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ARTICLE

Particulate matter and markers of glycemic control and insulin resistance in type 2 diabetic patients: result from Wellcome Trust Genetic study

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Abstract

There is growing evidence that air pollution is associated with increased risk of type 2 diabetes (T2DM). However, information related to whether particulate matter (PM) contributing to worsened metabolic control in T2DM patients is inconsistent. We examined the association of PM_{10} exposure with glucose-function parameters in young-onset T2DM patients. We investigated the association between a year ambient concentration of PM_{10} at residential places, using AERMOD dispersion model, with fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), 2 h post meal plasma glucose (2hPG), homeostasis model assessment of insulin resistance (HOMA-IR), β-cell function (HOMA-β) and disposition index (DI) in 1213 diabetic patients from the Wellcome Trust Genetic study at the Diabetes Unit, KEM Hospital Research Center, Pune, India. We used linear regression models and adjusted for a variety of individual and environmental confounding variables. Possible effect modification by age, gender, waist-to-hip ratio (WHR) and smoking status were investigated. Sensitivity analysis assessed the impact of relative humidity (RH) and temperature a day before examination and anti-diabetic and HHR medication (Hydralazine, Hydrochlorothiazide and Reserpine). We found that 1 SD increment in background concentration of PM_{10} at residential places (43.83 μg/m^3) was significantly associated with 2.25 mmol/mol and 0.38 mmol/l increase in arithmetic means of HbA1c and 2hPG, respectively. A similar increase in PM_{10} was also associated with 4.89% increase in geometric mean of HOMA-IR. The associations remained significant after adjustment to RH and temperature, and WHR and smoking enhanced the size of the effect. Our study suggests that long-term exposure to PM_{10} is associated with higher glycaemia and insulin resistance. In context of our previous demonstration of association of SO_2 and NO_x and plasma C-reactive protein, we suggest that air pollution could influence progression of diabetes complications. Prospective studies and interventions are required to define mechanism and confirm causality.

Keywords Particulate Matter · Diabetes Mellitus, Type 2 · glycemic control · Insulin Resistance · Glycated Hemoglobin A · disposition index

Introduction

Studies from developed nations suggest that air pollution may adversely influence glucose metabolism and diabetes-

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related mortality [1–5]. A recent study showed that particulate matter (PM) could increase the risk of acute metabolic complications of DM, such as coma and ketoacidosis [6], suggesting that PM might affect glucose homeostasis [7]. However, research investigating the association between long-term exposure to PM and glucose homeostasis has shown conflicting results [7–14].

It has been proposed that inhaled air pollutants cause the release of reactive oxygen species from cells in the lungs [15] and circulating immune cells [16]. We found that air pollution is associated with higher levels of circulatory inflammatory markers in diabetic patients [17]. Inflammation and oxidative stress have been shown to induce gluconeogenesis in muscle [18], lipolysis in adipose tissue [19], decreased insulin secretion from pancreatic β cells [20], and whole-body insulin resistance [21, 22].

In the Wellcome Trust Genetic (Well-Gen) Study, we have collected extensive phenotypic data on type 2 diabetic patients in Pune, including biomarkers of glycemic control, β-cell function and insulin action. Emission data for PM_{10} for Pune was available in the public domain from the Pune Regional Emissions Inventory Study (PREIS) [23]. We used this database to investigate the association between PM_{10} exposure at residential places and glycemic parameters in the WellGen study participants, at the same address.

Methods

Study population and design

Young-onset (46 years) type 2 diabetic patients attending the Diabetes Clinic of the King Edward Memorial Hospital in Pune were enrolled in the WellGen study. Details of the study are published elsewhere [17, 24]. For the current study, we included patients who were enrolled between March 2005 and May 2007, and residing in the Pune city boundary for the last 12 months.

Clinical and biochemical parameters

All patients answered a standard questionnaire that gave information about their residential address, age, sex, smoking history, alcohol consumption, and medical history, including date of diagnosis of diabetes. Height, weight, waist and hip circumferences were measured as per standard protocol. Fasting blood sample was drawn to examine various biochemical measurements, including fasting plasma glucose (FPG), HbA1c and C-peptide. Another blood sample was drawn to examine 2-h post meal plasma glucose (2hPG). Insulin resistance (HOMA-IR) and β-cell function (HOMA—β) was computed according to homeostatic model assessment using an online program (HOMA2, available online at http://www.dtu.ox.ac.uk/homa) using fasting glucose and C-peptide concentration, are widely used in epidemiological study for assessing the two physiological function [25]. Disposition index (DI) was calculated as HOMA—β / HOMA-IR [26] representing β-cell function in relation to the prevailing insulin resistance.

