



The Australian Child Health and Air Pollution Study (ACHAPS): A national population-based cross-sectional study of long-term exposure to outdoor air pollution, asthma, and lung function

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ABSTRACT

Most studies of long-term air pollution exposure and children's respiratory health have been performed in urban locations with moderate pollution levels. We assessed the effect of outdoor nitrogen dioxide (NO₂), as a proxy for urban air pollution, on current asthma and lung function in Australia, a low-pollution setting.

We undertook a national population-based cross-sectional study of children aged 7–11 years living in 12 Australian cities. We collected information on asthma symptoms from parents via questionnaire and measured children's lung function (forced expiratory volume in 1 s [FEV₁], forced vital capacity [FVC]) and fractional exhaled nitric oxide [FeNO]. We estimated recent NO₂ exposure (last 12 months) using monitors near each child's school, and used a satellite-based land-use regression (LUR) model to estimate NO₂ at each child's school and home.

Our analysis comprised 2630 children, among whom the prevalence of current asthma was 14.9%. Mean (± SD) NO₂ exposure was 8.8 ppb (± 3.2) and 8.8 ppb (± 2.3) for monitor- and LUR-based estimates, respectively. Mean percent predicted post-bronchodilator FEV₁ and FVC were 101.7% (± 10.5) and 98.8% (± 10.5), respectively. The geometric mean FeNO concentration was 9.4 ppb (± 7.1).

An IQR increase in NO₂ (4.0 ppb) was significantly associated with increased odds of having current asthma; odds ratios (ORs) were 1.24 (95% CI: 1.08, 1.43) and 1.54 (95% CI: 1.26, 1.87) for monitor- and LUR-based estimates, respectively. Increased NO₂ exposure was significantly associated with decreased percent predicted FEV₁ (−1.35 percentage points [95% CI: −2.21, −0.49]) and FVC (−1.19 percentage points [95% CI: −2.04, −0.35]), and an increase in FeNO of 71% (95% CI: 38%, 112%).

Exposure to outdoor NO₂ was associated with adverse respiratory health effects in this population-based sample of Australian children. The relatively low NO₂ levels at which these effects were observed highlight the potential benefits of continuous exposure reduction.

1. Introduction

Compared with adults, the growth and development that characterise childhood potentially places children at greater risk of adverse respiratory health effects due to air pollution (McConnell et al., 2002;

Morgenstern et al., 2007; Bateson and Schwartz, 2008; Goldizen et al., 2016). The evidence for acute, short-term (e.g., days to weeks) effects of air pollution on children has grown markedly in recent years (e.g. Samoli et al., 2011; Spira-Cohen et al., 2011). In comparison, studies on the association between long-term (i.e., one or more years') exposure to

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outdoor air pollution and children's respiratory health are relatively few, and largely confined to North American and European cities with moderate air pollution levels (e.g. McConnell et al., 2002; Morgenstern et al., 2007; Gauderman et al., 2015; Dales et al., 2008; Eckel et al., 2011; Gehring et al., 2013; Gauderman et al., 2004; Janssen et al., 2003; Jerrett et al., 2008; Penard-Morand et al., 2005; Penard-Morand et al., 2010; Peters et al., 1999). For example, most studies of childhood asthma have been performed in settings with annual average nitrogen dioxide (NO₂) levels between ~12 and ~30 ppb (Favarato et al., 2014). Empirical evidence on the effects of exposure below that range, and the extent to which the findings of those studies may be generalisable to lower levels, is comparatively limited (Khreis et al., 2017).

A potential limitation of some previous studies of childhood asthma is the reliance on surrogates of pollutants, mostly traffic sources (e.g., road density near the home), in lieu of pollutant measurements or modelled exposures. Surrogates may adequately reflect relatively high or low traffic-related exposures, but they do not inform the concentration-response function for specific air pollutants. This is relevant to health impact assessment and meta-analyses, which require health outcomes for a pollutant to be expressed on a continuous scale (e.g., per µg/m³ increase) (Favarato et al., 2014; Khreis et al., 2017; Khreis and Nieuwenhuijsen, 2017).

Moreover, most studies that did estimate pollutant exposure used a single method for assigning exposure. For example, in a meta-analysis of 18 studies on NO₂ and prevalent asthma in children, published in 2014, four different exposure assessment methods were used, but no study used more than one method (Favarato et al., 2014). A more recent systematic review of exposure assessment in 42 studies (cross-sectional, case-control, and cohort) of traffic-related air pollution (TRAP) and childhood asthma reported that 28/42 (66%) used a single exposure assessment method (Khreis and Nieuwenhuijsen, 2017). That review also found that only 10/42 (24%) studies considered both the home and school or daycare address when assigning exposure, which may more realistically reflect the exposures of school-aged children than home addresses alone (Khreis and Nieuwenhuijsen, 2017). More detailed exposure assessment methods have been suggested as one way to increase the utility and generalisability of studies assessing air pollution and childhood asthma, including in health impact assessments (Khreis and Nieuwenhuijsen, 2017).

Australia has a small population (~24.5 million in 2017), approximately 10% of which has prevalent asthma, one of the world's highest rates. Asthma is the leading contributor to disease burden in Australian children aged ≤ 14 years (AIHW, 2011). As an island continent, Australia is not subject to significant trans-boundary air pollution. Australia has relatively low pollutant levels compared with North America and many European countries (e.g., annual average NO₂ in urban areas during 2006–2011: ~7 ppb) (Knibbs et al., 2014).

Previous Australian investigations of air pollution and children's respiratory health have focused on short-term effects, mostly in small or localised studies (e.g. Henry et al., 1991; Jalaludin et al., 2000; Lewis et al., 1998; Pereira et al., 2010). An exception in both size and geographic extent was a large national time-series case-crossover study that examined the association between air pollutants and respiratory hospital admissions of children in five Australian (and two New Zealand) cities (Barnett et al., 2005). That study reported a 6.0% increase in asthma admissions (95% CI: 0.2, 12.1) for children (5–14 years old) per 5.1 ppb increase in 24-h NO₂. While short-term respiratory effects of air pollution on Australian children have been demonstrated, to our knowledge, there have been no nationally representative studies of long-term effects.

We sought to better define the role of long-term outdoor air pollution exposure on children's respiratory health in Australia via a national study. We sought to add to the international evidence, largely based in locations with higher concentrations than Australia, by focusing on a low pollution setting, using two exposure assessment methods, and estimating exposure at school and home.

2. Methods

2.1. Study design

2.1.1. Site selection

We undertook a national, cross-sectional study of Australian children aged 7–11 years during 2007–2008: the Australian Child Health and Air Pollution Study (ACHAPS). We targeted the six most populous states and territories of the eight in Australia (New South Wales, Victoria, Queensland, South Australia, Western Australia, and the Australian Capital Territory). Tasmania and the Northern Territory were excluded due to their small population and limited air quality monitoring.

We first identified all regulatory ambient air quality monitors that: (a) had at least five years' measurements of criteria pollutants using standard reference methods (ozone (O₃), carbon monoxide [CO], NO₂, sulphur dioxide [SO₂], particulate matter < 2.5 µm [PM_{2.5}] and < 10 µm [PM₁₀]); (b) had at least three potentially eligible primary (elementary) schools within approximately 2 km; and (c) were considered by the relevant pollutant monitoring authorities to be at a site representative of general population exposure in surrounding areas (e.g., not influenced by a major road or industrial emission source, for example).

We calculated the annual average levels of each pollutant during 2004–2005 and ranked the monitoring sites. We aimed to ensure maximum variability in the diversity of air pollutants and their concentrations. A quota of the highest- and lowest-ranked sites for each pollutant was selected (approximately six), which yielded 29 sites in total after allowing for overlap. We used the 2 km distance threshold as a balance between the need for a sufficient number of schools while aiming to limit exposure measurement error introduced due to spatial variability of pollutants. We also investigated an additional exposure assessment method (described in Section 2.4).

We targeted state government-run public schools, which educate approximately 71% of primary school students in Australia, and have sufficiently large numbers of children aged 7–11 years (Australian Bureau of Statistics, Schools, Australia, 2012). We also targeted independent (non-government) Catholic schools in the state of Victoria due to limited government schools proximate to each monitor. We randomly selected two schools per monitoring site to approach, then contacted the principal and invited their school to participate. Refusing schools were randomly replaced, where possible, and 86 schools were approached in total.

Fifty-five schools (64%) agreed to participate, all of which (except two) were within 2 km of a monitor. The remaining two schools were 2.1 and 2.8 km from the monitoring site, respectively. The median distance of schools from the monitoring site was 1.4 km. The 55 schools spanned the major state capital cities in Australia: Sydney (population in 2006 = 4.3 million; 6 schools), Melbourne (3.6 million; 10 schools), Brisbane (1.8 million; 6 schools), Perth (1.5 million; 7 schools), and Adelaide (1.1 million; 6 schools). Seven other cities (20 schools total) were also included, spanning a population range of ~20,000 to ~500,000; these cities are not named to minimise the potential for re-identification of schools. An overview map of the schools located in large cities is presented in Fig. 1.

2.1.2. Recruitment and questionnaire

We randomly selected whole classes within each of the 55 schools to obtain at least 100 children per school. No exclusions were made on the basis of race, ethnicity or socio-demographic factors. Background information, questionnaires and consent forms were distributed to parents. In total, 7618 children were invited to take part.

The questionnaire was derived from items in the International Study of Asthma and Allergies in Childhood (ISAAC) (ISSAC, 2000), and other relevant studies (Peters et al., 1999; Toelle et al., 2004; Marks et al., 2006; Centre for Epidemiology and Research, N. D. O. H., 2003). We

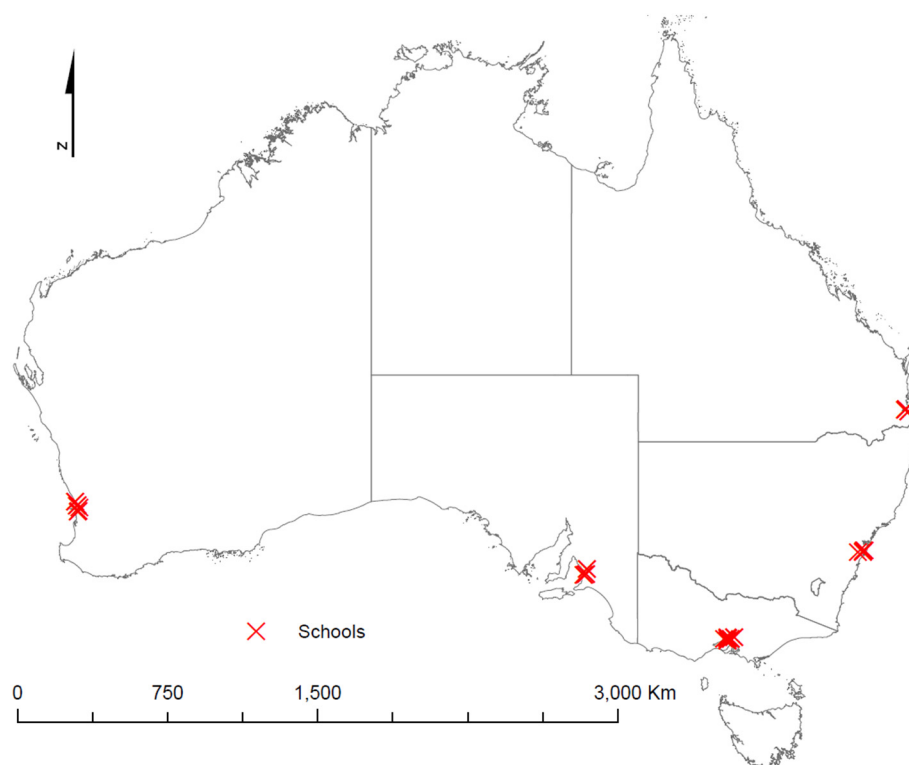


Fig. 1. The location of schools from which children were recruited. Schools ($n = 35$) in state capital cities are shown (clockwise from top: Brisbane, Sydney, Melbourne, Adelaide, and Perth). The remaining schools ($n = 20$) are not shown to prevent re-identification.

gave preference to the ISAAC questionnaire because of its widespread use (300,000+ respondents) and extensive validation. The final questionnaire included 70 items and sought, among other outcomes, information on whether a child had ever been diagnosed with asthma ('lifetime asthma'). This was based on the parent's response to the question "Have you ever been told by a doctor or nurse that your child has asthma?". Children who still have asthma ('current asthma') were defined based on the question "Does he/she still have asthma?". We also collected information on other potential covariates, including the use of asthma medication, symptoms of wheeze and cough, history of recurrent itchy rash (signifying eczema), parental smoking habits, pets, and sources of indoor pollutant exposure at home. The questionnaire we used is available online (ACHAPS study questionnaire, 2007).

