

Traffic-related air pollution and incident asthma in a high-risk birth cohort

Chris Carlsten,¹ Anne Dybuncio,¹ Allan Becker,² Moira Chan-Yeung,¹ Michael Brauer¹

¹Department of medicine, University of British Columbia, Vancouver, Canada

²Department of pediatrics, University of Manitoba, Winnipeg, Canada

Correspondence to

Chris Carlsten, Vancouver General Hospital, 2775 Laurel Street, 7th Floor (The Lung Center), Vancouver, BC V5Z 1M9, Canada; chris.carlsten@vch.ca

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ABSTRACT

Objectives The risk of incident asthma and bronchial hyper-reactivity associated with early life exposure to traffic-related air pollution has not been fully elucidated. We aimed to evaluate the hypothesis that the risk of new onset asthma is positively associated with early exposure to traffic-related air pollution in a well-characterised high-risk birth cohort.

Methods Infants at high-risk for asthma were recruited for an intervention study. Birth year exposures to NO, NO₂, black carbon and PM_{2.5} were estimated by land use regression. At 7 years of age, asthma was assessed by a paediatric allergist and bronchial hyper-reactivity was measured by methacholine challenge. Associations between exposures and outcomes were analysed by stepwise multiple logistic regression, adjusted for potential confounding variables.

Results Exposure estimates were available for 184 children; 23 were diagnosed with asthma and 68 with bronchial hyper-reactivity. The IQR (4.1 µg/m³) of birth year PM_{2.5} was associated with a significantly increased risk of asthma (OR 3.1, 95% CI 1.3 to 7.4) and with a trend to increased risk of bronchial hyper-reactivity. Similar findings were noted in association with NO and NO₂, while black carbon did not appear to confer increased risk.

Conclusion Modest elevations in exposure to some traffic-related air pollutants during the year of birth are associated with new onset asthma assessed at age 7. That significant associations were revealed in spite of a limited sample size emphasises the strengths of a high-risk birth cohort model, along with individual air pollution exposure estimates and well-characterised data on covariates and outcomes.

INTRODUCTION

It is generally appreciated that traffic-related air pollution is associated with asthma, but this has been most commonly demonstrated for asthma exacerbation or asthmatic symptoms.^{1–3} Evidence for traffic-related air pollution-associated asthma initiation is considerably less developed. Recently, the association between ambient air pollution and de novo asthma has been demonstrated in older children⁴ and adults.^{5–6} The study of a birth cohort has the distinct advantage of eliminating misclassification regarding the presence or absence of asthma at study initiation. Additionally, the use of birth cohorts allows consideration of exposures during the period of most intense immunological and anatomical development and therein provides insights of fundamental relevance to public health and preventive medicine.^{7–8}

The few studies to have so considered this relationship between traffic-related air pollution

What this paper adds

- ▶ Traffic-related air pollution is associated with asthma exacerbation, yet the association between traffic-related air pollution and new onset asthma is not well understood.
- ▶ This relationship has not previously been explored in the specific context of a high-risk population, although our ability to prevent incident asthma may depend on such understanding.
- ▶ Our data suggest an increased risk of incident asthma in high-risk children exposed to elevated traffic-related air pollution in the year of birth.
- ▶ This supports the notion that policies related to air pollution should consider effects most demonstrable in vulnerable populations

and incident asthma have been in populations of average-risk children. Morgenstern and colleagues⁹ followed 3066 German children from birth to age 6. They noted an increased risk of 'asthmatic bronchitis' (by parental questionnaire) with fine particulate matter (PM_{2.5}), although no association was found with nitrogen dioxide (NO₂). Brauer and colleagues¹⁰ documented new asthma at 4 years of age in 3538 children followed from birth in the Netherlands. They noted an increased risk of doctor-diagnosed asthma associated with both NO₂ and PM_{2.5}; similar findings were noted in follow-up of this cohort to 8 years of age.¹¹ In contrast to these studies, at least one other study¹² has failed to demonstrate an association between asthma (as assessed by parental questionnaire) and ambient nitrogen oxides.

