Air Pollution and Serum Glucose Levels

A Population-Based Study

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Abstract: Recent studies demonstrated an adverse effect of chronic exposure to air pollution (AP) on metabolic syndrome and its components. In a population-based study, we investigated the association between exposure to ambient AP and serum glucose (SG), among subjects with normal glucose, impaired fasting glucose (IFG), and diabetes mellitus (DM).

We included 1,063,887 SG tests performed in 131,882 subjects (years 2001–2012). Exposure data included daily levels of SO_2, NO_2 and other pollutants of industrial, traffic, and nonanthropogenic sources. Demographic, clinical, and medications purchase data were assessed. Log-transformed SG levels were analyzed by linear mixed models adjusted for seasonal variables and personal characteristics.

SG increases (%increase [95% CI]), among subjects with normal glucose, IFG, and DM, respectively, were associated with 6.36 ppb increase of NO_2 measured 24 to 72 hours before the test (0.40% [0.31%; 0.50%], 0.56% [0.40%; 0.71%], and 1.08% [0.86%; 1.29%]); and with 1.17 ppb increase of SO_2 measured 24 hours before the test (0.29% [0.22%; 0.36%], 0.20% [0.10%; 0.31%], and 0.33% [0.14%; 0.52%]). Among DM population, weakest association was observed among patients treated with Metformin (0.56% increase in SG [0.18%; 0.95%]).

In conclusion, NO_2 and SO_2 exposure is associated with small but significantly increased levels of SG. Although DM patients were found to be more susceptible to the AP induced SG variations, Metformin treatment seem to have a protective effect. Given the chronic lifetime exposure to AP and the broad coverage of the population, even small associations such as those found in our study can be associated with detrimental health effects and may have profound public health implications.

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Abbreviations: ADA = American Diabetes Association, AP = air pollution, CBS = central bureau of statistics, CHS = Clalit Health

Services, CI = confidence intervals, CV = coefficient of variance, DM = diabetes mellitus, HbA1c = glycosylated hemoglobin, HMO = Health Maintenance Organization, IFG = impaired fasting glucose, IQR = interquartile range, PM_{10} = particular matter smaller than 10 μm in diameter, $PM_{2.5}$ = particular matter smaller than 2.5 μm in diameter, SES = socioeconomic status, SG = serum glucose, SUMC = Soroka University Medical Center.

INTRODUCTION

Recent studies demonstrated an adverse effect of long-term exposure to air pollution (AP) on metabolic syndrome and its components, such as diabetes mellitus (DM) and hypertension,[1–3] adding risk to known factors such as lifestyle, obesity, and inactivity.[4]

The data on the effect of the specific pollutants on glucose homeostasis—a major component of the metabolic syndrome—are scarce. One study found positive association of fasting serum glucose (SG) only with ozone, and no other pollutants.[5] Others found positive significant associations between fasting SG levels, insulin resistance, and particular matter smaller than 10 μm in diameter (PM_{10}),[6] particular matter smaller than 2.5 μm in diameter ($PM_{2.5}$),[7,8] sulfur dioxide (SO_2),[6] and nitrogen dioxide (NO_2).[9–11] Studies suggested that the pathophysiology explaining a possible association between AP and glucose levels is linked to an inflammatory response which may disrupt the lipid and glucose metabolism process.[3,12,13]

Current evidence is highly diverse in terms of exposure assessment, outcome definitions, and the estimates of association found. The association between AP exposure and glucose homeostasis can be confounded by time factors,[5] seasonality factors,[5,7] and personal characteristics: age,[3,5,7,14,15] gender,[3,5,15] ethnicity,[7,15] comorbidities,[3] socioeconomic status (SES),[3,5,15] and other confounders.[3]

Trying to address the potential biases, we performed a population-based analysis of over 1 million tests, collected over 12 years in Southern Israel (Negev). We aimed to explore the association between AP (PM_{10}, carbon monoxide (CO), SO_2, NO_2, and O_3) and SG and glycosylated hemoglobin (HbA1c) variations, and to assess the potential interactions by the presence of diabetes and impaired glucose tolerance and type on antidiabetic treatment.

