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ARTICLE

Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts

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Abstract
Aims/hypothesis Epidemiological studies that have examined associations between long-term exposure to traffic-related air pollution and type 2 diabetes mellitus in adults are inconsistent, and studies on insulin resistance are scarce. We aimed to assess the association between traffic-related air pollution and insulin resistance in children.
Methods Fasting blood samples were collected from 397 10-year-old children in two prospective German birth cohort studies. Individual-level exposures to traffic-related air pollutants at the birth address were estimated by land use regression models. The association between air pollution and HOMA of insulin resistance (HOMA-IR) was analysed using a linear model adjusted for several covariates including birthweight, pubertal status and BMI. Models were also further adjusted for second-hand smoke exposure at home. Sensitivity analyses that assessed the impact of relocating, study design and sex were performed.
Results In all crude and adjusted models, levels of insulin resistance were greater in children with higher exposure to air pollution. Insulin resistance increased by 17.0% (95% CI 5.0, 30.3) and 18.7% (95% CI 2.9, 36.9) for every 2SDs increase in ambient NO_2 and particulate matter $\leq$10 μm in diameter, respectively. Proximity to the nearest major road increased insulin resistance by 7.2% (95% CI 0.8, 14.0) per 500 m.
Conclusions/interpretation Traffic-related air pollution may increase the risk of insulin resistance. Given the ubiquitous nature of air pollution and the high incidence of insulin resistance in the general population, the associations

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examined here may have potentially important public health effects despite the small/moderate effect sizes observed.

Keywords Air pollution · Children · Cohort study · HOMA-IR · Insulin resistance · Traffic

Abbreviations

ESCAPE	European Study of Cohorts for Air Pollution Effects
ETS	Environmental tobacco smoke
GINIplus	German Infant Study on the Influence of Nutrition Intervention plus Environmental and Genetic Influences on Allergy
GIS	Geographic information system
HOMA-IR	HOMA of insulin resistance
LISAplus	Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood
LUR	Land use regression
PM	Particulate matter
$PM_{2.5}$	Particulate matter ≤2.5 μm in diameter
PM_{10}	Particulate matter ≤10 μm in diameter

Introduction

Air pollution exposure increases the risk of cardiopulmonary morbidity, acute events [1] and mortality [2]. Recent studies also suggest that exposure to chronic traffic and air pollution influences the development and progression of atherosclerosis [3, 4], possibly via systemic oxidative stress and low-grade inflammation in endothelial cells and macrophages [5]. These underlying biological mechanisms are also involved in the pathogenesis of type 2 diabetes mellitus, particularly in the progression of insulin resistance [6]. It has also been shown in animal models that exposure to particulate matter 2.5 μm or less in diameter ($PM_{2.5}$) for 24 weeks exaggerates insulin resistance, visceral inflammation and adiposity in diet-induced obese mice [7]. Further exposure for a duration of 10 months led to oxidative stress, decreased mitochondrial count in visceral adipose depots and decreased mitochondrial size in interscapular adipose depots [8]. Adverse effects have been found to be associated with indoor air pollution exposure, for example between environmental tobacco smoke (ETS) exposure and type 2 diabetes mellitus incidence and susceptibility among adults [9] and adolescents [10]. It thus seems biologically plausible that air pollution may be a risk factor for insulin resistance and type 2 diabetes mellitus.

The few cross-sectional and longitudinal studies that have examined associations between exposure to air pollution and the development of type 2 diabetes mellitus in different adult age groups [11–17] have yielded inconsistent findings. As insulin resistance is considered to be a strong risk factor for the development of diabetes in adults, studying the effects of air pollution on insulin resistance in healthy children could lead to new insights into this complex disease.

To the best of our knowledge, no study has yet investigated the association between traffic-related air pollution and insulin resistance in school-aged children. The present study aimed to investigate the relation between long-term exposure to traffic-related air pollution (NO_2, $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance, and proximity to nearest major road) at the birth address and the HOMA of insulin resistance index (HOMA-IR) in 10-year-old children in two German birth cohorts.