There is considerable interest in understanding the risk due to environmental exposures within vulnerable populations. Children are among those so considered as particularly sensitive to toxic inhalants¹³; those children with first-degree relatives with asthma are known to have a considerably increased risk of asthma.¹⁴ Therefore, the objective of this study was to consider a population that encompasses both of these vulnerabilities; we hypothesised that the risk of new onset asthma would be positively associated with early exposure to traffic-related air pollution in a well-characterised high-risk birth cohort.^{15–16}

METHODS

Study subjects

As previously described,¹⁵ 272 high-risk infants from Vancouver were recruited (via their mothers,

Original article

upon registration at a maternity hospital) and randomised into usual care and intervention arms for a study of primary prevention of asthma. High risk was defined as having, according to parental report, at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic disease (atopic dermatitis, seasonal or perennial allergic rhinitis or food allergy). The multi-faceted intervention arm included avoidance of house dust mites, pet allergens and environmental tobacco smoke as well as encouragement of breast feeding (with formula supplementation if necessary) and delayed introduction of solid foods into the child's diet,¹⁵ the effect of which has been previously described.¹⁷

Overall study design

The main objective of our study was to determine the association between early life exposure to traffic-related air pollution and new onset asthma, in the context of a high-risk birth cohort. To do so, we estimated birth year (1995) exposure to NO, NO₂ and PM_{2.5} by land use regression and obtained paediatric allergist assessment of asthma diagnosis, along with methacholine-based measurements of airway reactivity, at 7 years of age.

Methods and analysis

Birth year exposures to traffic-related outdoor NO, NO₂ and PM_{2.5} were estimated using the residential address of each subject and a land use regression model, as previously developed, described and validated.¹⁸ Briefly, land use regression was performed as follows. NO, NO₂, black carbon and PM_{2.5} were directly sampled at multiple sites throughout the study area in the spring and autumn of 2003; black carbon data were collected at 39 sites, PM_{2.5} data at 25 sites, and NO and NO₂ data at 116 sites. Fifty-five variables describing each site in terms of location, surrounding land use, population density and traffic patterns were generated in a geographical information system. Linear regression was used to model concentrations of the pollutant as a function of the most predictive variables, and the geographical information system was used to render the model as high resolution (10 m) maps of annual (2003) average concentrations across the study region. As these maps describe annual averages for 2003, air pollution estimates for 1995 were generated by adjusting for temporal trends using the regulatory ambient air quality monitoring network data. Specifically, for each land use regression model, the corresponding monitoring network data for each pollutant were fit with monthly dummy variables and a covariate for linear trend (Times Series Forecasting System, SAS v 9.1). From these models, adjustment factors were applied to each surface to estimate the 1995 annual average. Using these data, we then computed individual subject exposure estimates based on their residential address at birth. This approach is supported by recent evidence of the stability of land use regression-based exposure estimates over several years in diverse settings.^{19 20}

Skin testing, performed at 1 year of age, was considered positive for atopy if both the histamine control and at least one of the panel of 12 common antigens, administered by skin prick, yielded a wheal of at least 3 mm.¹⁵

Outcomes were assessed at 7 years of age. The primary outcome was a diagnosis of asthma upon evaluation by a single paediatric allergist, who was blinded to the subject's group assignment, residential and pollution exposure information, and who did not provide healthcare to the child or their family. Asthma was defined as at least two or more distinct episodes of cough (each lasting at least 2 or more weeks), at least two distinct episodes of wheeze (each lasting at least 1 or more

