



Iranian population exposures to heavy metals, PAHs, and pesticides and their intake routes: a study protocol of a national population health survey

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Received: 1 October 2020 / Accepted: 7 December 2020 / Published online: 4 January 2021
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Abstract

Cancer is the second leading cause of death in the world and the third leading cause of death in Iran. It has been proven that numerous cancer cases are caused by exposure to environmental pollutants. There is a public health concern regarding an increase in exposure to carcinogens across Iran through different sources (air, food, and water) and a lack of research to address this issue. This study aims to gather data on exposure to heavy metals, polycyclic aromatic hydrocarbons (PAHs), and pesticides and their intake routes during the implementation of a national population health survey. This is a cross-sectional study of environmental pollutants in Iran, with a stratified multi-stage random sampling method, which led to 660 nationally representative samples in 132 clusters in three sequential parts. The first will be questionnaires to obtain demographics, assets, food records, air quality, and food frequency. The second will be physical measurements, including anthropometric and body composition. The third will be lab assessments that measure 26 types of environmental pollutants (7 heavy metals, 16 PAHs, and 3 pesticides) in urine, inhaled air, and consumed food and water of the population under study using ICP-MS and GS-MS devices. The results of this study will inform policymakers and the general population regarding the level of threat and will provide evidence for the development of interventional and observatory plans on the reduction of exposures to these pollutants. It could also be used to develop local standards to control contaminants through the three exposure routes. This study protocol will obtain data needed for policymakers to set surveillance systems for these pollutants at the national and provincial level to address the public concerns regarding the contamination of food, air, and water.

Keywords Environmental pollutants · Exposure pathways · Urine · Carcinogens · Iran

Responsible Editor: Lotfi Aleya

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Introduction

Increased industrial and agricultural developments have introduced environmental pollutants and exposures to heavy metals, pesticides, and polycyclic aromatic hydrocarbons (PAHs) (Forman and Silverstein 2012; Nicolopoulou-Stamati et al. 2016; Sansom et al. 2018; Goudarzi et al. 2018; Kelishadi and Poursafa 2010; Heidari Farsani et al. 2018; Kargarfard et al. 2011). These pollutants have various adverse health effects such as perinatal disorders, infant mortality, respiratory diseases, allergies, malignancies, cardiovascular disorders, increased oxidative stress, endothelial dysfunction, mental disorders, and various other harmful effects (Strosnider et al. 2017; Kelishadi and Poursafa 2010; Kargarfard et al. 2011; IARC 2012; IARC 2004; Badeenezhad et al. 2020; Soleimani et al. 2019a, b). Although the short-term effects of environmental pollutants are usually highlighted, the wide range of exposures from the early stages of life and their possible implications on chronic non-communicable diseases during adulthood also warrant study.

There are a few studies on the distribution of exposures to the abovementioned pollutants in Iran (Saeedi et al. 2012; Pirsahab et al. 2016), although none of them provides nationally representative estimates. Moreover, it is assumed that there are vast differences in exposure of these pollutants in different provinces and districts in Iran. For example, in Iran, dust pollution in the southwest (Neisi et al. 2017; Naimabadi et al. 2018), air pollution in metropolises (Omidi Khaniabadi et al. 2017; Dehghan et al. 2018; Bagherian Marzouni et al. 2017), water pollution in some provinces (such as high levels of arsenic in some cities in Kurdistan and Kerman Provinces), and the discharge of contaminated effluents into water resources highlight the need for a national-scale study.

This study will provide data to estimate the nation-scale exposures of environmental pollutants (heavy metals, PAHs, and pesticides) in Iranian adults. This study will also examine the level of the contaminants in drinking water, inhaled air, and consumed food by the study participants, which will provide data needed to set local standards for different routes in different regions in Iran.

In this paper, we introduce the study's scientific methods to include data collection, laboratory measurements, sampling methods, and statistical analysis.

Methods/design

Design and implementation process

This cross-sectional study was designed to determine the carcinogens' level (heavy metals, PAHs, and pesticides) in the

urine of the population under investigation. Additionally, we determine the population's environmental exposure to the carcinogens in air, food, and water. These evaluations enable us to modify the native standards by using the local coefficient for each contaminant in each route of the exposure. A representative sample size of 660 adults in 132 clusters at the national and regional levels is estimated based on the region's population within study and the current concentrations of the carcinogenic contaminants.