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METHODS

Study Population

We included all fasting SG tests of Clalit Health Services (CHS), Health Maintenance Organization (HMO) members, performed in southern Israel between the years 2001 and 2012. Health data were retrieved from CHS database. CHS is

the largest HMO in Israel; it insures approximately 70% of the Negev population of 730,000 residents.[16] All blood tests of CHS members in the Negev are analyzed by a single laboratory. The demographic, clinical, laboratory and medication prescription data of CHS members are fully computerized and are available at the patient level. We obtained the following patient data: age, gender, ethnicity, comorbidities, medications, and SES. The latter was stratified into 3 levels: low, intermediate, and high. SES was assigned based on the SES of the population residing in the close proximity to the subjects' primary clinic, according to the definitions of the central bureau of statistics (CBS). Ethnicity was assigned for each city or settlement of residence by the CBS and was determined according to the religion of the majority of the population residing in it.[17]

We excluded children (under 18 years of age), and those residing further than 20 km from the available monitoring stations. The population excluded was similar to the subjects represented in the study in terms of age, gender, and ethnicity distribution.

Clinical Definitions

We defined the patient DM or impaired fasting glucose (IFG) status in accordance to the American Diabetes Association (ADA) criteria.[18] *Diabetes diagnosis* was established if one of the following was present: documented physician confirmed diagnosis, antidiabetic medication purchase, more than 1 measurement of fasting SG equal or higher than 126 mg/dL or more than 1 measurement of HbA1c $\geq$6.5%. Patients were defined as having *IFG* if case of a record of more than 1 fasting SG between 100 and 125 mg/dL, or more than 1 measurement of HbA1c between 5.7% and 6.5%, or only 1 fasting SG level higher than 125 mg/dL, or only 1 HbA1c $\geq$6.5% in the presence of at least 1 additional fasting SG level between 100 and 125 mg/dL and at least 1 HbA1c level between 5.7% and 6.5%.[18] On an event of multiple tests available per a patient the most severe status of the disease was assigned, that is, patients meeting DM criteria once during the study period, were considered as such through the entire follow-up time.

Tests performed during hospitalizations were excluded from the analysis.

Air Pollution and Meteorological Data

Daily data on air pollutants and meteorological variables (air temperature and relative humidity) for the period of 2001 to 2012 were obtained from the monitoring site located in the center of the largest city (Beer-Sheva) in the Negev area. This monitoring station is simultaneously recording data (every 5 minutes) of the following pollutants: PM_{10}, CO, SO_2, NO_2, and O_3. Pollutants values higher than the 98th percentile were defined as outliers and were imputed with the value of the 98th percentile.

Blood tests are performed between 7:00 and 10:00 AM in all primary clinics in southern Israel. Since the exact time of the test was not available, we used the calculated averages of concentrations of the pollutants over 24 hours (from 10:00 in the previous day to 10:00 AM in the day of the test) as well as the temperature and relative humidity—24, 48, and 72 hours before the day of the test.

Statistical Analysis

Results are presented by mean $\pm$ SD, interquartile range (IQR) and range for continuous variables and as percentages for categorical data.

Coefficient of variation (CV) of SG was calculated for each subject. Low and high variability of SG results were defined according to CV values lower than the 10th percentile, and higher than the 90th percentile, respectively.

Analyses were performed separately among subjects with DM, IFG, and normal glucose. Log-transformed SG levels were modeled by mixed linear models, accounting for repeated tests within each subject. We used multipollutant models, inclusive of 24, 48, or 72 hours averages of pollutants. Models were adjusted for average value of temperature and relative humidity, day of the week, year, age, gender, hypertension, ethnicity, and SES. Models for DM patients were also adjusted for the purchase of anti diabetic drugs during the 3 preceding months. Coefficients were antilog transformed to the original units, and results are presented as percent change in SG levels and 95% confidence intervals (CI).

