ORIGINAL ARTICLE

The association of exposure to air pollution with changes in plasma glucose indices, and incidence of diabetes and prediabetes: A prospective cohort of first-degree relatives of patients with type 2 diabetes

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Background: Increasing incidence rates of diabetes related to air pollution have been reported in high-income countries. However, few studies evaluated air pollution effect on plasma glucose indices, in addition to diabetes and prediabetes incidence in developing countries. This study investigated the association between exposure to common air pollutants and the changes plasma glucose indices over time. The incidence of type 2 diabetes (T2D) and prediabetes in future were also examined in association with exposure to air pollution. **Materials and Methods:** A total of 3828 first-degree relatives of patients with T2D who were prediabetes or had normal glucose tolerance (NGT) were enrolled in this study. Cox regression was used to assess the relationships between particulate matter (PM2.5 and PM10), nitrogen monoxide (NO), nitrogen dioxide, nitric oxides, sulfur dioxide (SO2), and ozone exposure and the incidence of T2D and prediabetes. We also applied a linear mixed model to assess the association between exposure to these air pollutants and changes in plasma glucose indices over time. **Results:** Air pollutants showed a significant positive association with changes in fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and 2 h oral glucose tolerance (OGTT) in participants with NGT and prediabetes. The maximum increase in plasma glucose indices was associated with NO concentration. Our study also showed exposure to all air pollutants except SO2 was significantly associated with an increased risk of developing T2D and prediabetes (Hazard ratio > 1, $P < 0.001$). **Conclusion:** According to our results, exposure to air pollution increases the risk of T2D and prediabetes incidence in our population. The exposure to air pollutants was also associated with increasing trend in FPG, HbA1c, and OGTT levels in both groups of NGT and prediabetic participants.

Key words: Air pollution, diabetes, incidence, prediabetes

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INTRODUCTION

Various environmental and lifestyle variables including, obesity and overweight,[1,2] physical inactivity,[3,4] unhealthy eating habits,[5] and smoking[6] are associated with the risk of type 2 diabetes. Several epidemiologic evidence have confirmed a positive relationship between exposure to air pollutants and the risk of developing type 2 diabetes (T2D).[7-10] A systematic review and meta-analysis suggested a positive association between exposure to particulate matter ≤ 2.5 μm (PM2.5), nitrogen dioxide (NO2), and the increased risk of developing

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T2D.[9] The associations of increased gaseous NO2, sulfur dioxide (SO2), ozone (O3), and carbon monoxide (CO) with PM2.5, PM10, and diabetes-associated mortality were also reported.[9] Although most of the previous studies showed a significant association between exposed to air pollutants with changes in plasma glucose indices, especially with fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and homeostatic model assessment of insulin resistance (HOMA-IR),[11] still there are several studies that detect no significant association between air pollution and the incidence of T2D and changes in plasma glucose indices.[12-15]

Previous studies mainly focused on the effect of one or two air pollutants (mainly PM2.5, PM10, and NO2) and the researches were conducted in the urban areas of high-income countries in North America and Europe.[9] Although the air pollution levels in Asia are reported to be much higher than in North America and Europe,[16] the effects of air pollution on developing T2D have not been well studied in these regions.[11] In addition, previous reports conducted their research mostly on the normal population, with very few studies on individuals with prediabetes,[17,18] and first-degree relatives of patients with T2D that are considered high-risk groups.

Iran is one of the 19 countries of the International Diabetes Federation-Middle East and North Africa region and has been ranked third in the prevalence of diabetes in this region.[19] The National Program for Prevention and Control of Diabetes-2016 reported the prevalence of type 2 diabetes 11.4% in Iran.[20] Considering the high prevalence of T2D in our country, the urbanization phenomenon and the lack of optimization of fuel consumption in developing countries including Iran,[21] it is worth to investigate the relationship between air pollution and these complications. Due to the huge burden of diabetes in Iran and the scarcity of research results assessing the association of air pollutants with prediabetes and diabetes incidence and changes in plasma glucose indices, further studies are necessary. The potential link between ambient air pollution and diabetes is of significant public health concern as the global health and economic burden from each of these is large and expected to increase. Air pollutants do not affect all populations equally because there are differences among susceptible subpopulation in terms of sensitivity to these pollutants. Few studies examined the changes in some diabetes-related blood markers particularly glycemic indices that are important determinants of the risk of affecting by diabetes in high-risk populations such as first-degree relatives of T2D. Examining the association between exposure to common air pollutants and changes in plasma glucose levels over time in Iran particularly in Isfahan an area that is exposed to high levels of indoor and especially outdoor air pollutants among a high-risk population with at risk of unstable metabolic profile. Population with NGT and particularly those with prediabetes who are first-degree relatives of T2D patients, due to inheritance, are particularly susceptible to IR and earlier development of T2D in future than other population.

