Study Protocol

National and Sub-national Environmental Burden of Disease in Iran from 1990 to 2013–Study Profile

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Abstract

Background: Development of national evidence-based public health strategies requires a deep understanding of the role of major risk factors (RFs) and the burden of disease (BOD). In this article, we explain the framework for studying the national and sub-national Environmental Burden of Disease (EBD) in Iran as a part of the National and Sub-national Burden of Disease (NASBOD) study.

Methods: The distribution of exposures to environmental RFs and their attributable effect size over 1990–2013 will be estimated through comprehensive reviews of either published or unpublished sources. Statistical modeling will be used to impute missing data in the distribution of RFs exposures for each district-year. National and sub-national BOD attributable to these RFs will be estimated in the following metrics: prevalence, death, years of life lost due to premature death (YLL), years of life lost due to disability (YLD), and disability-adjusted life years lost (DALYs).The BOD attributable to the current distribution of exposures will be compared with a counterfactual exposure distribution scenario–here, the theoretical-minimum-risk exposure distribution. Inequalities in the distribution of exposure to RFs will be analyzed and manifested nationwide using geographic information systems.

Discussion: The EBD study aims to provide an official report to Iranian Ministry of Health and Medical Education, to publish a series of articles on the exposure trends of the selected environmental RFs, to estimate the BOD attributable to these RFs, and to assess inequalities and its determinants in the distribution of exposure to RFs. Iran's territory is large with diverse population, socioeconomic, and geographic areas. Results of this comparative risk assessment study may pave the way for health policy makers to plan more comprehensive and cost-effective evidence-based strategies.

Keywords: Burden of disease, environmental risk factors, Iran, Middle East, NASBOD, study profile

Cite this article as: Amini H, Shamsipour M, Sowlat MH, Parsaeian M, Kasaeian A, Hassanvand MS, et al. National and sub-national environmental burden of disease in Iran from 1990 to 2013–study profile. *Arch Iran Med*. 2014; **17(1):** 62 – 70.

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Accepted for publication: 3 December 2013

Introduction

Following the seminal work of Murray and Lopez[1] in estimating the burden of disease (BOD) attributable to ten major risk factors in global and regional scales using comparative risk assessment (CRA) methodology, subsequent studies with the same framework came through.[2–5] While these studies are interesting and useful for developing future global and regional health improvement strategies, due to some important limitations they may not be fully applicable for national and sub-national scales as policy support. First, only the major risk factors have been selected that either their exposure distributions are available or feasible to estimate. Meanwhile, the high-priority risk factors to be studied in national or sub-national scales may differ based on local concerns and situations. In addition, the reference population that will be used for standardizations in the national or sub-national analyses will be also different. Ultimately, the broad estimated global patterns may have masked or underestimated significant sub-national variations in risks.

Environmental risk factors play an important role in the burden of disease both globally and nationally.[5–7] In fact, one in four child deaths have been caused by unsafe and unhealthy environment, worldwide.[8] According to the global health risk assessment by

World Health Organization (WHO) climate change, indoor smoke from solid fuels, lead exposure, urban outdoor air pollution, and unsafe water/sanitation/and hygiene cause approximately 10 % of deaths and diseases burden and 25 % of disability-adjusted life years (DALYs) in children under five years old.[8] Global Burden of Disease (GBD) study also showed that from the ten leading risk factors in 2010 (ranked by attributable burden of death) two were environmental including household air pollution from solid fuels (ranked four) and ambient particulate matter pollution (ranked seven) (see the heat map from the permanent online link).[9] For Iran, similarly of the ten leading risk factors in 2010 (again ranked by attributable burden of death), two were environmental risk factors. However, as Iran has large natural gas reservoirs, majority of people use gas for cooking and heating; therefore, household air pollution from solid fuels was not among the top ten risk factors—ranked 20, indeed. In other words, ambient particulate matter pollution (ranked six) and lead exposure (ranked ten) were the leading environmental risk factors in Iran, 2010 (see the heat map from the permanent online link).[10] Generally, the proportion of ischemic heart disease (IHD) DALYs attributable to ambient particulate matter pollution, household air pollution from solid fuels, and lead exposure in 2010 was estimated to be 22 %, 18 %, and 4 %, respectively.[5] Fine particulate matter was also estimated to cause roughly 8 %, 5 %, and 3 % of lung cancer, cardiopulmonary deaths, and respiratory infection deaths, respectively.[8] Of the environmental risk factors, climate change also has a substantial impact on the burden of disease. It has been estimated that between 1990 and 2100, the global average temperature rises by 1.1 to 6.4 °C.[11] Nonetheless, CRA study of climate change indices, such as increased temperatures or floods, is challenging as there is considerable complexity and uncertainty in models of attributable avoidable impacts (*i.e.* establishing a counterfactual scenario).[8]