weeks), plus at least one of the following: nocturnal cough (at least once a week) in the absence of a cold, hyperpnoea-induced cough or wheeze at any time, or response to treatment with β -agonist and/or anti-inflammatory drugs. Secondary outcomes were bronchial hyper-reactivity, defined as a provocative concentration of methacholine resulting in a 20% decrease in forced expiratory volume from baseline (PC₂₀) of ≤ 2 mg/ml, and asthma defined as having both allergist-diagnosed asthma and a PC₂₀ of ≤ 2 mg/ml. For bronchial hyper-reactivity as the endpoint, sensitivity analysis at a higher PC₂₀ cut-off of 8 mg/ml, more commonly applied to adults,²¹ was performed. The paediatric allergist was blinded to the results of the methacholine challenge in his assessment of asthma, as such data are rarely available in typical clinical scenarios at 7 years of age.

All statistical analyses were performed using Stata, v 9.0. Fisher's exact test was used to evaluate potential differences between subsets of children (presented in table 1). The associations between exposure estimates and outcome measures were analysed by multiple logistic regression analysis, allowing an estimate of the ORs and 95% CIs associated with an IQR increase for each pollutant. For consistency in interpretation of ORs, and because IQRs did not differ considerably between analytical subgroups (data not shown), the IQRs determined from the total data of subjects were used in all presentations of ORs. We selected a number of potential confounders (maternal education, history of asthma (in mother, father or siblings), atopic status at 1 year) and entered these stepwise as covariates into regression models, with a threshold significance of $p < 0.05$ for entry into the model, while intervention status was forced into the model. A secondary model was run in which all covariates were included. The following sensitivity analyses were also performed: (a) for both asthma and bronchial hyper-reactivity, stratifications by intervention, gender, racial and atopic status, (b) quartile analyses for both asthma and bronchial hyper-reactivity, and (c) for asthma alone, stratification by bronchial hyper-reactivity status.

This study was approved by the Clinical Research Ethics Board at the University of British Columbia.

RESULTS

Overall, 233 of the cohort members from Vancouver were successfully contacted by telephone at 7 years of age; of these, 47 (21.2%) refused or were unable to travel to our study centre for paediatric allergist assessment. Therefore, 186 children were

Table 1 Characteristics of children successfully contacted at 7 years of age compared with Vancouver-based children in the original cohort

	With paediatric assessment (N = 186), n (%)	Without paediatric assessment (N = 47), n (%)	Original Vancouver cohort (N = 267), n (%)
Male	97 (52.2)*	17 (36.2)	129 (48.3)
Caucasian	130 (69.9)*	40 (85.1)	191 (71.5)
Family history of asthma	135 (72.6)	40 (85.1)	203 (76.0)
Maternal post-secondary education	155 (83.3)	41 (87.2)	227 (85.0)
Intervention group	100 (53.8)	27 (57.4)	138 (51.7)
Atopic at 12 months	50 (27.5)	7 (17.1)‡	62 (25.3)§

* $p < 0.05$ when compared to those without paediatric assessment.

†Percentages based on total subjects with available data for a given characteristic.

‡41/47 had a skin test done at 12 months.

§251/267 had a skin test done at 12 months.

available for follow-up at 7 years of age, representing 63% of the Vancouver cohort entering the study at its onset. Table 1 describes the key characteristics of those who returned for assessment and those who were unable to or refused; data for the Vancouver-based children in the original cohort are also provided. While those with paediatric assessment did not differ significantly from those in the original cohort, those not assessed by the allergist in this follow-up were disproportionately female, Caucasian, with a family history of asthma, born to well-educated mothers and non-atopic; all of these factors were included in regression models. Dog ownership was rare (4.9% of homes at any point in year 1) and did not alone significantly predict any of the endpoints (data not shown).