This study protocol covers the following areas of design and implementation of study: information technology, questionnaire, and guide for interviewers, physical measurements, laboratory measurements, sample banking (urine and food), training, supervision, sampling, statistical analyses, and ethics (Fig. 1).

Sampling

Overall, 660 households will participate in this survey. To sample the households, we designed a stratified multi-stage sampling frame (Lohr 2010; Skinner 1996). Before running the first stage, we will implement a cluster analysis in 30 provinces of Iran. Among different clustering methods, we will employ model-based clustering (Banfield and Raftery 1993; Scrucca et al. 2016) based on the Gaussian mixture models, which allow us to choose the appropriate model and number of clusters. The input covariates of the models include the particulate matter of 10 μm or less in diameter (PM_{10}); the incidence rate of all cancer groups and chronic respiratory diseases (CRDs); and the total usage of fungicides, herbicides, insecticides, and acaricides in all provinces (except Alborz, as we do not have the data for pesticides). We should point out that we will standardize the mentioned rates by the national population's sex-age structure, making different provinces comparable. As a result, we will categorize the provinces into six super-clusters (SCs)(Fig. 1). Each SC contains certain provinces in which we will select one province as the representative and consider its capital the primary sampling unit. The selected provincial capitals are Ardebil, Kermanshah, Mashhad, Zahedan, Tehran, and Yazd (Fig. 2). In each provincial capital, the fieldwork and supervision's responsible authority will be the local university of medical sciences.

In the second stage, we will define every five households (geo-locally near each other) as a cluster and consider the clusters as the secondary sampling units. Since all households' list is not available, we will systematically sample a specific number of clusters from each of the six cities. The allocated number of clusters for each town is proportional to the total population of people aged 25 years or older in the corresponding SC. We have summarized all the information regarding the SCs, clusters, and assigned sample sizes in Table 1.

To sample the clusters, we have defined a frame with a plausible range of latitudes and longitudes around every city. We will then generate random uniformly distributed latitudes

