



Longitudinal Associations Between Ambient Air Pollution With Insulin Sensitivity, β -Cell Function, and Adiposity in Los Angeles Latino Children

Tanya L. Alderete,¹ Rima Habre,¹ Claudia M. Toledo-Corral,^{1,2} Kiros Berhane,¹ Zhanghua Chen,¹ Frederick W. Lurmann,³ Marc J. Weigensberg,⁴ Michael I. Goran,^{5,6} and Frank D. Gilliland¹

Diabetes 2017;66:1789–1796 | <https://doi.org/10.2337/db16-1416>

Evidence suggests that ambient air pollution (AAP) exposure may contribute to the development of obesity and type 2 diabetes. The objective of this study was to determine whether exposure to elevated concentrations of nitrogen dioxide (NO₂) and particulate matter with aerodynamic diameter <2.5 (PM_{2.5}) had adverse effects on longitudinal measures of insulin sensitivity (S_I), β -cell function, and obesity in children at high risk for developing diabetes. Overweight and obese Latino children (8–15 years; *n* = 314) were enrolled between 2001 and 2012 from Los Angeles, CA, and followed for an average of 3.4 years (SD 3.1 years). Linear mixed-effects models were fitted to assess relationships between AAP exposure and outcomes after adjusting for covariates including body fat percent. Higher NO₂ and PM_{2.5} were associated with a faster decline in S_I and a lower S_I at age 18 years, independent of adiposity. NO₂ exposure negatively affected β -cell function, evidenced by a faster decline in disposition index (DI) and a lower DI at age 18 years. Higher NO₂ and PM_{2.5} exposures over follow-up were also associated with a higher BMI at age 18 years. AAP exposure may contribute to development of type 2 diabetes through direct effects on S_I and β -cell function.

In the U.S., prediabetes and type 2 diabetes have dramatically increased in adult populations and have

become more frequent in obese youth (1,2), presenting pressing clinical and public health problems. Although obesity, an unhealthy diet, and reduced physical activity contribute to the pathogenesis of type 2 diabetes, increased ambient and traffic-related air pollution exposures also contribute to disease risk (3). Epidemiological studies among adults have shown that higher exposure to nitric oxides, nitrogen dioxide (NO₂), and particulate matter with aerodynamic diameter <2.5 (PM_{2.5}) was associated with greater risk for type 2 diabetes (4–9). Supporting this, clinical studies in children and adults have found that higher ambient and traffic-related air pollution were associated with higher insulin resistance using the HOMA of insulin resistance (HOMA-IR) (10–13). These results suggest that increased air pollution exposure may adversely affect insulin sensitivity (S_I), but these results were limited by the use of a HOMA-IR that has known limitations compared with a frequently sampled intravenous glucose tolerance test (FSIVGTT) (14,15). As such, these studies did not examine the effects of ambient air pollution (AAP) exposure on direct measures of glucose homeostasis, including whole-body S_I, insulin secretion, and β -cell function.

Only two cross-sectional studies have examined whether increased air pollution exposure affects the underlying pathophysiology of type 2 diabetes, which included robust measures of whole-body S_I, acute insulin response to glucose (AIR_g), and pancreatic β -cell function

¹Department of Preventive Medicine, Division of Environmental Health, University of Southern California, Los Angeles, CA

²Department of Public Health, California State University, Los Angeles, CA

³Sonoma Technology, Inc., Petaluma, CA

⁴Department of Pediatrics, University of Southern California, Los Angeles, CA

⁵Department of Preventive Medicine, Diabetes and Obesity Research Institute, University of Southern California, Los Angeles, CA

⁶Department of Physiology and Biophysics, University of Southern California, Los Angeles, CA

Corresponding author: Michael I. Goran, goran@usc.edu.

Received 17 November 2016 and accepted 24 January 2017.

This article contains Supplementary Data online at <http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db16-1416/-/DC1>.

© 2017 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

See accompanying article, p. 1755.

using an FSIVGTT (16,17). In Hispanic adults, higher NO_2 and $\text{PM}_{2.5}$ exposure were associated with higher fasting glucose concentrations and a lower whole-body S_1 (16). In overweight and obese Latino and African American youth, average exposures to NO_2 and $\text{PM}_{2.5}$ in the year prior to participation were associated with higher fasting glucose and lower whole-body S_1 independent of adiposity (17). These findings suggest that elevated exposure to NO_2 and $\text{PM}_{2.5}$ adversely affects glucose metabolism starting early in life and that prolonged exposure in childhood may negatively affect pancreatic β -cell function and eventually lead to type 2 diabetes.

Recent studies have provided emerging evidence that NO_2 and $\text{PM}_{2.5}$ exposure affects risk for metabolic dysfunction (10–13,16–18). To date, no studies have examined the longitudinal effects of AAP exposure on longitudinal measures of glucose homeostasis that are risk factors for type 2 diabetes. The objective of this study was to examine the relationships between residential AAP and longitudinal measurements of fasting glucose, fasting insulin, and measures of S_1 , insulin secretion, and pancreatic β -cell function over follow-up in high-risk overweight and obese Latino children residing in urban Los Angeles, CA. We hypothesized that higher long-term NO_2 and $\text{PM}_{2.5}$ exposures would be associated with a faster increase in fasting glucose and a more rapid decrease in whole-body S_1 , insulin secretion, and pancreatic β -cell function and that these adverse effects were independent of adiposity.