As mentioned above, GBD studies have some uncertainties in their estimates. In fact, conducting national and sub-national BOD studies may better account indeterminacies and provide an opportunity to reassess GBD estimates. In order to develop effective policy measures, quantitative information about the extent of health impacts of different environmental stressors is needed. In this paper, we will introduce and discuss the general framework of the Environmental Burden of Disease (EBD) study in Iran, which is part of the National and Sub-national Burden of Disease study, with updated exposure estimates, updated effect sizes for risks, and more number of risk factors related to national and sub-national concerns. The first aim of EBD is to estimate exposure distribution of selected major environmental risk factors among the entire Iranian population from 1990 to 2013. The second aim is to estimate the burden of disease attributable to these risks using the following metrics: prevalence, death, years of life lost due to premature death (YLL), years of life lost due to disability (YLD), and DALYs. Finally, special focus will be placed on assessing national and sub-national inequalities of environmental risk factors.

Materials and Methods

Executive study phases

In order to design the study framework of EBD, an expert panel was formed consisting of six environmental health experts, three epidemiologists, and one biostatistician. According to a risk-based approach, the EBD expert panel listed the major environmental determinants of health (i.e. risk factors) from the full list of the GBD risk factors and other similar projects through comprehensive reviews of published works and numerous meetings. However, this list was finalized based on Iran's situation and priorities. Next, since it was not feasible to include all major risk factors in the EBD study, a novel justifiable protocol comprising two steps was developed by the expert panel to select the high-priority risk factors. The first step was scoring the four primary criteria (i.e. public health impact, high individual risk, high political or public concern, and economic significance) introduced by the European Burden of Disease study[6] from 0 to 100—this score was used as a weighting factor for the second step. In the second step, the four criteria were scored from 0 (low importance) to 10 (high importance) for each risk factor. Thereafter, they were multiplied by the weight given in the first step. Finally, the scores of each risk factor were summed and ranked to select the high-priority risk factors. The members of the internal EBD expert panel and those of the external EBD advisory board, who are introduced at the end of this article, fulfilled the scoring. The high-priority risk factors, ultimately, were selected based on the mentioned protocol. In addition, a technical team was then formed for each risk factor.

The selected high-priority risk factors (based on the developed protocol after scoring) were Particulate Matter with an aerodynamic diameter of ≤ 2.5 micrometers ($PM_{2.5}$), Tropospheric Ozone (O_3), Benzene, Second-hand Smoke, Ultraviolet Radiation (UV), Environmental Noise, Indoor Radon, Unsafe Water/Sanitation/and Hygiene, Drinking Water Fluoride, Dioxins and Furans, Climate Change Indices, and Sulfur Dioxide (SO_2), (Table 1). Noteworthy, we also took into account two more criteria for selecting the risk factors. The first was the accessibility of risk factors' data/proxy covariates or feasibility to access them; the other was the availability of evidence-based dose-response functions derived from WHO guidelines, meta-analyses, and/or credible current scientific literature including individual studies. Finally, each technical team drafted a proposal for their target risk factor, which was evaluated and confirmed by the EBD expert panel and the NASBOD core team.

