Asia Pacific **allergy**

Original Article

Residential NO$_2$ exposure is associated with urgent healthcare use in a thunderstorm asthma cohort

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ABSTRACT

Background: There is increasing interest in the role of traffic-related air pollution (TRAP) in allergic airway diseases. Few studies investigate the relationship between TRAP exposure and acute exacerbations of asthma.

Objective: The 2016 Melbourne thunderstorm asthma epidemic provided an opportunity to investigate the relationship between proxies of TRAP exposure and asthma exacerbation requiring urgent healthcare in the previous 12 months.

Methods: Current asthmatics who presented to the 3 Emergency Departments of Melbourne's second-largest health service with epidemic thunderstorm asthma in November 2016 were identified and completed a standard questionnaire. Their residential addresses were geocoded and the annual average nitrogen dioxide (NO$_2$) exposure for each patient was assigned using a validated satellite-based land use regression model. Residential distance to the nearest major road was calculated using ArcGIS. Multivariate logistic regression was used to investigate the relationship between each TRAP proxy and healthcare use, adjusting for potential confounders.

Results: From 263 thunderstorm asthma patients, 88 patients identified with current asthma were analysed. Those with higher mean annual residential NO$_2$ exposure had greater odds of urgent healthcare use in the previous year (odds ratio [OR], 3.45 per one interquartile-range increase; 95% confidence interval [CI], 1.31–9.10; p = 0.01), however distance from major road (OR, 0.95 per 100-m increase; 95% CI, 0.80–1.13; p = 0.57) and living <200 m from a major road (OR, 1.47; 95% CI, 0.29–7.45; p = 0.64) were not significantly associated.

Conclusion: In current asthmatics who presented during an epidemic thunderstorm asthma event, greater exposure to residential NO$_2$ was significantly associated with greater odds of asthma exacerbations requiring urgent healthcare in the previous 12 months.

Keywords: Asthma; Air pollution; Environmental exposure; Environmental pollutants; Bronchial spasm; Hypersensitivity

INTRODUCTION

Worldwide, the increasing burden of allergic respiratory diseases [1, 2] could potentially reflect contemporaneous increases in air pollution from motor vehicles. This observation has led to the hypothesis that traffic-related air pollution (TRAP) may contribute greatly to allergic respiratory diseases.

Key components of TRAP include oxides of nitrogen (nitric oxide [NO] and nitrogen dioxide [NO_2]), black carbon, and fine (<2.5 μm) and ultrafine (<100 nm) particulate matter. TRAP may contribute to airway sensitisation by impairing airway mucosa and mucociliary clearance, thus exposing inhaled allergens to the immune system [3, 4]. As a major pollutant from car exhaust, NO_2 is often used as a proxy for the broader TRAP mixture, alongside other proxies such as residential distance from a major road. A number of studies have already reported the association between NO_2 and incidence of asthma in children [5-7] and adults [8-10].

The current literature demonstrates a link between TRAP exposure and development of childhood asthma [5], long-term asthma risk [11] and increased mortality from respiratory and cardiovascular disease [12-15]. However, there are few studies investigating the relationship between TRAP exposure and acute exacerbations of asthma.

Thunderstorm asthma is defined as acute bronchospasm following a thunderstorm in the local vicinity. The world's largest and most catastrophic thunderstorm asthma epidemic occurred in Melbourne, Australia, on November 2016, precipitating several thousand acute respiratory presentations to hospital emergency departments and was associated with 10 deaths [16, 17]. Aeroallergen sensitisation is an individual susceptibility risk factor for thunderstorm asthma, and Australian episodes have exclusively been attributed to ryegrass pollen allergy [18, 19].

Given that air pollution may potentiate allergic sensitisation, this thunderstorm asthma event provided a unique opportunity to investigate the role of TRAP exposure in this cohort and the risk of asthma exacerbation requiring urgent healthcare in the 12 months prior to the epidemic. This provides an important understanding of the impact of TRAP exposure on healthcare service usage and risk of asthma exacerbation.

