Contents lists available at ScienceDirect





Environmental Research

journal homepage: www.elsevier.com/locate/envres

Health impacts quantification of ambient air pollutants using AirQ model approach in Hamadan, Iran



Farshad Bahrami Asl^a, Mostafa Leili^{b,*,1}, Yaser Vaziri^a, Soheila Salahshour Arian^c, Antonio Cristaldi^d, Gea Oliveri Conti^d, Margherita Ferrante^d

^a Department of Environmental Health Engineering, Students Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

^b Department of Environmental Health Engineering, School of Health, Hamadan University of Medical Sciences, Hamadan, Iran

^c Urmia University of Medical Sciences, Urmia, Iran

^d Environmental and Food hygiene Laboratories (LIAA)-Department of Medical, Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania,

Catania, Italy

ARTICLE INFO

Keywords: Criteria air pollutants AirQ model Health impacts quantification Hamadan Iran

ABSTRACT

Iranian western cities, including Hamadan, have been experiencing Middle East Dust Storms (MEDS) phenomenon problems in recent years, so the air quality is getting worse every year in these cities. The aim of this study was to evaluate the human health impacts of criteria air pollutants including PM_{10} , $PM_{2.5}$, NO_2 , SO_2 , CO and O_3 on the citizens of Hamadan using AirQ model software 2.2.3. Considering the determined baseline incidence (BI) and relative risk (RR) rate, the attributable proportion (AP) of deaths due to cardiovascular and respiratory mortality attributed to $PM_{2.5}$, PM_{10} , O_3 , NO_2 , and CO pollutants was estimated to be 4.42%, 3.37%, 1.75%, 1.74% and 0.92% (95% CI) of the total mortality and the excess death cases were respectively estimated to be 131.9, 100.4, 52.1, 51.9 and 27.3 persons. In addition, cardiovascular mortality brings more contribution than respiratory mortality in total death number. The results of our study also showed that $PM_{2.5}$ poses the greatest health effects on the citizens. Analyzing the average seasonal concentrations of studied pollutants (PM_{10} , $PM_{2.5}$, and NO_2) and the mean seasonal temperature values revealed a positive linear correlation. Significant negative correlations were observed between the studied pollutants (PM_{10} , $PM_{2.5}$ and NO_2) and relative humidity, and between PM and wind speed. This study, therefore, provides additional data in decision-makings for the development of strategies for reduction of ambient air pollution which will result in improvements of air quality.

1. Introduction

The World Health Organization (WHO) in 2012 estimated that approximately 3.7 million deaths can be attributed to outdoor air pollution each year (WHO, 2014). Acute and chronic impacts of human exposure to the polluted air have been intensively studied by many researchers (Landrigan, 2017; Stewart et al., 2015). Accordingly, many epidemiological studies on Iranian cities about the death's cases due to air pollutants (Landrigan, 2017), environmental particulate matters (Cascio, 2016; Rich, 2017) and mortality and morbidity due to exposure to outdoor air pollution have recently been carried out (Dehghani et al., 2017; Khaniabadi et al., 2017; Miri et al., 2016).

Previous studies showed that even if the concentration of particulate matters (Talbott et al., 2014); photochemical pollutants (Hallquist et al., 2016); urban traffic pollutants (Gauderman et al., 2007; Jerrett et al., 2008) and also, the six common pollutants (named by U.S.EPA

also as "criteria" air pollutants) (Zhao et al., 2017) are lower than the standard or guideline values for air quality, may still cause adverse health impacts. So, the actual national ambient air quality standards (NAAQS) may be unable to adequately protect the sensitive groups from the health impacts of air pollutants.

Although the ambient particulates were the most widely used pollution index among these studies, the gaseous pollutants such as nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃) and carbon monoxide (CO) also have direct impacts on the increased morbidity and mortality rate, hence, the effects of these pollutant have been extensively discussed in the literature (Boyce et al., 2015; Khaniabadi et al., 2017).

Atmospheric particulate matter (PM) may induces serious health hazards during short-and long-term exposure because of it's chemical characteristics (Leili et al., 2008). An increase in severity of mortality, increased rate of respiratory tract infections and incidence of asthma

* Corresponding author.

http://dx.doi.org/10.1016/j.envres.2017.10.050

E-mail addresses: mostafa.leili@gmail.com, m.leili@umsha.ac.ir (M. Leili).

¹ Postal address: School of Public Health, Hamadan University of Medical Sciences, Shaheed Fahmideh Ave., Hamadan 6517838695, Iran.

Received 23 May 2017; Received in revised form 3 October 2017; Accepted 30 October 2017 0013-9351/ © 2017 Elsevier Inc. All rights reserved.

and bronchitis are among the acute health impacts observed at high concentrations of small fractions of particulate matters (PM_{2.5}, with aerodynamic diameter less than 2.5 µm). Furthermore, the PM2.5 directly cause friction in the respiratory tract, blocking the air passages and damage pulmonary mucosal pathways (Griffin, 2016). Several studies have also shown that $PM_{2.5}$ can penetrate into the buildings and negatively affect the indoor air quality (Shahsavani et al., 2011; Wang et al., 2005). Nitrogen oxides (NO_x) are produced by high-temperature combustion processes such as the burning of fuel in motors vehicles and power plants. NO₂ toxicity is several times higher than that of NO and can causes many health impacts in human such as: changes in the tissues of the kidneys, liver and heart: reduced immunity against infectious diseases; and susceptibility to bacterial and viral infections (Griffin, 2016), pulmonary allergies and chronic obstructive pulmonary disease (COPD) (Mohammadi et al., 2016; Temam et al., 2017). Epidemiological studies conducted in the last decade have shown that SO₂induced air pollution can be associated with increased risk of mortality due to respiratory diseases and lung cancer (Yun et al., 2015). Lungs, therefore, are considered as the target organ in SO₂ pollution. Other health issues due to SO₂ exposure include: irritation, loss of mucosal transparency in the air passages and shortness of breath (Vallero et al., 2014).