Research objectives

I. National and sub-national exposure trends

- Determining national and sub-national trends of exposure to $PM_{2.5}$, O_3, Benzene, Second-hand Smoke, UV, Environmental Noise, Indoor Radon, Unsafe Water/Sanitation/and Hygiene, Drinking Water Fluoride, Dioxins and Furans, Climate Change, and SO_2 from 1990 to 2013

II. National and sub-national Burden of Disease

- Calculating national and sub-national Burden of Disease attributable to the above mentioned risk factors from 1990 to 2013.

III. National and sub-national inequality and its determinants assessment

- Determining national and sub-national inequalities in the exposure distribution of the above mentioned risk factors from 1990 to 2013.

Data sources

The information about the level of exposure to the risk factors, health endpoints, and the RRs of each outcome attributable to an environmental risk factor will be collected from: a) data published in peer reviewed papers through a systematic review and meta-

Table 1. The selected high-priority environmental risk factors in the EBD 1990-2013 study in Iran[a]

Risk factor	Variable Definition	Outcome(s)	Data Source	Exposure Assessment Method	Counterfactual	Source of Relative Risks
$PM_{2.5}$	Ambient particulate matter with an aerodynamic diameter of ≤ 2.5 µg/m³	Cardiovascular disease; cerebrovascular disease; chronic obstructive pulmonary disease (COPD); ischemic heart disease (IHD); lower respiratory infection; natural-cause mortality; respiratory disease; stroke; trachea, bronchus, and lung cancers	GBD 2010 estimates, National air quality monitoring network	Geo-statistical/geo-spatial modeling	-	Crouse et al (2012)[44] Hoek et al (2013)[45] Jerrett et al (2013)[46] Raaschou-Nielsen et al (2013)[47] Beelen et al (2013)[48] Latest meta-analyses
O_3	Tropospheric ozone in air measured in parts per billion (ppb)	Cardiovascular disease; COPD; IHD; lung cancer; respiratory disease; and stroke	GBD 2010 estimates, National air quality monitoring network	Geo-statistical/geo-spatial modeling	-	Jerrett et al (2013)[46] Jerrett et al (2009)[49]
Benzene	Benzene levels in outdoor air	Leukemia[6]	National air quality monitoring network and specific covariates	Geo-statistical/geo-spatial modeling	-	Hänninen and Knol (2011)[6]
Second-hand Smoke	Also called environmental tobacco smoke or passive smoking is the proportion of children and non-smoking adults who report exposure to second-hand smoke	*In children:* lower respiratory infections; upper respiratory infections; otitis media; asthma; and sudden infant death syndrome (SIDS) *In adults:* trachea, bronchus, and lung cancers; asthma; IHD; and cerebrovascular disease	Population surveys	-	No second-hand smoke exposure	-
UV Radiation	The intensity of UV radiation in outdoor environments	Skin cancers including basal cell carcinoma, squamous cell carcinoma, and melanoma	-	-	-	-
Environmental Noise	Noise emitted from all sources except industrial workplaces	Blood pressure; children's cognition and health; IHD; and myocardial infarction	-	-	-	-
Indoor Radon	Gaseous radon present in indoor environments measured in Bq/m³	Lung cancer	-	-	Zero	-

