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The respiratory health effects of nitrogen dioxide in children with asthma

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ABSTRACT: There is growing evidence that asthma symptoms can be aggravated or events triggered by exposure to indoor nitrogen dioxide (NO_2) emitted from unflued gas heating.

The impact of NO_2 on the respiratory health of children with asthma was explored as a secondary analysis of a randomised community trial, involving 409 households during the winter period in 2006 (June to September).

Geometric mean indoor NO_2 levels were 11.4 $\mu g \cdot m^{-3}$, while outdoor NO_2 levels were 7.4 $\mu g \cdot m^{-3}$. Higher indoor NO_2 levels (per logged unit increase) were associated with greater daily reports of lower (mean ratio 14, 95% CI 1.12–1.16) and upper respiratory tract symptoms (mean ratio 1.03, 95% CI 1.00–1.05), more frequent cough and wheeze, and more frequent reliever use during the day, but had no effect on preventer use. Higher indoor NO_2 levels (per logged unit increase) were associated with a decrease in morning (-17.25 mL, 95% CI -27.63– -6.68) and evening (-13.21, 95% CI -26.03– -0.38) forced expiratory volume in 1 s readings. Outdoor NO_2 was not associated with respiratory tract symptoms, asthma symptoms, medication use or lung function measurements.

These findings indicate that reducing NO_2 exposure indoors is important in improving the respiratory health of children with asthma.

KEYWORDS: Asthma, children, heating, nitrogen dioxide, randomised community trial

Asthma is one of the most prevalent chronic diseases in childhood. It imposes a heavy burden on healthcare expenditure and reduces quality of life for individuals and their families. There is growing evidence that asthma symptoms can be aggravated or even triggered by exposure to indoor nitrogen dioxide (NO_2) emitted from unflued gas heating and cooking appliances [1–4].

While human controlled-exposure studies have reported associations between NO_2 and respiratory symptoms such as wheeze and cough [5–7], epidemiological evidence for the association between NO_2 exposure and respiratory symptoms has been inconsistent. This inconsistency is partly due to methodological problems, confounding or effect modification by other pollutants, and a lack of prospective data [8, 9]. To some extent, this inconsistency in epidemiological studies also relates to the differences between the groups of people who have been studied. Populations have included healthy children [4, 10, 11], children with asthma [1, 12, 13], infants [14, 15] and adults with and without asthma [16–19].

Despite methodological differences, a systematic review, involving 23 outdoor and 36 indoor studies, assessed the role of NO_2 in respiratory diseases. The review concluded that respiratory effects were associated with levels of NO_2 encountered in common domestic and outdoor settings [20]. Another systematic review of the health effects caused by environmental NO_2 reported that there was moderate evidence that short-term exposure (24 h), even for mean values <50 $\mu g \cdot m^{-3}$ NO_2, increased both hospital admissions and mortality [21]. The review also reported that there was moderate evidence that long-term exposure to an NO_2 level below the World Health Organization (WHO) recommended air quality annual mean guideline of 40 $\mu g \cdot m^{-3}$ was associated with adverse health effects (respiratory symptoms/diseases, hospital admissions, mortality and otitis media).

Few community randomised controlled trials have been conducted on the effects of NO_2 on respiratory health. In 2004, PILOTTO *et al.* [2] reported the first randomised controlled trial. Their study intervention involved removing high exposures to NO_2 by replacing unflued gas heaters in schools with flued gas or electric heaters. The study reported a reduction in the rates of difficult breathing, chest tightness and daytime asthma attacks.

We report a secondary analysis of a clustered, randomised control trial (identifier NCT00489762)

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designed to assess the effects of a heating intervention. The Housing, Heating and Health Study [22] has previously shown that homes in this study with unflued gas heating had significantly higher levels of NO_2 in their living rooms than homes that did not use this form of heating [23]. The primary aim of our study was to investigate the impact of NO_2 on the respiratory health of children with asthma in the home environment. A secondary aim was to investigate the effect of outdoor NO_2 on these children.

METHODS

Study design

The Housing, Heating and Health Study [22] was carried out between June and September 2006 in five communities in New Zealand (Bluff, Dunedin, Christchurch, Porirua and the Hutt Valley). This study presents a secondary analysis of the impact of NO_2 on the health of children with asthma.

Study population

A flow chart of the recruitment and retention progress throughout the study is shown in figure 1.