Exposure assessment

We estimated background PM_{10} concentrations at the homes of subjects through atmospheric dispersion model using AERMOD [27]. These US EPA air dispersion models (AERMOD) are used to measure pollution concentration and deposition from a wide variety of sources. The input data files were prepared as per the specified format which included appropriate estimation of emissions from various sources based on the activity data and the relevant emission factors. The database was initially developed as part of a project entitled PREIS with support from the US Agency for International Development and the US–Asia Environmental Partnership in March 2004 [23]. A further refinement (the Improvement Program) estimated the annual mass of PM_{10} emitted per 2 km^2, dividing the city in to 189 grids [28]. The emission data were added to the AERMOD along with the onsite meteorological data. Geo-position information on the home location of subjects allowed us an estimation of a 1-year exposure to background PM_{10} concentration for the year 2005.

Statistical analysis

The data are presented as mean (±SD) or median (25th, 75th percentile). Skewed variables, (duration of diabetes since diagnosis, FPG, HOMA-IR, HOMA-β and DI) were log-transformed (ln) to obtain normal distribution.

Visual inspection of data ascertained linearity of the relationship, therefore we used multiple linear regression models to describe the association between residential exposure to PM_{10} and the glycemic indicators (FPG, 2hPG, HbA1c, HOMA-IR, HOMA-β and DI). We controlled for a variety of endogenous and exogenous confounding factors such as age, gender, education (years of educations), season of enrollment (monsoon [June–October], winter [November–February], and summer [March–May]), body mass index (BMI), waist-to-hip ratio (WHR), duration of diabetes, diet (lacto vegetarian, ovo-vegetarian and non-vegetarian), alcohol consumption and smoking (never, past and current') as an indicator variable. Model selections were based on minimum value of Akaik's Information Criterion [29]. Sensitivity of our models was investigated with additional adjustment for medication, temperature, relative humidity, and air quality (i.e., PM_{10}, nitrogen oxides, sulfur

dioxide) a day before the blood sample collection [30]. For normally distributed biomarkers (i.e., HbA1c and 2hPG) the results are given as absolute change in biomarkers, for 1 SD increment in PM_{10} and for those logarithmic transformed biomarkers we have reported percent change in geometric mean (change in GM = [e $^{(1SD \times b)}$−1] × 100) of the biomarkers, for 1 SD increment in PM_{10}, where "*b*" is regression coefficient.

To investigate possible effect modification by conditions such as age (below and above the median of 46 years), gender, central obesity (WHR for men = 0.90 and women = 0.80) [31], and current smoking status (yes vs. no), insulin treatment, Metformin, Glitazones and Sulfonylureas, we added an interaction term of indicator variable (above group) and exposure value (i.e., PM_{10}) simultaneously with the main effect terms in main model.

Results

Characteristic of the study population

Out of the 1700 diabetic patients who were enrolled between March 2005 and May 2007, we studied 1213 subjects whose home addresses did not change for the last 12 months and therefore PM_{10} concentration at their place of residence could be estimated. Table 1 shows the characteristics of study population ($n = 1213$). The mean age of patients at the time of enrolment was 46.65 years and 54% of the patients were males. Average duration of diabetes was 8 years. Forty-two and 15% of patients were overweight ($25 \geq BMI < 30$) and obese ($BMI \geq 30$), respectively. Smoking and alcohol intake were more prevalent in men than women. Almost a third were treated with insulin.

