Long-Term Exposure to PM2.5 and Cardiovascular Disease Incidence and Mortality in an Eastern Mediterranean Country: Findings based on a 15-Year Cohort Study

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Research

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Abstract

Background

Evidence concerning impact of long-term exposure to fine Particulate Matter<2.5 mm ($PM_{2.5}$) on Cardio-Vascular Diseases (CVDs) for those people subject to ambient air pollution in developing countries remains quite scant. This study assessed the relationship of 15-year $PM_{2.5}$ exposure and cardiovascular incidence and mortality rate in Isfahan province, Iran.

Methods

The cohort comprised 3081 participants over 35 years old and free of CVDs. They were selected through multi-stage cluster sampling in Isfahan, Iran. $PM_{2.5}$ exposure for each individual was determined using satellite-based spatiotemporal estimates according to their residential addresses. CVD is defined here as fatal and non-fatal Acute Myocardial Infarctions (AMI) or stroke and sudden cardiac death. The risk of CVD incidence and mortality was calculated based on average $PM_{2.5}$ exposure within a study period of 15 years using the Cox proportional hazard model upon adjusting individual risk factors. Annual averages of $PM_{2.5}$ and the follow-up data of each residential area were combined.

Results

Mean three-year $PM_{2.5}$ exposure was 45.28 µg/m3 in the cohort, ranging from 20.01 to 69.80 µg/m3. The median follow-up was 12.3 years for the whole population. It is notable that 105 cardiovascular and 241 all-cause deaths occurred among 393,786 person months (27 and 61 per 100,000 person months, respectively). In well-adjusted models, 10 µg/m3 increase in $PM_{2.5}$ corresponded to a 4% increase in the incidence rate of CVDs [0.95 CI=1.022, 1.054] (given p=0.0000014 per 10 µg/m3 increase in $PM_{2.5}$, the Hazard Ratio (HR) for AMI was 1.073 [0.95 CI=1.029, 1.119] and Ischemic Heart Disease (IHD) was 1.052 [0.95 CI=1.034, 1.071]. No consistent association was found between $PM_{2.5}$ concentration and CVD deaths (fatal AMI, fatal stroke, and SCD (Sudden Cardiac Death)).

Conclusions

The final results revealed that long-term exposure to ambient $PM_{2.5}$ with high concentrations correlated with IHD incidence and its major subtypes positively, except for mortality. This finding supports the already found pieces of evidence that $PM_{2.5}$ contributes to the high susceptibility of people in the eastern Mediterranean region to cardiovascular diseases after 15 years. The outcome accentuates the need for better air quality in many countries.

Background

The present ambient air pollution concentrations correspond too many different detrimental health effects including mortality and morbidity because of CVD. According to the epidemiological findings specific to western countries, elevated ambient particulate matter < 2.5 mm ($PM_{2.5}$) leads consistently to CVD incidence and death [1]. The fine particulate matter calculated as 2.5 $\mu g/m^3$ or less ($PM_{2.5}$) is closely in association with myocardial infarction, thrombosis, and stroke [2]. The mean of air pollutant concentrations in the USA [3] and European [4] countries is much lower than eastern Asia [5]. It should be noted that eastern Asia is subject to frequent Asian dust events from industrial facilities and the Gobi Desert in Central Asia, reportedly producing over 20% of the total global dust emissions through westerly wind [6, 7]. Over 90% of the world's population inhabit areas whose air quality exceeds the annual mean $PM_{2.5}$ standard defined at 10 $\mu g/m^3$ by the World Health Organization [8].

Furthermore, concentration-responsive detrimental impacts of long-term $PM_{2.5}$ exposure on cardiovascular mortality rates in countries exposed to higher air pollution levels have not been thoroughly investigated. Therefore, it is crucial to scrutinize the effects of such exposure carefully and develop fitting preventive strategies to reduce risks for the community.

Assessments formulated and performed in line with the Global Burden of Disease initiative demonstrate that ambient air pollution impacts the mortality rate significantly more than other major risk factors such as high cholesterol, high sodium intake, and low physical activity [9].

Nearly 50% of these estimated attributable deaths result from ischemic heart disease and stroke, to which countries with low and medium income and high outdoor $PM_{2\cdot5}$ levels are primarily subject [10].

Most air-pollution studies enjoying a large cohort have failed to make adjustments for detailed individual level risk factors (e.g., SES, health-related behaviors, or healthcare access) that may confound the associations between $PM_{2\cdot5}$ and CVD.

The aging population in conjunction with the fast-paced urbanization are contributing to the prevalence of cardiovascular diseases in Iran.

Based on the statistics obtained from the Iranian Journal of Cardiovascular Nursing, cardiovascular diseases were the most common cause of death in most countries including Iran in 2013; to be specific, cardiovascular disease cases were 172 (78.5%) in urban and 47 (21.5%) in rural areas with a steadily rising trend [11].

Precise assessment of $PM_{2.5}$ exposure can be carried out for medical studies using satellite data. The satellite observations measure the earth's optical radiations while the radiation affected by the aerosols. There are physical and acceptable statistical models to calculate PM2.5 density from the satellite observation [12].

The present study performs an inclusive study using a population-based cohort in order to find the relationship of long-term $PM_{2.5}$ exposure and all-cause mortality with CVD mobility and mortality. In addition, it investigates if a specific $PM_{2.5}$ concentration rate that could be closely associated with increased risks of mortality exists. Subgroup analysis is carried out to study the $PM_{2.5}$-induced mortality in accordance with cardiovascular comorbidities.

Backed by the datasets obtained from satellite-based high-quality $PM_{2.5}$ estimates with a 1×1 km spatial resolution as well as the prediction records of Cardiovascular Disease Risk in Iran (Isfahan Cohort Study (ICS)—an established prospective project), this study studies the connection between long-term ambient $PM_{2.5}$ exposure and the incidence of and mortality from CVDs, by subtypes and overall. It is hoped that findings will further conventional understanding of global impacts of $PM_{2·5}$-induced air pollution on CVDs as they capture different population communities subject to a wide range of $PM_{2·5}$ concentrations on a global scale and include standardized objective measures for CVD risk factors.

