

## The Association Between Air Pollution Exposure and Glucose and Lipids Levels

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**Context:** Evidence from recent decades supports a causal association between air pollution (particulate matter  $<10\ \mu\text{m}$  in diameter [ $\text{PM}_{10}$ ] and  $\text{PM} <2.5\ \mu\text{m}$  in diameter [ $\text{PM}_{2.5}$ ]) and oxidative stress, possibly involving impaired metabolism of glucose and lipids.

**Objective:** Using a satellite based model to assess PM exposure at 1-km spatial resolution, we examined the associations between PM and glucose, hemoglobin A1c (HbA1c), and lipids.

**Design:** Population-based retrospective cohort study of a 10-year period.

**Setting:** Members of the largest health care provider in Southern Israel.

**Participants:** We included all serum glucose, HbA1c, and lipids tests of subjects with known cardiovascular diseases and risk factors. Subjects' glycemic status was defined as normal or diabetes.

**Main Outcome:** Log-transformed glucose, HbA1c, and lipid values were explored by mixed models, with adjustment for personal and seasonal confounders.

**Results:** We assessed 73 117 subjects with over 600 000 samples. Three-month average concentration of  $\text{PM}_{10}$ , but not 1- to 7-d exposure, was associated with increases of serum glucose, HbA1c, low-density lipoprotein and triglycerides, and decrease of high-density lipoprotein. The strongest associations were observed among subjects with diabetes (percent increase [95% confidence interval], for interquartile range increase of  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$ ): 3.58% (1.03%; 6.20%) and 2.93% (0.35%; 5.59%) increase in HbA1c and 2.37% (2.11%; 2.63%) and 1.54% (1.26%; 1.83%) increase in low-density lipoprotein. Antidiabetic medications (other than insulin) attenuated the air pollution effect on serum glucose.

**Conclusions:** Intermediate-term, but not short term, exposure to PM is associated with alterations in glucose, HbA1c, and lipids, especially among people with diabetes. (*J Clin Endocrinol Metab* 101: 2460–2467, 2016)

**P**articulate matter (PM) is one of the leading risk factors for global disease burden (1). Cardiovascular, respiratory, and metabolic effects of air pollution have already been documented in several studies (2, 3). Evidence from recent decades supports a causal association between exposure to PM less than  $10\ \mu\text{m}$  in diameter ( $\text{PM}_{10}$ ) and PM

less than  $2.5\ \mu\text{m}$  in diameter ( $\text{PM}_{2.5}$ ) and oxidative stress (4), which may explain the association with an increased risk for cardiovascular morbidity (2, 5). Several biological pathways were proposed, among them: atherosclerosis acceleration (6), coagulation changes (7) and blood cells response (8), the development of dysfunctional high-density

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Abbreviations: AOD, Aerosol Optical Depth; BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; IR, insulin resistance; LDL, low-density lipoprotein; PM, particulate matter;  $\text{PM}_{10}$ , PM less than  $10\ \mu\text{m}$  in diameter;  $\text{PM}_{2.5}$ , PM less than  $2.5\ \mu\text{m}$  in diameter; SES, socioeconomic status.

lipoprotein (HDL) with impaired capacity to provide antioxidant protection (9), and endothelial dysfunction and vasoconstriction (10). The latter is supported by the evidence that the exposure to higher concentration of diesel exhaust particles reduces the endothelial relaxation evoked by nitric oxide, suggesting a direct effect of diesel exhaust particles on smooth muscles relaxation, mediated by the nitric oxide reduction (11).

Impaired metabolism of glucose and lipids associated with PM exposure and mediated by insulin resistance (IR) (12–14) contributes to the development of the cardiovascular disease. A recent animal study showed that mice who were exposed to PM<sub>2.5</sub> for 10 weeks displayed impaired hepatic glycogen storage, glucose intolerance, and IR (12). In another study, mice who were exposed to PM<sub>2.5</sub> for 10 weeks exhibited a reduced plasma HDL level and increased low-density lipoprotein (LDL) oxidation, free oxidized fatty acids, and triglycerides (15). However, current knowledge of the association of PM exposure and glucose metabolism (13, 16, 17), IR (18), hemoglobin A1c (HbA1c) levels (13, 16), or lipids (16, 19) levels in human studies, is scarce. Moreover, spatial estimates of particle exposure are imprecise and create exposure measurement errors (20). Furthermore, most previous studies tend to focus on the association between the acute exposure and clinical/laboratory outcomes.