The aim of the current study as the first one in Iran and worldwide is to investigate the effect of m exposure to air pollution overtime on the changes in plasma glucose and the incidence of prediabetes and T2D in Isfahan city, the largest centrally located city in Iran. All analyses of this study were conducted separately in both groups of participants with prediabetes and normal glucose tolerance (NGT).

MATERIALS AND METHODS

Study design and participants

The study population comprised participants of the Isfahan Diabetes Prevention Study (IDPS), an ongoing cohort study in the center of Iran. In the IDPS cohort study, the FDR of patients with T2D including siblings or children, were recruited between 2003 and 2005. The IDPS examined various potential risk factors for T2D in the first-degree relatives of subjects with T2DM. The sample of FDR was recruited between 2003 and 2018 and followed up. Participants who were diagnosed with diabetes at baseline were excluded and those patients who were prediabetes were tested annually, while individuals with NGT were tested every 3 years.[22] In the current study, a total of 3828 FDRs of patients with T2D who were diagnosed with prediabetes or those with NGT in 2012 were selected from IDPS participants and subjected to statistical analysis.

Assessment of variables

We collected demographic information including age, gender, education, physical activity (Min/week), anthropometric measures including body mass index (BMI), biochemical, and clinical data from the registry of the IDPS at the Isfahan Endocrine and Metabolism Research Center. The available data from NGT and prediabetic participants regarding basic demographic variables at entrance to the cohort study and biochemical data collected annually for patients with prediabetes and every 3 years for participants with NGT from 2012 to 2018 were used in the current secondary study.

Anthropometric measures were assessed by well-trained staff at the time of entry into the cohort study and subjects were minimally clothed and without footwear. Weight was measured using a Seca scale with stadiometer and recorded to the nearest 0.1 kg. Height was determined while subjects were in a normal standing position and recorded to the nearest 0.5 cm. BMI was calculated as weight (kg) divided by height squared (m^2).

All biochemical tests were measured using standard procedures in the central laboratory of the Isfahan Endocrine and Metabolism Research Center.[22] Biochemical tests included FPG, plasma glucose levels at 30, 60, and 120 min after oral glucose administration 2 h oral glucose tolerance (OGTT), HbA1c, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. To determine lipid profile and FPG, blood samples were collected from all participants after 10 to 12 h of overnight fasting. Post-glucose load was measured using venous blood sample at 30, 60, and 120 min after oral glucose (75 g) administration. Plasma glucose and lipid profile concentrations were determined using the enzymatic colorimetric method (ParsAzmoon, Tehran, Iran) adapted Selectra-2 auto-analyzer (Vital Scientific, Spankeren, Netherlands). Diastolic blood pressure and systolic blood pressure were also measured. Blood pressure was assessed two times (with at least 30 s intervals between measurements) using a mercury sphygmomanometer when participants were in a seated position for at least 10 min. The mean of two measurements was recorded as the level of blood pressure for our study samples.

Participants were categorized by the following criteria Impaired fasting glucose (IFG) was diagnosed if the FPG was between 100 mg/dL and 125 mg/dl, and 2-h post 75 g glucose load was <140 mg/dl. When the 2-h post glucose load was between 140 mg/dL and 199 mg/dL with normal fasting glucose (FPG <100 mg/dl), the patient was defined impaired glucose tolerance (IGT). Prediabetes were considered as either IFG or IGT or both.[23] Individuals were identified with diabetes, if the FPG was ≥126 mg/dl and/or the 2-h post glucose load was ≥200 mg/dl. The FPG <100 mg/dl and the 2-h post glucose load <140 mg/dl were considered as NGT.[18] We used annual data on plasma glucose indices, i.e., FPG, plasma glucose levels at 30, 60, and 120 min after oral glucose administration (OGTT), HbA1c from patients with prediabetes and those participants with NGT who had data on these indices during 2012–2018.

The Ethics Committee of the National Institute for Medical Research Development (NIMAD) approved the protocol of this (IR.NIMAD.REC.1397.250) and the tenants of the Declaration of Helsinki were followed. All participants had provided written informed consents.