Land use regression-based estimates were available for 184 children, of whom 23 (12.5%) were diagnosed with asthma. The mean (SD) values of each pollutant, each in $\mu\text{g}/\text{m}^3$ (except for black carbon which is in absorbance units (AU) of 10^{-5} m), in total and then stratified by asthma status were as follows (figure 1): $\text{PM}_{2.5}$ 5.6 (2.6) (5.4 in controls, 7.0 in asthmatics), NO 35.7 (14.8) (35.2 in controls, 39.4 in asthmatics), NO_2 32.6 (5.9) (32.4 in controls, 34.4 in asthmatics) and black carbon 1.6 (1.2)

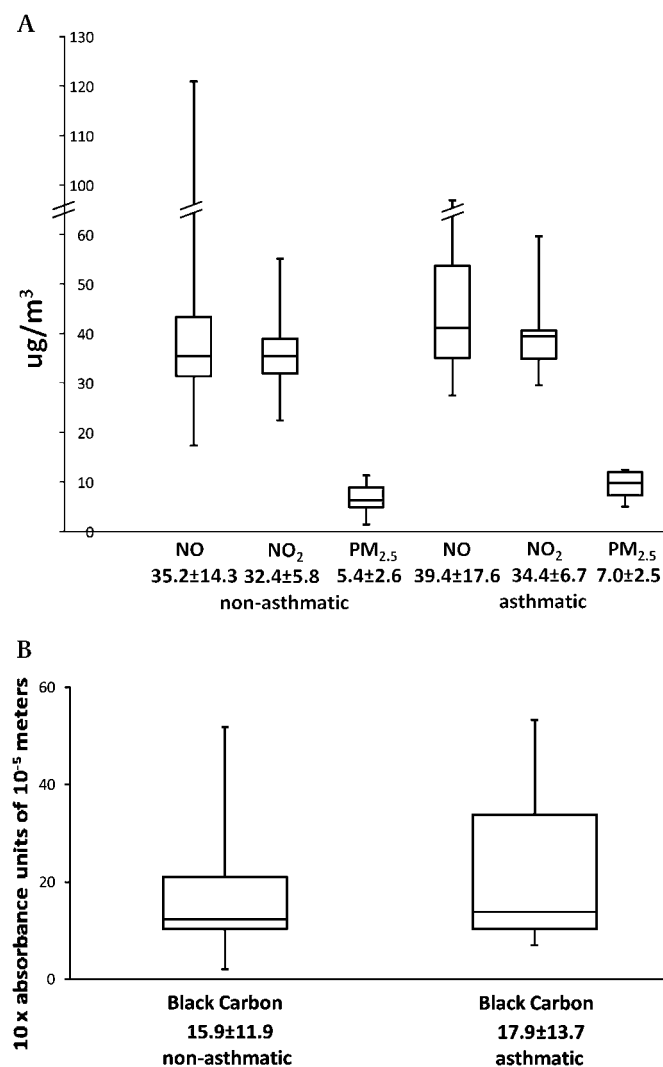


Figure 1 Characteristics of exposure estimates for the study cohort according to asthma status. The bars represent minimum and maximum values, the box represents the first and third quartile and the line within the box represents the median. (A) NO, NO_2 , $\text{PM}_{2.5}$; (B) black carbon.

(1.6 in non-asthmatics, 1.8 in asthmatics); IQRs for each were 4.1, 12.7, 7.2 and 1.2, respectively. Pearson correlations between pollutant measures were as follows: NO– NO_2 , $r=0.8$; NO_2 – $\text{PM}_{2.5}$, $r=0.7$; NO– $\text{PM}_{2.5}$, $r=0.5$; black carbon–NO, $r=0.5$; black carbon– NO , $r=0.3$; and black carbon– $\text{PM}_{2.5}$, $r=0.2$.

Table 2 describes the risk for asthma, at 7 years of age, associated with the IQR increase in the estimated exposure to each pollutant in the year of birth. Among these outdoor air pollutants, risk of asthma development is significantly ($p<0.05$) increased in association with increased $\text{PM}_{2.5}$, as noted in table 2. Although $\text{PM}_{2.5}$ had the largest effect estimates, there was a trend to similarly increased risk for asthma in association with an IQR increase in the levels of NO and NO_2 , but much less so for black carbon in the total group and control subgroup. These results did not change significantly when potential confounding variables were included in the models. When stratified by gender and by Caucasian (versus non-Caucasian) status, there was a suggestion of increased risk in males and Caucasians (data not shown).