NO_2 measurements

We piloted the use of passive diffusion tubes to measure NO_2 in 203 homes during the winter period in 2005 (June until September) [24]. Passive diffusion tubes consist of an acrylic tube with a mesh steel cap that is coated in an absorbent (triethanolamine) at one end and a removable cap at the other end which, once opened, starts the sampling period. These tubes were inserted into spacers that held the tubes 5 cm away from the wall at a height of 1.8 m from the ground. Over the 2006 winter, NO_2 was measured over four 4-week sampling periods in 349 living rooms. Outdoor NO_2 (from the back porches of the homes) was measured over the final 4-week sampling period.

After 4 weeks, the tubes were collected, sealed, and returned to the study centre. NO_2 concentrations were determined in a single laboratory colorimetrically as nitrite using Griess–Saltzman reagent [24]. The azo dye-forming reagent was prepared as described previously [24] and contained *N*-(1-naphthyl) ethylenediamine dihydrochloride, de-ionised water, orthophosphoric acid (H_3PO_4), and sulfanilic acid. The reagent was fresh for each analytical run.

Outcome measures

Our primary outcomes were measures of lung function: peak expiratory flow rate (PEFR) and forced expiratory volume in 1 s (FEV_1). Small hand-held spirometers, ''Piko-meters'', were given to each child and their correct use explained by community co-ordinators. During the winter of 2005 the Piko-meter's internal recording device was used to select the best of three blows every morning and evening from 297 children. However, due to the high number of implausible readings recorded during the winter of 2005 (>5%), in 2006 more emphasis was placed on teaching the children the correct technique, as well as asking them to record up to five blows (morning and evening) in a symptom diary. Symptom diaries were designed to record symptoms for the entire study period (112 days per child). Daily measures of asthma severity and upper respiratory tract symptoms were recorded in the symptom diaries by 360 children in 2006. Each respiratory

