Associations between ambient air pollution and noise from road traffic with blood pressure and insulin resistance in children from Denmark

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Background: Road traffic is a major source of air pollution and noise. Both exposures may contribute to increased blood pressure and metabolic disease; however, few studies have examined these relationships in children.
Objectives: We aimed to investigate whether long-term exposures to air pollution and noise from road traffic were associated with increased blood pressure and insulin resistance in children.
Methods: Cardiometabolic outcomes were derived from a follow-up examination of 629 children (10–15 years old) enrolled in the Danish National Birth Cohort. We evaluated associations with prenatal and postnatal residential exposure to nitrogen dioxide (NO_2) and noise from road traffic (L_{den}) using historical addresses and linear regression models.
Results: A 10-unit increase in postnatal exposure to NO_2 and L_{den} was associated with a 0.31 (–0.87, 1.48) and 0.18 (–0.61, 0.96) mmHg changes in diastolic blood pressure, respectively. In contrast, both exposures were associated with decreased systolic blood pressure. After adjustment and mutual adjustment for NO_2, exposure to L_{den} was associated with a statistical significant decrease in systolic blood pressure both during prenatal and postnatal life, but the majority of the associations evaluated did not reach statistical significance. Inverse associations were observed for plasma fasting glucose, insulin, and HOMA of insulin resistance for both exposures, exposure windows, before and after adjustment.
Conclusions: The findings do not support evidence of associations between long-term exposures to air pollution and road traffic noise, increased blood pressure, and a metabolic profile characteristic of increased risk for glucose intolerance or type 2 diabetes later in life.

Introduction

High blood pressure is the leading risk factor for morbidity and mortality worldwide, accounting for nearly half of all myocardial infarctions and strokes.[1] Blood pressure in children represent one of the most important measurable markers of cardiovascular risk later in life.[2] There is abundant evidence that ambient air pollution contributes to the risk of cardiovascular disease and associated mortality, supported by evidence of multiple mechanisms that may drive this association.[3] Epidemiological and experimental evidence demonstrating that exposure to ambient air pollution increases blood pressure in adults is accumulating,[3,4] but the findings from studies with children that examine associations between blood pressure and long-term residential exposure to ambient air pollution are scarce and inconsistent. Four-years mean exposure to ambient air pollution concentrations with nitrogen dioxide (NO_2) at the nearest routine air monitor have been associated with increases in both diastolic and systolic blood pressure in a study from China with 9,354 children 5–17 years old.[5] Associations between long-term exposure to NO_2 and diastolic, but not systolic blood pressure, has been found in a study with 12-year-old children (n = 1,147) from the Netherlands after restriction to 471 children who were still living at the same address as at the time of birth.[6] The association for NO_2 and diastolic blood pressure did not reach statistical significance for the full study population which included children who had changed home address.[6] A study with 1,102 newborn children from Boston has reported that exposure to black carbon late in pregnancy was associated with increase in systolic blood pressure, but this was not evident for prenatal exposure to NO_2.[7] No associations, or even inverse associations, between NO_2 and diastolic blood pressure

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What this study adds

In this study, we evaluate the associations of long-term exposures to ambient air pollution and noise from road traffic with increased blood pressure and insulin resistance in children from Denmark. In contrast to experimental and some of the epidemiological evidence, we found no evidence of adverse effects of exposures to ambient NO_2 and noise from road traffic.

have been found in a study with 2,368 children (10 years) from Germany.[8]

Although not only ambient air pollution but also noise from road traffic exposure at home has been associated with higher blood pressure in children,[8–10] only two of the above-mentioned studies has examined the associations between the joint exposures and blood pressure in children.[6,8] While road traffic noise was not associated with higher blood pressure in a study of 1,400 12-year-old Dutch children,[6] adverse effects of road traffic noise were suggested in a study of 605 children from the inner city of Munich in Germany also after adjustment of NO_2.[8]

Long-term exposures to ambient air pollution and noise from road traffic have also been associated with development of type 2 diabetes mellitus in some,[11,12] but not all,[13,14,15] studies with adults. A few studies have indicated that exposure to ambient air pollution may contribute to development of type 1 diabetes.[16,17] Higher exposure to air pollution have also been linked with higher levels of insulin resistance measured by the homeostasis model of insulin resistance (HOMA-IR), in children from Iran (n = 374) and Germany (n = 379), respectively, using the HOMA-IR, one of the important underlying conditions predisposing to type 2 diabetes mellitus.[18,19] Furthermore, exposure to air pollution have been associated with higher level of insulin measured in umbilical cord plasma from 590 placentas collected in Belgium,[20] and fasting blood samples from 314 children 8–15 years old living in Los Angeles.[21] Nevertheless, the independent and joint effect of exposure to road traffic noise and air pollution on biomarkers for development of diabetes have not yet been examined.