RESEARCH DESIGN AND METHODS

Participants

Analyses were conducted on participants from the Childhood Obesity Research Center Air Study, which is a longitudinal cohort that was recruited in two waves from 2001 to 2012. Participants included in this study lived in urban Los Angeles, CA, and were recruited mostly from local metabolic clinics but also through word of mouth, health fairs, and advertisements in the local communities. Inclusion criteria included Latino ethnicity (defined as self-reported race/ethnicity for all participants, parents, and grandparents), age- and sex-specific BMI of ≥ 85 th percentile, and absence type 1 or type 2 diabetes as assessed by an oral glucose tolerance test. Participants were excluded if they were using a medication or diagnosed with a condition known to influence insulin and/or glucose metabolism or body composition. Each participant had detailed phenotyping of body fat and risk factors for type 2 diabetes at each annual visit. The original sample size was 328, of which 314 children were included in the current analysis (182 males/132 females) based on availability of complete exposure and covariate data. Participants were followed for an average of 3.4 years (SD 3.1), providing up to 1,253 total observations. Before testing, informed written consent/assent was obtained from the parents/participant.

The University of Southern California Institutional Review Board approved these studies.

Residential AAP Exposure Assessment

Street-level residential addresses of participants were standardized and geocoded at the parcel level, and match codes were obtained using the Texas A&M Geocoder (<http://geoservices.tamu.edu/Services/Geocode/>). Addresses that did not match to a parcel centroid were corrected based on the best available knowledge of the participant's residence location. Monthly air pollution exposure data for up to 12 months prior to each visit were estimated for each participant. In brief, hourly air quality data from ambient monitoring stations were downloaded from the U.S. Environmental Protection Agency's Air Quality System (AQS, <http://www.epa.gov/ttn/airs/airsaqs>) for the relevant time period and averaged to daily level. In California, air monitor stations are spaced 20–30 km apart and provide a monitoring network with good characterization of the pollution gradients across Los Angeles. The air gases were measured using Federal Reference Method (FRM) continuous monitors, whereas PM data were restricted to FRM or Federal Equivalent Method (FEM) monitors. Non-FEM $\text{PM}_{2.5}$ data were used only when FRM/FEM measurement data were not available ($<20\%$). Monthly averages were calculated from the daily data using a 75% completeness criterion, and monthly exposure values were spatially interpolated from the air quality monitoring station's locations to the finest geographic resolution possible (usually parcel level) based on the participant's geocoded street-level residence using an inverse distance-squared weighting (IDW2) algorithm, as previously described (19). Data from up to four monitors were used to estimate exposure for each location. Due to the regional nature of NO_2 and $\text{PM}_{2.5}$, in Southern California, a maximum interpolation radius of 50 km was used for all pollutants. On the basis of previous methodological studies, when a residence was located within 5 km of one or more stations with valid observations, the interpolation was based solely on the concentrations from those stations. Prior work by our group has shown that the IDW2 method in California was robust to a leave one out validation for monthly monitoring AQS site data and performs as well as more sophisticated models that are limited by shorter spatial-temporal coverage. Specifically, results indicated that the IDW2 method estimates monthly NO_2 and $\text{PM}_{2.5}$ with <1 ppb and $1 \mu\text{g}/\text{m}^3$ biases on average and with $\pm 34\%$ and $\pm 31\%$ relative error on average, respectively (20).

Clinical Assessments

Participants attended clinical visits at either the Los Angeles County Hospital or the University of Southern California University Hospital each year. Each year, participants received a comprehensive medical history and physical examination where pubertal staging was determined by the Tanner method (21,22). Height and weight were measured to determine BMI and applied to Centers for Disease Control and Prevention age- and

sex-specific growth charts to determine BMI percentile and *z* score. A 2-h oral glucose tolerance test was conducted and ~2 weeks later, a 13-sample insulin-modified FSIVGTT was performed. After two fasting blood samples were taken at -15 and -5 min, glucose (0.3 g/kg body weight) was administered at time 0 over a 1-min period. Subsequent blood samples were collected at 2, 4, 8, and 19 min. Insulin (0.02 units/kg body weight, Humulin R; Eli Lilly and Company, Indianapolis, IN) was administered intravenously at 20 min, followed by blood sample collection at 22, 30, 40, 50, 70, 100, and 180 min. Glucose was assayed using a Yellow Springs Instruments analyzer (YSI Inc., Yellow Springs, OH) and insulin was assayed using an automated enzyme immunoassay (Tosoh AIA 600 II Analyzer; Tosoh Bioscience, Inc., South San Francisco, CA). Glucose and insulin from the FSIVGTT were entered into MINMOD software (version 6.02; RN Bergman, Los Angeles, CA) for calculation of whole-body S_I , AIR_g (area under the plasma insulin curve between 0 and 10 min), and the disposition index (DI). As the product of S_I and AIR_g , DI is used in research settings as an assessment of β -cell function. Total body fat percent was determined by DEXA using a Hologic QDR 4500 W (Hologic, Bedford, MA). Single-slice abdominal MRI scans were performed on a subset of participants ($n = 219$) using a General Electric 1.5 Signa LX-Echospeed device (Waukesha, WI) at the level of the umbilicus for cross-sectional area of subcutaneous abdominal adipose tissue (SAAT) and intra-abdominal adipose tissue (IAAT) (23).

