

Original Article



Residential NO₂ exposure is associated with urgent healthcare use in a thunderstorm asthma cohort

Vivien Wai Yun Lai¹, Gayan Bowatte², Luke David Knibbs³, Kanishka Rangamuwa⁴, Alan Young^{1,4}, Shyamali Dharmage², and Francis Thien^{1,4,*}

¹Monash School of Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia

²Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population & Global Health, The University of Melbourne, Melbourne, VIC, Australia

³School of Public Health, The University of Queensland, Brisbane, QLD, Australia

⁴Box Hill Hospital, Eastern Health, Box Hill, VIC, Australia

OPEN ACCESS

Received: Sep 27, 2018

Accepted: Sep 30, 2018

*Correspondence to

Francis Thien

Respiratory Medicine, Box Hill Hospital,
Eastern Health, 5 Arnold Street, Box Hill,
Melbourne 3128, VIC, Australia.

Tel: +613-9095-2415

Fax: +613-9899-6810

E-mail: frank.thien@monash.edu

Copyright © 2018. Asia Pacific Association of
Allergy, Asthma and Clinical Immunology.

This is an Open Access article distributed
under the terms of the Creative Commons
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>)
which permits unrestricted non-commercial
use, distribution, and reproduction in any
medium, provided the original work is properly
cited.

ORCID iDs

Francis Thien

<https://orcid.org/0000-0003-0925-6566>

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 (NO₂) 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 NO₂ 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 NO₂ 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

Author Contributions

Conceptualization: Francis Thien. Data curation: Vivien Wai Yun Lai, Francis Thien. Formal analysis: Vivien Wai Yun Lai, Gayan Bowatte, Luke David Knibbs. Investigation: Vivien Wai Yun Lai. Project administration: Francis Thien. Resources: Francis Thien. Supervision: Francis Thien. Validation: Vivien Wai Yun Lai, Francis Thien. Writing - original draft: Vivien Wai Yun Lai. Writing - review & editing: Gayan Bowatte, Luke David Knibbs, Kanishka Rangamuwa, Alan Young, Shyamali Dharmage, Francis Thien.

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 [NO₂]), 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, NO₂ 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 NO₂ 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

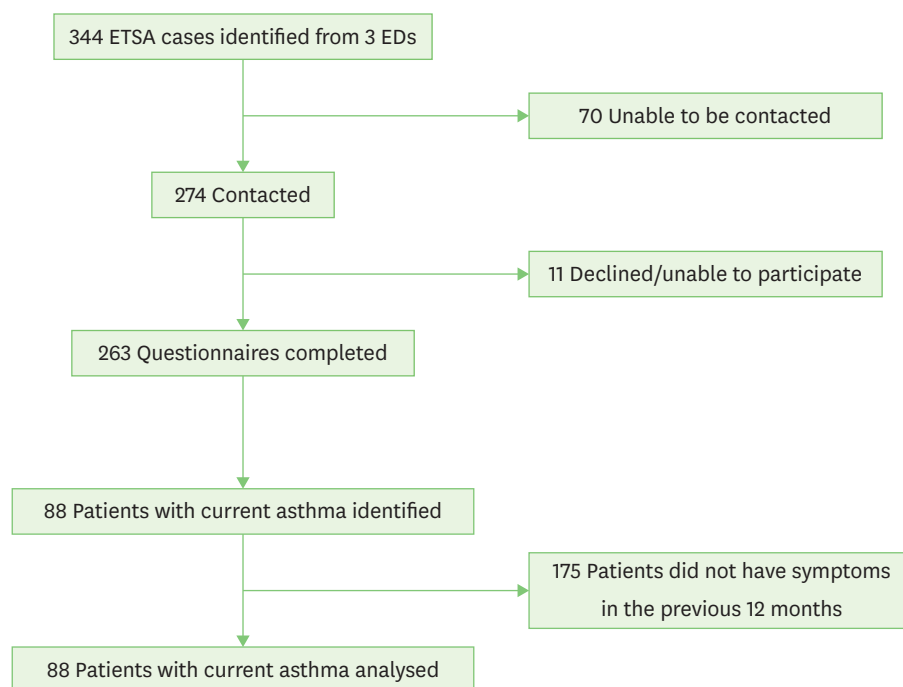


Fig. 1. Consort diagram of epidemic thunderstorm asthma patients. ETSA, Epidemic thunderstorm asthma; ED, Emergency Department.