In the present study, we aim to investigate whether long-term exposures to ambient air pollution and noise from road traffic are associated with increased blood pressure and insulin resistance in children living in Denmark. Both single and joint effect estimates of long-term exposure to ambient air pollution and road traffic noise will be investigated.

Methods

Study population

This study included children recruited from the Danish National Birth Cohort.[22] Briefly, all general practitioners in Denmark were invited to recruit pregnant women for the Danish National Birth Cohort. In total, 50% of the general practitioners participated, and 60% of the women invited agreed to participate. Enrollment occurred in gestational weeks 6–10 from 1996 to 2002 and computer-assisted telephonic interviews with follow-up interviews started around 12th gestational week. Women were only eligible if they spoke sufficient Danish and intended to carry their pregnancy to term. In the current study, children born by 1,350 women with a diagnosis of gestational diabetes mellitus (GDM) and 2,629 children of randomly selected women without a GDM diagnosis and their mothers were invited to participate in a clinical follow-up examination during March 2012 to April 2014 as described in detail previously.[23] A total of 1,234 children participated in the follow-up.[24] Since children of women with GDM was oversampled, the prevalence of GDM in the current study population is much higher than in the general Danish population. The study was approved by the Regional Scientific Ethics Committee for the municipalities of Copenhagen and Frederiksberg (H-4-2011-045 and H-4-2013-129). All study participants gave informed consent.

Measurement of blood pressure, glucose, and insulin levels

At the clinical examination, after 10 minutes, the resting blood pressure was measured with an Omron blood pressure device with the child in the supine position. All measurements were taken twice, and if the differences exceeded 5 mmHg, a third measurement was taken. In all analyses, the mean value of the measurements was used.

A fasting blood sample for glucose measurements was drawn in K-oxalat-Na-fluoride vials and in lithium-heparin vials for insulin.[24] Glucose and insulin levels were measured using standard laboratory methods on the Modular P-module (Roche, Mannheim, Germany). Coefficients of variance were 4%–5% for glucose and insulin. HOMA-IR was calculated as follows: ([(fasting plasma insulin (pmol/L) × fasting plasma glucose (mmol/L)]/22.5] × 0.144).[25]

The height of the children was measured, the children were weighed without shoes being lightly dressed and their pubertal staging were determined during the follow-up.[24]

Exposure assessment

The methods have previously been used in several epidemiological studies.[26–28] Briefly, maternal residential address history from conception until delivery and child residential address history from birth to age 7, including dates of moving, was collected from the Civil Registration System.[29] All home addresses were geocoded.

Ambient NO_2 concentration (μg/m³) was used as indicator for the mixture of outdoor air pollution from motorized road traffic, emissions from power plants and other combustion processes and calculated at high spatial (individual address level) and temporal level (1 hour) resolution using the advanced and successfully validated DEHM/UBM/AirGIS dispersion modeling system.[30–33] Information on emission factors as well as traffic data for individual roads, emission data from the Danish car fleet, street and building geometry, building height, and meteorological data were used to estimate the sum of local air pollution, urban background, and regional background levels.

Road traffic noise was calculated at the most exposed facade of each residential address using the Nordic prediction method, geographical coordinates and height (floor) for each residential address, and building polygons for all Danish buildings, as well as traffic information on road links (information on annual average daily traffic, vehicle distribution [light/heavy], travel speed, and road type) as described in details previously.[12,34] The following input variables were used for calculation of road noise: geocodes, road links with information on annual average daily traffic, vehicle distribution, travel speed as maximum allowed speed indicated on street signs, and road type and building polygons for all Danish buildings. Road traffic noise was calculated as the equivalent continuous A-weighted sound pressure level and expressed as L_{den}, which refers to average of day (L_d; 0700–1900 hours), evening (L_e;1900–2200 hours), and night (L_n; 2200–0700) in decibel (dB). L_{den} is highly correlated with L_n (0.97).[28]

Prenatal exposure to ambient air pollution with NO_2 and road traffic noise was calculated as time-weighted mean exposure during the time period between conception and birth and postnatal exposure refer to the time-weighted mean exposure from birth to age 7 (taking all present and historical addresses during each period into account). We calculated time-weighted mean exposures as the arithmetic mean of sound intensity, followed by transformation to the dB scale.