Social Position

A modified version of the Hollingshead Four-Factor Index of Social Status was used to assess socioeconomic status (24) in those participants where information was available ($n = 278$). This index takes into account the occupation and education of each parent/guardian residing in the child's home in order to generate a single measure of a family's social status. An education score of 1-7 was assigned to parents/guardians living in the household. An educational score of 1 corresponded to less than a seventh-grade education and 7 to graduate training. Homemakers, unemployed, or students did not have categories based on the Hollingshead method and would not be included in the household social position score. To prevent exclusion of this information, we utilized a modified scoring system where these individuals were assigned a score of 0 in order to retain them in our final score. This method was used in combination with the traditional occupation scores of 1-7, where 1 corresponded to an unskilled employee and 7 was assigned to those with employment roughly corresponding to higher executives and major professionals. Education and occupation scores were weighted to obtain a single score for each parent/guardian according to the Hollingshead method. For households with multiple caretakers, scores were averaged to obtain a single household social position score or index (Supplementary Table 1). Social position was categorized as ≤ 25 th percentile ($n = 90$), > 25 th percentile and

< 75 th percentile ($n = 132$), ≥ 75 th percentile ($n = 57$), and missing ($n = 35$). Those without social position data did not differ in any important physical or metabolic characteristics (data not shown).

Statistical Analysis

Exposure to NO_2 and $PM_{2.5}$ was modeled as long-term exposure, defined as yearly concentrations averaged over an individual's follow-up. Linear mixed-effects models were fitted to estimate longitudinal relationships between metabolic outcomes, pathophysiology end points for type 2 diabetes (i.e., S_I , AIR_g , and DI), and adiposity in relation to AAP exposure over time. We examined the associations of the longitudinal measurements of metabolic and adiposity outcomes with the 1) long-term exposure on the rate of change of the outcome and 2) long-term exposure on the attained level of the outcome at age 18 years. Tanner stage, body fat percent (where appropriate), the season of testing (warm/cold), variations in prior year exposure at each follow-up visit (average prior year concentration at each individual's visit subtracted from their long-term exposure), and study entry year were included in each model as covariates to adjust for confounding. Participant-specific intercepts were included and were a function of sex, social position category, study wave, and a participant-level random intercept. A full description of the modeling approach is described in the Supplementary Data, and results from each longitudinal model are presented in the tables (effects on growth) and figures (attained level at age 18 years). NO_2 and $PM_{2.5}$ were highly correlated (Pearson $r = 0.88$, $P < 0.001$), thus multipollutant models were not examined. Stratified analysis was conducted to explore heterogeneity in effects by sex, and effect modification was examined for extreme obesity (BMI percentile > 99 th; $n = 102$) compared with overweight/obese ($n = 212$) at baseline. Linear mixed-effect models were fitted to estimate the associations between body fat percent and metabolic outcomes at age 18 years. Tanner stage and study entry year were included in these models as covariates to adjust for confounding. Participant-specific intercepts were included and were a function of sex, social position category, study wave, and a participant-level random intercept. Statistical significance was based on a two-sided $P < 0.05$. Natural log transformations were performed on fasting glucose, fasting insulin, S_I , AIR_g , and DI to approximate normal distributions. Estimated effect estimates were reported for a 5-ppb difference in NO_2 and a 4 $\mu g/m^3$ difference in $PM_{2.5}$. All analyses were performed in SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Metabolic and obesity-related outcomes at baseline are reported in Table 1 along with the average levels of NO_2 and $PM_{2.5}$ over follow-up. At study entry, 58% of participants were male and the mean age was 11.3 years (range

Table 1—Baseline characteristics and previous year residential AAP concentrations in Latino children (n = 314) enrolled in the longitudinal study

General characteristics	
Age (years)	11.3 ± 1.7
Sex (males/females, %)	182/132, 58%
Tanner stage (n, %)	
Tanner 1	98, 31%
Tanner 2	110, 35%
Tanner 3	41, 13%
Tanner 4	42, 13%
Tanner 5	23, 7%
Metabolic indices	
Fasting glucose (mg/dL)	90.7 ± 6.5
Fasting insulin (μU/mL)*	15 ± 9.4
2-h glucose (mg/dL)†	127.3 ± 18.1
2-h insulin (μU/mL)‡	151.1 ± 125.5
S _I (×10 ⁻⁴ min ⁻¹)/(μU/mL)§	2.1 ± 1.4
AIR (μU/mL × 10 min)§	1,669.7 ± 1,203.1
DI§	2,451.4 ± 1,150.6
Adiposity	
BMI (kg/m ²)	28.5 ± 5.6
BMI percentile	98.4 (2.9)
BMI z score	2.1 ± 0.4
Total fat mass (kg)¶	25.6 ± 10.1
Total lean mass (kg)¶	37.8 ± 10.4
Body fat percent (%)¶	38.7 ± 5.9
SAAT (cm ²)#	344.1 ± 144.6
IAAT (cm ²)#	48.4 ± 21.5
Long-term average residential AAP	
NO ₂ (ppb)	27.6 ± 5.2
PM _{2.5} (μg/m ³)	17.8 ± 3.8

Data are reported as mean ± SD. *Sample size is 304. †Sample size is 312. ‡Sample size is 303. §Sample size is 291. ||Median (interquartile range). ¶Sample size is 299. #Sample size is 219.

7.9–14.9). Approximately 66% of the children were in prepuberty or early puberty (Tanner stages 1 and 2), and the average baseline BMI percentile was in the obese category (>95th percentile).