In a subgroup analysis among the DM patients, we stratified by the type of treatment: no medications, Insulin, Metformin, or other antidiabetic drugs (GLP1 agonists, DPP4 inhibitor, alpha glucosidase inhibitor, sulphonylurea, meglitinides, and thiazolidinediones).

The log-transformed HbA1c levels were modeled as well. Since HbA1c levels represent the mean SG levels over approximately 3 months, exposure to pollutants was assigned as a 3 months moving average of the pollutants concentrations.

Sensitivity Analysis

SES data were available for 87% of the study population. We performed sensitivity analyses to verify our results with the imputation of median and maximal SES levels.

Analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC) and R3.1.0 software.

The study has been approved by the institutional review board of Soroka University Medical Center (SUMC).

RESULTS

Population

We identified 1,063,887 SG tests of 131,882 region residents eligible for the study (Figure 1). DM patients (26,071 subjects) were 63 years old on average, 68% were treated with anti diabetic drugs. Subjects (105,811 subjects) with no evidence of DM or IFG were younger, and 2.22% (1961 subjects) were diagnosed with ischemic heart disease and/or myocardial infarction (Table 1).

Meteorological and Pollution Data

Table 2 shows summary statistics of AP and meteorology data during the study period. Air pollutants IQR during the study period were as follows: CO 0.19 ppm, NO_2 6.36 ppb, SO_2 1.17 ppb, O_3 13.79 ppb, and PM_{10} 26.44 µg/m³. The air temperatures are relatively high most of the year. The IQR of the 24-hour mean air temperature ranged between 14.4 and 24.9 °C reaching maximal mean air temperature of 33.7 °C (Table 2).

Estimating the Effect of Air Pollutants on SG and HbA1c

Linear mixed models were employed to estimate the association between AP exposure and SG levels and HbA1c in all study groups. AP and meteorological factors were not highly correlated in our data, with a highest correlation estimate observed for NO_2 and SO_2 (r = 0.34, $P < 0.01$).
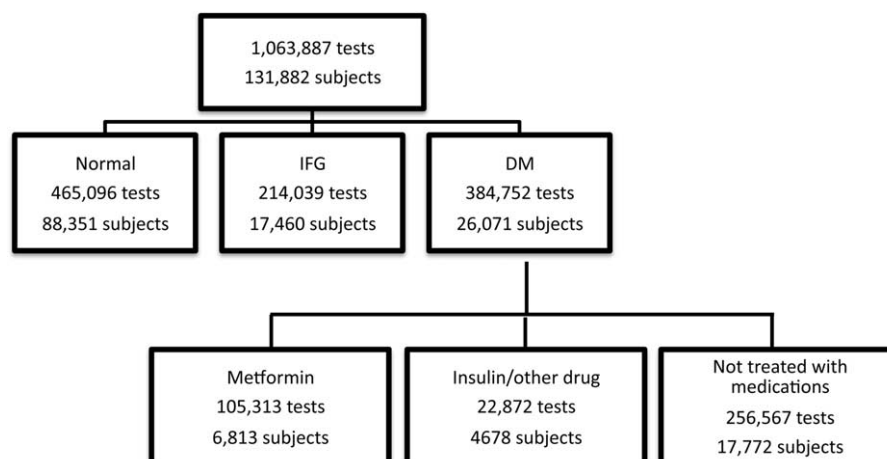
FIGURE 1. The total number of tests and subjects included in the study, by 3 comparison groups: subjects with normal glucose, impaired fasting glucose (IFG), and diabetes mellitus (DM). DM patients are stratified by the treatment type.

