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Exposure to ambient air pollution and noise in relation to adverse health effect in children

Dissertation
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1. Summary

Adverse health impacts of ambient air pollution and noise have been reported previously. However, many published studies were in adults or aged population, little attention has been paid to children and in particular to noise and the potential combined effect with air pollution. In addition, we considered health parameters, which are underinvestigated so far. In our study, we explored associations between ambient air pollution and noise with blood pressure (BP), and exhaled nitric oxide (eNO) in school-aged children, using data from two German birth cohorts.

Noise levels within a 50m buffer around each participant's home address were assessed using geographic information system. Exposure estimates of annual average concentrations of air pollution for each participant's residence were calculated using a land use regression model. Short-term concentrations of air pollution were collected from background monitoring sites. Information on BP and eNO was collected during a physical examination at the 10-year follow-up of the cohorts.

We studied the health impacts of ambient air pollution and noise in children from three different aspects. The association between traffic noise and BP was explored in 605 children, and the results showed that higher minimum levels of weighted day-evening-night noise and nighttime noise around the home residence may increase a child's BP. Based on this finding, we conducted a second analysis to figure out the combined associations between air pollution and noise with BP, and found that ambient air pollution was not consistently associated with BP with adjustment for noise. Furthermore, the effects of ambient air pollution on eNO were explored within 1985 children, and we observed a significant positive association between short-term, but not long-term, air pollution with childhood eNO.

In conclusion, our study provided more epidemiological evidence on the adverse health impacts of ambient air pollution and noise in school-aged children, and highlighted the confounding association between ambient air pollution and noise. More studies are needed to better assess the combined health effects of ambient air pollution and noise in children.

2. Zusammenfassung

Frühere Studien haben über die gesundheitsschädigende Wirkung von Luftschadstoffen und Lärm berichtet. Allerdings betrachteten viele bislang publizierte Studien Erwachsene oder die ältere Bevölkerung. Kinder und im Speziellen die gesundheitlichen Auswirkungen von Lärm, sowie die gemeinsame Wirkung von Luftschadstoffen und Lärm wurden hingegen bislang nur wenig untersucht. Das ist ein Ziel der vorliegenden Promotionsschrift. Zusätzlich haben wir Gesundheitsgrößen betrachtet, die bisher wenig erforscht wurden. In unserer Studie haben wir die Assoziationen zwischen Luftschadstoffen und Lärmbelastung und Blutdruck und exhaliertem Stickstoffmonoxid (eNO) bei Kindern im Schulalter untersucht. Wir konnten dabei auf Daten von zwei großen deutschen Geburtskohorten zurückgreifen.

Die Lärmbelastung innerhalb eines Umkreises von 50m um die Wohnadresse jedes Studienteilnehmers wurde anhand von Lärmpegelkarten im Geographischen Informationssystem modelliert. Schätzungen der mittleren jährlichen Konzentration von Luftschadstoffen an der jeweiligen Wohnadresse wurden anhand von „land use regression“ Modellen berechnet. Kurzzeit-Konzentrationen von Luftschadstoffen wurden mit Hilfe von Hintergrund Monitoring Stationen gesammelt. Informationen zu Blutdruck und eNO wurden während einer körperlichen Untersuchung beim Follow-up der Kohorten im Alter von 10 Jahren gemessen.

Wir haben die Auswirkungen von Luftschadstoffexposition und Lärmbelastung auf die Gesundheit von Kindern unter drei verschiedenen Aspekten betrachtet. Der Zusammenhang zwischen Verkehrslärm und Blutdruck wurde bei 605 Kindern untersucht und die Ergebnisse legen nahe, dass ein höherer Mindestpegel des gewichteten Tag-Abend-Nacht Lärmes und des Lärmes während der Nachtzeit um die Wohnung den Blutdruck der Kinder erhöhen könnte. Auf Grund dieser Erkenntnis haben wir eine zweite Auswertung durchgeführt um den gemeinsamen Zusammenhang zwischen Luftschadstoffbelastung und Lärm mit Blutdruck zu untersuchen und haben festgestellt, dass die Luftschadstoffexposition nach einer Adjustierung für Lärm nicht konsistent mit Blutdruck assoziiert war. Darüber hinaus wurden die Auswirkungen der Luftverschmutzung auf das eNO bei 1985 Kindern untersucht. Dabei wurde ein signifikanter, positiver Zusammenhang zwischen Kurzzeit-, jedoch nicht zwischen Langzeitexposition mit Luftschadstoffen und eNO beobachtet.

Zusammenfassend lässt sich festhalten, dass unsere Studie weitere epidemiologische Erkenntnisse über die negativen gesundheitlichen Auswirkungen von Luftverschmutzung und

Lärm bei Schulkindern geliefert hat. Insbesondere wird damit betont, dass Luftschadstoffe und Lärm wechselseitige Störgrößen in Assoziationen darstellen können. Allerdings sind weitere Studien notwendig, um gesundheitliche Auswirkungen von Luftschadstoffen auf die Knochenumsatzrate bei Kindern abschließend beurteilen zu können.

3. Introduction

3.1 Background

The health effects of traffic-related exposure, including traffic-related noise and air pollution, have been studied previously. Long-term exposure to noise may cause adverse health effects such as annoyance, disturbance of sleep or daily activities, hearing disorders, hypertension, ischemic heart disease[1], stress[2] and asthma[3]. Meanwhile, ambient air pollution has also been reported to be associated with hypertension[4-6], inflammation (indicated by exhaled nitric oxide [eNO][7-13], IL-6[14], C-reaction protein, etc.) and even bone health[14-16].

However, most of the afore-mentioned studies were conducted among adults or aged population. Studies in children are limited and no conclusive result can be achieved. For one side, less study have used health parameters, such as childhood blood pressure (BP) and eNO. For another, the potential combined effects of ambient air pollution and noise have rarely been considered.

In order to contribute more knowledge on the health impacts of ambient air pollution and noise in children, we conducted the present study using data from two German birth cohorts.

1) Noise exposure and blood pressure

Most previous epidemiological studies conclude that noise exposure may cause adverse health effects. However, studies on children are limited. To date, several epidemiological studies have examined the impact of road-traffic noise on BP in children, and have yielded somewhat mixed results. Most of these studies found positive associations between road-traffic noise and BP[2,17-21], but one study reported a negative association between noise and diastolic BP[19], another between noise and systolic BP[1], and there was an study reporting no associations between noise exposure and childhood hypertension in Germany[22].

Also, exposure to noise during nighttime[1] and the direction of child's bedroom[23], which are crucial factors for the association between noise and health effect, are rarely considered in previous studies.

2) Air pollution, noise and blood pressure

It has been proven that exposure to ambient air pollution[4-6] and/or noise[24] causes increase in BP. However, most of the published studies are on adults of the elderly, less has focused

on children. As childhood BP is a strong predictor for hypertension later in life[25], understanding the factors that influence childhood BP is important.

Furthermore, as traffic-related air pollution and noise share road traffic as a source, it is necessary to mutually adjust for these two factors when exploring their effects on BP. The potential confounding relationship between traffic-related air pollution and noise has been previously highlighted[26], but only two studies[27,28] have examined this issue among children. Bilenko et al.[27] reported a positive association between childhood BP and long-term NO_2, and no association with noise. Clark et al.[28] found no statistical associations between NO_2 and childhood BP before and after adjusting for road-traffic noise at school.

3) Air pollution and exhaled nitric oxide

The fractional concentration of eNO is a reliable and noninvasive marker of eosinophilic airway inflammation[29,30]. As it is easier and faster to obtain than other inflammation markers, such as sputum eosinophils level[29], it is widely used in epidemiological studies[8], especially those conduced in children[29].

Short-term air pollution is positively associated with eNO in children, especially those with asthma[7-13]. Studies in non-asthmatic children are rare. Furthermore, there have also been studies[31-34] reported that children living in areas with high traffic density and/or air pollution concentrations have chronically increased levels of eNO. However, few study has examined the effects of both short- and long-term exposure simultaneously. We investigated associations between short-term air pollution and eNO in both asthmatic and non-asthmatic children, taking long-term air pollution into consideration.

3.2 Method

Study population

The study population consists of children from two German birth cohorts of healthy full-term neonates. The German Infant Nutritional Intervention plus environmental and genetic influences on allergy development study (GINIplus) was designed to prospectively investigate the effects of a nutrition intervention during infancy, as well as air pollution and genetics, on allergy development. A total of 5991 newborns were recruited in obstetric clinics in Munich and Wesel, Germany, between September 1995 and July 1998. Follow-up occurred at the age of one, two, three, four, six and ten years of age. The Lifestyle-Related

factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics (LISAplus) population-based study aimed to assess the influence of lifestyle-related factors on the immune system, as well as the effects of air pollution and genetics on the development of allergies in childhood. In total, 3097 healthy full-term neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. Follow-up for this study occurred at the age of six, twelve and eighteen months, and two, four, six and ten years.

We included children at the age of 10 years, for whom data on ambient air pollution and/or noise are available. For both cohort studies, ethical approval was obtained by the medical ethical committees. Written informed consent was obtained from the parents of all participants.

Exposure assessment

Road-traffic noise

A GIS based noise model, including the entire Munich street network (around 2800 km) was used to estimate road traffic noise levels for the year 2007 on a 5 m grid, 4 m above ground level, in 5 dB(A)-intervals. Briefly, weighted equivalent noise levels in dB(A) over a full day (Lden, weighted yearly average noise level between 6 a.m. to 6 p.m., 6 p.m. to 10 p.m., and 10 p.m. to 6 a.m.) and at night (Lnight, yearly average noise level between 10 p.m. and 6 a.m., as German regulations stipulate) were modeled according to the European Noise Directive.

Maximum and minimum levels of noise within a 50 m buffer around each child's home address were used in this study. Maximum noise over a full day (Lden_max) was defined as the maximum noise level of Lden within a 50 m buffer around the selected building/house. Minimum noise over a full day (Lden_min), maximum noise at nighttime (Lnight_max) and minimum noise at nighttime (Lnight_min) were defined analogously.

Long-term (one-year) air pollution concentration

Estimates of modeled annual average concentrations of NO_2 and particulate matter (PM; including $PM_{2.5}$, $PM_{2.5-10}$, PM_{10} and $PM_{2.5}$ absorbance) were derived from city-specified land-use regression models developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) collaboration (http://www.escapeproject.eu/manuals).

In brief, NO_2 and PM were monitored at 40 and 20 sites, respectively, between October 2008 and November 2009. Each site was monitored for two consecutive weeks, three times (during warm, cold and intermediate temperature seasons). These discontinuous measurements were then adjusted for the actual long-term average of the observation period, according to data from one additional background site that measured air pollution concentrations using the same instruments continuously for a complete year. Using these data, land use regression models were developed and used to assign individual air pollution exposure estimates to each participant's home address at the age of 10 years.

Short-term air pollution concentrations

Concentrations of both NO_2 and PM_{10} mass for Munich were obtained from the same background monitoring site located in the Munich suburban area (Johanneskirchen), which is approximately nine kilometers in the northeast of the city. Concentrations of both NO_2 and PM_{10} mass for Wesel were obtained from 'The State Agency for Nature, Environment and Consumer Protection of North Rhine-Westphalia'. The data were collected in one monitoring site (WESE) that located in the suburban area of Wesel-Feldmark, it is approximately two kilometers in the northeast of the city.

Outcome measurement and covariates

Blood pressure, eNO and serum bone markers were measured at the 10-year physical examination. Demographic, health, and lifestyle information on the study participants was collected using self-administered questionnaires completed by the parents.

1) Blood pressure: Resting systolic and diastolic BP were measured twice in a sitting position from the right arm after five minutes rest. The elbow was relaxed at heart level to store (slightly bent) and the upper arm was bare during testing. A second measurement was taken after sitting for two minutes. An automatic BP monitor (Omron M5 Professional) was used for the measurements. The cuff size was selected according to the length and circumference of the upper arm of each child: the width was at least 2/3 of the length and the pressure bladder covered at least half of the circumference of the upper arm. BP was measured by one physician in Munich and one in Wesel. The average of the two BP measurements was used in all analyses.

2) Exhaled NO: Fractional eNO was determined in line with the current European Respiratory Society and American Thoracic Society recommendations during a controlled expiration over six seconds using the handheld device, NIOX MINO (Aerocrine[35]).

Briefly, the eNO measurement was performed in a standing position. The study participants were asked to inhale quickly to total lung capacity through the mouthpiece of the device so that the lung was filled with NO free air (NO scrubber). To avoid nasal inspiration a nose clip was used. The participant then exhaled slowly and evenly through the mouthpiece at a flow rate of 50 ± 5 ml/sec. The accurate flow rate was achieved by guidance of a sound and light signal from the device. The quality of the eNO measurement was automatically controlled by the device. Typically, one maneuver was performed and, upon acceptance for quality control, was used for analyses. Unacceptable maneuvers were repeated until acceptance, with a possible maximum of 5 repetitions.

In order to avoid the effects of factors known to influence eNO, we included only children who met the following requirements before the eNO measurement: no nitrite-rich food intake (e.g., green vegetables and fruits, smoked meats and spinach, etc.) for at least four hours prior to measurement; no anti-asthmatic and antiphlogistic medications in the last four hours; no measurements of lung function and no bronchial challenge prior to test.

Statistics analysis

The analyses were carried out using the statistical software R (version 2.14.1). Pearson's chi-square, the Student's t-test and the Wilcoxon rank sum test were used for categorical, normally distributed continuous variables, and continuous variables with a skewed distribution, respectively. Associations between exposure and health outcomes were explored with generalized additive models (MGCV package in R).

1) Noise exposure and blood pressure

The association between noise exposure and BP in children was studied in 605 children from Munich area. Cohort (GINIplus; LISAplus), sex, age, body mass index (BMI), season of physical examination, physical activity, maternal smoking during pregnancy, parental history of hypertension, and highest education level of either parent (low: both parents reported less than 10 years of school; medium: at least one parent had 10 years of school; high: one of the parents reported more than 10 years of school) were included as adjustment. The orientation of child's bedroom window (facing street or not) was considered in sensitivity analyses.

2) Air pollution, noise and blood pressure

We investigated associations between annual average concentrations of NO_2, $PM_{2.5}$, PM_{10} and $PM_{2.5}$ absorbance and BP in 2,368 children, independent of cohort, city, sex, age, BMI, physical activity, maternal smoking during pregnancy, highest education level of either

parent, parental history of hypertension, 7-day air pollution and 7-day temperature. We also studied this association with further adjustment of noise exposure in a subgroup of 605 children from Munich inner city.

3) Air pollution and exhaled nitric oxide

The association between ambient air pollution and eNO was investigated in 1985 children (asthmatics = 192, non-asthmatics = 1793). Average concentrations of NO_2 and PM_{10} in 24h before physical examination were included as main exposure. Cohort, city, sex, highest education level of either parent, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco smoke at 10 years of age, average ambient temperature in the last 24h, annual averages of ambient air pollution were included as adjustment.

3.3 Results

1) Noise exposure and blood pressure

Diastolic BP was significantly associated with Lden_min and Lnight_min. Specifically, diastolic BP increased by 0.67 and 0.89 mmHg for every 5 A-weighted decibels increase in Lden_min and Lnight_min. After adjusting for Lden_min (Lnight_min), diastolic BP of children whose bedroom window faced the street was 1.37 (1.28) mmHg higher than those whose bedroom window did not, these children showed statistically significant increased systolic BP for Lden_min (3.05 mmHg) and Lnight_min (3.27 mmHg) compared to children whose bedroom window did not face the street.

2) Air pollution, noise and blood pressure

In the overall analysis including 2368 children, NO_2, $PM_{2.5}$, PM_{10} and $PM_{2.5}$ absorbance were not associated with BP. When restricting the analysis to the subgroup of children with noise information (N = 605), a significant association between NO_2 and diastolic BP was observed (-0.88 (95% confidence interval: -1.67, -0.08)). However, upon adjusting the models for noise exposure, only noise remained independently and significantly positively associated with diastolic BP. Diastolic BP increased by 0.50 (-0.03, 1.02), 0.59 (0.05, 1.13), 0.55 (0.03, 1.07), and 0.58 (0.05, 1.11) mmHg for every five decibel increase in Lden and by 0.59 (-0.05, 1.22), 0.69 (0.04, 1.33), 0.64 (0.02, 1.27), and 0.68 (0.05, 1.32) mmHg for every

five decibel increase in Lnight, in different models of NO_2, $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance as the main exposure, respectively.

3) Air pollution and exhaled nitric oxide

In the total of 1985 children, robust associations between 24h NO_2 and eNO were observed in both single-pollutant (percentage change: 18.30%, 95% confidence interval: 11.63 – 25.37) and two-pollutant models (14.62%, 6.71 – 23.11). The association between 24h PM_{10} mass and eNO was only significant in the single-pollutant model (9.59%, 4.80 – 14.61). The same significant associations were also observed in 1793 non-asthmatic children, while they did not reach significant levels in 192 asthmatic children. Associations between annual averages of ambient air pollution (NO_2, $PM_{2.5}$, PM_{10} and $PM_{2.5}$ absorbance) and eNO were consistently null.