Associations for AAP With Risk Factors for Type 2 Diabetes

Higher NO₂ and PM_{2.5} exposure had adverse effects on the development of risk factors for type 2 diabetes (e.g., S_I, AIR_g,

and DI) after adjusting for confounders and body fat percent (Fig. 1 and Table 2). These longitudinal adverse effects in rate of change over the study period resulted in substantial differences in these measures at age 18 years in those with higher levels of exposure during follow-up compared with those with lower exposures. For S_I, a 5-ppb difference in long-term NO₂ (averaged exposure over follow-up) was associated with a 2.4% faster decline in S_I over the study period (*P* = 0.02), resulting in a 13% (*P* = 0.04) lower S_I at age 18 years. Similarly, a 4 μg/m³ higher long-term PM_{2.5} was associated with a 3.3% faster decline in S_I over the study period (*P* = 0.02), resulting in a 21.6% lower S_I at age 18 years (*P* = 0.01). Long-term exposure NO₂ and PM_{2.5} were positively associated with the rate of increase of AIR_g over the study period. Although these associations did not reach statistical significance (all *P* > 0.1), by age 18 years, the cumulative effects of chronic exposure to higher PM_{2.5} concentrations resulted in significant associations with higher AIR_g. As such, compensation for decreased S_I occurred via increased insulin secretion as a 4 μg/m³ difference in long-term PM_{2.5} was associated with a 28.5% higher AIR_g at age 18 years (*P* = 0.03). With prolonged exposure to AAP, there was evidence of β-cell function fatigue. Illustrating this, a 5-ppb difference in long-term NO₂ exposure was associated with a 2.3% faster decline in DI over follow-up (*P* = 0.02). At age 18 years, chronic exposure to higher NO₂ was associated with a lower β-cell function as a 5-ppb difference in long-term NO₂ exposure was associated with a 13% lower DI (*P* = 0.04).

Increased long-term averaged AAP exposure over the study period was also associated with elevations in fasting and 2-h insulin levels after adjusting for confounders and body fat percent (Fig. 2 and Table 2). For example, a 4 μg/m³ difference in long-term PM_{2.5} exposure was associated with a 2.9% faster increase in fasting insulin levels (*P* = 0.03) and 3.1% faster increase in 2-h insulin levels (*P* = 0.06). At age 18 years, a 4 μg/m³ difference in long-term PM_{2.5} exposure was associated with a 26.8% higher fasting insulin (*P* = 0.01) and a 35.6% higher 2-h insulin (*P* = 0.007). Similar relationships were observed for NO₂

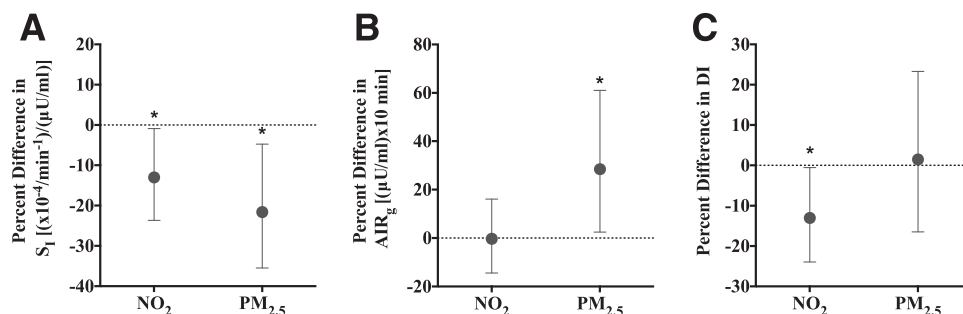


Figure 1—Effects of long-term average AAP exposure during follow-up on metabolic indices from an FSIVGTT at age 18 years in Latino children. The estimated percent difference in S_I (A), AIR_g (B), and DI (C) at age 18 years for a 5-ppb and 4 μg/m³ difference in long-term NO₂ and PM_{2.5} exposure, respectively. Results are displayed as the estimated percent difference with 95% CIs. Each model was adjusted for sex, Tanner stage, season of testing (warm/cold), social position, body fat percent, study wave, and study entry year. **P* < 0.05.

Table 2—Effects of long-term residential AAP exposure on clinical fasting glucose, fasting insulin, and metabolic indices (percent differences) from a FSIVGTT in Latino children

	NO ₂ (long-term)	PM _{2.5} (long-term)
Fasting glucose (mg/dL)	0.02 (−0.2, 0.3)	0.1 (−0.2, 0.4)
Fasting insulin (μU/mL)	1.7 (−0.4, 3.8)	2.9 (0.2, 5.6)
2-h glucose (mg/dL)	0.5 (−0.1, 1.1)	0.6 (−0.1, 1.4)
2-h insulin (μU/mL)	2.5 (0.01, 5.1)	3.1 (−0.2, 6.6)
S ₁ (×10 ^{−4} min ^{−1})/(μU/mL)	−2.4 (−4.4, −0.3)	−3.3 (−6, −0.6)
AIR _g (μU/mL × 10 min)	0.5 (−1.8, 2.9)	2.5 (−0.6, 5.7)
DI	−2.3 (−4.2, −0.3)	−1.1 (−3.8, 1.6)

