb, Cu and Mo were higher than world soil values [26]. Keshavarzi et al. found that in Ahvaz, the coefficient of variation (CV) for As, Hg, Pb, Ni was >100 that reflects the exceptionally high variability of production resources, also for Cr and Cd were $100 > CV > 50$ that shows the high variability of production resources [23]. This diversity in results can be due to the different heavy metal/metalloid resources in Ahvaz. The emitted heavy metals can float in the atmosphere or settle on the soil surface and enter children's bodies through respiration and direct contact. However, the Pb concentration in Golestan was higher ($p < 0.001$) than Padad. It could be due to high traffic jam of vehicles in Golestan. A study has shown that Pb is emitted from gasoline and diesel fuels [27]. Pb is the only heavy metal with an annual average of 0.5 µg/m³ that is registered in Iran's national atmosphere quality guideline. In the 1990s due to local regulations the use of leaded gasoline was banned in the developed countries and in 2002, the consumption of leaded gasoline in Iran was prohibited [22].

Pro-inflammatory biomarkers (IgE, IL-4 and IL-13) levels in children

Pro-inflammatory biomarkers were measured in order to determine the allergic and inflammatory status in children. Table 2 indicates the average concentration of pro-inflammatory biomarkers including IgE, IL-4 and IL-13 in children blood serum of the ages 6 to 9 years olds in different sampling areas. The results showed IgE, IL-4 and IL-13 levels of children from padad region were higher ($P = 0.003$), ($P < 0.001$) and ($P < 0.001$)

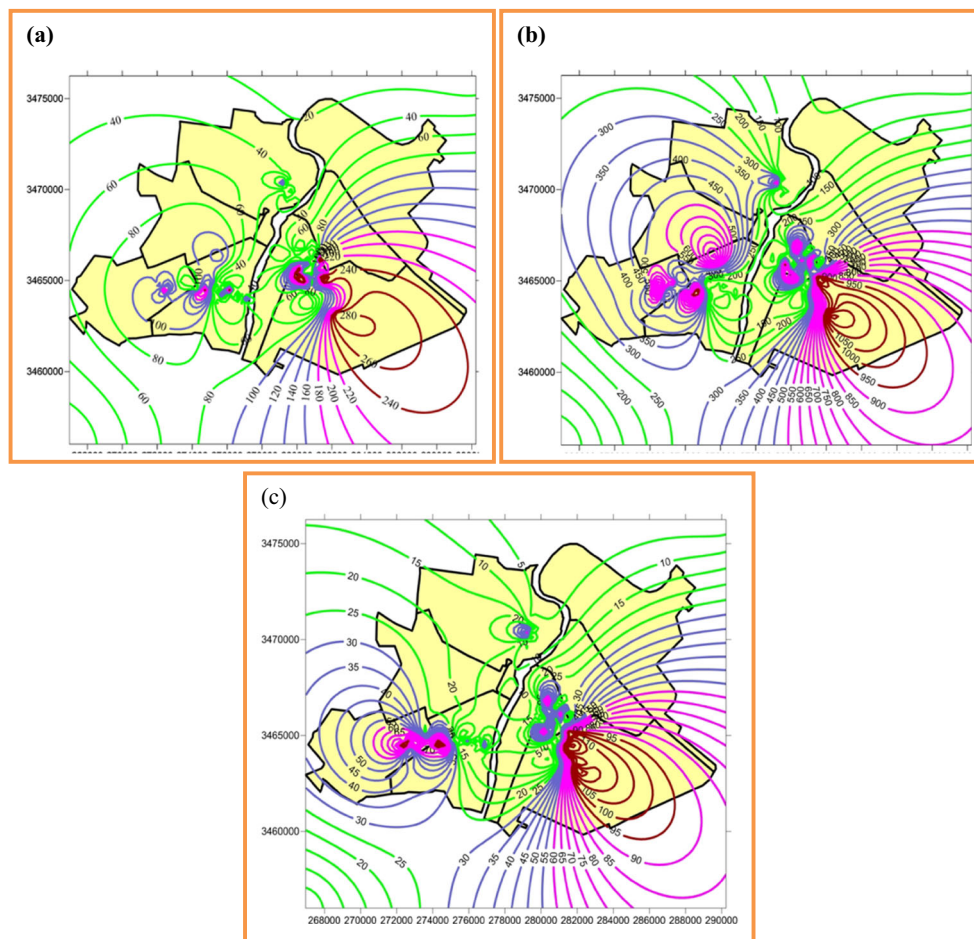
Fig. 2 Location of PM_{2.5}-bound metal(loid)s, industries and children blood IgE, IL-4 and IL-13 in studied areas