Carbon monoxide decreases the oxygen-carrying capacity of the blood and disrupts the mechanism of tissue oxygenation by forming carboxyhemoglobin in the blood leading to a reduction in oxygen supply to body and cerebral (Phung et al., 2016; USEPA, 1991). Indeed, some studies show that the exposure to high CO concentrations can cause damage to the central nervous system (CNS) and heart, but it has not been fully proven that how fundamental organs can be disrupted by low concentrations of this pollutant (Hampson et al., 2012). A significant relationship between mortality rate and ambient CO concentrations was observed in a previous study carried out in Toronto, where 4.7% of death cases was attributed to this pollutant (Burnett et al., 1998). Tropospheric O_3 is a reactive molecule able to produce secondary air pollutants and, epidemiological studies have shown to be one of the most toxic among the photochemical air pollutants and it is associated with increasing mortality (Boyce et al., 2015; Khaniabadi et al., 2017; Phung et al., 2016). According to studies carried out on humans and animals, exposure to high levels of O₃ causes inflammation reactions and destruction of lung epithelial cells (Depuydt et al., 2002); hence, it facilitates the respiratory infections and increases the production of pro-inflammatory cytokines from the infected cells especially by rhinovirus 16 (RV16) (Peng et al., 2013).

To evaluate the impacts of different air pollutants on human health, there are different approaches and models, most of which are of epidemiological statistics type which integrate the air quality data with the epidemiological parameters such as relative risk, baseline risk and attributable fraction at different concentrations and depict the results in a form of mortality graphs (Krzyzanowski et al., 2002; Oliveri Conti et al., 2017). However, Air $Q_{2.2.3}$ software is considered one of the valid and reliable tool to estimate the potential health effects of air pollutants, in which information on population exposure-response relationships are combined and then the expected health impacts are estimated. AirQ software 2.2.3 is a validated WHO software that enables users to evaluate potential health impacts arising from exposure to specific pollutants on humans in a specific geographic area in a time period of one year (WHO, 2001). Nowadays a new version is available (AirQ+) (WHO, 2016) but not is still performing for the SO₂ analysis. This software has recently been used in worldwide to quantify air pollutant health impact. The COPD attributed to O₃, NO₂ and SO₂ using AirQ Model in Tabriz, Iran has been evaluated during 2011-2012 and found that these pollutant have a significant impact on COPD hospitalization (Ghozikali et al., 2016). Fattore et al. (2011) estimated the human health risk from O₃, nitrogen dioxide, and particulate matter (PM₁₀) in two municipalities in an industrialized area of Northern Italy, showing that 433, 180, and 72 years of life lost in a year considering long term effects for mortality from all causes, cardiopulmonary diseases and lung cancer, respectively. Miri et al. (2016) have estimated the health impacts due to exposure to outdoor air pollution on the inhabitants of Mashhad, Iran, using the AirQ model approach. The results showed that the total mortality attributed to studied pollutants, including PM_{10} , $PM_{2.5}$, SO_2 , NO_2 and O_3 were 4.24%, 4.57%, 0.99%, 2.21%, 2.08%, and 1.61%, respectively.

Iranian western cities have been experiencing Middle East Dust Storm (MEDS) phenomenon problems in recent years, so the air quality getting worse every year in these cities (Marzouni et al., 2016; Soleimani et al., 2016). Hamadan is a very old Iranian city which was not an exception, in addition, our literature review revealed that health impacts on habitants of Hamadan due to exposure to PM_{10} , $PM_{2.5}$, NO_2 , SO_2 , CO and O_3 have not been systematically studied. Therefore, the aim of our study was to evaluate the health impacts of the listed pollutant in 2014–2015 using the WHO's validated AirQ 2.3.3 software through an ecological study. Furthermore, the effects of some meteorological parameters on air quality have been examined.

2. Materials and methods

2.1. Study area

Hamadan is located in western Iran and believed to be among the oldest Iranian cities, maybe one of the oldest in the world. Nowadays no data are available about the air pollution effects on its citizens. According to the last report of Statistical Center of Iran, its population was 548,000 people, WHOse 35, 000 are 65 years old and over that have been considered for CO impacts assessment. Hamadan province is located between 33° 59' to 35° 44' N latitude and 47° 47' to 49° 28' E longitude. The map of the city is shown in Fig. 1.

2.2. AirQ_{2.2.3} software

In this ecological cross-sectional study, AirQ software 2.2.3 model (WHO) was used to evaluate the health effects and death cases on citizens of Hamadan based on the attributable proportion (AP) to PM_{10} , $PM_{2.5}$, NO_2 , SO_2 , CO and O_3 exposure. AP can be calculated using the following equation (Miri et al., 2016):

$$AP = \left(\sum \{[RR(c) - 1 \times P(c)]\}/(\sum [RR(c) \times P(c)])\right)$$
(1)

where RR(c) and P(c) are the relative risk and the proportion of the target population for a certain health effect in the category "c" of exposure, respiratory (Miri et al., 2016; Naddafi et al., 2012).

If the baseline frequency of the health effect in the target population



Fig. 1. Map of the study area.

is identified, the amount attributable to the population exposure can be obtained by the Eq. (2):

$$IE = I \times AP \tag{2}$$

where, IE and I are the rate of the health effect attributable to the exposure, and the baseline frequency of the health effect in the studied population, respectively. Finally, considering the size of the target population, the total number of excess cases attributable to the exposure can be determined using following equation:

$$NE = IE \times N \tag{3}$$

where NE is the number of cases attributed to the exposure and N is considered as the total number of investigated residents (Gharehchahi et al., 2013; Naddafi et al., 2012). The RR gives the rate of the pollutant's health effects which related to the changes in the exposure to the air pollutants. Considering that so far no time-series study has been done in Iran, up to day, relative risk values that were used in this study are obtained from Fattore et al. (2011) and Naddafi et al. (2012) studies, which they summarize these values mainly from the largest multicity study related to the European population considered as an APHEA project (Gryparis et al., 2004; Samoli et al., 2006), from a quantitative meta-analysis of peer-reviewed studies focused on European investigations (Anderson et al., 2004), along with WHO Air Quality Guidelines for Europe (WHO, 2000). Although the use of RR values that obtained from the studies carried out in other regions may increase prediction error of the model, however, this error can be ignored given that it can provide valuable information on the health effects of air pollutants in the study area for policy-makers in order to minimize the health effects and applying a proper air quality management plan. The base line incidence (BI) was derived from the study conducted by Naddafi et al. (Naddafi and Hassanvand, 2012; Naddafi et al., 2012) in which the baseline rates of all mortality for the calendar year 2010 were obtained from death certificates recorded at the Civil Registration Office of Tehran, Iran but to make sure for accuracy and precision, the obtained values have been compared with those of World Bank values. Regarding that 72% of the Iran's populations were in the age ranges of 15-64 that is considered young population, thus the average BI was about 5 per 1000 people for Iran. The parameters needed for the AirQ model application to quantify the health impacts of air pollutants including the relative risk (RR) and baseline incidence (BI), as well as their various health endpoints are presented in Table 1.