Air pollution assessment

Information on air pollutants in Isfahan city from 2012 to 2018 was collected from the recorded data by the environmental protection agency of the province that monitors the air quality of the city. Currently, there are seven active air quality monitoring stations in Isfahan. The annual average concentrations of particulate matter with an aerodynamic diameter ≤1.0 μm and ≤2.5 μm (PM1 and PM2.5), SO2, nitrogen monoxide (NO), NO2 nitric oxides (NOx) (a collective term used to refer to NO and NO2 together), CO, and O3 were included in our study. The annual data on air pollutants were used for evaluating the association of concurrent changes in these indices with plasma glucose indices.

Statistical analysis

Basic and clinical continuous data and air pollution variables were reported as mean ± standard deviation (SD) or median (minimum–maximum). To assess the associations between air pollution exposures (PM2.5, PM10, NO, NO2, NOX, SO2, CO, O3) and indices of plasma glucose (FPG, OGTT, HbA1C), we applied linear mixed effects regression models with random intercepts. Results for the association of air pollutants with mean change in the outcome are presented as regression coefficients and 95% confidence intervals (CIs) for regression coefficients per one unit increase of the pollutants. We presented results in the final model, i.e., after adjustment for possible available confounders such as age, gender, education, physical activity, BMI, smoking and lipid profile, and blood pressure.

We also used Cox regression models with time-dependent covariate (the concentration of air pollutants was considered as time-varying covariate) to determine the association between the concentrations of pollutants and the risk of developing diabetes in participants with NGT and patients with prediabetes. This model also was used to investigate the risk of prediabetes in participants with NGT. The crude model and adjusted model by confounders were applied to each air pollutant. Age, sex, education, BMI, lipid profile (including triglycerides, cholesterol, HDL, and LDL), smoking, and physical activity, and blood pressure were considered confounders. Results of Cox regression were presented as hazard ratio (HR) and 95% confidence interval for HR. All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, Ill., USA).

RESULTS

Overall, participants included in the analysis (n = 3828) were around 43 years old at the baseline [Table 1]. On entering the cohort study, 70.4% (n = 2695) of the participants were female and 1752 were prediabetes. Tables 1 and 2 of the Supplementary Information shows mean and median (minimum–maximum) of air pollutants over the study period.

In the total population of our study, all air pollutants show a positive association with changes in FPG, HbA1c, and OGTT, irrespective of their status (NGT or prediabetic) [Table 2]. The strongest associations are listed here: The mean increase of FPG was 0.189 mmol/L (95% CIs:

Table 1: Demographic and basic clinical characteristics of participants

	Total	Normal	Prediabetes	IGT	IFG
n	3826	2074	1752	443	1309
Age (years)	43.10±6.25	42.69±6.03	43.59±6.46	42.70±5.97	43.90±5.97
BMI (kg/m^2)	29.29±4.10	29.17±4.19	29.44±3.99	29.24±3.72	29.50±4.08
FPG (mg/dL)	100.13±15.85	96.87±13.81	104.07±17.21	99.20±12.92	105.75±18.17
BS30 (mg/dL)	154.53±33.29	149.78±31.49	160.40±34.50	155.77±3072	162.09±35.65
BS60 (mg/dL)	160.22±44.08	151.96±41.76	170.51±44.73	171.55±40.29	170.14±46.23
OGTT (mg/dL)	127.15±39.34	121.11±35.34	134.49±42.59	144.93±41.75	130.74±42.28
HbA1c (%)	5.49±0.63	5.43±0.61	5.55±0.66	5.29±0.74	5.57±0.62
Triglyceride (mg/dL)	157.95±86.91	157.94±86.91	161.18±87.51	158.80±83.37	162.01±88.93
Cholesterol (mg/dL)	199.57±38.93	199.57±38.93	198.63±41.09	198.36±42.83	198.72±40.49
HDL (mg/dL)	45.26±10.91	45.26±10.91	44.81±11.16	45.90±11.18	44.44±11.32
LDL (mg/dL)	123.83±32.93	123.83±32.93	122.80±34.62	121.37±37.62	123.30±33.49
BP-maximum (mmHg)	115±15.39	114.97±15.34	115.53±15.46	114.42±15.36	115.90±15.47
BP-minimum (mmHg)	79±10.43	76.04±10.36	76.44±10.51	76.24±9.53	76.50±10.82