respectively than two other studied areas. Several studies have shown that the IL-6, IL-8 and IgE of the human population living in industrial areas were high [21, 27]. Few researches have

shown the effect of chromium on levels of serum IL-2 and IL-6 in pigs [28]. An in vitro experimental research showed that chromium could increase the level of IL-4 and IFN- γ [29]. In

Fig. 3 Spatial distribution of children's blood pro-inflammatory factors. **a** (IgE), **b** (IL-4) and **c** (IL-13)



addition, Richard Hayse reported a significant association between chromium concentrations in ambient air and lung cancer in industrial workers [30].

Spatial distribution of children's pre-inflammatory (IgE, IL-4 and IL-13) biomarkers

Children's life patterns in Ahvaz city indicated this group spends most of their after-school hours in outdoor playing different hobbies [31]. Therefore, children are highly susceptible to inhalation and contact with these contaminants. Figure 2 shows the location of PM_{2.5}-bound metal(loid)s sampling sites, industries and participants locations in different areas of Ahvaz. Blood samples were taken from children living in three areas: Padad (industrial), Golestan (vehicles traffic) and Kianpars (residential) and geographical information of each child was applied to compare the spatial distribution of pre-inflammatory (IgE, IL-4 and IL-13) biomarkers in the studied areas. Figures 3a to c show the spatial distribution of children's IgE, IL-4 and IL-13 in the studied areas. Green curves in maps indicate desirable concentrations of IgE and IL-4, blue curves indicate acceptable concentrations, while pink lines indicate IgE, IL-4 and IL-13 concentrations over the reference, moreover, a warning red lines show the hazard zone of very high levels of blood toxic metals. Figure 3a and c show an abnormal increase level of 240 to 400 pg/200land for IgE, 950 to 1400 pg/200land for IL-4 and 90 to 128 pg/200land in the Padad area. The increasing trend of children's IgE, IL-4 and IL-13 observed in the northwest of steel factory and west of carbon black and piping factories, are affected by prevailing wind speed and direction, which is from southeast to northwest [32]. In the present study, children from Padad had higher IgE, IL-4 and IL-13 compared to volunteers from the two other areas, which may point out that children living in industrial area were more at risk of allergic, atopic, asthmatic and other chronic diseases. Several studies demonstrated that living in industrial area poses harmful long-term effects on the health of the present and future generations [33, 34]. In addition, some researches showed the role of IgE and IL-4 secretion on allergic patients and childhood asthma and other chronic diseases [13, 35].

Conclusions

This was the first study that simultaneously surveyed the increasing of children's pre-inflammatory lung biomarkers (IgE, IL-4 and IL-13) in industrial, vehicle traffic and reference areas. Our findings suggested that in the industrial area exposure to As, Hg, Cr, Ni and Cd levels of PM_{2.5}-bound metal(loid)s were higher compared with the vehicle traffic and reference areas and there were significant relationships with IgE, IL-4 and IL-13. Our results indicated the children residing at

industrial areas are at very high risk of the allergic, asthmatic, atopic diseases, and early death. Due to the high quantity and diversity of pollutants in industrial areas it is recommended to evaluate other more potential confounders such as PAH markers and other blood heavy metals. The next step of the study could survey the levels of other pro-inflammatory biomarkers in connection with chronic and acute diseases.

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Authors' contributions Amir Zahedi: Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft. Mohammad Sadegh Hassanvand: Conceptualization, Methodology, Investigation, Writing - Original Draft. Nematollah Jaafarzadeh: Conceptualization, Methodology, Resources, Investigation, Supervision, acquisition, Project administration. Ata Ghadiri: Methodology, Investigation, Resources, Review & Editing. Mansour Shamsipour: Validation, Formal analysis. Mohamad Ghasemi Dehcheshmeh: Methodology, Resource.

Declarations

Competing interests The authors declare they have no conflict of interest in preparation of the manuscript.

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