Unsafe Water, Sanitation and Hygiene	Proportion of people using an unimproved water supply and/or an unimproved procedure of human excreta disposal and/or no personal hygiene practices	Ascariasis; hookworm; infectious diarrhea; malnutrition and consequences of malnutrition on most infectious diseases; schistosomiasis; trachoma; and trichuriasis	Population surveys and censuses, systematic review	Survey of water supply system, procedure of human excreta disposal and hand washing in the communities	Absence of transmission of infectious diarrhoeal disease through water and sanitation and hygiene	Cairncross et al (2006)[50] Cairncross et al (2010)[51] Ejemot-Nwadiaro et al (2012)[52] Prüss-Üstün et al (2004)[53]
Drinking Water Fluoride	Mineral fluoride in drinking water in parts per million	Dental fluorosis; skeletal fluorosis; teeth decay and DMFT (decayed, missing, and filled teeth)	National and sub-national water quality surveys	Water quality monitoring	-	-
Dioxins and Furans	Daily intake of dioxins and furans expressed as toxic equivalent (TEQ)	Total cancer	-	Survey studies on food consumption Human bio-monitoring investigation of human milk or blood levels	Zero	NAS (2006)[54] Hänninen and Knol (2011)[6] Leino et al (2008)[55] US EPA (2003)[56]
Climate Change Indices	Apparent temperature, humidity	Malnutrition (under 5); morbidity from cardio and cerebrovascular disease; mortality and morbidity from hydro-meteorological disasters; mortality and morbidity from water & food-born disease; mortality from Respiratory disease; and vector-born disease	National Meteorological Organization, MOH, MOI	Time-series models with spline smoothing Mathematical models	-	Baker et al (2000)[57] McMichael et al (2000)[58] Patz et al (2000)[59] Rosenzweig and Parry (1994)[60] Shindell et al (1998)[61]
SO_2	SO_2 in air measured in parts per billion (ppb)	Asthma; lower respiratory tract infections; lung cancer; still birth; low birth weight; preterm labor; heart rate variability; IHD; cardiovascular diseases; migraine; death	National air quality monitoring network	Geo-statistical/geo-spatial modeling	-	Lai et al (2013)[62] Lewtas (2007)[63] Dales et al (2009)[64] Sunyer et al (2003)[65] Cao et al (2011)[66] Kan et al (2010)[67]

These environmental risk factors were also considered for scoring but finally were not selected to be studied in the EBD 1990–2013 study based on the developed protocol: lead exposure, home injuries, driving injuries, electromagnetic fields, fecal coliform, total organic carbons (TOCs), trihalomethanes (THMs), arsenic, chromium, nitrate, polycyclic aromatic hydrocarbons (PAHs), pesticides, and parasite oocytes. [a]Each piece of this table may be updated during the study.

analysis (if necessary); b) data from national or sub-national surveys, which partly have been collected by the Center for Environmental and Occupational Health of Ministry of Health and Medical Education (CEOH-MOHME) and Institute for Environmental Research (IER), available via National Comprehensive System of Environmental Health Information;[12] and c) other sources, such as data collected by government organizations or by Department of Environment (DOE), or unpublished international, national, and sub-national data. Details of each source(s) are described below.

I. Systematic review

In order to collect exposure data from 1990 to 2013, a systematic review will be conducted following the requirement and decision of technical teams for each risk factor to compile all relevant data. In other words, systematic reviews and meta-analyses will be conducted to obtain RRs of each risk factor attributable to the outcomes, if needed. Meanwhile, if there are credible and reliable recently published systematic reviews and/or meta-analyses, the technical teams may decide to use their results.

Search strategy

Systematic reviews will be conducted mainly through the available online national and international databases and indexing services. The national target databases are Scientific Information Database (SID), IranMedex, and Irandoc. SID is the largest up-to-date Iranian data bank, started in 2004. This database makes it possible to search amongst more than 130,000 and 200,000 Persian and English Iranian articles, respectively. IranMedex contains over 70,000 Iranian articles from about 228 medical/health oriented journals. Irandoc, also, covers more than 120,000 Iranian theses, 15,000 theses of Iranian students who have been graduated in foreign universities, 90,000 research projects, 140,000 Persian articles, 28,000 governmental reports, and 106,000 presented articles in scientific congresses. The international databases are Web of Science, PubMed, and Scopus. To find all relevant data and information, the technical teams will define a detailed search strategy based on Medical Subject Headings (MeSH),[13] Emtree (the Embase thesaurus), and/or other pertaining keywords for each risk factor. The other sources of systematic reviews are: a) abstracts and proceedings of national and international conferences; b) PhD or DSc dissertations and MD, MPH, MSc, or MSPH theses within national relevant departments; c) accepted manuscripts which are published online and are available through some publications; and finally d) complementary data obtained from researchers through contacting the author.