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.

NO₂ exposure

Mean annual residential NO₂ 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 NO₂ levels from a combination of predictors including tropospheric NO₂ columns observed by satellite, land use and roads. This model has been both internally and externally validated across 68 and 123 different NO₂ monitoring sites, respectively, across all Australian states [24, 25]. The model captures 66%–81% of spatial variability in annual NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 (%).

NO₂, 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; NO₂, 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 NO₂ 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 NO₂ has been reported in a few studies [29–31], with a systematic review summarising significant positive associations in 10 of 11 studies investigating NO₂ and asthma symptoms in paediatric patients [32]. Another pooled study from six European cohorts reported a borderline association between NO₂ and incidence of asthma [8]. Additionally, our study provides evidence that greater NO₂ 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 NO₂ from an

internally and externally-validated national LUR model able to predict NO₂ exposure levels across Australia with low error rates [24].

However, our proxy markers for TRAP—annual mean NO₂ 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 NO₂ 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 NO₂ exposure and asthma exacerbation across an annual period using patients from the thunderstorm asthma cohort, as opposed to acute NO₂ 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 NO₂ exposure increasing risk of presentation with thunderstorm asthma. However, it adds to the epidemiological evidence of NO₂ 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 NO₂ 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.

REFERENCES

1. Woolcock AJ, Peat JK. Evidence for the increase in asthma worldwide. *Ciba Found Symp* 1997;206:122-34.
[PUBMED](#)
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
[PUBMED](#) | [CROSSREF](#)
3. D'Amato G, Cecchi L. Effects of climate change on environmental factors in respiratory allergic diseases. *Clin Exp Allergy* 2008;38:1264-74.
[PUBMED](#) | [CROSSREF](#)