NO_2

In all groups, SG levels were positively associated with IQR elevations of average NO_2 concentrations 48 and 72 hours before the blood test. Stronger associations were observed with NO_2 concentrations 72 hours before the blood test. Association observed among subjects with DM were stronger: 1.08% increase (95% CI: 0.86%; 1.29%), compared to 0.40% increase (95% CI: 0.31%; 0.50%) among subjects with normal glucose levels; and 0.56% increase (95% CI: 0.40%; 0.71%) among subjects with IFG.

SO_2

In all groups, SG increases were more pronounced when assessing exposure to SO_2 concentrations 24 hours before the blood test, compared to prolonged periods of exposure. The highest increase in SG was observed among subjects with DM: 0.33% increase (95% CI: 0.14%; 0.52%), compared to 0.29% increase in SG (95% CI: 0.22–0.36%) among subjects with normal glucose levels; and 0.20% increase in SG (95% CI: 0.10–0.31%) among subjects with IFG (Table 3).

No associations were found with CO, PM_{10}, or O_3 average concentrations 24 to 72 hours before the test, in all study subgroups.

Identification of Susceptible Population

To evaluate possible interactions with the type of treatment among DM patients, we compared the percent change in SG levels among DM patients treated only with Metformin, insulin, or other oral medications, and patients that are not treated with antidiabetic medications. Weaker associations with NO_2 were observed among untreated patients (1.16% increase in SG, 95% CI: 0.90–1.42%) and among patients treated with Metformin (0.56% increase in SG, 95% CI: 0.18–0.95%), compared to patients treated with Insulin (1.81% increase in SG, 95% CI: 0.26–3.38%) or other antidiabetic medications (2.12% increase in SG, 95% CI: 0.82–3.44%). No significant associations with SO_2 were found in any of the sub groups (Figure 2).

Comparing the lowest and highest quantiles of coefficient of variance (CV) values, we found stronger association with NO_2 among patients presented high variability in SG (1.53% increase in SG, 95% CI 0.42–2.65%), compared to the lowest

quantile of SG variability (0.79% increase in SG, 95% CI: 0.34–1.25%). No significant associations were observed with SO_2.

No effect modification was found in analyses stratified by age or ethnicity.

Approximately 4% (4756 subjects) of the study population had available HbA1c tests within the study period (a total of 5715 tests). HbA1c level ranged between 4% and 20.3%, with a median value of 6.7%. No associations were found between the different pollutants and HbA1c levels.

Sensitivity Analysis

As a sensitivity analysis, we repeated the analyses using 2 methods of SES imputation: by assigning the most frequent SES level (low) and the highest SES level. The results were consistent with the main results and showed no difference in the inference.

DISCUSSION

In this population-based study of 131,882 subjects with over 1 million glucose tests, we were able to detect associations of AP exposure and SG levels. We found positive associations between SG levels and NO_2 and SO_2, among subjects with normal glucose levels, IFG and diabetes. The association with NO_2 was especially pronounced among DM patients; however, Metformin treatment ameliorated the negative effect of the pollutant.

Short-Term Exposure

In the last few decades, studies have provided findings linking environmental exposures to IR, SG levels, and metabolic diseases.[2,20,21] Yet, the evidence regarding the association of AP and glucose metabolism are sparse.[1,5,9,10,12,21]

Kim et al found positive associations of PM_{10}, O_3, and NO_2 with IR. The authors contributed the lack of association found with SO_2 to the different sources of the pollutants: while PM_{10}, O_3, and NO_2 are emitted mostly from traffic sources, SO_2 is known to be a combustion product in industries.[9] We found positive associations between SG levels and NO_2 and SO_2, 72 and 24 hours concentrations before the test. In Southern Israel, other than natural dust and traffic as AP sources, another