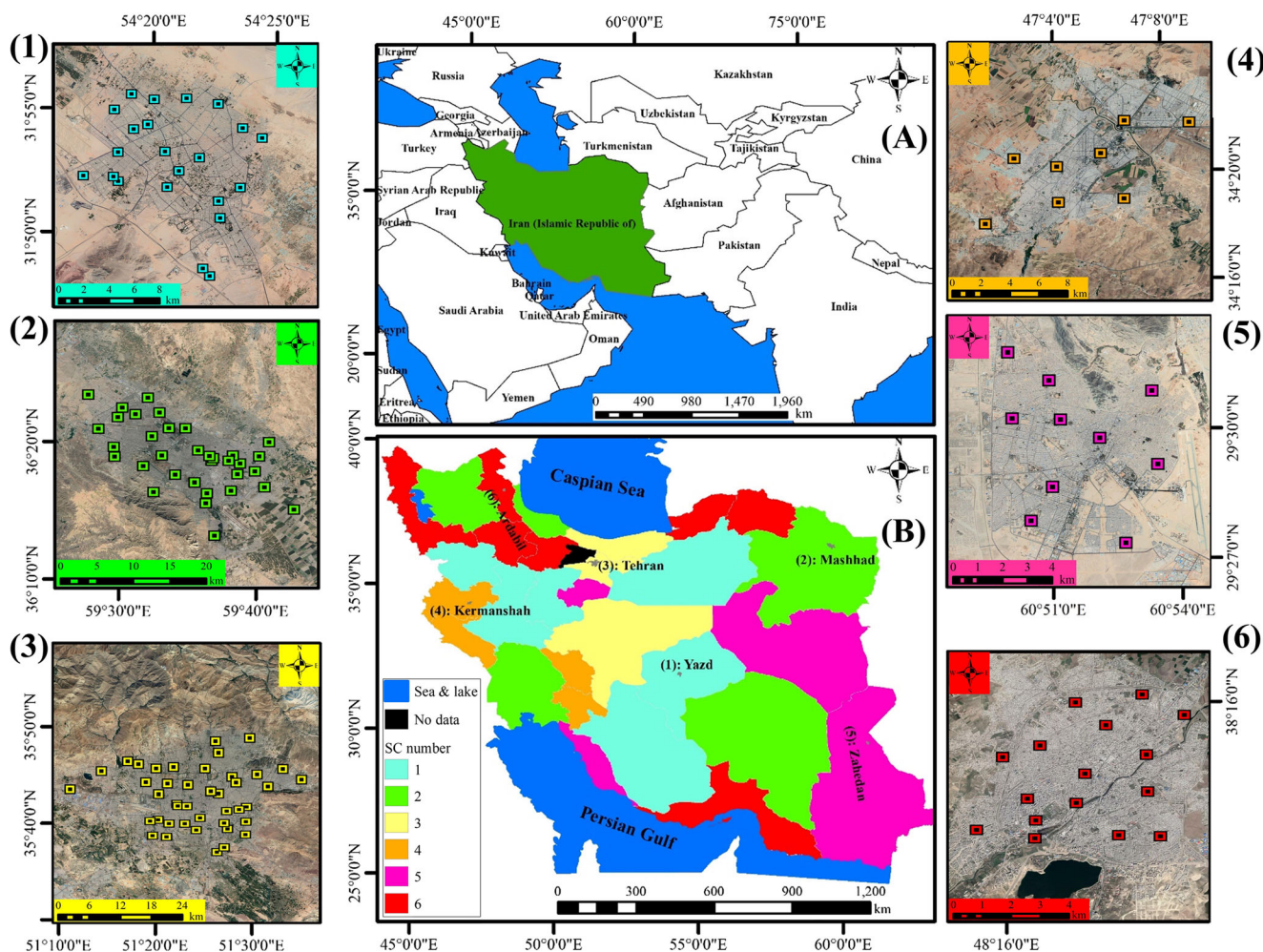


Fig. 1 Geographical distribution of the six super-clusters (SCs) and the selected provinces and capitals for sampling in Iran. A: Location of Iran country in regional scale, B: Geographical distribution of SCs, (1): Yazd, (2): Mashhad, (3): Tehran, (4): Kermanshah, (5): Zahedan, (6): Ardebil

and longitudes, which together construct the coordinates of our potential clusters (Bivand et al. 2018). If a cluster is not within our sampling frame, we will replace it with an alternative coordinate.

Finally, we will select one participant from all the eligible members of every household.

To gather a representative sample of our population, we have determined the eligibility criteria for the individuals within a household using the inclusion and exclusion criteria shown in Table 2. We will collect the questions regarding these criteria in a single questionnaire. It should be noted that only urban areas will be in the sampling frame, and subsequently, no individual will be outside the cities.

Sample size calculation

Since no previous national study has measured the mean intake of heavy metals, PAHs, and pesticides, we

considered the baseline prevalence of the attributes as 50%. According to Cochran's formula for large populations (Cochran 2007), we calculated a sample size of 383, assuming a 95% confidence level and a maximum margin of error of 5%. To adjust the sample size based on our cluster sampling framework, we considered a design effect of 1.5 (Salganik 2006) and a response rate of 85% (Dey 1997), which leads to 660 samples in 132 clusters.

Information technology

In this study, to accelerate and facilitate the implementation of the processes and increase and improve data registration and transmission accuracy, we use the DIGIT Platform as a service (<https://rabit.info>). DIGIT creates electronic questionnaires with measures that ensures data quality. This platform combines multiple questionnaires

