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Vehicle exhaust outside the home and onset of asthma among adults

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ABSTRACT: Few studies have investigated the relationship between vehicle exhaust and the new onset of asthma among adults. The aim of the present prospective cohort study was to investigate the relationship between the cumulative incidence of asthma and onset of asthma among adults and vehicle exhaust concentrations at home.

Participants from three Swedish cities included in the Respiratory Health in Northern Europe cohort constituted the study population. Exposure at each participant's home was calculated using dispersion models. We also used <50 m distance to nearest major road as a more simple indicator of exposure. The adjusted model included 3,609 participants, of which 107 were classified as onset cases and 55 as true incident cases of asthma.

There was a positive association between asthma onset (odds ratio (OR) per 10 $\mu g \cdot m^{-3}$ 1.46, 95% confidence interval (CI) 1.07–1.99) and incident asthma (OR per 10 $\mu g \cdot m^{-3}$ 1.54, 95% CI 1.00–2.36) and the levels of nitrogen dioxide (NO_2), which remained statistically significant after adjusting for potential confounders. The relationship between asthma and NO_2 was not significantly modified by sex, hay fever or wheeze. The risk of developing asthma was also significantly related to living close to a major road.

The current study suggests that elevated levels of vehicle exhaust outside the home increase the risk of onset and incident asthma among adults.

KEYWORDS: Adults, asthma, cohort, incidence, vehicle exhaust

The adverse health impact of air pollution is well known, and previous epidemiological studies have suggested that both cardiovascular and respiratory hospital admissions, as well as total mortality, increase with increasing levels of air pollution [1].

The prevalence of asthma and asthmatic symptoms has increased over the last decades, and is a global health issue [2]. Asthma is considered a multifactor disease with different phenotypes and air pollution has been suggested as one important factor. Recent studies have shown that air pollution is related to the prevalence of asthmatic symptoms and hospital admissions for asthma [3–5]. The relationship, however, is ambiguous, since there are studies also showing no relationship to the prevalence of asthma [6]. Previous studies have shown that children living closer to high traffic flow areas have a higher incidence of asthma in comparison with children living further away [7, 8]. Adverse effects of air pollution on lung function have also been shown [9]. However, few studies have investigated the relationship between air pollution and the onset of asthma among adults. One study from the USA, showed a nonsignificant increased risk of developing asthma among adults exposed to high levels of particles [10], while a Swedish study showed similar results for adults living close to roads with high traffic levels [11]. The incidence of asthma associated with traffic-related air pollution has been poorly investigated, largely due to a lack of usable prospective cohorts. The lack of population cohorts coupled with exposure misclassification have been mentioned as two important shortcomings linking traffic-related air pollution to respiratory health effects [12].

Earlier studies of traffic-related air pollution and health impacts have used relatively coarse measures of exposure, often at a city level, while more recent studies have tried to increase the spatial resolution of the exposure information [7, 11, 13, 14]. High spatial resolution exposure data are needed for vehicle exhaust when there are large within-city gradients in pollution levels. They are

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necessary for identifying relatively weak effects and also for specifying exposure–response relationships to facilitate impact assessment for such sources.

The aim of the present study was to assess the relationship between traffic-related air pollution levels and the cumulative number of onset and incident cases of asthma among adults. We used a prospective cohort and validated meteorological dispersion models to calculate the levels of nitrogen dioxide (NO_2) with high spatial resolution outside each participant's home. We also used a distance <50 m from home to nearest major road with ⩾8,000 vehicles per 24 h as a more simple measure of exposure.

METHODS

Study design and subjects

The Respiratory Health in Northern Europe (RHINE) cohort has been previously described [15]. Basically, the RHINE cohort is based on the random sample of people receiving the first screening questionnaire sent out within the European Community Respiratory Health Survey (ECRHS). The questionnaire was sent out in 1990 and included questions regarding respiratory symptoms such as wheezing, attacks of asthma and current use of asthma medication. All participants who answered the first questionnaire received the follow-up questionnaire in 1999, a procedure that differentiates the RHINE cohort from the ECRHS cohort, where only a subsample of the participants that received the first survey were included in the follow-up. The RHINE cohort includes five northern countries (Estonia, Denmark, Iceland, Norway and Sweden), each with one representative city with the exception of Sweden where three cities were used (Gothenburg, Umeå, and Uppsala). In the current study, we have used the results from the three Swedish cities. The study population in Sweden consisted of 10,800 participants, born between 1945 and 1973, from the municipalities of Gothenburg, Uppsala and Umeå, the latter being the main city in the southern part of Västerbotten County.