PM exposure is a major issue in countries located in desert areas. In Eastern Asia, the frequent dust events, which originate in the Chinese and Mongolian desert, in combination with the anthropogenic air pollution, have become a major concern for public health (21). Studies conducted in Asia has linked between dust exposure and asthma episodes (21), mortality (22), blood pressure, serum lipids, and glucose (13). If, as this study suggests, these high particle levels are also increasing IR, they may accelerate the already increasing levels of diabetes in those countries.

The Negev region (Southern Israel) is located in the global dust belt, which extends from West Africa to the Arabian Desert. PM<sub>10</sub> and PM<sub>2.5</sub> concentrations in the area can reach extremely high levels (23). In a recent study, which included real-time measurements of PM<sub>10</sub> and PM<sub>2.5</sub> levels measured simultaneously in outdoor and indoor air during dust events in the Negev, the observed average outdoor concentrations for PM<sub>10</sub> and PM<sub>2.5</sub> reached 551 and 299  $\mu\text{g}/\text{m}^3$ , respectively. Indoor levels were similar (517 and 282  $\mu\text{g}/\text{m}^3$ , respectively), suggesting high pollution infiltration into the houses (24).

We have recently presented a new method of assessing spatiotemporal resolved PM<sub>2.5</sub> and PM<sub>10</sub> exposures in the Negev (25). In contrast to many commonly used exposure models, our model makes use of satellite Aerosol Optical

Depth (AOD) measurements as well as land use terms, which allow us to estimate spatially resolved PM<sub>10</sub> on a daily basis across Israel and include populations in rural areas not living nearby monitoring stations.

As a part of the possible theory linking the association of PM exposure and cardiovascular diseases, we sought to investigate if this association might be mediated through the well-established cardiovascular risk factors such as abnormal lipid and glucose metabolism. We make use of the aforementioned model, and rich individual clinical and sociodemographic data from over 70 000 participants and 600 000 blood samples. Across 10 years of follow-up, we aim to investigate the effects of both short- and intermediate-term exposure to PM on serum glucose, HbA1c, triglycerides, HDL, and LDL.

## Materials and Methods

### Study population

The study population comprised adult subjects residing in Southern Israel between the years 2003 and 2012 and diagnosed with one of the following: stroke, ischemic heart disease, dyslipidemia, diabetes, hypertension, or being known smokers. We included all glucose, HbA1c, and lipids samples of subjects with available geocoded addresses, insured by Clalit Health Services. Clalit Health Services is the largest health care provider in the area, covering approximately 70% of a population of 730 000 residents in the Negev.

All blood tests were performed between 7 and 10 AM in the primary clinics in Southern Israel and were analyzed by a single laboratory, located in Soroka University Medical Center. Patients scheduled to undergo the aforementioned tests are routinely guided to fast 8 hours before a glucose test and 12 hours before lipids test. Computerized individual demographic, clinical, laboratory, and medication prescription data were fully available. We obtained the following patient data: age, gender, ethnicity, comorbidities, body mass index (BMI), smoking status, medications, and socioeconomic status (SES). SES was assigned based on the subjects' home address and stratified according to the definitions of the Central Bureau of Statistics assigning SES level in a scale of 1–10 (26).

We excluded children (under 18 y of age), and patients whose blood tests were performed in the presence of a known acute illness (ie, tests performed during hospitalization or tests performed in primary clinics with additional test result of white blood cells count higher above 10 800  $\text{mm}^{-3}$ ).

### Clinical definitions

#### Study groups

Diabetes diagnosis was established in the presence of one of the following: physician confirmed diagnosis, antidiabetic medication purchase between the years 2003 and 2013, and 2 or more measurement of fasting glucose more than or equal to 126 mg/dL or HbA1c more than 6.5% (27). In the event of multiple tests available, patient meeting diabetes criteria once during the

study period was assigned to diabetes group for the entire study period.