Our cross-sectional study aimed to investigate the relationship between proxy markers of TRAP exposure and urgent presentation to healthcare services, in patients with existing asthma who presented to hospital during the thunderstorm asthma epidemic.

MATERIALS AND METHODS

Study population and data collection

The study sample comprised a subset of patients with current asthma from a larger study of the 344 patients who presented to our health service with 'thunderstorm asthma' (**Fig. 1**) [17]. Patients who presented to the 3 Emergency Departments of our health service with asthma symptoms on the 21st or 22nd November 2016 were identified. Follow-up was conducted 1 month after the event over a 2-week period through a standardised telephone questionnaire that included information on asthma diagnosis, symptoms, medication use, healthcare
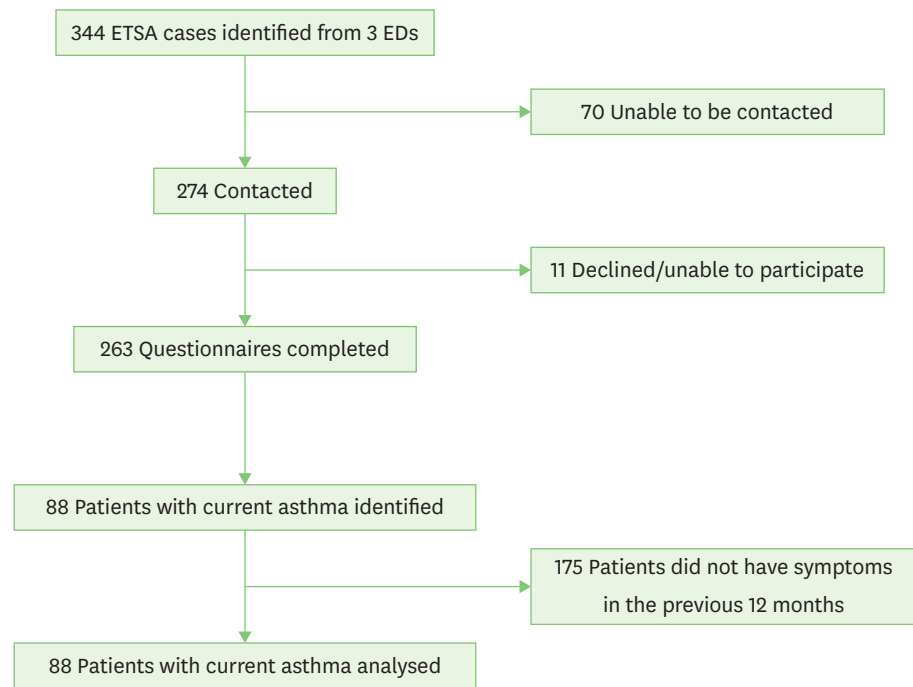
Fig. 1. Consort diagram of epidemic thunderstorm asthma patients. ETSA, Epidemic thunderstorm asthma; ED, Emergency Department.

use, sociodemographic characteristics and residential address. All identified patients were telephoned; those unable to be contacted were sent a paper questionnaire.

Ethical approval for this study was received from Eastern Health Human Research Ethics Committee LR02/2017.

Definition of current asthma
Current asthma was defined as a diagnosis of asthma by a medical practitioner, and having had asthma symptoms in the previous 12 months. Symptoms included wheeze, cough, chest tightness, and shortness of breath, with or without exercise or colds.

Definition of urgent healthcare use
Urgent healthcare use was defined as requiring any of the following medical services within the previous 12 months: urgent general practitioner visit for asthma, hospital or Emergency Department visit for asthma or spending at least one night in hospital for asthma.