2.3. Air pollution monitoring station data and exposure assessment

The selected pollutants data and the meteorological parameters (temperature, barometric pressure, wind speed, and relative humidity) from March 21, 2014 to March 20, 2015 (Farvardin 01, 1393 to Esfand 29, 1393, according to Persian calendar), was obtained by the air quality monitoring station of Hamadan's Department of Environment (DoE) and by Meteorological Organization, respectively. The air pollutants data were reported in Microsoft Excel file format, so, these data were converted to the format that required by the model. Before analysis, data must be evaluated according to criteria listed by WHO (Naddafi and Hassanvand, 2012; Naddafi et al., 2012; WHO, 2001, 2014). Since, determining the adverse health impacts is related to the mass of inhaled pollutants, in AirQ software data units were converted based on temperature and pressure conditions for the gaseous pollutant, reported on the Microsoft Excel and were later converted based on V-W unit $(g/\mu m^3)$ and then they classified at the intervals of 10 $\mu g/m^3$ (Miri et al., 2016). The required statistical indices, including annual mean, warm season mean, cold season mean, annual 98th percentile of pollutants, annual maximum, warm season maximum and cold season maximum were calculated to enter into the software using Microsoft Excel software after converting the data unit. The 8-h "moving average" and 1 h average have been used for O₃ and NO₂, respectively, and daily average was used for the other pollutants (Table 1). All information on the population required by the model were taken from Statistical Center of Iran. Finally, after entering the processed data in the AirQ software, results were obtained as death cases described in tables and graphs which have subsequently been interpreted.

3. Results and discussion

3.1. Seasonal variation of the studied pollutants

It was evident that ambient weather conditions such as temperature, wind speed, relative humidity, short wave radiation, etc. can influence atmospheric chemical reactions; hence, formation of secondary pollutants or pollutant concentration changes. To show meteorological influence on air quality, the pollutants concentrations in various seasons and temperatures, wind speed, relative humidity and their fluctuations during the sampling period was depicted in Fig. 2. Summary of the measured parameters were also presented in Table 2.

It should be noted that spring, summer, fall and winter are defined

Table 1

Relative risks (RR) with 95% confidence intervals (95% CI) and baseline incidences used in AirQ_{2.2.3} software for the health endpoint estimates.

Health endpoint	Baseline incidence ^a	Pollutant	RR (95% CI) per 10 $\mu g/m^3$ b
Total Mortality	543.5	NO2 ^d	1.003 (1.002–1.004) ^e
		SO_2^{f}	1.004 (1.003-1.0048)
ICD-9-cm < 800 ^c		O ₃ ^g	1.003 (1.002-1.005)
		PM_{10}^{f}	1.006 (1.004-1.008)
		$PM_{2.5}^{f}$	1.015 (1.011-1.019)
Cardiovascular Mortality	231	NO_2^d	1.004 (1.003-1.005)
		SO ₂ ^f	1.008 (1.002-1.012)
ICD-9-cm 390-459		O ₃ ^g	1.005 (1.002-1.007)
		CO ^d	1.007 (1.002-1.012)
		PM_{10}^{f}	1.009 (1.005-1.013)
Respiratory Mortality	48.8	SO ₂ ^f	1.01 (1.006-1.014)
ICD-9-cm 460-519		O ₃ ^g	1.013 (1.007-1.015)
		PM ₁₀ ^f	1.013 (1.005–1.02)

^a Crude rate per 100,000 inhabitants.

^c International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-cm).

^d 1 h average.

^e The values in parentheses represent the low and high Relative risks.

f 24 h average.

g 8 h average "moving average".

^b For CO RR (95%CI) defined per 1 mg/m³.



Table 2Seasonal variation of the studied parameters.

Season	Studied pollutant concentrations (µg/m ³)					
	PM ₁₀	PM _{2.5}	NO_2	SO_2	СО	O ₃
Spring Summer Fall Winter	67.25 80.65 56.78 67.41	40.79 47.90 33.95 41.45	57.21 105.15 41.23 75.12	39.68 23.24 29.27 36.89	1.58 2.6 3.14 2.93	79.40 65.34 70.16 78.58

as beginning on 21 March, 21 June, 21 September and 21 December, respectively. As seen in Fig. 2, PM_{10} , $PM_{2.5}$ and NO_2 concentrations are the highest in summer that experienced higher temperatures and lower wind speed compared to other seasons. Furthermore, one-way ANOVA, followed by the post hoc Tukey's test, and Pearson's correlation coefficient analysis were used to describe the relation between the meteorological variables and the studied pollutants. The analysis of the average seasonal concentrations of studied pollutants (PM_{10} , $PM_{2.5}$, and NO_2) and the mean seasonal temperature values showed a positive linear correlation with the corresponding correlation coefficient values of r = 0.456, 0.455 and 0.353, respectively. The increases in photochemical activity during the days with high temperatures due to increased solar intensity, the lack of enough rainfall, low wind speed and the severity of dust storms experienced in this session (in the case of

Fig. 2. Average seasonal temperatures, wind speed, relative humidity, and mean PM₁₀, PM_{2.5}, NO₂, SO₂, CO and O₃ concentration for the period of sampling.