Continuous and categorical data were reported as mean±SD and frequency (%), respectively. BS30 and BS60, plasma sugar level after 30 and 60 min oral glucose administration. SD=Standard deviation; BMI=Body mass index; FPG=Fast plasma sugar; BP=Blood pressure; IGT=Impaired glucose tolerance; IFG=Impaired fasting glucose; OGTT=2 hours oral glucose tolerance; HbA1c=Glycated hemoglobin; HDL=High-density lipoprotein; LDL=Low-density lipoprotein

Table 2: Association of exposures to air pollutants with plasma glucose indices in the total population (normal glucose tolerance and prediabetes)

	FPG			HbA1C			OGTT		
	B (SE)	95% CI	*P*	*B* (SE)	95% CI	*P*	*B* (SE)	95% CI	*P**
O3 (ppm)	0.102 (0.008)	0.088-0.120	<0.001	0.00014 (1.284E-5)	0.00012-0.00017	<0.001	0.602 (0.049)	0.512-0.706	<0.001
NO (ppm)	0.189 (0.135)	0.164-0.217	<0.001	0.00029 (2.046E-5)	0.00023-0.00031	<0.001	1.128 (0.080)	0.980-1.299	<0.001
NO_2 (ppm)	0.050 (0.005)	0.040-0.063	<0.001	6.895E (9.476E-5)	5.266E-9.026E	<0.001	0.353 (0.037)	0.287-0.434	<0.001
NOx (ppm)	0.029 (0.002)	0.024-0.034	<0.001	4.129E (4.079E-5)	3.402E-5.011E	<0.001	0.189 (0.016)	0.160-0.222	<0.001
PM10 (μg/m^3)	0.010 (0.000)	0.008-0.012	<0.001	2.202E (1.527E-5)	1.922E-2.522E	<0.001	0.069 (0.005)	0.058-0.081	<0.001
PM2.5 (μg/m^3)	0.060 (0.004)	0.051-0.07	<0.001	8.628E (7.921E-5)	7.207E-0.0001	<0.001	0.399 (0.030)	0.344-0.464	<0.001
SO_2 (ppm)	0.056 (0.005)	0.046-0.067	<0.001	8.387E (9.057E-5)	6.786E-0.0001	<0.001	0.291 (0.296)	0.239-0.356	<0.001

*Resulted from linear mixed effects models. All regression coefficients are from fully adjusted models for age, sex, education, BMI, lipid profile (including triglycerides, cholesterol, HDL, LDL), smoking, and physical activity, and BP. B=Regression coefficient; SE=Standard error of regression coefficient; CI=Confidence interval for *B*; FPG=Fast plasma glucose; OGTT=2 hours oral glucose tolerance; HbA1c=Glycated hemoglobin; O3=Ozone; NO=Nitrogen monoxide; NO_2=Nitrogen dioxide; NOx=Nitric oxides; SO_2=Sulfur dioxide; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; BP=Blood pressure; BMI=Body mass index

0.164, 0.121) per 1 μg/m^3 increase in NO. OGTT showed a significant positive association with the NO concentration. A 1 μg/m^3 increase in NO was associated with a mean increase of 1.128 mmol/L (95% CIs: 0980, 1.299) in OGTT level. Furthermore, the significant associations were found between HbA1c and the concentration of air pollutants in which, we observed an average 0.00029 (95% CIs: 0.00023, 0.00031) increase in HbA1c per 1 μg/m3 increase in NO concentrations. The associations of all air pollutants with changes in plasma glucose indices are shown in Table 2.

A positive association was observed between all air pollutants and FPG, OGTT, and HbA1c in participants with prediabetes [Table 3]. A high significant association was observed between OGTT and NO concentration in which an average increase of 1.311 mmol/L (95% CIs: 1.066, 1.611) was detected per 1 μg/m^3 increase in the concentration of NO. Similarly, FPG and HbA1c showed significant association with the increased concentration of NO compared to other pollutants, which is 0.213 mmol/L and 0.0002% per 1 μg/m^3 increases in NO concentration, respectively [Table 3].

Similarly, we observed a significant association between all air pollutants and FPG, OGTT and HbA1c in NGT participants [Table 4]. A significant association of the OGTT with the concentration of NO was observed; in which an average 1.128 mmol/L (95%CIs: 0980, 1.299) was detected per 1 μg/m^3 increment in NO. The FPG and HbA1c also significantly increased with an increase in NO concentration, in which their values were increased by an average of 0.142 mmol/L and 0.0002% per 1 μg/m^3 increases in NO concentration, respectively [Table 4].