Statistical analysis

We used linear regression models to calculate beta-coefficients (β) and their 95% confidence intervals (CIs). The assumption of linearity (on a log scale) of air pollution and noise from traffic in relation to the outcomes was evaluated by fitting models with the exposure variables on a continuous scale simultaneously with a quadratic term of the exposure variables. Several of the associations for NO_2 deviated significantly from linearity ($P < 0.05$, eTable 1; http://links.lww.com/EE/A62) and therefore

we analyzed effect estimates of exposure divided into quartiles using the lowest quartile as referent exposure quartiles in addition to effect estimates of linear exposure variables fitted on continuous scales for a 10-μg/m^3 increase in NO$_2$ and a 10-dB increase in L$_{den}$.

Analyses were done without adjustment. We selected covariates a priori. Adjusted models included information on child's age at the follow-up, sex, height (cm), weight (kg), maternal active smoking during pregnancy obtained from the first interview (none, occasional, <15 cigarettes/day, ≥15 cigarettes/day), maternal education the year before last menstrual period (low, middle, high), and household disposable income (after taxation and interest per person, adjusted for number of household persons and divided into tertiles based on Danish background population) the year before last menstrual period and area-specific income gathered from Statistic Denmark.

Associations with air pollution and road traffic noise was estimated by fitting models for the two exposures separately as well as jointly. Potential interaction between air pollution and noise was evaluated by including an interaction term between air pollution and noise using Wald test. Potential effect modification by sex, puberty, GDM, maternal pre-pregnancy BMI, maternal education, and area of living.

In sensitivity analyses, we repeated the analyses for the smaller sample which excluded the children who moved after age 7 and children of women with GDM. Metabolic differences between GDM-exposed children and children of the control groups has been reported.[24]

The differences in characteristics of the study population by moving status and between the included and excluded population were assessed through P-values from Chi-square. Correlations between exposures were assessed with Spearman Rank Correlations Coefficient.

We performed all record linkage and statistical analyses on Statistic Denmark's server using SAS version 9.3 (SAS Institute Inc. Cary, NC). We used an alpha level of 5% for statistical significance.

Results

Study population

We excluded children due to multiple pregnancies (n = 36), children from later pregnancies for women who had participated with more than one child to avoid correlated measures between siblings (n = 40), and children with missing information on blood pressure (n = 126), prenatal exposure (n = 33), and postnatal exposure (n = 370). This rendered a total of 629 children in the present study. Table 1 summarizes the characteristics of the study population, which consisted of almost half boys and girls 10–15 years old, mostly with residence outside greater Copenhagen. Children estimated to be exposed to the highest concentration of NO$_2$ postnatally (i.e., greater than the median concentration of 11.5 μg/m^3) were less likely to have a mother of high BMI, with GDM and high income and education and to live in areas with high-income than those with the lowest exposure (Table 1). Plasma fasting glucose, insulin, and HOMA-IR concentrations were lower in the highest NO$_2$ exposed children when compared with the lowest exposed children. Maternal smoking, low income, and low education was more frequent for children with highest L$_{den}$ exposure and the systolic blood pressure were lower in these children as compared with the level of the children exposed to lowest L$_{den}$ levels.

The included children were more frequent boys, older, heavier, taller, and with a nonsmoking lean mother free of GDM with higher income than those excluded (eTable 2; http://links.lww.com/EE/A62). The biomarker levels, especially the insulin concentrations were higher in the included children than in the excluded children, but there were no statistical significant differences in terms of exposure to air pollution and noise between

the included and excluded children from whom exposure were available.

The correlations between NO$_2$ and L$_{den}$ were 0.54 and 0.51 for the prenatal and postnatal periods, respectively. Prenatal and postnatal exposure to NO$_2$ and L$_{den}$ were highly correlated (eTable 3; http://links.lww.com/EE/A62).

Associations between long-term exposure to ambient air pollution and road traffic noise, blood pressure, and insulin resistance

Table 2 shows the associations between postnatal exposure to ambient air pollution, road traffic noise, blood pressure, and markers of insulin resistance. Overall, the results provide no evidence of prohypertensive or diabetogenic effect of long-term exposures to these environmental exposures.