Methods

Study area and study population The study population consists of a subsample of children living in Munich, South Germany, and Wesel, West Germany, who participated in the 10-year follow-up of two birth cohorts. In both cohorts, only healthy full-term neonates were recruited. The German Infant Study on the Influence of Nutrition Intervention plus Environmental and Genetic Influences on Allergy (GINIplus) is a multicentre, two-armed study consisting of 5,991 newborns. One study arm is a prospective, double-blind, randomised intervention trial with hypoallergenic formulae, while the second arm is observational and does not include an intervention. The study design has been previously described in detail [18]. The Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood (LISAplus) Study consists of 3,097 healthy neonates, recruited at birth, who have a birthweight >2,500 g. LISAplus was designed as a population-based observational study, and children have been followed-up at the age of 6, 12 and 18 months and 2, 4, 6 and 10 years [19]. The regional ethics committees approved both studies, and parents gave written informed consent.

At the age of 10 years, children from both cohorts were randomly assigned to one of two groups based on the last digit of their identification number. The first group did not undergo any further selection and will hereafter be referred to as the population-based sample. This population-based sample was enriched with a potentially sensitive subgroup consisting of children with a BMI at age 10 years above the 85th percentile selected from the second group (enrichment sample). A random subset of children from both the population-based sample and the enrichment sample were invited for fasting blood sampling at the age of 10 years.

The present study population consists of 397 children without diabetes (type 1 or 2) for whom air pollution exposure data at birth and insulin and glucose measurements are available.

Laboratory analyses Glucose measurements in blood were performed by standard laboratory methods by the individual hospitals. Fasting insulin in serum was measured centrally by the fully mechanised system, LIAISON (DiaSorin, Saluggia, Italy). The lower limit of detection for this method was 3.5 pmol/l. Quality control samples showed intra- and inter-assay coefficients of variation below 5.8%. HOMA-IR was calculated as described by Matthews et al [20].

Exposure assessment We used land use regression (LUR) models to estimate long-term spatial variability of NO_2, PM_{10}, $PM_{2.5}$ and $PM_{2.5}$ absorbance at the birth address of each individual. The LUR models were developed in the framework of an ongoing European Study of Cohorts for Air Pollution Effects (ESCAPE; (15/10/2012): www.escapeproject.eu). The development of the LUR models has been described in previous publications [21–24]. Briefly, concentrations of NO_2 were measured at 40 monitoring sites, and concentrations of $PM_{2.5}$ and filter absorbance of $PM_{2.5}$ at 20 monitoring sites in Munich-Augsburg and the Ruhr area. The measurement period in Munich was between October 2008 and November 2009, and measurements at all selected sites were carried out three times for 14 consecutive days, in different seasons. All air pollution measurements were performed according to standard operating procedures available on the ESCAPE project website (www.escapeproject.eu/manuals/), accessed 15 October 2012.

Europe-wide geographic information system (GIS) data (such as digital road network, land use data CORINE [CO-ordination and INformation on the Environmental program, initiated by the European Commission] and population density data), centrally provided within the framework of the ESCAPE study, was used to generate potential predictor variables that describe each monitoring site in terms of location, surrounding land use, population density and traffic patterns.

The measured air pollutant concentrations and the GIS-generated predictor variables were used to develop local LUR models for each study centre. A detailed description of the LUR model development process and predictors are provided in Beelen et al [21] and Eeftens et al [22]. The final LUR models were used to estimate outdoor air pollution concentrations at the addresses of study participants.

In addition, local GIS data for the Munich and Wesel study areas were collected and used to estimate the distance between the child's birth address and the centre of the nearest major road defined as a road with traffic intensity >5,000 vehicles/day.

Covariate assessment All adjustment covariates were selected a priori. Socioeconomic status was defined as the largest number of years of education of either parent (low, <10 years of school; medium, 10–11 years of school; high, ≥12 years of school). Onset (yes/no) of puberty was assessed via a questionnaire (signs of puberty, e.g. pubic hair or menarche). Height and weight at age 10 years were measured by a physician during a clinical examination in the study centres by standard procedures. Exposure to second-hand smoke (ETS) was ascertained at several time points between birth and the age of 10 years (details provided previously [25]), and the percentage of years during which the parents or another person smoked in the home was classified into three mutually exclusive categories: no ETS, ≤50% or >50% of years recorded.