The associations between each of the seven air pollutants and the risk of developing diabetes and prediabetes have been presented by HR and 95% CI for HR in crude and adjusted Cox regression models in Table 5. There were statistically significant positive associations between PM2.5, NO, NO2, NOX concentrations and the incidence of diabetes in participants with NGT and patients with prediabetes. One unit increase in the concentration of NO showed a significantly increased risk of the incidence of diabetes in both groups of participants with NGT and

Table 3: Associations between exposures to air pollutants and plasma glucose indices in prediabetic participants

	FPG			HbA1C			OGTT		
	B (SE)	95% CI	*P*	*B* (SE)	95% CI	*P*	*B* (SE)	95% CI	*P*
O3 (ppm)	0.109 (0.013)	0.085-0.140	<0.001	0.0001 (1.0843E-5)	0.00010-0.00018	<0.001	0.670 (0.812)	0.526-0.849	<0.001
NO (ppm)	0.213 (0.023)	0.172-0.263	<0.001	0.0002 (2.986E-5)	0.0002-0.0003	<0.001	1.311 (0.138)	1.066-1.611	<0.001
NO_2 (ppm)	0.069 (0.010)	0.052-0.092	<0.001	6.357E (1.303E-5)	4.255E-5-9.499E-5	<0.001	0.469 (0.065)	0.358-0.615	<0.001
NOx (ppm)	0.034 (0.004)	0.024-0.044	<0.001	3.896E (5.750E-5)	2.917E-5-5.202E-5	<0.001	0.233 (0.027)	0.186-0.293	<0.001
PM10 ($\mu g/m^3$)	0.014 (0.002)	0.011-0.017	<0.001	1.972 (2.081E-5)	1.603E-5-2.422E-5	<0.001	0.076 (0.009)	0.060-0.096	<0.001
PM2.5 ($\mu g/m^3$)	0.068 (0.008)	0.054-0.086	<0.001	7.717E (1.071E-5)	5.879E-5-0.0001	<0.001	0.504 (0.054)	0.410-0.622	<0.001
SO_2 (ppm)	0.069 (0.010)	0.052-0.092	<0.001	7.995E (1.149E-5)	6.031E-5-0.0001	<0.001	0.350 (0.052)	0.262-0.468	<0.001

*Resulted from linear mixed effects models. All regression coefficients are from fully adjusted models for age, sex, education, BMI, lipid profile (including triglycerides, cholesterol, HDL, LDL), smoking, and physical activity, and BP. *B*=Regression coefficient; SE=Standard error of regression coefficient; CI=Confidence interval for *B*; FPG=Fast plasma glucose; OGTT=2 hours oral glucose tolerance; HbA1c=Glycated hemoglobin; O3=Ozone; NO=Nitrogen monoxide; NO_2=Nitrogen dioxide; NOx=Nitric oxides; SO_2=Sulfur dioxide; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; BP=Blood pressure; BMI=Body mass index

Table 4: Associations of exposures to air pollutants with plasma glucose indices in normal glucose tolerance participants

	FPG			HbA1C			OGTT		
	B (SE)	95% CI	*P*	B (SE)	95% CI	*P*	B (SE)	95% CI	*P*
O3 (ppm)	0.109 (0.013)	0.085-0.140	<0.001	0.0001 (1.725E-5)	0.00010-0.00018	<0.001	0.505 (0.054)	0.409-0.624	<0.001
NO (ppm)	0.142 (0.014)	0.118-0.172	<0.001	0.0003 (2.704E-5)	0.0002-0.0003	<0.001	0.878 (0.086)	0.725-1.064	<0.001
NO_2 (ppm)	0.024 (0.006)	0.018-0.041	<0.001	8.183E-5 (1.405E-5)	5.845E-5-0.0001	<0.001	0.241 (0.039)	0.175-0.332	<0.001
NOx (ppm)	0.020 (0.002)	0.015-0.264	<0.001	4.551E-5 (5.683E-5)	3.564E-5-5.814E-5	<0.001	0.138 (0.017)	0.109-0.175	<0.001
PM10 ($\mu g/m^3$)	0.007 (0.001)	0.005-0.009	<0.001	2.350E-5 (2.148E-5)	1.964E-5-2.810E-5	<0.001	0.065 (0.007)	0.052-0.079	<0.001
PM2.5 ($\mu g/m^3$)	0.068 (0.008)	0.054-0.086	<0.001	7.717E-5 (1.071E-5)	5.879E-5-0.0001	<0.001	0.279 (0.031)	0.224-0.348	<0.001
SO_2 (ppm)	0.069 (0.010)	0.052-0.092	<0.001	9.814E-5 (1.553E-5)	7.197E-5-0.0001	<0.001	0.236 (0.031)	0.183-0.305	<0.001