3.4 Discussion

We explored health impacts of ambient air pollution and noise in school-aged children from three different aspects, with consideration of health parameters that are underinvestigated so far. Noise was observed as an independent factor that is positively associated with diastolic BP. On the other side, ambient air pollution was not consistently associated with BP with adjustment for noise. In addition, we also found adverse health effects of ambient air pollution on airway inflammation in children.

The present study is unique in the following aspects. First, it is a study on the health impacts in school-aged children. Many published studies were in adults or aged population, and less in children. Second, it is one of the few studies that have considered the combined association between ambient air pollution and noise, which share traffic as the same source. Third, some health parameters that are underinvestigated previously have been included in the present study using a rather large sample.

However, there are also limitations which should be considered when interpreting the presenting results. There is a potential selection bias. The study participants were collected from two German birth cohorts at the tenth year, and not all children from the original cohort population could be included due to the availability of data. Furthermore, exposure misclassification may be a concern in the current study. Ten-year old children spend much daytime at school, thus ambient air pollution and noise levels assessed at the home address may not accurately reflect a child’s true daytime exposure.

3.5 Conclusion

It is concluded from the study that exposure to ambient air pollution and noise inversely associated with children's health, including elevated BP levels and airway inflammation. Moreover, a confounding association between air pollution and noise with childhood BP was supported by the results. Overall, the present study provided further epidemiological evidence on the health impacts of ambient air pollutants and noise in school-aged children. The observed confounding association highlighted the importance of including both ambient air pollution and noise in future studies. More studies including various health parameters are needed to better assess the health impacts of ambient air pollution and noise in children.

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4. The Association between road traffic noise exposure and blood pressure among children in Germany: The GINIplus and LISAplus studies

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The association between road traffic noise exposure and blood pressure among children in Germany: The GINIplus and LISAplus studies

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Abstract

Studies examining the association between road traffic noise and blood pressure in children are scarce. Nighttime noise levels and window orientations have not been considered in most previous studies. Investigate the association between road traffic noise exposure and blood pressure among children, and investigate the impact of bedroom window direction on this association. We measured blood pressure in 605 children aged 10 years from two Munich cohorts. Demographic and health information was collected by parent completed questionnaires. Road traffic noise levels were assessed by day-evening-night noise indicator "Lden" and night noise indicator "Lnight". Minimum and maximum levels within a 50 m buffer around child's home address were derived. Generalized additive models were applied to explore effect of noise levels on systolic and diastolic blood pressure (SBP and DBP). The orientation of child's bedroom window was considered in sensitivity analyses. DBP was significantly associated with the minimum level of noise during 24 h (Lden_min) and nighttime (Lnight_min). Specifically, DBP increased by 0.67 and 0.89 mmHg for every 5 A-weighted decibels increase in Lden_min and Lnight_min. After adjusting for Lden_min (Lnight_min), DBP of children whose bedroom window faced the street was 1.37 (1.28) mmHg higher than those whose bedroom window did not, these children showed statistically significant increased SBP for Lden_min (3.05 mmHg) and Lnight_min (3.27 mmHg) compared to children whose bedroom window did not face the street. Higher minimum levels of weighted day-evening-night noise and nighttime noise around the home residence may increase a child's blood pressure.

Keywords: Blood pressure, children, nighttime, road traffic noise, windows

Introduction

Transportation is the main source of environmental noise pollution.[1] Approximately 54% of European Union (EU) citizens that live in major agglomerations (>500,000 inhabitants) are exposed to road traffic noise with a weighted day-evening-night equivalent sound pressure level of 55 A-weighted decibels [dB(A)] or more, whereas 15% are exposed to levels above 65 dB(A). Along densely traveled roads, levels can exceed 75 dB(A). During nighttime, more than 18% of EU citizens are exposed to night noise levels of 55 dB(A) or more.[2] Long-term exposure to noise may cause adverse effects on health such as annoyance, disturbance of sleep or daily activities, hearing disorders, hypertension and ischemic heart disease.[3]

Most previous epidemiological studies conclude that noise exposure may cause adverse health effects. However, studies on children are limited, especially with respect to road-traffic-related noise as most previous studies have focused on aircraft noise.[4] To date, there have been seven reliable epidemiological studies on road-traffic noise and blood pressure in children. However, no unequivocal conclusions can be drawn from these results; Two of the seven studies found positive and significant associations between

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noise exposure and diastolic blood pressure (DBP),[5,6] one study found negative and significant associations between noise and DBP,[7] four studies found positive and significant associations between noise and systolic blood pressure (SBP),[6-9] one study found a positive but non-significant association between noise and SBP[10] and one study found a negative and significant associations for SBP.[3]

The effect of nighttime noise exposure on health has been seldom explored in children.[3] Belojevic *et al*.[7] reported a positive correlation between SBP and noise during the day, but not at night. Paunovic *et al*.[6] found the same result in their study, as well as a similar correlation between DBP and noise (again, only the day noise was correlated positively). Furthermore, the direction of child's bedroom is rarely considered among studies on noise and health.[11]

According to Sorensen *et al*.,[12] exposure to noise during the night may cause sleep disturbance, potentially resulting in a stress reaction which activates the sympathetic and endocrine system ultimately leading to changes in blood pressure. As explained by van Kempen *et al*.,[13] we are exposed to noise during sleep, which may cause the fluctuation of blood pressure in the body. As also suggested in the paper, although the change in blood pressure caused by noise exposure may be small, this increase, which could affect the prevalence of cardiovascular disease, may still have an important impact as a large percent of the population is exposed.

The aim of the present study is to investigate the association between modeled road traffic noise exposure (noise levels for both 24 h and nighttime) and blood pressure among children aged 10 years, and to investigate the impact of the direction of the bedroom window on this association.

Methods

Study population

The study population consists of participants from two German birth cohorts of healthy full-term neonates (gestational age ≥ 37 weeks).

The German Infant Nutritional Intervention plus (GINIplus) environmental and genetic influences on allergy development study was initiated to prospectively investigate the influence of a nutrition intervention during infancy, as well as the effects of air pollution and genetics on allergy development. Details of the design, recruitment and follow-up of this intervention study have been previously published.[14,15] In brief, a total of 5991 newborns were recruited in obstetric clinics in Munich and Wesel, Germany, between September 1995 and July 1998. Follow-up occurred at the age of 1-4, 6 and 10 years of age. Fifty-five percent of those originally recruited at birth could be followed until the age of 10 years.

The lifestyle-related factors on the immune system and the development of allergies in childhood plus the influence of traffic emissions and genetics (LISAplus) population-based study was designed to assess the influence of lifestyle-related factors on the immune system, air pollution, and genetics on the development of allergies in childhood. In total, 3095 healthy full-term neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999 (original recruitment was 3097 children, but two withdrew their consent to participate). Follow-up for this cohort occurred at the age of 6, 12 and 18 months, and 2, 4, 6 and 10 years. Fifty-seven percent of the original population could be followed until the age of 10 years. A detailed description of screening and recruitment is described elsewhere.[16,17]

We restricted our present analysis to the Munich area for which a road traffic noise map was available. To be included, a child must have reported their home address to be within Munich at birth and at the 10 year follow-up (GINIplus $N = 709$, LISAplus $N = 444$, total $N = 1153$). Of these children, 52% participated in a clinical physical examination in the 10th year of follow-up during which blood pressure measurements were taken (GINIplus 405, LISAplus 200 in total $N = 605$). Figure 1 shows the overall design of the study population.

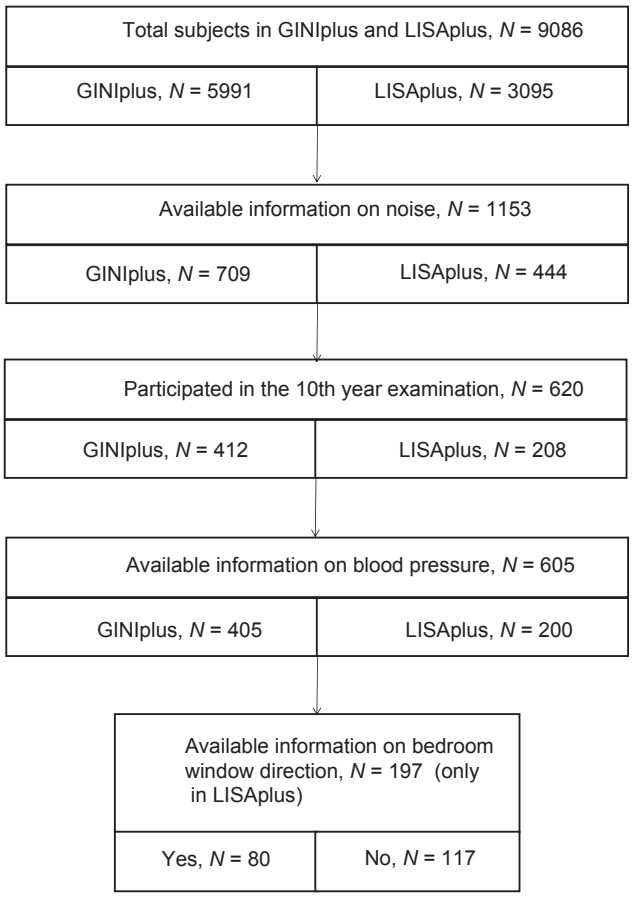

Figure 1: Design of study population

For both cohort studies, ethical approval was obtained by the medical ethical committees of all participating institutes and the medical association of the state of Bavaria (Landesaerztekammer). Written informed consent was obtained from all active participating families.

Outcome definition and covariates

At the 10-year follow-up, blood pressure, height, weight, and age (in months) were collected during a physical examination. Resting blood pressure measurements, including SBP and DBP, were carried out twice following standardized guidelines: Blood pressure was measured on the right arm, except in the case of injuries or other obstacles (e.g., gypsum) when it was measured on the left arm. The measurement was performed with the child in a sitting position after 5 min rest. The elbow was relaxed, at heart level, and slightly bent, and the upper arm was bare during testing. A second measurement was taken after sitting for a further 2 min. An automatic blood pressure monitor (Omron M5 Professional) was used for the blood pressure measurements. The cuff size was selected according to the length and circumference of the upper arm of each child: the width was at least 2/3 the length and the pressure bladder covered at least half of the circumference of the upper arm. All the blood pressure measurements were conducted between 7:00 a.m. and 8:30 p.m. by the same physician. The average of the two measurements was used throughout this analysis, regardless of the difference between the two records (we excluded 11 subjects who had only one measurement).

Demographic, health, and lifestyle information on the subjects was collected using self-administered questionnaires completed by the parents [gender, physical activity (hours per week), maternal smoking during pregnancy (yes/no), parental history of hypertension (neither parent is hypertensive; at least, one of the parents is hypertensive), and the highest educational level of parents (low: Both parents with less than 10 years of school; medium: 10 years of school; high: One of the parents with more than 10 years of school)].

Geographic information system modeled road traffic noise exposure

A GIS based noise model, including the entire Munich street network (around 2800 km) was used to estimate road traffic noise levels for the year 2007 on a 5 m grid, 4 m above ground level, in 5 dB(A)-intervals. Details of the modeling approach have been published previously.[18] Briefly, weighted equivalent noise levels in dB(A) over a full day (Lden, weighted yearly average noise level between 6 a.m. to 6 p.m., 6 p.m. to 10 p.m., and 10 p.m. to 6 a.m.) and at night (Lnight, yearly average noise level between 10 p.m. and 6 a.m., as German regulations stipulate) were modeled according to the European Noise Directive.[19]

Maximum and minimum levels of noise within a 50 m buffer around each child's home address were used in this study. Maximum noise over a full day (Lden_max) was defined as the maximum noise level of Lden within a 50 m buffer around the selected building/house. Minimum noise over a full day (Lden_min), maximum noise at nighttime (Lnight_max) and minimum noise at nighttime (Lnight_min) were defined analogously.

Statistical analysis

The descriptive analysis was carried out using the statistical software package SPSS 17.0. Pearson's Chi-square, the Student's *t*-test, and Wilcoxon rank sum test were used to assess differences of baselines characters between GINIplus and LISAplus; one-way ANOVA was used to analysis distribution of blood pressure between different levels of noise, which were divided into three categories based on quartiles with cutoffs at the 25th and 75th percentile.

Given that the correlation between noise and blood pressure was nearly linear, we explored the effect of road-traffic noise (as a linear term) on blood pressure using generalized additive models (GAM), other confounders [age of child, body mass index (BMI) of child at the age of 10 and physical activity], which were not found to be in a linear relationship with blood pressure were analyzed using splines.

Three models were used to test associations. The first model included adjustments for cohort (GINIplus; LISAplus), gender, age of child, BMI at the age of 10, time of physical examination (divided into four groups January to April, May to July, August to September and October to December), physical activity, maternal smoking during pregnancy, parental history of hypertension, and parental educational level (Model 1; included participants for both cohorts combined). The second model included the same covariates as Model 1, but was restricted to the LISAplus participants (Model 2). The third model (Model 3) was the same as model 2, but also included an adjustment for the direction of the child's bedroom window (facing street, not facing street). As window direction was only available for the LISAplus participants, Model 2 was necessary to accurately assess the impact of incorporating the direction of the bedroom window (comparing Models 2 and 3). All risk estimates were modeled per 5 dB(A) increase in noise exposure. All results are presented as coefficients with corresponding 95% confidence intervals (95% CI). *P* values below 0.05 were used to indicate conventional statistical significance. All models were constructed using the MGCV package in the R statistical software.

Results

Among the 1153 subjects with available noise measurements, 605 of them participated in the 10-year physical examination and provided two blood pressure measurements (GINIplus 405, LISAplus 200; Figure 1).

Basic characteristics of the participants, stratified by cohort and pooled are shown in Table 1. In general, Lnight_max is approximately 10 dB(A) lower than Lden_max [spearman correlation coefficient is 0.965 (*P* value < 0.001); for Lden_min and Lnight_min, the spearman correlation coefficient is 0.915 (*P* value < 0.001)]. GINIplus study have significantly higher BMI and SBP compared to LISAplus participants.

The distribution of blood pressure levels across noise exposure categories is presented in Table 2. DBP appears to increase across increasing Lden_max, Lden_min and Lnight_min noise categories, the latter of which is statistically significant (*P* value = 0.019). In addition, SBP increases across increasing Lnight_min categories, and the association is not significant.

Associations between road traffic noise exposure and blood pressure are presented in Table 3. No significant associations between maximum noise exposure and blood pressure were observed. For minimum noise exposure, DBP was significantly associated with Lden_min and Lnight_min after confounder adjustment [0.67 (0.11, 1.24) mmHg and 0.89 (0.20, 1.58) mmHg increase per 5 dB(A), respectively]. The associations between DBP and Lden_min and Lnight_min remained significant after adjusting for the direction of the bedroom window [Model 3, β = 1.14 (0.21, 2.07); β = 1.73 (0.57, 2.88), respectively].

SBP was not associated with any measure of noise exposure (Models 1 and 2). However, after taking the direction of the child's bedroom window into account, a statistically significant association was observed between SBP and Lnight_min [Model 3, β = 1.62 (0.16, 3.09)].

Table 3 also shows that, after adjusting for Lden_min and other variables, the SBP of children whose bedroom window faced the street was 3.05 (0.10, 6.00) mmHg higher compared to children whose bedroom window did not. For Lnight_min, the SBP of children whose bedroom window faced the street was 3.27 (0.34, 6.20) mmHg higher compared to those whose bedroom window did not.