All outcomes were transformed using the natural log. Results are displayed as the estimated percent difference with 95% CIs for the effects of long-term exposure on the percent difference in the yearly rate of change (growth) of fasting glucose, fasting insulin, 2-h glucose, 2-h insulin, S₁, AIR_g, and DI. Each model was adjusted for sex, Tanner stage, season of testing (warm/cold), prior year exposure at each follow-up visit, social position, body fat percent, study wave, and study entry year. Bold font indicates results that were statistically significant based on a two-sided $P < 0.05$.

exposure as a 5-ppb difference in long-term exposure was associated with an 18.4% higher fasting insulin ($P = 0.01$) and an 18.6% higher 2-h insulin ($P = 0.03$) at age 18 years. Fasting glucose levels were not associated with AAP; however, increased long-term AAP exposure was associated with impaired glucose regulation after an oral glucose challenge. As an example, a 5-ppb difference in long-term NO₂ exposure was associated with a 0.5% faster increase in 2-h glucose levels ($P = 0.1$) over follow-up and a 5.1% higher 2-h glucose ($P = 0.01$) at age 18 years. There was little evidence to support differences in the effects of AAP on metabolic outcomes by sex or obesity status, and the study findings did not substantially change when adjusting for other measures of adiposity (data not shown).

For metabolic outcomes, the magnitude of the effects of higher long-term NO₂ and PM_{2.5} exposures on attained level at age 18 years was comparable to and, in some instances, larger than the effect of a 5% increase in body fat percent on attained level at age 18 years. For example, a 5% increase in body fat percent was associated with a 16.7% lower S₁ at age 18 years ($P < 0.001$). This effect size was similar to the 13% and 21.6% lower S₁ observed at age 18 for NO₂ and PM_{2.5}, respectively. Additionally, a 5% increase in body fat percent was associated with a 10.2% higher AIR_g ($P < 0.001$) and 6.9% lower DI ($P = 0.01$) at age 18 years. The effect size corresponding to a 5% increase in body fat percent for AIR_g was about one-third of that observed for PM_{2.5}, and for DI, it was about one-half of that observed for NO₂. For fasting insulin, a 5% increase in body fat percent was associated with a 30% higher fasting insulin ($P < 0.001$) at age 18 years, which was similar to the effect size for PM_{2.5}.

Associations for AAP With Measures of Obesity

Higher NO₂ and PM_{2.5} exposures were also associated with more rapid increases in BMI and central adiposity in children who were already overweight and obese at study entry. For example, a 4 μg/m³ difference in long-term PM_{2.5} was associated with a 3.8 kg/m² faster increase in BMI over the study period ($P = 0.006$) and a 3 kg/m² higher BMI at

age 18 years ($P = 0.0003$). There were also significant associations between AAP exposures with body fat percent and SAAT (Fig. 3 and Table 3). Whereas a 4 μg/m³ difference in long-term PM_{2.5} was associated with a 2% higher body fat percent at age 18 years ($P = 0.047$), this same difference in PM_{2.5} was associated with an 8.1 cm³ faster increase in SAAT over the study period ($P = 0.03$) and a 51.4 cm³ higher SAAT at age 18 years ($P = 0.05$). The effects of AAP on body fat percent varied by sex (interactions on level and growth $P < 0.001$) but not BMI, SAAT,

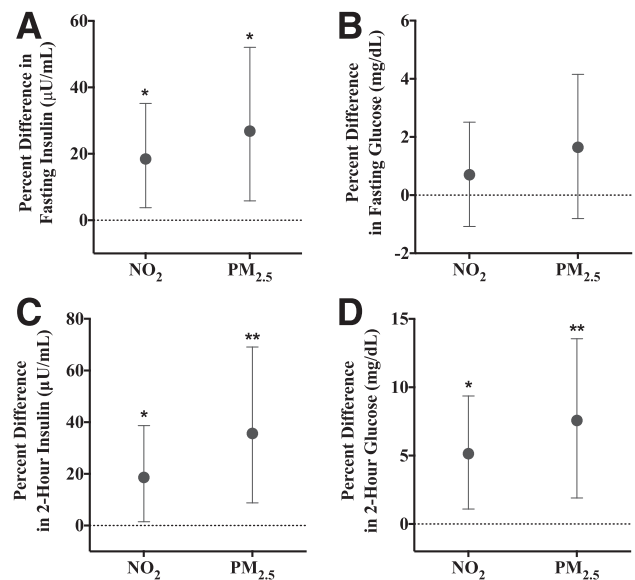


Figure 2—Effects of long-term average AAP exposure during follow-up on fasting and 2-h insulin and glucose measures from an OGTT at age 18 years in Latino children. The estimated percent difference with 95% CIs are shown for fasting insulin (A), fasting glucose (B), 2-h insulin (C), and 2-h glucose (D) at age 18 years for a 5-ppb and 4 μg/m³ difference in long-term NO₂ and PM_{2.5} exposure, respectively. Each model was adjusted for sex, Tanner stage, season of testing (warm/cold), social position, body fat percent, study wave, and study entry year. * $P < 0.05$; ** $P < 0.01$.

or IAAT. A $4 \mu\text{g}/\text{m}^3$ difference in long-term $\text{PM}_{2.5}$ exposure during the study period was associated with a 3.1% increase in body fat percent ($P = 0.04$) in females and a 1.4% increase in males ($P = 0.31$) at age 18 years.