Table 1 Characteristics of type 2 diabetic patients in Wellcome Trust Genetic study

Age (years)	46.6 (9.3)
Male, *n* (%)	655 (54)
Body mass index (kg/m²)	26.1 (4.2)
Waist–hip ratio	0.9 (0.7)
Duration of diabetes (years)	8.2 (3.0,15.1)
Current smoking, *n* (%)	125 (10)
Current alcohol, *n* (%)	256 (21.1)
Dietary habit	
Lacto-vegetarian, *n* (%)	435 (36)
Ovo-vegetarian, *n* (%)	81 (7)
Non-vegetarian, *n* (%)	694 (57)
Years of Education (years)	11.9 (4.7)
FPG (mmol/l), $n = 991$	8.6 (6.9, 11.3)
2hPG (mmol/l), $n = 1212$	13.5 (4.5)
HbA1c (mmol/mol)—$n = 924$	74 (22.9)
HOMA-IR, $n = 985$	5.6 (3.9, 8.1)
HOMA-β, $n = 985$	120.1 (70.9, 180.8)
Disposition index	20.5 (13.1, 31.4)
Insulin treatment (%)	397 (32)

FPG fasting plasma glucose, *2hPG* 2-h post meal plasma glucose, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model assessment of insulin resistance, *HOMA-β* homeostasis model assessment of β-cell insulin secretion, *Disposition index* HOMA—β/HOMA-IR

Values are presented as mean (SD), median (25th, 75th percentile), and number (%) as appropriate.

Markers of glycemic control, HOMA-IR and HOMA-β

Sixty-nine percent ($n = 955$) of patients had FPG > 7 mmol/l and 82% had HbA1c > 53 mmol/mol, indicating uncontrolled diabetes. Multivariate analysis indicated that FPG, 2hPG, and HbA1c were not related to age, gender, BMI and smoking but were significantly correlated directly with WHR and duration of diabetes. We observed that these patients are substantially insulin resistant (mean HOMA-IR = 5.6) and appear to have enhanced β cell function (HOMA-β = 120%) which however is not enough to match the insulin resistance, as evident in low DI (=21%) [32]. We did not find sex related differences in the estimated HOMA-IR, HOMA-β and DI. We found that younger patients and those with shorter duration of diabetes were more insulin resistant and had higher B-cell function, which reflected in a higher DI in those with shorter duration of diabetes. We observed higher HOMA-IR in subjects who were currently smoking (geometric mean of IR for current smoker 5.8 vs. non-smoker 5.5, $P = 0.008$). We found that the level of FPG, HbA1c, HOMA-IR, and HOMA-β are significantly higher in winter than other seasons ($P < 0.05$), however, there were no seasonal difference in levels of 2hPG and DI (winter = 20.40 (1.027) vs. other season = 19.16 (1.032), *p*-value = 0.933).

Exposure to PM_{10}

We estimated the background PM_{10} concentration at the homes of 1213 patients. Average estimated PM_{10} concentrations were 172.5 μg/m^3 (±43.83). Estimated PM_{10} concentrations ranged from 17.62 to 299.32. The average PM_{10} exceeded recommended standards (of 60 μg/m^3 according to national ambient air quality standards [33]) by almost 3 times, and 99% of patients exceeded this exposure. Map of Pune, the location of patients and the background concentration of PM_{10} are depicted in supplemental figure S1. The modeled monthly mean values of PM_{10} when compared with measurements from one of the air quality monitoring stations located on Karve Road,

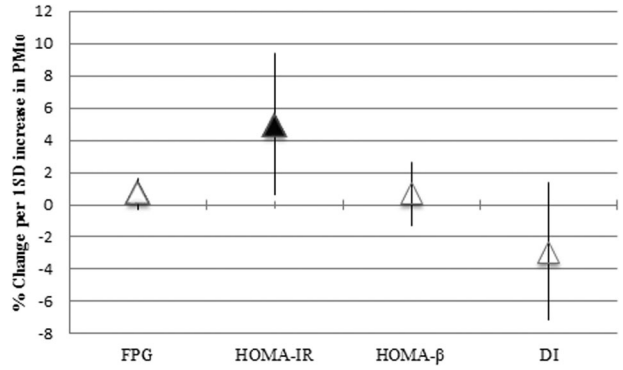

Fig. 1 Association between exposure to PM10 and biomarkers of glycemic control, HOMA-IR, HOMA-β and DI, adjusted to age, sex, season of enrolment, duration of diabetes, WHR, and smokingThe estimates are given as percent change in biomarkers per 1 SD (=43.83 μg/m^3) increase of PM10. Error bar indicates 95% CI. Black triangle indicates significant association ($P < 0.05$)