Definitions of TRAP exposure measures
Distance from major road
The distance from each participant's residential address to the nearest major road was calculated using ArcGIS v10.1 software (Environmental Systems Research Institute, Redlands, CA, USA). Major roads were defined as those with Australian transport hierarchy codes 301 and 302 according to standard definitions used by the Public Sector Mapping Agencies. These include freeways, highways and arterial roads – roads which are a principal avenue of transport between two cities or key towns [20, 21].

Living <200 m from a major road
Previous studies have demonstrated a decay in levels of most pollutants in TRAP to near-background concentrations at approximately 200 m [22, 23]. Patients were therefore categorised into 2 groups to investigate this relationship: (1) living <200 m and (2) living >200 m from a major road.

NO$_2$ exposure
Mean annual residential NO$_2$ exposures were assigned to each participant's geocoded address through a satellite-based land-use regression (LUR) model [24]. The LUR model estimates mean annual NO$_2$ levels from a combination of predictors including tropospheric NO$_2$ columns observed by satellite, land use and roads. This model has been both internally and externally validated across 68 and 123 different NO$_2$ monitoring sites, respectively, across all Australian states [24, 25]. The model captures 66%–81% of spatial variability in annual NO$_2$ in urban locations, with a prediction error of 19%–25% [24, 25].

Definitions of confounders
We controlled for potential confounders including asthma control, reliever use, preventer use, smoking, and socioeconomic status.

Asthma control was rated categorically from 1 to 5 from not controlled at all to completely controlled in the 4 weeks before the event. Reliever use was rated categorically from 1 to 5 from more frequent use (3 or more times per day) to not at all in the 4 weeks before the event.

Preventer use was rated categorically from 0 to 4 from less frequent use (not prescribed preventers) to more frequent use (5 or more days per week) in the 4 weeks before the event. Smoking was categorically either: never smoked, smoked in the past but not currently, or current smoker.

Area-level socioeconomic status was determined by mapping each patient's residential address to their corresponding Australian Bureau of Statistics index of relative socio-economic advantage and disadvantage [26], which are derived from 25 socio-economic variables collected in the 2011 national census.

Statistical analysis
To investigate differences in mean annual residential NO$_2$ exposure between patients with and without urgent healthcare use, a Mann-Whitney *U* test was first performed comparing the two data sets. The same test was applied to investigate differences in distance from major road between the 2 groups. Additionally, living <200 m from a major road was fitted as a binary categorical variable and a chi-square test was used to investigate its relationship with urgent healthcare use.

Multiple logistic regression models were then fitted to the dataset to determine odds ratios between the independent variables (mean annual residential NO$_2$ exposure, distance to major road and living <200 m from a major road) and the binary dependent variable, urgent healthcare use, adjusting for the potential confounders described previously. An analysis was performed on each confounder separately to examine the effect of each on the univariate model. The final multivariate analysis adjusted for all these confounders.

All statistical analyses were performed using Stata ver. 12 (StataCorp LP., College Station, TX, USA).

RESULTS

Study population

A total of 88 patients with current asthma were analysed from 263 thunderstorm asthma patients. Baseline characteristics of patients with and without urgent healthcare use are displayed in **Table 1**.

Association between NO_2 exposure and urgent healthcare use

As shown in **Table 1**, patients with urgent healthcare use were more likely to have a higher mean annual residential NO_2 exposure, compared to those that did not (p = 0.02). However, while patients requiring urgent healthcare lived closer to major roads (mean, 321 m) compared to those who did not (mean, 415 m) this difference was not statistically significant. Similarly, the binary outcome of living <200 m from a major road was not significantly associated with urgent healthcare use.

The results of the univariate and multivariate logistic regression models are summarised in **Table 2**. Mean annual residential NO_2 exposure was significantly associated with more than a 3-fold increased odds of urgent healthcare use for every one interquartile-range increase (odds ratio [OR], 3.45; 95% confidence interval [CI], 1.31–9.10; p = 0.01). However, neither distance from major road nor living <200 m from a major road were associated with urgent healthcare use (**Table 2**).