*Resulted from linear mixed effect models. All regression coefficients are from fully adjusted models for age, sex, education, BMI, lipid profile (including triglycerides, cholesterol, HDL, LDL), smoking, and physical activity, and BP. *B*=Regression coefficient; SE=Standard error of regression coefficient; CI=Confidence interval for *B*; FPG=Fast plasma glucose; OGTT=2 hours oral glucose tolerance; HbA1c=Glycated hemoglobin; O3=Ozone; NO=Nitrogen monoxide; NO_2=Nitrogen dioxide; NOx=Nitric oxides; SO_2=Sulfur dioxide; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; BP=Blood pressure; BMI=Body mass index

Table 5: Hazard ratios and 95% confidence intervals for hazard ratio of the associations between air pollutants and the risks of developing type 2 diabetes and prediabetes in participates with prediabetes and normal glucose tolerance, during the study period

	T2D risk in NGTs	Prediabetes risk in NGTs	T2D risk in prediabetes
O3 (ppm)			
Crude	1.102 (1.074-1.113)	1.095 (1.081-1.109)	1.092 (1.074-1.100)
Adjusted	0.990 (0.923-1.063)	1.071 (1.033-1.110)	1.097 (1.056-1.140)
NO (ppm)			
Crude	1.772 (1.589-1.978)	1.761 (1.664-1.863)	1.757 (1.631-1.892)
Adjusted	1.371 (1.044-1.799)	1.678 (1.445-1.949)	1.768 (1.495-2.091)
NO_2 (ppm)			
Crude	1.099 (1.079-1.119)	1.126 (1.113-1.140)	1.079 (1.068-1.090)
Adjusted	1.112 (1.043-1.189)	1.118 (1.085-1.152)	1.075 (1.051-1.101)
NOx (ppm)			
Crude	1.097 (1.079-1.116)	1.120 (1.180-1.132)	1.079 (1.069-1.089)
Adjusted	1.105 (1.037-1.177)	1.113 (1.083-1.143)	1.077 (1.055-1.100)
PM10 ($\mu g/m^3$)			
Crude	1.084 (1.053-1.115)	1.085 (1.069-1.102)	1.092 (1.072-1.112)
Adjusted	1.064 (0.972-1.164)	1.080 (1.032-1.130)	1.097 (1.052-1.144)
PM2.5 ($\mu g/m^3$)			
Crude	1.113 (1.090-1.136)	1.139 (1.124-1.154)	1.089 (1.079-1.102)
Adjusted	1.132 (1.047-1.223)	1.131 (1.094-1.170)	1.088 (1.059-1.117)
SO_2 (ppm)			
Crude	0.997 (0.987-1.006)	0.995 (0.990-1.000)	1.000 (0.993-1.006)
Adjusted	0.998 (0.958-1.039)	0.992 (0.978-1.007)	1.003 (0.989-1.017)

The presented data are HR and 95% CI for HR. All HR are based on fully adjusted models for age, sex, education, BMI, lipid profile (including triglycerides, cholesterol, HDL, LDL), smoking, and physical activity, and BP. T2D=Type 2 diabetes; NGT=Normal glucose tolerance; HR=Hazard ratio; CI=Confidence interval; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; BP=Blood pressure; BMI=Body mass index; O3=Ozone; NO=Nitrogen monoxide; NO_2=Nitrogen dioxide; NOx=Nitric oxides; SO_2=Sulfur dioxide

prediabetic (HR = 1.371; 95% CI: 1.044–1.799 in NGTs and HR = 1.678; 95% CI: 1.445–1.949 in patients with prediabetes). The exposure to PM2.5, NO, NO_2, NO_X pollutants was also significantly associated with the increased risk of developing prediabetes in participants with NGT, with an adjusted HR of 1.768 (1.495–2.091). Our study showed no significant association between the concentration of SO2 and the risk of developing T2D and prediabetes.