The population at risk were those who had negative answers to the questions ''Have you had an attack of asthma during the last 12 months?'' and ''Are you currently taking any medicine for asthma?'' in the first survey, and also had answers to either of those questions at follow-up together with at least one answer to either of the questions ''Have you ever had asthma?'' or ''Have you ever had asthma diagnosed by a doctor?'' To be defined as an onset case of asthma observed during the follow-up period, the participant had to have negative answers to the questions on attacks of asthma during the last 12 months and current use of asthma medication in the first survey, followed by a positive answer to at least one of these questions at the follow-up, followed by a positive answer to either ''Do you have or have you ever had asthma?'' or ''Have you ever had asthma diagnosed by a doctor?'' In addition to the definition of onset asthma, a more strict definition of cases (incident asthma) was used, where reporting the age at onset of asthma symptoms within the follow-up period was needed for being classified as a case.

The centre point of each participant's home address at inclusion in the cohort was georeferenced as the x- and y-coordinates of the estate within the Swedish coordinate system (RT 90). Georeferencing was performed by local authorities in each of the three municipalities of Gothenburg, Uppsala and Umeå.

Exposure

The vehicle exhaust levels outside each participant's home were indicated by the winter half-yr concentration (October–March) of NO_2 from dispersion models. Within Gothenburg, Uppsala and Umeå the concentration gradients are primarily caused by traffic flow. Our rationale for using winter half-yr values was that the majority of historical measurements available for validation of the models were from that part of the year, when levels are about 10–20% higher. Meteorological dispersion models were used to calculate the levels within each city, at a resolution of 50×50 m. The models were based on detailed information regarding meteorology, topography, emission sources and emission factors for different sources (traffic, heating and industry), which were combined to predict the spatial distribution of the urban background levels. In the current study the input data for the models were based on information from the year 1990, to correspond to the georeferenced addresses from the beginning of the follow-up period. For Gothenburg and Uppsala, locally adapted models managed by the cities authorities were used, while an external model was used for Umeå (Gothenburg: Enviman; Uppsala: Airviro; and Umeå: The Air Pollution Model) [16–18]. In a recent research project financed by the Swedish Environmental Protection Agency, the models for Gothenburg and Uppsala were evaluated, showing the modelled levels to be highly correlated to measured values; the degree of explained variation (r^2) was 0.79 and 0.71, respectively [19]. The Umeå model was fine tuned using measured levels, which resulted in an absolute correction of background levels upwards. The r^2 value between modelled and measured values (24 sites) in Umeå was 0.68. Figure 1 illustrates the exposure gradients in Umeå.

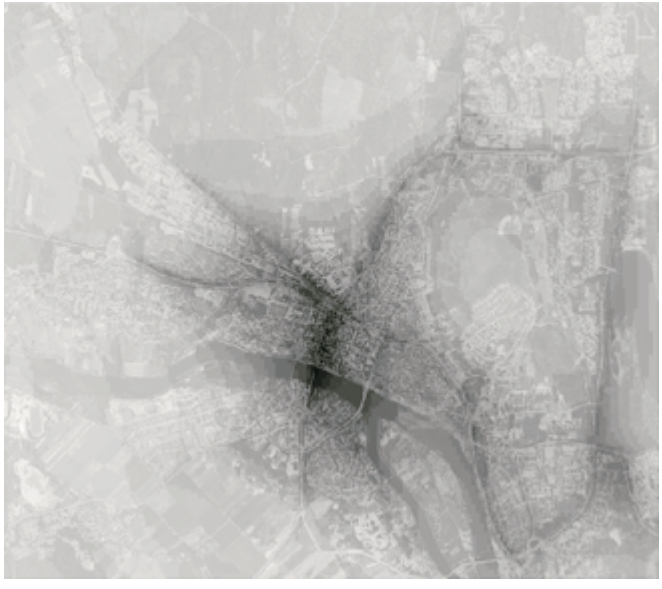

FIGURE 1. A map illustrating the results from the dispersion model for Umeå in 50-m squares. Darker colours indicate higher winter mean levels of nitrogen dioxide.

The results from the dispersion models were linked to the coordinates of each participant's home at inclusion in the cohort, resulting in a specific level of exposure for each participant.