Of all potential confounders, reliever use had the greatest effect on the univariate model. Socioeconomic status had minimal confounding effect, as did asthma control.

Table 1. Characteristics of current asthmatics who presented to 3 Emergency Departments during 2016 Melbourne thunderstorm asthma epidemic

Characteristic	Patients with urgent healthcare use (n = 19)	Patients without urgent healthcare use (n = 69)	p value
Age (yr)	40.84 ± 25.7	35.52 ± 18.0	
Male sex	10 (53)	45 (65)	
Preventer use*	12 (63)	14 (20)	
Reliever use[†]	6 (32)	5 (7)	
Well or completely controlled asthma[‡]	9 (47)	56 (81)	
Current smoker	0 (0)	4 (6)	
Socioeconomic class[§]	1,029 (76)	1,043 (64)	
Distance from nearest road	320.57 ± 261.9	414.56 ± 604.7	0.85
Living close to a major road	9	26	0.45
NO_2 exposure	6.74 ± 1.5	5.80 ± 1.7	0.02

Values are presented as mean ± standard deviation or number (%).
NO_2, nitrogen dioxide.
*Preventer use of 5 or more days per week 4 weeks before thunderstorm asthma epidemic. [†]Reliever use of 3 or more times per day 4 weeks before thunderstorm asthma epidemic. [‡]Well or completely controlled asthma 4 weeks before thunderstorm asthma epidemic. [§]Socioeconomic class defined as Index of Relative Socio-Economic Advantage and Disadvantage score, derived from the Australian Bureau of Statistics. This index ranks areas on a continuum from most disadvantaged (low score) to most advantaged (high score).

Table 2. Logistic regression analysis of the association between proxy measures of traffic-related air pollution exposure and urgent healthcare use

Variable	Univariate analysis*		Multivariate analysis[†]	
	OR (95% CI)	p value	OR (95% CI)	p value
Mean annual residential NO_2 exposure[‡]	1.69 (1.02–2.80)	0.04	3.45 (1.31–9.10)	0.01
Distance from major road[§]	0.96 (0.84–1.09)	0.52	0.95 (0.80–1.13)	0.57
Living <200 m from major road	1.49 (0.54–4.14)	0.45	1.47 (0.29–7.45)	0.64

OR, odds ratio; CI, confidence interval; NO_2, nitrogen dioxide.
*Univariate analysis included only the independent variable listed, with the dependent variable, urgent healthcare use. [†]Multivariate analysis adjusted for socioeconomic status, smoking use, reliever use, preventer use and asthma control. [‡]Per one interquartile-range increase. [§]Per 100-m increase.

DISCUSSION

This study contributes to the growing body of evidence demonstrating an association between TRAP exposure and various negative asthma outcomes. Previous studies have demonstrated an association between TRAP exposure and childhood allergic respiratory diseases [5-7], poor lung function and persistent symptoms in adult asthma [20, 27]. This study extends these observations in a cohort of thunderstorm asthma patients and explores associations with asthma exacerbations severe enough to require urgent healthcare utilisation.

We found that thunderstorm asthma patients presenting to our health service with a higher annual mean residential NO_2 exposure were more likely to have experienced asthma exacerbation requiring urgent healthcare in the previous 12 months (OR, 3.45 per one interquartile-range increase; 95% CI, 1.31–9.10; p = 0.01). However, our other proxy markers for TRAP exposure - distance from major road and living <200 m from a major road – had no significant association with urgent healthcare use in our cohort of thunderstorm asthma patients.