2.2. Clinical measurements

We measured each child's lung function and the fractional nitric oxide concentration in exhaled breath (Fe_{NO}). Children with completed questionnaires were eligible for these clinical measurements, provided: (i) the child was present on the day of testing at the school; (ii) their parent provided written consented; (iii) the child assented; (iv) the child was physically able to complete the tests, and; (v) the child had not recently been absent from school due to, or currently had signs of, a respiratory illness.

2.2.1. Spirometry

We measured forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and FEV_1/FVC . Trained fieldworkers measured lung function before and after bronchodilator, in accordance with the European Respiratory Society and American Thoracic Society recommendations for standardisation of spirometry (Miller et al., 2005).

We used a Spirocard spirometer and SpiroScore+ V2.6 software (Bird Healthcare, Melbourne, Australia). We requested that participants withhold short-acting bronchodilators for 6 h and long-acting bronchodilators for 12 h prior to the baseline measurements. Measures were

repeated at least three times (up to a maximum of eight times) to achieve reproducibility of ≤ 100 mL between the best and the second-best FEV_1 . Immediately after the baseline spirometry was completed, participants received salbutamol (200 μ g Ventolin®; 100 μ g $\times$ 2, 1 min apart), administered by a tube spacer. Post-bronchodilator measurements were made 10 min later using the same procedure.

Each child's standing height (without shoes) was measured using a stadiometer, and weight was measured using calibrated digital scales. Measured FVC, FEV_1 and FEV_1/FVC for each child were converted to a percentage of predicted values for a given sex, age and height using the Global Lung Function Initiative reference values for Caucasian males and females (Quanjer et al., 2012).

2.2.2. Fe_{NO}

We measured Fe_{NO} , a marker of eosinophilic airway inflammation (Dweik et al., 2011), using an offline technique (Massaro and Gaston, 1995; Salome et al., 1999). Before collection, children took three breaths through an NO scrubber to filter ambient NO. After a maximal inspiration, participants exhaled at a flow of 12 L/min against a small resistance to their residual volume. The exhaled breath was collected in an NO impermeable polyethylene bag (Scholle Industries Pty Ltd., SA, Australia). The first 2 s of the exhalation were diverted from the collection bag, using a three-way tap, to exclude dead space air (Paredi and Loukides, 1998). The procedure was repeated until there was sufficient air in the bag for the measurement. The exhaled gas was analysed within 6 h of collection using a reference chemiluminescence analyser (Thermo Environmental Instruments Model 42i, Franklin, MA, USA).

We defined 'high' Fe_{NO} in our study population as the 97.5th percentile of measured Fe_{NO} , calculated as the antilog of mean ($\log(Fe_{NO}) + 1.96 \times SD(Fe_{NO})$) among children who were non-atopic (a negative response to eight common allergens based on a skin prick test [details in (ACHAPS final report, 2012)]), and had not had rhinitis or asthma in the last 12 months (Dweik et al., 2011; Buchvald et al., 2005).

2.3. Approvals

Our study was approved by the Human Research Ethics Committees of the University of Queensland (Ref: 2006000592) and University of Sydney (Ref: 10050), the Departments of Education in each of the six jurisdictions, and the Catholic Education Office of Victoria. Project staff obtained working with children checks and national police clearances.

2.4. Exposure assessment

We focused on NO₂ as the main exposure variable in our study. While no single commonly monitored air pollutant is an ideal proxy for air pollution exposure (Health Effects Institute, 2010), we used NO₂ because: (i) of the routinely measured pollutants, NO₂ is the most useful surrogate for the complex mixture of combustion-derived air pollutants, including vehicle emissions (Khreis et al., 2017; Khreis and Nieuwenhuijsen, 2017); (ii) NO₂ has been associated with current asthma, lung function, and Fe_{NO} in children (e.g. Gauderman et al., 2015; Favaro et al., 2014; Delfino et al., 2006) and; (iii) it is generally more spatially heterogeneous than other criteria pollutants in urban areas. In Australia, the major sources of nitrogen oxides are vehicle emissions and coal-fired power generation (Australian Bureau of Statistics, Year Book Australia, 2012). We used two methods for assigning NO₂ exposure and compared their effects on the outcomes we measured.

2.4.1. Measured NO₂

We obtained hourly outdoor NO₂ measurements during 1995 through 2007–2008 for each of the 29 selected regulatory monitoring sites. NO₂ was measured using the standard chemiluminescence reference method at all sites (Thermo Environmental Instruments Model 42i, Franklin, MA, USA). We linked NO₂ monitoring sites to their associated school sites, and, in turn, to children. Although primary school-aged children tend to live near their school, the monitors were selected based on their proximity to schools rather than homes. As such, we used ArcGIS v.10.3 (ESRI, Redlands, CA, USA) to calculate the distance from each child's home address to the NO₂ monitor used to estimate their exposure. These distances were used in sensitivity analyses (Section 2.5).

We assessed exposures in three time windows during each child's residence at their address. We defined the period of residence as the time from the child's date of birth, if the child had lived at that address all their life, or January 1 of the year in which the parent reported they had moved to that address, to the date the spirometry was measured. Daily NO₂ levels were averaged over all days of residency ('lifetime exposure'), for the period of residence except the last year ('previous exposure'), and for the last year ('recent exposure').

Measurements of other pollutants using standard methods at each regulatory monitoring site were obtained (O₃, SO₂, CO, PM_{2.5}, PM₁₀, and light-scattering particles measured by a nephelometer). These measurements were used in two-pollutant models (Section 2.5).

2.4.2. Modelled NO₂

We matched each child's residential and school address to the Australian geocoded national address file (G-NAF), a database of all 14.1 million addresses in Australia (Public Sector Mapping Agencies, 2013). We then estimated NO₂ concentrations at school and home using a validated satellite-based land-use regression (LUR) model that had spatial (national) and temporal (2006–2011) coverage that included our study locations and time period (Knibbs et al., 2014). The LUR model used spatial predictors of NO₂ (i.e., independent variables), including relatively coarse satellite observations of tropospheric NO₂ abundance (13 × 24 km) combined with more finely-resolved local-scale predictors including major and minor roads, industrial land use, and point-source emissions (Knibbs et al., 2014). It captured 76% of the spatial variability in monthly average NO₂ during 2006–2011, with a

mean prediction error of 27% (1.9 ppb) (Knibbs et al., 2014). We used LUR model estimates as an additional source of NO₂ exposure information to complement the fixed-site regulatory measurements.

Monthly estimates of NO₂ exposure were averaged over the months included in the most recent year of the child's residency, for both school- and home-based estimates. A combined measure was also calculated based on a weighted mean reflecting the approximate time children spent in the two locations (75% home, 25% school).

We had LUR estimates of the last 12 months' ('recent exposure'), which we could compare with NO₂ measurements taken over the same time period. We did not have historical satellite-based monthly estimates of NO₂ (i.e., for 'lifetime exposures' or 'previous exposures'), or LUR estimates of other pollutants.

2.5. Statistical analysis

Our analysis was restricted to children who completed the spirometry examination and returned a valid questionnaire. We used standard statistical measures to describe the characteristics of the children, their respiratory health history, and the results of clinical assessment (i.e., lung function and Fe_{NO}). As Fe_{NO} values were positively skewed, the values were log-transformed for analysis.

2.5.1. Analysis

Analyses were conducted using SAS v.9.4 (SAS Institute, Cary, NC, USA), with procedures SURVEYREG and SURVEY LOGISTIC used for modelling. Hierarchical models, with city as stratum and school as cluster, were used to examine the association between NO₂ exposure and the outcome variables: lung function and respiratory symptoms. We assessed non-linearity by incorporating quadratic and cubic polynomial terms for the pollutants (after centring), as well as fitting splines to residuals.

2.5.2. Covariates

All models included age and sex as covariates. Because of potential confounding by socioeconomic status, we used parental education (i.e., completed 12 years of formal education, for mothers and fathers separately) as well as two area-level socioeconomic indices based on each child's residential address. These standard indices were obtained from the Australian Bureau of Statistics (ABS) and used information collected in the 2006 national census (Australian Bureau of Statistics, 2006). We used the Index of Education and Occupation (IEO), which includes census variables related to educational and occupational characteristics of areas, such as the proportion of people who are employed, their educational qualifications, and those working in skilled occupations. Additionally, we used the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), derived from variables related to both advantage and disadvantage and expressed on a continuous scale (e.g., single-parent households with low income working in unskilled occupations through to high-income couples with no dependents working in professional occupations).

Models assessing lung function and Fe_{NO} included the monthly (for month of testing) and annual average daily mean temperature (°C), based on standard data from the Australian Bureau of Meteorology (Australian Government, Bureau of Meteorology, n.d.). Children's height was included for lung function measures that were not already height-adjusted (e.g., percent predicted FEV₁ inherently accounted for age, sex and height).

2.5.3. Sensitivity analyses

We undertook several sensitivity analyses to assess their effects on respiratory symptoms and lung function: (1) adjustment for indoor exposure to second-hand smoke and gas combustion products from stoves and heaters, as potentially the most relevant sources of indoor exposure from the questionnaire; (2) adjustment for air conditioning in the home and the age of the dwelling; (3) adjustment for additional

Table 1
Characteristics of the ACHAPS study population.

Item	n/N (%) or mean $\pm$ SD (N)
Socio-demographic	
Age (years)	10.1 $\pm$ 1.2 (2630)
Female	1339/2612 (51.3)
Born in Australia	2425/2627 (92.3)
Speak language other than English at home	442/2572 (17.2)
Mother completed 12 years of high school	1908/2560 (74.5)
Father completed 12 years of high school	1801/2431 (74.1)
Index of relative socio-economic advantage and disadvantage	1022 $\pm$ 75 (2630)
Index of education and occupation	1024 $\pm$ 90 (2630)
Mother - history of asthma	543/2504 (21.7)
Father - history of asthma	437/2376 (18.4)
Indoor exposure sources	
Indoor exposure to gas cooking - first year of life	1604/2546 (63.0)
Indoor exposure to gas cooking - currently	1768/2602 (68.0)
Indoor exposure to gas heating - first year of life	880/2630 (33.5)
Indoor exposure to gas heating - currently	875/2630 (33.3)
Mother smoked during pregnancy	357/2503 (14.3)
Indoor exposure to second-hand smoke - currently	225/2614 (8.6)
Had a cat - first year of life	703/2082 (33.8)
Currently have a cat	751/2108 (35.6)
Had a dog - first year of life	1053/2086 (50.5)
Currently have a dog	1282/2110 (60.8)
Asthma history and medication use - recent	
Current asthma	385/2593 (14.9)
Any asthma/wheezing medication in the last 12 months	574/2479 (23.2)
Visit doctor for asthma last 12 months	322/2394 (13.5)
Current wheeze	438/2601 (16.8)
Wheeze after exercise last 12 months	304/2250 (13.2)
Itchy rash for 6 months in the last 12 months	440/2616 (16.8)
Rhinitis last 12 months	823/2617 (31.5)
Cough last 12 months	1882/2620 (71.8)
Dry cough at night last 12 months	605/2614 (23.1)
Asthma history and medication use - lifetime	
Lifetime asthma	739/2603 (28.4)
Any asthma medication ever	974/2478 (39.3)
Ever admitted to hospital for breathing problems	352/2592 (13.6)
Lifetime wheeze	922/2604 (35.4)
Itchy rash for 6 months ever	619/2620 (23.6)
Rhinitis ever	884/2617 (33.8)
Parent-reported doctor-diagnosed eczema/atopic dermatitis	610/2561 (23.8)
Clinical measurements	
Height (cm)	141.1 $\pm$ 9.1 (2619)
Weight (kg)	37.6 $\pm$ 9.9 (2617)
BMI (kg/m ²)	18.7 $\pm$ 3.3 (2616)
Lung function and Fe_{NO}	
FEV ₁	
Pre-bronchodilator (L)	2.01 $\pm$ 0.39 (2621)
Pre-bronchodilator (% predicted)	98.3 $\pm$ 10.3 (2592)
Post-bronchodilator (L)	2.08 $\pm$ 0.40 (2599)
Post-bronchodilator (% predicted)	101.7 $\pm$ 10.5 (2570)
% change: Pre- to post-bronchodilator	3.64 $\pm$ 5.33 (2595)
FVC	
Pre-bronchodilator (L)	2.29 $\pm$ 0.47 (2489)
Pre-bronchodilator (% predicted)	97.7 $\pm$ 10.5 (2462)
Post-bronchodilator (L)	2.32 $\pm$ 0.46 (2513)
Post-bronchodilator (% predicted)	98.8 $\pm$ 10.5 (2485)
FEV ₁ /FVC ratio	
Pre-bronchodilator (%)	87.9 $\pm$ 6.5 (2489)
Pre-bronchodilator (% predicted)	100.1 $\pm$ 7.3 (2462)
Post-bronchodilator (%)	90.0 $\pm$ 5.4 (2513)
Post-bronchodilator (% predicted)	102.5 $\pm$ 6.0 (2485)
Fe _{NO} (ppb)	9.4 $\pm$ 7.1 (1815)
High Fe _{NO}	135/1815 (7.4)