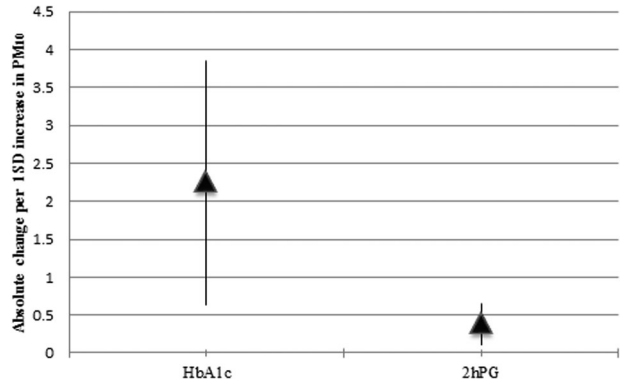

Fig. 2 Association between exposure to PM10 and biomarkers of glycemic control (i.e., 2hPG, HbA1c) adjusted to age, sex, season of enrolment, duration of diabetes, WHR, and smokingThe estimates are given as absolute change in biomarkers per 1 SD (=43.83 μg/m^3) increase of PM10. Error bar indicates 95% CI. Black triangle indicates significant association ($P < 0.05$)

yielded a high correlation coefficient ($r = 0.86$, $P < 0.001$). This model has already been validated in a previous study [34].

Association between PM_{10} and biomarkers of glycemic control

We found that the concentration of PM_{10} at the homes of patients significantly associated with HbA1c, 2hPG, and HOMA—IR after adjustment for age, gender, duration of diabetes, WHR, smoking and season of enrolment (see Figs. 1, 2). For instance, we found 1 SD increment in PM_{10} was associated with 2.25 mmol/mol (95% CI, 0.64–3.86) and 0.38 mmol/l (0.11–0.65) increase in arithmetic means of HbA1c and 2hPG, respectively. Similar increase in PM_{10} was also associated with 4.89% (0.59–9.37) increase in geometric mean of HOMA—IR. Residential PM_{10} level was not associated with FPG, HOMA—β and DI. Additional adjustment for medication, meteorological variables (i.e., temperature and relative humidity) and air quality did not show significant effect on the response.

Effect modification analysis

We present the effect modification only for the variables which were significantly associated with residential PM_{10} level, and the rest are provided as online supplementary material (Supplementary figures 2, 3 and 4). Enhanced association between residential PM_{10} and 2hPG were observed among patients with central obesity and patients who were currently smoking (Fig. 3). Similarly, WHR and smoking were important modifiers of the association between PM_{10} and HbA1c (Fig. 4). We have also observed that association between PM_{10} and HbA1c were significantly higher among those patients who were on oral anti-diabetic treatment (i.e., Glitazones and Sulfonylureas), but insulin treatment mitigates the association. On the other hand, the effects of PM_{10} on HOMA-IR were significantly higher in female subjects and those who were centrally obese (see Fig. 5).

Discussion

We have shown that 1 SD increment in PM_{10} (43.83 μg/m^3) in a residential place over a period of 1 year is associated with an increase in HbA1c (2.25 mmol/mol, equivalent to 9.6 % change in SD), 2hPG (0.38 mmol/l, equivalent to 8.5 % change in SD), and HOMA—IR (0.27 units, equivalent to 4.89 % change in GM) in Indian type 2 diabetic patients. These associations were robust to different modeling approaches (additional adjustment for temperature and relative humidity and medication). We did not find an association between PM_{10} and levels of FPG, HOMA—β and DI. Effect modification analysis revealed a significant interaction, such that PM_{10} had a larger effect on 2hPG and HOMA-IR among centrally obese participants and smokers. Also we have found that patients who were treated with insulin—unlike those who were on Glitazones and Sulfonylureas—show a reduced effect from PM_{10} on HbA1c. Hyperglycemia is a potent risk factor for diabetic vascular complications [35]. Our findings thus raise the possibility that long-term exposure to PM_{10} could worsen the risk of diabetes complications [36] especially in the centrally obese and smokers. Even though the size of the effect is modest, it adds to the list of modifiable risk factors for diabetic vascular complications.