Materials And Methods

Study population

Isfahan Cohort Study (ICS) was employed to investigate the incidence of CVD and the corresponding risk factors involved for Iranian population. A full description of study design was published elsewhere. Briefly, ICS was conducted in Isfahan, Najafabad, and Arak, all located in central Iran. In ICS, subjects aged at least 35 years old without CVD who lived in one of these three cities were included. In this study, the data of Isfahan and Najafabad were employed because we could access the addresses and study their association with $PM_{2.5}$. A total of 3081 adults were initially enrolled for baseline examination from both rural and urban areas in Isfahan and Najafabad. Multi-stage cluster random sampling was employed to select participants in terms of gender, age, and residence status distribution (urban/rural). They were followed up for major cardiovascular events every two years from 2001 to 15 years later by phone calls and verbal autopsy and for measuring risk factors and complete physical examination every 5 years [13].

Risk factors measurements

Similar methods at baseline and follow-up surveys were applied for selecting all participants. Professional healthcare staff were given a standardized questionnaire to glean data on personal characteristics, medical history, and lifestyle risk factors. Smoking statuses are classified by smokers (one cigarette a day at least), ex-smokers (one cigarette a day in the past at least), and non-smokers. Participants' fasting blood samples (10 ml) were acquired to gauge their total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDLC), and triglycerides. The ratio of LDL to HDL was divided into three categories: Normal (< 5.4), Borderline (5.4-7), and Abnormal (> 7). In case of FBS ≥ 126 mg/dl or taking oral hypoglycemic agents, diabetes was considered [14]. The anthropometric parameters including height and weight were measured by standard protocol. Obesity, overweight, and normal weight constitute the Body Mass Index: (BMI) ≥ 30 kg/m^2, 25 ≤ BMI < 29.9 kg/m^2, and BMI < 24.9 kg/m^2 [15].

Systolic and diastolic blood pressure rates were calculated by trained personnel in line with standard protocols. Based on the WHO definition, people with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 or hypertensive drug users were assumed hypertensive [16].

A validated Food Frequency Questionnaire (FFQ) was employed to evaluate participants' dietary behaviors [17]. The Mediterranean diet pattern was considered here as a protective regime against CVD mortality (healthy diet behavior, maintaining and enhancing the general body health, providing the body with the necessary nutrients, fluids, amino acids and fatty acids, vitamins and minerals, as well as calories, and meeting basic body needs without the risk of causing overweight or ill), while other dietary patterns were assumed to be characterized by poor dietary behavior [18].

A validated International Physical Activity Questionnaire (IPAQ) was employed here to assess physical activity [19] which was divided into three categories: low (less than 600 Met-min/Week), medium (at least 600 Met-min/Week), and high (at least 3000 Met-min/Week) [18].

This research was endorsed by Isfahan University of Medical Sciences and approved by the Health Sciences Research Ethics Board with code number 399099. Written informed consent was received from each participant before data collection.

Outdoor $PM_{2·5}$ Air Pollution Exposure Assessment

A satellite-based spatiotemporal model was used to measure ambient $PM_{2.5}$ levels at a spatial resolution of 1×1 km. $PM_{2.5}$ modeling refers to those within Land Use Regression (LUR) models that have drawn much attention in recent years because of their critical role in understanding and assessing air pollution [12, 20].

We use MODIS (Moderate Resolution Imaging Spectroradiometer) aerosol product MOD04 and MAIAC (Multi-Angle Implementation of Atmospheric Correction algorithm) which is a multispectral sensor onboard two Terra and Aqua satellites. The satellites overpass the study area about 10:30 and 13:30 local time every day [21]. The statistical model to convert statistical observations to PM2.5 is referenced from Kong et al. [22].

Three-year rolling average $PM_{2·5}$ estimates were available for the years 2001, 2007, and 2013 at an approximate resolution of 1x1 km.

Outcomes

Total CVD events included fatal and non-fatal Acute Myocardial Infraction (AMI), fatal and non-fatal stroke, Sudden Cardiac Death (SCD), and Unstable Angina (UA). Fatal cardiovascular disease was defined as an illness resulting from fatal strokes, fatal MIs, and sudden cardiac death in our study [13]. Ischemic Heart Disease (IHD) included MI, definitive or probable UA, and SCD. Diagnosis of stroke which is a permanent neurological disorder for at least 24 hours complied with the definition put forward by the World Health Organization [13]. Two distinct groups of experts, made up of four cardiologists and

neurologists, managed to review all patient records (original questionnaires, medical records, secondary interviews, verbal autopsy, or death certificates) to make final decisions on the CVD events and subtypes. Total CVD, CVD Deaths, stroke, AMI, ACS, and IHD were included separately in different models.

Statistical Analysis

A description of the baseline characteristics of the participants was given based on means and standard deviation for continuous variables and percentages of categorical variables. This study modeled the associations between ambient $PM_{2.5}$ levels and CVD events using Cox Proportional Hazards frailty models with R 4.0.3 software. Baseline explanatory variables and 3-year mean $PM_{2·5}$ levels were used in different model strategies. Annual $PM_{2.5}$ averages were combined with the annual follow-up of individuals in each residential area. In the multivariate adjusted Cox models, a priori hypothesized covariates that could potentially confound the relation between $PM_{2.5}$ concentration and CVD was incorporated. We added the following four models using the covariates gathered at baseline.

Model 1 includes such clusters as age, gender, geographic area (urban/rural status), and living areas as random effects (according to the national population census conducted blocks). These census blocks were randomly selected from each county with a probability of selection proportional to the expected number of households and were divided into clusters of approximately 1000 households. Nearly 5–10% of the households were randomly selected for enumeration in each cluster.