With respect to the covariates, parental hypertension had a significant effect on SBP [mean β = 3.20, all *P* value =

Table 1: Baseline characteristics of the study participants

Covariates	LISAplus (*N*=200)		GINIplus (*N*=405)		Total (*N*=605)	
	n/N or *N*	% or mean±SD	*n/N* or *N*	% or mean±SD	*n/N* or *N*	% or mean±SD
Gender, male	109/200	54.5	211/405	52.1	320/605	52.9
Age, months	200	121.60±1.98	405	122.06±3.42	605	121.91±3.03
Height, cm	200	142.35±6.39	405	142.87±6.49	605	142.70±6.45
Weight, kg*	199	33.89±5.82	405	35.59±6.66	604	35.03±6.44
BMI, kg/m²*	199	16.64±1.90	405	17.34±2.41	604	17.11±2.28
Activities per week, h	200	17.04±12.14	405	17.23±12.34	605	17.16±12.27
Parental education[a]						
Low, %	6	3.0	24	5.9	30	5.0
Medium, %	35	17.5	59	14.6	94	15.5
High, %	159	79.5	322	79.5	481	79.5
Smoking during pregnancy	32/182	17.6	56/402	13.9	88/584	15.1
Hypertension of parents	39/198	19.7	102/405	25.2	141/603	23.4
Child's bedroom window facing street[b]	80/197	40.6	NA	NA	80/197	40.6
Month of blood pressure measurement						
January-April	49	24.5	135	33.3	184	30.4
May-July	67	33.5	106	26.2	173	28.6
August-September	39	19.5	68	16.8	107	17.7
October-December	45	22.5	96	23.7	141	23.3
Road traffic noise, dB(A)						
Lden_max	200	58.30±10.44	405	57.66±9.74	605	57.87±9.97
Lnight_max	200	49.08±9.87	405	48.39±9.20	605	48.62±9.43
Lden_min	200	45.25±5.88	405	45.93±5.92	605	45.71±5.91
Lnight_min	200	37.23±4.99	405	37.72±4.93	605	37.56±4.95
Systolic blood pressure, mmHg*	200	109.11±8.61	405	110.95±9.44	605	110.34±9.21
Diastolic blood pressure, mmHg	200	62.90±6.89	405	63.26±8.16	605	63.14±7.76

BMI = Body mass index, LISAplus = The lifestyle-related factors on the immune system and the development of allergies in childhood plus the influence of traffic emissions and genetics, GINIplus = The german infant nutritional intervention plus environmental and genetic influences on allergy development, NA = Not available, Lden_max/Lden_min: Maximum/minimum of annual average of weighted yearly average day-evening-night equivalent noise levels in dB(A) within a 50 m buffer around the selected building/house. Lnight_max/Lnight_min = Maximum/minimum of equivalent yearly average noise levels in dB(A) at nighttime (10 p.m. to 6 a.m.) within a 50 m buffer around the selected building/house. [a]The highest educational level of either parent was considered: low if both parents have less than 10 years of school, medium = 10 years of school, high: more than 10 years of school, [b]Only available in LISAplus.*Significant difference between the GINIplus and LISAplus study

Table 2: Distribution of blood pressure across levels of noise exposure

Noise level[a]	*N*	Systolic blood pressure (*N*=605)			Diastolic blood pressure (*N*=605)		
		Mean±SD	*F*	*P* value[c]	Mean±SD	*F*	*P* value[c]
Lden_max			2.08	0.126		2.00	0.137
Low (<52.5 dB(A))	124	108.86±8.62			61.96±7.38		
Medium	333	110.81±9.46			63.31±8.05		
High (>62.5 dB(A))	148	110.53±9.03			63.76±7.34		
Lnight_max[b]			0.76	0.470		2.43	0.089
Low (<42.5 dB(A))	90	109.52±8.75			61.64±6.82		
Medium	404	110.66±9.29			63.57±8.12		
High (>57.5 dB(A))	111	109.86±9.29			62.80±7.01		
Lden_min			1.22	0.297		2.03	0.132
Low (<42.5 dB(A))	107	109.24±9.02			62.04±7.78		
Medium	357	110.78±9.51			63.12±7.77		
High (>47.5 dB(A))	141	110.09±8.51			64.04±7.66		
Lnight_min[b]			2.49	0.084		3.99	0.019*
Low (<32.5 dB(A))	3	98.67±9.29			53.50±8.19		
Medium	551	110.37±9.26			63.02±7.79		
High (>42.5 dB(A))	51	110.78±8.34			65.07±6.94		

Lden_max/Lden_min = Maximum/Minimum of annual average of weighted yearly average day-evening-night equivalent noise levels in dB(A) within a 50 m buffer around the selected building/house. Lnight_max/Lnight_min = Maximum/Minimum of equivalent yearly average noise levels in dB(A) at nighttime (10 p.m. to 6 a.m.) within a 50 m buffer around the selected building/house. [a]Divided based on quartiles with the cut-off of 25% and 75%. [b]Distribution is skewed (Lnight_max to right and Lnight_min to left). [c]Assessed with One-way ANOVA.*Significant difference between levels

Table 3: The association between traffic noise exposure and blood pressure

Source of exposure	Outcome	Model 1[a] (*N*=514)		Model 2[b, d] (*N*=154)		Model 3[c, d] (*N*=151)	
		β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Lden_max							
Noise exposure	Systolic blood pressure	0.17 (-0.23, 0.57)	0.578	0.26 (-0.41, 0.92)	0.600	0.31 (-0.37, 0.98)	0.453
	Diastolic blood pressure	0.28 (-0.05, 0.62)	0.149	0.44 (-0.09, 0.96)	0.101	0.40 (-0.14, 0.93)	0.139
Windows direction	Systolic blood pressure					2.57 (-0.36, 5.50)	0.085
	Diastolic blood pressure					0.89 (-1.44, 3.22)	0.455
Lnight_max							
Noise exposure	Systolic blood pressure	0.06 (-0.36, 0.49)	0.948	0.23 (-0.48, 0.95)	0.642	0.29 (-0.43, 1.00)	0.526
	Diastolic blood pressure	0.28 (-0.08, 0.64)	0.190	0.47 (-0.09, 1.02)	0.095	0.43 (-0.14, 0.99)	0.130
Windows direction	Systolic blood pressure					2.60 (-0.34, 5.53)	0.085
	Diastolic blood pressure					0.90 (-1.43, 3.23)	0.448
Lden_min							
Noise exposure	Systolic blood pressure	0.20 (-0.48, 0.88)	0.689	0.63 (-0.54, 1.79)	0.407	0.90 (-0.30, 2.09)	0.207
	Diastolic blood pressure	0.67 (0.11, 1.24)	0.030	1.05 (0.14, 1.97)	0.009	1.14 (0.21, 2.07)	0.006
Windows direction	Systolic blood pressure					3.05 (0.10, 6.00)	0.045
	Diastolic blood pressure					1.37 (-0.97, 3.71)	0.252
Lnight_min							
Noise exposure	Systolic blood pressure	0.34 (-0.48, 1.17)	0.536	1.18 (-0.15, 2.72)	0.116	1.62 (0.16, 3.09)	0.041
	Diastolic blood pressure	0.89 (0.20, 1.58)	0.020	1.57 (0.45, 2.69)	0.004	1.73 (0.57, 2.88)	0.003
Windows direction	Systolic blood pressure					3.27 (0.34, 6.20)	0.030
	Diastolic blood pressure					1.28 (-1.02, 3.59)	0.278

CI = Confidence interval, *N* = Sample size in the models, *β* = Estimated change in blood pressure per 5 dB(A) increase in noise, 95% CI = 95% confidence intervals, Lden_max/Lden_min = Maximum/minimum of annual average of weighted yearly average day-evening-night equivalent noise levels in dB(A) within a 50 m buffer around the selected building/house, Lnight_max/Lnight_min = Maximum/minimum of equivalent yearly average noise levels in dB(A) at nighttime (10 p.m. to 6 a.m.) within a 50 m buffer around the selected building/house. [a]Adjusted for cohort study, gender, age of child, BMI, time of physical examination, physical activities, maternal smoking during pregnancy, parental education level, parental history of hypertension. [b]Model 1 covariates excluding cohort study. [c]Model 2 covariates plus with windows direction [d]Applied only to LISA plus study

0.001 across the four different noise factors] and DBP [mean β = 1.82, range of *P* values (0.024, 0.030) across the four different noise factors]. The gender of the child also had a significant effect on DBP [mean β = 1.80, range of *P* values (0.008, 0.009) across the four different noise factors].

Discussion

We investigated associations between road traffic noise and blood pressure among 605 children aged 10 years. DBP was associated with Lden_min and Lnight_min after adjusting for

relevant covariates, and the associations remained significant after considering the direction of the bedroom window. No significant associations between SBP and noise exposures were found in the basic models, but a significant association between SBP and Lnight_min was observed after adjusting for the direction of the window in the child's bedroom. We also found that, after adjusting for noise levels and other covariates, children whose window faced a street had a significantly higher SBP compared to those whose bedroom did not.

Although negative associations between noise and blood pressure have been previously reported, the positive association between DBP and noise in our study is in agreement with most past studies. For example, Belojevic *et al*. reported a 3 mmHg significant difference in DBP between children from noisy schools and residences (57.18 mmHg) compared to those living in more quiet environments (60.18 mmHg).[20] Conversely, in a study of 1542 children aged 3-7 years in the Slovak Republic, association between 24-h equivalent urban traffic noise around kindergartens/residences and blood pressure was explored, the DBP of children living in noisy homes was 2 mmHg higher than those living in quiet homes.[5] In addition, Paunovic *et al*. explored the effect of road traffic noise on blood pressure among 856 children aged 7-11 years, using noise levels at schools during the day and at the home address during the night as the exposure. This study found a positive and significant association between DBP and noise levels at schools, mean levels of blood pressures for children at noisy and quiet schools were 60.0 mmHg and 58.2 mmHg, respectively.[20] Babisch *et al*.[9] also reported similar results in their study, in which 1048 children aged 8-14 were investigated and noise levels in front of child's (bed-) room between 8:00 and 23:30 were recorded. In this study, a 1.0 mmHg difference in DBP between children from residences located at busy-traffic (65.9 mmHg) and low-traffic (64.8 mmHg) streets was found. This study also reported a significant increase in DBP (0.61 mmHg, 95% CI: 0.08-1.15 mmHg) per 10 dB(A) increase in average noise level around the child's (bed-) room.

In our study, noise was more strongly associated with DBP than with SBP. One explanation may be that noise exposure increases peripheral vascular tone, which has been observed by Andren *et al*.[21] and Neus *et al*.[22] under experimental laboratory conditions. Another explanation may be a reduction of "dipping" due to noise exposure, such as was reported by Haralabidis *et al*.[23] In their study, the authors suggested that blood pressure during sleep show a physiological decline with reference to daytime values ("dipping"), the extent of which is associated with noise (a 0.8% less dipping in DPB per 5 dB(A) increase in measured road traffic noise was reported).[23] These studies support the relationship between both Lden_min and Lnight_min and DBP observed in our work.

This study has several important limitations. First, there is a potential for selection bias, as only 12.7% (1153 out of 9086) of the original GINIplus and LISAplus populations could be included in this study due to the availability of the noise exposure levels (only available for the city of Munich). In addition, only 52.47% (605 out of 1153) of the selected subjects underwent blood pressure measurements 10 years later. However, there were no significant differences between noise levels of children who provided blood pressure information and those who did not. Nevertheless, we found that children who underwent blood pressure measurements were more physically active ($P < 0.01$) and their parents were less likely to have hypertension ($P < 0.01$) or have a high level of education ($P = 0.037$). Second, we do not have information on the hearing levels (abilities) of the children. Children with and without hearing deficiencies could be differently affected by similar noise levels. Third, as mentioned by van Kempen *et al*.,[13] a common problem of this and most past study is that not all relevant noise information is examined [e.g., fluctuation of noise levels or frequency distribution (Hz)]. Fourth, although we did collect information on the direction of the child's bedroom window for the LISAplus cohort, we did not collect information on window opening habits, which may be a key factor in this study. For example, it is possible that people are exposed to higher levels of noise when they leave the windows open at night during warm periods.[12] Furthermore, due to the small number of children who have information on the windows direction ($N = 197$ in LISAplus), we were unable to directly explore the interaction between noise levels and the window direction in our models. Fifth, as previously mentioned, exposure misclassification is a concern in these types of studies. The noise levels used in this study are outdoor noise levels within a 50 m buffer of the child's home, without considering directionality. Thus, it is not clear if the assigned noise level (maximum or minimum) is the noise level actually outside of the child's bedroom. It is possible that a child with a high maximum noise level may actually be sleeping in a quieter part of the house, and thus the noise exposure would be overestimated (and vice versa). It is quite conceivable that the maximum noise level registered in our study is away from the child's bedroom (for example, in front of the house), which may explain why we did not observe an association between Lnight_max and blood pressure. Furthermore, 10-year-old children spend most of their time at school, thus noise levels at home might not reflect a child's actual daytime exposure. This type of exposure misclassification may have contributed to the lack of association between Lden_max/Lden_min and SBP observed in this study. This lack of association with noise exposures assessed at the home address has also been documented by others. For example, Regecova and Kellerova[5] found that children's SBP was significantly associated with noise levels at schools but not at residences. Evans *et al*.[10] also reported non-significant differences in SBP in children exposed to low compared to high noise levels at residences.

Despite the limitations, this study also has important strengths. Firstly, this study is unique in examining the association between blood pressure and individual noise exposure levels during night time. Night-time noise has only been considered by two other studies, which dichotomized noise levels into noisy and quiet areas.[20] Secondly, this study is one of the few studies that have considered the direction of the child's bedroom window in the analyses. To our knowledge, only one other recently published paper[24] has incorporated this factor in their analyses. Belojevic and Evans studied the effects of traffic noise on blood pressure among 250 African-American children of low-socioeconomic status, aged 6-14 years. They found no significant effect of noise exposure at home/school on blood pressure [for SBP, β (95% CI) = 0.0007 (-0.003, 0.004); for DBP, β (95% CI) = 0.0009 (-0.004, 0.002)]. When examining the impact of the orientation of the child's bedroom and living room on these associations, no interaction with noise at home was found on blood pressure [for SBP, β (95% CI) = -0.007 (-0.053, 0.038); for DBP, β (95% CI) = 0.011 (-0.026, 0.047)].

The World Health Organization[25] has recognized noise as an important factor that may affect health, and previous epidemiological studies have provided evidence to support this claim, as do the results of our current study. Although it is unclear how the long-term effects of early noise exposure may affect the cardiovascular systems of children, it is conceivable that noise-induced elevations of blood pressure may cause adverse effects later in their life.[9,26]

In order to better understand the association between noise and blood pressure in children, we recommend that future studies pay particular attention to the exposure assessment; noise exposure should be assessed at kindergartens and schools during daytime and at the home residence at night. In addition, the direction of the bedroom window should be considered as a potential factor in future studies, especially given the strong associations with this covariate documented in this study.

Conclusions

The results of this study suggest that road traffic noise may increase blood pressure in children, especially DBP. The level of minimum noise at home appears to be important. Our finding that the direction of the child's bedroom affects the modeled estimates highlights the importance of including this factor in future studies.

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5. The associations between traffic-related air pollution and noise with blood pressure in children: Results from the GINIplus and LISAplus studies

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The associations between traffic-related air pollution and noise with blood pressure in children: Results from the GINIplus and LISAplus studies

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Abstract

Although traffic emits both air pollution and noise, studies jointly examining the effects of both of these exposures on blood pressure (BP) in children are scarce. We investigated associations between land-use regression modeled long-term traffic-related air pollution and BP in 2,368 children aged 10 years from Germany (1,454 from Munich and 914 from Wesel). We also studied this association with adjustment of long-term noise exposure (defined as day-evening-night noise indicator “Lden” and night noise indicator “Lnight”) in a subgroup of 605 children from Munich inner city. In the overall analysis including 2,368 children, NO_2, $PM_{2.5}$ mass (particles with aerodynamic diameters below 2.5 μm), PM_{10} mass (particles with aerodynamic diameters below 10 μm) and $PM_{2.5}$ absorbance were not associated with BP. When restricting the analysis to the subgroup of children with noise information (N = 605), a significant association between NO_2 and diastolic BP was observed (-0.88 (95% confidence interval: -1.67, -0.08)). However, upon adjusting the models for noise exposure, only noise remained independently and significantly positively associated with diastolic BP. Diastolic BP increased by 0.50 (-0.03, 1.02), 0.59 (0.05, 1.13), 0.55 (0.03, 1.07), and 0.58 (0.05, 1.11) mmHg for every five decibel increase in Lden and by 0.59 (-0.05, 1.22), 0.69 (0.04, 1.33), 0.64 (0.02, 1.27), and 0.68 (0.05, 1.32) mmHg for every five decibel increase in Lnight, in different models of NO_2, $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance as the main exposure, respectively. In conclusion, air pollution was not consistently associated with BP with adjustment for noise, noise was independently and positively associated with BP in children.

Key words: road traffic**,** air pollution, noise, blood pressure, children

Introduction

Several reviews on the effects of air pollution (Brook and Rajagopalan, 2009; Brook et al., 2011; Brunekreef and Holgate, 2002) and road-traffic noise (van Kempen and Babisch, 2012) on blood pressure (BP) have concluded that exposure to air pollution and/or traffic noise causes increase of BP. Most previous studies have been on adults or the elderly, while less has focused on children. As childhood BP is a strong predictor for hypertension later in life (Lauer et al., 1991), understanding the factors that influence childhood BP is important.

Few study has previously examined the association between air pollution and childhood BP. Sughis et al (Sughis et al., 2012) explored the effect of particulate air pollution on BP among 179 Pakistani children aged 8-12 years. Two schools were studied; one in a highly polluted area (n = 100, PM_{10} mass [particles with aerodynamic diameters below 10 μm] = 728.6 $\mu g/m^3$ and $PM_{2.5}$ mass [particles with aerodynamic diameters below 2.5 μm] = 183.0 $\mu g/m^3$) and the other in an area with lower pollution concentrations (n = 79, PM_{10} mass = 223.0 and $PM_{2.5}$ mass = 28.5 $\mu g/m^3$). The BP of children from the school in the highly polluted area was significantly higher than that of children attending the school in the less polluted area (115.9/70.9 and 108.3/66.4 mmHg, respectively), with adjustment of age, sex, height, weight, social-economic status, passive smoking and the urinary concentrations of Na, K and creatinine. Although informative, this study did not consider the effect of traffic noise on the results.

Seven epidemiological studies have examined the impact of road-traffic noise on BP in children, and have yielded somewhat mixed results. Most of these studies found positive associations between road-traffic noise and BP (Babisch et al., 2009; Belojevic et al., 2008a; Belojevic et al., 2008b; Evans et al., 2001; Paunovic et al., 2009; Regecova and Kellerova, 1995), but one study reported a negative association between noise and diastolic BP

(Belojevic et al., 2008a), and another between noise and systolic BP (van Kempen et al., 2006).