Data for the secondary endpoint bronchial hyper-reactivity were available for 169 children; bronchial hyper-reactivity was present in 40% of these children at 7 years of age. There was little risk association between bronchial hyper-reactivity and traffic-related air pollution in terms of NO or NO_2 IQRs (respective ORs 1.1, 95% CI 0.8 to 1.5 and 1.0, 95% CI 0.6 to 1.5) or of black carbon IQR, but there was an increased risk of borderline significance associated with $\text{PM}_{2.5}$ IQR (OR 1.4, 95% CI 1.0 to 2.1). The use of higher PC_{20} cut-offs did not significantly change these results. When stratified by bronchial hyper-reactivity status, the risk of asthma associated with $\text{PM}_{2.5}$ was increased in those 68 subjects with bronchial hyper-reactivity (OR 15.5 (95% CI 1.9 to 109.0) per IQR increase in $\text{PM}_{2.5}$) but not in those 101 subjects without bronchial hyper-reactivity; for neither NO, black carbon nor NO_2 did this stratification reveal a subgroup at significant risk.

There were 13 children with both allergist-diagnosed asthma and bronchial hyper-reactivity ($\text{PC}_{20} \leq 2 \text{ mg}/\text{ml}$). The risk for such dual conditions at year 7 associated with the IQR in estimated exposure to each pollutant in the year of birth contrasted somewhat with the risks, noted above, for asthma alone. Notably, each of the risk estimates (for each pollutant and for each group (total, control and intervention) was somewhat increased in children with both conditions relative to those having defined asthma by allergist diagnosis alone. In particular, the risks associated with NO in both the total and control groups achieved statistical significance (ORs 1.8, 95% CI 1.1 to 2.9 and 2.5, 95% CI 1.2 to 5.2, respectively), the risk associated with NO_2 in the total group achieved borderline statistical significance (OR 2.3, 95% CI 1.0 to 5.1; $p=0.05$) and the $\text{PM}_{2.5}$ -associated OR, including the lower end of the CI, increased to 14.1 although with a wide CI (2.2 to 88.8), reflecting instability in this estimate due to the small number of children with both conditions. The risk associated with black carbon remained insignificant.

Regarding analyses by exposure quartile, risk for asthma increased monotonically with increasing exposure quartiles for NO and $\text{PM}_{2.5}$. No such clear dose–response trend was evident for NO_2 , although risk estimates for the second and higher quartiles were elevated relative to the first quartile. While there was no clear dose-related effect on bronchial hyper-reactivity risk alone, the risk for the combined condition of allergist-diagnosed asthma and bronchial hyper-reactivity was most elevated in the higher exposure quartiles (table 3). Given the relatively attenuated risks noted above in association with black carbon, black carbon quartiles were not included in this analysis.

Table 2 ORs* (95% CIs) for allergist-diagnosed asthma, per IQR increase in to outdoor NO, NO₂, black carbon and PM_{2.5}

Pollutant (IQR)	NO (12.7 µg/m ³)	NO ₂ (7.2 µg/m ³)	Black carbon (1.2 AU)	PM _{2.5} (4.1 µg/m ³)
Total (n=184)	1.2 (0.9 to 1.7)	1.5 (0.9 to 2.5)	1.1 (0.7, 1.9)	3.1 (1.3 to 7.4)
Control (n=84)	1.7 (1.0 to 2.8)	1.9 (0.9 to 4.0)	1.2 (0.6, 2.3)	4.1 (1.2 to 13.8)
Intervention (n=100)	0.8 (0.4 to 1.6)	1.3 (0.6 to 2.9)	1.1 (0.5, 2.5)	2.1 (0.6 to 7.1)

NO, nitric oxide; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter of mean aerodynamic diameter ≤ 2.5 µm.