TABLE 1. Study Population Characteristics

Study Population Characteristics	Study Groups		
	Normal Glucose, 88,351 Subjects (460,096 Tests)	IFG, 17,460 Subjects (214,039 Tests)	DM, 26,071 Subjects (384,752 Tests)
Anti diabetic medications			
Insulin, % (n)	0 (0)	0 (0)	4.51 (1177)
Metformin, % (n)	0 (0)	0 (0)	26.2 (6813)
Other, % (n)	0 (0)	0 (0)	13.4 (3501)
Age, mean ± SD	44.71 ± 18.7	59.24 ± 17.4	63.03 ± 15.3
Male gender, % (n)	36.53 (32,270)	38.99 (6808)	41.7 (10,877)
Chronic conditions:			
Ischemic heart disease	0.78 (693)	3.31 (578)	5.88 (1532)
Myocardial infarction	1.64 (1449)	5.49 (958)	10.13 (2640)
Hypertension	0.22 (192)	0.86 (150)	1.37 (357)
Type of locality, % (n)			
Jewish, urban	68.33 (60,370)	82.69 (14,438)	79.04 (20,638)
Jewish, rural	2.19 (1939)	2.28 (398)	2.39 (623)
Bedouin, urban	24.81 (21,922)	13.02 (2273)	16.21 (4226)
Bedouin, rural	4.66 (4120)	2.01 (351)	2.24 (584)
SES, % (n)[*]			
Low	68.41 (52,160)	62.11 (9163)	67.54 (15,295)
Intermediate	25.16 (19,183)	31.17 (4598)	27.69 (6272)
High	6.43 (4901)	6.72 (991)	4.77 (1080)

DM = diabetes mellitus, IFG = impaired fasting glucose, SES = socio economic status.
[*] SES—socioeconomic status, defined as the socioeconomic status of population residing in the proximity of the person's primary clinic.

potential source is the emissions from an industrial site located approximately 15 km from the largest city in the area.

In accordance with our findings, a recent meta-analysis found a pooled relative risk of 1.08 (95% CI: 1.00, 1.17) for type 2 diabetes per 10 $\mu g/m^3$ increase in NO_2.[3] Since the majority of NO_2 emissions originate in traffic, the lack of significant associations reported in other studies[22,23] may be due to low pollution levels and lower effect sizes.[10]

Susceptible Populations

Previously, the majority of the epidemiological studies investigating AP effect on glucose homeostasis have focused on diabetic patients, as a group with particularly high susceptibility to AP-triggered cardiovascular events.[25–28] Supporting the

hypothesis of higher vulnerability of patients with DM, our study showed higher associations with both NO_2 and SO_2.

The association with NO_2 was less pronounced among DM patients who presented low variability in SG results as well as among those treated with Metformin. The same inflammatory mechanism of AP associated with cardiovascular damage, is also believed to be involved in the promotion of IR and Type 2 diabetes.[22,29] In the present study, we have shown that among patients with diabetes, those receiving Metformin treatment were resistant to the AP effect on glucose levels. Insulin sensitizers (eg, Metformin) suppress proinflammatory genes, therefore may enhance the antiinflammatory response occurring in the presence of AP exposure. Rioux and colleagues[30] found lower c-reactive protein (CRP) levels among DM patients residing in proximity to main roads and treated with oral

TABLE 2. Summary Statistics for Daily 24 hours Average Air Pollutant and Meteorological Data (2001–2012)

Daily Levels	Mean ± SD	Interquartile Range	Maximal Value
PM_{10} ($\mu g/m^3$)	51.41 ± 42.38	28.52–54.94	240.00
NO_2 (ppb)	10.83 ± 4.64	7.26–13.62	21.00
CO (ppm)	0.85 ± 0.36	0.85–1.04	1.89
SO_2 (ppb)	1.86 ± 0.84	1.22–2.39	4.00
O_3 (ppb)	35.54 ± 10.02	28.80–42.59	57.00
Air temperature (°C)	19.64 ± 5.74	14.40–24.94	33.72
Relative humidity (%)	66.81 ± 15.57	59.75–76.70	100.00

CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = particular matter smaller than 10 μm in diameter, SD = standard deviation, SO_2 = sulfur dioxide.
Pollutants' values above the 98th percentile were defined as outliers and were imputed with the 98th percentile value.