Effect estimates for both exposures were elevated for diastolic blood pressure, but the difference did not reach statistical significance (adjusted β: 0.31 [95% CI = –0.87, 1.48] and 0.18 [95% CI = –0.61, 0.96] for 10-units increase in postnatal exposure to NO$_2$ and L$_{den}$, respectively) and the corresponding effect estimates for systolic blood pressure were not elevated (adjusted β: –0.17 [95% CI = –1.81, 1.46] and 1.09 [95% CI = –2.18, 0.01] for 10-units increase in postnatal exposure to NO$_2$ and L$_{den}$, respectively).

Inverse associations were observed for plasma fasting glucose, insulin, and HOMA of insulin resistance for both types of exposure, both exposure windows as well as before and after adjustment, but the 95% CI most often included the null (Table 2). An inverse association between postnatal exposure to L$_{den}$ and HOMA-IR, however, reached statistical significance (adjusted β: –0.16 [95% CI = –0.30, –0.03]). This association did, nevertheless, not follow a clear monotonic dose–response relationship with decreases of 0.33, 0.14, and 0.29, respectively, for the second, third, and fourth quartiles as compared with the lowest quartile of exposure.

All effect estimates for the associations between ambient air pollution, road traffic noise, and blood pressure were greater in crude than adjusted models. Most of the effect estimates were reduced when the two exposures were jointly fitted (Table 2).

Results for prenatal exposure to NO$_2$ and L$_{den}$ were very similar to those of postnatal exposures (eTable 4; http://links.lww.com/EE/A62), that is, generally null.

There were no statistically significant interactions between exposure to NO$_2$ and L$_{den}$ (eTable 5; http://links.lww.com/EE/A62). The effect estimates associated with ambient NO$_2$ and noise from road traffic exposures were also not modified by maternal BMI, education, and area of living.

There was no overall tendency for higher effect estimates in non-movers as compared with the full population which included 140 children who had changed address and results were overall very similar after excluding GDM offspring (eTable 6; http://links.lww.com/EE/A62). The statistical significance of the inverse associations observed for postnatal exposure to L$_{den}$ increased for systolic blood pressure and decreased for HOMA-IR after excluding GDM offspring.

Discussion

We assessed associations of long-term exposure to air pollution and noise from road traffic with blood pressure and markers of prediabetes in 10- to 15-year-old children living in Denmark. We assessed both prenatal and postnatal exposure at the home addresses and found little or no evidence of adverse effects of these common environmental exposures on these cardiometabolic markers.

In accordance with the findings of our study of 629 children, overall no adverse effects have been reported in the previous studies on long-term exposure to NO$_2$ and blood pressure

Table 1

Study Population Characteristics for All and by Low Versus High Postnatal Exposure Levels