### Air pollution and meteorological data

PM<sub>10</sub> and PM<sub>2.5</sub> daily average concentrations were estimated using a hybrid satellite based model incorporating daily satellite remote sensing data at 1 × 1-km spatial resolution (28). Briefly, we use an algorithm developed by NASA-Multi-Angle Implementation to Atmospheric Correction (29), which provides AOD data at a high resolution. We then used mixed models to regress daily PM<sub>10</sub> (or PM<sub>2.5</sub>) mass concentration from the Ministry of Environmental Protection monitors against: AOD, traditional land use regression terms, and temporal predictors. When AOD were not available, we fitted a generalized additive model using nearby monitors and a thin plate spline term of latitude and longitude to interpolate PM<sub>10/2.5</sub> estimates. Good model performance was achieved, with out-of-sample cross validation R<sup>2</sup> values of 0.79 and 0.72 for PM<sub>10</sub> and PM<sub>2.5</sub>, respectively. Model predictions had little bias, with cross-validated slopes (predicted vs observed) of 0.99 for both models. Exposure estimates were assigned for each patient based on his/her geocoded home address. Further details have been previously published (28).

Daily data on air temperature and relative humidity for the study period were obtained from the monitoring site located in the center of the largest city in Southern Israel.

### Statistical analysis

Results are presented by mean ± SD and interquartile range (IQR) for continuous variables and as percentages for categorical data. Log-transformed glucose and lipid values were modeled by mixed models with random intercepts for each participant. We modeled the associations with PM<sub>10</sub> and PM<sub>2.5</sub> separately. Each model was adjusted for personal characteristics (age, gender, SES, BMI, smoking status, diabetes status, and the purchase of antidiabetic medications 3 mo before the test), seasons, year, and moving average of temperature and relative humidity. When examining the association with blood lipids, models were adjusted for the purchase of lipid modifying agents 3 months before the test.

Coefficients were antilog transformed to the original units, and results are presented as percent change in the outcome and 95% confidence intervals (CIs) for increases of IQR of the pollutants.

### Serum HbA1c

HbA1c levels were available for 12.76% of the patients diagnosed with diabetes. To avoid selection bias, due to the availability of the HbA1c results only in this group, we used stabilized inverse probability weights. Probabilities of having a test were modeled accounting for the subjects' age, gender, ethnicity, SES, cardiovascular illness, dyslipidemia, and the purchase of antidiabetic drugs.

### Exposure windows

For the associations with glucose and lipids, we have a priori defined short-term exposure periods to PM<sub>10</sub> or PM<sub>2.5</sub> as 1-day, 2- to 3-day, and 1-week moving average concentrations preceding the laboratory test. Because HbA1c levels reflect the mean serum glucose levels over approximately 3 months, short-term exposure to PM was not linked to HbA1c

levels. We used a 3-month moving average of the PM<sub>10</sub> or PM<sub>2.5</sub> pollutants concentrations to define an intermediate-term exposure. Intermediate-term exposure, for the association with glucose and lipids, was defined as 3-month moving average concentrations preceding the laboratory test to match the period with a glucose control time interval reflected in HbA1c.

### Stratified analyses

In a subgroup analysis we repeated the analysis among subjects with and without diabetes separately. We additionally stratified the tests performed by patients with diabetes by the type of treatment: no medications, insulin, metformin, or other antidiabetic drugs (glucagon-like peptide-1 receptor agonists, inhibitors of dipeptidyl peptidase 4, α-glucosidase inhibitor, sulfonylurea, meglitinides, and thiazolidinediones).

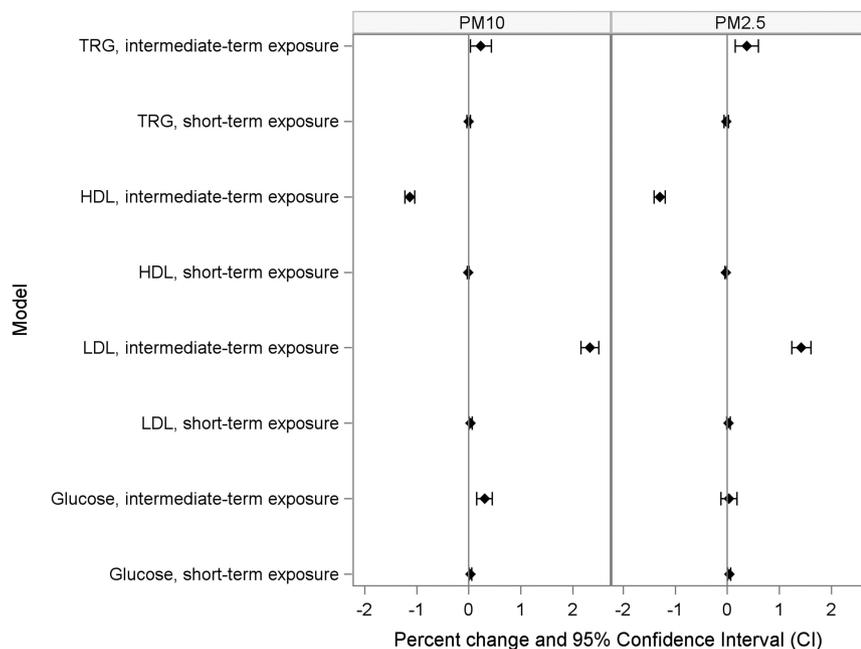
Analyses were performed in SAS 9.4 (SAS Institute, Inc) and R3.1.0 software.