TABLE 3. The Percent Change in Serum Glucose Levels, Associated With NO_2 and SO_2 Concentrations, Among Subjects With Normal Glucose Levels; Impaired Fasting Glucose and Diabetes Patients

Pollutants 24–72 hours Average Concentrations	Percent Change in Serum Glucose Levels (95% Confidence Intervals)		
	Normal Glucose Levels	**Impaired Fasting Glucose**	**Diabetes Mellitus**
NO_2 24 hours	0.20% (0.13%; 0.28%)[*]	0.43% (0.32%; 0.54%)[*]	0.09 % (−0.10%; 0.29%)
NO_2 48 hours	0.25% (0.17%; 0.34%)[*]	0.49% (0.34%; 0.63%)[*]	0.84 % (0.64%; 1.03%)[*]
NO_2 72 hours	0.40% (0.31%; 0.50%)[*]	0.56% (0.40%; 0.71%)[*]	1.08 % (0.86%; 1.29%)[*]
SO_2 24 hours	0.29% (0.22%; 0.36%)[*]	0.20% (0.10%; 0.31%)[*]	0.33 % (0.14%; 0.52%)[*]
SO_2 48 hours	0.12% (0.05%; 0.20%)[*]	0.04% (−0.07%; 0.16%)[*]	0.27 % (0.09%; 0.44%)[*]
SO_2 72 hours	−0.04% (−0.07%; 0.07%)	−0.05% (−0.18%; 0.06%)	0.18 % (0.00%; 0.37%)[*]

This table shows the percent change in serum glucose levels for interquartile range (IQR) elevation of SO_2 (1.17 ppb) and NO_2 (6.36 ppb) average concentrations 24–72 hours before the test, with 95% confidence intervals. The coefficients were back-transformed using the following formula: EXP $((\beta^{*}IQR) - 1) \times 100$. Where EXP = exponential value, β = the regression coefficient, and IQR = the pollutants' interquartile range. Models were performed separately in subjects with normal glucose levels; impaired fasting glucose treated and untreated diabetes, and were adjusted for day of the week, year, average temperature and relative humidity, gender, age, hypertension, and socioeconomic status. Among patients with diabetes, models were also adjusted for the purchase of antidiabetic drugs 3 months before the test.
[*] $P < 0.05$.

hypoglycemic medications versus nontreated, supporting the hypothesis of an antiinflammatory downregulation process.

Health Implications

Assessing the results of our study, the main question that can be asked by the clinicians is: what is the health effect of these relatively numerically small observed associations between the air pollutants and glucose levels? The answer is 2-fold: the effect is clinically significant both on a population and individual levels. Given the broad extent of exposed population and the continuous nature of exposure, even small adverse associations represent a public health concern and may have implications on public health policies.[20] Because the whole population is exposed, even small effects can be translated into substantial attributable adverse health outcomes.[31]

Another aspect that should be considered on an individual level is the chronic exposure effect. As short-term studies describe only part of the air-pollution-related adverse outcomes,[31] while the cumulative lifetime risk is probably larger than the usually assessed acute risk. The cumulative adverse health effects are related to a combination of exposure intensity and duration. Therefore, even numerically small acute effects, such as observed in our study, can be translated into a profound detrimental clinical effect over longer period.