questionnaire-derived covariates on maternal smoking during pregnancy, premature birth, and if the child attended day care in their first year of life; (4) adjustment of NO₂ for other pollutants in two-pollutant models using measured PM_{2.5}, PM₁₀, CO, O₃, SO₂, and light-scattering particles; (5) adjustment of lung function models for measured NO₂

concentrations on the day of, or day prior to, spirometry (measured as that day's deviation from mean lifetime, previous, or recent exposure), and; (6) exclusion of participants whose home address was above the third distance quartile from an NO₂ monitoring site for all outcomes using measured NO₂ as the exposure variable.

Table 2
Nitrogen dioxide exposure estimates based on monitors and LUR predictions.

Measure	N sites	Median exposure duration	1st to 3rd quartile of exposure duration	Mean exposure (ppb)	Median exposure (IQR) (ppb)	Between-site SD (ppb)	Between-site minimum to maximum (ppb)	Mean within-site SD (ppb)
NO ₂ at nearest monitor to school								
Lifetime	29	5.7 y	3.2 to 8.3 y	9.3	8.8 (4.3)	3.6	3.0 to 17.1	0.50
Previous	29	4.7 y	2.3 to 7.4 y	9.5	9.0 (4.1)	3.6	3.0 to 17.7	0.52
Recent	27	11.7 m	10.4 to 12.0 m	8.8	7.9 (4.0)	3.2	3.4 to 15.6	0.21
Satellite-based LUR NO ₂								
School	55	12 m	n/a	8.8	8.4 (2.9)	2.2	4.2 to 13.1	–
Residence	2630	12 m	n/a	8.8	8.3 (3.4)	2.4	2.9 to 24.1	–
Combined	2630	12 m	n/a	8.8	8.3 (3.3)	2.3	3.2 to 21.3	–

Table 3
Effect estimates for respiratory outcomes associated with an IQR (4.03 ppb) increase in monitored NO₂ (lifetime, previous, and recent exposure). Bold text denotes statistical significance at the 5% level.

Outcome	NO ₂ at nearest monitor to school					
	Lifetime exposure		Previous exposure		Recent exposure	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratios ^a for IQR increase:						
Current asthma	1.19 (1.04, 1.38)	0.014	1.21 (1.05, 1.41)	0.010	1.24 (1.08, 1.43)	0.003
Lifetime asthma	1.06 (0.98, 1.16)	0.17	1.09 (1.00, 1.19)	0.045	1.08 (0.98, 1.19)	0.13
High Fe _{NO}	1.56 (1.17, 2.07)	0.003	1.54 (1.16, 2.05)	0.003	1.77 (1.32, 2.38)	< 0.001
Current wheeze	1.13 (1.01, 1.27)	0.036	1.12 (1.00, 1.26)	0.048	1.17 (1.03, 1.33)	0.014
Current cough	0.98 (0.86, 1.12)	0.78	0.99 (0.86, 1.14)	0.94	1.00 (0.87, 1.15)	0.98
Visit to doctor for asthma last 12 months	1.12 (0.91, 1.36)	0.28	1.11 (0.92, 1.35)	0.29	1.15 (0.93, 1.43)	0.19
Beta-agonist (short-term) last 12 months	1.08 (0.95, 1.23)	0.23	1.11 (0.97, 1.26)	0.14	1.09 (0.96, 1.25)	0.18
Wheeze after exercise last 12 months	1.23 (1.10, 1.38)	< 0.001	1.24 (1.10, 1.39)	< 0.001	1.29 (1.12, 1.48)	< 0.001
Itchy rash for 6 months last 12 months	1.01 (0.87, 1.19)	0.87	1.02 (0.87, 1.19)	0.80	1.03 (0.86, 1.23)	0.78
Rhinitis last 12 months	0.95 (0.83, 1.10)	0.51	0.99 (0.86, 1.14)	0.87	0.93 (0.79, 1.09)	0.39
Change ^b per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	−1.03 (−1.89, −0.17)	0.020	−0.96 (−1.82, −0.10)	0.029	−1.23 (−2.08, −0.39)	0.005
FEV ₁ Post-bronchodilator (% predicted)	−1.11 (−1.91, −0.30)	0.008	−1.13 (−1.97, −0.30)	0.009	−1.35 (−2.21, −0.49)	0.003
FVC Pre-bronchodilator (% predicted)	−0.95 (−1.71, −0.19)	0.015	−0.82 (−1.62, −0.02)	0.046	−1.11 (−1.87, −0.34)	0.006
FVC Post-bronchodilator (% predicted)	−1.02 (−1.84, −0.20)	0.016	−1.00 (−1.83, −0.16)	0.020	−1.19 (−2.04, −0.35)	0.007
FEV ₁ /FVC Pre-bronchodilator (% predicted)	−0.09 (−0.69, 0.51)	0.77	−0.14 (−0.74, 0.45)	0.63	−0.10 (−0.58, 0.38)	0.68
FEV ₁ /FVC Post-bronchodilator (% predicted)	0.02 (−0.49, 0.52)	0.95	−0.03 (−0.52, 0.46)	0.90	−0.10 (−0.50, 0.30)	0.62
Fe _{NO} (% increase)	32 (14,53)	< 0.001	32 (14,52)	< 0.001	37 (19,58)	< 0.001

^a Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD).

^b Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature.

3. Results

3.1. General and respiratory health results

Of 7618 children invited to take part in the study, 2880 (37.8%) returned a parent-completed questionnaire. Of those, 2630 (91.3%) had at least one valid spirometry result; these children comprised our analysis dataset. Due mainly to equipment malfunction, only 1815 (69%) of these children had valid results for Fe_{NO}.

Table 1 summarises the socio-demographic characteristics of the children and their parents and the main results of the questionnaire and clinical assessment. The mean ($\pm$ SD) age was 10.1 ($\pm$ 1.2) years and 51.3% were female. Most (92.3%) children were born in Australia, while 17.2% spoke a language other than English at home. The majority of parents had completed high school education (74.5% of mothers, 74.1% of fathers). Table S1 summarises the characteristics of the participants, stratified by NO₂ exposure.

Of the children, 28.4% had a history of asthma (lifetime asthma), 14.9% still had asthma (current asthma), 35.4% had experienced wheezing during their lives, and 16.8% had wheeze currently (Table 1). Lung function results were consistent with population reference values. Of the 1815 children with Fe_{NO} measurements (median Fe_{NO}: 7.5 ppb, IQR: 6.3 ppb), 573 (31.6%) were non-atopic and had not had rhinitis or asthma

in the last 12 months. Based on that group, the threshold we used to define ‘high’ Fe_{NO} was 19.4 ppb, consistent with results suggesting that Fe_{NO} of approximately 15–25 ppb is the upper limit of normal in healthy children aged 4–17 years (Buchvald et al., 2005). Among all children with Fe_{NO} measurements, 135 (7.4%) had high Fe_{NO}.

3.2. NO₂ exposures

All 29 monitoring sites had NO₂ data available during the period preceding the study, although some sites had periods with missing data. As a result, 1.7% of children had no estimate for lifetime exposure, 5.8% had no estimate for previous exposure, and 5.3% had no estimate for recent exposure. The median distance between the home addresses and the NO₂ monitoring site used to estimate exposure was 1.7 km (5th percentile: 0.6 km, 95th percentile: 6.3 km). The 75th percentile, which we used to exclude participants located further away in sensitivity analyses, was 2.44 km.

The mean ($\pm$ SD) NO₂ concentration for lifetime exposure was 9.3 ($\pm$ 3.6) ppb, ranging from 3.0 to 17.1 ppb, and the median duration of lifetime exposure was 5.7 years (Table 2). These concentrations were similar to those for previous exposure (median duration: 4.7 years), while recent exposure (median duration: 11.7 months) was slightly lower (Table 2).

Table 4

Effect estimates for respiratory outcomes associated with a 4.03 ppb (IQR for measured NO₂) increase in satellite-based LUR NO₂ (recent exposure only; school, home, and combined exposure). Bold text denotes statistical significance at the 5% level.

Outcome	NO ₂ from satellite-based LUR					
	School address		Home address		Combined (school and home)	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratios ^a for IQR increase:						
Current asthma	1.46 (1.20, 1.79)	< 0.001	1.49 (1.23, 1.81)	< 0.001	1.54 (1.26, 1.87)	< 0.001
Lifetime asthma	1.22 (1.02, 1.47)	0.031	1.27 (1.07, 1.52)	0.008	1.29 (1.06, 1.56)	0.010
High Fe _{NO}	3.34 (1.90, 5.85)	< 0.001	2.45 (1.55, 3.86)	< 0.001	2.83 (1.70, 4.71)	< 0.001
Current wheeze	1.19 (0.97, 1.47)	0.10	1.24 (0.99, 1.54)	0.06	1.25 (0.99, 1.57)	0.06
Current cough	0.89 (0.72, 1.12)	0.32	0.85 (0.70, 1.05)	0.13	0.85 (0.69, 1.05)	0.14
Visit to doctor for asthma last 12 months	1.36 (0.99, 1.85)	0.06	1.27 (0.97, 1.66)	0.09	1.31 (0.97, 1.76)	0.07
Beta-agonist (short-term) last 12 months	1.23 (1.02, 1.49)	0.032	1.32 (1.09, 1.58)	0.004	1.33 (1.09, 1.61)	0.004
Wheeze after exercise last 12 months	1.55 (1.26, 1.92)	< 0.001	1.54 (1.28, 1.86)	< 0.001	1.60 (1.32, 1.95)	< 0.001
Itchy rash for 6 months last 12 months	1.40 (1.07, 1.84)	0.015	1.36 (1.11, 1.67)	0.003	1.40 (1.11, 1.78)	0.005
Rhinitis last 12 months	1.01 (0.79, 1.29)	0.92	1.14 (0.94, 1.38)	0.20	1.12 (0.90, 1.39)	0.31
Change ^b per IQR in:						
FEV1 Pre-bronchodilator (% predicted)	−1.09 (−2.66, 0.48)	0.17	0.17 (−1.01, 1.36)	0.77	−0.09 (−1.41, 1.22)	0.89
FEV1 Post-bronchodilator (% predicted)	−1.39 (−2.75, −0.03)	0.045	−0.14 (−1.18, 0.90)	0.79	−0.42 (−1.56, 0.71)	0.45
FVC Pre-bronchodilator (% predicted)	−0.91 (−2.28, 0.45)	0.19	0.24 (−0.83, 1.31)	0.65	0.01 (−1.17, 1.18)	0.99
FVC Post-bronchodilator (% predicted)	−1.11 (−2.42, 0.21)	0.10	−0.11 (−1.15, 0.92)	0.83	−0.34 (−1.47, 0.79)	0.55
FEV1/FVC Pre-bronchodilator (% predicted)	−0.28 (−1.20, 0.64)	0.54	−0.03 (−0.91, 0.84)	0.94	−0.09 (−1.01, 0.83)	0.84
FEV1/FVC Post-bronchodilator (% predicted)	−0.21 (−0.95, 0.53)	0.57	0.01 (−0.63, 0.66)	0.96	−0.03 (−0.73, 0.66)	0.92
Fe _{NO} (% increase)	71 (38, 112)	< 0.001	52 (24, 86)	< 0.001	60 (30, 98)	< 0.001

^a Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD).