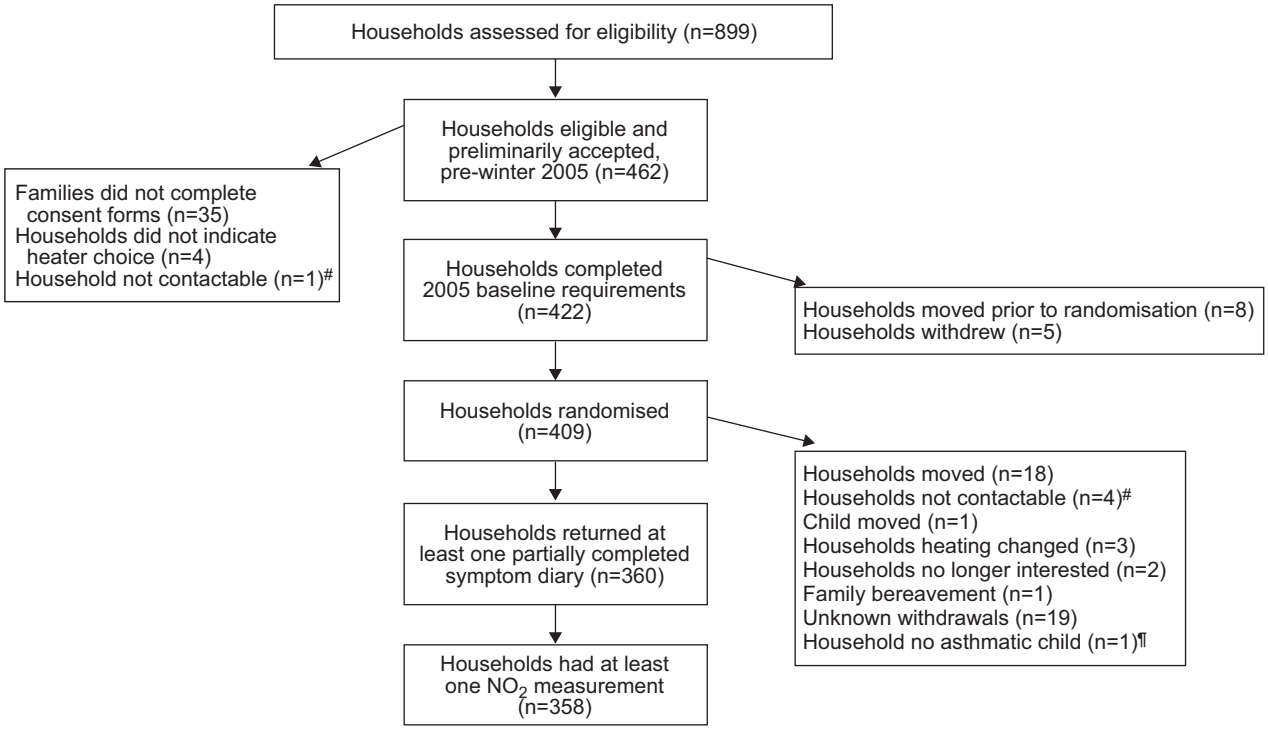

FIGURE 1. Flow chart of the recruitment and retention progress throughout the study. #: unable to make contact after at least three phone calls, two letters and community-coordinator visits, it is probable that these households have moved but we are unable to confirm this; ¶: did not meet entry criteria (child with asthma) and were dropped when this finally became clear after cross checking with the community coordinator.

symptom was recorded on a nominal severity scale from 0 to 3 as used by CHAUHAN *et al.* [12], with ''0'' representing the absence of a symptom and ''3'' representing the greatest severity level. Symptoms of cough at night, cough on waking, wheeze at night and wheeze on waking were recorded each morning. Cough and wheeze during the day and number of preventer and reliever puffs were recorded in the evening. Lower respiratory symptoms were defined as cough on waking, wheeze on waking, night-time cough and wheeze during the night, while upper respiratory tract symptoms were defined as having a runny nose or sneezing, blocked or stuffy nose, sore throat or hoarse voice, headaches or face aches, and aches and pains elsewhere. The median return for recorded symptoms was 81 days and lung function measures were recorded over a median of 72 days.

Ethical approval

Multi-region ethics approval was obtained before recruitment commenced. Parents signed consent forms on behalf of their children.

Statistical analysis

Data were cleaned and analysed using R version 2.9.1 (www.r-project.org). NO_2 measurements were log normally distributed, so the analysis was based on log-transformed NO_2 measures. The maximum morning and evening FEV1 and PEFR were used in the analysis. Reported daily health symptoms and spirometry were matched to the NO_2 level measured in the corresponding month. For example, an FEV1 or PEFR reading taken on day 10 was matched to the NO_2 level measured during the first 4-week period of the study.

During 2006 (study year), outcomes and NO_2 measurements were used in the models, the 2005 (pilot year) outcomes were not included in order to reduce model complexity. Linear mixed-effects models were used to analyse the data. These models consisted of two levels. The first level consisted of the random effects of the repeated measures on the same individuals. The second level captured the fixed linear effects of NO_2 on health outcomes. Outcomes for the linear mixed-effects models were daily maximum FEV1 and PEFR, and daily symptom scores.

TABLE 1 Participants characteristics, nitrogen dioxide (NO_2) levels and temperature during the winter of 2006

Subjects n	349
Males	58.6
Mean age at baseline yrs	9.6
Mäori children	35.0
New Zealand-European children	63.0
Pacific children	16.9
Other ethnicity	13.5
Indoor NO_2 level $\mu g \cdot m^{-3}$	11.4
Outdoor NO_2 level $\mu g \cdot m^{-3}$	7.4
Mean indoor temperature °C	16.5

Data are presented as % or geometric mean for NO_2 levels, unless otherwise stated.

The results are presented as the mean change in lung function per logged unit of NO_2 or the change in mean symptom rate per unit increase in logged NO_2. A one-unit change in NO_2 is approximately the same as moving from the 25th percentile to the 75th percentile. Indoor NO_2 was measured for up to 16 weeks (112 days) per child and outdoor NO_2 was measured for one 4-week period in September 2006. A sensitivity analysis was performed to assess the presence of a threshold effect of NO_2 exposure, but no threshold effect was found. Because of differences in the period of measurement between indoor and outdoor NO_2, the models with indoor NO_2 cover the entire winter period and have four times as many data points as models that include outdoor NO_2, which only cover the final 4 weeks of the winter period.