Statistical analysis Children were included in the analysis if they had valid measurements of both fasting blood insulin and glucose as well as information on at least one exposure variable. The HOMA-IR was log-transformed to base *e*, as its distribution was skewed. For the exposure variables, extreme observations exceeding mean ± 4SD were excluded (n=1 for NO_2 and $PM_{2.5}$ absorbance, and n=7 for distance to the nearest major road). Generalised additive models (gam), as implemented in R [26] (library mgcv, gam procedure), were used to assess the linearity of associations between insulin resistance and air pollutants. These models allow the use of smooth functions for covariates or exposures that may have a non-linear relationship with the outcome. Subsequently, linear regression models were used to analyse the relationship between insulin resistance quantified by HOMA-IR and exposure to traffic-related air pollution. Models were adjusted for sex, age, study (including GINIplus intervention status), parental education, study centre, study design, BMI, puberty status, birthweight and ETS at home during childhood. In addition, analyses were performed separately in the population-based sample and the enrichment sample, as well as stratified by sex and relocations (never moved, moved before the age of 3, or moved after the age of 3). Results are presented as percentage differences with 95% CI, which correspond to the back-transformed β-coefficients from the linear regression analyses on log-transformed HOMA-IR multiplied by 100 [27]. Effect sizes correspond to a 2SD increase in traffic-related air pollutant or a 500 m decrease in distance to the nearest major road. Statistical significance was defined by a two-sided α level of 5%. All statistical analyses were performed using R 2.14 [26].

Results

The characteristics of the study population are summarised in Table 1. Measured fasting blood insulin and glucose levels and geocoded residential address information at birth were available for 397 children. The majority (82.1%) were recruited in Munich. Children living in Wesel were more likely to have been exposed to ETS at home between birth and 10 years of age, and their families were more likely to be

Table 1 Characteristics of the total and city-specific populations

Characteristic	Total (n=397)	Munich (n=326)	Wesel (n=71)
Design			
Enrichment sample[a]	167 (42.1)	117 (35.9)	50 (70.4)
Population-based	230 (57.9)	209 (64.1)	21 (29.6)
Study			
GINI observation	125 (31.5)	84 (25.8)	41 (57.7)
GINI intervention	131 (33.0)	114 (35.0)	17 (23.9)
LISA	141 (35.5)	128 (39.3)	13 (18.3)
Socioeconomic status[b,c]			
Low	26 (6.6)	19 (5.9)	7 (9.9)
Medium	83 (21.1)	51 (15.8)	32 (45.1)
High	285 (72.3)	253 (78.3)	32 (45.1)
Sex			
Male	175 (44.1)	147 (45.1)	28 (39.4)
Female	222 (55.9)	179 (54.9)	43 (60.6)
Birthweight (kg)	3.5±0.5	3.4±0.5	3.6±0.5
% of years with ETS at home			
No ETS	256 (64.5)	224 (68.7)	32 (45.1)
≤50%	66 (16.6)	51 (15.6)	15 (21.1)
>50%	75 (18.9)	51 (15.6)	24 (33.8)
Puberty started[d,e]			
No	252 (64.6)	202 (63.3)	50 (70.4)
Yes	138 (35.4)	117 (36.7)	21 (29.6)
Age of the child (years)	10.2±0.2	10.2±0.3	10.3±0.2
BMI at 10 years (kg/m^2)	18.3±2.9	18.3±2.9	18.2±2.9
HOMA-IR (GM)	1.5±1.8	1.5±1.8	1.5±1.8
Distance to major road (m) (GM)	190.2±3.3	175.0±3.1	280.8±3.7
NO_2 (μg/m^3)	21.7±5.3	21.2±5.5	24.0±3.1
PM_{10} (μg/m^3)	21.2±3.0	20.3±2.4	25.5±1.2
$PM_{2.5}$ (μg/m^3)	14±1.9	13.3±1.0	17.5±0.7
$PM_{2.5}$ absorbance (10^{-5}/m)	1.6±0.3	1.7±0.2	1.2±0.2

Values are n (%) or mean ± SD

[a] BMI at 10 years >85th percentile

[b] Highest number of years of education of either parent

[c] Information was missing for n=3 children

[d] Defined as a parental report of signs of puberty (e.g. pubic hair, menarche)