As traffic-related air pollution and traffic noise share road traffic as a source, it is necessary to mutually adjust for these two factors when exploring their effects on BP. The potential confounding relationship between traffic-related air pollution and noise has been previously highlighted (Allen and Adar, 2011), but only two studies (Bilenko et al., 2013; Clark et al., 2012) have examined this issue among children. Bilenko et al. (Bilenko et al., 2013) reported a positive association between childhood BP and long-term NO_2, and no association with noise. Clark et al. (Clark et al., 2012) found no statistical associations between NO_2 and childhood BP before and after adjusting for road-traffic noise at school.

Given the inconsistency of studies which have examined the joint effects of traffic-related air pollution and noise on BP and the scarcity of such studies in children, we investigated the effects of long-term traffic-related air pollution (NO_2, $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance) on the BP of 10 year-old children and, in a subsample, accounted for the effects of long-term road-traffic noise exposure.

Methods

Study Population

The study population consists of children from two German birth cohorts of healthy full-term neonates. The German Infant Nutritional Intervention plus environmental and genetic influences on allergy development study (GINIplus) was designed to prospectively investigate the effects of a nutrition intervention during infancy, as well as air pollution and genetics, on allergy development. Details on the design, recruitment and follow-up of this intervention study have been previously published (Filipiak et al., 2007; von Berg et al., 2010). Briefly, a total of 5991 newborns were recruited in obstetric clinics in Munich and

Wesel, Germany, between September 1995 and July 1998. Follow-up occurred at the age of one, two, three, four, six and ten years of age. The Lifestyle-Related factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics (LISAplus) population-based study aimed to assess the influence of lifestyle-related factors on the immune system, as well as the effects of air pollution and genetics on the development of allergies in childhood. In total, 3097 healthy full-term neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef between November 1997 and January 1999. Follow-up for this study occurred at the age of six, twelve and eighteen months, and two, four, six and ten years. A detailed description of the screening and recruitment has been described elsewhere (Heinrich et al., 2002; Zutavern et al., 2007).

We included children who lived in Munich or Wesel at the age of 10 years, for which air pollution estimates at the home address were available. In total, 2,368 children (Munich 1,454, Wesel 914) had available data on BP measurements and long-term air pollution. Noise exposure information was only available for children living in the Munich inner city. As such, only 605 children from the Munich inner city could be included in the analyses in which road-traffic noise is considered. Fig. 1 shows the selection of the study population.

For both cohort studies, ethical approval was obtained by the medical ethical committees. Written informed consent was obtained from all participating families.

Air Pollution

Long-term (one-year) air pollution concentrations

Estimates of modeled annual average concentrations of NO_2 and particulate matter (PM; including $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance) are used in this study. All data were derived from land-use regression models (different models had been applied for Munich and

Wesel) developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) collaboration (http://www.escapeproject.eu/manuals).

In brief, NO_2 and PM were monitored at 40 and 20 sites between October 2008 and November 2009, respectively. Each site was monitored for two consecutive weeks three times (during warm, cold and intermediate temperature seasons). These discontinuous measurements were then adjusted for the true long-term average of the observation period, according to data from one additional background site which measured air pollution concentrations using the same instruments continuously for a complete year. Finally, exposure estimates of annual average concentrations of air pollution for each participant's residence were calculated using a land use regression model. Details of this procedure have been previously published (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a; Eeftens et al., 2012b).

Short-term (7-day) air pollution concentrations

Concentrations of both NO_2 and PM_{10} mass for Munich were obtained from the same background monitoring site located in the Munich suburban area (Johanneskirchen), which is approximately nine kilometers in the northeast of the city. Concentrations of both NO_2 and PM_{10} mass for Wesel were obtained from 'The State Agency for Nature, Environment and Consumer Protection of North Rhine-Westphalia' (http://www.lanuv.nrw.de/luft/temes/tagaus.htm). The data were collected in one monitoring site (WESE) that located in the suburban area of Wesel-Feldmark, it is approximately two kilometers in the northeast of the city. An average of seven days (Baccarelli et al., 2011; Hampel et al., 2011) before BP measurements was calculated and used to adjust the models for the short-term effects of air pollution on BP.

Road Traffic Noise

A geographic information system (GIS) based noise model that includes the street network for the Munich inner city (around 2800 km) was used to estimate road traffic noise levels in 2007 on a 5m grid, 4m above ground level, in 5 A-weighted decibel-intervals [dB(A)]. Details of the modeling approach have been published previously (Birk et al., 2011). Briefly, weighted equivalent noise levels in dB(A) over a full day (Lden, weighted yearly average noise level between 6 a.m. to 6 p.m., 6 p.m. to 10 p.m., and 10 p.m. to 6 a.m.) and at night (Lnight, yearly average noise level between 10 p.m. to 6 a.m.) were modeled according to the European Noise Directive (The European Parliament and The Council of the European Union 2002). The annual average lowest level of noise over a full day or night within a 50m buffer around each child's home address (Lden_min and Lnight_min, respectively) were used in this study, as we previously reported significantly positive associations between these noise exposures and BP (Liu et al., 2013).

Outcome Definition and Covariates

At the 10-year follow-up, BP, height, weight, and age (in months) data were collected during a physical examination. The height and weight measurements were used to calculate body mass index (BMI). Resting systolic and diastolic BP were measured twice in a sitting position from the right arm after five minutes rest. The elbow was relaxed at heart level to store (slightly bent) and the upper arm was bare during testing. A second measurement was taken after sitting for two minutes. An automatic BP monitor (Omron M5 Professional) was used for the measurements. The cuff size was selected according to the length and circumference of the upper arm of each child: the width was at least 2/3 of the length and the pressure bladder covered at least half of the circumference of the upper arm. BP was measured by one physician in Munich and one in Wesel. The average of the two BP measurements was used in

all analyses, regardless of the difference between the two records (we excluded 14 subjects (11 from Munich and three from Wesel) who had only one BP measurement).

Demographic, health, and lifestyle information on the subjects were collected using self-administered questionnaires completed by the parents (gender, physical activity [hours per week], maternal smoking during pregnancy [yes/no], parental history of hypertension [neither parent is hypertensive; at least one of the parents is hypertensive], and the highest educational level of either parent[low: both parents reported less than 10 years of school; medium: 10 years of school; high: one of the parents reported more than 10 years of school]).

Statistical analysis

The analysis was carried out using the R statistical software (version 2.14.1). Pearson's chi-square, the Student's t-test and the Wilcoxon rank sum test were used to assess differences between Munich and Wesel, between subgroups of children with and without noise information, for categorical, normally distributed continuous variables, and continuous variables with a skewed distribution, respectively. Correlations between annual noise and air pollution concentrations were assessed with Spearman's rank correlation coefficient.

The effects of air pollution on BP were explored with generalized additive models (GAM, MGCV package in R). GAM provides a flexible method to predict the quality of a dependent variable Y from different distributions with exponential family models and other likelihood-based regression models (Trevor and Robert, 1986). Air pollution and noise were included as linear terms, after testing their linearity with BP using GAM plots.

Four models were used to investigate the independent associations between road traffic noise and air pollution with BP in children. Model 1 explored association between each of the four air pollutants (NO_2, $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance) with BP, with adjustment of cohort (GINIplus; LISAplus), gender, age, BMI, physical activity, maternal

smoking during pregnancy, parental history of hypertension, parental educational level, 7-day temperature (Adams and Leverland, 1985; Fuks et al., 2011) and 7-day air pollution concentrations (7-day NO_2 was included in the NO_2 models and 7-day PM_{10} was included in the $PM_{2.5}$ mass, PM_{10} mass and $PM_{2.5}$ absorbance models). The combined models were additionally adjusted for city (Munich or Wesel). Model 2 was identical with model 1 but restricted to a subgroup of 605 children with available noise information. Model 3 and Model 4 included additional adjustment of Lden_min and Lnight_min on the basis of Model 2, respectively.

All air pollution and traffic noise risk estimates are presented per interquartile range (IQR, 6.43 μg/m³ for NO_2, 4.07 μg/m³ for $PM_{2.5}$ mass, 4.84 μg/m³ for PM_{10} mass and 0.44×10^{-5} m^{-1} for $PM_{2.5}$ absorbance in the total data) increase and per five dB(A) increase, respectively. All results are presented as coefficients with corresponding 95% confidence intervals (CI). *P*-values below 0.05 were used to indicate conventional statistical significance.

Results

In total, 2,368 children (74.4% and 25.6% come from GINIplus and LISAplus studies, respectively) were included in this study, 25.5% (605 out of 2368) of them were from the Munich inner city and had noise data (Figure 1). Baseline characteristics of the study population, stratified by area and pooled, are given in Table 1. Children from Wesel have significantly higher blood pressure levels (113.23 and 66.07 mmHg for systolic and diastolic BP, respectively) than children from Munich (110.23 and 63.06 mmHg for systolic and diastolic BP, respectively). The distribution of annual and 7-day average concentrations for the air pollutants are presented in Table 2. Mean annual average concentrations of NO_2, $PM_{2.5}$ mass and PM_{10} mass were significantly higher in Wesel, while the mean concentration of $PM_{2.5}$ absorbance was significantly higher in Munich.

The study characteristics of children with and without noise information are provided in the Supplemental Material (Table S-1, Table S-2). Mean annual average concentrations of NO_2 and $PM_{2.5}$ absorbance were higher among children with noise information, while the mean concentrations of $PM_{2.5}$ and PM_{10} mass were higher among children without noise information. The noise variables (Lden_min and Lnight_min) were highly correlated (spearman correlation coefficient is 0.92, *P*-value < 0.001). Correlations between noise and air pollution variables were low (ranging from -0.14 to 0.26; Supplemental Material, Table S-3).

Figure 2 illustrates the pooled and area-specific associations between long-term traffic-related air pollution and BP. In the pooled population (N = 2,368), none of the air pollutants were associated with BP in any of the models (crude and basic results not shown). Similar results were observed for Munich and Wesel in the analyses stratified by area (Supplemental Material, Table S-4).

When restricting the analysis to a subgroup of 605 children, for whom noise exposure data were available, diastolic BP was observed to decrease significantly (-0.88 mmHg, 95% CI: -1.67, -0.08) with every IQR (6.43 $\mu g/m^3$) increase in NO_2 before adjusting for noise (Model 2, Table 3). However, when the models were further adjusted for noise exposure (Table 3, model 3 for Lden_min and model 4 for Lnight_min), the significantly negative association between NO_2 and diastolic BP was attenuated to null. Meanwhile, a statistically significant increase in diastolic BP was observed per 5 dB(A) increase in the minimal noise exposure (increase of 0.50-0.59 and 0.59-0.69 mmHg for Lden_min and Lnight_min, respectively, across the four different air pollution variables).

Finally, children with parental history of hypertension had a statistically significantly higher systolic (mean β = 2.44, *P*-values < 0.001 across the four different air pollution

variables) and diastolic BP (mean β = 1.35, *P*-values < 0.001 across the four different air pollution variables).

Discussion

In the present paper, we investigated the associations between long-term traffic-related air pollution and BP among 2,368 children aged 10 years. We also investigated these associations in a subgroup of 605 children with adjustment for long-term road-traffic noise. Among total children, null associations between air pollution and BP were observed for the total study population, and nor for children from Munich and Wesel. For the subgroup of 605 children living in the Munich inner city with available noise information, a negative association between NO_2 and diastolic BP was observed before adjustment for noise. However, when road-traffic noise was additionally included in the model, the association between NO_2 and diastolic BP was attenuated to null. Both Lden_min and Lnight_min were significantly and positively associated with diastolic BP.

To the best of our knowledge, only two previous studies (Bilenko et al., 2013; Clark et al., 2012) have reported on the association between traffic-related air pollution and BP in children, after accounting for road-traffic noise. But no constant results were reported. Clark et al. (Clark et al., 2012) explored association between NO_2 at school and BP in 276 children aged 9-10 years, taking noise exposure at school as adjustment, and no statistical associations were reported. Bilenko et al (Bilenko et al., 2013) recently reported a positive association between diastolic BP and long-term NO_2 in children who did not change address since birth. This study was conducted among 1400 children aged 12-year, diastolic BP was found to increase 0.83 mmHg with every 7.8 μg/m³ increase in NO_2. No association was found between noise exposure and BP.

Studies on the effects of long-term air pollution and traffic exposure indicators on BP in adults are also limited, and no universal conclusions can be drawn. One study reported positive associations (Fuks et al., 2011), while another study reported the inverse (Sorensen et al., 2012). Fuks et al (Fuks et al., 2011) explored effects of long-term PM on BP among 4,291 participants aged 45-75 years. The authors reported that after adjusting for traffic noise, mean systolic and diastolic BP increased by 1.4 mmHg (95% CI: 0.5, 2.3) and 0.9 mmHg (95% CI: 0.4, 1.4), respectively, per 2.4 $\mu g/m^3$ increase in $PM_{2.5}$ mass. However, the authors did not report on the specific risk estimates of noise with BP in their results. In contrast, Sorensen et al (Sorensen et al., 2012) reported negative effects of both traffic-related NO_x and traffic exposure indicators (whether there is a major road within 50 meters; traffic load within 200 meters) on BP among 57,053 participants aged 50-64 years.

In this study, air pollution did not have a significant effect on BP in the total study population. However, we observed a negative association between annual NO_2 and diastolic BP among a subgroup of 605 children living in the Munich inner city, before adjusting for road-traffic noise. This subgroup finding may be due to chance as only a small number of study participants are included. Another possible explanation may be that the air pollution levels between the Munich inner city and suburbs are somehow different. Children from the Munich inner city are exposed to significantly higher NO_2 concentrations compared to those living in the Munich suburbs.

After adjusting the Munich inner city models for noise, the afore-mentioned association between NO_2 and diastolic BP in the subgroup of children was attenuated to null. However, positive associations between noise and diastolic BP were observed, which is consistent with our previous study in which we had not considered the effects of air pollution as a covariate (Liu et al., 2013). Based on these results, it appears that noise may play a more important role than air pollution on childhood BP.

This study has several limitations. First, there is a potential for selection bias, as only 26.1% (2,368 out of 9,086) of the original GINIplus and LISAplus populations were included in this study due to data availability and loss of follow-up. The children selected into analyses tend to take more physical activities and have higher parental education level and lower parental hypertension level. Furthermore, only 25.5% (605 out of 2,368) of these children had available noise data. The subgroup children with available noise information had lower BMI, take less physical activities, and have higher parental education levels and blood pressure levels compared to children without noise data (Supplemental Material, Table S-1). Averages of annual air pollution are significantly different between children with and without noise data (Supplemental Material, Table S-2). Second, we do not have information on the hearing levels (abilities) of the children. Although the proportion of children with hearing deficiencies is likely low at age of 10 years, it remains possible that children with and without hearing deficiencies may be differently affected by similar noise levels, which may introduce bias into the results. The inclusion of children with hearing deficiencies may tend to a null association between road traffic noise and BP in children. Third, exposure misclassification may be a concern in the current study. Ten year-old children spend much of their daytime at school, thus air pollution and noise levels assessed at the home address may not accurately reflect a child's true daytime exposure. Furthermore, the noise levels used in this study are noise levels within a 50m buffer of the child's home, and it is not clear if the assigned minimum noise level is similar to that outside of the child’s bedroom. It is possible that a child with an assigned minimum noise level may actually be sleeping in a noisier (quieter) part of the house, and thus the noise exposure would be underestimated (overestimated). Forth, some potential confounders (e.g. breathing rate, indoor air pollution, the time of BP measurement during the day, etc.) were not well adjusted in this study. Fifth, three

measurements of BP are recommended (Paunovic et al., 2011), but only two records were available in this study.

Despite the limitations discussed above, this study has several strengths. First, this is one of the few studies to explore the combined effects of traffic-related air pollution and road traffic noise on the BP of children. Second, all exposure data used are based on GIS modeling and were individually assigned to each participants' home address. Third, in a subgroup of the study population, an adjustment for both 24-hour and nighttime noise levels was possible. As nighttime noise has been reported to play an important role on the effect of BP (Belojevic et al., 2008c; Haralabidis et al., 2011), the inclusion of this exposure is a particular strength of this study. Last, both short-term temperature and air pollution, which have been shown to be associated with BP (Brook et al., 2011; Madsen and Nafstad, 2006), were included as covariates in the present study.

Although it has been suggested that air pollution, especially PM, is particularly harmful to children (Heinrich and Slama, 2007), there are few epidemiological studies that have assessed associations with BP in children with consideration of noise. Due to the inconsistent findings with previous studies (Bilenko et al., 2013; Clark et al., 2012), more such studies are needed to disentangle the potential confounding relationship between traffic-related air pollution and road traffic noise with BP in children.

Conclusion

Air pollution was not consistently associated with BP in children. However, a statistically significant and positive effect of minimum noise levels on diastolic BP was observed in a subgroup of children living in the Munich inner city. Further studies are necessary to disentangle the effects of air pollution and noise on childhood BP.