PM₁₀ and PM₂₅) can cause it (Kartal and Özer, 1998; Leili et al., 2008; Maleki et al., 2016; Marzouni et al., 2016). A significant negative correlation was observed only for SO₂ and temperature (P = 0.008, r =-0.721). The lowest and highest mean of SO₂ concentrations were measured during summer and spring, and we found significant differences between mean concentration during spring, winter and summer (P < 0.05). Igarashi et al. (2004) measured higher winter concentration of SO₂ than the summer. Akpinar et al. (2008) were also investigated the effects of meteorological conditions on the SO₂ concentration and found the maximum concentration at colder air temperature of around 0 °C. Wind speed considered as one of the most important meteorological parameters that affects and control pollutant concentrations. Pearson's correlation coefficient analysis results showed a negative correlation between PM, including both PM_{10} (r = -0.317), $PM_{2.5}$ (r = - 0.328), and wind speed, because dispersion or dilution of the polluted air are controlled by wind speed and its directions. Similar results were observed in the study conducted by Akpinar et al. (2008) and Marcazzan et al. (2001). Post hoc Tukey's analysis of NO₂ concentration during the studied seasons showed that fall and summer have the lowest and highest concentrations and the difference was significant (P < 0.05). In the case of ozone, maximum 1 h concentration in wintertime was slightly higher than the summertime, which this atmospheric condition has only recently been documented (Kalabokas et al., 2013; Ooka et al., 2011), and it is mainly due to increasing use of home heaters and increasing level of CO in the wintertime (Ghanbari

Table 3

Required statistical indexes for model to estimate attributable deaths to criteria air pollutants exposure.

Statistical Index	PM ₁₀ (μg/m ³)	PM _{2.5} (µg/m ³)	$NO_2 (\mu g/m^3)$	SO ₂ (μg/m ³)	CO (mg/m ³)	O_3 (µg/m ³)
Annual mean	68	41	69	32	2.5	73
Winter mean	62	37	58	33	3	74
Summer mean	73	44	81	31	2	72
Annual 98th percentile	133	80	179	59	6	104
Annual maximum	200	120	220	80	9	144
Winter maximum	200	120	182	80	9	144
Summer maximum	172	103	220	44	5	111

Pollutant	Standard values	Averaging period	Pollutant concentration/ Standard values
PM ₁₀	A: 50 (μg/m ³)	24 h	1.36
	B: 150 (μg/m ³)	24 h	0.45
PM _{2.5}	B: 35 (μg/m ³)	98th percentile of 24 h	2.28
NO_2	A & B: 200 (μg/m ³)	98th percentile of Maximum daily 1 h	0.9
SO_2	A: 125(μg/m ³)	24 h	0.25
	B: 400 (μg/m ³)	24 h	0.08
O ₃	A: 120 (μg/m ³)	Maximum daily 8 h	1.2
	B: 150 (μg/m ³)	Maximum daily 8 h	0.96
CO	B: 40 (mg/m ³)	1 h	0.02

Table 4

Ratios of studied pollutants concentration to the standard values*.

A: European Union Standards (2016).

B: U.S. EPA-National Ambient Air Quality Standards (NAAQS).

* Iran's Department of Environment also adhere and implement the U.S. EPA national ambient air quality standards for criteria air pollutants.

Ghozikali et al., 2014).

Significant negative correlations were observed between studied pollutants, PM₁₀, PM_{2.5}, NO₂, concentration with relative humidity (P < 0.05) with the corresponding correlation coefficient values of -0.723, -0.733 and -0.580, respectively, since it controls the rate of absorption of pollutants (Kartal and Özer, 1998). Moreover, the results showed a linear correlation between PM₁₀ and PM_{2.5} (r =1) and between PM and NO₂ (r = 0.424) concentrations.

3.2. AirQ model analysis

Data validation have shown the validity of results. All indicators required by the model were reported in Table 3. The provided values were determined according to the processing steps that well described in other similar studies (Ghanbari Ghozikali et al., 2014; Naddafi and Hassanvand, 2012). The seasonal variation of the pollutants that presented in Tables 2, 3, were described in previous section. The calculated annual average values were also compared with available guideline values and standards (Table 4). Both the number of excess cases and the attributable proportions (percent) for the health impacts of the six pollutants that obtained by the AirQ software are summarized in Table 5.

From the Table 4, we observed that PM₁₀ and SO₂ concentrations were respectively 1.36 and 0.25 times greater than the EUS and the average annual concentration of PM2.5 and NO2 were 2.28 and 0.9 times greater than both EUS and NAAQS. Also, 1 h CO concentration was 40 mg/m³ (0.017 times greater than NAAQS). Regarding O₃, pollutant concentration/standard values ratios for maximum daily 8-h concentration were respectively 1.2 and 0.96 time greater than the EUS and NAAQS of 120 and 150 μ g/m³. These results represent the undeniable contribution of these pollutants on the total mortality and death cases caused by cardiovascular diseases (see Table 5). However, some authors reported harmful health impacts of pollutants at lower concentration than the common air pollution guidelines, which indicates that the available standards may not been sufficiently protective from the public health point of view (Mamta and Bassin, 2010; Ozcan, 2012). Our results showed that during the study period, the highest PM₁₀, PM_{2.5}, SO₂ concentrations (on 24-h average); NO₂, CO concentrations (on 1-h average); and O₃ concentrations (on 8-h average) were respectively in the ranges of $60-69 \,\mu g/m^3$, $40-49 \,\mu g/m^3$, 20–29 μ g/m³, 40–49 μ g/m³, < 1 μ g/m³ and 70–79 μ g/m³, respectively.

Relative risks were determined and were reported for every $10 \mu g/m^3$ increases in pollutants concentration at three levels of lower (5%), central (50%) and upper (95%) categories of the relative risk (Table 1). To explain this parameter, for example, one can say that by taking into account central relative risk for a every $10 \mu g/m^3$ increases in the PM₁₀, PM_{2.5}, NO₂, O₃ and SO₂ concentration, the relative risk of total death cases will be increased by 0.6%, 1.5%, 0.3%, 0.3% and 0.4%,

Table 5

Estimated Attributable Proportion (AP) and number of excess cases in a year due to short-term exposure to criteria pollutants.