*ORs for total group adjusted for intervention group, atopy at 12 months, ethnicity, gender, mother, father or sibling history of asthma, and maternal post-secondary education.

IQR, interquartile range, based on data from all subjects.

DISCUSSION

In children at high risk for asthma, exposure to elevated PM_{2.5}, even at relatively low levels, is associated with risk of new onset asthma. To our knowledge, this study is the first to have used a high-risk birth cohort to examine the effect of traffic-related air pollution on incident asthma and one of the first birth cohort analyses associating traffic-related air pollution with incident asthma in North America. The use of a high-risk design enriches the cohort for asthma cases and empowers the study to detect effect even with a relatively modest sample size. Compared to a study of children drawn from the general population that yielded similar risk estimates,¹⁰ our high-risk population had three times the prevalence of asthma. Other strengths of this study, to which our positive results likely are in part attributable, include the use of a unique and blinded paediatric allergy specialist to administer a structured interview for the clinical diagnosis of asthma; it has been shown that allergy specialists' diagnoses differ considerably from those of generalists.²² Furthermore, the use of land use regression to obtain more precise individual exposure estimates may account in part for our ability to document significant risk in this population.

The sensitivity analyses on the risk of asthma are supportive of the overall findings, in particular the finding that asthma risk was greatest in the control subset and that this was true for each pollutant, although most clearly apparent for PM_{2.5}. There was concern that the intervention, in spite of having been accounted for in multivariate regression, could distort analytical results, yet

this concern is moderated in the control group subset analysis. Furthermore, the finding of increased risk in the control group is concordant with the hypothesis of synergy between allergens and non-allergen pollutants.²³ In previous analyses, we have shown that exposures to classical aeroallergens (ie, dog allergen) that could so synergistically interact with particulate matter or nitrogen oxide exposure were reduced by the study intervention and were consequently higher in the control group.¹⁷ One might further speculate on why the control group demonstrated higher risk. For example, it is possible that breast feeding (part of the intervention) in some way protected against asthma. However, our study design does not allow formal testing for such hypotheses. While it is possible that unmeasured confounding could affect our results, we have tried to limit this by our consideration and inclusion, in analyses, of covariates.

That the association with asthma was stronger for PM_{2.5} than for nitrogen oxides reflects a pattern noted by the most similar prior studies to date^{9 10} and thereby bolsters the suggestion that the particulate pollution related to traffic may be somewhat more potent in terms of asthma initiation. This may have important public health, policy and regulatory implications and so should be further investigated.

The suggestion of increased bronchial hyper-reactivity risk associated with PM_{2.5} in the context of a birth cohort, although of borderline statistical significance, is particularly noteworthy in that it is rare to obtain such data at this age; one prior similar analysis did not find increased risk.¹¹ The risk of bronchial hyper-reactivity associated with each of the measured pollutants was modest relative to that noted for asthma. There are several possible explanations for this. The most likely reason for the discrepancy between traffic-related air pollution-associated risk of asthma versus that of bronchial hyper-reactivity is that the diagnosis of asthma is a clinical one reflecting a complex set of pathophysiological processes that, in some, are highlighted by active inflammation rather than airway reactivity alone.²⁴ This notion is supported by the markedly increased risk estimate (admittedly, with a large CI) for the condition of both paediatrician-diagnosed asthma and bronchial hyper-reactivity. An alternative explanation is that there was a bias towards over-diagnosis of asthma, disproportionately in those with higher traffic-related air pollution levels, but we can find no credible hypothesis to support such a bias in this blinded clinical evaluation. Regardless, evaluation of risk associated with the condition of having both allergist-diagnosed asthma and bronchial hyper-reactivity, perhaps the most robust definition of clinically-relevant asthma, showed the most pronounced traffic-related air pollution-related risk.