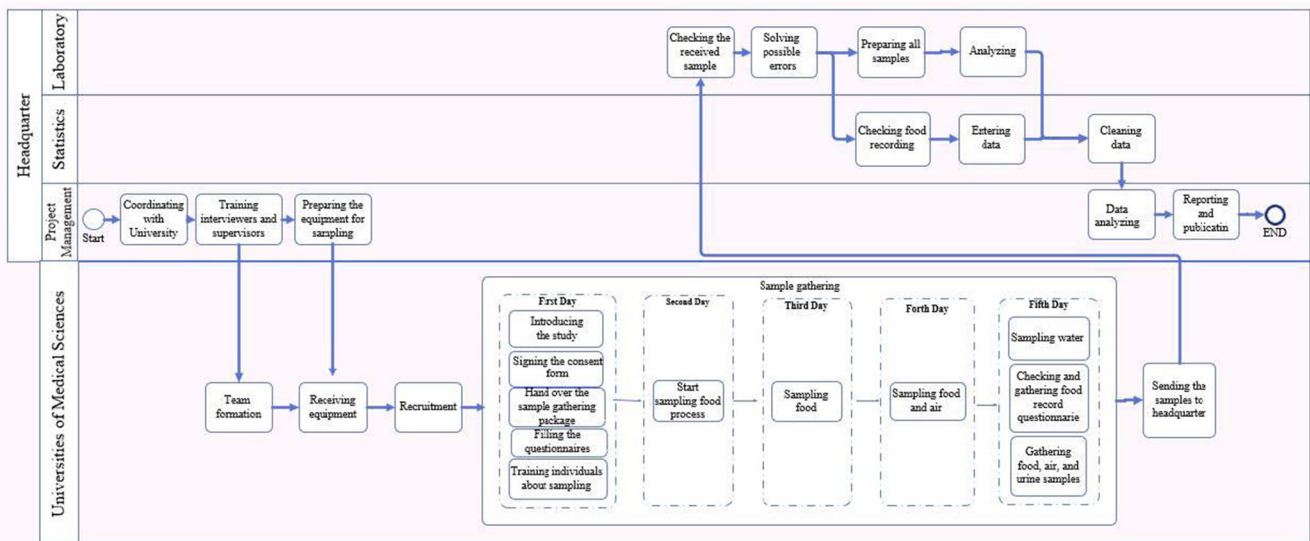


Fig. 2 Implementation process chart

and converts them into a survey project. DIGIT also provides a network of interviewers to collect field data. This approach contains an android application for data gathering of four questionnaires and a website for management, monitoring, and reporting. All communications between the android tablets and the server use the HTTPS protocol (<https://rabit.info>).

Training

A training session for each selected university will be conducted at the study’s headquarters (NCDRC). During that session, all steps of scientific and executive

procedures (introduction; interview procedures, using the tablet’s application; physical measurements; sampling of air, water, food, and urine) will be presented. This session also will contain multiple workshops and a competence examination.

Recruitment

The interviewers will recruit eligible individuals based on addresses, randomly selected according to the sampling method. Two copies of the consent form will be filled out and signed by each participant. Afterward, the interview and anthropometric measurements will be conducted. The subjects will be

Table 1 Descriptive statistics on super-clusters (SCs), clusters, and the assigned number of samples

SC number	Provinces	Selected province	Provincial capital	Weight	Total clusters	Total samples
1	Fars, Hamadan, Kurdistan, Lorestan, Markazi, Semnan, and Yazd	Yazd	Yazd	0.17	22	110
2	East Azarbayejan, Gilan, Kerman, Khorasan-e-Razavi, and Khuzestan	Khorasan-e-Razavi	Mashhad	0.26	34	170
3	Isfahan, Mazandaran, and Tehran	Tehran	Tehran	0.32	42	210
4	Chahar Mahaal and Bakhtiari, Ilam, Kermanshah, and Kohgiluyeh and Boyer-Ahmad	Kermanshah	Kermanshah	0.06	8	40
5	Bushehr, North Khorasan, South Khorasan, Qom, and Sistan and Baluchistan	Sistan and Baluchistan	Zahedan	0.07	10	50
6	Ardebil, West Azarbayejan, Golestan, Hormozgan, Qazvin, and Zanjan	Ardebil	Ardebil	0.12	16	80
	Total			1	132	660

Table 2 Inclusion and exclusion criteria in this study

Inclusion	Exclusion	Explain
Individuals should be at least 25 years old.		—
Individuals should be non-smoker and have no contact with smokers.	Having contact with smokers in home and work place during the study.	—
Individuals should be apparently healthy and not pregnant.	Gets sick during the study.	—
Individuals should not take any medications within the last month.	—	—
Individuals should not have a history of any chemotherapy or radiotherapy throughout their lifetime.	—	—
Occupational exposures are not allowed.	Having an occupational exposure.	Individuals' occupation should not include the following items: casting, metallurgy, welding, and soldering rubber, asphalt, and coke industries pesticide manufacturing industries agriculture and greenhouse cooking (in large restaurants)

asked to collect and provide samples of food and urine and help the survey staff collect water and air samples over 4 days. Details of necessary actions to be taken in the coming days will be described, and individuals will be provided with sampling packages (brochure, sampling containers, and ID labels).