Model 2 incorporates individual risk factors (smoking status, physical activity, healthy eating index, obesity, Social Economic Status (SES), and hypertension).

Subjects were purposefully assigned to different multiple clusters. Factors varying across clusters may have significant and distinct influence on the outcomes of CVDs. Accordingly, independent variables cannot explain all the variability in the observed time-to-event outcome. In the analysis of multistage cluster sampling with time-to-event outcome, the shared frailty model is a viable and attractive tool employed to address the heterogeneity of clusters or urban/rural areas.

However, given that the proposed analysis was used to examine a wide range of PM2·5 exposures for the populations living in diverse clusters and urban/rural communities, we conducted extensive sensitivity analyses to evaluate unmeasured characteristics that might modify the associations between PM2·5 levels and individual CVD risk. In some cases, we ran models with random effect by clusters and urban/rural areas. This model controls possible variations in the sampling strategy by different centers and urban/rural areas. Another strategy entails including a “fixed effect” to clusters or urban/rural areas; this strategy controls the unmeasured factors between centers and, therefore, relies primarily on PM2·5 variation in each center.

Model 3 is similar to Model 2 in that clusters have fixed effects with the urban/rural status as random effect.

Model 4 is further adjusted in terms of diabetes, total cholesterol, triglycerides, LDL-to-HDL ratio, history of heart disease in the family, urban/rural status fixed effect, and cluster random effect.

Kaplan Meyer survival curves were drawn for all CVD fatal and non-fatal events, CVD mortality, AMI, and non-fatal stroke. In addition, the participants were categorized into three groups according to $PM_{2.5}$ tertiles (i.e., < 38.20, 38.20–51.60, and > 51.60 $\mu g/m^3$). Considering $PM_{2.5}$ a continuous variable here, we reported the hazard ratio (HR) of CVD incidence in Model 6. Adjusted HRs and the confidence intervals of 95% (CIs) were presented per 10 $\mu g/m^3$ increase in $PM_{2·5}$.

Results

Over a 15-year course of following up with the 3081 subjects, we found 241 deaths, among which 105 were CVD deaths (fatal AMI, fatal stroke, and SCD). There were 441 CVD events (fatal and non-fatal incidence of AMIs and strokes) comprising 73 AMIs and 92 strokes. The mean (SD) three-year $PM_{2.5}$ concentration at the study baseline was 45.28 $\mu g/m^3$ (11.63), ranging from a low of 20.01 $\mu g/m^3$ in Najafabad to a high of 69.80 $\mu g/m^3$ in Isfahan. There was a substantial variation in individual and geographic characteristics by $PM_{2·5}$ levels (Table 1). For example, 2429 (78.8%) of the study participants were urban dwellers, among whom 983 (95.8%) of the subjects were exposed to the lowest $PM_{2·5}$ tertile, 825 (80.4%) to the middle tertile, and 621(60.3%) to the highest $PM_{2·5}$ tertile. In addition, the difference between current smokers and cholesterol variables in different tertiles was significant, while the difference between current smokers and other variables in different tertiles was not significant.

Table 1
Summary of individual characteristics for the 3081 participants across long-term $PM_{2.5}$ exposure tertiles.

		$PM_{2.5}$ ($\mu g/m^3$) Tertiles			p-value
	All Study Participants	T1 (< 38.2041)	T2 (38.2041–51.6069)	T3 (> 51.6069)	
No. Individuals	3081	1026	1026	1029	
No. Clusters	37	26	35	32	
No. Events [a]	1060	307	300	453	
Age($\bar{x}$, sd)	49.55(11.57)	50.11(11.72)	49.56(11.54)	48.99(11.43)	0.090
Female (%)	1589(51.6)	556(54.2)	517(50.4)	516(50.1)	0.121
Low SES (%)	1045(33.9)	323(31.5)	344(33.5)	378(36.7)	0.079
Current Smoker (%)	517(16.8)	144(14.0)	188(18.3)	185(18.0)	0.049
Low Physical Activity (%)	772(25.1)	267(26.0)	270(26.3)	235(22.8)	0.373
Poor diet (%)	296(9.6)	109(10.6)	89(8.7)	98(9.5)	0.320
BMI					0.399
Overweight [b] (%)	1223(40.7)	425(42.2)	387(38.8)	411(41.0)	
Obesity [c] (%)	774(25.7)	260(25.8)	270(27.1)	244(24.3)	
History of heart disease in the family (%)	162(5.3)	52(5.1)	45(4.4)	65(6.3)	0.138
Hypertension [d] (%)	771(25.0)	266(25.9)	238(23.2)	267(25.9)	0.254
Diabetes (%)	233(7.6)	80(7.8)	84(8.3)	69(6.8)	0.422
Cholesterol ($\bar{x}$, sd)	217.85(50.22)	215.80(48.71)	221.63(49.11)	216.16(52.56)	0.014
Triglycerides ($\bar{x}$, sd)	203.82(124.14)	204.53(127.50)	202.15(128.60)	204.76(116.11)	0.872
Normal LDL to HDL ratio (%)	2710(97.6)	901(97.8)	904(97.1)	905(97.7)	0.425
Urban (%)	2429(78.8)	983(95.8)	825(80.4)	621(60.3)	< 0.001

[a] CVD Death(n = 105) + Major CVD Events(n = 441) + AMI(n = 73) + Stroke(n = 92) + IHD(n = 349)

[b] $25 \leq$ Body Mass Index $< 29.9 \raisebox{1ex}{\$kg\$} \left/ \raisebox{-1ex}{\$m^2\$} \right.$

[c] Body Mass Index $\geq 30 \raisebox{1ex}{\$kg\$} \left/ \raisebox{-1ex}{\$m^2\$} \right.$

[d] Diastolic Blood Pressure > 90 mmHg or Systolic Blood Pressure > 140 mmHg or if the patients were receiving antihypertensive drugs

Model results of mortality and CVD events are presented in Table 2. In Model 1, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was significantly associated with an HR of 1.024 (0.95 CI = 1.015, 1.033) for CVD, which was reduced to 1.025 (0.95 CI = 1.016, 1.034) in Model 2. When the random effect of geographical variable was added (Model 3), the value of HR was reduced to 1.039 (0.95 CI = 1.025, 1.054) for CVD events. In the fully adjusted models (Model 4), the most significant association was observed for AMIs and the HR of 1.031 (0.95 CI = 1.005, 1.057) and for IHDs and the HR of 1.028 (0.95 CI = 1.017, 1.039). No risk associations were observed between $PM_{2.5}$ and CVD mortality.