Hypotheses exist for air pollutants promoting acute asthma exacerbations through increased oxidative stress resulting in airway sensitisation, impaired mucociliary clearance and mucosal damage of the airway [28]. The role of NO_2 has been reported in a few studies [29-31], with a systematic review summarising significant positive associations in 10 of 11 studies investigating NO_2 and asthma symptoms in paediatric patients [32]. Another pooled study from six European cohorts reported a borderline association between NO_2 and incidence of asthma [8]. Additionally, our study provides evidence that greater NO_2 exposure is also associated with greater odds of asthma exacerbations requiring urgent healthcare use.

We found reliever use the most influential confounder on our initial univariate model. Increased reliever use was associated with increased urgent healthcare use. This is more likely to be potential marker for underlying disease severity and a consequence rather than a cause for increased use of healthcare services. The fact that asthma control was only a mild confounder in our analysis also supports the notion that reliever use is more likely to be a consequence of the association, rather than a cause. However, the role of increased beta-agonist reliever use and its contribution to increased asthma severity and mortality is acknowledged, and reverse causation cannot be entirely excluded in our analysis [33]. There was little confounding from socioeconomic status, making our findings applicable to all social classes.

It has previously been reported that distance from major road and living <200 m may better capture other important constituents of TRAP such as volatile organic compounds, black carbon, fine and ultrafine particles, and freshly-produced pollutants closely associated with reactive compounds that cause negative health outcomes [20, 34]. One potential reason for our result to be nonsignificant in this study is related to the study size. A previous study, for example, examined a sample size of 689 patients to report a positive association between distance from major road and persistent new asthma [20].

Our study has a number of strengths and limitations. A strength is that our cohort is derived from three separate emergency departments in Melbourne's second largest metropolitan public health network. We utilised the largest cohort of epidemic thunderstorm asthma patients reported worldwide. A comprehensive questionnaire was developed and administered in a systematic and consistent method. Furthermore, we derived NO_2 from an

internally and externally-validated national LUR model able to predict NO_2 exposure levels across Australia with low error rates [24].

However, our proxy markers for TRAP—annual mean NO_2 exposure and mean distance from major roads—have limitations. Firstly, distance from major roads may inaccurately measure TRAP when variables altering TRAP levels are not accounted for, such as traffic volume, exhaust composition, climate (including wind, rainfall and humidity), land and topography characteristics [35]. Secondly, whilst we found an association between annual mean residential NO_2 exposure and urgent healthcare use, there may be a different component of TRAP that explains the increase in asthma exacerbations. Other constituents of TRAP, such as particulate matter, may be more relevant and chemically reactive air pollutants in the context of airway damage [36].

Our cross-sectional study examines the relationship between NO_2 exposure and asthma exacerbation across an annual period using patients from the thunderstorm asthma cohort, as opposed to acute NO_2 exposure changes on the day of the epidemic. We did not have a control cohort of people with current asthma in the same geographic location who did not present with thunderstorm asthma with which to compare. Hence, we cannot draw conclusions about acute NO_2 exposure increasing risk of presentation with thunderstorm asthma. However, it adds to the epidemiological evidence of NO_2 exposure increasing risk of recent asthma exacerbation with reference to this particular cohort.

Previous studies investigating environmental factors contributing to thunderstorm asthma strongly suggest a link to grass pollens [28, 37-39] as a cause of allergic respiratory symptoms in presensitised individuals. We do not have data on allergic sensitisation in our cohort, but ryegrass sensitisation was confirmed in almost all thunderstorm asthma patients tested in neighbouring metropolitan health services [18, 19]. One previous retrospective study following a thunderstorm asthma epidemic in London 1994 found only an association between increases of sulphur dioxide the previous day and acute asthma presentations [37]. Further research is required to determine whether acute changes in TRAP exposure is related to asthma exacerbation in thunderstorm asthma epidemics.

In a cohort of thunderstorm asthma patients, those exposed to higher annual average residential NO_2 were more likely to experience asthma exacerbation requiring urgent healthcare in the previous 12 months. A better understanding of this interaction may assist with identifying high-risk asthmatics in regions with higher TRAP to help implement preventative strategies.

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