Assessment of anthropometric indices and body composition

Anthropometric measurements, including body weight and height, will be conducted by a trained assistant. Body weight will be measured using a portable body composition scale (Omron, BF 511) with 100-g precision. The mobile body composition scale is an 8-sensor bioelectrical impedance analyzer that can report body fat (in %), skeletal muscle (in %), and visceral fat. The gender, age, and height of the participants will be entered manually.

Participants will be asked to remove any heavy clothing and socks to make skin contact with the device's metal pads. Height will be measured using an unstretched meter with a precision of 0.5 cm while individuals stand against a wall with their shoulders and head in a normal position. Then, body mass index (BMI) will be calculated by dividing body weight (in kilograms) by squared height (in meters).

Questionnaires

The first step in the recruitment process will be to check the inclusion criteria for the study's application.

Five valid and reliable questionnaires (demographic, anthropometry, air quality, food frequency, food record) will be completed. The demographic questionnaire will collect information about age, gender, education, and career. Anthropometry will gather the anthropometric indices and body composition that will be measured by interviewers. The air quality questionnaire focuses on several factors that influence indoor air quality, such as the size of the kitchen area, use of pesticides, type of air conditioner, and owning houseplants. Moreover, we will ask about the hours a subject spends outdoors to estimate air contaminant intake. Food frequency questionnaire will be completed about the use of 167 food items. Tablets will be used to gather all questionnaires and food record questionnaires. The food record will be in paper form and will be filled out during the sampling period (3 days).

Data collection

Assessment of pollutants in food, water, air, and urine

In this study, food, water, air, and urine pollutant sampling will be conducted according to the protocol in Fig. 3.

Sampling and measurement of pollutants in food

The method to assess dietary intake includes three sections: duplicate portion sampling (DPS), food record, and the food frequency questionnaire (FFQ).

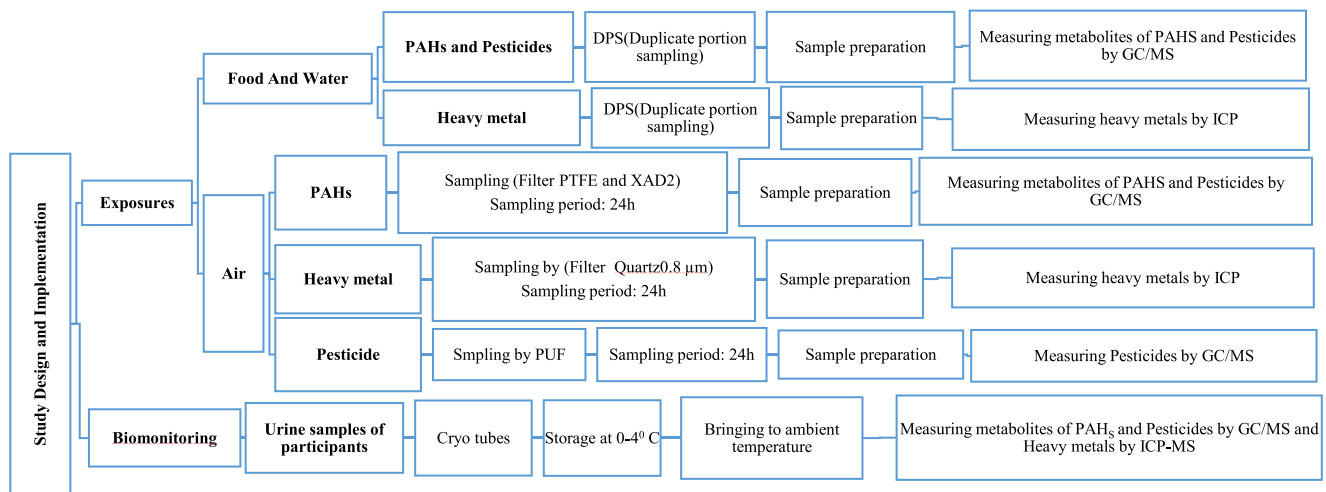


Fig. 3 Sampling method and measurement of pollutants in food, water, air, and urine