Acknowledgements

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Table 1 Baseline characteristics of the study participants of GINIplus and LISAplus: Munich and Wesel

	Munich (N=1454)		Wesel (N=914)		Total (N=2368)	
	n/N or N	% or mean ± SD	n/N or N	% or mean ± SD	n/N or N	% or mean ± SD
Cohort, GINIplus *	966/1454	66.4	795/914	87.0	1761/2368	74.4
Gender, male	751/1454	51.7	459/914	50.2	1210/2368	51.1
Age, month *	1454	121.82 ± 2.82	914	122.63 ± 2.34	2368	122.13 ± 2.67
Height, cm *	1454	142.96 ± 6.47	914	144.68 ± 6.48	2368	143.62 ± 6.53
Weight, kg *	1452	35.13 ± 6.58	914	37.80 ± 7.41	2366	36.16 ± 7.03
BMI, kg/m² *	1452	17.09 ± 2.31	914	17.95 ± 2.64	2366	17.42 ± 2.48
Physical activity per week, hours *	1454	17.75 ± 12.41	914	22.34 ± 18.24	2368	19.52 ± 15.10
Parental education [a] *						
low, %	63/1450	4.3	88/911	9.7	151/2361	6.4
medium, %	254/1450	17.5	368/911	40.4	622/2361	26.3
high, %	1133/1450	78.2	455/911	49.9	1588/2361	67.3
Smoking during pregnancy	169/1404	12.0	128/889	14.4	297/2293	13.0
Hypertension of parents	342/1449	23.6	191/914	20.9	533/2363	22.6
7-day temperature, ℃ *	1454	10.71 ± 7.39	914	12.31 ± 6.28	2368	11.33 ± 7.02
road traffic noise, dB(A)						
Lden_min	605	45.71 ± 5.91	NA	NA	605	45.71 ± 5.91
Lnight_min	605	37.56 ± 4.95	NA	NA	605	37.56 ± 4.95
Systolic blood pressure, mmHg *	1454	110.23 ± 9.59	914	113.23 ± 10.24	2368	111.38 ± 9.95
Diastolic blood pressure, mmHg *	1454	63.06 ± 7.47	914	66.07 ± 7.00	2368	64.22 ± 7.44

N: total number of study samples; n: number of children with relative information; BMI: body mass index. dB(A): A-weighted decibel. Lden_min: minimum of weighted yearly average day-evening-night equivalent noise levels in dB(A) within a 50 meter buffer around the selected building/house. Lnight_min: minimum of equivalent yearly average noise levels in dB(A) at nighttime (10 p.m. to 6 a.m.) within a 50 meter buffer around the selected building/house.

[a] Parental education: low if both parents have less than 10 years of school; medium: 10 years of school; high: at least one parent has more than 10 years of school. * Significant difference between Munich and Wesel

Table 2. Annual and 7-day average concentrations of air pollutants

Exposure	Munich (N = 1454)	Wesel (N = 914)	Total (N = 2368)
Annual level			
NO_2 (µg/m³)			
Mean	19.78	23.73	23.31
5th percentile	13.65	19.92	14.06
Median	18.85	23.20	21.54
95th percentile	28.83	28.88	28.84
Interquartile range	6.72	3.26	6.43
$PM_{2.5}$ mass (µg/m³)			
Mean	13.29	17.41	14.88
5th percentile	11.86	16.37	12.09
Median	13.24	17.27	13.97
95th percentile	14.84	18.75	18.26
Interquartile range	1.05	0.84	4.07
PM_{10} mass (µg/m³)			
Mean	20.02	25.47	22.12
5th percentile	16.25	23.98	16.66
Median	20.37	25.19	21.77
95th percentile	23.54	28.05	26.79
Interquartile range	2,93	1.54	4.84
$PM_{2.5}$ absorbance (10^{-5} m^{-1})			
Mean	1.65	1.20	1.48
5th percentile	1.39	0.99	1.03
Median	1.63	1.16	1.52
95th percentile	1.96	1.53	1.90
Interquartile range	0.21	0.21	0.44
7-day level (mean ± SD, µg/m³)			
NO_2	29.39 ± 9.50	25.04 ± 9.39	27.71 ± 9.69
PM_{10}	24.65 ± 13.06	24.57 ± 9.43	24.62 ± 11.78

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 µm. PM_{10}: particulate matter with aerodynamic diameter ≤ 10 µm.

Table 3. Estimated change in blood pressure (mmHg, with 95% CI) per corresponding interquartile range increase of exposure to air pollution and/or per 5 dB(A) of noise

	Model 1[a] (N=2368)	Model 2[b] (N=605)	Model 3[c] (N=605)	Model 4[d] (N=605)
Effects on systolic blood pressure				
NO_2	0.11(-0.45, 0.67)	-0.24(-1.17,0.69)	-0.20(-1.14,0.73)	-0.19(-1.13,0.75)
+Lden_min	--	--	0.23(-0.39,0.84)	--
+Lnight_min	--	--	--	0.29(-0.46,1.03)
$PM_{2.5}$ mass	1.01(-0.90, 2.92)	0.40(-0.58,1.39)	0.32(-0.70,1.34)	0.32(-0.69,1.33)
+Lden_min	--	--	0.19(-0.45,0.83)	--
+Lnight_min	--	--	--	0.26(-0.50,1.02)
PM_{10} mass	0.25(-0.71, 1.21)	-0.21(-0.90,0.48)	-0.20(-0.90,0.49)	-0.20(-0.89,0.49)
+Lden_min	--	--	0.24(-0.37,0.85)	--
+Lnight_min	--	--	--	0.31(-0.43,1.05)
$PM_{2.5}$ absorbance	-0.20(-1.11, 0.72)	-0.37(-1.16,0.41)	-0.44(-1.23,0.36)	-0.42(-1.21,0.37)
+Lden_min	--	--	0.30(-0.32,0.92)	--
+Lnight_min	--	--	--	0.37(-0.37,1.12)
Effects on diastolic blood pressure				
NO_2	-0.06(-0.48, 0.36)	-0.88(-1.67,-0.08)*	-0.79(-1.58,0.00)	-0.77(-1.57,0.03)
+Lden_min	--	--	0.50(-0.03,1.02)	--
+Lnight_min	--	--	--	0.59(-0.05,1.22)
$PM_{2.5}$ mass	-0.19(-1.63, 1.24)	0.07(-0.77,0.91)	-0.18(-1.04,0.69)	-0.14(-0.99,0.72)
+Lden_min	--	--	0.59(0.05,1.13)*	--
+Lnight_min	--	--	--	0.69(0.04,1.33)*
PM_{10} mass	-0.34(-1.06, 0.38)	-0.51(-1.10,0.08)	-0.49(-1.08,0.09)	-0.48(-1.07,0.11)
+Lden_min	--	--	0.55(0.03,1.07)*	--
+Lnight_min	--	--	--	0.64(0.02,1.27)*
$PM_{2.5}$ absorbance	-0.48(-1.17, 0.20)	-0.05(-0.72,0.62)	-0.17(-0.85,0.50)	-0.15(-0.82,0.53)
+Lden_min	--	--	0.58(0.05,1.11)*	--
+Lnight_min	--	--	--	0.68(0.05,1.32)*

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 μm. PM_{10}: particulate matter with aerodynamic diameter ≤ 10 μm.

[a] Model 1adjusted for cohort study, area, gender, age of child, BMI, physical activity, maternal smoking during pregnancy, parental education level, parental history of hypertension, 7-day level of air pollutants, 7-day temperature. [b] Model 2 restricted to children from the Munich city area in which noise variables are available. [c] Model 3 additionally adjusted for Lden_min. [d] Model 4 additionally adjusted for Lnight_min.

* *P*-value < 0.05

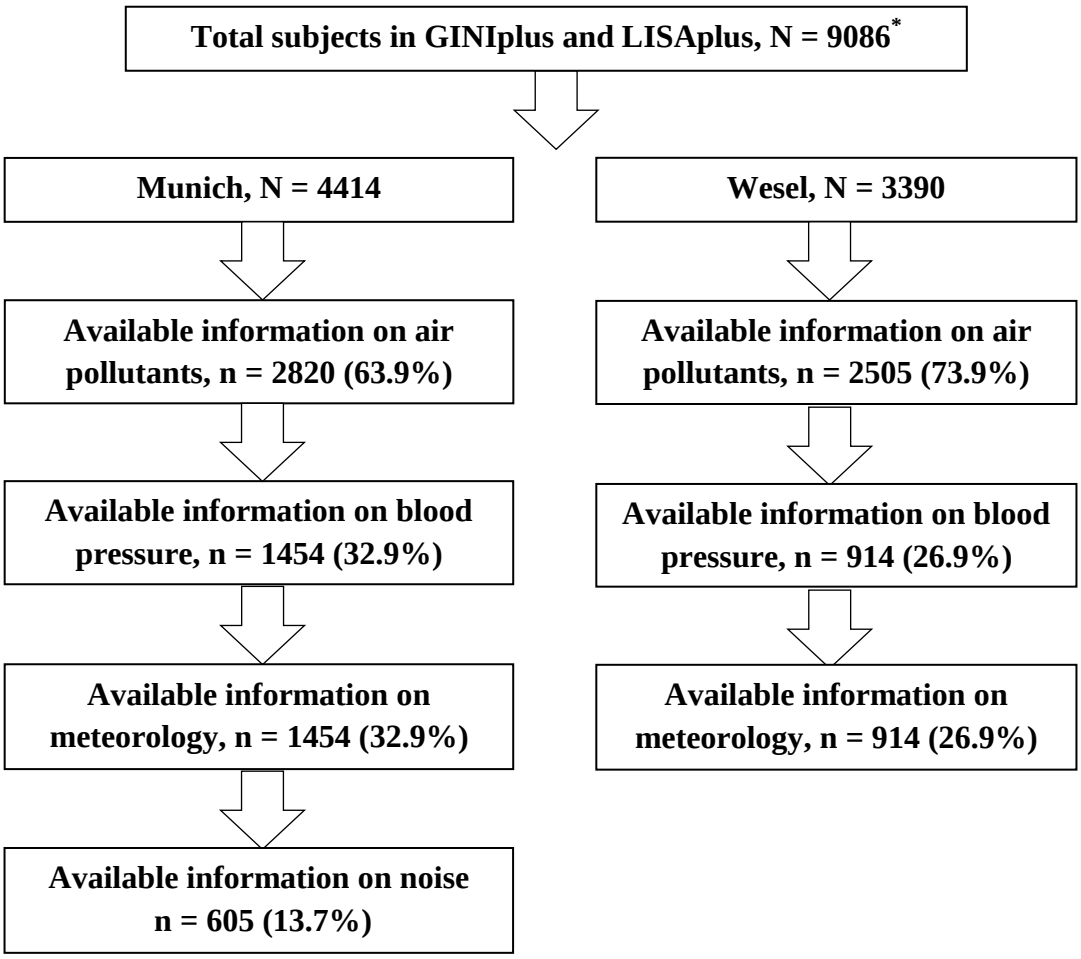

Figure 1. Selection of study participants

*1282 children (976 from Leipzig and 306 from Bad Honnef) of the original cohorts are not shown in the flow chart

n, the number of study population in each subgroup; %, the percentage of children from the total original samples.

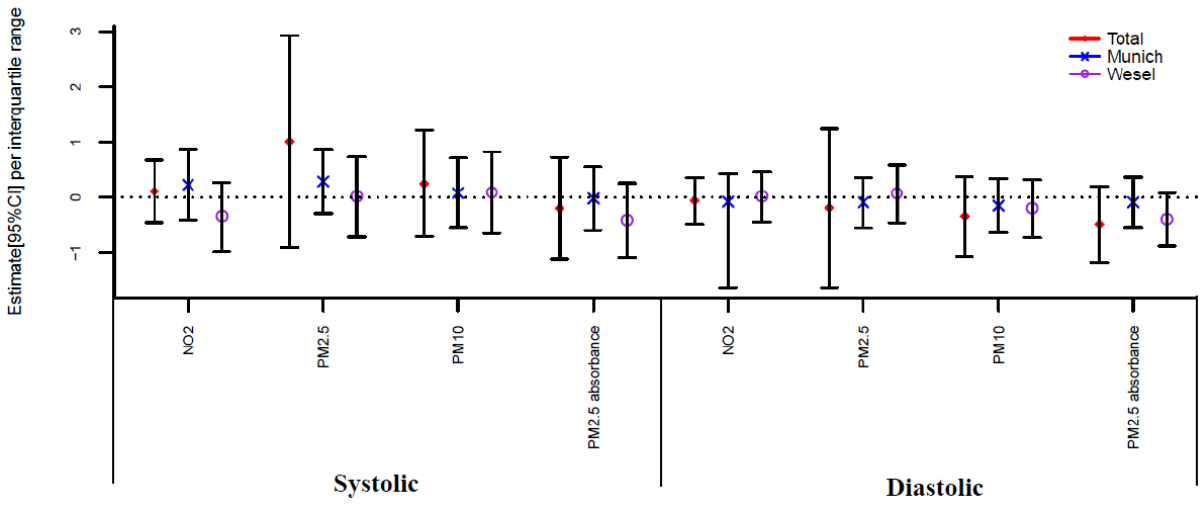

Figure 2. Estimated change in blood pressure (mmHg, with 95% CI) per interquartile range increment of annual mean of traffic-related air pollution. Models adjusted for cohort study, gender, age of child, body mass index, physical activity, maternal smoking during pregnancy, parental education level, parental history of hypertension, 7-day air pollution and 7-day temperature, area (total models only).

Supplemental material Table S1. Comparison of the baseline characteristics in different subgroups

	subgroup with noise (N=605)		subgroup without noise (N=1763)	
	n/N or N	**% or mean ± SD**	**n/N or N**	**% or mean ± SD**
Cohort, GINIplus	405/605	66.9	1356/1763	76.9
Gender, male	320/605	52.9	890/1763	50.5
Age, month*	605	121.91 ± 3.03	1763	122.21 ± 2.54
Height, cm*	605	142.70 ± 6.45	1763	143.94 ± 6.52
Weight, kg*	604	35.03 ± 6.44	1762	36.54 ± 7.19
BMI, kg/m²*	604	17.11 ± 2.28	1762	17.53 ± 2.53
Physical activity per week, hours*	605	17.16 ± 12.27	1763	20.33 ± 15.88
Parental education [a] *				
low, %	30	5.0	121/1756	6.9
medium, %	94	15.5	528/1756	30.1
high, %	481	79.5	1107/1756	63.0
Smoking during pregnancy	88/584	15.1	209/1709	12.2
Hypertension of parents	141/603	23.4	392/1760	22.3
7-day temperature, ℃	605	10.87 ± 7.37	1763	11.49 ± 6.89
Systolic blood pressure, mmHg*	605	110.34 ± 9.21	1763	111.74 ± 10.17
Diastolic blood pressure, mmHg*	605	63.14 ± 7.76	1763	64.59 ± 7.29

BMI: body mass index. dB(A): A-weighted decibel. Lden_min: minimum of weighted yearly average day-evening-night equivalent noise levels in dB(A) within a 50 meter buffer around the selected building/house. Lnight_min: minimum of equivalent yearly average noise levels in dB(A) at nighttime (10 p.m. to 6 a.m.) within a 50 meter buffer around the selected building/house.

[a] Parental education: low if both parents have less than 10 years of school; medium: 10 years of school; high: at least one parent has more than 10 years of school.* Significant difference between Munich inner city and suburbs

Supplemental material Table S2. Annual and 7-day average concentrations of air pollution in different subgroups

Exposure	subgroup with noise (N = 605)	subgroup without noise (N = 1763)
Annual level		
NO_2 (μg/m³)		
Mean	23.67	20.49
5th percentile	16.79	13.83
Median	23.36	20.67
95th percentile	31.07	27.33
Interquartile range	6.16	6.71
$PM_{2.5}$ mass (μg/m³)		
Mean	13.11	15.48
5th percentile	11.56	12.64
Median	13.03	16.29
95th percentile	14.88	18.39
Interquartile range	1.39	3.95
PM_{10} mass (μg/m³)		
Mean	20.57	22.65
5th percentile	16.88	16.59
Median	20.45	24.01
95th percentile	23.97	27.11
Interquartile range	2.00	5.04
$PM_{2.5}$ absorbance (10^{-5} m^{-1})		
Mean	1.69	1.40
5th percentile	1.41	1.02
Median	1.66	1.42
95th percentile	2.04	1.82
Interquartile range	0.22	0.47
7-day level (mean ± SD, μg/m³)		
NO_2	29.33 ± 9.76	27.16 ± 9.61
PM_{10}	24.58 ± 13.73	24.63 ± 11.04

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 μm. PM_{10}: particulate matter with aerodynamic diameter ≤ 10 μm.