Of the initial 10,800 participants, 7,424 had answers from both surveys, and of these 6,832 fulfilled the criteria for inclusion in the population at risk. Of these, 4,736 could be georeferenced based on the local registry of dwellings. The dispersion models did not cover the outskirts, which reduced the number of participants with a modelled value of NO_2 to 3,824 subjects. There was no significant difference in the proportion of onset asthma cases among those who did receive a modelled value of NO_2 and those who did not ($p=0.86$).

As a more simple indicator of exposure, the distance between each participant's address and the closest major road was measured. A major road was defined as a road with $\geqslant$8,000 vehicles per 24 h. Of the participants included in the population at risk, 4,736 had geocoded addresses, which made it possible to calculate the distance from the home to the closest major road.

Statistical analysis

In order to determine whether a significant relationship between NO_2 and asthma occurred, we used multiple logistic regression with asthma as the dichotomous dependent variable. The analysis was made for both outcome variables (onset and incident asthma). The results are presented as odds ratios (OR) per 10 $\mu g \cdot m^{-3}$ change in the NO_2 levels [20]. The analysis was first done with NO_2 at home grouped into tertiles, with the first tertile used as a reference.

In addition to analyses of the whole study population, separate analyses were performed on a portion of the population based on sex, presence of hay fever and wheeze at inclusion, by including variables estimating the NO_2 effect for each stratum, separately. Each of the variables was also tested for interactive effects on the relationship between NO_2 on asthma. The analysis based on distance to a major road was made by comparing those living close to a major road, defined as $<$50 m, with those living further away.

All analyses were made both unadjusted and adjusted. The adjustment was made by including a predetermined set of potential confounding variables: body mass index (BMI), sex, age, smoking, water damage or mould in the home at any time during the last 8 yrs, and city, simultaneously in the main analysis. Socioeconomic index (SEI) based on job title was used for ~80% of the participants to classify five categories, and was only used for sensitivity analysis [21]. Smoking was divided into three categories (nonsmokers, former smokers and current smokers), while BMI and age were included as continuous variables. We used Pearson's Chi-squared tests to compare participants with and without modelled values of NO_2 with regard to the number of asthma cases, and to compare cases with and without asthma. Pearson's Chi-squared test was also used to compare smoking habits and the prevalence of hay fever among participants included in the study with those who were excluded. Mean values were compared using an unpaired t-test. For evaluation of statistical significance, we used the 95% confidence level. Analyses were made using SPSS 14.0 statistical software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 represents the 3,824 participants at risk with a modelled NO_2 value, and the distribution of the covariates separately for both definitions of cases and noncases of asthma. The follow-up study showed that females developed asthma more frequently than males ($p_{onset}=0.01$, $p_{incidence}=0.02$), and hay fever at inclusion was more common among cases. 116 onset cases and 58 incident cases corresponds to a cumulative incidence of 3.0% (116 out of 3,824) and 1.5% (58 out of 3,824), respectively. The mean follow-up period was 8.2 yrs.

Of the 3,824 participants, 107 onset cases and 55 incident cases had information on all covariates and could be included in the analysis. The cases occurred among 3,609 subjects with all data needed for inclusion in the adjusted model. There was no

TABLE 1 Characteristics of cases and noncases from the population at risk

	Onset asthma			Incident asthma		
	Cases	Noncases	p-value	Cases	Noncases	p-value
Total n	116	3708		58	3766	
Males n	41	1739		18	1762	
Females n	75	1969	0.01[¶]	40	2004	0.02
BMI mean $kg \cdot m^2$	25.4	24.7	0.06[+]	25.3	24.7	0.26[+]
Age in 1999 mean yrs	39.4	39.7	0.61[+]	39.7	39.7	0.97[+]
Smoking % never/former/current	46/29/25	51/25/24	0.50[§]	41/32/27	51/25/24	0.32[§]
Hay fever %	48.7	18.6	<0.00[§]	40.4	19.2	<0.00[§]
Water/mould[#] %	24.3	23.2	0.74[§]	20.7	23.3	0.76[§]

The table includes those who received a modelled value of nitrogen dioxide and could be classified as cases or noncases according to the definition of onset and incident asthma. BMI: body mass index. [#]: water damage or mould in the home at any time during the last 8 yrs; [¶]: Pearson's Chi-squared test comparing the proportional difference of males and females among cases; [+]: unpaired t-test comparing cases with asthma with those without asthma; [§]: Pearson's Chi-squared test comparing cases with asthma with those without asthma.