4. D'Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, Liccardi G, Popov T, van Cauwenberge P. Allergenic pollen and pollen allergy in Europe. *Allergy* 2007;62:976-90.
[PUBMED](#) | [CROSSREF](#)
5. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ Int* 2017;100:1-31.
[PUBMED](#) | [CROSSREF](#)
6. Favarato G, Anderson HR, Atkinson R, Fuller G, Mills I, Walton H. Traffic-related pollution and asthma prevalence in children. Quantification of associations with nitrogen dioxide. *Air Qual Atmos Health* 2014;7:459-66.
[PUBMED](#) | [CROSSREF](#)
7. Anderson HR, Favarato G, Atkinson RW. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Qual Atmos Health* 2013;6:47-56.
[CROSSREF](#)
8. Jacquemin B, Siroux V, Sanchez M, Carsin AE, Schikowski T, Adam M, Bellisario V, Buschka A, Bono R, Brunekreef B, Cai Y, Cirach M, Clavel-Chapelon F, Declercq C, de Marco R, de Nazelle A, Ducret-Stich RE, Ferretti VV, Gerbase MW, Hardy R, Heinrich J, Janson C, Jarvis D, Al Kanaani Z, Keidel D, Kuh D, Le Moual N, Nieuwenhuijsen MJ, Marcon A, Modig L, Pin I, Rochat T, Schindler C, Sugiri D, Stempfelet M, Temam S, Tsai MY, Varraso R, Vienneau D, Vierkötter A, Hansell AL, Krämer U, Probst-Hensch NM, Sunyer J, Künzli N, Kauffmann F. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;123:613-21.
[PUBMED](#) | [CROSSREF](#)
9. Modig L, Torén K, Janson C, Jarvholm B, Forsberg B. Vehicle exhaust outside the home and onset of asthma among adults. *Eur Respir J* 2009;33:1261-7.
[PUBMED](#) | [CROSSREF](#)
10. Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 2014;190:914-21.
[PUBMED](#) | [CROSSREF](#)
11. Bowatte G, Erbas B, Lodge CJ, Knibbs LD, Gurrin LC, Marks GB, Thomas PS, Johns DP, Giles GG, Hui J, Dennekamp M, Perret JL, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *Eur Respir J* 2017;50.
[PUBMED](#) | [CROSSREF](#)
12. Künzli N, Kaiser R, Medina S, Studnicka M, Chanel O, Filliger P, Herry M, Horak F Jr, Puybonnieux-Texier V, Quénel P, Schneider J, Seethaler R, Vergnaud JC, Sommer H. Public-health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet* 2000;356:795-801.
[PUBMED](#) | [CROSSREF](#)
13. Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;329:1753-9.
[PUBMED](#) | [CROSSREF](#)
14. Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. *Epidemiology* 2005;16:41-8.
[PUBMED](#) | [CROSSREF](#)
15. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71-7.
[PUBMED](#) | [CROSSREF](#)
16. Thien F, Beggs PJ, Csutoros D, Darvall J, Hew M, Davies JM, Bardin PG, Bannister T, Barnes S, Bellomo R, Byrne T, Casamento A, Conron M, Cross A, Crosswell A, Douglass JA, Durie M, Dyett J, Ebert E, Erbas B, French C, Gelbart B, Gillman A, Harun NS, Huete A, Irving L, Karalapillai D, Ku D, Lachapelle P, Langton D, Lee J, Looker C, MacIsaac C, McCaffrey J, McDonald CF, McGain F, Newbigin E, O'Hehir R, Pilcher D, Prasad S, Rangamuwa K, Ruane L, Sarode V, Silver JD, Southcott AM, Subramaniam A, Suphioglu C, Susanto NH, Sutherland MF, Taori G, Taylor P, Torre P, Vetro J, Wigmore G, Young AC, Guest C. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. *Lancet Planet Health* 2018;2:e255-63.
[PUBMED](#) | [CROSSREF](#)
17. Rangamuwa KB, Young AC, Thien F. An epidemic of thunderstorm asthma in Melbourne 2016: asthma, rhinitis, and other previous allergies. *Asia Pac Allergy* 2017;7:193-8.
[PUBMED](#) | [CROSSREF](#)
18. Lee J, Kronborg C, O'Hehir RE, Hew M. Who's at risk of thunderstorm asthma? The ryegrass pollen trifecta and lessons learnt from the Melbourne thunderstorm epidemic. *Respir Med* 2017;132:146-8.
[PUBMED](#) | [CROSSREF](#)