## Results

We included 73 117 subjects with 618 483 glucose samples, 480 669 LDL samples, 473 551 HDL samples, and 476 556 triglycerides and 4179 HbA1c samples performed between the years 2003 and 2012. The median and IQR of samples per subject were: 7 (3; 12) for glucose, 5 (2; 10) for lipids, and 1 (1; 1) for HbA1c tests. Subjects with diabetes comprised 36% of the study cohort (Table 1).

**Table 1.** Population Characteristics

Population Characteristics	Diabetes	
	No (46 894 Subjects)	Yes (26 223 Subjects)
Glucose tests, n	329 934	288 549
Tests per subject, median (IQR)	5 (2; 10)	10 (5; 16)
Median value (IQR) (mg/dL)	87 (78; 96)	115 (96; 143)
LDL tests, n	253 174	227 495
Tests per subject, median (IQR)	4 (2; 8)	8 (4; 13)
Median (IQR) (mg/dL)	114 (92; 138)	99 (79; 124)
HDL tests, n	249 347	224 204
Tests per subject, median (IQR)	4 (2; 8)	8 (4; 12)
Median (IQR) (mg/dL)	50 (42; 59)	46 (39; 55)
Triglycerides tests, n	250 375	226 181
Tests per subject, median (IQR)	4 (2; 8)	8 (4; 13)
Median (IQR) (mg, dL)	121 (90; 165)	138 (102; 186)
Age, years mean ± SD	55.2 ± 18.5	64.8 ± 14.0
Male gender, % (n)	44.8 (21 015)	44.1 (11 571)
CVD, % (n)	62.4 (29 276)	87.1 (23 116)
HTN, % (n)	59.2 (27 765)	86.2 (22 616)
Dyslipidemia, % (n)	66.6 (31 256)	89.2 (23 383)
BMI, % (n)	27.5 ± 5.4	30.3 ± 5.7
Smoking, % (n)	34.0 (15 183)	21.6 (5328)
Medications, % (n)		
Insulin	0 (0)	14.0 (3678)
Metformin	0 (0)	43.3 (11 320)
Other antidiabetic drug	0 (0)	24.7 (6461)
Statins	19.0 (8379)	46.2 (11 767)



**Figure 1.** The association between short- and intermediate-term exposure to PM<sub>10</sub> and PM<sub>2.5</sub> and glucose and lipids levels. The figure shows the percent change in glucose, LDL, HDL, and TRG (triglycerides), for IQR increase in 1 day (short-term exposure) and 3-month average (intermediate-term exposure) concentrations of PM<sub>10</sub> (20  $\mu\text{g}/\text{m}^3$ ) and PM<sub>2.5</sub> (7  $\mu\text{g}/\text{m}^3$ ), obtained from mixed models. All models are adjusted for personal characteristics (age, gender, SES, BMI, smoking status, diabetes status, and the purchase of antidiabetic medications 3 mo before the test), seasons, year, and moving average of temperature and relative humidity 3 months before the test. When examining the association with blood lipids, models were adjusted for the purchase of lipid modifying agents 3 months before the test.

During the study period, the IQR of the mean daily temperature ranged between 14.60°C and 25.10°C, reaching maximal mean temperature of 33.48°C. The IQR of relative humidity ranged between 59% and 77%. Three-month moving average of PM<sub>10</sub> and PM<sub>2.5</sub> levels in the study period ranged between 3.4 and 244.4  $\mu\text{g}/\text{m}^3$  (mean, 54.08  $\mu\text{g}/\text{m}^3$ ) and between 8.8 and 87.1  $\mu\text{g}/\text{m}^3$  (mean, 22.3  $\mu\text{g}/\text{m}^3$ ), respectively.