Health Endpoint	Pollutant	Relative Risk	Estimated AP (%)	Estimated number of excess cases
Total Mortality	NO_2	Lower	1.17	34.8
		Central	1.74	51.9
		Upper	2.31	68.7
	SO_2	Lower	0.69	20.5
		Central	0.92	27.3
		Upper	1.1	32.7
	O ₃	Lower	1.17	34.9
		Central	1.75	52.1
		Upper	2.88	85.8
	PM_{10}	Lower	2.27	67.7
		Central	3.37	100.4
		Upper	4.44	132.3
	PM _{2.5}	Lower	3.29	97.9
		Central	4.42	131.9
		Upper	5.54	165.1
Cardiovascular	NO_2	Lower	1.74	22
Mortality		Central	2.31	29.2
		Upper	2.87	36.3
	SO_2	Lower	0.46	5.8
		Central	1.81	23
		Upper	2.7	34.2
	O ₃	Lower	1.17	14.8
		Central	2.88	36.5
		Upper	3.99	50.5
	CO	Lower	0.09	0.2
		Central	0.31	0.5
		Upper	0.54	0.9
	PM_{10}	Lower	2.82	35.7
		Central	4.97	62.9
		Upper	7.02	88.9
Respiratory	SO_2	Lower	1.37	3.7
Mortality		Central	2.26	6
		Upper	3.13	8.4
	O ₃	Lower	3.99	10.7
		Central	7.16	19.1
		Upper	8.17	21.9
	PM_{10}	Lower	2.82	7.6
		Central	7.02	18.8
		Upper	10.41	27.8

respectively. As seen in Table 5 and according to the baseline incidence and central relative risk values given in Table 1, the attributable proportion (AP) estimated for total number of deaths attributable to $PM_{2.5}$, PM_{10} , O_3 , NO_2 , and SO_2 pollutants were respectively 4.42, 3.37, 1.75, 1.74, 0.92% (95% CI) of the total mortality and the corresponding excess cases of death were estimated 131.9, 100.4, 52.1, 51.9 and 27.3 persons, respectively. The AP estimated for total number of deaths caused by cardiovascular diseases attributed to PM_{10} , O_3 , NO_2 , SO_2 , and



Fig. 3. Relationship between cumulative number of cardiovascular mortality and atmospheric pollutants concentration of A) CO, B) NO₂, C) O₃, D) PM₁₀, and E) SO₂.

CO pollutants were respectively 4.97%, 2.88%, 2.31%, 1.81% and 0.31% (95% CI) of the total mortality and corresponding excess death cases were respectively estimated 62.9, 36.5, 29.2, 23 and 0.5 persons (see Fig. 3 and Table 5). Regarding respiratory mortality, AP for total number of deaths associated with O_3 , PM_{10} , and SO_2 were estimated respectively 7.16%, 7.02%, and 2.26% (95% CI) of the total mortality with the excess death cases of 19.1, 18.8, and 6 person, respectively (Table 5).

A literature review showed that in the Kinney and Özkaynak (1991) study, the relative risk for total mortality was about 0.26% for a 10 μ g/m³ increases in NO₂ concentration. Goudarzi et al. (2015) also reported the relative risk (central RR category) of 1% and 0.44% for every 10 μ g/m³ increases in SO₂ concentration for the total number of, respectively, respiratory and hospitalization death cases due to COPD. In the other study, Goudarzi et al. (2013) assessed the health impacts of NO₂ on Tehran residents and found that about 3.4% of total cases of death

attributed to cardiovascular diseases, heart attacks and hospital admissions due to COPD by NO₂ exposure having concentrations more than 60 μ g/m³. Miri et al. (2016) carried out a similar study in Mashhad city, northeastern Iran, and reported that 4.24%, 4.57%, 0.99%, 2.21% and 2.08% of non-accidental deaths were attributed to PM₁₀, PM_{2.5}, SO₂, NO₂ and O₃, respectively.

The relationship between the cumulative number of total deaths caused by cardiovascular diseases attributable to the different concentrations of these pollutants along with upper, central and lower domains of relative risk have been shown in Fig. 3. Results tabulated in Table 5 and Fig. 3 showed that $PM_{2.5}$ and PM_{10} have had a greater effect on total, cardiovascular and respiratory mortality rates. Furthermore, $PM_{2.5}$ excess cases and attributable proportion estimated for all death cases were higher respect to PM_{10} , because $PM_{2.5}$ is more toxic than larger particles (Cifuentes et al., 2000; T. Burnett et al., 2000) due to its characteristics and higher ability to penetrate into the respiratory

tract (Dockery et al., 1993).

A study carried out by the researchers of Harvard University on PM_{2.5} in six cities of United States (Dockery et al., 1993), showed that the annual average concentration of this pollutant was 18 μ g/m³, which is far less than the average concentration obtained in Hamadan. Results of Naddafi and colleagues study were consistent with our study, where they found that PM10 and PM2.5 accounted for largest contribution of health impacts attributed to air pollutants in Tehran, and the number of total death cases attributed to $PM_{2.5}$ and PM_{10} were estimated 2318 and 2194 cases, respectively, which accounted for 4.74% and 4.6% of all deaths in Tehran, respectively (excluding deaths from accidents) (Naddafi et al., 2012). Another study conducted in United States showed that a decrease in PM2.5 concentration was associated with reduced mortality rate. It was also found that for each $10 \,\mu\text{g/m}^3$ increases in average PM2.5 concentration, 2732 excess deaths would be expected (Laden et al., 2006). The results of a study on impacts of daily or short-term exposure to pollutants in two industrial cities in northern Italy showed that PM2.5, with an attributable fraction of 4.5%, accounted for 8 deaths out of 177 deaths per year for a population of 24,000 citizens and had the greatest effect among the studied pollutants (Fattore et al., 2011). Tominz et al. (2004) investigated health impacts of PM₁₀ in Trieste, Italy, using the AirQ software and found that 1.8% of all cardiovascular deaths has been attributed to concentrations higher than 20 µg/m³. Goudarzi et al. (2013) evaluated the health impacts of NO2 pollutant in Ahvaz (Iran) and reported that the cumulative number of cases of myocardial infarction and cardiovascular deaths have estimated 9 and 19 persons, respectively. Ghanbari Ghozikali et al. (2014) concluded in his paper that for every $10 \,\mu g/m^3$ increase in O₃ concentration, total risk of death (considering upper limit relative risk) was also increased by 0.45%.

According to Fig. 3, the increase of NO₂ concentrations leads to increasing also of adverse effects with a gentle slope; however, adverse effects of other pollutants increased with a steep slope only up to a concentration of about 40–50 μ g/m³, and then it was almost constant. Therefore, it can be concluded that NO₂ concentration distribution is wider than other pollutants.