^b Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature.

All schools and 97.8% of homes were geocoded to a building-level match; other homes were geocoded to either a street-level (0.6%) or postcode-level match (1.5%). Our satellite-based LUR estimates had less variability than measured data for recent NO₂ exposures (Table 2). LUR estimates at schools had a mean of 8.8 (± 2.1) ppb and ranged from 4.2 to 13.1 ppb. These results were similar to those for combined exposure at school and home (Table 2). LUR-based estimates at the schools were slightly higher than the nearby monitor-based estimates at lower concentrations, and vice-versa (R² = 0.56, supplement, Fig. S1). At the individual level, LUR estimates were correlated with monitor-based exposures; Pearson's *r* = 0.75, 0.64, and 0.68 for the school, home and combined exposure estimates, respectively. School- and home-based exposure estimates from the LUR model were well-correlated (*r* = 0.88).

3.3. NO₂ and respiratory symptoms

Table 3 contains the associations between measured NO₂ and parent-reported respiratory symptoms, after adjustment for age, sex, parental education and area-level socio-economic indices. For consistency, we scaled all effect estimates to an IQR increase in measured NO₂ in the last 12 months (4.03 ppb; hereafter denoted 4 ppb). We found that a 4 ppb increase in recent exposure to NO₂ was significantly associated with greater odds of current asthma and current wheeze. Most of the significant associations we observed for recent exposure were also present for previous and lifetime exposure to NO₂; the effect estimates were slightly larger for recent exposure (Table 3).

Table 4 contains associations between satellite-based LUR estimates of recent NO₂ exposure at the school and home address and respiratory symptoms. A 4 ppb increase in NO₂ exposure at school, home and combined (75% home, 25% school) were all significantly associated with increased odds of current asthma. These results were mostly consistent with those using measured NO₂, but the three LUR-based exposures generally had larger effect estimates, and, for most outcomes, the combined exposure yielded larger effect estimates than the school or residential exposures alone (Table 4). There were three other outcomes for which we only observed consistent evidence of significant associations when using the LUR-based estimates; lifetime asthma,

current short-acting beta-agonist use, and itchy rash for six of the last twelve months.

3.4. NO₂, lung function and Fe_{NO}

Table 3 contains associations between measured NO₂ and lung function after adjustment for age, sex, parental education, area-level socioeconomic indices, and monthly (for month of testing) and annual average daily mean temperature. A 4 ppb increase in recent NO₂ exposure was significantly associated with a decrease in percent predicted FEV₁ and FVC (pre- and post-bronchodilator). An increase in recent NO₂ exposure was also significantly associated with increased Fe_{NO}, expressed as a percentage increase and categorically (i.e., high Fe_{NO}). All significant associations for recent exposure were also observed for previous and lifetime exposure; the effects of recent exposure were slightly larger (Table 3).

Table 4 shows the associations between satellite-based LUR estimates of recent NO₂ exposure and lung function. With the exception of Fe_{NO} and a single result for FEV₁, the significant associations observed using monitored NO₂ were not observed when using LUR-based estimates of exposure.

3.5. Diagnostics and sensitivity analyses

We did not observe any evidence of significant non-linearity in the models, as assessed by quadratic and cubic terms. When we adjusted both parent-reported and lung function outcomes for other measured pollutants in two-pollutant models, the effect estimates we observed for NO₂ were mostly stable (supplement, Figs. S2–S4). Similarly, adjustment for indoor exposure to gas combustion and second-hand smoke did not change the associations for our main outcomes (supplement, Tables S2–S3). The lung function results observed in our main analysis were similar to those adjusted for NO₂ on the day prior to, and day of, clinical assessment (Tables S4–S5). Excluding participants whose home address was above the third distance quartile from a monitor (2.44 km) led to increased effect sizes for lifetime, previous and recent measured NO₂ exposure and some parent-reported and lung function outcomes (Table S6). Finally, adjustment for other covariates including maternal

smoking, premature birth, and day care attendance in the first year of life did not substantively change our main findings (Tables S7–S8).

4. Discussion

4.1. Main findings

In this cross-sectional, multi-city study of 2630 Australian children aged 7–11 years, we found strong evidence that an increase in outdoor NO₂ concentrations in the last 12 months ('recent' exposure) was associated with an increase in the odds of current asthma. We also found that NO₂ was associated with a decrease in both FEV₁ and FVC, and an increase in FeNO. Similar associations were observed with estimated lifetime exposure, but the effect sizes were smaller.

4.2. Effects of NO₂ on current asthma

Our findings add to the existing evidence by demonstrating adverse effects of low-level NO₂ on current asthma in children. Australian cities have low NO₂ concentrations compared with other high income countries. For example, the mean NO₂ concentration in our study (~9 ppb, median: 8 ~ ppb, IQR: ~4 ppb) was lower than that in 18 comparable studies (~20 ppb, median: ~19 ppb, IQR: ~8 ppb); twelve from Europe, three from Asia and three from the USA (Favarato et al., 2014). Using those same studies, a meta-analysis on recent NO₂ exposure and current asthma symptoms in children found borderline-significant fixed- and random-effects: ORs of 1.04 (95% CI: 1.00, 1.08) and 1.06 (95% CI: 1.00, 1.11) per ~5.3 ppb increase in NO₂, respectively (Favarato et al., 2014). We found strong evidence of associations; ORs of 1.54 (CI: 1.26, 1.87) and 1.24 (CI: 1.08, 1.43) per 4 ppb increase in LUR- and monitor-based exposures, respectively.

None of the 18 studies meta-analysed used two NO₂ exposure assessment methods. Studies of air pollution and prevalent asthma within communities sharing a common airshed (i.e., pollutant source and dispersion characteristics) that use fine-scale exposure assessment to capture spatial contrasts often report positive associations (Anderson et al., 2013a). Conversely, the same associations are less frequently observed in between-community studies that represent each community and its airshed as a whole (i.e., by assigning exposure to all subjects in a community using the same measurements) (Favarato et al., 2014; Anderson et al., 2013a). One explanation proposed in the literature is that the finely-resolved exposure estimates used in most within-community studies (e.g., LUR modelling) are necessary to demonstrate such associations (Khreis and Nieuwenhuijsen, 2017; Anderson et al., 2013a). Our study is best described as a within-community study where multiple communities were assessed (i.e., 12 cities each with a distinct airshed) and residential- and school-based exposures were estimated using an LUR model. The larger effects of recent NO₂ exposure on current asthma we observed when using LUR estimates, compared with fixed-site monitors, could potentially be due to reduced exposure misclassification (Penard-Morand et al., 2005; Penard-Morand et al., 2010; Khreis and Nieuwenhuijsen, 2017; Anderson et al., 2013a).

Notably, four recent meta-analyses have reported significant associations between outdoor air pollutants and incident asthma (Khreis et al., 2017; Anderson et al., 2013b; Bowatte et al., 2015; Gasana et al., 2012). Their selection criteria and analytical approaches differed, but the sum of evidence generally supports an association between NO₂, or the complex pollutant mixtures it represents, and increased risk of incident asthma. Because the prevalence of asthma reflects the varying contributions of incidence, remission, relapse, and changes in severity, one possible implication for our study of NO₂ and prevalent asthma is that the effects we observed may be partially due to increased incidence (Favarato et al., 2014; Anderson et al., 2013b). It remains to be elucidated whether incident asthma represents an effect of NO₂ that would not have occurred in its absence, or the expedited development of clinically-apparent asthma that was already underway due to other

causes (Khreis et al., 2017; Anderson et al., 2013b).

Among the parent-reported outcomes described here, our main focus was current asthma. Other outcomes significantly associated with a 4 ppb increase in NO₂ were: lifetime asthma (mostly for LUR-based exposure estimates), itchy rash for six of the last twelve months (LUR-based estimate only), beta-agonist use in the last twelve months (LUR-based estimate only), wheeze after exercise in the last twelve months (monitor and LUR-based estimates), and current wheeze (monitor-based estimate only). Taken together with our main findings, these results support a non-spurious association between NO₂ and indicators of asthma in Australian children.

4.3. Effects of NO₂ on lung function and FeNO

We found statistically significant reductions in percent predicted FEV₁ and FVC per 4 ppb increase in NO₂. These effects were observed for lifetime, previous, and recent exposure, but only when using monitor-based exposures. This finding was in contrast to our results for current asthma and other parent-reported outcomes, where LUR-estimated recent exposures generally led to larger effects than those from monitor-based estimates. One possible explanation that lung function may be more sensitive than parent-reported outcomes to variability in NO₂ that is not captured by the monthly LUR estimates to the same extent as the hourly NO₂ measurements, both of which were then averaged over different exposure windows. Another possible explanation is that school-based exposures, which the monitors were well-placed to capture (median distance: 1.4 km), could be more relevant for lung function outcomes. For example, outdoor activities during school time can involve brief but vigorous physical activity during PE classes or recesses, and a child's respiratory ventilation rate can increase up to 17-fold during exercise (McConnell et al., 2002).

Previous studies have reported associations between increased exposure to air pollutants, including NO₂, and small but statistically significant decreases in lung function among non-asthmatic and asthmatic school children (e.g. Gehring et al., 2013; Ierodiakonou et al., 2016; Urman et al., 2014; Wang et al., 2015; Steerenberg et al., 2001). The converse has also been demonstrated; that reductions in NO₂ and PM_{2.5} in Southern California over 1998–2011 were associated with improvements in FEV₁ and FVC (Gauderman et al., 2015). Our findings add to the existing evidence by demonstrating that relatively low levels of outdoor NO₂ are associated with statistically significant reductions in percent predicted FVC and FEV₁ in this population-based cross-sectional study of 2630 Australian children.

We found that increased NO₂ exposure had a significant association with increased FeNO; from 32% (95% CI: 14, 53%) to 37% (95% CI: 19%, 58%) per 4 ppb for lifetime and recent exposure, respectively, based on monitored NO₂. The effect size was larger for LUR-based estimates of recent exposure: 71% (95% CI: 38%, 112%), 52% (95% CI: 24%, 86%) and 60% (95% CI: 30%, 98%) for school, home, and combined exposures, respectively. Moreover, a 4 ppb increase in NO₂ was strongly associated with greater odds of having high FeNO (> 19.4 ppb). That finding was consistent across all exposure time windows using monitored NO₂, and all LUR-based estimates of recent exposure.

FeNO is a marker of eosinophilic airway inflammation, with which TRAP has been associated in asthmatic and non-asthmatic school children (e.g. Dales et al., 2008; Eckel et al., 2011; Delfino et al., 2006; Steerenberg et al., 2001). Pro-oxidant components of TRAP, including PM_{2.5}, can generate reactive oxygen species that deplete ascorbate and glutathione, and have been associated with increased FeNO in children with asthma (Maikawa et al., 2016). Some children have greater genetic and epigenetic susceptibility to such pro-oxidants on FeNO, which reflects their NOS2 haplotype that encodes inducible nitric oxide synthase (iNOS) (Zhang et al., 2017). Although we did not collect genetic data in this study, our results add further evidence that NO₂, as a proxy for urban pollutant mixtures, is associated with eosinophilic airway inflammation in children, as measured by FeNO.