[e] Information was missing for n=10 children

GM, geometric mean

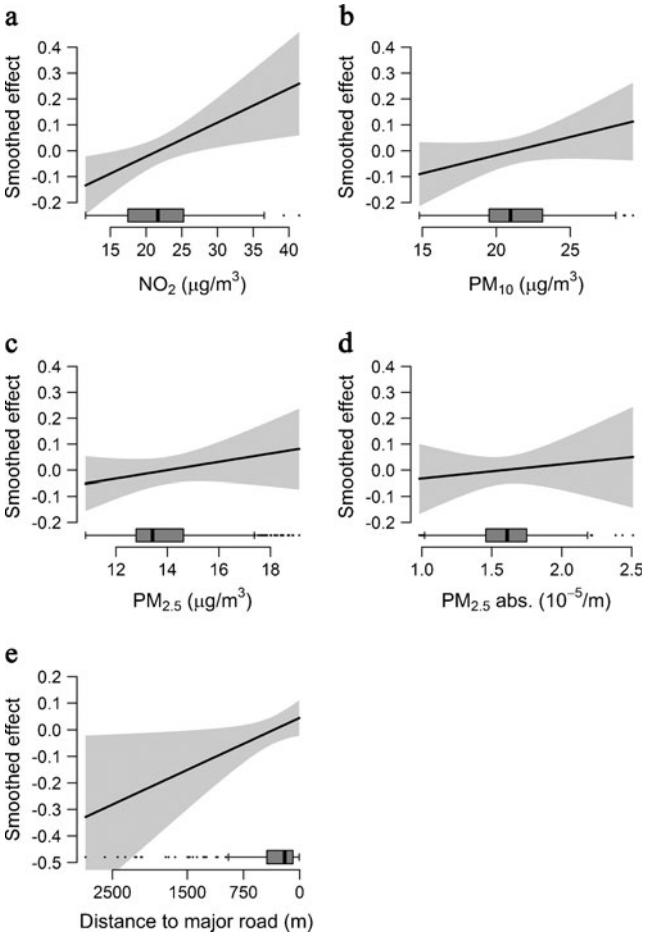

Fig. 1 Smooth associations between insulin resistance and exposure variables assessed using generalised additive models adjusted for sex, age and BMI. Box plots on the x-axis show the distribution of the exposure variables NO_2 (**a**), PM_{10} (**b**), $PM_{2.5}$ (**c**), $PM_{2.5}$ absorbance (**d**) and distance to the nearest major road (**e**); abs., absorbance

of lower socioeconomic status. However, there were no differences in age, BMI and HOMA-IR between children living in Munich and Wesel. All pollutant concentrations, except for $PM_{2.5}$ absorbance, were higher in Wesel than in Munich. Children from Wesel tended to live further away from a major road. All exposure measures were linearly associated with insulin resistance by generalised additive modelling (Fig. 1).

Table 2 shows the percentage differences in HOMA-IR per 2SD increase for NO_2, PM_{10}, $PM_{2.5}$ and $PM_{2.5}$ absorbance concentrations, as well as a 500 m decrease in distance to the nearest major road after adjustment for different sets of covariates. All estimates for the association between air pollutants and insulin resistance were greater than 0.0%. Insulin resistance was statistically significantly increased by 17.0% (95% CI 5.0, 30.3) per 2SD increase in NO_2 after adjustment for sex, birthweight, study centre, parental education, study, study design, age, puberty status and BMI (adjustment 1). The association of insulin resistance and PM_{10} was also significant (increase of 18.7% [95% CI 2.9, 36.9] per 2SD increase in PM_{10}). Effect estimates for $PM_{2.5}$ (22.5%, 95% CI −0.9, 51.5) and $PM_{2.5}$ absorbance (8.6%, 95% CI −5.7, 25.0) were elevated, but the difference did not reach statistical significance.

Log-transformed (to the base e) distance to the nearest major road correlated with modelled NO_2 (r=−0.50, p<0.001), PM_{10} (r=−0.17, p<0.001), $PM_{2.5}$ (r=−0.10, p=0.04) and $PM_{2.5}$ absorbance (r=−0.56, p<0.001). Insulin resistance was significantly increased by 7.2% (95% CI 0.8, 14.0) per 500 m decrease in distance to a major road. All

Table 2 Percentage difference (95% CI) in insulin resistance (HOMA-IR) per 2SD increase in traffic-related air pollutants and per 500 m decrease in distance to the nearest major road

Exposure	Adjustment 1[a]		Adjustment 2[b]	
	% (95% CI)	*p* value	% (95% CI)	*p* value
Per 2SD increase in				
NO_2 (μg/m^3)	17.0 (5.0, 30.3)	0.005	15.8 (3.8, 29.1)	0.009
PM_{10} (μg/m^3)	18.7 (2.9, 36.9)	0.019	17.5 (1.9, 35.6)	0.027
$PM_{2.5}$ (μg/m^3)	22.5 (−0.9, 51.5)	0.062	20.5 (−2.6, 49.0)	0.087
$PM_{2.5}$ absorbance (10^{-5}/m)	8.6 (−5.7, 25.0)	0.254	7.1 (−7.1, 23.5)	0.343
Per 500 m decrease in distance to major road (m)	7.2 (0.8, 14.0)	0.028	6.7 (0.3, 13.5)	0.040