TABLE 2 Descriptive information on the modelled winter average levels of nitrogen dioxide for cities and for onset and incident cases and noncases

	Mean±SD	Percentiles			Minimum	Maximum	p-value#
		25th	50th	75th			
Total	17.9±6.4	12.9	17.2	21.9	3.3	45.6	
Gothenburg	19.1±6.8	13.1	18.3	24.4	3.3	45.6	
Umeå	18.9±5.8	15.0	18.5	22.4	7.9	41.4	
Uppsala	14.6±4.7	10.8	14.7	17.8	5.4	28.7	
Onset asthma							
Noncases	17.9±6.4	12.9	17.1	21.8	3.3	45.0	0.03
Cases	19.2±7.1	13.7	17.8	24.0	6.8	45.6	
Incident asthma							
Noncases	17.9±6.4	12.9	17.1	21.8	3.3	45.6	0.12
Cases	19.2±6.1	15.6	18.2	24.1	6.8	33.7	
Distance to major road <50 m							
Onset cases	25.1±7.8	21.7	23.2	29.4	12.7	45.6	
Onset noncases	24.1±6.8	19.8	23.1	27.3	9.6	44.6	
Incident cases	24.3±6.0	21.1	24.4	29.1	12.7	32.7	
Incident noncases	24.1±6.9	20.0	23.1	27.3	9.6	45.6	

Data are given in $\mu g \cdot m^{-3}$ as winter half-yr concentrations, unless otherwise stated. #: unpaired t-test comparing the mean value for cases and noncases.

significant difference in the proportion of males and females included in the study in comparison with those excluded (p=0.10), and no significant difference existed when the prevalence of smoking and water damage or mould at home was considered.

Table 2 shows the distribution of NO_2 levels as mean values and percentiles for cases and noncases separately. The overall winter half-yr concentration mean level was 18 $\mu g \cdot m^{-3}$ in total, 19 $\mu g \cdot m^{-3}$ in Gothenburg and Umeå and 15 $\mu g \cdot m^{-3}$ in Uppsala. When all subjects were included in the analysis, the onset cases had a higher mean level of NO_2 outside the home compared with the noncases (p=0.03), while there was no significant difference for incident cases (p=0.12).

Table 3 shows the distribution of onset and incident cases in each of the exposure categories based on the distance to the nearest major road. 146 onset cases and 68 incident cases could be classified based on the distance to the nearest major road. Of these, 135 onset cases and 64 incident cases had information on all covariates and could be included in the fully adjusted analysis. The cases occurred among 4,460 subjects with all data needed for inclusion in the adjusted model.

TABLE 3 The number of cases and noncases for two definitions of asthma in relation to the distance to the nearest major road

Distance to major road#	Onset asthma		Incident asthma	
	Cases	Noncases	Cases	Noncases
⩾50 m	129	4370	58	4441
<50 m	17	220	10	227

#: ⩾8,000 vehicles per 24 h.

The analysis of the relationship between onset and incident cases of asthma and the levels of NO_2 outside the home showed a positive and significant coefficient, indicating an increased risk of developing asthma among adults with increasing levels of NO_2 outside the home (table 4). The OR in the fully adjusted model was 1.46 (95% confidence interval (CI) 1.07–1.99) for the onset definition and 1.54 (95% CI 1.00–2.36) for the incident definition of cases per 10 $\mu g \cdot m^{-3}$ increase

TABLE 4 Associations between exposures to nitrogen dioxide (NO_2), distance to nearest major road and the onset and incidence of asthma

	Onset asthma		Incident asthma	
	OR	95% CI	OR	95% CI
Crude#				
NO_2 per 10 $\mu g \cdot m^{-3}$	1.39	1.05–1.84	1.36	0.92–2.02
Distance to nearest major road <50 m¶	2.81	1.66–4.76	3.55	1.78–7.01
Fully adjusted+				
NO_2 per 10 $\mu g \cdot m^{-3}$	1.46	1.07–1.99	1.54	1.00–2.36
Distance to nearest major road <50 m¶	2.92	1.70–4.98	3.88	1.93–7.82

OR: odds ratio; CI: confidence interval. #: includes the same population as in the fully adjusted model; ¶: yes *versus* no, major road is defined as ⩾8,000 vehicles per 24 h; +: including city, sex, body mass index, age, smoking history, water damage or mould in the home at any time during the last 8 yrs.