### The association between PM exposure, glucose, and lipids; short- and intermediate-term effects

We observed no association or negligible associations between acute exposures to PM<sub>10</sub> (1 d before the blood test) and glucose (% [95% CI]: 0.03% increase [0.003%; 0.057%]), LDL (0.03% increase [0.01%; 0.06%]), triglycerides (0.00% decrease [-0.04%; 0.03%]), and HDL (0.01% decrease [-0.02%; 0.00%]). The associations observed with PM<sub>2.5</sub> and the associations observed with 2- and 3-day and 1-week average concentrations of the pollutants were similar.

When assessing the effect of intermediate-term exposure (3-mo average concentration of PM<sub>10</sub> and PM<sub>2.5</sub>), we found 0.30% (0.153%; 0.452%) and 0.02% (-0.12%; 0.18%) increases in glucose, 2.32% (2.15%; 2.49%) and 1.42% (1.23%; 1.60%) increases in LDL, 0.23% (0.02%;

0.42%) and 0.37% (0.14%; 0.59%) increases in triglycerides, and 1.13% (-1.23%; -1.03%) and 1.30% (-1.40%; -1.19%) decreases in HDL (Figure 1).

### Stratified analyses

#### Diabetes

We observed statistically significant interaction between PM<sub>10</sub> exposure and diabetes, in the association with glucose, HDL, and triglycerides ( $P < .05$ ), and between PM<sub>2.5</sub> exposure and diabetes in the association with HDL ( $P < .05$ ). Nearly significant interaction was observed between PM<sub>10</sub> and PM<sub>2.5</sub> exposure and diabetes in the association with LDL ( $P = .080$  for both comparison). We therefore repeated the analysis with stratification by diabetes status in order to assess modification of the association between the intermediate exposure to PM and glucose or lipids levels. In both groups, IQR increases of 3-month average concentration of PM<sub>10</sub> and PM<sub>2.5</sub> were associated with increases of serum glucose, HbA1c, LDL, and triglycerides and decreases of HDL. The strongest associations were observed among subjects with diabetes (percent increase [95% CI], for IQR increase of PM<sub>10</sub> and PM<sub>2.5</sub>): 3.58% (1.03%; 6.20%) and 2.93% (0.35%; 5.59%) increase in HbA1c, and 2.37% (2.11%; 2.63%) and 1.54% (1.26%; 1.83%) increase in LDL. Among subjects without diabetes IQR increases in 3-month average concentration of PM<sub>10</sub> and PM<sub>2.5</sub> were associated with 2.28% (2.05%; 2.50%) and 1.28% (1.03%; 1.52%) increases in LDL. The associations with glucose and triglycerides were weaker compared with those observed among subjects with diabetes (Table 2).

No significant associations were observed with PM<sub>10</sub> or PM<sub>2.5</sub> concentrations 1–7 days before the test.

No significant associations were observed with PM<sub>10</sub> or PM<sub>2.5</sub> concentrations 1–7 days before the test.

#### Type of treatment

To evaluate possible modification by the type of treatment among subjects with diabetes, we compared the percent change in serum glucose among patients treated only with insulin, only with metformin or only with any other antidiabetic drug, and patients who are not treated with antidiabetic medications. We observed a statistically signif-

**Table 2.** Percent Change in Serum Glucose, LDL, HDL, and Triglycerides Associated With an IQR Increase of PM<sub>10</sub> and PM<sub>2.5</sub>, Among Subjects With and Without Diabetes