4.4. Strengths and limitations

The design of this study has four main strengths. First, we recruited 2630 children from 12 urban locations throughout Australia, ranging from regional cities (population: ~20,000 to ~500,000) through to large metropolitan hubs like Sydney (population: ~4.3 million). Second, we purposefully selected schools through which children were recruited based on proximity to pollutant monitors that maximised the variability of pollutant concentrations. Third, we used two methods to assess NO₂ exposure; monitor-based measurements within 2 km of each school and a validated national satellite-based LUR model that allowed us to estimate spatial contrasts in exposure using both school and home addresses across the 12 cities. Fourth, we based questionnaire items on large international studies (primarily ISAAC), which have been validated and have adequate sensitivity and specificity for doctor-diagnosed asthma (e.g. Hederos et al., 2007; Nwaru et al., 2011).

Our study has four main limitations. First, we used a cross-sectional design that precluded the assessment of a causal association between NO₂ and respiratory outcomes. Our analysis of effects for lifetime exposures and lifetime asthma, and, separately, for recent exposures and recent outcomes attempted to provide additional information on the role of different exposure time windows, within the limitations of a cross-sectional study. Second, due mainly to equipment malfunction, we did not have FeNO observations for about 30% of children. While unfortunate, these missing measurements merely limit the statistical power of the study for FeNO, since the losses were unrelated to the true level of FeNO. Third, because we selected schools based on proximity to regulatory air monitors, it is difficult to judge the representativeness of the sample of children in relation to the target population of all urban primary-school aged children in 2007–2008. Moreover, the questionnaire response rate was 37.8%, which could reflect selection bias. The characteristics of our sample, in terms of asthma prevalence and other conditions, were consistent with published estimates from national surveys at the time of our study (AIHW, Australian Centre for Asthma Monitoring, 2007).

Finally, we used NO₂ as a proxy for complex urban pollutant mixtures from traffic and other combustion emissions. It can mask confounding by correlated pollutants, including black carbon (Favarato et al., 2014; Khreis et al., 2017; Khreis and Nieuwenhuijsen, 2017). Although our main findings remained consistent when NO₂ was adjusted for other measured pollutants, it is not possible to state the extent to which the effects we observed are attributable to NO₂, as distinct from unmeasured pollutants like black carbon.

5. Conclusions

We found strong evidence of a positive association between exposure to outdoor NO₂ and increased odds of current asthma in Australian children aged 7–11 years during 2007–2008. We also found an association with decreased FEV₁ and FVC, and with increased FeNO, a marker of airway inflammation commonly associated with asthma. These effects were observed in relatively low-pollution settings with an annual mean NO₂ concentration of ~9 ppb. Gradual but consistent reductions in pollutant concentrations in Australian cities, which have been observed in recent years since our study, may therefore yield benefits for children's respiratory health. Follow-up studies to quantify the effects of such reductions would be useful.

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Appendix A. Supplementary information

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SUPPLEMENT

The Australian Child Health and Air Pollution Study (ACHAPS): a national population-based cross-sectional study of long-term exposure to outdoor air pollution, asthma, and lung function

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Table S1. Characteristics of the ACHAPS study population overall and by NO₂ exposure tertile (based on recent exposure estimates derived from monitored NO₂).

Item		n/N (%) or mean $\pm$ SD (N)			
Socio-demographic		Overall	1st tertile	2nd tertile	3rd tertile
	Age (years)	10.1 $\pm$ 1.2 (2630)	10.2 $\pm$ 1.2 (844)	10.1 $\pm$ 1.2 (882)	10.2 $\pm$ 1.2 (881)
	Female	1339/2612 (51.3)	433/837 (51.7)	456/872 (52.3)	440/880 (50)
	Born in Australia	2425/2627 (92.3)	754/838 (90)	780/863 (90.4)	782/861 (90.8)
	Speak language other than English at home	442/2572 (17.2)	106/832 (12.7)	138/857 (16.1)	194/860 (22.6)
	Mother completed 12 years of high school	1908/2560 (74.5)	553/831 (66.6)	649/854 (76)	662/852 (77.7)
	Father completed 12 years of high school	1801/2431(74.1)	523/771 (67.8)	613/821 (74.7)	629/820 (76.7)
	Index of relative socio-economic advantage and disadvantage	1022 $\pm$ 75 (2630)	993 $\pm$ 76 (844)	1025 $\pm$ 67 (882)	1051 $\pm$ 67 (881)
	Index of education and occupation	1024 $\pm$ 90 (2630)	985 $\pm$ 83 (844)	1020 $\pm$ 74 (882)	1068 $\pm$ 89 (881)
	Mother - history of asthma	543/2504 (21.7)	183/802 (22.8)	194/839 (23.1)	160/843 (19)
	Father - history of asthma	437/2376 (18.4)	135/743 (18.1)	151/798 (18.9)	147/818 (18)
Indoor exposure sources					
	Indoor exposure to gas cooking - first year of life	1604/2546 (63)	498/812 (61.3)	507/856 (59.2)	585/857 (68.3)
	Indoor exposure to gas cooking - currently	1768/2602 (68)	534/832 (64.2)	586/874 (67.1)	635/874 (72.7)
	Indoor exposure to gas heating - first year of life	880/2630 (33.5)	239/519 (46.1)	186/554 (33.6)	243/550 (44.2)
	Indoor exposure to gas heating - currently	875/2630 (33.3)	243/525 (46.3)	219/552 (39.7)	251/553 (45.4)
	Indoor exposure to second-hand smoke - currently	225/2614 (8.6)	94/841 (11.1)	48/877 (5.5)	77/874 (8.8)
	Had a cat - first year of life	703/2082 (33.8)	275/709 (38.8)	238/723 (32.9)	183/630 (29.1)
	Currently have a cat	751/2108 (35.6)	269/716 (37.6)	258/729 (35.4)	218/642 (34)
	Had a dog - first year of life	1053/2086 (50.5)	404/712 (56.7)	377/718 (52.5)	260/635 (40.9)
	Currently have a dog	1282/2110 (60.8)	462/722 (64)	453/723 (62.7)	355/645 (55)
Asthma history and medication use - recent					
	Current asthma	385/2593 (14.9)	102/830 (12.3)	139/865 (16.1)	137/875 (15.7)
	Any asthma/wheezing medication in the last 12 months	574/2479 (23.2)	166/791 (21)	211/832 (25.4)	191/833 (22.9)

Visit doctor for asthma last 12 months	322/2394 (13.5)	93/761 (12.2)	109/811 (13.4)	114/802 (14.2)
Current wheeze	438/2601 (16.8)	123/835 (14.7)	157/869 (18.1)	150/874 (17.2)
Wheeze after exercise last 12 months	304/2250 (13.2)	83/724 (11.5)	103/750 (13.7)	112/758 (14.8)
Itchy rash for 6 months in the last 12 months	440/2616 (16.8)	148/838 (17.7)	131/875 (15)	158/880 (18)
Rhinitis last 12 months	823/2617 (31.5)	261/841 (31)	291/875 (33.3)	266/879 (30.3)
Cough last 12 months	1882/2620 (71.8)	616/841 (73.3)	623/875 (71.2)	624/881 (70.8)
Dry cough at night last 12 months	605/2614 (23.1)	191/840 (22.7)	201/874 (23)	201/878 (22.9)
Asthma history and medication use - lifetime				
Lifetime asthma	739/2603 (28.4)	234/835 (28)	247/868 (28.5)	245/877 (27.9)
Any asthma medication ever	974/2478 (39.3)	301/791 (38.1)	341/832 (41)	318/832 (38.2)
Ever admitted to hospital for breathing problems	352/2592 (13.6)	118/835 (14.1)	113/863 (13.1)	112/871 (12.9)
Lifetime wheeze	922/2604 (35.4)	289/836 (34.6)	318/869 (36.6)	301/876 (34.4)
Itchy rash for 6 months ever	619/2620 (23.6)	198/840 (23.6)	194/876 (22.2)	223/881 (25.3)
Rhinitis ever	884/2617 (33.8)	283/839 (33.7)	308/875 (35.2)	286/881 (32.5)
Parent-reported doctor-diagnosed eczema/atopic dermatitis	610/2561 (23.8)	183/821 (22.3)	206/863 (23.9)	217/855 (25.4)
Clinical measurements				
Height (cm)	141.1 ± 9.1 (2619)	141.3 ± 9.1 (842)	140.8 ± 9.1 (876)	141.3 ± 9.3 (878)
Weight (kg)	37.6 ± 9.9 (2617)	37.7 ± 9.9 (841)	37.4 ± 10.2 (875)	37.7 ± 9.5 (878)
BMI (kg/m ²)	18.7 ± 3.3 (2616)	18.7 ± 3.3 (841)	18.6 ± 3.5 (875)	18.7 ± 3.2 (877)
Lung function and Fe_{NO}				
FEV₁				
Pre-bronchodilator (L)	2 ± 0.4 (2621)	2 ± 0.4 (842)	2 ± 0.4 (877)	2 ± 0.4 (879)
Pre-bronchodilator (% predicted)	98.3 ± 10.3 (2592)	98.8 ± 10 (833)	98.8 ± 10.3 (861)	97.2 ± 10.6 (875)
Post-bronchodilator (L)	2.1 ± 0.4 (2599)	2.1 ± 0.4 (831)	2.1 ± 0.4 (872)	2.1 ± 0.4 (873)
Post-bronchodilator (% predicted)	101.7 ± 10.5 (2570)	102.4 ± 10.2 (822)	102.1 ± 10.3 (856)	100.7 ± 10.7 (869)
% change: Pre- to post- bronchodilator	3.6 ± 5.3 (2595)	3.7 ± 5.4 (831)	3.5 ± 5.2 (869)	3.7 ± 5.4 (872)

FVC				
Pre-bronchodilator (L)	2.3 ± 0.5 (2489)	2.3 ± 0.5 (792)	2.3 ± 0.5 (827)	2.3 ± 0.5 (847)
Pre-bronchodilator (% predicted)	97.7 ± 10.5 (2462)	98.4 ± 10.6 (784)	98.1 ± 10.4 (812)	96.5 ± 10.5 (843)
Post-bronchodilator (L)	2.3 ± 0.5 (2513)	2.4 ± 0.5 (793)	2.3 ± 0.5 (841)	2.3 ± 0.5 (856)
Post-bronchodilator (% predicted)	98.8 ± 10.5 (2485)	99.6 ± 10.6 (785)	98.9 ± 10.2 (825)	97.9 ± 10.6 (852)
FEV₁/FVC ratio				
Pre-bronchodilator (%)	87.9 ± 6.5 (2489)	87.9 ± 7.2 (792)	87.9 ± 6.1 (827)	87.9 ± 6.2 (847)
Pre-bronchodilator (% predicted)	100.1 ± 7.3 (2462)	100 ± 8 (784)	100.1 ± 6.8 (812)	100.2 ± 6.9 (843)
Post-bronchodilator (%)	90.0 ± 5.4 (2513)	89.9 ± 5.4 (793)	90.2 ± 5.5 (841)	89.9 ± 5.4 (856)
Post-bronchodilator (% predicted)	102.5 ± 6.0 (2485)	102.4 ± 6 (785)	102.6 ± 6.1 (825)	102.4 ± 5.9 (852)
Fe _{NO} (ppb)	9.4 ± 7.1 (1815)	8.4 ± 7.2 (689)	9.1 ± 6.2 (611)	11.1 ± 7.7 (492)
High Fe _{NO}	135/1815 (7.4)	40/689 (5.8)	38/611 (6.2)	55/492 (11.2)

Table S2. Effect estimates for respiratory outcomes associated with an IQR (4.03 ppb) increase in monitored NO₂ (lifetime, previous, and recent exposure), adjusted for indoor exposure