DISCUSSION

In this study, we observed significant increases in FPG, HbA1c, OGTT, associated with increased in concentrations of air pollutants over 7 years in both groups of NGT and prediabetic participants. The associations were more pronounced between FPG, OGTT, HbA1c level, and NO concentration. Few studies evaluate the impact of air pollution on glucose indices.[13,16,24] According to a recent meta-analysis, 14 out of 17 studies on FPG have reported increased risk of developing diabetes for at least one of the investigated pollutants; in seven out of eight studies, increased level of HbA1c was associated with air pollution concentrations. In eight out of 10 studies HOMA-IR was also increased with increased exposure to air pollution.[11] PM2.5, PM10, and NO2 are the most frequent air pollutants that have been examined in those studies.[11] Some previous studies found that PM2.5, PM10, NO2, O3, and SO_2 positively associated with changes in FPG.[25,26] However, some others reported no association between FPG and PM2.5, PM10, NO2.[27,28] Several studies in accordance with our study results showed increased in HbA1C by PM2.5, PM10, NO2, with increasing O3 exposure.[24-26,28,29] While some literature report, no significant association between OGTT and PM2.5 and NO2,[11,27] others evidenced that PM1, PM2.5, PM10, and NO2 were associated with higher concentrations of OGTT.[16,28]

Previous studies showed the association of pathophysiologic pathways and glucose metabolism with air pollution. Exposure to air pollutants leads to an increase in oxidative stress and inflammation in the lungs and damages other organ systems, including the adipose tissue.[30] Insulin signaling pathways that regulate glucose metabolism affected negatively by the induced inflammation and this leads to disruption of glucose regulation as well as an abnormal increase in glucose level. This phenomenon has been observed in patients with diabetes or prediabetes that suffered from high insulin insensitivity, with a dramatic increase in FPG and HbA1c levels. Inhaled air pollutants change endothelial function in both animals and humans. Changing in endothelial function, often precede alterations in IR, and have been implicated in reduced peripheral glucose uptake. A direct link has been observed between inhalational exposure of $PM_{2.5}$ and an increase in fasting, postprandial glucose, insulin, and HOMA-IR measures.[31-33]

NO2 or nitrogen oxide is one of the key lead pollutants that often serve as a proxy for traffic-related pollution. Epidemiologic studies about the evidence for pathophysiologic pathways for NO2 or nitrogen oxide on glycemic indices and T2D are limited because these types of pollutants react with and correlate with other pollutants and they are highly spatially variable, thus, both exposure estimation and their effects on health outcomes, specifically, are difficult to distinguish from other pollutants. However, recent technical studies suggest some support for adverse effects on inflammation, airway hyperresponsiveness, and oxidative stress as potential pathophysiological mechanisms resulting in adverse human health effects. It is well known that both oxidative stress and inflammation have been linked to IR and metabolic dysfunction.[34]

O3, formed by photochemical reactions on emissions from fossil fuel combustion and industrial and vehicular activities, has been linked to poor FPG, insulin levels, and HOMA indices among older adults, with stronger associations observed among those with a history of diabetes or increased susceptibility to oxidative stress.[34]

We showed that the exposure to PM2.5, NO, NO2, and NOX was associated with increased risk of developing diabetes in participants with NGT and patients with prediabetes. We also observed a positive association between these pollutants and diabetes incidence in participants with NGT. NO concentration shows the highest HR in all three groups of our study. According to a recent meta-analyses,[11] significant associations were observed between PM2.5 and T2D incidence (11 studies; HR = 1.10, 95% CI = 1.04–1.17 per 10 μg/m^3 increment; I^2 = 74.4%) and prevalence (11 studies; odds ratio [OR] = 1.08; 95% CI = 1.04–1.12 per 10 μg/m^3 increment; I^2 = 84.3%). The meta-analyses of 6 studies showed the association of PM10 with T2D prevalence (OR = 1.10; 95% CI = 1.03–1.17 per 10 μg/m^3 increment; I^2 = 89.5%) and incidence (HR = 1.11; 95% CI = 1.00–1.22 per μg/m^3 increment; I^2 = 70.6%). In addition, eleven studies evidenced the relation between NO2 and T2D prevalence (OR = 1.07; 95% CI = 1.04–1.11 per 10 μg/m^3 increment; I^2 = 91.1%).[11] Although in our study, O3 and PM10 showed no association with the incidence rate of diabetes in participants with NGT, a few studies have reported a positive association between these pollutants and the incidence rate or prevalence of diabetes.[16,35,36] We have also detected no association between SO2 exposure and diabetes incidence in participants with NGT and patients with prediabetes, as well as prediabetes incidence

in participants with NGT. On the contrary, a recent study has demonstrated that the exposure to SO2 was associated with a higher risk of developing early-onset T2D in adults aged between 30 and 50 years.[36]