Table 2
Associations between outdoor $PM_{2.5}$ exposure with mortality and CVD events.

	n	Events	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
CVD Death [a]	3081	105	0.995(0.978,1.013)	0.955(0.977,1.012)	0.970 *(0.94 5,0.997)	0.998(0.979,1.017)	0.965 * (0.936,0.995)	0.997(0.978,1.0
Major CVD Events [b]	3081	441	1.024 * (1.015,1.033)	1.025 * (1.016,1.034)	1.039 * (1.025,1.054)	1.026(1.016,1.036)	1.038 * (1.022,1.054)	1.026 * (1.016,1.036)
AMI [c]	3081	73	1.019 (0.997,1.041)	1.019 (0.997,1.041)	1.045 * (1.009,1.082)	1.031 * (1.005,1.057)	1.073 * (1.029,1.119)	1.030 * (1.005,1.057)
Stroke	3081	92	1.018 (0.999,1.037)	1.017 (0.999,1.036)	0.998(0.971,1.026)	1.018 (0.999,1.039)	0.999(0.971,1.028)	1.018 (0.998,1.038)
IHD [d]	3081	349	1.026 * (1.016,1.037)	1.027 * (1.017,1.038)	1.053 * (1.036,1.070)	1.028 * (1.017,1.039)	1.052 * (1.034,1.071)	1.028 * (1.017,1.039)

Model 1: $PM_{2.5}$, age, sex, urban/rural status fixed effect and cluster random effect.

Model 2: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, SES, hypertension status, urban/rural status fixed effect and cluster random effect.

Model 3: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, SES, hypertension status, cluster fixed effect and urban/rural status random effect.

Model 4: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, SES, hypertension status, diabetes, cholesterol, triglycerides, LDL to H ratio, History of heart disease in the family, urban/rural status fixed effect and cluster random effect.

Model 5: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, SES, hypertension status, diabetes, cholesterol, triglycerides, LDL to H ratio, History of heart disease in the family, cluster fixed effect and urban/rural status random effect.

Model 6: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, hypertension status, diabetes, cholesterol, triglycerides, LDL to HDL ratio, History of heart disease in the family, cluster random effect and urban/rural status random effect.

[a] Death from cardiovascular causes and myocardial infarction, stroke, and heart failure, each sub-category includes fatal and non-fatal events.

[b] CHD + stroke

[c] Acute myocardial infarction

[d] MI + SCD + UAP

* Statistically significant (0.05)

According to the results of performed geographic sensitivity analyses, especially upon the inclusion of cluster fixed effect and urban/rural status random effect (model 5), we observed increased associations between some outcomes with the most significant changes in the values of AMI and IHD. Herein, the HR value per 10 μg/m^3 increase in $PM_{2.5}$ was 1.073 (0.95 CI = 1.029, 1.119) for AMIs and 1.052 (0.95 CI = 1.034, 1.071) for IHDs. For CVD events, the estimated value of HR increased to 1.038 (0.95 CI = 1.022, 1.054) per 10 μg/m^3 increase in $PM_{2.5}$, which was higher than those obtained by the previous four models. In Model 6, the risk ratio for each event was reduced more than that in Model 5.

Sub-group analyses for CVD mortality, CVD, AMI, and stroke events revealed modest differences in terms of individual and geographic characteristics (Table 3). Across CVD mortality, CVD events, and MI and stroke, men older than 60 years, current smokers, individuals with comorbidity diseases, and individuals with a history of heart disease in the family respectively experienced higher HRs associated with $PM_{2.5}$ exposures (p for heterogeneity < 0·05). The highest HRs were observed for CVD mortality among individuals older than 60 years (HR: 6.943, 0.95 CI = 4.182, 11.527 per 10 μg/m^3 increase in $PM_{2.5}$) (p for heterogeneity < 0·05).

Table 3. Sub-group analyses by individual and clinical variables for the associations of $PM_{2.5}$ with CVD events and separately for AMI and Stroke.