DISCUSSION

In this pediatric cohort study, our results demonstrate significant effects of elevated NO_2 and $\text{PM}_{2.5}$ on insulin homeostasis, S_1 , and β -cell function that were independent of body fat percent. Higher long-term exposure to AAP was associated with a faster decrease in S_1 over the study period and a lower S_1 at age 18 years. We found evidence that Latino youth compensate for AAP exposure-related declines in S_1 via increases in insulin secretion, including increased fasting insulin levels and AIR_g . Indicative of β -cell fatigue, long-term AAP exposure was associated with a faster decrease in DI over the study period and a lower DI at age 18 years. Importantly, the adverse effects of NO_2 and $\text{PM}_{2.5}$ on insulin homeostasis, S_1 , and β -cell function were independent of adiposity. The clinical significance of these results is that the magnitude of the effects was similar to those from significant excess weight gain. For example, the magnitudes of metabolic effects reported for NO_2 and $\text{PM}_{2.5}$ were similar and, in some cases, larger than those of a 5% increase in body fat percent on the same metabolic outcomes. These findings suggest that in response to AAPs, metabolic regulation of

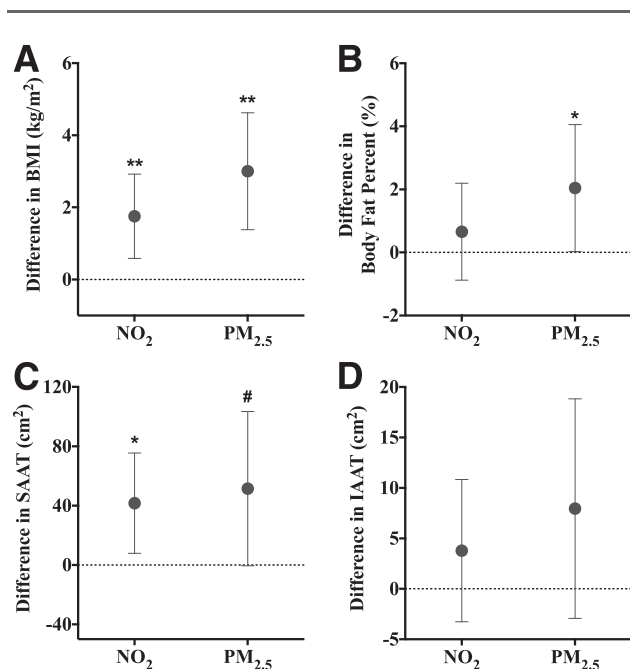


Figure 3—Effects of long-term AAP exposure during follow-up on BMI and adiposity at age 18 years in Latino children. The estimated difference with 95% CIs are shown for BMI (A), body fat percent (B), SAAT (C), and IAAT (D) at age 18 years for a 5-ppb and $4 \mu\text{g}/\text{m}^3$ difference in long-term NO_2 and $\text{PM}_{2.5}$ exposure, respectively. Each model was adjusted for sex, Tanner stage, season of testing (warm/cold), social position, body fat percent (where appropriate), study wave, and study entry year. * $P < 0.05$; ** $P < 0.01$; # $P = 0.05$.

Table 3—Effects of long-term residential AAP exposure on BMI and adiposity in Latino children

	NO_2 (long-term)	$\text{PM}_{2.5}$ (long-term)
BMI (kg/m^2)	2.1 (0.1, 4.1)	3.8 (1, 6.6)
Body fat percent (%)	0.1 (−0.1, 0.3)	0.1 (−0.1, 0.4)
SAAT (cm^2)	6.5 (1.6, 11.3)	8.1 (0.6, 15.7)
IAAT (cm^2)	0.9 (−0.1, 1.9)	1.2 (−0.4, 2.8)

Results are displayed as the estimated difference with 95% CIs for the effects of long-term exposure on the yearly rate of change (growth) of BMI, body fat percent, SAAT, and IAAT. Each model was adjusted for sex, Tanner stage, season of testing (warm/cold), prior year exposure at each follow-up visit, social position, body fat percent (where appropriate), study wave, and study entry year. Bold font indicates results that were statistically significant based on a two-sided $P < 0.05$.

glucose is maintained via robust increases in insulin levels during adolescence (25); however, with long-term exposure to AAP, β -cell function is impaired. These results suggest that prolonged AAP exposure may result in further declines in β -cell function and reduction in the ability to compensate for decreased S_1 , thereby contributing to type 2 diabetes (26,27). Higher NO_2 and $\text{PM}_{2.5}$ exposures were also associated with higher BMI, body fat percent, and central adiposity over follow-up and at age 18 years in this group of children who already were overweight and obese at study entry.

Only a few cross-sectional studies have reported associations between AAP and insulin resistance using HOMA-IR in pediatric populations (10,12,18,28). In overweight and obese minority youth, we previously reported that higher prior year exposure to NO_2 and $\text{PM}_{2.5}$ was unrelated to adiposity but was associated with lower S_1 and higher AIR_g (17). The current study found that increased longitudinal exposure to AAP was associated with longitudinal declines in S_1 , which were accompanied by increased AIR_g and fasting insulin levels to compensate for reduced S_1 . With prolonged AAP exposure, there were significant declines in β -cell function during the study follow-up. These findings build upon previous work by illustrating that long-term exposure to increased AAP, independent of adiposity, contributes to the underlying pathophysiology of type 2 diabetes. In the current study, we also observed significant relationships between increased AAP exposure and higher BMI, body fat percent, and SAAT, all of which are important risk factors for cardiometabolic disease (29). The effect of increased AAP on increased adiposity was stronger among female compared with male youth, suggesting that there may be sex differences in exposure responses. Obesity status did not modify the effect of AAP exposure on risk factors for type 2 diabetes; however, this study only included overweight or obese youth. Future studies should include participants with varying levels of adiposity in order to examine whether obesity and increased AAP

exposure synergistically impact metabolic health in youth.