Supplemental material Table S3. Correlations (Spearman's rank correlation coefficient) between noise and long-term air pollution

Noise[a]	Lden_min	NO_2	$PM_{2.5}$ mass	PM_{10} mass	$PM_{2.5}$ abs
Lden_min	1.00	-0.13**	0.26***	0.01	0.17***
Lnight_min	0.92***	-0.14***	0.23***	-0.01	0.13***

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 µm. PM_{10}: particulate matter with aerodynamic diameter ≤ 10 µm. Abs = absorbance
Significance Level: *P<0.05, **P<0.01, ***P<0.001
a. Categories: Lden_min: 32.5, 37.5, 42.5, 47.5, 52.5, 57.5, 62.5 dB(A);
Lnight_min: 27.5, 32.5, 37.5, 42.5, 47.5, 52.5 dB(A)

Supplemental material Table S4. Associations between blood pressure and long-term traffic-related air pollution

Source of exposure	Outcome	Total (N = 2368)		Munich (N = 1454)		Wesel (N = 914)	
		β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
NO_2	systolic BP	0.11 (-0.45, 0.67)	0.697	0.23 (-0.41, 0.87)	0.481	-0.35 (-0.98, 0.27)	0.269
	diastolic BP	-0.06 (-0.48, 0.36)	0.770	-0.08 (-0.58, 0.43)	0.766	0.01 (-0.44, 0.46)	0.973
$PM_{2.5}$ mass	systolic BP	1.01 (-0.90, 2.92)	0.302	0.29 (-0.29, 0.87)	0.324	0.01 (-0.72, 0.73)	0.989
	diastolic BP	-0.19 (-1.63, 1.24)	0.791	-0.09 (-0.55, 0.36)	0.682	0.06 (-0.46, 0.58)	0.815
PM_{10} mass	systolic BP	0.25 (-0.71, 1.21)	0.612	0.08 (-0.54, 0.71)	0.794	0.08 (-0.65, 0.82)	0.826
	diastolic BP	-0.34 (-1.06, 0.38)	0.354	-0.15 (-0.64, 0.34)	0.549	-0.20 (-0.73, 0.32)	0.451
$PM_{2.5}$ absorbance	systolic BP	-0.20 (-1.11, 0.72)	0.672	-0.02 (-0.60, 0.55)	0.940	-0.41 (-1.08, 0.26)	0.234
	diastolic BP	-0.48 (-1.17, 0.20)	0.166	-0.09 (-0.54, 0.37)	0.707	-0.40 (-0.88, 0.08)	0.103

$PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 µm. PM_{10}: particulate matter with aerodynamic diameter ≤ 10 µm.
BP = blood pressure, N = sample size, β = estimated change in blood pressure per interquartile range increment of long-term traffic-related air pollution, 95% CI = 95% confidence intervals
Adjusted for cohort study, gender, age, body mass index, physical activity, maternal smoking during pregnancy, parental education level, parental history of hypertension, 7-day air pollution and 7-day temperature, and area (total models only)

6. Effects of air pollution on exhaled nitric oxide in children: Results from the GINIplus and LISAplus studies

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International Journal of Hygiene and Environmental Health

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Thank you for submitting your work to International Journal of Hygiene and Environmental Health.

Yours sincerely,

Lars Jurzik
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Effects of Air Pollution on Exhaled Nitric Oxide in Children: Results from the GINIplus and LISAplus Studies

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Abstract

Most previous studies which have investigated the short-term effects of air pollution on airway inflammation, assessed by an increase of exhaled nitric oxide (eNO), have been conducted among asthmatic children. Few studies have considered this potential association among non-asthmatics. Furthermore, although both short- and long-term effects of air pollution on eNO had been reported separately, studies which include both are scarce. We explored associations between 24h NO_2 and PM_{10} (particles with aerodynamic diameters below 10 µm) mass with eNO in 1,985 children (192 asthmatics and 1,793 non-asthmatics) aged 10 years and accounted for the long-term effects of air pollution by adjusting for annual averages of NO_2, PM_{10} mass, $PM_{2.5}$ mass (particles with aerodynamic diameters below 2.5 µm) and $PM_{2.5}$ absorbance, using data from two German birth cohorts in Munich and Wesel. In total, robust associations between 24h NO_2 and eNO were observed in both single-pollutant (percentage change: 18.30%, 95% confidence interval: 11.63 - 25.37) and two-pollutant models (14.62%, 6.71 - 23.11). The association between 24h PM_{10} mass and eNO was only significant in the single-pollutant model (9.59%, 4.80 - 14.61). The same significant associations were also observed in non-asthmatic children, while they did not reach significant levels in asthmatic children. Associations between annual averages of ambient air pollution (NO_2, PM_{10} mass, $PM_{2.5}$ mass and $PM_{2.5}$ absorbance) and eNO were consistently null. In conclusion, significantly positive associations were observed between short-term ambient air pollution and eNO. No long-term effects of air pollution on eNO were found in this study.

Keywords: air pollution, exhaled nitric oxide, short-term exposure, long-term exposure, children's respiratory health, environmental epidemiology

Introduction

The fractional concentration of exhaled nitric oxide (eNO) is a reliable and noninvasive marker of eosinophilic airway inflammation (La Grutta et al., 2012; Sandrini et al., 2010). As it is easier and faster to obtain than other inflammation markers, such as sputum eosinophils level (La Grutta et al., 2012), it is widely used in epidemiological studies (Delfino et al., 2006), especially those conduced in children (La Grutta et al., 2012).

Recent studies have provided evidence that short-term air pollution is positively associated with eNO in children, especially those with asthma (Barraza-Villarreal et al., 2008; Delfino et al., 2006; Flamant-Hulin et al., 2010; Koenig et al., 2005; Liu et al., 2009; Mar et al., 2005; Renzetti et al., 2009). Studies in non-asthmatic children are rare. Only two previous studies have examined the association between short-term exposure to particulate matter and eNO in both asthmatic and non-asthmatic children, and both reported positive significant associations (Flamant-Hulin et al., 2010; Berhane et al., 2011).

There have also been studies (Dales et al., 2008; Eckel et al., 2011; Graveland et al., 2011; Holguin et al., 2007) which report that children living in areas with high traffic density and/or air pollution concentrations have chronically increased levels of eNO. However, only one study has examined the effects of both short- and long-term exposure simultaneously (Graveland et al., 2011). Graveland et al (2011) investigated associations between eNO and both short-term (0-3 days) concentrations of outdoor PM_{10} (particles with aerodynamic diameters below 10 μm) mass and long-term traffic exposures (traffic counts, distances of children's residence/school to motorways, etc.) among 812 children aged 7-11 years. This study found that eNO was positively and significantly associated with short-term ambient PM_{10} mass. A positive but non-significant association with long-term exposure was found only among 86 asthmatic children (Graveland et al., 2011).

Given the lack of studies including both asthmatic and non-asthmatic children, and considering the effects of short- and long-term air pollution on airway inflammation, we studied associations between short-term (24h before eNO measurements) NO_2 and PM_{10} mass with eNO in both asthmatic and non-asthmatic children participating in two German birth cohorts, and included adjustments for long-termNO_2, PM_{10} mass, $PM_{2.5}$ mass (particles with aerodynamic diameters below 2.5 μm) and $PM_{2.5}$ absorbance.

Methods

Study Population

The study population consists of children from two German birth cohorts of healthy full-term neonates. The German Infant Nutritional Intervention plus environmental and genetic influences on allergy development study (GINIplus) was designed to prospectively investigate the effects of a nutrition intervention during infancy, as well as of air pollution and genetics on allergy development. Details of the design, recruitment and follow-up of this intervention study have been previously published (Filipiak et al., 2007; von Berg et al., 2010). Briefly, a total of 5991 newborns were recruited in obstetric clinics in Munich and Wesel, Germany, between September 1995 and July 1998. Follow-up occurred at the age of one, two, three, four, six and ten years of age. The Lifestyle-Related factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics (LISAplus) population-based study aimed to assess the influence of lifestyle-related factors on the immune system, as well as the effects of air pollution and genetics on the development of allergies in childhood. In total, 3097 healthy full-term neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel and Bad Honnef, Germany, between November 1997 and January 1999. Follow-up for this study occurred at the age of six, twelve and eighteen months, and two, four, six and ten years. A detailed description of

the screening and recruitment has been published elsewhere (Heinrich et al., 2002; Zutavern et al., 2007).

The current study is restricted to children from Munich and Wesel as long-term air pollution data were only available for these two areas. In total, 1,985 children (asthmatic children = 192, non-asthmatic children = 1,793) were included in this analysis as they had available data on eNO, short-term (24h) air pollution concentrations, and asthmatic history (Figure 1). For both cohort studies, ethical approval was obtained by the local medical ethical committees (Bavarian Board of Physicians, University of Leipzig, Board of Physicians of North-Rhine-Westphalia). Written informed consent was obtained from all participating families.

Air Pollution

Short-term air pollution concentrations

Concentrations of both NO_2 and PM_{10} mass for Munich were obtained from the same background monitoring site located in the Munich suburban area (Johanneskirchen), which is approximately nine kilometers in the northeast of the city. Concentrations of both NO_2 and PM_{10} mass for Wesel were obtained from 'The State Agency for Nature, Environment and Consumer Protection of North Rhine-Westphalia' (2012). The data were collected in one monitoring site (WESE) that located in the suburban area of Wesel-Feldmark, it is approximately two kilometers in the northeast of the city.

Long-term (one-year) air pollution concentrations

Estimates of modeled annual average concentrations of NO_2 and particulate matters (PM_{10} mass, $PM_{2.5}$ mass and $PM_{2.5}$ absorbance) were used to adjust for the long-term effects of NO_2 and particulate matters on eNO in this study. These data were derived from land-use regression (LUR) models (different models had been applied forMunich and Wesl) developed

as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) collaboration (http://www.escapeproject.eu/manuals).

In brief, NO_2 was monitored at 40 sites and particulate matters were monitored at 20 sites between October 2008 and November 2009. Each site was monitored for two consecutive weeks three times (during warm, cold and intermediate temperature seasons). These discontinuous measurements were then adjusted for the true long-term average of the observation period, according to data from one additional background site which measured concentrations of air pollution using the same instruments continuously for a complete year. Finally, exposure estimates of annual average concentrations of air pollution for each participant's residence were calculated using a LUR model. Details of this procedure have been previously published (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a; Eeftens et al., 2012b).

Measurement of eNO

Fractional eNO was determined in line with the current European Respiratory Society and American Thoracic Society recommendations during a controlled expiration over six seconds using the handheld device, NIOX MINO (Aerocrine (Maestrelli et al., 2007)).

Briefly, the eNO measurement was performed in a standing position. The study participants were asked to inhale quickly to total lung capacity through the mouthpiece of the device so that the lung was filled with NO free air (NO scrubber). To avoid nasal inspiration a nose clip was used. The participant then exhaled slowly and evenly through the mouthpiece at a flow rate of 50 ± 5 ml/sec. The accurate flow rate was achieved by guidance of a sound and light signal from the device. The quality of the eNO measurement was automatically controlled by the device. Typically, one maneuver was performed and, upon acceptance for

quality control, was used for analyses. Unacceptable maneuvers were repeated until acceptance, with a possible maximum of 5 repetitions.

In order to avoid the effects of factors known to influence eNO, we included only children who met the following requirements before the eNO measurement: no nitrite-rich food intake (e.g., green vegetables and fruits, smoked meats and spinach, etc.) for at least four hours prior to measurement; no anti-asthmatic and antiphlogistic medications in the last four hours; no measurements of lung function and no bronchial challenge prior to test.

Other covariates

Demographic, health and lifestyle information on the study participants was collected using self-administered questionnaires completed by the parents (sex, highest educational level of either parent [low: both parents reported less than 10 years of school; medium: 10 years of school; high: at least one of the parents reported more than 10 years of school], maternal smoking during pregnancy [yes/no], exposure to tobacco smoke at 10 years of age [yes/no], indoor gas pollution [yes/no, using gas as fuel for indoor cooking and/or heating], current pet ownership [yes/no], parental history of atopy [neither parent is atopic; at least one of the parents is atopic], anti-asthma medication in the past one year [yes/no], time of last infection [infection within recent four weeks versus four weeks ago] and physician diagnosed asthma in the past ten years [yes/no]). IgE levels were measured at the 10^{th} year to determine atopy status of children. Atopy was defined as inhalation mixture positive (IgE > 0.35 kU/L) or food mixture positive (IgE > 0.35 kU/L).

Statistical analysis

The analysis was carried out using the R statistical software (version 2.14.1) (R Development Core Team, 2011). Pearson’s chi-square test, the Student’s t-test and the Wilcoxon rank sum

test were used to assess differences between asthmatic and non-asthmatic children for categorical, normally distributed continuous variables, and continuous variables with a skewed distribution, respectively. Correlations between short- and long-term air pollution concentrations were assessed with Spearman's rank correlation coefficient.

We ln-transformed the eNO measurements to normalize the distribution of the outcome variable. The associations between short-term NO_2 (PM_{10} mass) with ln-transformed eNO were explored with generalized additive models (GAM, MGCV package in R (Wood, 2011)). GAM provides a flexible method to predict the quality of a dependent variable from different distributions with exponential family models and other likelihood-based regression models (Trevor and Robert, 1986). Air pollution concentrations were included as linear terms, after testing their linearity with ln-transformed eNO (GAM plots are not shown).

First, we ran models including adjustment for physician diagnosed asthma in the past ten years in the total population to find the strongest associations between short-term (24h and moving averages of one to seven days) NO_2 and PM_{10} mass with eNO.

Second, two models were used to test associations between 24h ambient air pollution and eNO among total and asthma-stratified children. Model 1 (crude model) included only the 24h air pollutant of interest. Model 2 (adjusted model) included the main exposure and adjustment for cohort (GINIplus versus LISAplus), city, sex, parental educational level, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco smoke at 10 years of age and average ambient temperature in the last 24h (Delfino et al., 2006). We also further adjusted the models for anti-asthma medication in the past one year (for models in asthmatic children only). Annual averages of NO_2 or/and particulate matters concentrations was also additionally included in the adjusted model (model 2) to assess the impact of long-term effects of air pollution on the investigated associations.

In the sensitivity analyses, stratified analyses according to atopy status and the time of last infection (within the past 4 weeks [yes/no]) were applied to look for potential effect modification. Furthermore, spatial clustering of study samples was explored by adding random area level intercepts (zip-code and community) and intervention effects in GINIplus study was explored by adding the intervention status. For all the afore-mentioned models, both single- ($PM_{2.5}$ mass or NO_2) and two-pollutant models ($PM_{2.5}$ mass and NO_2) were applied.

All air pollution risk estimates were modeled per interquartile range (IQR; 17.60 μg/m³ for 24h NO_2 and 17.04 μg/m³ for 24h PM_{10} mass in the total population) increase. All results are presented as percentage change of eNO with corresponding 95% confidence intervals (CI). *P*-values below 0.05 were used to indicate conventional statistical significance.

Results

Characteristics of study population and eNO

In total, 1,985 children were included in this study, 9.67% (N = 192) and 90.33% (N = 1,793) of which were asthmatic and non-asthmatic, respectively. Baseline characters of the study participants are given in Table 1. 49.5% of the asthmatic children come from Munich and 50.5% from Wesel; while for non-asthmatic children, more of them are from Munich (64.2%) than Wesel (35.8%). There is no significant difference for the distribution of parental education, parental atopy history, exposure to tobacco smoke, indoor gas pollution and current pet ownership between asthmatic and non-asthmatic children. Characteristics of children from the two baseline cohorts are shown in Supplemental Material, Table S1. Children who are included into analyses tend to have higher parental education level, and they are less exposed to tobacco smoke and indoor air pollution compared to the unselected children.

Table 2 summarizes eNO and ambient air pollution concentrations. The distribution of eNO was skewed, ranging from 1.00 to 174.00 part per billion (ppb) among total children (1.00 to 174.00 ppb for asthmatic children and 1.00 to 144.00 ppb for non-asthmatic children). Asthmatic children had significantly higher levels of eNO compared to non-asthmatic children ($P < 0.01$, median is 18.00 ppb for asthmatic children and 12.00 ppb for non-asthmatic children). Mean and standard deviation of 24h air pollution concentrations were 30.55 ± 12.56 μg/m³ for NO_2 and 23.36 ± 13.90 μg/m³ for PM_{10} mass ; for annual average levels, they are 21.24 ± 4.82 μg/m³ for NO_2 and 22.07 ± 3.21 μg/m³ for PM_{10} mass among total children. The 24h NO_2 and PM_{10} mass concentrations were moderately correlated (spearman correlation coefficient is 0.586). The 24h air pollution concentrations were not correlated with long-term air pollution concentrations, see Supplemental Material Table S2.

Associations between air pollutants and eNO parameters

Figure 2 shows the effects of varying short-term air pollution averages on eNO in children. The strongest association was observed between NO_2 averaged over the last 24 hours and eNO. The same was true for PM_{10} mass. As such, the average over the last 24 hours was used for all short-term air pollution concentrations in all models.

Based on the results from Figure 2, further covariates were adjusted. Table 3 summaries the crude and adjusted associations between 24h NO_2 and PM_{10} mass with eNO.

Among the total children, there were significantly positive associations between 24h NO_2 and PM_{10} mass with eNO across single-pollutant models. In the fully adjusted single-pollutant models (model 2), eNO increased by 18.30% (95% CI, 11.63 - 25.37) and 9.59% (4.80 - 14.61) per IQR increase of 24h mean NO_2 and PM_{10} mass, respectively. In the two-pollutant models, the association between eNO and 24h NO_2 remained statistically

significant (14.62%, (95% CI, 6.71 - 23.11)) but the association with 24h PM_{10} mass was attenuated and no longer significant (4.36%, (-1.35 - 10.40)). For non-asthmatic children, the associations between ambient air pollution and eNO are the same as that in total; for asthmatic children, positive but not significant associations between 24h NO_2 and PM_{10} mass with eNO are observed across different models. Overall, asthmatic children have approximately 40% higher level of eNO compared to non-asthmatic children.

Long-term effects of air pollution

After further adjusting the models for annual mean of NO_2 and particulate matters, associations between 24h NO_2 and PM_{10} mass with eNO did not change substantially. All associations between long-term NO_2 and PM_{10} mass with eNO were null (Figure 3). Also null associations were observed between long-term $PM_{2.5}$ mass and $PM_{2.5}$ absorbance with eNO (data not shown).