Glucose levels increasing due to the AP both within and above normal range can contribute to the development of vascular morbidity. As reported in the findings of the Honolulu Heart Study, the risk of CHD increases continuously as glucose levels increases,[32] emphasizing the importance of glycemic control and glucose reduction, even in small amount and within
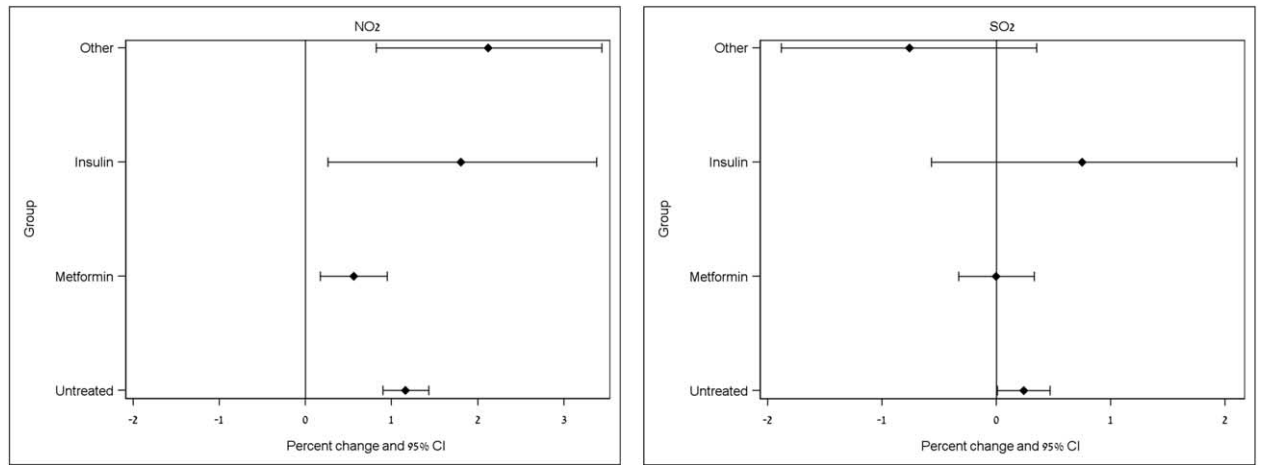
FIGURE 2. The percent change in serum glucose levels for IQR elevation of NO_2 (6.36 ppb) and SO_2 (1.17 ppb) concentration 72 hours before the test, with 95% confidence intervals. The coefficients were back-transformed using the following formula: EXP $((\beta^{*}IQR) - 1) \times 100$. Where EXP = exponential value, β = the regression coefficient, and IQR = the pollutants' interquartile range. Models were performed separately among untreated patients with diabetes, and among patients treated with Insulin, Metformin, or other antidiabetic medications. Models were adjusted for day of the week, year, average temperature and relative humidity, gender, age, ethnicity, socioeconomic status, hypertension, and the purchase of antidiabetic medications 3 months before the test. IQR = interquartile range; [*] $P < 0.05$.

the normal range. Furthermore, higher glucose levels were reported to be associated with cardiovascular disease, even within the range of normal glucose levels.[33] That said, the AP related increases in glucose found in our study were relatively small. In order to establish cardiovascular risk the effect of lifetime chronic exposure should be estimated.

LIMITATIONS

Our study had a number of limitations. First, AP data for our study period were available only from 1 monitoring site, located in the center of the largest city in the region. To reduce exposure measurement error we excluded subjects residing farther than 20 km from the monitoring site. Therefore, the rural and suburban population is underrepresented in our study. In addition, using this method, we were unable to estimate the variations in AP in rural versus urban locations. Second, the use of medications and laboratory results for DM definition might have resulted in misclassification, as well. Both limitations might have decreased the magnitude of the associations estimated in the study.

In addition, data of potential confounders such as BMI and smoking status were not available in this study, which precluded a more detailed adjustment of the study finding. SES level was assigned based on the SES of the population residing in the close proximity to the subjects' primary clinic, but we did not have data regarding the exact estimated SES of each subject, therefore residual confounding by SES might still be present. Lastly, given the small amount of available HbA1c tests in our study, the analysis might not had the power required to detect relatively small differences and long-term associations.

CONCLUSION

In summary, in this population-based study, we found small but consistent increases in SG associated with short-term exposure to NO_2 and SO_2; especially pronounced among patients with DM who were not treated with Metformin. Given the chronic lifetime exposure to AP and the broad extent of exposed population, even small associations such as those found in our study may have profound public and individual health implications.

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