TABLE 5 Results from the adjusted logistic regression model, describing the relationship between nitrogen dioxide and the risk of onset and incident asthma among males and females and subjects with and without hay fever and wheeze

Strata	Onset asthma			Incident asthma		
	OR#	95% CI	p-value for interaction	OR#	95% CI	p-value for interaction
Females	1.30	0.96–2.04	0.71	1.67	0.98–2.74	0.63
Males	1.57	0.97–2.52		1.32	0.64–2.74	
Hay fever	1.31	0.85–2.04	0.58	1.15	0.59–2.24	0.30
No hay fever	1.55	1.03–2.35		1.79	1.04–3.05	
Wheeze	1.62	1.03–2.57	0.53	2.08	1.12–3.87	0.18
No wheeze	1.34	0.90–2.00		1.19	0.66–2.12	

OR: odds ratio; CI: confidence interval. #: per 10 $\mu g \cdot m^{-3}$ from the fully adjusted model including city, sex, body mass index, age, smoking history and water damage or mould in the home at any time during the last 8 yrs.

in NO_2 level (see online supplementary material table 4a for results for covariates). When NO_2 was grouped into tertiles there was a dose–response pattern, with higher estimates for the third tertile (OR_{onset} 1.58, 95% CI 0.96–2.6; $OR_{incident}$ 2.06, 95% CI 0.98–4.32) than for the second tertile (OR_{onset} 1.17, 95% CI 0.70–1.94; $OR_{incident}$ 1.77, 95% CI 0.86–3.64), and with the first tertile used as a reference.

There was a significant risk for developing asthma when a participant lived <50 m from a major road. The OR for onset and incident asthma was 2.92 (95% CI 1.70–4.98) and 3.88 (95% CI 1.93–7.82), respectively (see online supplementary material table 4b for results for covariates).

We do not have the full residential history. However, when excluding the large proportion of persons with a different address at follow-up and inclusion (~60%), relative risks tended to increase. Including SEI in the model marginally changed the NO_2 estimate. The mean NO_2 level in the five SEI categories was similar: 17.1, 17.6, 17.5, 18.1 and 17.3 $\mu g \cdot m^{-3}$.

Separate estimates were made for males and females, participants with and without hay fever, and with and without reported wheeze in 1990 (table 5). There were no significant effects on the relationship between NO_2 and asthma associated with sex, hay fever or wheeze, which was true for both the onset and the incident asthma definition (onset: p=0.71, p=0.58 and p=0.53 and incident: p=0.63, p=0.30 and p=0.18, respectively).

DISCUSSION

This prospective study of young adults, aged 20–44 yrs at inclusion, shows that the risk of developing asthma increases with the levels of NO_2 outside the home.

Although the literature is scarce and not unanimous, our results confirm the findings of previous longitudinal studies among adults suggesting that air pollution is a risk factor for asthma [10, 11, 22, 23]. Studies based on the nonsmoking cohort of the Seventh-day Adventists from California reported associations between ozone and particulate matter and asthma. This study assessed the exposure by interpolating levels from fixed monitoring stations. A recent study showed incident asthma among adults in the ECRHS to be significantly related to estimated values of NO_2 [23]. A part of our study population was included in the ECRHS study and although the previous study used a less detailed exposure model, the results were strikingly similar. The Swedish case–control study showed a nonsignificant relationship between incident asthma in adults and proximity to high traffic flow areas, while the same tendency could not be shown for NO_2 [11]. These results are similar to the findings in the current study except that we now find significant results for both NO_2 and the more simple proximity indicator of exposure. Some previous prevalence studies have shown no significant relationship between asthma and objective measures of exposure to vehicle exhaust [6, 24]. Results comparisons between studies built on different designs and exposure metrics and resolutions are difficult. Our study and other recent findings highlight the need for more longitudinal studies with high-resolution exposure data.

We used two different definitions of asthma. The first (onset) aimed to identify incident cases, but also included subjects that had an onset of asthma symptoms during follow-up related to pre-existing asthma. The cumulative incidence of onset with our definition was 3.0% after 8.2 yrs of follow-up, which is slightly higher than result of 2.1% presented by TORÉN *et al.* [15] for the entire RHINE population using a somewhat different case definition. By including only those cases reporting an age of onset of asthmatic symptoms within the follow-up period, our second definition (incident asthma) becomes more specific towards selecting only true incident cases of asthma. Almost half of the cases available using our wider definition were lost when the stricter definition was applied, resulting in a cumulative incidence rate of 1.5%. As a result, the effect estimate increased but was only borderline significant, which we expected since a more strict definition both lowers the number of cases and the misclassification of cases and noncases. This effect was also observed in the study by JACQUEMIN *et al.* [23] as an increase in the effect estimate when excluding cases with an asthma onset 1 yr before the start of the follow-up. The use of a stricter definition of onset asthma strengthened the effect, which supports the conclusion that the results are due to a real effect of vehicle exhaust on asthma and asthma-related symptoms and not due to misclassification.