Sensitivity analyses

City-stratified analysis shows systematically different associations between ambient air pollution and eNO in different areas (Figure 4). Significantly positive associations are observed among children from Munich, which are the same as the findings in the total children. Null associations are found for children from Wesel.

No systematically different associations are observed among children with different atopy status and last infection time. Associations between ambient NO_2 and PM_{10} mass with eNO tend to be stronger among non-atopy children and children who did not get infection in recent four weeks (Figure 5).

No indication of spatial clustering of study samples and intervention effects in GINIplus study is found. We find no substantial change in the associations between ambient air

pollution and eNO after including random area level intercept in total children and the intervention effects in children from GINIplus study (data not shown).

Discussion

In the present study, we investigated associations between 24h NO_2 and PM_{10} mass with eNO, as a surrogate for airway inflammation, among 1,985 children aged 10 years, 192 of which were asthmatics. Significantly positive associations were found between 24h NO_2 and PM_{10} mass with eNO among the total children, the same findings were also observed among non-asthmatic children, while the associations between short-term ambient air pollution and eNO did not reach significant level among asthmatic children. After adjusting for the long-term effects of NO_2 and particulate matters, the associations between short-term air pollution and eNO did not change substantially, and no independent effect of these long-term air pollutants was found.

The effects of air pollution on eNO in children have been summarized in a recent review (La Grutta et al., 2012). Positive and significant associations have been reported in most studies, the majority of which have focused on allergic children (La Grutta et al., 2012). Few studies have considered both asthmatic and non-asthmatic children. Of these, Flamant-Hulin et al. (2010), who recruited 104 children (34 asthmatic children and 70 non-asthmatic children), reported significant positive effects of 5-day average school yard and school $PM_{2.5}$ mass on eNO in both asthmatic and non-asthmatic children. In another study, which was conducted among 2,240 school children from 13 Southern Californian communities, the authors also reported positive effects of short-term $PM_{2.5}$ mass, PM_{10} mass and O_3 on airway inflammation, indicated by an increase of eNO, independent of asthma status (Berhane et al., 2011).

Although most previous studies have concluded that exposure to short-term air pollution leads to an increase of eNO among asthmatic children (La Grutta et al., 2012), null associations had also been found (Liu et al., 2009). In the current study, non-significant but positive associations were found between 24h NO_2 and PM_{10} mass with eNO among asthmatic children, one possible interpretation for this might be the number of asthmatic children was not large enough to reach statistical significance. Another reason might be that the measurement of eNO used in our study did not capture lower airway inflammation in children. Barregard et al. reported that increased eNO caused by exposure to wood smoke can only be measured and captured at a flow rate of 270 ml/sec, but not 50 ml/sec, as was used here (Barregard et al., 2008).

In this study, we also included the annual averages of NO_2 and particulate matters, as adjustments for the long-term effects of air pollution on eNO. No previous study has included both short- and long-term ambient air pollution concentrations. Only one published paper (Graveland et al., 2011) included short-term air pollution concentrations together with traffic characteristics as indicators of long-term exposure. Graveland et al. (2011) found that the eNO of 812 school children was significantly associated with 0-3 day averages of ambient PM_{10} mass levels, but not with traffic characteristics, the latter of which were considered as the long-term exposure indicators. This result is similar to the findings of the present study, in that associations between short-term but not long-term air pollution concentrations with eNO were observed.

The present study has several strengths. First, this study is the first to explore associations between short-term air pollution and eNO in both asthmatic and non-asthmatic children, while simultaneously considering the effects of long-term air pollution exposure. Second, LUR modeled long-term air pollution concentrations, which have been successfully applied in many past studies on associations between long-term exposure to outdoor air pollution and

health effects (Hoek et al., 2008), were individually assigned to cohort participants. LUR modeled data, which can represent more accurate exposure estimates than a single traffic-related indicator (e.g. traffic counts, distance to the road, etc.), might help to reveal a clearer association between long-term traffic-related air pollution and eNO (Graveland et al., 2011).

However, our study is not without limitations. First, the selection bias may exist in this study. The participants have higher parental education level than the others in the source cohorts. Second, the long-term ambient air pollution data in the current study was modeled using home addresses but not school addresses. As children at 10 year of age spend most of their daytime at school, there might be an exposure bias for long-term effect of ambient air pollution on eNO**,** although a null association between air pollution exposure at school and eNO has been reported (Holguin et al., 2007). Third, although air pollution concentrations at monitoring stations have been widely used in previous studies on health effects of short-term air pollution, exposure misclassification is possible as these estimates are not assigned at the individual-level (Holguin et al., 2007). In Delfino et al.'s study, although similar effects were observed for both individually assigned and ambient NO_2 on eNO, the results with individually-assigned $PM_{2.5}$ mass were more robust (Delfino et al., 2006). Forth, the eNO was measured with NIOX MINO machine, we do not have record of the actual flow rate and thus we cannot include it as adjustment. As eNO is highly flow rate dependent, the limitation caused by using such device should be kept in mind in future studies. Fifth, we do not have repeated measurements of eNO, which is ideal to study short-term effects.

As stated by Berhane et al., it is likely that children have different susceptibilities to the inflammatory effects of air pollution (Berhane et al., 2011). Our study provides further evidence to the growing body of evidence that short-term air pollution may increase in eNO. As the biological mechanism by which air pollution may increase bronchial inflammation and thus eNO has not been fully established (Bernstein et al., 2004), further studies are needed,

particularly on individuals with differing susceptibilities (e.g. people with and without asthma).

Conclusion

Significantly positive associations were observed between short-term air pollution and eNO. However, associations between long-term air pollution concentrations and eNO were null.

Acknowledgements

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Table 1 Baseline characteristics of the study participants

	Total (N = 1985)		Asthmatic (N = 192)		Non-asthmatic (N = 1793)	
	n/N or N	% or mean (SD)	n/N or N	% or mean (SD)	n/N or N	% or mean (SD)
Cohort, GINIplus	1460/1985	73.6	160/192	83.3	1300/1793	72.5
City*						
Munich	1246/1985	62.8	95/192	49.5	1151/1793	64.2
Wesel	739/1985	37.2	97/192	50.5	642/1793	35.8
Sex, male	1012/1985	51.0	120/192	62.5	892/1793	49.7
Parental education [a]						
low, %	114/1978	5.8	13/191	6.8	101/1787	5.7
medium, %	511/1978	25.8	62/191	32.5	449/1787	25.1
high, %	1353/1978	68.4	116/191	60.7	1237/1787	69.2
Parental history of atopy, yes	1252/1976	63.4	139/191	72.4	1113/1785	62.4
Exposure to tobacco smoke						
Maternal smoking during pregnancy	238/1924	12.4	21/187	11.2	217/1737	12.5
Passive smoke of child at 10 years	326/1962	16.6	31/191	16.2	295/1771	16.7
Indoor gas pollution	322/1911	16.8	28/173	16.2	294/1739	16.9
Current pet ownership	776/1924	40.3	59/185	31.9	717/1739	41.2
24h temperature, ℃	1985	11.41 ± 6.89	192	11.67 ± 6.61	1793	11.38 ± 6.92

[a] Parental education: low if both parents have less than 10 years of school; medium: 10 years of school; high: at least one parent has more than 10 years of school.

* *P*-value < 0.05

Table 2. Distribution of air pollutants and exhaled NO

	Mean	5th percentile	Median	95th percentile	Interquartile range
Total children (N = 1985)					
24h air pollution (μg/m³)					
NO_2	30.55	13.00	29.15	51.17	17.60
PM_{10} mass	23.36	7.00	20.00	48.21	17.04
Annual average of air pollution					
NO_2 (μg/m³)	21.24	14.05	21.46	28.85	6.51
PM_{10} mass (μg/m³)	22.07	16.69	21.69	26.69	4.76
$PM_{2.5}$ mass (μg/m³)	14.82	12.14	13.92	18.20	4.00
$PM_{2.5}$ abs (10^{-5} m^{-1})	1.48	1.03	1.52	1.91	0.43
Exhaled NO (ppb)	18.39	5.00	13.00	54.00	11.00
Asthmatic children (N = 192)					
24h air pollution (μg/m³)					
NO_2	29.83	12.00	27.60	55.89	16.34
PM_{10} mass	25.12	8.16	23.00	54.90	16.39
Annual average of air pollution					
NO_2 (μg/m³)	21.75	13.93	22.26	28.31	5.05
PM_{10} mass (μg/m³)	22.84	16.67	24.01	26.89	7.85
$PM_{2.5}$ mass (μg/m³)	15.40	12.22	15.89	18.41	4.09
$PM_{2.5}$ abs (10^{-5} m^{-1})	1.42	1.04	1.43	1.90	0.46
Exhaled NO (ppb)	26.83	4.65	18.00	73.75	27.25
Non-asthmatic children (N = 1793)					
24h air pollution (μg/m³)					
NO_2	30.62	13.00	29.42	51.00	17.60
PM_{10} mass	23.17	6.98	20.00	48.00	17.58
Annual average of air pollution					
NO_2 (μg/m³)	21.18	14.06	21.34	28.88	6.64
PM_{10} mass (μg/m³)	21.99	16.69	21.62	26.67	4.78
$PM_{2.5}$ mass (μg/m³)	14.75	12.11	13.86	18.19	3.97
$PM_{2.5}$ abs (10^{-5} m^{-1})	1.49	1.03	1.53	1.91	0.43
Exhaled NO (ppb)	17.50	5.00	12.00	50.30	10.00

PM_{10}: particulate matter with aerodynamic diameter ≤ 10 μm. $PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 μm

Table 3. Estimated percent change (95% CI) of exhaled NO per corresponding interquartile range increase in *24h* air pollution, stratified by history of physician-diagnosed asthma

	Total (N = 1985)			Asthmatics (N = 192)			Non-asthmatics (N = 1793)		
	% change	95% CI		*% change*	95% CI		*% change*	95% CI	
Model 1									
NO2									
Single-pollutant	15.58*	10.35	21.07	13.46	-3.43	33.30	15.65*	10.27	21.28
Two-pollutant	12.05*	5.74	18.73	4.85	-15.23	29.68	12.97*	6.42	19.92
PM10 mass									
Single-pollutant	10.99*	6.68	15.47	11.32	-3.55	28.49	11.32*	6.71	16.12
Two-pollutant	5.93*	0.72	11.42	15.38	-4.28	39.09	4.98	-0.51	10.78
Model 2									
NO2									
Single-pollutant	18.30*	11.63	25.37	21.19	-5.11	54.79	17.36*	10.69	24.44
Two-pollutant	14.62*	6.71	23.11	9.93	-19.25	49.64	14.57*	6.54	23.21
PM10 mass									
Single-pollutant	9.59*	4.80	14.61	11.61	-4.67	30.66	9.56*	4.55	15.00
Two-pollutant	4.36	-1.35	10.40	15.86	-5.27	41.70	3.33	-2.68	9.72
Model 3									
NO2									
Single-pollutant	NA	NA	NA	22.66	-3.52	55.95	NA	NA	NA
Two-pollutant	NA	NA	NA	13.01	-16.55	53.05	NA	NA	NA
PM10 mass									
Single-pollutant	NA	NA	NA	11.04	-4.92	29.61	NA	NA	NA
Two-pollutant	NA	NA	NA	13.74	-6.68	38.62	NA	NA	NA

PM_{10}: particulate matter with aerodynamic diameter ≤ 10 μm. 95% CI = 95% confidence intervals. NA: not available.

Model 1, crude model; Model 2, adjusted for cohort, city, sex, parental education level, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco at 10 years and 24h average ambient temperature; Model 3, additionally adjusted for anti-asthma medication in the past year. Asthmatic status was additionally adjusted across all the three models among total children.

* *P*-value<0.05

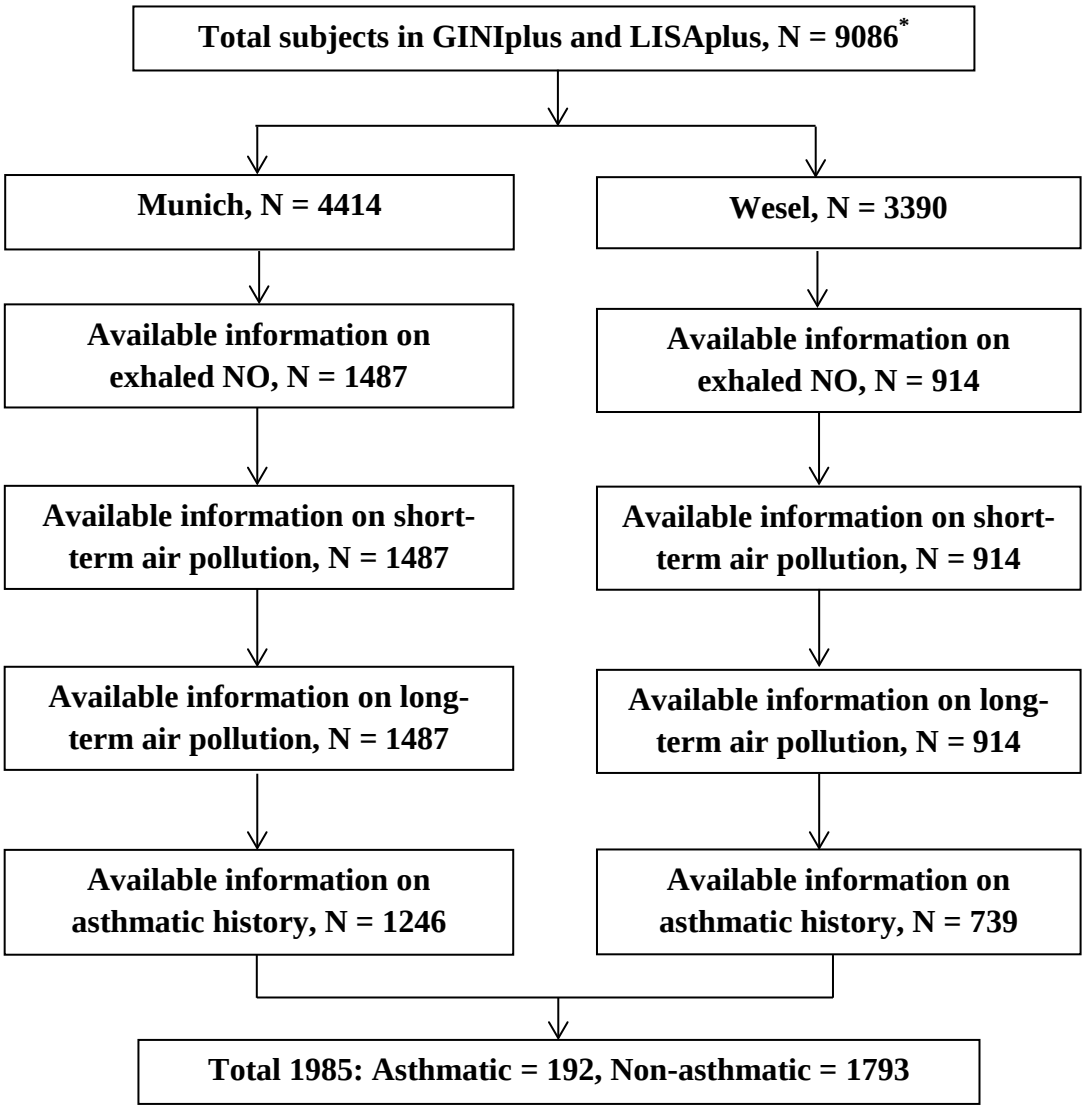

Figure 1. Selection of study participants

*1282 children (976 from Leipzig and 306 from Bad Honnef) of the original cohorts are not shown in the flow chart