Although attenuated by the above-noted strengths, the greatest study limitation is probably the modest sample size, which limits precision in effect estimates. Notably, however, even the lower confidence limit for the risk of asthma associated with the PM_{2.5} IQR (1.3) is of significant public health concern and is remarkably consistent with estimates from several studies

Table 3 Risk (OR† (95% CI)) of asthma, bronchial hyper-reactivity (BHR) and both conditions by quartile (relative to first quartile) for NO, NO₂ and PM_{2.5}

	Asthma	BHR (PC ₂₀ ≤2)	Asthma and BHR
NO			
≤27.7	1	1	1
27.7–32.4	0.8 (0.2 to 3.3)	1.0 (0.4 to 2.4)	2.1 (0.3 to 15.1)
32.4–40.3	1.4 (0.4 to 5.2)	1.1 (0.5 to 2.6)	1.8 (0.2 to 12.8)
>40.3	1.8 (0.5 to 6.1)	1.0 (0.4 to 2.2)	3.3 (0.5 to 20.5)
NO ₂			
≤28.4	1	1	1
28.4–32.2	1.9 (0.3 to 5.7)	0.8 (0.3 to 2.0)	0.9 (0.1 to 7.7)
32.2–35.6	3.4 (0.8 to 14.0)	0.8 (0.3 to 1.9)	2.3 (0.4 to 15.1)
>35.6	2.1 (0.5 to 8.4)	0.7 (0.3 to 1.7)	3.1 (0.5 to 19.3)
PM _{2.5} *			
≤3.70	1	1	1
3.70–5.11	2.3 (0.4 to 13.4)	0.7 (0.3 to 1.7)	—
5.11–7.79	3.4 (0.6 to 18.7)	1.5 (0.6 to 3.5)	4.9 (0.8 to 29.5)
>7.79	7.0 (1.4 to 36.0)	1.4 (0.6 to 3.5)	11.7 (2.1 to 65.5)

NO, nitric oxide; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter of mean aerodynamic diameter ≤2.5 µm.*Analysis performed based on lnPM_{2.5} given skewed distribution of PM_{2.5}; equivalent quartiles presented here.

†ORs adjusted for intervention group, atopy at 12 months, ethnicity, gender, mother, father or sibling history of asthma, and maternal post-secondary education.

with larger sample sizes that also used land use regression to assess traffic-related air pollution exposure as summarised by a recent report.²⁵ Our population was at higher risk for asthma than a population-based cohort in the same geographical area using the same land use regression model²⁶ and by Brauer *et al* in a larger birth cohort¹⁰; this may contribute to the higher overall estimate of risk in our study. Another potential limitation is extrapolation of the land use regression-based estimates over time; however as previously noted, recent evidence suggests that such extrapolation is reasonable over relatively few years as in our study.^{19 20} Although it appears that there have not been major changes in the road network between 1995 and 2003, this issue of temporal stability of land use regression models is a subject of current research by our group as well as others.

In summary, the IQR of PM_{2.5} (4.1 µg/m³) among children with a family history of asthma in Vancouver, British Columbia was associated with increased risk of new-onset asthma (OR 3.1, 95% CI 1.3 to 7.4) and a suggestion of increased risk of bronchial hyper-reactivity. This has important implications for public health, particularly regarding the protection of sensitive populations regarding ambient air pollution. The pollutant inter-quartile ranges in our study are modest by international standards but similar to those in related European studies,^{6 7} suggesting that even current ambient traffic-related air pollution levels in the developed world may require further control.

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Competing interests None.