Selection criteria and variables

For international data sources, studies published over 1990 to 2013 will be selected, while for national data sources, those published in the corresponding national calendar year will be included. Each technical team is free to define other selection criteria. The major variables are exposure levels, sample size of studies, health related endpoints, effect size, standard deviation (SD), and confidence interval (CI) or standard error (SE) of the effect for the mentioned risk factors and outcomes.

Quality assessment of the articles

In order to assess the quality of the source(s), two reviewers within each technical team will independently evaluate them and conclude whether they qualify to be involved in the study using critical appraisal instruments. Finally, an expert or the head of each technical team controls and confirms reviewers' decision about involving the collected sources based on the defined selection criteria. If there is a disagreement between the reviewers, the third reviewer will finalize the decision. Noteworthy, each technical team is free to assess the methodology quality of the sources.

II. Other sources

Several databases have measured or estimated the required data, namely CEOH-MOHME, DOE, and Global Burden of Disease (GBD) 2010. So far, we have acquired the data about globally estimated $PM_{2.5}$ and O_3 risk factors in 1990, 2005, and 2010 from the corresponding author of that study, and we have obtained permission to use them for EBD-NASBOD study.[14–15]

Statistical methods and analysis plans

Within the context of our extensive research to access all national and sub-national data, some provinces are expected to lack environmental risk factors exposure data. Additionally, many surveys do not include all age groups, both sexes, and rural/urban areas of residence. Therefore, two distinct statistical models, i.e. spatiotemporal and Bayesian autoregressive multilevel models,[16–17] were developed to estimate mean (whatever the measure is) and its uncertainty interval for each sex, age, year, and province of residence. The models will employ data of a specific age, year, and province along with data from other ages, other years, and other provinces. There exists the issue of misaligned areal units for the provinces separated in the desired period, which will be tackled in both models. We are using two models to verify that the results are not model-dependent.

Spatiotemporal model

We should take into consideration the temporal and spatial correlations, because the majority of environmental exposure data, such as air pollution, noise, etc., will be collected across time and space. One of the conventional frameworks for this type of data is spatiotemporal Bayesian hierarchical modeling with conditional autoregressive prior for spatial random effects.[16] In the spatial framework, it is assumed that the observations closer in space are more correlated than those far in space. Therefore, using this framework, the model is permitted to borrow information from neighboring areal units, which improves the estimates for areas with missing values and/or those with small number of observations. In addition, in order to combine incompatible areal units between data sources and/or over the years, spatiotemporal misalignment modeling will be used, which includes covariates effects, non-linear age trend, and study quality and source of data variations. Finally, this model can arbitrarily accommodate the missing data.

Bayesian Autoregressive Multilevel model

Another advanced method to handle the challenges mentioned earlier is the Bayesian Autoregressive Multilevel model.[17] This framework nests observations hierarchically in districts, provinces, sub-regions, regions, and national levels, respectively. In addition, in this hierarchical model, lower levels borrow information from higher levels; furthermore, depending on the degree of data availability, units of each level lend information to each other. Several components, such as linear time trends, nonlinear change over time, covariate effects, nonlinearity associated with age, heterogeneity of data sources, and age-by-study variability, are included in this model. To offer a natural solution to the mentioned problems, Bayesian autoregressive multilevel model merges information from several data sources and also from available prior information. If necessary, estimates will be obtained using time-varying district-level or province-level covariates.

For both of the abovementioned modeling frameworks, we will use the Markov Chain Monte Carlo (MCMC) method to perform Bayesian inference, due mainly to its general applicability and ease of implementation. All of the programs will be developed in R statistical packages.[18]

In addition to these challenges, another problem is related to the summary statistics reported with different classifications. This problem will be tackled by cross walking between continuous and categorical measures of the target variables.