Lockwood [37] first demonstrated a significant relationship between 1999 US state-wide Toxics Release Inventory

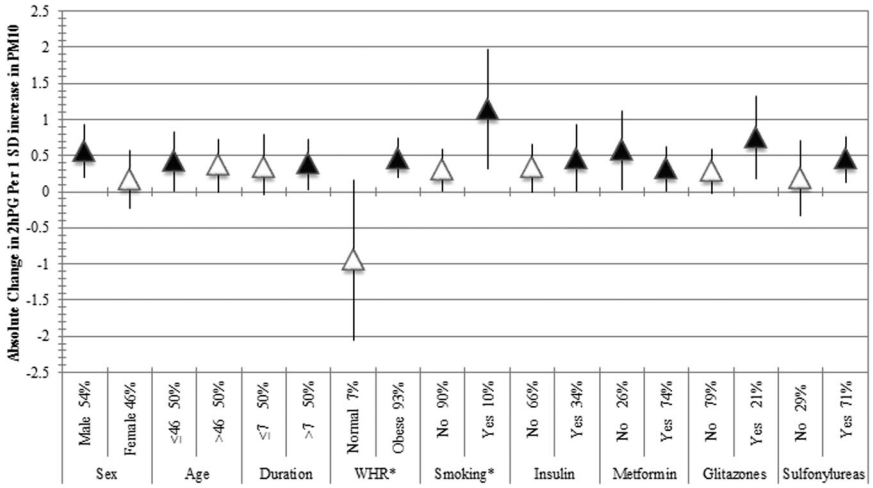

Fig. 3 Effect modificationThe estimates are given as absolute change in 2hPG per 1 SD (=43.83 μg/m^3) increase of PM10. Error bar indicates 95% CI. Black triangle indicates significant association ($P < 0.05$). * indicates significant interaction

and the prevalence of self-reported diabetes from the Behavioral Risk Factor Surveillance System. A number of other studies reported an association between air pollution and diabetes incidence [2, 7, 38–40]. However, only a few studies have investigated whether air pollution is associated with poor metabolic control in type 2 diabetic patients [9, 10, 13].

Chuang et al. investigated the association between 1-year average air pollutants exposure and FPG and HbA1c in 1023 adults (aged ≤54). FPG and HbA1c was accessed from the database of the Social Environment and Biomarkers of Aging Study in Taiwan and air pollutant obtained from 72 monitoring stations of Taiwan administration environmental protection agency (nearest station for each person). They reported that 20.42 μg/m^3 increment in 1 year background exposure to $PM_{2.5}$ was associated with 1.92 mmol/l increase in FPG and 22.95 mmol/mol increase in HbA1c (these changes represent >30% increase in the mean values of FPG and HbA1c) [10]. Mexican Americans study among 1023 young obese women with history of GDM reported that 3.6 μg/m^3 increment in a 12 months' cumulative exposure to ambient $PM_{2.5}$ (obtained from monitoring station and assigned to residential address of subjects) prior to blood sample associated with 0.08 mmol/L increase in absolute FPG and 5.81% increase in geometric mean of HOMA-IR [8].

Another study [9] among newly diagnosed type 2 diabetic patients in Germany showed higher adjusted mean HbA1c levels (56 mmol/mol) in the highest quartiles of exposure to PM_{10} (21.10 μg/m^3) compared to a level of 52 mmol/mol in lowest quartile (16.40 μg/m^3) of exposure. A recent nation-wide survey from China ($n = 17{,}708$, age ≥ 45) also indicated a significant association between $PM_{2.5}$ and FPG and HbA1c. The effect estimate for a 41.1 μg/m^3 increment in $PM_{2.5}$ were associated with increase of a 0.26 mmol/L and 0.08% in FPG and HbA1c, respectively [11]. However, other studies from Iran [13] and Germany [12] using different methodological approach for exposure assessment, found no convincing evidence between exposure to PM and HbA1c in young subjects with diabetes type I ($n = 330$).