RESULTS

At baseline 58.6% of children were male and the average age was 9.6 yrs (range 6–13 yrs) (table 1). The study had a higher proportion of Mäori and Pacific children than the national average of children aged 5–14 yrs (22.5% and 11.1%, respectively), but the percentage of New Zealand-European participants was similar to the national average of 61.7%. The indoor NO_2 geometric mean was 11.4 $\mu g \cdot m^{-3}$ while the outdoor NO_2 geometric mean was 7.4 $\mu g \cdot m^{-3}$.

The mean of the cough symptom scores ranged between 0.44 and 0.59 on a scale of 0 to 3 (table 2). Similarly for wheeze, the average scores ranged between 0.27 and 0.37. Among all children the mean FEV1 morning and evening readings were 2,065 mL and 2,507 mL, respectively, and the mean PEFR morning and evening readings were 282.7 $L \cdot min^{-1}$ and 283.0 $L \cdot min^{-1}$, respectively.

The effects per logged unit increase in NO_2 on daily symptom scores are reported as mean ratios in table 3. This table shows a consistent and significant increase in lower (change in mean symptom rate per unit increase in NO_2 1.14, 95% CI 1.12–1.16)

TABLE 2 Mean daily respiratory symptom scores, medication use and lung function measurements during the winter of 2006

Health event	Child days n	Subjects n	Mean
Cough at night	26546	344	0.45
Cough during the day	27364	358	0.59
Cough on waking	26528	344	0.44
Wheeze at night	26421	343	0.29
Wheeze during the day	27133	356	0.37
Wheeze on waking	26431	343	0.27
Preventer use	27583	356	1.56
Reliever puffs per day	27277	357	1.08
Lower respiratory symptoms	23475	337	2.40
Upper respiratory symptoms	26860	353	1.57
Evening FEV1 mL	23428	357	2507
Morning FEV1 mL	22163	347	2065
Evening PEFR $L \cdot min^{-1}$	23435	357	282.7
Morning PEFR $L \cdot min^{-1}$	22456	348	283.0

FEV1: forced expiratory volume in 1 s; PEFR: peak expiratory flow rate.

TABLE 3 Effect per logged unit increase in indoor nitrogen dioxide (NO_2) on daily asthma symptom scores and medication use during the winter of 2006

Health event	Child days n	Subjects n	Change in mean symptom rate per unit increase in NO_2	95% CI
Cough at night	25528	344	1.16	1.12–1.21
Cough during the day	26329	358	1.12	1.08–1.16
Cough on waking	25513	344	1.16	1.11–1.20
Wheeze at night	25406	343	1.12	1.06–1.19
Wheeze during the day	26101	356	1.06	1.01–1.12
Wheeze on waking	25417	343	1.12	1.06–1.18
Preventer use	26522	356	0.99	0.98–1.01
Reliever puffs per day	26234	357	1.14	1.11–1.17
Lower respiratory symptoms	22756	337	1.14	1.12–1.16
Upper respiratory symptoms	25857	353	1.03	1.00–1.05

and upper (change in mean symptom rate per unit increase in NO_2 1.03, 95% CI 1.00–1.05) respiratory tract symptoms with exposure to increased NO_2. The change in mean symptom rate per unit increase in NO_2 was also significant for the positive associations between indoor NO_2 and all cough and wheeze symptoms. An increase in indoor NO_2 exposure was also significantly related to reliever use during the day. Indoor NO_2 had no effect on preventer use.

A log scale was used as NO_2 is log normally distributed. To help interpret the tables a one unit change in both outdoor and indoor NO_2 is approximately the same as moving from the 25th percentile to the 75th percentile *i.e.* if someone was to move from a ''low'' NO_2 (5.5 $\mu g \cdot m^{-3}$) house or area to a ''high'' NO_2 (15.9 $\mu g \cdot m^{-3}$) house or area this would, on average, result in increasing their cough at night symptoms by 1.16 times.

The results for the association between indoor NO_2 and lung function are reported in table 4. These show a consistent decrease in lung function with increasing indoor NO_2, which is significant for morning and evening FEV_1 readings.

Outdoor NO_2 was measured only during the last 4-weeks of the winter period. Table 5 shows that in this restricted sample mean outdoor NO_2 was not significantly associated with any of the asthma symptoms or medication use.

The results for the association between outdoor NO_2 and lung function are reported in table 6. A unit change in outdoor NO_2 was associated with a greater change in lung function than a unit change in indoor NO_2, although none of the outdoor NO_2 associations were significant.