Ethical considerations

Since the present work is a secondary study, there are no specific ethical considerations. However, the publication of the results will depend on the permission of the study funders. Likewise, Tehran University of Medical Sciences' Institutional Review Board approved this study for ethical considerations.

Discussion

This is the first study on the burden of disease attributable to the major environmental risk factors in Iran using a comparative risk assessment framework. Generally, there are a number of studies that have assessed burden of disease in national or sub-national scales from Australia,[19–22] Ghana,[23] India,[24] Iran,[25–26] Japan,[27] Kenya,[28] Mexico,[29–30] Nairobi,[31] Netherlands,[32–33] New Zealand,[34] Pakistan,[35] South Africa,[36–37] Thailand,[38] UK,[39] USA,[40–41] and Vietnam.[42] Of these, several have included burden of disease attributable to environmental risk factors. In brief, Begg and colleagues (2008) have assessed burden of disease attributable to outdoor air pollution in Australia in 2003. Indeed, they have found that 0.8 % of Australian's health loss (DALYs per 1000 people) due to cancers and 2.7 % due to cardiovascular diseases were attributable to outdoor air pollution.[19] Smith (2000) also reported burden of disease attributable to indoor air pollution from solid fuels in India. In fact, it has been estimated that, roughly 400 – 500 thousand premature deaths annually within subgroups of adult males and children fewer than 5 years old are attributable to indoor air pollution from solid fuels. Consequently, indoor air pollution causes about 4 % – 6 % of total DALYs in India. Smith also reported that approximately 9.6 to 14 million DALYs due to acute respiratory infection, 0.39 to 0.68 million DALYs due to chronic obstructive pulmonary diseases, 0.004 to 0.009 million DALYs due to lung cancer, 0.064 to 0.13 million DALYs due to blindness, and 0.27 to 0.68 million DALYs due to asthma are attributable to indoor air pollution from solid fuels.[24] Noteworthy, as Iran has large natural gas reservoirs, this risk factor has much less contribution in the burden of disease nationwide—it is ranked 20 in 2010 GBD.[43] Overall, the burden of disease in India due to indoor air pollution, which is estimated to be 5.9 % – 9.2 % of total India's BOD, is nearly rivaling poor water, sanitation, and hygiene risk factors.[24] Snow, et al. (1998) also estimated burden of malaria in Kenya and reported that each day approximately 72 – 400 children younger than 5 years old die or develop clinical stages of malaria.[28] In Mexico, Stevens and colleagues (2008) assessed burden of disease due to unsafe water/sanitation/and hygiene, urban and indoor air pollution and found that 1.6 % of total deaths have occurred due to urban air pollution in 2004.[30] The long-term effects of particulate air pollution, in Netherlands, have been estimated to cause 60 % of the total environment-related health loss. Besides, environmental noise and indoor air pollution (including second-hand smoke, humidity, radon, as well as drinking water lead) have been estimated to cause about 4 % and 6 % of total health loss, respectively. Overall, less than 5 % of total annual burden of disease in Netherlands was attributable to the studied environmental risk factors.[32] Additionally, Hänninen and Knol (2011) reported that 3 % – 7 % of the burden of disease in six European countries (Belgium, Finland, France, Germany, Italy, and the Netherlands) is associated with nine environmental risk factors ($PM_{2.5}$, benzene, dioxin and furans, non-smokers exposure to second-hand smoke, formaldehyde, lead, transportation noise, ozone, and radon).[6]

To our best knowledge, some of the selected environmental risk factors in Iran, including O_3, UV Radiation, Drinking Water Fluoride, Climate Change indices and SO_2 have not yet been studied at sub-national levels for their burden of disease using a comparative risk assessment framework. To select these risk factors, we have developed a novel approach, which is described above. Notably, albeit based on GBD 2010 study lead exposure ranked 10 out of 20 among Iran's leading risk factors, based on our developed protocol it was not chosen to be studied in EBD-NASBOD 1990 – 2013 study. This is mainly due to the importance of other unstudied risk factors in the GBD based on the developed protocol and national priorities.