Epidemiological studies that examined associations between long-term exposure to air pollution and insulin resistance are limited. Along with BetaGene study [8], the analysis of 10-year-old children ($n = 397$) in two prospective German birth cohorts [21] that showed a 2 SD (=6 μg/m^3) increment in ambient PM_{10} at residential places (estimated with land use regression models) was associated with 18.7% (95% CI 2.9, 36.9) increase in HOMA-IR. Recently, Latino children study in Los Angeles, CA investigated the link between ambient exposure to $PM_{2.5}$, and insulin sensitivity and β cell function. Children were followed for the average period of 3.4 years and observed that a higher exposure to $PM_{2.5}$ (=4 μg/m^3) during the follow-up period was associated with 2.9% higher fasting insulin and 3.3% lower insulin sensitivity. Similar to our finding in this study, there were no significant association between exposure to ambient PM and DI [14]. As per our review, no study has yet investigated the long-term effect of PM_{10} on HOMA-IR in diabetic patients or reported PM_{10} levels as high as that in our study (172.48 ± 43 μg/m^3). Nevertheless, low magnitude of effect we have detected (4.89%) in comparison to BetaGen and German birth cohort study may be due to method of exposure assessment, health status of the study population, and composition or size of PM [41]. Also the small effect size in our study may be similar as those time-series studies done in high-polluted area, where local people may be adapted to the pollution.

Air pollutants contain free radicals or have the ability to drive free radical synthesis [42] that act directly on lipids and proteins, or indirectly through the activation of intracellular oxidant pathways [17, 43, 44]. Oxidative stress caused by exposure to air pollutants may therefore play a role in dysregulation of glucose homeostasis including insulin signaling abnormalities and development of insulin

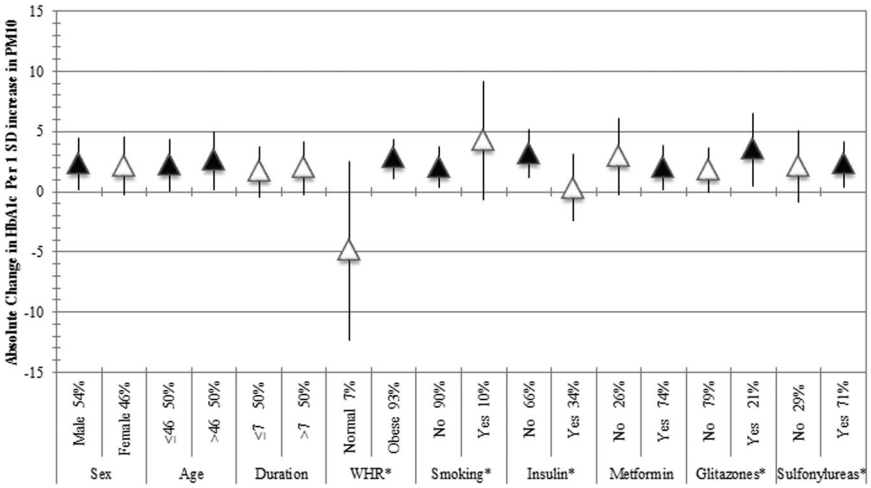

Fig. 4 Effect modificationThe estimates are given as absolute change in HbA1c per 1 SD (=43.83 μg/m^3) increase of PM10. Error bar indicates 95% CI. Black triangle indicates significant association ($P < 0.05$). * indicates significant interaction

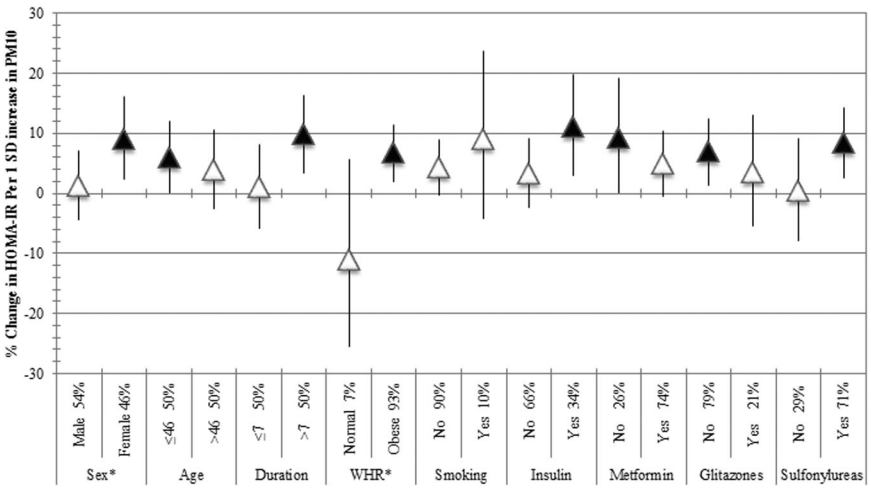

Fig. 5 Effect modificationThe estimates are given as percent change in geometric means of HOMA-IR per 1 SD (=43.83 μg/m^3) increase of PM10. Error bar indicates 95% CI. Black triangle indicates significant association ($P < 0.05$).* indicates significant interaction