Although there is no conclusive study, many of them support an association between air pollutants, particularly traffic-related sources, and T2D. The varying results regarding the association between air pollution and T2D among conducted studies might relate to differences, including the population characteristics, risk factors, individual susceptibilities, validness of the cohort data, prevalence of type 2 DM, availability of data and the exposure assessment methodologies, pollutants' types/sources, and the severity and duration of exposure to air pollutants. In some instances, sex-specific differences were detected that may relate to true differences in biological susceptibility in some subpopulation. Possibly, sex differences in terms of susceptibility may relate to exposure assessment error because males tend to be more mobile than females and as a result, they are more vulnerable to air pollutants exposure. In our study population, the majority of participants were female (about two-third of total sample). Additional considerations should be highlighted here, particularly in underdeveloped and developing countries, are the importance of factors such as low socioeconomic status, stress, and poorly measured pollutants often pervasive in the urban areas.[37]

A previous study in Iran on the association of geographical distribution of air quality index and incidence rate of T2D using a geographic information system[38] showed that the number of participants with diabetes was higher in highly polluted areas compared to areas with the lower levels of air pollution, however, there was no significant correlation between the distribution of patients with diabetes and air pollution level. It is worth noting that the influence of air pollutants on the incidence rate of diabetes mellitus or blood parameters was not assessed.[38] Another study in Iran[15] investigated the association of T2D prevalence with exposure to high levels of PM10 in adults between 2006 and 2011 in five large cities (Tehran, Ahwaz, Shiraz, Kermanshah, and Isfahan),[15] grouping the cities to Group 1 (Tehran, Shiraz with PM10 concentration <100 μg/m^3), and Group 2 (Kermanshah, Ahwaz, Esfahan, with PM10 concentration >100 μg/m^3). The 5-year average of PM10 concentration was higher in Group 2 compared to group 1. The prevalence of T2D in Group 2 was 13.8%, while it was 10.7% in Group 1 (P = 0.01), OR = 1.32 (95% CI 1.03–1.69).[15] The results of data collected from the urban area of 31 provinces of Iran, showed a weak positive correlation between PM2.5 level and diabetes prevalence, and no significant association was detected with prediabetes prevalence.[39] The effect of air pollution on HbA1C level was not significant in 330 people diagnosed with diabetes mellitus who were followed for at least 12 months.[40]

Differences in results in various studies worldwide in this regard could be due to the differences in studied populations, levels of air pollution, and duration of exposure in the studied populations.

Study strengths and limitations

We examined the concurrent association of changes in a wide range of air pollutants with the changes in plasma glucose indices in a longitudinal setting and with the incidence of T2D and prediabetes in a high-risk group, first-degree relatives of patients with T2D. Having a large sample size is another strength of our study. Only few previous studies evaluated the impact of air pollution on plasma glucose indices, globally. Hence, we detailed the relation between air pollution and FPG, HbA1c, OGTT.

Due to the lack of information on insulin level, we were unable to evaluate the IR related to the air pollution. Our ability to characterize pollutants and diabetes, concentration–response relationship, could be improved if more time-activity patterns for each individual and occupational exposures data were available. Another limitation should be mentioned is the lack of data for some air pollutants for some few years of study.

CONCLUSION

Our results indicated that exposure to air pollution, the majority of air pollutants, is a risk factor for developing T2D and prediabetes, the exposure to air pollutants was significantly associated with increase in FPG, HbA1c, and OGTT levels in NGT and prediabetic participants. These findings suggest that air pollution could be considered a key risk factor for abnormal glucose metabolism and diabetes. Our findings have significant public health implications, suggesting that the environmental risk factors may contribute to diabetes, and continued efforts are required to minimize such risk.

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Ethics approval

The Ethics Committee of the National Institute for Medical Research Development (NIMAD) approved the protocol of this (IR. NIMAD. REC.1397.250)

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Conflicts of interest

There are no conflicts of interest.

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