Approximately half of onset cases reported wheeze in the initial survey. Wheeze is a known risk factor for asthma and is

thought to be a potential early stage in the development of asthma [15]. One could argue that participants reporting wheeze at inclusion should be excluded on the premise that they are more or less asthmatics. This study, however, showed that 16% (866) of the population at risk reported wheeze in the initial survey, and of these 866 persons ~8% were classified as onset cases of asthma at follow-up. Furthermore, the results from the analysis of interaction showed that there was no significant interaction between wheeze and NO_2.

Adult onset asthma is a heterogenic disease with many factors contributing to different phenotypes of the disease [25]. Despite the fact that many risk factors for asthma have been identified, the actual mechanisms causing the asthma symptoms are still under investigation. The difference between allergic and nonallergic asthma has been widely discussed. Although these two phenotypes show obvious clinical differences, including differences in trigger factors, they seem to share many immunological and pathological mechanisms, meaning that they cannot be fully separated as two different mechanisms causing asthma [26]. In the current study, there was no significant difference in the effect of NO_2 on developing asthma when comparing those who reported hay fever and those who did not. In a selected subsample with a large proportion of symptomatic participants, 60% of the immunoglobulin E positive patients reported hay fever (results not shown). Consequently, the degree to which self-reported hay fever is a good marker of atopy has to be further evaluated before any conclusions can be drawn from these results.

In the present study, NO_2 was used as a marker for vehicle exhaust, which is common in epidemiological studies of vehicle-related air pollution. Previous studies have shown measured levels of NO_2 to be correlated to other vehicle-related air pollutants [27]. The frequent measurement of NO_2 by both local and national authorities has created a large quantity of data at various locations, which is crucial for validation of dispersion models. Most pollutants, such as NO_2 and fine particles, penetrate indoors. The indoor/outdoor ratio for NO_2 in Umeå was 0.4–0.7 [28]. A certain amount of uncertainty exists when using indicators to compare cities or areas because different amounts and patterns of traffic may affect the pollution mix. This is also a problem when comparing results from studies using other measures of exhaust fumes [11]. As we also used proximity to a major road as a more simple measure of exposure, we can conclude that the findings in this study are consistent regarding the direction of the effect.

Dispersion models, in relation to other exposure measures, are seldomly used in this type of study, possibly due to the complexity of the models and the need for large amounts of information regarding emission factors, traffic counts and meteorological data [14, 29]. In this study, the levels of NO_2 were modelled in 50-m squares, which allowed for a high degree of variation in exposure levels between study subjects. We used the pollution levels outside homes to indicate the exposure to vehicle exhaust, which is an approximation of the actual exposure, best shown by personal measurements. However, recent studies have evaluated alternative measures of living in close proximity to traffic against personal measurements and have shown reasonable agreement [30]. In comparison with distance to closest major road, the results from the dispersion model accounts for all nearby sources and does not explicitly focus only on the major roads as the source of exposure. Large roads are the most influential in dispersion models but other factors modify the levels, *e.g.* wind patterns and other factors influencing the dispersion.

The dispersion models did not include the outskirts of the municipalities, which posed a limitation to the study by reducing the number of subjects that could be included in the analysis. The difference in the proportion of incident asthmatics was only marginal when comparing those with and without a modelled value of NO_2.

Although one of the main strengths in the current study design is the possibility to follow subjects prospectively over a period of time, studying the development of asthma among adults adds uncertainties regarding their exposure before the initial survey. We used the exposure levels at baseline to represent the exposure during the entire follow-up. Among incident cases, 70% reported onset between 1990 and 1995. This, coupled with the premise that the induction of asthma is not related to a very short period of exposure, was the motivation for using 1990 as the year for exposure modelling.

In summary, this prospective cohort study adds to the growing evidence that vehicle exhaust may not only worsen existing respiratory symptoms but also induce asthma. Although this study does not indicate which specific part of the vehicle exhaust causes the effects, the results demonstrate the general impact of vehicle exhaust on development of asthma in adults.

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