	CVD Death	CVD Events	Forest plot for all CVD fatal and non-fatal events	AMI Events	Stroke Events
$PM_{2.5}$	0.997(0.978,1.016)	1.026 *(1.016,1.036)		1.030 *(1.005,1.057)	1.018 (0.998,1.038)
Gender					
Female	Ref.	Ref.		Ref.	Ref.
Male	1.712 *(1.020,2.873)	1.351 *(1.051,1.735)		2.167 *(1.148,4.090)	1.153(0.678,1.958)
Age					
≤60	Ref.	Ref.		Ref.	Ref.
>60	6.943 *(4.182,11.527)	2.524 *(2.005,3.177)		1.903 *(1.045,3.468)	4.687 *(2.880,7.628)
Smoking Status					
Never smoker	Ref.	Ref.		Ref.	Ref.
Ever smoker	1.336(0.803,2.221)	1.411 *(1.07,1.817)		1.410(0.755,2.634)	1.577(0.926,2.687)
Physical Activity					
Low	Ref.	Ref.		Ref.	Ref.
Moderate	0.870(0.548,1.379)	0.889(0.701,1.127)		1.193(0.639,2.228)	0.926(0.574,1.495)
High	0.402 *(0.193,0.837)	0.627 *(0.457,0.859)		0.402(0.157,1.032)	0.435*(0.205,0.920)
Healthy Eating Index					
Poor diet	Ref.	Ref.		Ref.	Ref.
Healthy diet	1.104(0.551,2.211)	1.087(0.778,1.520)		0.692(0.324,1.478)	1.067(0.530,2.148)
Hypertension Status					
No	Ref.	Ref.		Ref.	Ref.
Yes	1.809 *(1.161,2.818)	1.783 *(1.431,2.223)		1.394(0.782,2.485)	1.924 *(1.210,3.059)
Diabetes					
No	Ref.	Ref.		Ref.	Ref.
Yes	3.964 *(2.437,6.448)	2.238 *(1.675,2.991)		3.650 *(1.877,7.099)	3.255 *(1.888,5.611)
Cholesterol	1.003(0.998,1.008)	1.002 *(1.000,1.005)		1.010 *(1.005,1.015)	0.997(0.992,1.002)
Triglycerides	0.997(0.994,1.001)	1.000(0.999,1.002)		0.998 (0.994,1.001)	1.000(0.997,1.003)
LDL to HDL ratio					
Unnormal	Ref.	Ref.		Ref.	Ref.
Borderline	0.335(0.032,3.498)	1.625(0.205,12.849)		-	-
Normal	0.145(0.016,1.319)	1.252(0.170,9.253)		-	-
Obesity					
No	Ref.	Ref.		Ref.	Ref.
Yes	0.865(0.478,1.563)	1.125(0.877,1.443)		1.022(0.529,1.974)	1.508(0.902,2.520)
History of heart disease in the family					
No	Ref.	Ref.		Ref.	Ref.
Yes	1.133(0.540,2.378)	1.109(0.754,1.630)	0 5 10	1.037(0.367,2.925)	0.978(0.420,2.280)

Model 6: $PM_{2.5}$, age, gender, smoking status, physical activity, healthy eating index, obesity, hypertension status, diabetes, cholesterol, triglycerides, LDL to HDL ratio, History of heart disease in the family, cluster random effect and urban/rural status random effect.
* Statistically significant (0.05).

Figure 1 shows that the probability of survival decreases over time for CVD events and the corresponding subgroups (CVD death, AMI events, and stroke events).

In some subgroups, an increase in $PM_{2.5}$ maximized the risk of CVD (Forest plot). Significantly higher trends of increased risk of CVD among men, older subjects (60 years), subjects with a history of hypertension, diabetes, and cholesterol were seen, given these groups were at a high risk of CVD occurrence. For example, these correlations were maximized for smokers rather than non-smokers [HR was 1.411 (0.95 CI = 1.07, 1.817)] (Forest plot).

Discussion

Given alarming concerns over the detrimental air pollution effects on human health are increasing, the issue has drawn a greater deal of academic research on a global scale, implying that air pollution, especially $PM_{2.5}$, is among the most significant causes of cardiovascular diseases and death [23].

PM is of particular importance due to its specific characteristics such as composition and size distribution. This pollutant is characterized by a very high surface area and can adsorb many diverse organic materials such as polycyclic aromatic hydrocarbons, nitro-polycyclic aromatic hydrocarbons, heavy metals, pathogens, and radioactive materials. It contains very fine particles that penetrate into the lower respiratory system and also the blood as well as migrate to other organs, even brain [24].

According to the WHO recommendation, long-term exposure to extreme levels of $PM_{2.5}$, over 10–25 μg/m³, can potentially impair coagulation process, reduce inflammation, damage blood vessels, and eventually cause cardiovascular disease. Several pathways that could help justify the strong link between $PM_{2.5}$ and cardiovascular diseases were identified [25, 26].

In Europe, $PM_{2.5}$ concentration in the air of urban areas has been increasing, and some recent cohort studies have approved the relation between long-term $PM_{2.5}$ exposure and increased mortality rate. Such studies have confirmed the strong correlation between PM concentration and the number of hospital admissions due to heart and respiratory problems [27]. Similar studies have been carried out worldwide (China, Italy, and Mexico) to determine the short-term effects of PM using the AirQ model [28, 29, 30].

According to the findings of Hoek et al., the pooled effect estimate expressed as excess risk per 10 μg/m3 increase in $PM_{2.5}$ exposure was 6% (0.95 CI = 4–8%) for all-cause mortality and 11% (0.95 CI = 5–16%) for cardiovascular mortality [11].

Chen et al. (2008) conducted a systematic review of the relationship between long-term exposure to ambient pollution and chronic diseases and found that such $PM_{2·5}$ exposure would increase the risk of cardiovascular mortality by nearly 12–14% per 10-μg/m3 increase in $PM_{2·5}$, independent of age, gender, and geographic region [31].

The existence of vast deserts in the surrounding areas and so many large industries in the suburb of Isfahan city have made this city one of the most polluted cities in Iran [32].

High $PM_{2.5}$ levels in Isfahan can be attributed to the growing emergence of deserts and mines, especially lead and zinc mines, as well as energy conversion sectors such as power plants and oil refineries around the city. In addition to the above, in Isfahan province, wind direction changes seasonally, meaning that the wind blows from west to east except in summer. Due to the adaptation of wind currents to the degraded areas caused by the activities of gypsum, clay, sand mines as well as related industries in more than 12,900 hectares (6800 hectares of gypsum and 6100 hectares of clay and sand), a significant impact on air quality, especially due to the concentration of suspended particles, in Isfahan was observed. Further to this, experts' estimates and the study of the amount of dust and suspended particles in the main stations of Isfahan indicated that more than 30% of the increase in dust in summer resulted from the workings of local centers. These particles are produced in the east and through summer winds [33].