Our study provide for the first time data on health impacts on Hamadan residents by exposure to six criteria air pollutants. However there are some limitations: health impacts were estimated based on a single pollutant exposure and every pollutant act as an indicator of a mixture of several pollutants but the impacts of one pollutant are actually not independent of other pollutants in a pollutants mixture. In fact, interactions between different contaminants have been ignored in quantitative assessments of health effects. Thus, studies on the impacts of pollutants on each other and changes in their impacts on humans have been carried out and still are required (Ibald-Mulli et al., 2004; Sillanpaa et al., 2004; Ying et al., 2013; Yun et al., 2015). Franklin et al. (2007) investigated the relationships between PM_{2.5} and all-causes and specific-causes of mortality in the US communities and found an univariate association between particulate matter and mortality, but, it is not confounded by other pollutants. The second limitation was due to the RR estimations, as they derived from different studies with different climate and demographic characteristics. The third limitation is arisen from populations and individual differences between various regions while they have also been ignored in this model. The last limitation is due to considering a single sampling site for the measurement of all parameters, together with a few mobile sampling point only for PM₁₀ and PM_{2.5}, as a representative to conduct the target population average exposure assessment. Regarding that the concentrations that were measured in sampling stations are representative of the average exposure of the people and the uniform exposure is the very basic assumption of this approach in quantifying the health impacts and there are variability in exposure within the city, so the establishment of further sampling stations in different areas made the results more reliable and made the corresponding health effects estimation will be more realistic.

4. Conclusions

AirQ model software is considered the most suitable tool for quantification of the deterministic effects of air pollution, so, it was used to estimate the air pollution effects on Hamadan inhabitants. Overall, PM2.5 and PM10 showed the greatest health impact on the Hamadan citizens. Their concentration in 248 days out of 346 days, during which the data were recorded, have been exceeded from available standards. It was observed that PM2.5 and SO2 pollutants concentrations were respectively 1.36 and 0.25 times greater than the EUS and the average annual concentration of PM_{2.5} and NO₂ were 2.28 and 0.9 times greater than both EUS and NAAOS. Our findings suggest that even at current ambient concentrations. PM air pollution continues to pose a public health risk because it's concentrations continue to rise. According to the BI and RR values, the AP estimated for total number of deaths attributable to $PM_{2.5}$, PM_{10} , O_3 , NO_2 , and SO_2 pollutants in Hamadan were respectively 4.42%, 3.37%, 1.75%, 1.74% and 0.92% and the corresponding excess cases of death were estimated as 131.9, 100.4, 52.1, 51.9 and 27.3 persons, respectively. Pearson's correlation coefficient analysis results showed that PM10, PM2.5 and NO2 concentrations and the mean seasonal temperature values have a positive linear correlation. A negative correlation were observed between SO₂ and temperature, and between PM concentrations and wind speed. The findings of our study are in line with those of other studies conducted in other countries, and despite the mentioned limitations, have indicated that this model explore many benefits which could be helpful in decision-making and air quality management program.

Acknowledgements

The authors would like to thank the Hamadan University of Medical Sciences and Hamadan's Department of Environment (HDoE) for providing us the required data of studied pollutants and all other people WHO have contributed in this study. The authors are grateful to Dr. Salvatore Napoli for suggestions about the paper's formatting.

References

- Akpinar, S., Oztop, H.F., Akpinar, E.K., 2008. Evaluation of relationship between meteorological parameters and air pollutant concentrations during winter season in Elazığ, Turkey. Environ. Monit. Assess. 146 (1–3), 211–224.
- Anderson, H.R., Atkinson, R.W., Peacock, J.L., Marston, L., Konstantinou, K., 2004. Meta-Analysis of Time Series Studies of Particulate Matter (PM) and Ozone (O3). WHO Europe Report of a WHO task group (EUR/04/5042688).
- Boyce, C.P., Goodman, J.E., Sax, S.N., Loftus, C.T., 2015. Providing perspective for interpreting cardiovascular mortality risks associated with ozone exposures. Regul. Toxicol. Pharm. 72 (1), 107–116.
- Burnett, R.T., Brook, J., Dann, T., Delocla, C., Philips, O., Cakmak, S., et al., 2000. Association between particulate-and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal. Toxicol. 12 (sup4), 15–39.
- Burnett, R.T., Cakmak, S., Raizenne, M.E., Stieb, D., Vincent, R., Krewski, D., et al., 1998. The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manag. Assoc. 48 (8), 689–700.
- Cascio, W.E., 2016. Proposed pathophysiologic framework to explain some excess cardiovascular death associated with ambient air particle pollution: insights for public health translation. Biochim. Biophys. Acta (BBA)-Gen. Subj. 1860 (12), 2869–2879.
- Cifuentes, L.A., Vega, J., Köpfer, K., Lave, L.B., 2000. Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago. Chile. J. Air Waste Manag. Assoc. 50 (8), 1287–1298.
- Dehghani, M., Keshtgar, L., Javaheri, M.R., Derakhshan, Z., Oliveri Conti, G., Zuccarello, P., et al., 2017. The effects of air pollutants on the mortality rate of lung cancer and leukemia. Mol. Med. Rep. 15 (5), 3390–3397.
- Depuydt, P., Lambrecht, B., Joos, G., Pauwels, R., 2002. Effect of ozone exposure on allergic sensitization and airway inflammation induced by dendritic cells. Clin. Exp. Allergy 32 (3), 391–396.
- Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., et al., 1993. An association between air pollution and mortality in six US cities. N. Engl. J. Med. 329 (24), 1753–1759.
- Fattore, E., Paiano, V., Borgini, A., Tittarelli, A., Bertoldi, M., Crosignani, P., et al., 2011. Human health risk in relation to air quality in two municipalities in an industrialized area of Northern Italy. Environ. Res. 111 (8), 1321–1327.
- Franklin, M., Zeka, A., Schwartz, J., 2007. Association between PM_{2.5} and all-cause and specific-cause mortality in 27 US communities. J. Expo. Sci. Environ. Epidemiol. 17 (2), 279–287.