Duplicate portion sampling

The DPS method will be used to determine the amount of pesticides and environmental pollutants obtained from the diet. DPS is considered the gold standard way to assess dietary intake at the individual level. However, it is more expensive and challenging to execute than other nutritional assessments (JointFAO et al. 1985; Domingo et al. 2012; Navarro-Alarcon et al. 2012; Ortega et al. 2015). In this method, participants are asked to prepare twice the usual portions of food they consume daily. For the present study, all consumed foods over 24 h with the same amount and preparation method (boiled, raw, fried, etc.) will be collected over 3 consecutive days (2 workdays, 1 non-working day).

Verbal and written instructions on how to gather food will be presented to the participants. The critical points that participants needed to preform carefully are as follows:

- All fruits and vegetables of the same meal should be collected in separate bags.
- Each bag (labeled with date and ID) should be put in a bigger dark bag and then kept in the freezer until collection by the research team.
- Whole duplicate portions for each day should be collected in a separate big dark bag in the freezer.

As the type of food container can affect the amount of pollutants in food, we recommend polyethylene bags for food collection.

Collected DPS will be transferred to the laboratory in cool boxes (0–4 °C). In the lab, the DPS for each participant will be weighed. The next step will be weighing and blending fruits and vegetables to get the pesticide sample. The remains of that mix,

along with other food samples, will then be homogenized in a blender. A 10-g food sample and 5 g mix of fruits and vegetables and a representative sample of the 3-day intake will be separated and considered for analysis. Finally, the samples will be poured into a tube and covered by foil, and prepared for analysis.

Determination of heavy metals, PAHs, and pesticides in food

Heavy metals, PAHs, and pesticides will be measured according to AOAC-2015 and EN-15662, respectively (AOAC 2015; BS EN 15662 2018).

Sampling and measurement of pollutants in water

Water quality sample collection strategies for heavy metals, PAHs, and pesticides will vary by site. If a cluster has been selected for water sampling, then the composite sampling method will be applied. This will be conducted as high-frequency discrete and/or composite sampling will provide information regarding the variability in water analyses due to random and systematic influences. The sampling method will be based on standard methods (Rice et al. 2017; EPA Guidelines 2007). All samples will be transported to the laboratory in a refrigerator (cooled between 1 and 4 °C). According to established procedures, water samples will be extracted using a solid-phase extraction (SPE) system (Li and Lee 2001).

Determination of heavy metals, PAHs, and pesticides in water

The EPA extraction methods 8270C and 8141B will be selected to determine PAHs and pesticides, respectively (EPA 2007; EPA 1996). The extract will then be poured into a microvial (100 μL) and preserved in the refrigerator until

being injected into the GC/MS instrument. The ASTM C1111 method has been selected to determine metals in water by the ICP-MS (Agilent Technology 7500, USA) (ASTM C1111 2015).

Sampling and measurement of pollutants in the air

Simultaneous indoor and outdoor 24-h PM₁₀ samples will be collected on Quartz (for metals) and PTFE (for PAHS) filter papers (25 µm dia., 0.5 µm pore size, from SKC) using low-volume air samplers (NIOSH 2014; EPA 1990), operating at flow rates of 3 L/min, 0.8 L/min, and 3 L/min for each cyclone, XAD2 adsorbent, and PUF adsorbent which will be used for gas PAHs and organophosphate pesticide, respectively. The indoor sampling device will be set where the participants will be stationary in the room at a height of approximately 150 cm above the ground. Also, outdoor air samples will be collected. Local weather data, including temperature and relative humidity in both indoors and outdoors, will be measured using meteorological sensors. Mass concentrations of PM₁₀ will be gravimetrically determined by weighing the PTFE and Quartz filters before and after the sampling on a microbalance (Mettler-Toledo Inc.) with a sensitivity of 0.0001 g. An equilibrating time of 48 h will be used under the controlled relative humidity (25–30%) and temperature (20–25 °C) before the weighting of PM and blank filters. The filters will then be packed in Petri dishes then covered in aluminum foils, and stored at –20 °C until the extraction and chemical analysis.