Empirical scientific evidence on the burden of disease attributable to the major risk factors and health status of general population in national or local scales provide a crucial baseline for policy support. Results of EBD study may underscore priority risk factors to be tackled in national or sub-national levels. Meanwhile, one of the most important achievements of the EBD study is that during the progression of the study, flaws of the national health information system will be detected. In other words, we will find out which risk factors and their health endpoints and how, especially in a sub-national scale, should be measured or registered. Finally, we will provide recommendations to improve the national and sub-national health information system. In order to attain the mentioned objectives, especially improving the national health information system, at the end of the study, the EBD and NASBOD contributors will be able to disseminate their knowledge to the whole country levels through presenting workshops, symposiums, and so forth.

The EBD study has some limitations. First, there might be problems regarding missing data, especially for sub-national levels. We will try to impute missing data using statistical methods, or using proxy covariates and extrapolating to each district-year. In the absence of reliable evidence for etiological effects from Iran, large meta-analyses of regional or international cohorts are the best sources of etiological effect sizes but transportability of effects from one population to another may be a weak assumption and depends on similarity of populations with regard to effect modifier and version of exposures.

The EBD will try to determine burden of disease attributable to major environmental risk factors. This achievement will help to broaden our knowledge about the most important risk factors in Iran. We will also determine national and sub-national inequalities in exposure distribution of the selected risk factors and their determinants. This will guide national and sub-national policy makers to invest more on priority risk factors and intervene effectively through cost-effective measures.

Contributors

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Competing interests

All of the authors declare that they have no actual or potential personal or financial competing interests.

Abbreviations

BOD: Burden of Disease; CRA: Comparative Risk Assessment; DALYs: Disability Adjusted Life Years; EBD: Environmental Burden of Disease; GBD: Global Burden of Disease; NASBOD: National and Sub-national Burden of Disease; RR: Relative Risk. YLD: years of Life Lost due to Disebility; YLL: years of Life Lost due to Premature Death.

Authors' contributions

General designing of the paper was by the NASBOD core team and the EBD expert panel. The primary draft was prepared by Hassan Amini and revised by all co-authors. All authors have given approval to the final version of the manuscript.

Acknowledgements

The study is granted by Ministry of Health and Medical Education of Islamic Republic of Iran; Setad-e-ejraie farmane Imam. The authors thank the Institute for Environmental Research's (IER) and Non Communicable Disease Research Center's staff for their wholehearted cooperation. We also acknowledge collaboration of numerous organizations and researchers that provided necessary data to conduct this study. Additionally, the authors extend their sincerest gratitude to Prof. Michael Brauer (School of Population and Public Health, The University of British Columbia, Vancouver, Canada) for providing us with the global ambient air pollution exposure estimates of the GBD 2010 study.

Funding

Institute for Environmental Research (IER), an associated institute of Tehran University of Medical Sciences, has supported financially the Environmental Burden of Disease study. The contract numbers (principal investigator(s)—risk factor) are: 92-01-46-21312 (H Kashani—second-hand smoke); 92-01-46-21327 (M Shamsipour and H Amini—$PM_{2.5}$); 92-01-46-21328 (H Amini and M Shamsipour—O_3); 92-01-46-21339 (M Shamsipour and H Amini—benzene); 92-01-46-21343 (M Mosaferi—drinking water fluoride); 92-01-46-21424 (R Saeedi—unsafe water, sanitation and hygiene); 92-01-46-21472 (MS Hassanvand—dioxins and furans); 92-01-46-21487 (MH Sowlat—UV); 92-01-46-21488 (MH Sowlat—indoor radon); 92-01-46-22067 (P Nowrouz—environmental noise) and 92-01-46-22194 (E Ahmadnezhad—climate change).

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