Characteristics	All (N = 629)	Low NO_2 (n = 315)	High NO_2 (n = 314)	P	Low L_{den} (n = 315)	High L_{den} (n = 314)	P
Sex				0.94			0.23
Boy	329 (52.3)	51.5	52.6		49.8	54.6	
Girl	300 (47.7)	48.1	47.5		50.2	45.4	
Puberty started				0.31			0.44
No	123 (19.5)	18.2	21.6		20.1	19.1	
Yes	360 (57.2)	60.2	54.1		58.8	55.6	
Missing	146 (23.2)	21.7	24.8		21.1	25.4	
Maternal smoking				0.73			0.02
No	462 (73.5)	73.6	73.3		75.1	71.8	
Yes	150 (23.9)	23.3	24.5		22.8	27.0	
Missing	17 (2.7)	3.2	2.2		4.2	1.3	
Maternal BMI (kg/m^2)				0.02			0.48
<25 kg/m^2	406 (64.6)	59.6	69.4		63.9	65.1	
≥25 kg/m^2	197 (31.3)	36.6	26.1		31.0	31.8	
Missing	26 (4.1)	3.8	4.5		5.1	3.2	
Maternal GDM				0.01			
No	464 (73.8)	67.8	79.6		68.4	79.0	0.002
Yes	165 (26.3)	32.2	20.4		31.6	21.0	
Household disposable income				0.01			0.03
Low	115 (18.3)	15.0	21.7		13.7	22.9	
Middle	179 (28.5)	33.8	23.0		31.3	25.4	
High	327 (52.0)	50.0	54.0		53.7	50.5	
Missing	8 (1.3)	1.3	1.3		1.3	1.3	
Maternal education				0.71			0.06
Low	77 (12.4)	12.4	12.1		10.5	14.0	
Middle	303 (48.2)	48.1	48.1		45.7	50.5	
High	237 (37.7)	38.2	37.3		42.5	33.0	
Missing	12 (1.9)	1.3	2.6		1.3	2.5	
Area of living				<0.001			<0.001
Greater Copenhagen	128 (20.4)	3.2	37.3		45.7	20.6	
Big cities and suburbs	268 (42.6)	34.1	50.6		41.5	43.2	
Provincial and rural	233 (37.0)	62.1	12.1		12.1	28.3	
Area-level income				<0.001			0.008
Low	232 (36.9)	33.4	40.0		38.3	35.6	
Medium-low	140 (22.3)	27.7	16.9		23.0	21.6	
Medium-high	155 (24.6)	29.2	34.7		19.2	29.8	
High	102 (16.2)	14.3	7.0		19.5	13.0	
Moved after age 7				0.03			0.04
No	489 (77.7)	81.2	74.2		81.2	74.3	
Yes	140 (22.3)	18.8	25.8		18.9	25.7	
Age (years)	12.7 (10.1–14.9)	12.8 (10.1–14.9)	12.7 (10.0–15.0)	0.73	12.7 (10.2–14.9)	12.7 (10.0–15.0)	0.96
Weight (kg)	47.0 (32.5–71.0)	47.8 (32.9–74.0)	46.7 (32.0–70.0)	0.76	47.7 (35.5–71.0)	46.7 (32.5–73.0)	0.95
Height (cm)	159.8 (142.0–177.0)	159.2 (142.6–177.0)	161.1 (141.1–177.6)	0.50	159.8 (172.6–176.0)	159.9 (141.7–180)	0.93
Systolic blood pressure (mmHg)	109 (97–126)	109 (97–125)	108 (4–127)	0.15	110 (97–127)	108 (47–122)	0.01
Diastolic blood pressure (mmHg)	62 (54–72)	62 (54–71)	62 (54–73)	0.56	62 (54–73)	62 (55–72)	0.90
Plasma fasting glucose (mmol/L)	4.8 (4.2–5.6)	5.0 (4.2–5.8)	4.7 (4.1–5.5)	<0.001	4.9 (4.2–5.8)	4.8 (4.2–5.6)	0.003
Insulin (pmol/L)	21 (3–38)	21 (4–38)	19.5 (2.00–38.0)	0.05	20.0 (3.0–38.0)	2.1 (2.0–3.8)	0.62
HOMA-IR	2.0 (0.9–4.6)	2.1 (1.0–4.6)	1.9 (0.7–4.3)	0.006	2.0 (0.9–4.8)	2.0 (0.9–4.3)	0.89
Prenatal exposure to NO_2 (µg/m^3)	11.5 (7.5–28.0)	7.7 (6.8–15.6)	15.2 (9.2–34.1)	<0.001	10.4 (7.2–19.5)	13.8 (7.8–32.1)	<0.001
Postnatal exposure to NO_2 (µg/m^3)	10.7 (9.3–20.9)	9.7 (9.2–10.5)	13.1 (10.8–23.6)	<0.001	9.8 (9.3–15.4)	11.9 (9.4–23.4)	<0.001
Prenatal exposure to L_{den} (dB)	57.7 (49.7–70.3)	55.0 (47.8–66.1)	61.2 (52.0–72.1)	<0.001	54.0 (47.8–64.3)	62.3 (53.7–74.5)	<0.001
Postnatal exposure to L_{den} (dB)	58.1 (50.1–68.8)	55.2 (48.3–65.1)	60.1 (52.6–70.8)	<0.001	53.9 (48.3–57.8)	62.4 (58.5–71.0)	<0.001

n (%) P50 (P5–P95). P-values from chi-square and Kruskal–Wallis test.

in 1,147, 2,368, and 1,102 children from the Netherlands, Germany, and the United States which are based on assessment of individual exposure assessed at the home address.[6–8] However, ambient air pollution with NO_2 has been associated with increased blood pressure in a cross-sectional study of >9,000 children from seven cities in China characterized by higher ambient air pollution exposure as compared with the above-mentioned studies,[5] but this study relied on air pollution concentrations from centralized monitors and fine-scale variation in air pollution as well as other risk factors that may have varied within smaller areas such as noise and area-specific socio-economic factors which were not taken into account and may have confounded or modified the reported associations with air pollution.