Exposure	Percent Change and 95% Confidence Intervals	
	Normal Glucose Levels	Diabetes
PM <sub>10</sub>		
Serum glucose	0.28% (0.14%; 0.42%) <sup>a</sup>	0.57% (0.29%; 0.85%) <sup>a</sup>
HbA1c	—	3.58% (1.03%; 6.20%) <sup>a</sup>
LDL	2.28% (2.05%; 2.50%) <sup>a</sup>	2.37% (2.11%; 2.63%) <sup>a</sup>
HDL	−1.13% (−1.26%; −0.99%) <sup>a</sup>	−1.13% (−1.27%; −0.99%) <sup>a</sup>
Triglycerides	0.16% (−0.12%; 0.45%)	0.31% (0.02%; 0.61%) <sup>a</sup>
PM <sub>2.5</sub>		
Serum glucose	−0.55% (−0.69%; −0.41%) <sup>a</sup>	0.41% (0.12%; 0.69%) <sup>a</sup>
HbA1c	—	2.93% (0.35%; 5.59%) <sup>a</sup>
LDL	1.28% (1.03%; 1.52%) <sup>a</sup>	1.54% (1.26%; 1.83%) <sup>a</sup>
HDL	−1.29% (−1.43%; −1.15%) <sup>a</sup>	−1.31% (−1.47%; −1.16%) <sup>a</sup>
Triglycerides	0.28% (−0.03%; 0.59%)	0.41% (0.09%; 0.74%) <sup>a</sup>

Percent change in glucose and lipids, for IQR increase in 3-month average concentrations of PM<sub>10</sub> (20 μg/m<sup>3</sup>) and PM<sub>2.5</sub> (7 μg/m<sup>3</sup>), obtained from mixed models. All models are adjusted for personal characteristics (age, gender, SES, BMI, smoking status), seasons, year, and moving average of temperature and relative humidity 3 months before the test. Among patients with diabetes, models are adjusted for the purchase of antidiabetic medications 3 months before the test. When examining the association with blood lipids, models were adjusted for the purchase of lipid modifying agents 3 months before the test.

<sup>a</sup> *P* < .05.

icant interaction between PM<sub>10</sub> exposure and metformin (*P* = .038) or antidiabetic drugs other than insulin (*P* = .007) and between PM<sub>2.5</sub> exposure and insulin (*P* < .01) or other medications (*P* = .006). We found that metformin and antidiabetic medications other than insulin had a protective effect against air pollution induced increases in serum glucose: an IQR increase of PM<sub>10</sub> was associated with 0.56% increase (0.03%; 1.15%) in serum glucose among patients treated with metformin, whereas no association was observed among patients treated with other medications. No statistically significant interaction with PM<sub>2.5</sub> was observed in both groups. Stronger effect estimates were observed among patients treated with Insulin (% [95% CI]: 1.47% increase [−0.37%; 3.36%] and 1.13%

increase [−0.72%; 3.03%], respectively) and among untreated patients (0.86% increase [0.52%; 1.20%] and 1.70% increase [1.37%; 2.04%], respectively) (Table 3).

## Discussion

In this study, we examined the associations between PM exposure and serum glucose, HbA1c, and lipids levels. We observed significant increase in glucose, HbA1c, LDL, and triglycerides and decrease in HDL levels, associated with increases of PM average concentrations in the 3 months preceding the test. The associations were more pronounced among patients with diabetes. The weaker asso-

**Table 3.** Percent Change in Serum Glucose Associated With an IQR Increase of PM<sub>10</sub> and PM<sub>2.5</sub>, Among Subjects With Diabetes, Stratified by Treatment

	n	Percent Change and 95% Confidence Intervals
PM <sub>10</sub>		
No medications	18 689 subjects, 168 636 tests	0.86% (0.52%; 1.20%) <sup>a</sup>
Insulin	1820 subjects and 12 167 tests	1.47% (−0.37%; 3.36%)
Metformin	8495 subjects and 51 859 tests	0.56% (0.03%; 1.15%) <sup>a</sup>
Other	2264 subjects and 9774 tests	−0.20% (−1.17%; 1.40%)
PM <sub>2.5</sub>		
No medications	18 689 subjects, 168 636 tests	1.70% (1.37%; 2.04%) <sup>a</sup>
Insulin	1820 subjects and 12 167 tests	1.13% (−0.72%; 3.03%)
Metformin	8495 subjects and 51 859 tests	−0.01% (−0.57%; 0.56%)
Other	2264 subjects and 9774 tests	0.34% (−1.27%; 1.98%)

Percent change in glucose for IQR increase in 3-month average concentrations of PM<sub>10</sub> (20 μg/m<sup>3</sup>) and PM<sub>2.5</sub> (7 μg/m<sup>3</sup>), obtained from mixed models. All models are adjusted for personal characteristics (age, gender, SES, BMI, smoking status), seasons, year, and moving average of temperature and relative humidity 3 months before the test.