Outcome	NO ₂ at nearest monitor to school					
	Lifetime exposure		Previous exposure		Recent exposure	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratio^a for IQR increase:						
Current asthma	1.20 (1.04, 1.39)	0.014	1.22 (1.05, 1.42)	0.009	1.25 (1.07, 1.45)	0.004
Lifetime asthma	1.07 (0.98, 1.16)	0.14	1.10 (1.01, 1.20)	0.038	1.08 (0.98, 1.19)	0.10
High Fe _{NO}	1.60 (1.20, 2.14)^c	0.001	1.59 (1.19, 2.12)^c	0.001	1.86 (1.39, 2.49)^c	< 0.001
Current wheeze	1.14 (1.02, 1.28)	0.027	1.13 (1.01, 1.27)	0.034	1.18 (1.04, 1.33)	0.010
Current cough	0.98 (0.86, 1.11)	0.73	0.99 (0.86, 1.14)	0.89	0.99 (0.86, 1.14)	0.91
Visit to doctor for asthma last 12 months	1.12 (0.92, 1.38)	0.26	1.12 (0.92, 1.37) ^d	0.25	1.16 (0.93, 1.44) ^d	0.19
Beta-agonist (short-term) last 12 months	1.09 (0.96, 1.24)	0.20	1.12 (0.98, 1.28)	0.11	1.10 (0.97, 1.25)	0.15
Wheeze after exercise last 12 months	1.24 (1.10, 1.39)	< 0.001	1.25 (1.11, 1.40)	< 0.001	1.29 (1.13, 1.48)	< 0.001
Itchy rash for 6 months last 12 months	1.01 (0.87, 1.18)	0.85	1.02 (0.87, 1.19)	0.79	1.03 (0.86, 1.22)	0.78
Rhinitis last 12 months	0.95 (0.82, 1.09)	0.44	0.98 (0.85, 1.13)	0.79	0.92 (0.78, 1.09)	0.33
Change^b per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	-1.03 (-1.87,-0.19)	0.017	-0.96 (-1.80,-0.12)	0.026	-1.23 (-2.08,-0.39)	0.005
FEV ₁ Post-bronchodilator (% predicted)	-1.09 (-1.90,-0.29)	0.009	-1.12 (-1.95,-0.29)	0.009	-1.34 (-2.21,-0.47)	0.003
FVC Pre-bronchodilator (% predicted)	-0.94 (-1.67,-0.21)	0.013	-0.81 (-1.58,-0.03)	0.042	-1.09 (-1.85,-0.34)	0.006
FVC Post-bronchodilator (% predicted)	-1.01 (-1.83,-0.18)	0.018	-0.98 (-1.82,-0.14)	0.023	-1.17 (-2.02,-0.32)	0.008
FEV ₁ /FVC Pre-bronchodilator (% predicted)	-0.10 (-0.70, 0.50)	0.75	-0.15 (-0.74, 0.44)	0.61	-0.11 (-0.59, 0.37)	0.64
FEV ₁ /FVC Post-bronchodilator (% predicted)	0.02 (-0.49, 0.53)	0.94	-0.03 (-0.52, 0.46)	0.90	-0.11 (-0.52, 0.31)	0.60
Fe _{NO} (% increase)	32 (14, 52)	< 0.001	32 (14, 52)	< 0.001	38 (19, 59)	< 0.001

a. Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD), exposure to indoor smoking and exposure to gas used for heating and/or cooking.

b. Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, exposure to indoor smoking and exposure to gas used for heating and/or cooking.

c. Exposure to indoor smoking significant

d. Exposure to gas cooking/heating significant

Table S3. Effect estimates for respiratory outcomes associated with a 4.03 ppb (IQR for measured NO₂) increase in satellite-based LUR NO₂ (recent exposure only; school, home, and combined exposure), adjusted for indoor exposure

Outcome	NO ₂ from satellite-based LUR					
	School Address		Home Address		Combined (school and home)	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratio^a for IQR increase:						
Current asthma	1.47 (1.18, 1.84)	< 0.001	1.49 (1.22, 1.83)	< 0.001	1.54 (1.25, 1.90)	< 0.001
Lifetime asthma	1.25 (1.03, 1.51)	0.025	1.29 (1.08, 1.54)	0.005	1.31 (1.08, 1.59)	0.007
High Fe _{NO}	3.42 (1.93, 6.08)^c	< 0.001	2.54 (1.59, 4.04)^c	< 0.001	2.94 (1.74, 4.95)^c	< 0.001
Current wheeze	1.20 (0.96, 1.49)	0.11	1.24 (0.99, 1.55)	0.06	1.25 (0.99, 1.57)	0.06
Current cough	0.89 (0.71, 1.11)	0.31	0.85 (0.69, 1.05)	0.13	0.85 (0.68, 1.06)	0.14
Visit to doctor for asthma last 12 months	1.33 (0.97, 1.82)	0.07	1.23 (0.93, 1.63)	0.14	1.27 (0.94, 1.72)	0.12
Beta-agonist (short-term) last 12 months	1.23 (1.01, 1.49)	0.039	1.31 (1.09, 1.58)	0.005	1.32 (1.09, 1.60)	0.005
Wheeze after exercise last 12 months	1.55 (1.24, 1.92)	< 0.001	1.53 (1.26, 1.84)	< 0.001	1.59 (1.30, 1.94)	< 0.001
Itchy rash for 6 months last 12 months	1.39 (1.07, 1.80)	0.013	1.36 (1.11, 1.66)	0.003	1.40 (1.12, 1.76)	0.004
Rhinitis last 12 months	1.00 (0.78, 1.28)	1.00	1.13 (0.93, 1.38)	0.22	1.11 (0.89, 1.38)	0.34
Change^b per IQR in:						
FEV1 Pre-bronchodilator (% predicted)	-1.15 (-2.68, 0.37)	0.14	0.12 (-1.04, 1.27)	0.84	-0.15 (-1.44, 1.13)	0.81
FEV1 Post-bronchodilator (% predicted)	-1.41 (-2.75, -0.06)	0.040	-0.17 (-1.21, 0.87)	0.74	-0.46 (-1.59, 0.68)	0.42
FVC Pre-bronchodilator (% predicted)	-0.95 (-2.26, 0.36)	0.15	0.18 (-0.86, 1.21)	0.73	-0.06 (-1.20, 1.08)	0.92
FVC Post-bronchodilator (% predicted)	-1.12 (-2.42, 0.19)	0.09	-0.13 (-1.17, 0.90)	0.80	-0.36 (-1.48, 0.76)	0.52
FEV1/FVC Pre-bronchodilator (% predicted)	-0.30 (-1.24, 0.63)	0.52	-0.02 (-0.90, 0.86)	0.96	-0.09 (-1.01, 0.84)	0.85
FEV1/FVC Post-bronchodilator (% predicted)	-0.22 (-0.96, 0.52)	0.55	0.01 (-0.63, 0.65)	0.98	-0.04 (-0.73, 0.65)	0.91
Fe _{NO} (% increase)	72 (38, 113)	< 0.001	53 (24, 87)	< 0.001	61 (31, 99)	< 0.001

- Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD), exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Exposure to indoor smoking significant.
- Exposure to gas cooking/heating significant.

Table S4. Effect estimates for respiratory outcomes associated with an IQR (4.03 ppb) increase in monitored NO₂ (lifetime, previous, and recent exposure), adjusted for monitored exposure on day of, or day before, spirometry measurement.

Outcome	NO ₂ at nearest monitor to school					
	Lifetime exposure		Previous exposure		Recent exposure	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Change^a per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	-1.08 (-1.92,-0.25)	0.012	-0.94 (-1.80,-0.07)	0.035	-1.12 (-2.03,-0.22)	0.017
FEV ₁ Post-bronchodilator (% predicted)	-1.21 (-2.05,-0.36)	0.006	-1.18 (-2.07,-0.28)	0.012	-1.25 (-2.16,-0.33)	0.009
FVC Pre-bronchodilator (% predicted)	-1.06 (-1.85,-0.27)^c	0.010	-0.87 (-1.74,-0.00)^c	0.049	-1.02 (-1.83,-0.20)^c	0.016
FVC Post-bronchodilator (% predicted)	-1.14 (-1.99,-0.28)	0.011	-1.05 (-2.00,-0.09)	0.032	-1.09 (-1.99,-0.20)	0.018
FEV ₁ /FVC Pre-bronchodilator (% predicted)	0.04 (-0.45, 0.53) ^c	0.88	0.02 (-0.51, 0.55) ^c	0.95	-0.07 (-0.57, 0.43) ^c	0.77
FEV ₁ /FVC Post-bronchodilator (% predicted)	-0.01 (-0.44, 0.42) ^c	0.97	-0.07 (-0.50, 0.37) ^c	0.76	-0.12 (-0.54, 0.30) ^c	0.56
Fe _{NO} (% increase)	37 (23, 53)	< 0.001	37 (23, 52)	< 0.001	40 (24, 58)	< 0.001
Change^b per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	-1.09 (-1.93,-0.26)	0.012	-0.96 (-1.82,-0.09)	0.031	-1.13 (-2.04,-0.21)	0.017
FEV ₁ Post-bronchodilator (% predicted)	-1.23 (-2.09,-0.37)	0.006	-1.21 (-2.12,-0.30)	0.011	-1.27 (-2.21,-0.33)	0.009
FVC Pre-bronchodilator (% predicted)	-1.12 (-1.92,-0.33)	0.007	-0.95 (-1.81,-0.09)	0.032	-1.06 (-1.87,-0.25)	0.012
FVC Post-bronchodilator (% predicted)	-1.19 (-2.04,-0.33)	0.008	-1.11 (-2.05,-0.16)	0.024	-1.13 (-2.03,-0.24)	0.015
FEV ₁ /FVC Pre-bronchodilator (% predicted)	0.09 (-0.42, 0.60)	0.72	0.07 (-0.47, 0.62)	0.79	-0.03 (-0.54, 0.47)	0.89
FEV ₁ /FVC Post-bronchodilator (% predicted)	0.03 (-0.41, 0.47)	0.90	-0.03 (-0.47, 0.41)	0.89	-0.10 (-0.53, 0.33)	0.65
Fe _{NO} (% increase)	37 (22, 54)^d	< 0.001	37 (23, 53)^d	< 0.001	41 (25, 59)^d	< 0.001

- Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, same day value for exposure.
- Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, value for exposure on day before measurement
- Same day exposure significant
- Day before exposure significant

Table S5. Effect estimates for respiratory outcomes associated with a 4.03 ppb (IQR for measured NO₂) increase in satellite-based LUR NO₂ (recent exposure only; school, home, and combined exposure), adjusted for monitored exposure on day of, or day before, spirometry measured.

Outcome	NO ₂ from satellite-based LUR					
	School Address		Home Address		Combined (school and home)	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Change^a per IQR in:						
FEV1 Pre-bronchodilator (% predicted)	-0.88 (-2.21, 0.45)	0.19	0.29 (-0.70, 1.28)	0.55	0.06 (-1.02, 1.13)	0.91
FEV1 Post-bronchodilator (% predicted)	-1.39 (-2.55,-0.22)	0.021	-0.21 (-1.14, 0.72)	0.65	-0.49 (-1.45, 0.48)	0.31
FVC Pre-bronchodilator (% predicted)	-1.13 (-2.17,-0.08)	0.035	-0.04 (-0.93, 0.86)	0.93	-0.28 (-1.23, 0.67)	0.55
FVC Post-bronchodilator (% predicted)	-1.25 (-2.23,-0.27)	0.014	-0.32 (-1.19, 0.56)	0.46	-0.55 (-1.44, 0.34)	0.22
FEV1/FVC Pre-bronchodilator (% predicted)	0.15 (-0.46, 0.77)	0.62	0.34 (-0.35, 1.03)	0.32	0.33 (-0.34, 1.00)	0.32
FEV1/FVC Post-bronchodilator (% predicted)	-0.11 (-0.73, 0.50)	0.71	0.13 (-0.34, 0.60)	0.58	0.09 (-0.41, 0.59)	0.73
Fe _{NO} (% increase)	65 (40, 94)	< 0.001	44 (19, 73)	< 0.001	52 (26, 84)	< 0.001
Change^b per IQR in:						
FEV1 Pre-bronchodilator (% predicted)	-0.96 (-2.26, 0.34)	0.14	0.26 (-0.72, 1.24)	0.59	0.02 (-1.05, 1.08)	0.98
FEV1 Post-bronchodilator (% predicted)	-1.39 (-2.56,-0.22)	0.02	-0.18 (-1.11, 0.76)	0.71	-0.46 (-1.42, 0.51)	0.35
FVC Pre-bronchodilator (% predicted)	-1.14 (-2.26,-0.02)	0.045	0.02 (-0.81, 0.86)	0.96	-0.23 (-1.14, 0.68)	0.61
FVC Post-bronchodilator (% predicted)	-1.21 (-2.27,-0.14)	0.028	-0.23 (-1.04, 0.58)	0.57	-0.46 (-1.30, 0.38)	0.27
FEV1/FVC Pre-bronchodilator (% predicted)	0.12 (-0.54, 0.79)	0.71	0.28 (-0.51, 1.07)	0.47	0.27 (-0.51, 1.05)	0.48
FEV1/FVC Post-bronchodilator (% predicted)	-0.15 (-0.75, 0.45)	0.61	0.07 (-0.45, 0.60)	0.78	0.03 (-0.52, 0.58)	0.91
Fe _{NO} (% increase)	59 (31, 92)	< 0.001	37 (9, 72)	0.009	45 (15, 83)	0.003

a. Adjusted for age, sex, parental education, IEO, IRSEAD, same day value for exposure.

b. Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, value for exposure on day before measurement.