While table 4 shows the effect of indoor NO_2 on lung function, it was also of interest how much of this relationship was due to outdoor NO_2. As outdoor NO_2 was measured in the final 4 weeks of the study rather than over the entire study period, it was necessary to restrict the analysis of indoor NO_2 adjusted for outdoor NO_2 to the final 4 weeks of the study. When this restriction was applied to the results in table 4, the sample size was greatly reduced and, thus, there was a reduction in power; this is seen in the reduction in number of child days (*e.g.* 22,516 to 5,257, for evening FEV_1). However, the adjustment for outdoor NO_2 did not significantly reduce the effect size of indoor NO_2 on symptoms or lung function, indicating that the effect of indoor NO_2 on lung function was independent of the effect of outdoor NO_2. Similarly, the effect of outdoor NO_2 was independent of the effect of indoor NO_2 (data not shown).

The results presented in tables 3–6 were also adjusted for a range of confounders (age, sex, smoking, the outcome at baseline, parental history of asthma, region, ethnicity, the effect of the intervention and low income). These adjustments made no substantial change to the results. However, when the models were adjusted for temperature, while most results were unchanged, the significant association between indoor NO_2 and wheezing disappeared and the association between indoor NO_2 and preventer use became significant.

TABLE 4 Effect per logged unit increase of indoor nitrogen dioxide (NO_2) on daily lung function measures in children during the winter of 2006

Lung function measurement	Child days n	Subjects n	Effect size	95% CI
Evening FEV_1 mL	22516	346	-13.21	-26.03– -0.38
Morning FEV_1 mL	21335	337	-17.25	-27.63– -6.88
Evening PEFR $L \cdot min^{-1}$	22518	346	-0.97	-2.29–0.36
Morning PEFR $L \cdot min^{-1}$	21619	338	-1.33	-2.69–0.02

FEV_1: forced expiratory volume in 1 s; PEFR: peak expiratory flow rate.

TABLE 5 Effect per logged unit increase of outdoor nitrogen dioxide (NO_2) on daily asthma symptom scores and medication use over 4 weeks in September 2006[#]

Health event	Child days n	Subjects n	Change in mean symptom rate per unit increase in NO_2	95% CI
Cough at night	6104	294	1.07	0.79–1.45
Cough during the day	6433	299	0.95	0.73–1.24
Cough on waking	6098	293	0.82	0.61–1.12
Wheeze at night	6072	293	1.23	0.82–1.85
Wheeze during the day	6413	298	1.18	0.83–1.68
Wheeze on waking	6082	292	1.12	0.76–1.65
Preventer use	6530	299	1.47	0.96–2.26
Reliever puffs per day	6443	298	1.46	0.94–2.27
Lower respiratory symptoms	6359	296	1.09	0.78–1.51
Upper respiratory symptoms	5479	283	1.09	0.82–1.44

[#]: during the period when outdoor NO_2 was measured.

DISCUSSION

The NO_2 levels reported in this study are higher than those previously reported indoors in the UK (Ashford), Spain (Menorca) and Sweden (Uppsala) [25, 26], and are comparable to those previously measured in New Zealand (Nelson), Italy (Po River Delta) and the USA [3, 27, 28]. However, NO_2 levels in our study were lower than those reported in Barcelona (Spain) [25]. The WHO annual average outdoor NO_2 guideline of 40 $\mu g \cdot m^{-3}$ [29] was exceeded during the 2006 winter period in 13.8% of homes and 1.9% of the outdoor samples.

Our findings that indoor NO_2 was associated with greater daily reports of lower and upper respiratory tract symptoms, more frequent coughing and wheezing and a reduction in morning and evening FEV_1 are consistent with previous findings from observational studies [1, 12, 20, 28, 30]. The conclusion of one systematic review stated that average hourly NO_2 values of 80 ppb (~154 $\mu g \cdot m^{-3}$) are likely to cause respiratory symptoms in the general population of children [20]. Furthermore, a study by JARVIS *et al.* [31] reported a 3.1% reduction in the lung function (FEV_1 % predicted) of females who used gas stoves in comparison to females who used other forms of cooking. In a later publication by JARVIS *et al.* [32], it was noted that burning gas appliances indoors may produce more of an effect on respiratory health than is reflected by NO_2 levels due to the failure to account for the adverse effects of nitrous acid, which is generated directly from gas combustion and indirectly from NO_2.