- Gauderman, W.J., Vora, H., McConnell, R., Berhane, K., Gilliland, F., Thomas, D., et al., 2007. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet 369 (9561), 571–577.
- Ghanbari Ghozikali, M., Mosaferi, M., Nadafi, K., 2014. Quantification of the health effects of exposure to ozone in tabriz by using AIRQ model. Urmia Med. J. 25 (6), 521–530.
- Gharehchahi, E., Mahvi, A.H., Amini, H., Nabizadeh, R., Akhlaghi, A.A., Shamsipour, M., et al., 2013. Health impact assessment of air pollution in Shiraz, Iran: a two-part study. Iran. J. Environ. Health Sci. Eng. 11 (1), 11–19.
- Ghozikali, M.G., Heibati, B., Naddafi, K., Kloog, I., Conti, G.O., Polosa, R., et al., 2016. Evaluation of chronic obstructive pulmonary disease (COPD) attributed to atmospheric O₃, NO₂, and SO₂ using Air Q Model (2011–2012 year). Environ. Res. 144, 99–105.
- Goudarzi, G., Mohammadi, M., Ahmadi Angali, K., Mohammadi, B., Soleimani, Z., Babaei, A., et al., 2013. Estimation of number of cardiovascular death, myocardial infarction and Chronic Obstructive Pulmonary Disease (COPD) from NO₂ exposure using Air Q Model in Ahvaz city during 2009. Iran. J. Health Environ. 6 (1), 91–102.
- Goudarzi, G.R., Geravandi, S., Salmanzadeh, S., Mohammadi, M.J., 2015. An estimation of respiratory deaths and COPD related to SO₂ pollutant in Tabriz, northwest of Iran (2011). Razi J. Med. Sci. 22 (131), 44–50.

Griffin, R.D., 2016. Principles of Air Quality Management. CRC Press.

- Gryparis, A., Forsberg, B., Katsouyanni, K., Analitis, A., Touloumi, G., Schwartz, J., et al., 2004. Acute effects of ozone on mortality from the "air pollution and health: a European approach" project. Am. J. Respir. Crit. Care Med. 170 (10), 1080–1087. Hallquist, M., Munthe, J., Hu, M., Wang, T., Chan, C.K., Gao, J., et al., 2016.
- Photochemical smog in China: scientific challenges and implications for air-quality policies. Natl. Sci. Rev (nww080).
- Hampson, N.B., Piantadosi, C.A., Thom, S.R., Weaver, L.K., 2012. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am. J. Respir. Crit. Care Med. 186 (11), 1095–1101.
- Ibald-Mulli, A., Timonen, K.L., Peters, A., Heinrich, J., Wölke, G., Lanki, T., et al., 2004. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. Environ. Health Perspect. 112 (3), 369–377.
- Igarashi, Y., Sawa, Y., Yoshioka, K., Matsueda, H., Fujii, K., Dokiya, Y., 2004. Monitoring the SO₂ concentration at the summit of Mt. Fuji and a comparison with other trace gases during winter. J. Geophys. Res.: Atmos. 109 (D17), 1–21.
- Jerrett, M., Shankardass, K., Berhane, K., Gauderman, W.J., Künzli, N., Avol, E., et al., 2008. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ. Health Perspect. 116 (10), 1433–1438.
- Kalabokas, P.D., Cammas, J.P., Thouret, V., Volz-Thomas, A., Boulanger, D., Repapis, C.C., 2013. Examination of the atmospheric conditions associated with high and low summer ozone levels in the lower troposphere over the eastern Mediterranean. Atmos. Chem. Phys. 13 (20), 10339–10352.
- Kartal, S., Özer, U., 1998. Determination and parameterization of some air pollutants as a function of meteorological parameters in Kayseri, Turkey. J. Air Waste Manag. Assoc. 48 (9), 853–859.
- Khaniabadi, Y.O., Goudarzi, G., Daryanoosh, S.M., Borgini, A., Tittarelli, A., De Marco, A., 2017. Exposure to PM₁₀, NO₂, and O₃ and impacts on human health. Environ. Sci. Pollut. Res. 24 (3), 2781–2789.
- Kinney, P.L., Özkaynak, H., 1991. Associations of daily mortality and air pollution in Los Angeles County. Environ. Res. 54 (2), 99–120.
- Krzyzanowski, M., Cohen, A., Anderson, R., 2002. Quantification of health effects of exposure to air pollution. Occup. Environ. Med. 59 (12), 791–793.
- Laden, F., Schwartz, J., Speizer, F.E., Dockery, D.W., 2006. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am. J. Respir. Crit. Care Med. 173 (6), 667–672.
- Landrigan, P.J., 2017. Air pollution and health. Lancet Public Health 2 (1), e4-e5.
- Leili, M., Naddafi, K., Nabizadeh, R., Yunesian, M., Mesdaghinia, A., 2008. The study of TSP and PM10 concentration and their heavy metal content in central area of Tehran, Iran. Air Qual. Atmos. Health 1 (3), 159–166.
- Maleki, H., Sorooshian, A., Goudarzi, G., Nikfal, A., Baneshi, M.M., 2016. Temporal profile of PM 10 and associated health effects in one of the most polluted cities of the world (Ahvaz, Iran) between 2009 and 2014. Aeolian Res. 22, 135–140.

Mamta, P., Bassin, J., 2010. Analysis of ambient air quality using air quality index-A case study. Int. J. Adv. Eng. Technol. 1 (2), 106–114.

- Marcazzan, G.M., Vaccaro, S., Valli, G., Vecchi, R., 2001. Characterisation of PM_{10} and $PM_{2.5}$ particulate matter in the ambient air of Milan (Italy). Atmos. Environ. 35 (27), 4639–4650.
- Marzouni, M.B., Alizadeh, T., Banafsheh, M.R., Khorshiddoust, A.M., Ghozikali, M.G., Akbaripoor, S., et al., 2016. A comparison of health impacts assessment for PM₁₀ during two successive years in the ambient air of Kermanshah, Iran. Atmos. Pollut. Res. 7 (5), 768–774.
- Miri, M., Derakhshan, Z., Allahabadi, A., Ahmadi, E., Conti, G.O., Ferrante, M., et al., 2016. Mortality and morbidity due to exposure to outdoor air pollution in Mashhad

metropolis, Iran. The AirQ model approach. Environ. Res. 151, 451–457.