Determination of heavy metals, pesticides, and PAHs in air

The NIOSH-7304 method has been selected to determine the composition of metals in PM₁₀ of Quartz filters. The extracted solution will be filtered through a 0.45-µm pore size, and the filtrate will then be analyzed with an ICP-MS instrument (NIOSH 2014). The method of sampling and monitoring of PAHs and organophosphorus pesticides in the air will be conducted according to NIOSH-5515 and EPA IP-8 (NIOSH 2014, EPA 1990, and ASTM D4861-17 2017).

Sampling and measurement of pollutants in urine

We will measure metabolized PAHs, pesticides, and metals in each urine sample. Our analysis will include a 300-ml baseline of morning urine samples, which will be collected on the fourth sampling day. Samples will be delivered to the laboratory in a cooling box (4 °C). The models will then be separated into aliquots and stored at –20 °C for a few days before being transferred to a –80 °C storage unit.

Determination of heavy metals, PAHs, and pesticides in urine

We have selected NIOSH-8310 and NIOSH-8321 methods. Organophosphate metabolites will be extracted from urine samples using a procedure previously validated for the simultaneous extraction of polar and non-polar pesticides in urine samples by Arcury et al. (2007) (NIOSH 1994; NIOSH 2017).

Creatinine in urine

The creatinine concentration will be used to adjust the effect of urine dilution. The urinary creatinine concentration will be determined in fresh urine samples immediately. This will be done based on the colorimetric method using a biochemistry autoanalyzer (BT-1500, Italy).

Equipment

The PAH and pesticide extracts will be analyzed with the Agilent 7890 gas chromatography and 5975 mass spectrometer systems (GC-MS), equipped with a 30 m × 0.25 mm column and liquid chromatography-mass spectrometry (LC-MS), respectively. The samples' heavy metals will be analyzed by the Agilent 7500× ICP-MS instrument (Agilent, Santa Clara, CA, USA) using a standardized protocol.

Standardization of calibration and quality control

For quality assurance and quality control (QA/QC), laboratory and field blanks and spiked samples and spiked samples will be analyzed. The international standard reference materials will be applied for the analytical control of all compounds. Limit of detection (LOD) values will be set three times the standard deviation of the blank values. The average of the blank values will then be subtracted from all concentrations above the LOD values.

Supervision

We will use online and direct observation through field visits for oversight in the study. Online supervision will focus on collected data, such as the completion of each questionnaire and the interviewers' activities. Direct observation via field visits will focus on the sampling methods for air, water, food, and urine collection; completion of food records by participants; and sample transportation to the laboratory. After the supervision of data collection, all recorded data will be reviewed and missed data will be collected through direct contact with participants.

Statistical analysis

We will aggregate the data and calculate descriptive statistics (e.g., mean, standard deviation) on the demographic variables, anthropometry, and laboratory-based variables at the national level. To make more representative estimates for the target population, we will incorporate a self-weighting sampling design in our study. First, we will define nine adjustment weights to build our desired sampling weights. Our nine adjustment weights will reflect various types of non-response rates and include three questionnaire-based non-response weights (one for each of the demographic, food frequency, and food diary questionnaires), four source-specific laboratory non-response weights (one for each of the studied sources: air, food, water, and urine), anthropometry non-response weight, and individual non-response weight. We will also construct a series of variable-specific weights to use when analyzing one goal-variable only (e.g., aluminum), independent from others.

We will define the individual non-response weight as the inverse of the non-response rate in a cluster. The non-response rate is the proportion of eligible people in the cluster who participate in the study but later refuse to cooperate in the procedures (including questionnaires, anthropometry, and laboratory tests). The above definition will be consistent for all other eight weights and will only be limited to the corresponding procedure variables.

It should be noted that the sample assignments will be proportional to the size of the SCs. As a result, the within-SC weight, which is calculated as the SC population-to-sample size ratio, will be equal in all SCs. Therefore, we will not assume any within-SC weight in our design. In all analytical processes, we will consider a p value of less than 0.05 statistically significant.