2SDs correspond to 10.6 μg/m^3 for NO_2, 6 μg/m^3 for PM_{10}, 3.7 μg/m^3 for $PM_{2.5}$ and 0.5×10^{-5}/m for $PM_{2.5}$ absorbance

[a] Adjustment 1: sex, birthweight, study centre, parental education, study, study design, puberty status, age and BMI

[b] Adjustment 2: adjustment 1 plus ETS

associations were slightly attenuated, but remained elevated, after additional adjustment for ETS (Table 2, adjustment 2).

Figure 2 shows the results from the stratified analyses. Effect estimates tended to be higher in children who had never moved between birth and 10 years than in children who had moved (Fig. 2a). Specifically, the point estimates for proximity to a major road and $PM_{2.5}$ absorbance were only elevated in 'never movers'. Less heterogeneity was observed between moving strata for NO_2, PM_{10} and $PM_{2.5}$ exposure.

Effect estimates for NO_2, $PM_{2.5}$ absorbance and distance to the next major road also tended to be higher in the enrichment sample with children of higher BMI compared with the population-based sample (Fig. 2b). We did not observe any evidence of effect modification by sex (Fig. 2c).

Discussion

We assessed associations between long-term exposure to traffic-related air pollutants and insulin resistance in school-aged children. We found consistent linear effects for NO_2 and PM_{10}, as well as suggestive evidence for other pollutants and distance to a major road. Effect estimates for exposure to NO_2 and PM_{10}, as well as living close to a major road, were statistically significant. Associations were robust to additional adjustment for ETS.

To the best of our knowledge, no study has yet investigated the long-term effects of air pollution on insulin resistance in children.

In order to understand the role of traffic-related air pollution exposure in the pathogenesis of insulin resistance, we also review here the evidence for an association between traffic-related air pollution and type 2 diabetes mellitus in adults, which has been investigated in several studies [11–17]. However, it remains difficult to completely reconcile our results with those of these other studies, as diabetes is a complex disease caused by multiple factors, not only insulin resistance.

Recently, Andersen et al [11] reported borderline significant associations between confirmed diabetes cases and NO_2 exposure in participants of the Danish Diet, Cancer and Health Cohort Study. Larger effects were observed in

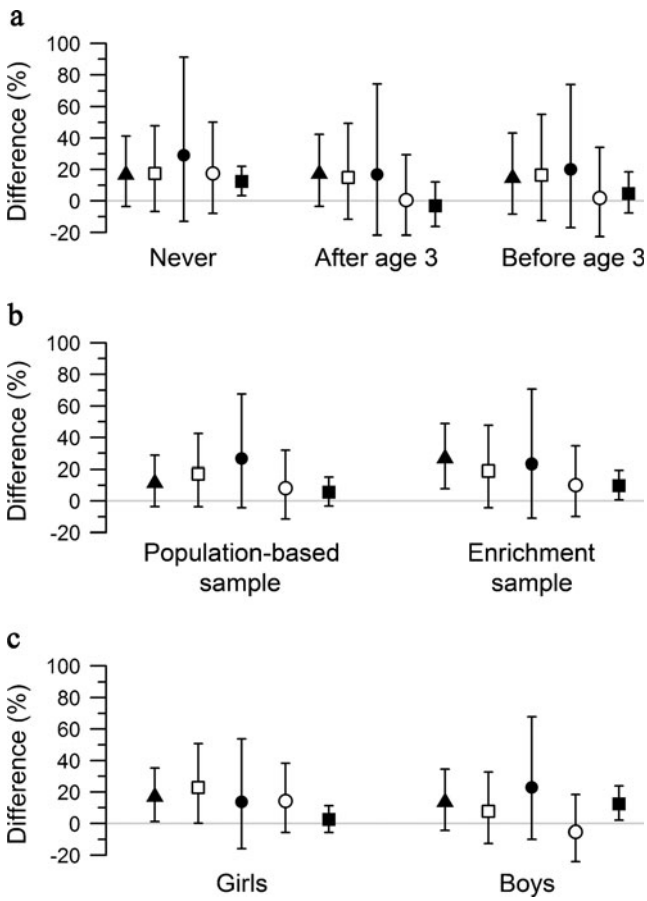

Fig. 2 Percentage difference in HOMA-IR per 2SD increase in NO_2 (black triangle), PM_{10} (white square), $PM_{2.5}$ (black circle), $PM_{2.5}$ absorbance (white circle), and per 500 m decrease in distance to the nearest major road (black square) stratified by moving house (**a**), study design (**b**) and sex (**c**)