Increasing levels of outdoor NO_2 were not significantly associated with an increase in respiratory symptoms or a reduction in lung function. The relatively large estimated effect for reduced lung function may be an accidental finding due to the smaller sample size for outdoor NO_2 measurement or it may be a consequence of the respiratory effects of other combustion products and fine particulates associated with outdoor sources of NO_2 [33]. The effect estimates of both indoor and outdoor NO_2 changed little when mutually adjusted, indicating that these factors may be independent. This suggests that indoor NO_2 mainly reflects differing sources and/or mechanisms for reducing lung function than outdoor NO_2.

The pathophysiological effect of NO_2 on the respiratory system may include early alterations in airway calibre and/or viscoelastic properties of the peripheral lung and delayed or impaired gas exchange and pulmonary function abnormalities [34]. Children are particularly vulnerable to the effects of air pollution as they breathe 50% more air per kg of body weight than adults [35]. Our findings are based on a *post hoc* secondary analysis of a study designed to investigate the effects of a heating intervention. We acknowledge the shortcomings of this design for investigating the study hypothesis, but are also aware that due to having two groups with different heating

TABLE 6 Effect per logged unit increase of outdoor nitrogen dioxide (NO_2) on daily lung function measures in children over 4 weeks in September 2006[#]

Lung function measurement	Child days n	Subjects n	Effect size	95% CI
Evening FEV_1 mL	5257	286	-87.91	-191.02–15.23
Morning FEV_1 mL	4858	279	-76.17	-168.70–16.36
Evening PEFR $L \cdot min^{-1}$	5257	286	-10.17	-21.33–0.98
Morning PEFR $L \cdot min^{-1}$	5007	280	-9.60	-20.71–1.51

FEV_1: forced expiratory volume in 1 s; PEFR: peak expiratory flow rate. [#]: during the period when outdoor NO_2 was measured.

systems, we are guaranteed a large spread of indoor NO_2, and increased power. Furthermore, while the heating intervention itself was not quite significant in improving lung function ($p=0.051$) [22], the overall negative effect of indoor NO_2 on lung function suggests that the intervention may have been effective in those houses where there was a marked reduction in NO_2.

A further limitation of our study is that while we took daily health measures, the NO_2 levels were measured as 4-week averages. Therefore, in the analysis the daily outcome from the first day of a sampling period is associated with a 4-week average that includes future NO_2 levels. Another limitation of this study is that short-term peak levels of exposure were not measured. Repeated exposures to short-term peaks of NO_2 have been suggested to be a more important determinant of airway symptoms than total dose or absolute background exposure levels [36–38]. PILOTTO *et al.* [39] reported that exposure to hourly peak levels of ~80 ppb in comparison to background levels of 20 ppb were associated with an increase in sore throats, colds and absences from school in children aged 6–11 yrs. However, as the design of our study was a household intervention trial involving 409 homes, measuring NO_2 peak levels was not practical.

Another limitation of this study was that ventilation rates were not measured. However, in the New Zealand population, people tend to ventilate a dwelling at levels higher than the natural ventilation rates of an unoccupied, fully closed-up building [40]. Furthermore, as New Zealand homes are generally built out of timber frames with single glazing, they tend to be draughty.

The final limitation of this study was that participants were not blinded to the replacement of their heater, which could have affected the reporting of symptoms and led to an over-estimation of the effect of reduced NO_2 exposure. However, outcome measures also included objective (PEFR and FEV_1) measures and these also declined with increasing NO_2. Moreover, after randomisation, children in both groups had similar characteristics, including previous use of gas heaters, parental history of asthma, smoking indoors and sex, thus, confounding by indoor factors is unlikely to explain the findings. We did not collect information on potential outdoor confounders or effect modifiers, such as traffic volume, which may explain the influence of outdoor NO_2 on lung function measurements.

Indoor NO_2 was significantly associated with an increase in asthma symptoms and reduced lung function (FEV_1), while outdoor NO_2 was not significantly associated with reduced lung function (FEV_1 and PEFR) or asthma symptoms. These findings indicate that reducing NO_2 exposure indoors is important in improving the respiratory health of children with asthma.

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CLINICAL TRIAL

This study is registered at ClinicalTrials.gov with the identifier NCT00489762.

STATEMENT OF INTEREST

A statement of interest for P. Howden-Chapman can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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