19. Sutherland MF, Portelli EL, Collins AL, Rahman MA, McDonald CF. Patients with thunderstorm asthma or severe asthma in Melbourne: a comparison. *Med J Aust* 2017;207:434-5.
[PUBMED](#) | [CROSSREF](#)
20. Bowatte G, Lodge CJ, Knibbs LD, Erbas B, Perret JL, Jalaludin B, Morgan GG, Bui DS, Giles GG, Hamilton GS, Wood-Baker R, Thomas P, Thompson BR, Matheson MC, Abramson MJ, Walters EH, Dharmage SC. Traffic related air pollution and development and persistence of asthma and low lung function. *Environ Int* 2018;113:170-6.
[PUBMED](#) | [CROSSREF](#)
21. Assessing the Feasibility of a National Road Classification: Report to the ICSM on National Road Classification Developments [Internet]. Canberra (Australia): Intergovernmental Committee on Surveying and Mapping; 2006 Oct [cited 2018 Aug 7]. Available from: http://icsm.gov.au/sites/default/files/Assessing_Feasibility_National_Road_Classification.pdf
22. Brugge D, Durant JL, Rioux C. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. *Environ Health* 2007;6:23.
[PUBMED](#) | [CROSSREF](#)
23. Dadvand P, Ostro B, Figueras F, Foraster M, Basagaña X, Valentín A, Martínez D, Beelen R, Cirach M, Hoek G, Jerrett M, Brunekreef B, Nieuwenhuijsen MJ. Residential proximity to major roads and term low birth weight: the roles of air pollution, heat, noise, and road-adjacent trees. *Epidemiology* 2014;25:518-25.
[PUBMED](#) | [CROSSREF](#)
24. Knibbs LD, Hewson MG, Bechle MJ, Marshall JD, Barnett AG. A national satellite-based land-use regression model for air pollution exposure assessment in Australia. *Environ Res* 2014;135:204-11.
[PUBMED](#) | [CROSSREF](#)
25. Knibbs LD, Coorey CP, Bechle MJ, Cowie CT, Dirgawati M, Heyworth JS, Marks GB, Marshall JD, Morawska L, Pereira G, Hewson MG. Independent validation of national satellite-based land-use regression models for nitrogen dioxide using passive samplers. *Environ Sci Technol* 2016;50:12331-8.
[PUBMED](#) | [CROSSREF](#)
26. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) 2011 Technical Paper. Belconnen (Australia): Australian Bureau of Statistics; 2013.
27. Bowatte G, Lodge CJ, Knibbs LD, Lowe AJ, Erbas B, Dennekamp M, Marks GB, Giles G, Morrison S, Thompson B, Thomas PS, Hui J, Perret JL, Abramson MJ, Walters H, Matheson MC, Dharmage SC. Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *J Allergy Clin Immunol* 2017;139:122-9.
[PUBMED](#) | [CROSSREF](#)
28. D'Amato G. Urban air pollution and plant-derived respiratory allergy. *Clin Exp Allergy* 2000;30:628-36.
[PUBMED](#) | [CROSSREF](#)
29. Arnedo-Pena A, García-Marcos L, Carvajal Urueña I, Busquets Monge R, Morales Suárez-Varela M, Miner Canflanca I, Batlles Garrido J, Blanco Quirós A, López-Silvarrey Varela A, García Hernández G, Aguinaga Ontoso I, González Díaz C. Air pollution and recent symptoms of asthma, allergic rhinitis, and atopic eczema in schoolchildren aged between 6 and 7 years. *Arch Bronconeumol* 2009;45:224-9.
[PUBMED](#)
30. Hwang BF, Lee YL, Lin YC, Jaakkola JJ, Guo YL. Traffic related air pollution as a determinant of asthma among Taiwanese school children. *Thorax* 2005;60:467-73.
[PUBMED](#) | [CROSSREF](#)
31. Linares B, Guizar JM, Amador N, Garcia A, Miranda V, Perez JR, Chapela R. Impact of air pollution on pulmonary function and respiratory symptoms in children. Longitudinal repeated-measures study. *BMC Pulm Med* 2010;10:62.
[PUBMED](#) | [CROSSREF](#)
32. Pollock J, Shi L, Gimbel RW. Outdoor environment and pediatric asthma: an update on the evidence from North America. *Can Respir J* 2017;2017:8921917.
[PUBMED](#) | [CROSSREF](#)
33. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockcroft D, Blais L, McNutt M, Buist AS, Spitzer WO. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):604-10.
[PUBMED](#) | [CROSSREF](#)
34. Sioutas C, Delfino RJ, Singh M. Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. *Environ Health Perspect* 2005;113:947-55.
[PUBMED](#) | [CROSSREF](#)
35. Brauer M. How much, how long, what, and where: air pollution exposure assessment for epidemiologic studies of respiratory disease. *Proc Am Thorac Soc* 2010;7:111-5.
[PUBMED](#) | [CROSSREF](#)

36. D'Amato G. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. *Multidiscip Respir Med* 2011;6:28-37.
[PUBMED](#) | [CROSSREF](#)
37. Celenza A, Fothergill J, Kupek E, Shaw RJ. Thunderstorm associated asthma: a detailed analysis of environmental factors. *BMJ* 1996;312:604-7.
[PUBMED](#) | [CROSSREF](#)
38. Knox RB. Grass pollen, thunderstorms and asthma. *Clin Exp Allergy* 1993;23:354-9.
[PUBMED](#) | [CROSSREF](#)
39. Venables KM, Allitt U, Collier CG, Emberlin J, Greig JB, Hardaker PJ, Highham JH, Laing-Morton T, Maynard RL, Murray V, Strachan D, Tee RD. Thunderstorm-related asthma--the epidemic of 24/25 June 1994. *Clin Exp Allergy* 1997;27:725-36.
[PUBMED](#)