According to the results given in Table 1, 78.8% of the cohort population lived in the city; however, in the third tertile, this number was 60.3% and the difference between the two mentioned values was significant. Regional characteristics of Isfahan are the cause of the higher percentage of $PM_{2.5}$ concentration in the nearby rural areas. Based on the information collected and the results of the project, Mazloumi et al. identified the eastern and northeastern regions of Isfahan as the most polluted areas with a large number of nearby rural areas. This phenomenon occurring in the suburbs can be attributed to the proximity of these areas to such areas as Sajzi, Nain, Gavkhoni swamps. Sajzi and Nain are desert areas that have remained subject to wind erosion and due to the prevailing wind direction in these areas blowing from east to west in summer, considerable suspended particles move towards the city and cause air pollution. Gavkhoni Wetland, an area to which excess water from the Zayandeh River has been flowing in recent years and a place for trapping suspended particles, has dried up due to reduced rainfall and improper farming and irrigation methods; thus, it has become a breeding ground for dust particles. Also, the existence of sand mines and brick kilns located in the east and northeast of the city (villages around Isfahan) is an important generating source of dust particles polluting the air of Isfahan [34].

In ICS comprising 3081 adults living in 37 clusters across Isfahan province, long-term outdoor $PM_{2·5}$ exposure corresponded to increased major CVD events. Our findings reveal new information on the relationship between ambient $PM_{2·5}$ exposure and CVD over a wide range of $PM_{2.5}$ concentrations (20.01 to 69.80 μg/m^3) and in diverse areas and urban/rural populations while adjusting an extensive set of individual, household, and community CVD risk factors.

A recent meta-analysis has pinpointed 53 studies on long-term PM2·5 and mortality, among which only six were conducted outside of North America and Europe and the mean PM2·5 concentration was 15·7 μg/m3 in all these studies. The weighted mean $PM_{2·5}$ concentration for world's population in 2017 was 46 μg/m3 with over 54% of them living in areas above 35 μg/m3, i.e., the WHO Interim Target-1 [10]. To date, only three CVD studies have been conducted at high PM2·5 concentrations, all in China, and the mortality rate estimated per 10% increase in PM2·5 at a mean exposure of 10 μg/m3 was a 14·6% (0.95 CI = 12·5–16·7%) increase in CVD mortality. They also identified low risk at higher PM2·5 concentrations [35]. In our study, we observed the mean (SD) 3-year $PM_{2·5}$ concentration of 45.28 μg/m^3 (11.63) and the HR value of 1.026 (0.95 CI = 1.016, 1.036) per 10 μg/m^3 increase in $PM_{2·5}$ for all CVD events (Table 2). These estimates were considerably smaller than those cited above from the meta-regression analyses and might be justified by the constraints in our study and the level of covariate adjustment compared to the previous studies.

In the study of Abdolahnejad et al., Relative Risk (RR) demonstrated the increased risk resulting from exposure to pollutants, as obtained through time-series experiments. They evaluated the daily connection of air pollution and health effects, such as mortality due to cardiovascular and respiratory diseases. In Isfahan, after each 10 μg/m3 increase in the pollutant amount, the value of RR per increase in the total mortality induced by $PM_{2.5}$ was 0.5% [36]. In our study, per 10 μg/m3 increase in $PM_{2.5}$, HR was 0.997 ((0.95 CI = 0.978, 1.016); therefore, we did not observe any evidence of a risk association between the mentioned $PM_{2.5}$ increase and CVD death.

Tertile models (Table 4) demonstrated a strong, steadily increasing exposure-response relationship for CVD deaths, CVD events, MI, and stroke in the model and then, $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, hypertension status, diabetes, cholesterol, triglycerides, LDL-to-HDL ratio, history of heart disease in the family, cluster random effect, and urban/rural status random effect were adjusted. In the fully adjusted model, only CVD events and stroke demonstrated a significant strong dose-response relationship: HRs related to the 3rd tertile of $PM_{2·5}$: 1.652 (0.95 CI = 1.269, 2.150) for all CVD events and 1.791 (0.95 CI = 1.036, 3.097) for stroke events. Taken together, our study results reinforce the evidence of increased CVD risk, especially for stroke, at high $PM_{2·5}$ concentrations; however, this relationship is not significant.

Table 4
Sub-group analyses by individual and clinical variables for the associations of tertiles of $PM_{2.5}$ versus CVD events and separately for AMI and Stroke.

	CVD Death	CVD Events	AMI Events	Stroke Events
Tertiles of $PM_{2.5}$				
1st Tertile	Ref.	Ref.	Ref.	Ref.
2nd Tertile	0.796(0.472,1.345)	0.982(0.748,1.289)	0.941(0.470,1.884)	1.005(0.567,1.784)
3rd Tertile	1.239(0.729,2.106)	1.652 *(1.269,2.150)	1.583(0.806,3.111)	1.791 *(1.036,3.097)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	1.795 *(1.068,3.018)	1.394 *(1.084,1.793)	2.242 *(1.185,4.242)	1.208(0.709,2.058)
Age				
≤ 60	Ref.	Ref.	Ref.	Ref.
> 60	6.995 *(4.218,11.601)	2.497 *(1.984,3.142)	1.871 *(1.027,3.409)	4.624 *(2.844,7.518)
Smoking Status				
Never smoker	Ref.	Ref.	Ref.	Ref.
Ever smoker	1.299(0.780,2.162)	1.401*(1.089,1.802)	1.407(0.753,2.629)	1.536(0.902,2.615)
Physical Activity				
Low	Ref.	Ref.	Ref.	Ref.
Moderate	0.847(0.533,1.344)	0.859(0.677,1.090)	1.138(0.609,2.127)	0.890(0.550,1.439)
High	0.387 *(0.186,0.808)	0.612 *(0.446,0.840)	0.389 *(0.151,0.999)	0.421 *(0.199,0.892)
Healthy Eating Index				
Poor diet	Ref.	Ref.	Ref.	Ref.
Healthy diet	1.101(0.549,2.207)	1.091(0.780,1.525)	0.697(0.327,1.489)	1.063(0.528,2.138)
Hypertension Status				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.832 *(1.177,2.853)	1.754*(1.407,2.185)	1.376(0.773,2.448)	1.914 *(1.206,3.039)
Diabetes				
No	Ref.	Ref.	Ref.	Ref.
Yes	4.179 *(2.555,6.833)	2.278 *(1.705,3.045)	3.688 *(1.897,7.169)	3.375 *(1.952,5.838)
Cholesterol	1.003(0.998,1.009)	1.003 *(1.000,1.005)	1.010 *(1.005,1.015)	0.997(0.992,1.002)
Triglycerides	0.997(0. 994,1.000)	1.000(0.999,1.002)	0.998(0.994,1.001)	1.000(0.997,1.003)
LDL to HDL ratio				
Unnormal	Ref.	Ref.	Ref.	Ref.
Borderline	0.440(0.041,4.682)	1.512(0.192,11.141)	-	-
Normal	0.184(0.020,1.708)	1.190(0.161,8.778)	-	-
Obesity				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.904(0.498,1.638)	1.141(0.889,1.465)	1.027(0.531,1.988)	10541(0.921,2.580)
History of heart disease in the family				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.066(0.507,2.242)	1.100(0.748,1.618)	1.044(0.371,2.942)	0.965(0.415,2.247)