- Mohammadi, A., Azhdarpoor, A., Shahsavani, A., Tabatabaee, H., 2016. Investigating the health effects of exposure to criteria pollutants using AirQ2.2.3 in Shiraz, Iran. Aerosol Air Qual. Res. 16 (4), 1035–1043.
- Naddafi, K., Hassanvand, M.S., 2012. Quantification of Health Effects of Tehran Air Pollution in 2011–2012. Air Pollution Research Center (APRC). Institute for Environmental Research, Tehran University of Medical Sciences, pp. 2011–2012.
- Naddafi, K., Hassanvand, M.S., Yunesian, M., Momeniha, F., Nabizadeh, R., Faridi, S., et al., 2012. Health impact assessment of air pollution in megacity of Tehran, Iran. Iran. J. Environ. Health Sci. Eng. 9 (1), 28–35.
- Oliveri Conti, G., Heibati, B., Kloog, I., Fiore, M., Ferrante, M., 2017. A review of AirQ Models and their applications for forecasting the air pollution health outcomes. Environ. Sci. Pollut. Res. 24 (7), 6426–6445.
- Ooka, R., Khiem, M., Hayami, H., Yoshikado, H., Huang, H., Kawamoto, Y., 2011. Influence of meteorological conditions on summer ozone levels in the central Kanto area of Japan. Procedia Environ. Sci. 4, 138–150.
- Ozcan, H.K., 2012. Long term variations of the atmospheric air pollutants in Istanbul city. Int. J. Environ. Res. Public Health 9 (3), 781–790.
- Peng, R.D., Samoli, E., Pham, L., Dominici, F., Touloumi, G., Ramsay, T., et al., 2013. Acute effects of ambient ozone on mortality in Europe and North America: results from the APHENA study. Air Qual. Atmos. Health 6 (2), 445–453.
- Phung, D., Hien, T.T., Linh, H.N., Luong, L.M., Morawska, L., Chu, C., et al., 2016. Air pollution and risk of respiratory and cardiovascular hospitalizations in the most populous city in Vietnam. Sci. Total Environ. 557, 322–330.
- Rich, D.Q., 2017. Accountability studies of air pollution and health effects: lessons learned and recommendations for future natural experiment opportunities. Environ. Int. 100, 62–78.
- Samoli, E., Aga, E., Touloumi, G., Nisiotis, K., Forsberg, B., Lefranc, A., et al., 2006. Shortterm effects of nitrogen dioxide on mortality: an analysis within the APHEA project. Eur. Respir. J. 27 (6), 1129–1138.
- Shahsavani, A., Yarahmadi, M., Jafarzade Haghighifard, N., Naimabadie, A., Mahmoudian, M.H., Saki, H., et al., 2011. Dust Storms: environmental and Health impacts. J. North Khorasan Univ. Med. Sci. 2 (4), 45–56.
- Sillanpaa, M., Frey, A., Hillamo, R., Salonen, R., 2004. Particulate elemental carbon and organic matter during contrasting urban air pollution situations in Europe (PAMCHART). J. Aerosol Sci. 35 (Suppl. 2), S1081–S1082.
- Soleimani, Z., Goudarzi, G., Sorooshian, A., Marzouni, M.B., Maleki, H., 2016. Impact of Middle Eastern dust storms on indoor and outdoor composition of bioaerosol. Atmos. Environ. 138, 135–143.
- Stewart, J.A., Mitchell, M.A., Edgerton, V.S., VanCott, R., 2015. Environmental Justice and Health Effects of Urban Air Pollution. J. Natl. Med. Assoc. 107 (1), 50–58.
- Talbott, E.O., Rager, J.R., Benson, S., Brink, L.A., Bilonick, R.A., Wu, C., 2014. A casecrossover analysis of the impact of PM_{2.5} on cardiovascular disease hospitalizations for selected CDC tracking states. Environ. Res. 134, 455–465.
- Temam, S., Burte, E., Adam, M., Antó, J.M., Basagaña, X., Bousquet, J., et al., 2017. Socioeconomic position and outdoor nitrogen dioxide (NO₂) exposure in Western Europe: a multi-city analysis. Environ. Int. 101, 117–124.
- Tominz, R., Mazzoleni, B., Daris, F., 2004. Estimate of potential health benefits of the reduction of air pollution with PM₁₀ in Trieste, Italy. Epidemiol. e Prev. 29 (3–4), 149–155.
- USEPA, 1991. Air Quality Criteria for Carbon Monoxide. Washington, DC. Publication No: EPA – 600/B- 90/045F.
- Vallero, D., Boubel, R.W., Fox, D.L., Turner, B., Stern, A.C., 2014. Fundamentals of Air Pollution, 5th edition. Academic Press.
- Wang, Y.Q., Zhang, X.Y., Arimoto, R., Cao, J.J., Shen, Z.X., 2005. Characteristics of carbonate content and carbon and oxygen isotopic composition of northern China soil and dust aerosol and its application to tracing dust sources. Atmos. Environ. 39 (14), 2631–2642.
- WHO (World Health Organization Regional Office for Europe Copenhagen), 2000. Air Quality Guidelines for Europe, Second ed. WHO Regional Publications.
- WHO, 2001. Quantification of Health Effects of Exposure to Air Pollution: Report on a WHO Working Group. Bilthoven, Netherlands, 20–22 November 2000.
- WHO, 2014. Burden of disease from Ambient Air Pollution for 2012. World Health Organization, Geneva.
- WHO, AirQ+. (http://www.euro.who.int/en/health-topics/environment-and-health/airquality/activities/airq-software-tool-for-health-risk-assessment-of-air-pollution). 2016.
- Ying, Z., Xu, X., Chen, M., Liu, D., Zhong, M., Chen, L.-c., et al., 2013. A synergistic vascular effect of airborne particulate matter and nickel in a mouse model. Toxicol. Sci. 135 (1), 72–80.
- Yun, Y., Gao, R., Yue, H., Li, G., Zhu, N., Sang, N., 2015. Synergistic effects of particulate matter (PM₁₀) and SO₂ on human non-small cell lung cancer A549 via ROS-mediated NF-κB activation. J. Environ. Sci. 31, 146–153.
- Zhao, R., Chen, S., Wang, W., Huang, J., Wang, K., Liu, L., et al., 2017. The impact of short-term exposure to air pollutants on the onset of out-of-hospital cardiac arrest: a systematic review and meta-analysis. Int. J. Cardiol. 226, 110–117.