<sup>a</sup> *P* < .05.

ciations found among patient treated with antidiabetic medications (other than insulin) suggest that these medications have a protective effect against the air pollution induced changes in serum glucose. We found no acute effect of PM (exposure of 1–7 d) on any of the parameters measured.

### Short- and intermediate-term effects

In accordance with previous studies, we found positive associations with serum glucose and lipids (13, 16, 17). The aforementioned studies, which found positive associations with exposure to PM<sub>2.5</sub> and PM<sub>10</sub> up to 6 days before the test, did not assess the possible intermediate-term effect of the pollutants (13, 17). Chuang et al, who did assess the association with annual average concentrations of PM<sub>10</sub> and PM<sub>2.5</sub>, concluded that long-term exposure is associated with increases of serum glucose, HbA1c, and total cholesterol (16).

Similar to the current study, a previous study performed in the Negev revealed no effect of short-term exposure to PM<sub>10</sub> on serum glucose levels. In addition, no association between 3-month average concentrations of PM<sub>10</sub> and HbA1c was found in the aforementioned study (30). Using spatially resolved satellite-based estimates, in the current study, we were able to identify the associations between the tested markers and PM<sub>10</sub> or PM<sub>2.5</sub> intermediate-term exposures.

PM can generate oxidative stress and systemic inflammation, which may be the mechanism by which it may lead to IR, and modify glucose and lipids metabolism (12, 15).

### Modification of the effect by the glycemic status and the type of treatment

Several studies found patients with diabetes to be more susceptible to the air pollution effect (17, 31, 32). Current evidence suggests that inflammatory and coagulation mechanisms, resulting in IR and vascular dysfunction, contribute to the vulnerability of these patients (31).

Similar to a previous study performed among the Negev population, we found stronger associations with air pollution exposure among patients with diabetes, with the exception of patients who were treated with metformin. This association may be explained by the enhanced antiinflammatory response occurring after the treatment of insulin sensitizers (eg, metformin), which may increase the resistance to the air pollution effect (33). That said, due to the weaker associations observed among patients who were treated with other antidiabetic medications as well, it is possible that other common characteristic of the treated patients, who are

not insulin dependents, made them less vulnerable to the air pollution effect.

### Health implications

As seen in many environmental studies, the health effects reported in our study are relatively small. Yet, when applied to large populations the overall effect, impairing glucose and lipids levels, can be translated into adverse health outcomes (34). In addition, when addressing health implications of environmental exposures, both the broad extent of exposed population and the continuous nature of exposure must be considered, beyond the individual risk (35).

Although genetics play a major role in the development of diabetes, recent studies linked between air pollution exposure and the development of diabetes (34) and diabetes-related deaths (36). Small differences in the glycemic control and glucose even within the normal range are translated into the clinically meaningful variation in cardiovascular disease risk (37).

High LDL, high triglycerides, and low HDL are well-established risk factors for coronary heart disease (38, 39). Several major trials provide robust evidence that lowering LDL cholesterol by a small amount of approximately 1 mmol/L leads to a reduction in vascular mortality and morbidity by 25% in a diverse range of patients treated with statins (40). In a cumulative lifetime exposure to air pollution, the increases of LDL and triglycerides and decreases of HDL may increase the risk of the development of cardiovascular events.

### Limitations

Our study had a number of limitations. First, the study population comprises mostly unhealthy subjects. Although this limitation may decrease generalizability of findings it also strengthens the validity of our findings by reducing comorbidities confounding by design (41). Second, the use of medications and laboratory results for diabetes definition might have resulted in misclassification in study group assignment. However, the completeness of the medical and laboratory data and the use of spatial estimates of PM in a high resolution of 1 × 1 km markedly decrease the potential exposure and outcome misclassifications. Lastly, HbA1c was available only for 12.76% of the patients with diabetes in our sample. We used stabilized inverse probability weights to reduce selection bias, but bias may still be present. In addition, given the small amount of HbA1c tests we were not able to stratify the association between PM and HbA1c by the type of treatment.

## Conclusion

Intermediate-term, but not short-term, exposure to PM is associated with alterations in serum glucose, HbA1c, and lipids, especially among patients with diabetes. Metformin and antidiabetic medications other than insulin seem to attenuate the association between air pollution and serum glucose increase.

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