In a subset of the children from the Dutch PIAMA cohort who lived at the same address since birth, NO_2 was, however, associated with higher diastolic but not systolic blood pressure.[6] This study relied on exposure estimated at the home address at the time of birth and other addresses was not taking into account. We also noted a minor increase in the mean effect estimate of postnatal exposure to NO_2 for diastolic blood pressure from 0.31 (–0.87, 1.48) to 1.22 (–0.29, 2.73) when we restricted to the subset of 489 non-movers. Bilenko et al. proposed that the stronger effects observed in non-movers may suggest that chronic exposure is of greater relevance than more recent exposure. Although, the 95% CI was wide and we cannot preclude that these could be random findings, the fact that we observe the same pattern may also reflect true adverse effects

Table 2

Postnatal Exposure to Ambient Air Pollution and Road Traffic Noise in Associations with Blood Pressure and Insulin Resistance

	NO$_2$						L$_{den}$					
	Unadjusted		Adjusted		Adjusted + L$_{den}$		Unadjusted		Adjusted		Adjusted + NO$_2$	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Systolic blood pressure (mmHg)												
Per 10 unit increment	−0.84	(−2.42, 0.75)	−0.17	(−1.81, 1.46)	0.83	(−1.03, 2.71)	−1.39	(−2.48, −0.30)	−1.09	(−2.18, 0.01)	−1.36	(−2.62, −0.11)
Quartile 1 (lowest)	Ref		Ref		Ref		Ref		Ref		Ref	
Quartile 2	−1.85	(−3.70, 0.00)	−0.74	(−2.57, 1.10)	−0.57	(−2.40, 1.26)	0.74	(−1.11, 2.59)	1.13	(−0.64, 2.90)	1.06	(−0.72, 2.84)
Quartile 3	−1.92	(−3.77, −0.07)	−0.49	(−2.31, 1.33)	0.08	(−1.80, 1.96)	−0.78	(−2.63, 1.06)	−0.88	(−2.62, 0.86)	−1.02	(−2.80, 0.75)
Quartile 4 (highest)	−1.18	(−3.03, 0.67)	0.03	(−1.88, 1.94)	1.10	(−1.00, 3.21)	−1.63	(−3.47, 0.22)	−1.45	(−3.26, 0.36)	−1.78	(−3.76, 0.20)
Diastolic blood pressure (mmHg)												
Per 10 unit increment	0.51	(−0.36, 1.66)	0.31	(−0.87, 1.48)	0.23	(−1.12, 1.59)	0.15	(−0.59, 0.89)	0.18	(−0.61, 0.96)	0.10	(−0.81, 1.01)
Quartile 1 (lowest)	Ref		Ref		Ref		Ref		Ref		Ref	
Quartile 2	0.62	(−0.62, 1.86)	0.44	(−0.88, 1.75)	0.45	(−0.89, 1.76)	−0.32	(−1.57, 0.92)	−0.03	(−1.31, 1.25)	−0.06	(−1.34, 1.23)
Quartile 3	0.21	(−1.03, 1.45)	0.01	(−1.29, 1.32)	0.01	(−1.34, 1.34)	−0.68	(−1.92, 0.57)	−0.49	(−1.75, 0.77)	−0.53	(−1.82, 0.75)
Quartile 4 (highest)	1.12	(−0.12, 2.36)	0.83	(−0.55, 2.20)	0.82	(−0.70, 2.34)	0.27	(−0.97, 1.51)	0.26	(−1.05, 1.57)	0.15	(−1.28, 1.59)
Plasma fasting glucose												
Per 10 unit increment	na		na		na		−0.14	(−0.21, −0.07)	−0.13	(−0.20, −0.05)	−0.07	(−0.16, 0.02)
Quartile 1 (lowest)	Ref		Ref		Ref		Ref		Ref		Ref	
Quartile 2	−0.21	(−0.33, −0.09)	−0.16	(−0.28, −0.04)	−0.16	(−0.28, −0.04)	−0.10	(−0.22, 0.02)	−0.10	(−0.23, 0.02)	−0.09	(−0.21, 0.04)
Quartile 3	−0.34	(−0.45, −0.22)	−0.26	(−0.39, −0.14)	−0.25	(−0.38, −0.12)	−0.21	(−0.33, −0.09)	−0.22	(−0.34, −0.10)	−0.18	(−0.30, −0.06)
Quartile 4 (highest)	−0.42	(−0.54, −0.31)	−0.37	(−0.50, −0.24)	−0.34	(−0.49, −0.20)	−0.20	(−0.32, −0.08)	−0.19	(−0.31, −0.06)	−0.10	(−0.24, 0.03)
Insulin												
Per 10 unit increment	−1.57	(−3.67, 0.49)	−2.42	(−4.47, −0.38)	−2.26	(−4.61, 0.10)	−1.08	(−2.58, 0.42)	−0.98	(−2.36, 0.39)	−0.23	(−1.81, 1.34)
Quartile 1 (lowest)	Ref		Ref		Ref		Ref		Ref		Ref	
Quartile 2	−2.14	(−4.67, 0.39)	−0.61	(−2.91, 1.69)	−0.55	(−2.86, 1.75)	−3.59	(−6.12, −1.06)	−3.04	(−5.27, −0.81)	−2.79	(−5.02, −0.56)
Quartile 3	−2.82	(−5.35, −0.28)	−0.72	(−3.01, 1.56)	−0.52	(−2.89, 1.85)	−0.82	(−3.35, 1.70)	−0.94	(−3.13, 1.25)	−0.45	(−2.67, 1.78)
Quartile 4 (highest)	−3.06	(−5.59, −0.53)	−2.21	(−4.60, 0.18)	−1.83	(−4.47, 0.82)	−1.94	(−4.47, 0.58)	−1.80	(−4.07, 0.48)	−0.66	(−3.14, 1.83)
HOMA-IR												
Per 10 unit increment	−0.18	(−0.39, 0.03)	−0.37	(−0.58, −0.20)	−0.33	(−0.57, −0.10)	−0.16	(−0.33, −0.03)	−0.16	(−0.30, −0.03)	−0.05	(−0.21, 0.10)
Quartile 1 (lowest)	Ref		Ref		Ref		Ref		Ref		Ref	
Quartile 2	−0.27	(−0.52, −0.00)	−0.14	(−0.36, 0.09)	−0.13	(−0.36, 0.10)	−0.35	(−0.61, −0.09)	−0.33	(−0.55, −0.11)	−0.30	(−0.52, −0.07)
Quartile 3	−0.41	(−0.66, −0.15)	−0.22	(−0.44, 0.01)	−0.19	(−0.42, 0.05)	−0.13	(−0.39, 0.12)	−0.14	(−0.36, 0.08)	−0.07	(−0.29, 0.15)
Quartile 4 (highest)	−0.43	(−0.69, −0.18)	−0.41	(−0.65, −0.18)	−0.36	(−0.62, −0.10)	−0.29	(−0.55, −0.03)	−0.29	(−0.51, −0.06)	−0.13	(−0.37, 0.12)