Ethics approval This study was conducted with the approval of the University of British Columbia Clinical Research Ethics Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Trasande L**, Thurston G. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol* 2005;**115**:689–99.
2. **Schildcrout J**, Sheppard L, Lumley T, *et al*. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. *Am J Epidemiol* 2006;**164**:505–17.
3. **McCreanor J**, Cullinan P, Nieuwenhuijsen M, *et al*. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;**357**:2348–59.
4. **Jerrett M**, Shankardass K, Berhane K, *et al*. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008;**116**:1433–8.
5. **Modig L**, Torén K, Janson C, *et al*. Vehicle exhaust outside the home and onset of asthma among adults. *Eur Respir J* 2009;**33**:1261–7.
6. **Jacquemin B**, Sunyer J, Forsberg B, *et al*. Association between modelled traffic related air pollution (NO₂) and asthma score in ECHRS. *Eur Respir J* 2009;**34**:834–42.
7. **Frank J**, Di Ruggiero E, McInnes R, *et al*. Large life-course cohorts for characterizing genetic and environmental contributions: the need for more thoughtful designs. *Epidemiology* 2006;**17**:595–8.
8. **Martinez FD**. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009;**6**:272–7.
9. **Morgenstern V**, Zutavern A, Cyrys J, *et al*. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008;**177**:1331–7.
10. **Brauer M**, Hoek G, Smit H, *et al*. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007;**29**:879–88.
11. **Gehring U**, Wijga AH, Brauer M. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010;**181**:596–603.
12. **Melen E**, Nyberg F, Lindgren C, *et al*. Interactions between GSTP1, TNF, and traffic related air pollution for development of childhood allergic disease. *Environ Health Perspect* 2008;**116**:1077–84.
13. **Landrigan PJ**. Children as a vulnerable population. *Int J Occup Med Environ Health* 2004;**17**:175–7.
14. **Burke W**, Fesinmeyer M, Reed K, *et al*. Family history as a predictor of asthma risk. *Am J Prev Med* 2003;**24**:160–9.
15. **Chan-Yeung M**, Manfreda J, Dimich-Ward H, *et al*. A randomized clinical trial on the effectiveness of a multifaceted intervention measures in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med* 2000;**154**:657–63.
16. **Becker A**, Watson W, Ferguson A, *et al*. The Canadian primary prevention of asthma study—outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;**113**:650–6.
17. **Chan-Yeung M**, Ferguson A, Dimich-Ward H, *et al*. Effectiveness of intervention measures in reducing allergen levels in a primary prevention of asthma study. *Ann Allergy Asthma Immunol* 2002;**88**:52–8.
18. **Henderson S**, Beckerman B, Jerrett M, *et al*. Application of land use regression to estimate long-term concentrations of traffic-related nitrogen oxides and fine particulate matter. *Environ Sci Technol* 2007;**41**:2422–8.
19. **Eeftens M**, Beelen R, Brunekreef B, *et al*. Extrapolation of land-use regression models in time. *Epidemiology* 2009;**20**:S69.
20. **Porta D**, Cesaroni G, Badaloni C, *et al*. Nitrogen dioxide spatial variability in Rome (Italy): an application of the lur model over a decade. *Epidemiology* 2009;**20**:S121.
21. **Godfrey S**, Springer C, Bar-Yishay E, *et al*. Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. *Eur Respir J* 1999;**14**:659–68.
22. **Pellicer C**, Ramirez R, Perpiñá M, *et al*. Gain, loss and agreement between respiratory specialists and generalists in the diagnosis of asthma. *Arch Bronconeumol* 2001;**37**:171–6.
23. **Tunnicliffe W**, Burge P, Ayres J. Effect of domestic concentrations of nitrogen dioxide on airway response to inhaled allergen in asthmatic patients. *Lancet* 1994;**344**:1733–6.
24. **Smith L**, McFadden E. Bronchial hyperreactivity revisited. *Ann Allergy Asthma Immunol* 1995;**74**:454–69.
25. **Health Effects Institute**. *Traffic-related air pollution: a critical review of the literature on emissions, Exposure and Health Effects*. Boston, MA: Health Effects Institute, 2010.
26. **Clark NAC**, Demers PA, Karr CJ. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010;**118**(2):284–90.



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