never smokers and physically active people, but not for all diabetes cases. Furthermore, in the same cohort, NO_2 and traffic load within a 200 m buffer were associated with diabetes-associated mortality [12]. An analysis of two large prospective cohorts [13] did not provide conclusive evidence for an association between exposure to PM in the previous 12 months and incident diabetes, but an association with distance to road was found in women. In our study, we also observed an association with distance to major road, especially in children who had not moved since birth.

While a study in a semirural area in the Netherlands [14] did not find any consistent associations between type 2 diabetes mellitus prevalence and exposure to traffic-related air pollution, despite some indications for an association with traffic within a 250 m buffer, a study conducted in the highly industrialised Ruhr district [15] found a significantly increased hazard for diabetes associated with increasing $PM_{2.5}$ absorbance and NO_2, as well as with proximity to a major road, but only among women with a low educational level. Moreover, Krämer et al [15] reported interaction effects between traffic-related air pollution exposure and the complement factor C3c, a surrogate marker for subclinical inflammation.

In summary, results in adults are inconsistent, especially for PM exposure. Observed effects were higher for NO_2 exposure than for PM_{10} exposure [15], and risk estimates for NO_x were only marginally attenuated when modelled together with $PM_{2.5}$ [16]. The observations that home proximity to a major road is associated with adverse effects in women [13, 15], and that there are indications of a relationship between type 2 diabetes mellitus and traffic within a 250 m buffer [14], imply that traffic-related air pollution could be responsible for associations of air pollution with type 2 diabetes mellitus in adults. This hypothesis is consistent with the associations between traffic-related air pollution and insulin resistance reported in the present study.

The short-term effects of traffic-related air pollution in youth age 10–18 years have been studied by Kelishadi et al [28]. Air pollution (Pollutant Standard Index, CO and PM_{10}) in the 7 days before blood sampling was significantly associated with HOMA-IR in their study, but NO_2 was not. We stratified our analyses on the basis of the time a child had lived at the birth address after birth. Effect estimates tended to be larger in children who lived longer at the birth address and who had not moved. Unfortunately, the low sample size did not allow an examination of whether children moved to a less or more polluted location. Nevertheless, we observed a slight increase in insulin resistance for children who were exposed to higher levels of NO_2, PM_{10} and $PM_{2.5}$ at birth, but moved before the age of 3 years.

Studies on air pollution and insulin resistance in humans are scarce, but associations between air pollution and metabolic outcomes have been studied using several animal models. For example, $PM_{2.5}$ increased HOMA-IR in rats fed a high-fat diet for 6 weeks but not in rats fed a normal diet [29]. Furthermore, ambient air pollution exaggerated adipose inflammation and insulin resistance in diet-induced obese mice [7]. In our study, we found a tendency for larger effect estimates in the subset of children with higher BMIs (enrichment sample) than in the population-based sample.

A previous study including both men and women [17] found significant associations between type 2 diabetes mellitus and air pollutants only among women. Other studies, in which only a female population was recruited a priori, found indications for an association between air pollution and type 2 diabetes mellitus [15, 16]. In our study, which is restricted to children, we did not find any indications for a risk-modifying effect of sex. However, the speculation that the air pollution exposure assessment may be more accurate for adult women, who are more likely to spend a greater proportion of time at home, than for adult men is not applicable to our study population.

There is some evidence that air pollution is associated with lower birthweight and growth restrictions [30, 31]—also shown previously in one of the cohorts of the present study [32]—which are known risk factors for type 2 diabetes mellitus [33]. Thus, one may speculate that lower birthweight is an intermediate phenotype between air pollution and insulin resistance. However, we found no evidence to suggest that this may be true in our cohort of children with birthweights >2,500 g.