Discussion

This study will aim to estimate the concentrations of Al, Pb, Cr, Cd, As, Ni, Hg, and organophosphate pesticides and PAHs in air, food, water, and urine in Iranian adults. The results of this study will be of use for at least three groups that include policymakers, responsible organizations, and the general population in the aspects of governance, guideline development, and intervention.

There are two major responsible entities that have the most effluence remediating these types of environmental problems. The first one is the Iranian Non-Communicable Diseases Committee (INCDC) of MOHME which focuses on the prevention, control, and monitoring the 6 major groups of diseases and risk factors in Iran (Peykari and Larijani 2019). The other one is the Supreme Council for Health and Food

Security (SCHFS), which focuses on inter- and intra-sectorial collaboration for maintaining public health (Hsu et al. 2020; Farshad et al. 2020). Both bodies are key policymakers and involved in the health legislation processes. The results of this study will provide these entities with the information needed for baseline evaluation of contamination at the national level and to estimate the attributable health risks. To control contamination levels, responsible organizations such as the Supreme Council of Environment Protection will be able to use this study's results to revise their guidelines.

General population awareness is another by-product of publishing such results. Increasing society's sensitivity towards the effects of pollutants on health, and individual and household level intervention efforts for controlling the amount of contamination exposures are possible. Following the rise of public awareness, demand for government intervention will drive policymakers towards controlling exposures through intra-sectorial collaboration. Moreover, routine surveys and complementary studies to identify the levels and sources of all environmental risk factors will focus on responsible organizations.

This study can help set standards using carcinogen levels in individuals' source routes (food consumed, water drunk, and air inhaled). For example, suppose in some areas exposure to an extra pollutant from one or two pathways is unavoidable. In that case, the other route(s) have to be controlled to address total recommended exposure thresholds. Depending on the main local pollutant, each part of the country will need different water, air, and food guidelines. It will also determine the relationship between the intake of heavy metals, PAHs, and pesticides and their concentration in Iranian adults' urine.

The strengths of the study are as follows:

For the first time, we will be simultaneously sampling all three routes of exposure to pollutants and comparing them with biomarkers in urine samples at a national scale. The DPS method used for food sampling will be applied for 3 consecutive days. Also, vegetables and fruits will be gathered and analyzed separately from other foods to detect pesticides.

The limitations in storing and transferring beverages, except for drinking water, are negligible due to technical and practical difficulties. Detecting different categories of pesticides will need different procedures, which this study's funding does not cover. Thus, the researchers decided to focus on the most commonly used pesticide chemical, organophosphate, as it is widely used in Iran.

Conclusion

This study is the first survey that measures these contaminants in the three matrix of food, drinking water, and air of

an individual at the same time at the national level. After publishing the results, we will use all networks available to inform policymakers regarding the threats' level, and provide solutions for the health problem. Given the public concerns regarding food, air, and water contamination, convincing policymakers to set surveillance systems for these pollutants at national and provincial levels seems quite likely. Also, by using the contaminant doses in the samples and carcinogenicity of them and matching them with mortality and morbidity level of related diseases such as cancers, we can estimate environmental risk factors for the Burden of Diseases study.

Acknowledgments We would like to thank National Institute for Medical Research Development (NIMAD) Iran for funding this study by the grant number 964655. Also, we would like to express our gratitude to Dr. Dale W. Griffin from the US Geological Survey for the help in conducting the present survey.

Authors' contributions Zahra Soleimani has drafted the work and contributed in designing the work.

Rosa Haghshenas has contributed in designing the work.

Masoud Masinaei has made substantial contributions to the sampling and statistical analysis.

Kazem Naddafi, Masud Yunesian, and Ramin Nabizadeh have drafted the work (section of air and water) and substantively revised it.

Nazli Namazi, Abolghasem Djazayeri, and Hamed Pouraram have drafted the work (section of the food) and substantively revised it.

Mohammad Javad Hajipour and Arezou Dilmaghani-Marand have drafted the work (section of laboratory).

Alireza Mesdaghinia and Farshad Farzadfar formed the concept, supervised all steps, and reviewed and finalized the manuscript.

Funding This research was funded by Grant 964655 from the National Institute for Medical Research Development (NIMAD) Iran.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Consent to participate Not applicable.

Code availability Not applicable.

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