Model 6: $PM_{2.5}$, age, sex, smoking status, physical activity, healthy eating index, obesity, hypertension status, diabetes, cholesterol, triglycerides, LDL to HDL ratio, History of heart disease in the family, cluster random effect and urban/rural status random effect.

* Statistically significant (0.05).

In addition to the diverse geographical population and large $PM_{2·5}$ concentration range, the ICS is unique in its depth of individual variables available to adjust the potential confounding factors. Besides the long-term follow-up (15 years), ICS considered a range of sociodemographic, behavioral, metabolic, and clinical variables that affect CVD, an issue that most large cohort studies examining air pollution did not measure [34].

In the analysis controlling for center urban and rural random effects (Model 5, Table 2), we observed a substantial change in the estimated HR for AMI and IHD, implying the existence of unmeasured important factors at the center level for the two above events.

From the results, one can conclude that long-term outdoor $PM_{2·5}$ is a significant contributing factor in CVD in Iran. This research enjoys a number of advantages including a longitudinal study with the 15-year follow-up, enough number of samples and comprehensive outcomes, and sufficient urban and rural population exposed to high PM2·5 concentrations for the whole study period, uniform assessment of long-term PM2·5 exposure using estimation methods, objective measurement of a comprehensive suite of individual CVD risk factors, and standardized collection of data on household and community characteristics, and prospective recording of fatal and non-fatal events that were evaluated through standard definitions. Further to the above, our research was subject to potential limitations. We could not control the acute (i.e., daily) variations in $PM_{2·5}$ exposures and their impacts. Further, we assigned $PM_{2·5}$ to study communities, representing neighborhoods in urban areas and small villages in rural areas. While it is unlikely that outdoor $PM_{2·5}$ concentrations would vary substantially over such small areas, some exposure misclassifications exist that could bias estimates towards the null.

Models were sensitive to geographical adjustments as we compared PM2·5 concentrations and CVD events across different areas. While residual confounding cannot be ruled out, we adjusted more individual CVD risk factors than previous studies; the analyses controlling for unmeasured factors between centers using random effects demonstrated larger estimates of the effect. We could not examine specific causes of non-CVD deaths due to the smaller number of events, but these analyses can be done in the future with additional follow-up and more events.

Conclusions

Our study showed that long-term ambient PM2·5 exposure was associated with the increased risk of CVDs including AMI and strokes. Our data support the assumption that PM2·5 is an important risk factor for CVD.

Limitations

Our study was subject to the following limitations. First, $PM_{2.5}$ was not considered in relation to ground stations in the proposed statistical models, because available data did not amount to 15 years and also, they were not satisfactory in terms of quality. Second, there was lack of data on indoor air pollution sources such as household use of solid fuels, which are not common in this area in Iran. Third, the exposure to ambient $PM_{2.5}$ was estimated based on the participants' residential addresses regardless of their daily activities and location.

Abbreviations

$PM_{2.5}$: Particulate Matter<2.5 mm

CVD: Cardio-Vascular Disease

AMI: Acute Myocardial Infarction

IHD: Ischemic Heart Disease

CHD: *Coronary Heart Disease*

MI: Myocardial Infarction

SCD: Sudden Cardiac Death

UAP: unstable angina pectoris

HR: Hazard Ratio

Declarations

Ethics approval and consent to participate

Study protocols were reviewed and approved by the Research and Ethics Council of Isfahan University of Medical Sciences (code number 399099) and conformed to the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJ, MK, MM, and NS participated in conceptualization. MT, MM and SA contributed in data curation. SJ and MM participated in formal analysis. MK, NS, MM, and MM participated in investigation. MM, and NS were responsible for methodology. MT and NS developed the software. MM, MK, and NS supervised the project. All authors read and approved the final version of the manuscript and agreed for all aspects of the work.