No significant effects of same day or day before exposure

Table S6. Effect estimates for respiratory outcomes associated with an IQR (4.03 ppb) increase in monitored NO₂ (lifetime, previous, and recent exposure), excluding participants for which distance between residence and monitor was greater than 2.44 km.

Outcome	NO ₂ at nearest monitor to school					
	Lifetime exposure		Previous exposure		Recent exposure	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratio^a for IQR increase:						
Current asthma	1.25 (1.04, 1.50)	0.017	1.26 (1.05, 1.51)	0.011	1.32 (1.09, 1.61)	0.005
Lifetime asthma	1.14 (1.01, 1.28)	0.034	1.18 (1.04, 1.33)	0.009	1.15 (1.01, 1.30)	0.030
High Fe _{NO}	1.65 (1.07, 2.53)	0.022	1.59 (1.03, 2.46)	0.034	1.95 (1.21, 3.14)	0.006
Current wheeze	1.22 (1.05, 1.43)	0.012	1.21 (1.04, 1.40)	0.015	1.27 (1.05, 1.53)	0.013
Current cough	0.98 (0.86, 1.12)	0.77	1.01 (0.86, 1.17)	0.95	0.96 (0.84, 1.11)	0.60
Visit to doctor for asthma last 12 months	1.21 (0.99, 1.49)	0.06	1.18 (0.97, 1.43)	0.09	1.28 (1.02, 1.60)	0.036
Beta-agonist (short-term) last 12 months	1.12 (0.97, 1.29)	0.12	1.14 (1.00, 1.30)	0.046	1.13 (0.98, 1.31)	0.10
Wheeze after exercise last 12 months	1.38 (1.14, 1.66)	< 0.001	1.36 (1.14, 1.63)	< 0.001	1.47 (1.18, 1.84)	< 0.001
Itchy rash for 6 months last 12 months	1.12 (0.95, 1.31)	0.17	1.12 (0.96, 1.31)	0.14	1.16 (0.96, 1.40)	0.13
Rhinitis last 12 months	0.93 (0.81, 1.06)	0.26	0.97 (0.85, 1.11)	0.64	0.91 (0.78, 1.06)	0.21
Change^b per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	-1.52 (-2.33,-0.70)	< 0.001	-1.43 (-2.21,-0.65)	< 0.001	-1.86 (-2.60,-1.11)	< 0.001
FEV ₁ Post-bronchodilator (% predicted)	-1.41 (-2.14,-0.68)	< 0.001	-1.42 (-2.15,-0.70)	< 0.001	-1.74 (-2.36,-1.12)	< 0.001
FVC Pre-bronchodilator (% predicted)	-1.19 (-1.94,-0.44)	0.002	-1.05 (-1.81,-0.29)	0.008	-1.43 (-2.07,-0.79)	< 0.001
FVC Post-bronchodilator (% predicted)	-1.18 (-1.96,-0.40)	0.004	-1.13 (-1.91,-0.36)	0.005	-1.38 (-2.04,-0.71)	< 0.001
FEV ₁ /FVC Pre-bronchodilator (% predicted)	-0.34 (-0.91, 0.23)	0.24	-0.39 (-0.94, 0.16)	0.16	-0.43 (-0.87, 0.02)	0.06
FEV ₁ /FVC Post-bronchodilator (% predicted)	-0.16 (-0.68, 0.36)	0.54	-0.20 (-0.71, 0.31)	0.43	-0.35 (-0.79, 0.09)	0.12
Fe _{NO} (% increase)	36 (16, 59)	< 0.001	36 (16, 59)	< 0.001	44 (22, 70)	< 0.001

a. Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD).

b. Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature.

Table S7. Effect estimates for respiratory outcomes associated with an IQR (4.03 ppb) increase in monitored NO₂ (lifetime, previous, and recent exposure), adjusting for indoor exposure (gas/smoking) + additional questionnaire covariates

Outcome	NO ₂ at nearest monitor to school					
	Lifetime exposure		Previous exposure		Recent exposure	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratio^a for IQR increase:						
Current asthma	1.18 (1.02, 1.37)^{eh}	0.029	1.22 (1.05, 1.42)	0.009	1.20 (1.02, 1.40)	0.025
Lifetime asthma	1.06 (0.97, 1.17) ^h	0.21	1.11 (1.01, 1.21)^h	0.034	1.06 (0.94, 1.18) ^h	0.36
High Fe _{NO}	1.52 (1.17, 1.96)	0.002	1.52 (1.17, 1.96)^c	0.001	1.72 (1.31, 2.26)	< 0.001
Current wheeze	1.09 (0.96, 1.24)	0.17	1.10 (0.97, 1.25)	0.14	1.10 (0.96, 1.27)	0.17
Current cough	0.98 (0.85, 1.12)	0.727	1.00 (0.86, 1.16)	0.98	0.99 (0.85, 1.14)	0.84
Visit to doctor for asthma last 12 months	1.10 (0.89, 1.36) ^e	0.40	1.11 (0.91, 1.36) ^d	0.31	1.09 (0.86, 1.39) ^e	0.46
Beta-agonist (short-term) last 12 months	1.08 (0.94, 1.23) ^h	0.28	1.12 (0.98, 1.27) ^{ch}	0.10	1.05 (0.92, 1.22) ^h	0.46
Wheeze after exercise last 12 months	1.20 (1.05, 1.37)^h	0.006	1.23 (1.08, 1.41)^h	0.002	1.21 (1.04, 1.41)^h	0.012
Itchy rash for 6 months last 12 months	1.01 (0.85, 1.20) ^{fg}	0.89	1.03 (0.86, 1.24) ^{fg}	0.72	1.01 (0.83, 1.24)	0.89
Rhinitis last 12 months	0.92 (0.80, 1.07)	0.29	0.97 (0.83, 1.12) ^e	0.65	0.90 (0.76, 1.07)	0.24
Change^b per IQR in:						
FEV ₁ Pre-bronchodilator (% predicted)	-1.02 (-1.81,-0.23)^{eh}	0.013	-0.97 (-1.77,-0.17)^h	0.019	-1.23 (-2.01,-0.46)^{eh}	0.003
FEV ₁ Post-bronchodilator (% predicted)	-1.16 (-1.97,-0.36)^h	0.006	-1.21 (-2.05,-0.38)^h	0.005	-1.43 (-2.29,-0.57)^h	0.002
FVC Pre-bronchodilator (% predicted)	-1.05 (-1.76,-0.34)^{hi}	0.005	-0.92 (-1.64,-0.19)^{hi}	0.014	-1.25 (-2.02,-0.48)^{ehi}	0.002
FVC Post-bronchodilator (% predicted)	-1.08 (-1.89,-0.27)^{hi}	0.010	-1.06 (-1.87,-0.26)^{hi}	0.011	-1.28 (-2.11,-0.46)^{hi}	0.003
FEV ₁ /FVC Pre-bronchodilator (% predicted)	-0.02 (-0.68, 0.63) ^{hi}	0.94	-0.10 (-0.74, 0.53) ^{hi}	0.75	-0.00 (-0.50, 0.49) ^{hi}	0.99
FEV ₁ /FVC Post-bronchodilator (% predicted)	-0.02 (-0.55, 0.50) ⁱ	0.94	-0.08 (-0.58, 0.43) ⁱ	0.76	-0.12 (-0.53, 0.29) ^{hi}	0.55
Fe _{NO} (% increase)	29 (13, 49)^e	< 0.001	29 (13, 49)^e	< 0.001	35 (17, 55)^e	< 0.001

- Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD), exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Exposure to indoor smoking significant (t)

- d. Exposure to gas cooking/heating significant (g)
- e. House has air conditioning significant (h)
- f. House is less than 5 years old significant (n)
- g. Child attended day care first year of life significant (k)
- h. Child born premature significant (p)
- i. Mother smoking in pregnancy significant (m)

Table S8. Effect estimates for respiratory outcomes associated with a 4.03 ppb (IQR for measured NO₂) increase in satellite-based LUR NO₂ (recent exposure only; school, home, and combined exposure), adjusting for indoor exposure (gas/smoking) + additional questionnaire covariates

Outcome	NO ₂ from satellite-based LUR					
	School Address		Home Address		Combined (school and home)	
	Effect (95% CI)	P	Effect (95% CI)	P	Effect (95% CI)	P
Odds ratio^a for:						
Current asthma	1.41 (1.10, 1.80)^h	0.006	1.44 (1.16, 1.79)^h	0.001	1.48 (1.17, 1.87)^h	0.001
Lifetime asthma	1.21 (0.96, 1.53) ^h	0.10	1.27 (1.03, 1.57)^h	0.022	1.28 (1.02, 1.61)^h	0.031
High Fe _{NO}	3.29 (1.99, 5.45)	< 0.001	2.41 (1.57, 3.70)	< 0.001	2.79 (1.74, 4.46)	< 0.001
Current wheeze	1.10 (0.87, 1.40) ^h	0.42	1.19 (0.93, 1.52) ^h	0.18	1.18 (0.92, 1.53) ^h	0.20
Current cough	0.93 (0.73, 1.19)	0.55	0.87 (0.70, 1.08)	0.20	0.87 (0.69, 1.10)	0.24
Visit to doctor for asthma last 12 months	1.33 (0.97, 1.82) ^e	0.08	1.23 (0.94, 1.63) ^e	0.14	1.27 (0.94, 1.72) ^e	0.11
Beta-agonist (short-term) last 12 months	1.19 (0.96, 1.46) ^h	0.11	1.28 (1.05, 1.55)^h	0.015	1.28 (1.04, 1.58)^h	0.019
Wheeze after exercise last 12 months	1.43 (1.12, 1.82)^h	0.004	1.44 (1.18, 1.76)^h	< 0.001	1.49 (1.20, 1.84)^h	< 0.001
Itchy rash for 6 months last 12 months	1.38 (1.06, 1.80)^{fg}	0.017	1.38 (1.13, 1.69)^{fg}	0.001	1.42 (1.13, 1.78)^{fg}	0.003
Rhinitis last 12 months	0.96 (0.76, 1.20)	0.71	1.12 (0.93, 1.34)	0.25	1.09 (0.89, 1.34)	0.42
Change^b per IQR in:						
FEV1 Pre-bronchodilator (% predicted)	-1.14 (-2.65, 0.37) ^{eh}	0.13	0.16 (-0.97, 1.30) ^{eh}	0.77	-0.11 (-1.37, 1.15) ^{eh}	0.86
FEV1 Post-bronchodilator (% predicted)	-1.46 (-2.91,-0.01)^h	0.049	-0.20 (-1.28, 0.89) ^h	0.72	-0.49 (-1.68, 0.70) ^h	0.42
FVC Pre-bronchodilator (% predicted)	-1.03 (-2.41, 0.35) ^{ehi}	0.14	0.18 (-0.87, 1.22) ^{hi}	0.73	-0.07 (-1.23, 1.09) ^{hi}	0.90
FVC Post-bronchodilator (% predicted)	-1.17 (-2.59, 0.25) ⁱ	0.10	-0.13 (-1.21, 0.95) ⁱ	0.81	-0.37 (-1.56, 0.82) ⁱ	0.54
FEV1/FVC Pre-bronchodilator (% predicted)	-0.19 (-1.15, 0.76) ^{hi}	0.68	0.02 (-0.89, 0.94) ^{hi}	0.96	-0.02 (-0.98, 0.94) ^{hi}	0.97
FEV1/FVC Post-bronchodilator (% predicted)	-0.25 (-1.02, 0.52) ⁱ	0.51	-0.06 (-0.72, 0.60) ⁱ	0.86	-0.10 (-0.82, 0.61) ⁱ	0.77
Fe _{NO} (% increase)	67 (36, 107)^e	< 0.001	49 (23, 80)^e	< 0.001	57 (29, 91)^e	< 0.001

- Adjusted for age, sex, parental education, index of education and occupation (IEO), and index of relative socio-economic advantage and disadvantage (IRSAD), exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Adjusted for age, sex, parental education, IEO, IRSEAD, monthly (for month of testing) and annual average daily mean temperature, exposure to indoor smoking and exposure to gas used for heating and/or cooking.
- Exposure to indoor smoking significant

- d. Exposure to gas cooking/heating significant
- e. House has air conditioning significant
- f. House is less than 5 years old significant
- g. Child attended day care first year of life significant
- h. Child born premature significant
- i. Mother smoking in pregnancy significant

Figure S1. Comparison of monitored and satellite-based LUR NO₂ estimates (at the location of each of the 55 schools) of recent exposure (i.e., averaged over last 12 months). The red line shows the linear regression ($R^2 = 56\%$, RMSE = 1.40 ppb, coefficient = 0.52 ppb, intercept = 4.24). The black line is the line of agreement.