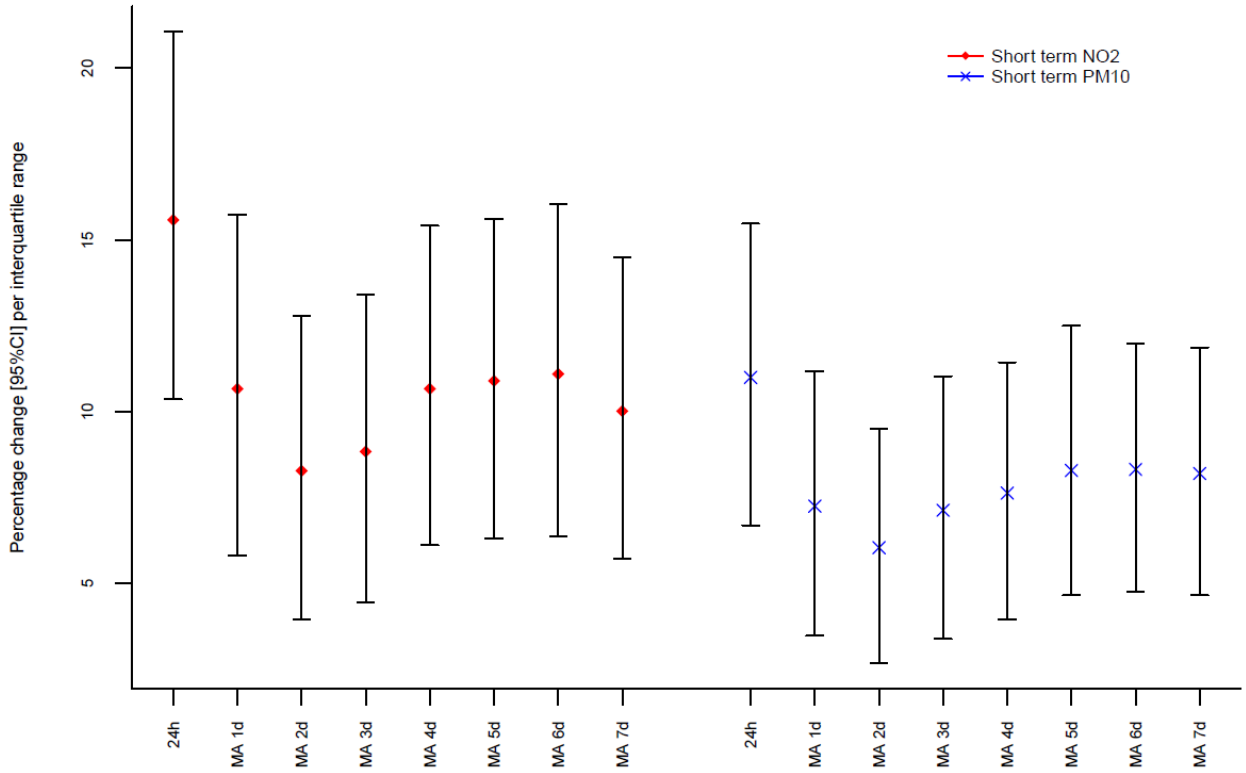

Figure 2. Percentage change of exhaled NO per interquartile range increase in short-term air pollution, adjusted for physician diagnosed asthma, MA: moving average

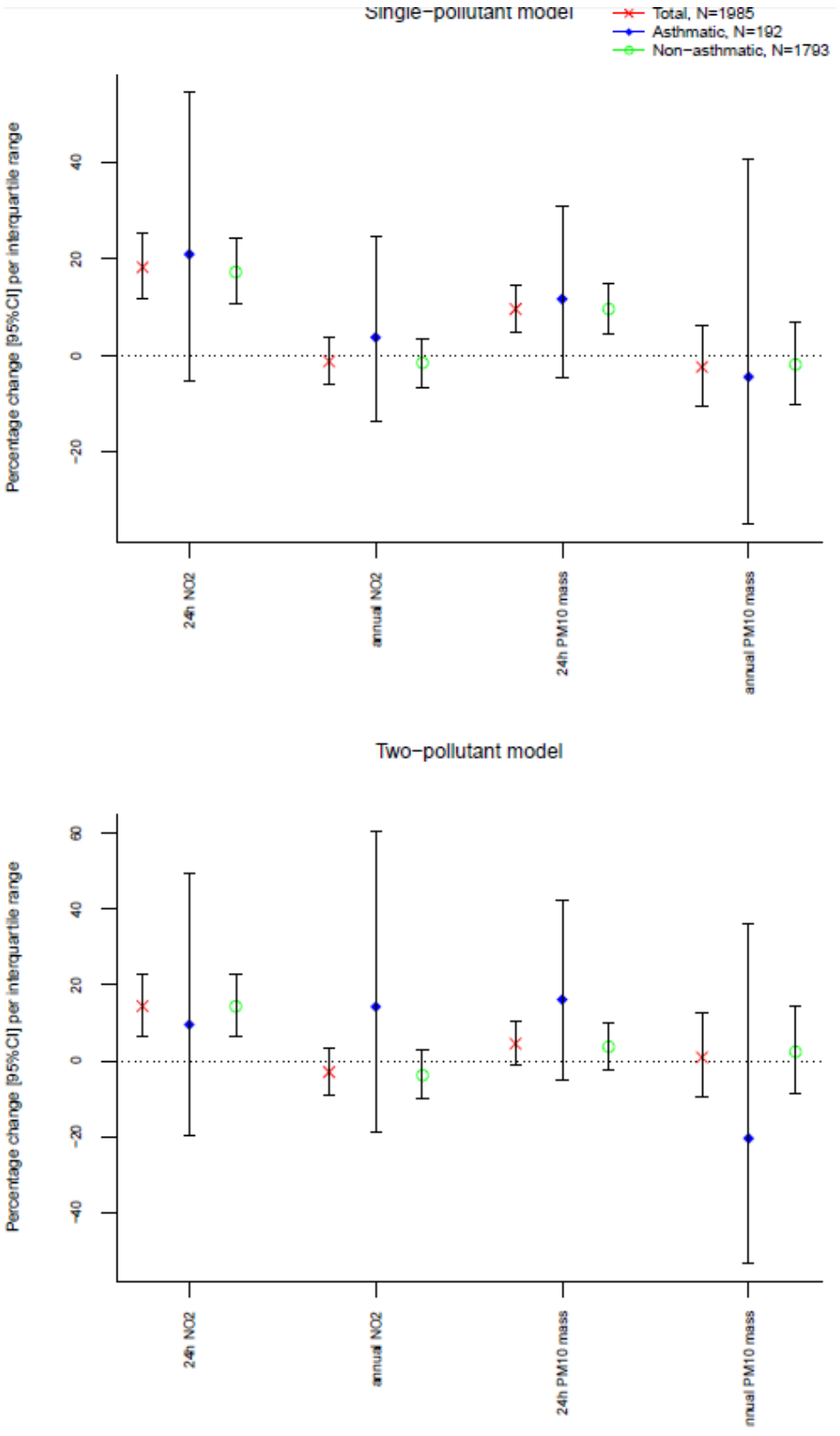

Figure 3. Percentage change of exhaled NO per interquartile range increase of ambient air pollution concentrations, adjusted for cohort, city, sex, parental education level, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco at 10 years, 24h average ambient temperature, 24h or annual average of NO_2 or/and PM_{10} mass

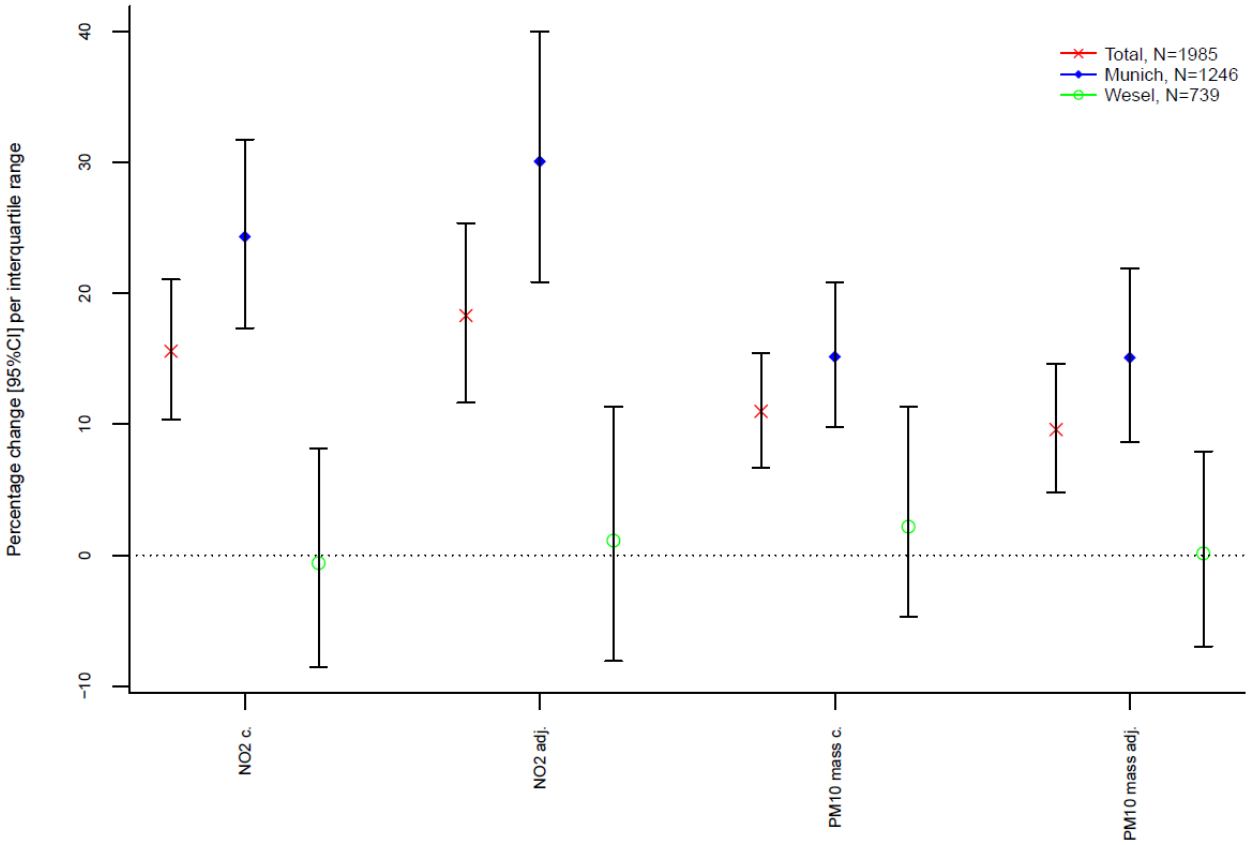

Figure 4. Percentage change of exhaled NO per interquartile range increase of average 24h air pollution concentrations, stratified by city, adjusted for cohort, sex, parental education level, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco at 10 years and 24h average ambient temperature. City was additionally adjusted in the total children

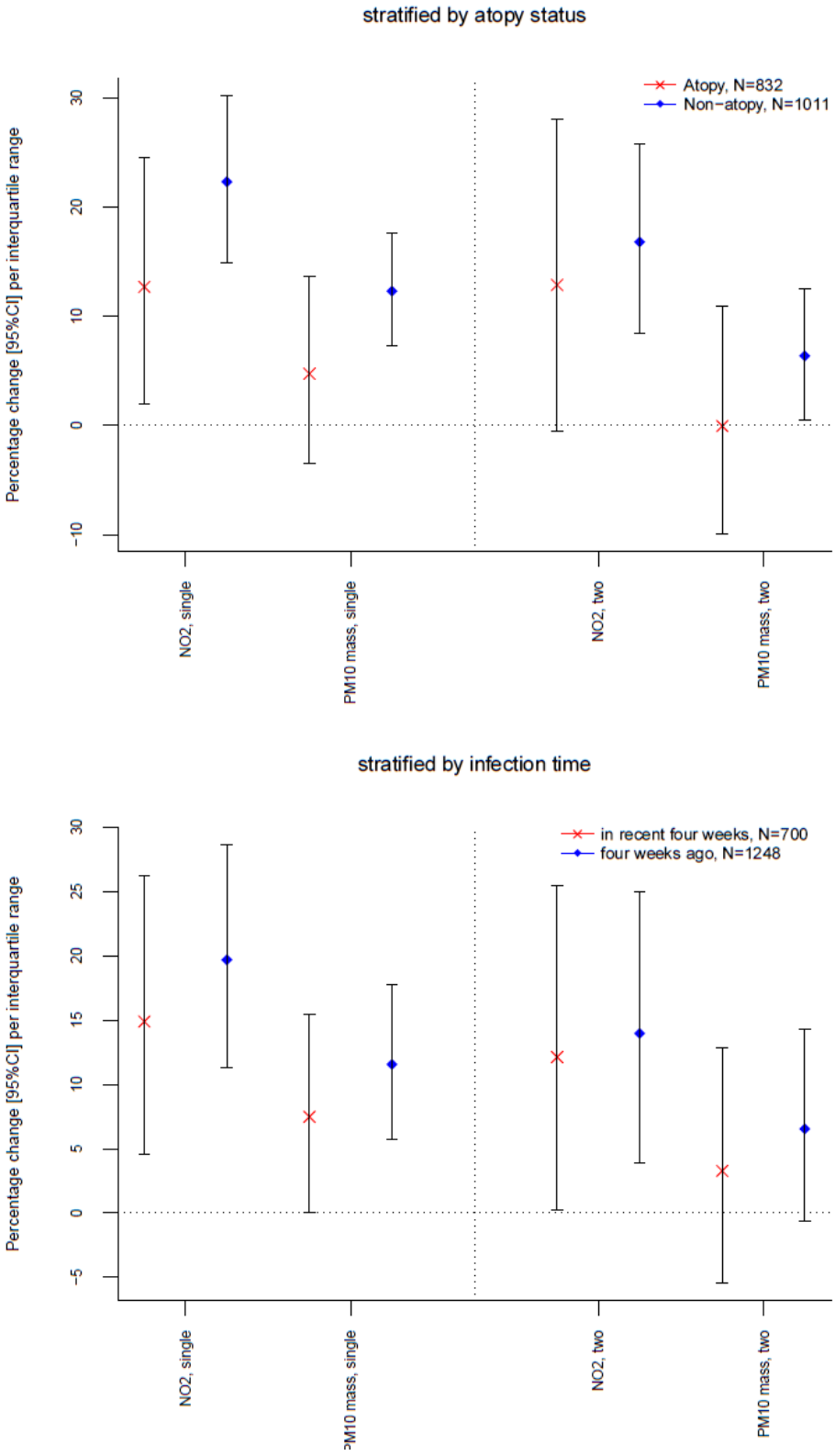

Figure 5. Percentage change of exhaled NO per interquartile range increase of average 24h air pollution concentrations, stratified by atopy status and last infection time, adjusted for cohort, city, sex, parental education level, parental history of atopy, indoor gas pollution, current pet ownership, maternal smoking during pregnancy, exposure to tobacco at 10 years and 24h average ambient temperature

Supplemental Material Table S1. Comparison between selected and unselected children from GINIplus and LISAplus studies

	selected (N = 1985)		unselected (N = 7101)	
	n/N	**%**	**n/N**	**%**
Cohort, GINIplus*	1460/1985	73.6	4531/7101	63.8
City*				
Munich	1246/1985	62.8	3168/7101	44.6
Leipzig	NA	NA	976/7101	13.7
Bad Honnef	NA	NA	306/7101	4.3
Wesel	739/1985	37.2	2651/7101	37.3
Sex, male	1012/1985	51.0	3564/6940	51.4
Parental education a*				
low, %	114/1978	5.8	855/7027	12.2
medium, %	511/1978	25.8	2145/7027	30.5
high, %	1353/1978	68.4	4027/7027	57.3
Parental history of atopy, yes*	1252/1976	63.4	3590/6947	51.7
Exposure to tobacco smoke				
Maternal smoking during pregnancy*	238/1924	12.4	1012/5725	17.7
Passive smoke of child at 10 years*	326/1962	16.6	590/2975	19.8
Indoor gas pollution*	322/1911	16.8	587/2884	20.4
Current pet ownership*	776/1924	40.3	1323/2943	45.0

[a] Parental education: low if both parents have less than 10 years of school; medium: 10 years of school; high: at least one parent has more than 10 years of school.

[*] *P*-value < 0.05

Supplemental material Table S2. Pearson correlation between ambient air pollution

	24h NO_2	24h PM_{10} mass
24h NO_2	1	0.586
24h PM_{10} mass	0.586	1
annual NO_2	-0.132	0.022
annual PM_{10} mass	-0.215	0.030
annual $PM_{2.5}$ mass	-0.232	0.046
annual $PM_{2.5}$ absorbance	0.171	-0.018

PM_{10}: particulate matter with aerodynamic diameter ≤ 10 μm. $PM_{2.5}$: particulate matter with aerodynamic diameter ≤ 2.5 μm

7. Curriculum Vitae

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1. **Liu, C.**, Flexeder C., Fuertes, E., Cyrys J., Bauer, C.P., Koletzko, S., Hoffmann B., von Berg A., Heinrich, J., **Effects of Air Pollution on Exhaled Nitric Oxide in Children: Results from the GINIplus and LISAplus Studies**. International Journal of Hygiene and Environmental Health, October 3. 2013, as available at http://dx.doi.org/10.1016/j.ijheh.2013.09.006 [Epub ahead of print].

2. Liu, C., Fuertes, E., Tiesler, C.M., Birk, M., Babisch, W., Bauer, C.P., Koletzko, S., von Berg A., Hoffmann B., Heinrich, J., **The associations between traffic-related air pollution and noise with blood pressure in children: Results from the GINIplus and LISAplus studies**. International Journal of Hygiene and Environmental Health, October 9. 2013, as available at http://dx.doi.org/10.1016/j.ijheh.2013.09.008 [Epub ahead of print].

3. **Liu, C.**, Fuertes, E., Tiesler, C.M., Birk, M., Babisch, W., Bauer, C.P., Koletzko, S., Heinrich, J., **The association between road traffic noise exposure and blood pressure among children in Germany: the GINIplus and LISAplus studies**. Noise Health, 2013. 15(64): p. 165-72.

4. **Liu, C.**, Liu M., Bo S., **Study on the Medical Rehabilitation and Related Factors of Disabled Children Aged 0-18 in Guangzhou and Dongying City**. Chinese Journal of Rehabilitation Medicine, 2011,26(8):754-758. [Article in Chinese]

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Eidesstattliche Versicherung

Liu Chuang

Name, Vorname

Ich erkläre hiermit an Eides statt,

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Exposure to ambient air pollution and noise in relation to adverse health effect in children

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