Biological mechanisms Measured NO_2 concentration is considered an indicator for the complex mixture of various gaseous and particulate components originating from both traffic combustion and wear of road and vehicles. PM may also originate from these sources, but also industry. In particular, the Wesel study area is located in proximity to the highly industrialised Ruhr area in Germany, and the air pollution estimates for this city probably reflect pollution originating from a mixture of industrial sources, long-range transportation, atmospheric chemistry and local mobile traffic. Sources of air pollution in Munich are more likely to be dominated by local traffic exhaust (for detailed information on the local LUR models, see Beelen et al [21] and Eeftens et al [22]). Although toxicity differs between air pollutants, they are all considered potent oxidisers that act either directly on lipids and proteins or indirectly through the activation of intracellular oxidant pathways [34, 35]. The oxidative potential of PM from traffic sources on protein and lipid oxidation in young adults has been shown previously [36], as have NO_2 effects on levels of oxidised LDL in adolescents [28]. Oxidative stress caused by exposure to air pollutants may therefore play a major role in the development of insulin resistance.

In addition, some studies have reported that short-term and long-term increases in PM and NO_2 exposure lead to elevated inflammatory biomarkers [28, 37–39]. For children, adverse effects were also shown for C-reactive protein, TNF-α and IL-1 β [40]. However, there are also large studies that have not found evidence for a relationship between PM and inflammation [41, 42]. A possible explanation for these diverging findings may be variation in the particulate size and the structure and chemistry of the pollutant, which may lead to differences in the inflammatory response depending on the susceptibility of the exposed individual.

Strength and limitations The primary strengths of this study are the prospective design and the availability of data on lifestyle and multiple risk factors such as exposure to ETS, which allowed us to adjust for many factors that may confound the association between insulin resistance and traffic-related air pollution. However, an important limitation of this study is the potential for exposure misclassification, as the modelling of air pollution estimates at the birth address was based on air pollution concentrations that were measured some years after the birth of the children. Changes in infrastructure—for example, related to road transport, such as noise protection or bypasses, or related to housing, such as additional housing blocks—may have hampered the correct estimation of air pollution concentrations at the birth address. Changes in the residential address may also be a source of exposure misclassification.

However, in a birth cohort study in Ohio, USA, differences in the results for exposure to diesel exhaust particles estimated via LUR models at the birth address and the time-weighted average of exposure at all addresses (including day care and moving) until the age of 3 years were found to be small for the total population [43], and in a birth cohort study in Stockholm, Sweden, strong correlations between early and later air pollution exposure, modelled at residential, day care and school addresses, up to the age of 8 years (r=0.70–0.89) were observed [44]. Recent studies have also shown that LUR models are temporally stable over at least an 8-year period [45, 46].

These results suggest that exposure assessment at the residential address at birth may be a good approximation of perinatal and early childhood exposure. We were particularly interested in investigating associations with exposures at the birth address, as this corresponds to a developmental period when children are probably more vulnerable and a time when children spend the majority of their time at the home address.

The degree of exposure misclassification resulting from changes in the residential address after birth depends on the age of the child at the first move. We addressed this issue in a sensitivity analysis (see Fig. 2a) and observed a tendency for lower effect estimates in movers than non-movers. We assume that the reported estimates for the total population may thus be biased towards the null because of potential exposure misclassification.

A further limitation of this study is related to the enrichment of the population-based sample with a susceptible group of children, which may have overexaggerated the true effect sizes. However, the stratified sensitivity analysis also shows elevated estimates in the population-based sample, although the effect sizes were larger in the enrichment sample.

To our knowledge, this is the first prospective study that investigated the relationship of long-term traffic-related air pollution and insulin resistance in children. Insulin resistance levels tended to increase with increasing traffic-related air pollution exposure, and this observation remained robust after adjustment for several confounding factors, including BMI and passive smoking.

Conclusions In conclusion, our data suggest that air pollution exposure at the birth address may increase the risk of insulin resistance at the age of 10 years. Given the ubiquitous nature of air pollution and the high incidence of insulin resistance in the general population, the associations examined here may have potentially important public health effects despite the small/moderate effect sizes observed.

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Contribution statement ET carried out the statistical analysis and drafted the manuscript. JC wrote the exposure assessment section of the manuscript. JK measured insulin levels. JH and CM were involved in the conception and design of the insulin resistance substudy. JH, BH, DB, AvB, SK and C-PB designed and/or conducted the birth cohort studies. All authors contributed substantially to the interpretation of the data and its discussion, revised the manuscript critically for important intellectual content, and approved the final version.

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