[a]Adjusted for child's age, sex, height, weight, maternal active smoking during pregnancy, maternal education, household disposable income, and area-income. NA refers not applicable as the dose–response relationship in these cases appeared to be non-linear.

of NO_2 on blood pressure which only are apparent at low exposure settings in the children with the most accurate exposure assessment. Although, the 95% CIs was wide and we cannot preclude that these could be random findings, the fact that we observe the same pattern may also reflect true adverse effects of NO_2 on blood pressure which only are apparent at low exposure settings in the children with the most accurate exposure assessment. Although the observed effect in our study and the reported increase in blood pressure associated with NO_2 is small on the individual level,[6] since exposure to ambient air pollution is widespread and because a rise in blood pressure on the populational level will result in a substantial increase in number of children with higher blood pressure and hypertension ambient air pollution may have a large population-attributable risk for hypertension and related disorders.

We do not have any explanation of the differential association of traffic exposure with systolic and diastolic blood pressure. Our findings for NO_2 are in agreement with those of the children from the PIAMA cohort,[6] but differential results are not observed in other studies,[5,8] and results for diastolic blood pressure is not always reported.[7] Similar to the results for systolic blood pressure in our study, statistically significant inverse associations between long-term exposure to NO_X and blood pressure in the participants of the Danish Diet and Cancer Cohort Study have previously been observed,[35] but in this population NO_X was also associated with decreased diastolic blood pressure.

The results of previous studies on the effects of long-term exposure at home to road traffic noise on blood pressure in children are contradictory. This could partly be due to differences in terms of methods used for noise estimation and party due to small, if any, impact of exposure.