resistance [18–20, 45]. Condition such as obesity and exposure to cigarette smoke, which is associated with increase in free radical and oxidative stress [46], therefore could enhance the susceptibility for effect from PM exposure [47]. Previous studies detected that smoker are more likely to live in residential area with higher ambient air pollution levels [48]. However, we did not find statistically significant difference in the amount of ambient exposure between smoker and non-smoker in our study (PM_{10} concentration for smoker = 165.87 vs. non-smokers = 173.17, p-value > 0.05).

Interestingly we found that those on insulin treatment (which have anti-oxidant action) [49] had smaller rise in HbA1c in relation to PM_{10} exposure compared with those who were not treated with insulin. However, regardless of anti-inflammatory and antioxidant properties of Glitazones and Sulfonylureas we have found that use of such agents trigger the effects of PM_{10} on HbA1c. Indeed, findings from several studies demonstrated that Glitazones and sulfonylureas associated with increased body weight [50]. Therefore, we speculated probability of such explanation for the enhanced association among patient on any of Glitazones or Sulfonylureas medication, but our data did not support.

Assessing individual exposure to air pollution requires extensive resources. Therefore, most studies have assessed exposure to air pollution using outdoor monitoring stations. Although concentrations of pollutants measured by ambient monitors may correspond to air pollution exposure at regional levels, this may not represent individual exposure [41]. We had data on dietary habit (vegetarian/lacto-veg/non-vegtarian/ovo-veg and alcohol consumption status) and years of education. However, these variables were excluded from our final models based on minimum value of Akaik's Information Criterion [29]. Also other study did not show strong association between regional pollutant (i.e., $PM_{2.5}$) and socio–economic status [51]. However, we did not account for physical activity, which may confound the association. We also know one more source of bias exists due to the fact that we have not assigned a standard meal to

the participants before the 2 h of blood withdrawal and this could have confounding effect in the association between PM_{10} and 2hPG.

Personal exposure measurements can be performed directly or indirectly. In the direct approach exposure levels are determined on an individual (by using a personal sampler or a biological marker), and in the indirect approach exposure levels are either determined by measuring stationarity or by models [52].

We believe that the strength of the current study lies in the method of exposure assessment, where we used dispersion models, which is a more precise method to estimate individual exposure data from the central monitoring station.

For outdoor pollutants, sophisticated dispersion models (e.g., Gaussian models), which incorporate meteorological variables and chemical processes, have been developed and used not only for exposure assessment but also for regulatory purposes across the globe. They can be used to predict outdoor spatial and temporal behavior of pollutants (Hanna et al., 1982). Their most important shortcoming is the need for detailed emission inventories. However, we accept the limitation of our study is that for the exposure assessment we had emission inventory data only for the baseline year (i.e., 2005) and used this as an indicator of the historical exposure for the further years, assuming that the annual exposure (spatially) varied a little in years 2005 and 2007. Also we have adjusted possible seasonal variation in the PM concentration in our analysis models. We adjusted the effect of clinical and environmental covariates in our analysis but, like any observational study, residual confounding is possible and causality is difficult to establish because of cross-sectional analysis.

Conclusions

Our study suggests that long-term exposure to PM_{10} could influence glycemic level and IR in diabetic patients. In combination with our previous demonstration of association of air pollution with inflammatory state, our results raise the possibility that air pollution exposure could contribute to increased risk of diabetic complications. Prospective large-scale studies and interventions are needed to confirm and establish causality of these interesting findings.

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Author contributions MAK and CSY researched, wrote, discussed and edited the manuscript. SSS and AO contributed to the discussion and edited the manuscript. BK and SDG contribute to the data analyses and edited the manuscript. CSY is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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