The mechanisms linking increased AAP to obesity and risk for type 2 diabetes remain to be fully determined. Rodent studies suggest that increased exposure to air pollution may result in metabolic dysfunction and obesity via increased adipose tissue inflammation, hepatic lipid accumulation, and decreased glucose utilization in skeletal muscle (30,31). Prolonged exposure to combustion-related air pollutants may also increase oxidative stress and systemic inflammation, resulting in activation of stress kinases that lead to defective insulin receptor signaling that results in peripheral insulin resistance (30,32,33). Future studies should examine these outcomes in conjunction with systemic markers of inflammation in order to explore whether inflammatory processes mediate any of these observed relationships.

Despite the strengths of this study, diet and physical activity measures were unavailable. Consequently, residual confounding may have affected the study findings since poor diet and lack of physical activity are associated with increased risk of obesity and metabolic dysfunction and could be correlated with residential proximity to sources of air pollution (34–37). Nevertheless, the results are unlikely to be explained by confounding by these factors since each model adjusted for social position, a strong determinant of these factors (34). Exposure misclassification may have occurred with residential-based estimates of AAP exposure, yet likely diminishes observed effects (38). This study also lacked information regarding other potential confounders, including smoking, passive smoking, and exposure to noise. Studies suggest that exposure to tobacco smoke and near-roadway air pollution have synergistic effects on the development of childhood obesity (39). Findings from this study may only be generalizable to overweight and obese Latino youth mostly of a lower social position. Despite this, these results have significant public health implications since lower socioeconomic status and minority communities may have some of the largest environmental toxin burdens and suffer from the greatest health disparities in obesity and type 2 diabetes (40–42).

Our results demonstrate that increased exposure to NO_2 and $\text{PM}_{2.5}$ disrupts glucose regulation through a lower S_1 and results in decreased β -cell function, a known risk factor for type 2 diabetes development. Each of these effects was independent of adiposity and the impacts of AAP on risk factors for type 2 diabetes were comparable to and, in some instances, larger than the influence of body fat percent on these traits. Additionally, increased NO_2 and $\text{PM}_{2.5}$ exposures were associated with increased obesity and abdominal adiposity. On the basis of these findings, prolonged exposure to increased AAP appears to independently contribute to decreased S_1 , a strong compensatory insulin response that contributes to β -cell exhaustion, and greater adiposity in youth. In conclusion, this study

supports an important role for AAP exposure in the etiology of type 2 diabetes in youth.

Funding. This work was funded by the following agencies: National Institute of Environmental Health Sciences (Ruth L. Kirschstein National Research Service Award Institutional Research Training Grant T32ES013678 to T.L.A., Southern California's Children's Health Center P01ES022845 and 5P30ES007048 to F.D.G., Maternal and Developmental Risks from Environmental and Social Stressors Center P50ES026086 and 83615801-0 to F.D.G.), National Center on Minority Health and Health Disparities (P60MD002254 to M.J.W. and M.I.G.), National Institute of Diabetes and Digestive and Kidney Diseases (R01DK59211 to M.I.G.), and Environmental Protection Agency (RD83544101 and 83615801 to F.D.G.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.L.A. conceived the research question and study design, collected and reviewed data, ran analysis, and wrote the manuscript. R.H. assembled residential data, guided geocoding efforts, designed and created the final analysis data set combining exposures and clinical outcomes, and contributed to analysis and writing of methods. C.M.T.-C. collected and reviewed data and contributed to manuscript writing. K.B. and Z.C. provided statistical consultation and carefully reviewed results and the manuscript. F.W.L. provided air pollution exposure data and contributed to manuscript writing. M.J.W., M.I.G., and F.D.G. conceived the primary study design. All authors reviewed the article. T.L.A. and F.D.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this work have been presented at the 28th Annual Conference of the International Society for Environmental Epidemiology, Rome, Italy, 1–4 September 2016; the National Institute of Environmental Health Sciences FEST, Durham, NC, 5–8 December 2016; and the 14th Annual Academic Pediatric Association Environmental Health Scholars Retreat, Arlington, VA, 6–8 January 2017.

References

1. D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. *Diabetes Care* 2011;34(Suppl. 2):S161–S165
2. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* 2015;314:1021–1029
3. Rao X, Patel P, Puett R, Rajagopalan S. Air pollution as a risk factor for type 2 diabetes. *Toxicol Sci* 2015;143:231–241
4. Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS. Association between fine particulate matter and diabetes prevalence in the U.S. *Diabetes Care* 2010;33:2196–2201
5. Andersen ZJ, Raaschou-Nielsen O, Ketzel M, et al. Diabetes incidence and long-term exposure to air pollution: a cohort study. *Diabetes Care* 2012;35:92–98
6. Coogan PF, White LF, Jerrett M, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. *Circulation* 2012;125:767–772
7. Chen H, Burnett RT, Kwong JC, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect* 2013;121:804–810
8. Park SK, Adar SD, O'Neill MS, et al. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. *Am J Epidemiol* 2015;181:327–336
9. Weinmayr G, Hennig F, Fuks K, et al.; Heinz Nixdorf Recall Investigator Group. Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a cohort study: effects of total and traffic-specific air pollution. *Environ Health* 2015;14:53

10. Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. *Atherosclerosis* 2009;203:311–319
11. Teichert T, Vossoughi M, Vierkötter A, et al. Association between traffic-related air pollution, subclinical inflammation and impaired glucose metabolism: results from the SALIA study. *PLoS One* 2013;8:e83042
12. Thiering E, Markevych I, Brüske I, et al. Associations of residential long-term air pollution exposures and satellite-derived greenness with insulin resistance in German adolescents. *Environ Health Perspect* 2016;124:1291–1298
13. Wolf K, Popp A, Schneider A, et al.; KORA-Study Group. Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation and adipokines. *Diabetes* 2016;65:3314–3326
14. Adam TC, Hasson RE, Lane CJ, et al. Fasting indicators of insulin sensitivity: effects of ethnicity and pubertal status. *Diabetes Care* 2011;34:994–999
15. Thompson DS, Boyne MS, Osmond C, et al. Limitations of fasting indices in the measurement of insulin sensitivity in Afro-Caribbean adults. *BMC Res Notes* 2014;7:98
16. Chen Z, Salam MT, Toledo-Corral C, et al. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. *Diabetes Care* 2016;39:547–554
17. Toledo-Corral CM, Alderete TL, Habre R, et al. Effects of air pollution exposure on glucose metabolism in Los Angeles minority children. *Pediatr Obes*. 6 December 2016 [Epub ahead of print]. DOI: 10.1111/ijpo.12188
18. Thiering E, Cyrys J, Kratzsch J, et al. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAPlus birth cohorts. *Diabetologia* 2013;56:1696–1704
19. Wong DW, Yuan L, Perlin SA. Comparison of spatial interpolation methods for the estimation of air quality data. *J Expo Anal Environ Epidemiol* 2004;14:404–415
20. Eckel SP, Cockburn M, Shu Y-H, et al. Air pollution affects lung cancer survival. *Thorax* 2016;71:891–898
21. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23
22. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303
23. Ross R, Léger L, Morris D, de Guise J, Guardo R. Quantification of adipose tissue by MRI: relationship with anthropometric variables. *J Appl Physiol* (1985) 1992;72:787–795
24. Hollingshead AB. Four factor index of social status. Smith P, ed. *Yale Journal of Sociology* 2011;8:21–52
25. Kelly LA, Lane CJ, Weigensberg MJ, Toledo-Corral CM, Goran MI. Pubertal changes of insulin sensitivity, acute insulin response, and β -cell function in overweight Latino youth. *J Pediatr* 2011;158:442–446
26. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes* 2002;51(Suppl. 1):S212–S220
27. Lillioja S, Mott DM, Spraul M, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med* 1993;329:1988–1992
28. Fleisch AF, Luttmann-Gibson H, Perng W, et al. Prenatal and early life exposure to traffic pollution and cardiometabolic health in childhood. *Pediatr Obes* 2017;12:48–57
29. Maligie M, Crume T, Scherzinger A, Stamm E, Dabelea D. Adiposity, fat patterning, and the metabolic syndrome among diverse youth: the EPOCH study. *J Pediatr* 2012;161:875–880
30. Sun Q, Yue P, Deiluiis JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009;119:538–546
31. Liu C, Xu X, Bai Y, et al. Air pollution-mediated susceptibility to inflammation and insulin resistance: influence of CCR2 pathways in mice. *Environ Health Perspect* 2014;122:17–26
32. Kelishadi R, Hashemi M, Javanmard SH, et al. Effect of particulate air pollution and passive smoking on surrogate biomarkers of endothelial dysfunction in healthy children. *Paediatr Int Child Health* 2014;34:165–169
33. Matthews NC, Pfeffer PE, Mann EH, et al. Urban particulate matter-activated human dendritic cells induce the expansion of potent inflammatory Th1, Th2, and Th17 effector cells. *Am J Respir Cell Mol Biol* 2016;54:250–262
34. Hajat A, Diez-Roux AV, Adar SD, et al. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect* 2013;121:1325–1333
35. Hsieh S, Klassen AC, Curriero FC, et al. Fast-food restaurants, park access, and insulin resistance among Hispanic youth. *Am J Prev Med* 2014;46:378–387
36. Hsieh S, Klassen AC, Curriero FC, et al. Built environment associations with adiposity parameters among overweight and obese Hispanic youth. *Prev Med Rep* 2015;2:406–412
37. Fram MS, Ritchie LD, Rosen N, Frongillo EA. Child experience of food insecurity is associated with child diet and physical activity. *J Nutr* 2015;145:499–504
38. Nerriere E, Zmirou-Navier D, Blanchard O, et al. Can we use fixed ambient air monitors to estimate population long-term exposure to air pollutants? The case of spatial variability in the Genotox ER study. *Environ Res* 2005;97:32–42
39. McConnell R, Shen E, Gilliland FD, et al. A longitudinal cohort study of body mass index and childhood exposure to secondhand tobacco smoke and air pollution: the Southern California Children's Health Study. *Environ Health Perspect* 2015;123:360–366
40. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;311:806–814
41. OOEHA. Analysis of CalEnviroScreen 2.0 scores and race/ethnicity, 2014. Available from <http://oehha.ca.gov/media/downloads/calenviroscreen/report/ces20final-raceethnicity.pdf>. Accessed 22 December 2016
42. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. *Environ Health Perspect* 2012;120:1699–1704