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Figures

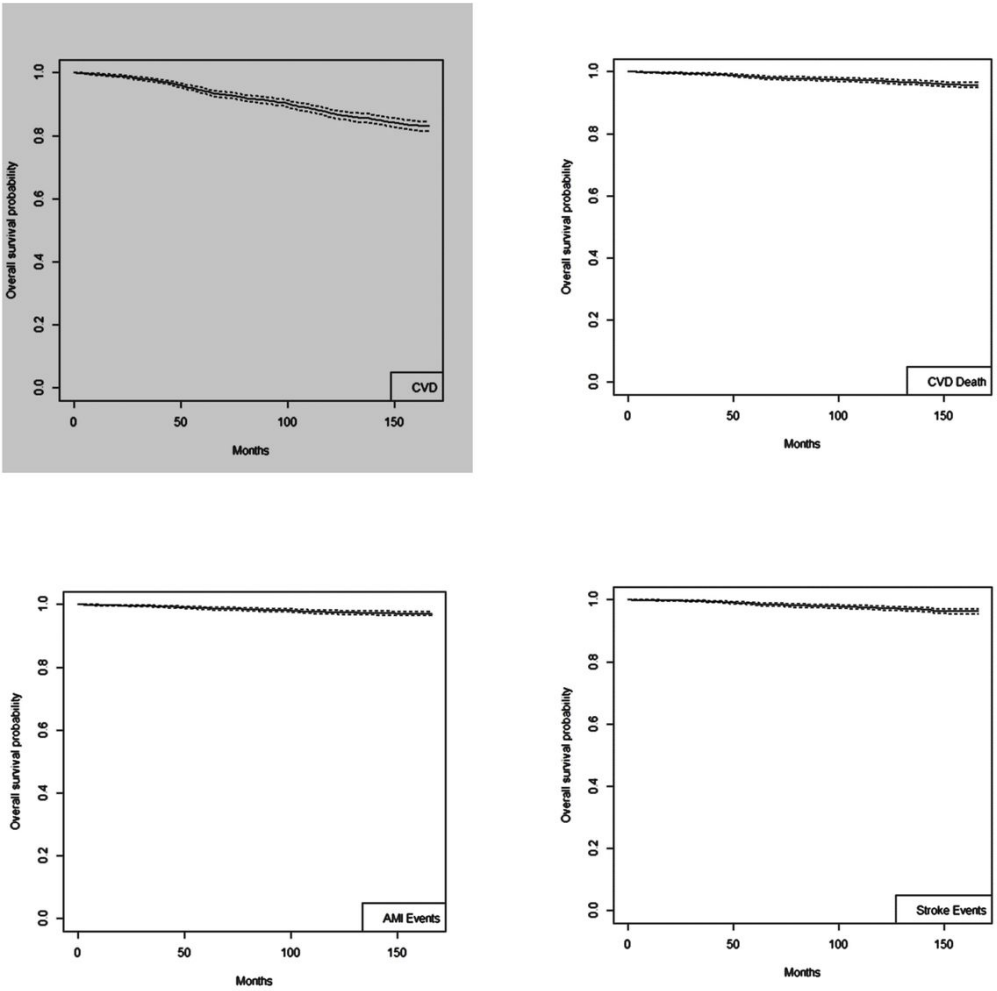

Figure 1

Kaplan Meyer survival curves for CVD events, CVD mortality, AMI and non-fatal stroke.

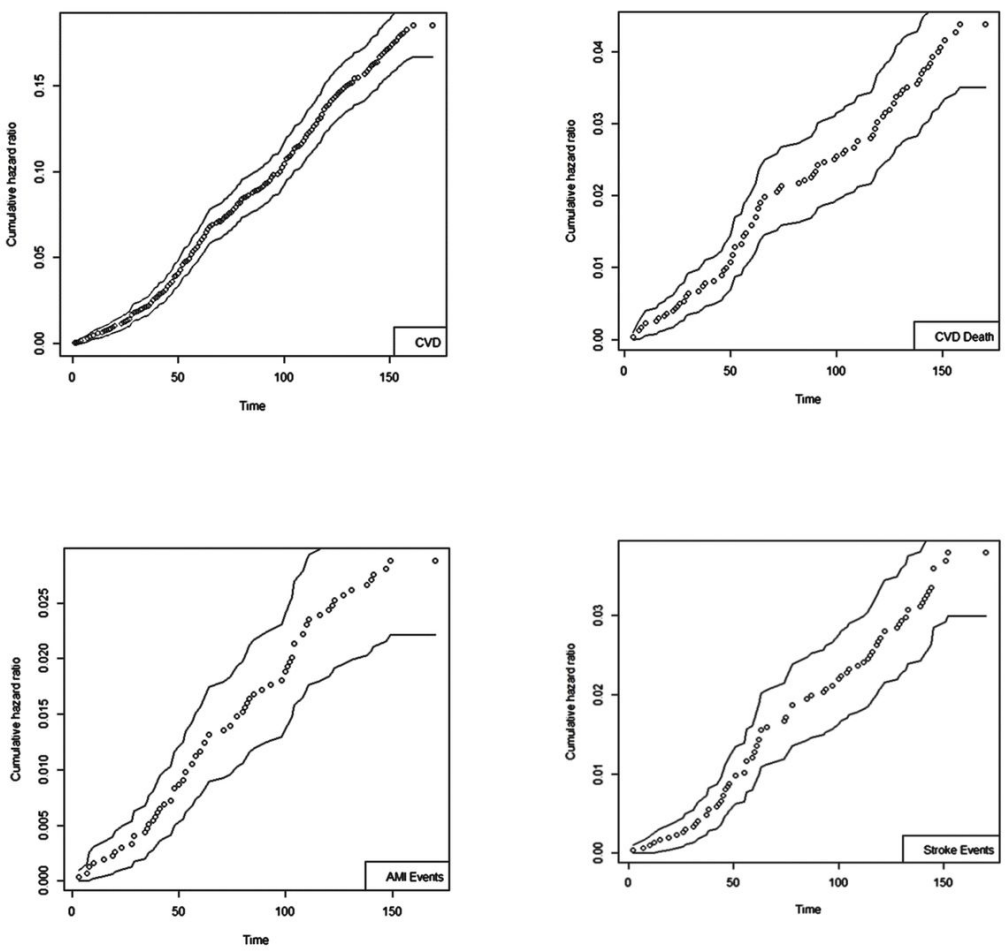

Figure 2

Cumulative hazard estimates with 95% confidence interval for different events (Model 6).