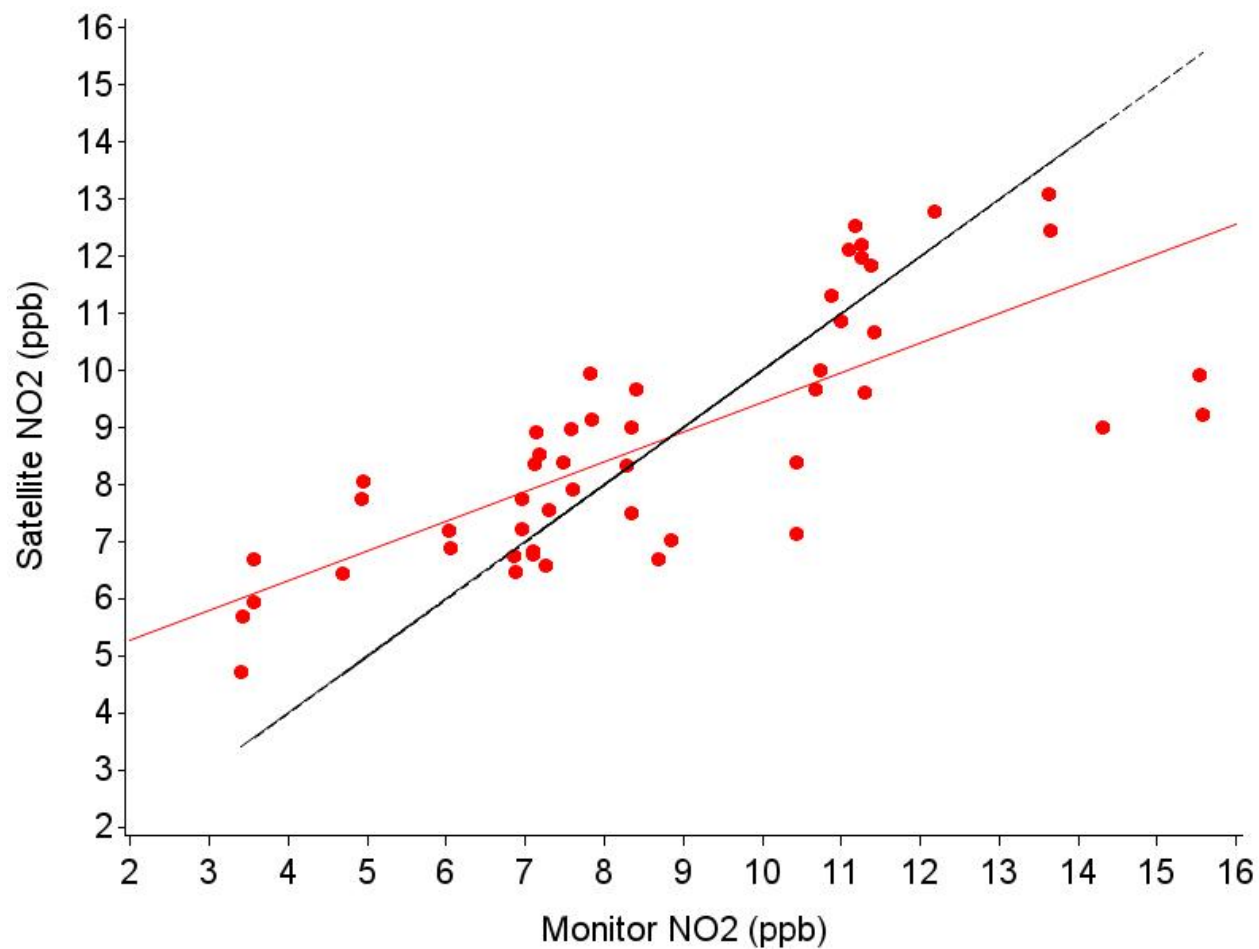


Figure S2. Two-pollutant model results (pre-bronchodilator FEV₁ percent predicted per 4.03 ppb increase in NO₂). Left panel is for monitored NO₂, right panel is for LUR-estimated NO₂. Note: we considered two-pollutant models for all outcomes; a selection are presented here but none changed the main findings appreciably.

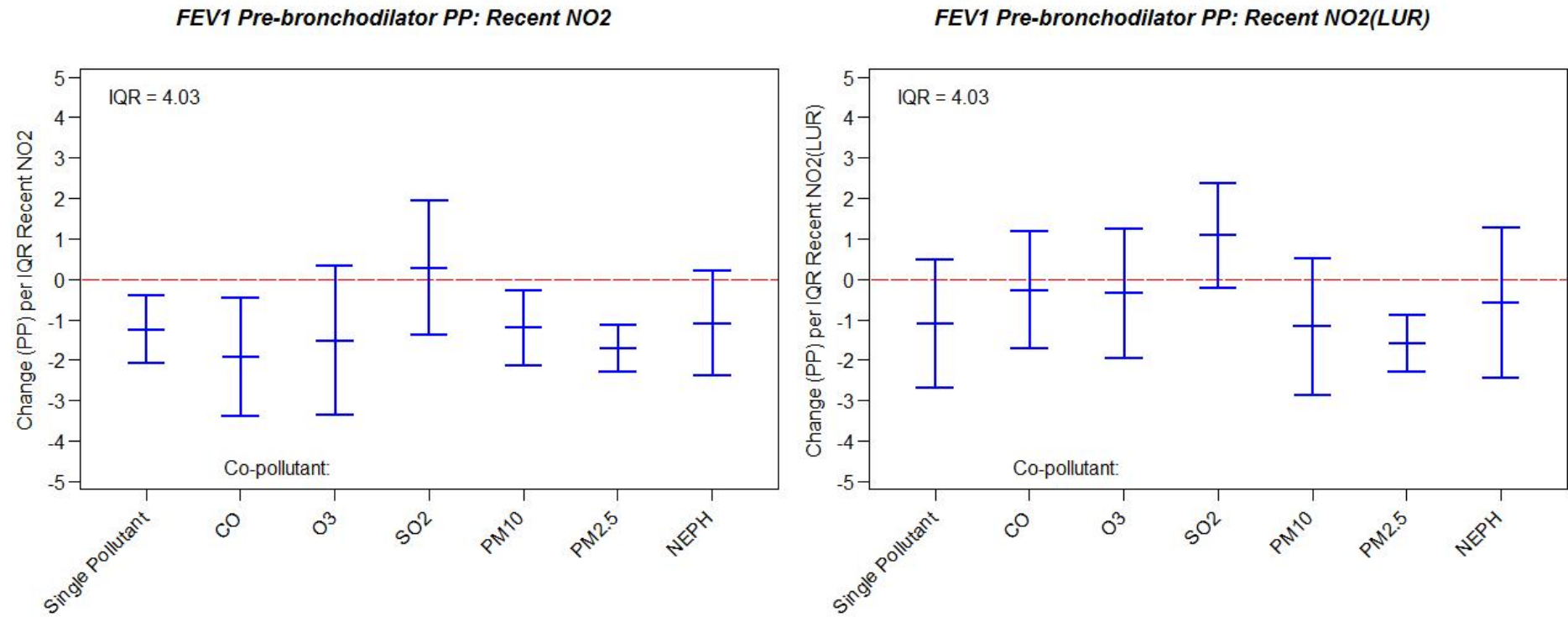


Figure S3. Two-pollutant model results (post-bronchodilator FEV₁ percent predicted per 4.03 ppb increase in NO₂). Left panel is for monitored NO₂, right panel is for LUR-estimated NO₂.

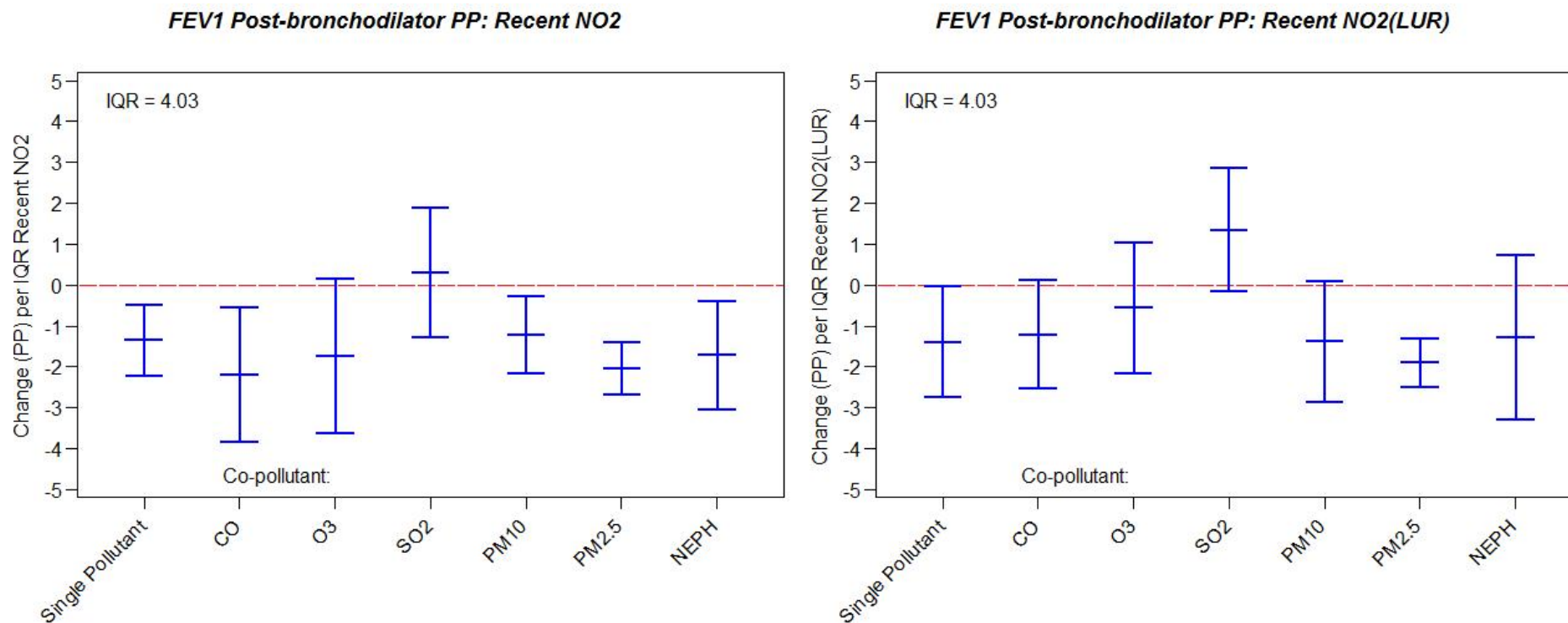


Figure S4. Two-pollutant model results (current asthma per 4.03 ppb increase in NO₂). Left panel is for monitored NO₂, right panel is for LUR-estimated NO₂.