Our lack of associations for noise and blood pressure is in line with the findings of two previous studies based on similar noise model methods which included children from both urban and rural areas of the Netherlands.[6,36] Positive results have, however, been reported in a German study of children from urban area based on a GIS noise model.[8] Borderline higher blood pressure among Austrian children living in areas with community noise level above 60 dB as compared with those living in neighborhoods below 50 dB.[37] Higher blood pressure has also been reported in children with extremely busy traffic street as compared with those with no street has been reported in a study based on parental classifications of the traffic levels in front of their children's room.[9]

The observed inverse associations between road traffic noise, systolic blood pressure, and insulin resistance are in conflict with our hypothesis, and with the majority of experimental and epidemiological studies investigating effects on noise on these markers, hypertension, and type 2 diabetes,[14,38,39] including studies with adults from Denmark and a similar exposure assessment of long-term exposure to road traffic noise.[11,12,40] As both inverse associations did not follow clear monotonic dose–responses together with the relatively small size of our cohort (629 children), we cannot preclude chance as a like explanation to these findings.

In contrast to the findings summarized in a recent meta-analysis of six cohort studies of children and adults,[41] including those from the previous studies on HOMA-IR,[18,19] the findings from our study are not supportive of associations between ambient NO_2 and noise from road traffic exposure and insulin resistance. One potential explanation for the lack of association in the present study may relate to low and narrow range of exposure to NO_2 and L_{den} as compared with the cross-sectional study of 374 children 10–18 years old from Iran in which the mean exposure to NO_2 for these children were three times higher than the one of the present study.[18] The air pollutant concentrations from centralized air monitoring stations were combined into quartiles of a pollution score of multiple air pollutants, the

individual associations with NO_2, and exposure to noise were not evaluated.

Our study has several limitations. Although our study was larger than previous studies[8,19] that have reported, effects supportive of associations the small study size limits our study. Further, variation in biomarkers related to other factors including unknown factors and known factors such as the sex, age, height, and body weight of the children, which varied widely and may not have been taken appropriately into account potentially masking any of the investigated exposure induced changes in the blood pressure and markers of diabetes. Our exposure assessment was limited to exposure at home addresses and exposures occurring elsewhere was not included. Therefore, our exposure assessment may suffer from exposure misclassification. Besides from not being able to assess the exposure to other relevant air pollutants such as particulate matter, which has been linked with the investigated outcomes,[3,41] exposures at the schools of the children, during their commute, etc., we had no information on the most recent exposure at their home, time spent at home, exposure at location of the children's bedrooms, ventilation habits, indoor sources to air pollution, and noise barriers such as noise-blocking windows in their homes. Furthermore, since motorized road vehicles is a major source of both air pollution and noise from road traffic, similar traffic indicators were used in the modeling resulting in modest correlations between the exposures (eTable 3; http://links.lww.com/EE/A62) which complicate differentiation between the effects of these exposures and could contribute to unstable models when having a smaller study population. The null finding of our study preclude meaningful interpretation of the exact observed effect estimates and for instance the observed change in the effect of NO_2 on systolic blood pressure from –0.17 to 0.83 together with the wider 95% CI after mutual adjustment for L_{den} illustrate that the results were unstable.

Finally, we do suggest future studies to separate out the effect of traffic related NO_2 from total NO_2 when possible to further understand the contribution from motorized road vehicle emissions.

The strengths of this study include the possibility to estimate individual exposure and risk factors during time periods that preceded the clinical follow-up of the children and wealth of information on both the mothers and their children over the 9–16 years of follow-up. This allowed us to consider and evaluate many covariates as potential confounders and minimize residual confounding. This information included objective indicators of socioeconomic status and detailed smoking data from early pregnancy. We used clinical data for the outcomes and this may have minimized the likelihood of differential measurement error and provided us with an outcome closer to the physiologic points of interest. The inclusion of GDM pregnancies is a unique feature in itself. It allowed us to examine the associations for a susceptible group of children. Opposite to previous studies, we were able to take into account all the home addresses from conception to 2011; however, a subset of 140 children had changed address during the last 1–3 years up till the clinical follow-up and our sensitivity analysis were suggestive of larger effect estimates for non-movers so in future studies we do recommend to include life-long exposure.

To conclude, our findings do not support evidence of associations between long-term exposures to ambient air pollution with NO_2 and road traffic noise, increased blood pressure, and a metabolic profile characteristic of increased risk for glucose intolerance and prediabetes later in life.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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