

The relationship between low level nitrogen dioxide exposure and child lung function after cold air challenge

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Summary

Background Nitrogen dioxide (NO₂) or home gas appliance use has been inconsistently associated with adverse respiratory outcomes in childhood.

Objectives (i) To examine the contribution of home gas appliance type and personal NO₂ exposure. (ii) To examine the relationship between NO₂ exposure and child lung function and respiratory history. (iii) To assess whether these relationships vary by house dust mite sensitization status.

Methods A cross-sectional survey of 344 children (71% of the eligible group) with a mean age of 9.1 years from four randomly selected schools in the Australian Capital Territory from July to September 1999. Study measurements included a parental questionnaire, NO₂ exposure by passive gas samplers, skin prick testing for 10 aeroallergens and lung function at rest and after cold air challenge.

Results Total NO₂ exposure was low with a mean concentration of 10.1 ppb. No associations were found between NO₂ exposure or gas appliance use and asthma, wheeze or baseline lung function. Personal NO₂ exposure was associated with a reduction in forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) after cold air challenge (adjusted difference – 0.12% (– 0.23% to – 0.01%) per 1 ppb increase). After exclusion of children who had home heating changed because of asthma, gas heater use was also significantly associated with a reduction in this measure (adjusted difference – 2.0% (– 3.7% to – 0.2%)). There was some evidence that these reductions were greater among the non-mite-sensitized children.

Conclusions The effect of low-level NO₂ exposure on these respiratory outcomes was not marked. The possible effect of low-level NO₂ exposure on non-specific bronchial reactivity requires confirmation. Future studies on NO₂ and respiratory health should include measures of house dust mite sensitization and bronchial hyper-responsiveness.

Keywords: nitrogen dioxide, respiratory symptoms, house dust mite, allergic sensitization, lung function

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Introduction

The possible contribution of indoor air pollution to childhood allergic disease, including asthma, has received considerable attention [1]. In particular, the role of nitrogen dioxide (NO₂), a fossil fuel combustion product, has been a

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focus of research [2]. A meta-analysis summary odds ratio of 1.18 (1.08–1.30) for child respiratory illness was reported when the results of 11 studies were combined which all measured high NO₂ exposure by a surrogate only, e.g. gas cooker use, but when four studies actually measuring NO₂ were combined, the risk estimate was increased to 1.27 [3]. However, the epidemiological evidence linking home gas appliance use or nitrogen dioxide exposure to adverse respiratory health has been inconsistent [1]. This inconsistency has partially reflected methodological problems including the definition of exposure and outcome, confounding or effect modification by other pollutants [2,4] and a lack of prospective data. In addition, randomised controlled trial data have shown that high levels of NO₂ inhalation can enhance allergen-induced late-phase airway changes in house dust mite (HDM) sensitized asthmatics [5,6]. Thus, part of the inconsistency of previous studies may also reflect that the effect of gas exposure on respiratory health may differ by atopic sensitization status [7].

Using a prospective infant cohort in Tasmania, Australia, we have previously reported that home gas appliance use measured at one month of age was associated with increased asthma prevalence by age 7 years [8]. The type of gas home heating in those studies was predominantly combustion gas heaters rather than modern flued gas-central heating [8]. In Canberra, Australia, we conducted a cross-sectional study during the winter of 1999. The aims of the study were: (1) to examine the contribution of home heating, gas cooking and parental smoking to personal NO₂ child exposure; (2) to examine the relationship between NO₂ exposure, home gas appliance use and child lung function or respiratory symptoms with a primary focus on the relationship between NO₂ exposure and subsequent time-lagged dynamic lung function; and (3) to examine the effect of HDM sensitization on the association between gas exposure and adverse respiratory outcomes.

Methods

Study sample

The source population was children born in 1989–90 who attended school in the Australian Capital Territory in 1999. The eligible study sample consisted of children who attended one of four randomly selected schools (3 government, 1 private) that were a subset of randomly selected primary schools involved in a larger study of childhood atopic disease (the ACT Childhood Allergy and Respiratory Health Study).

Exposure measurements

The primary variable of interest was personal exposure to

NO₂ measured by passive gas samplers [9]. The Commonwealth Scientific and Industrial Research Organisation (CSIRO) Division of Atmospheric Research provided passive gas samplers to measure ambient concentrations of the pollutant NO₂ using integrated sampling. The NO₂ measurements were conducted from July to September 1999. Each child wore a sampler from the end of the school day (1515 h) until the start of the next school day (0900 h) for two consecutive days. The sampler was pinned onto the child's clothing immediately after the last class of the school day and removed after the child arrived at his or her classroom the next morning. This was done to ensure NO₂ exposure during travel to and from school would be captured. The sampler was the size of a conference name-badge and was attached to the child's clothes or placed on a table near the head of the child's bed while the child was sleeping. Thus a large proportion of the non-school sampling occurred overnight during sleep. The passive NO₂ diffusion sampler has been validated under Australian conditions and shown to have a satisfactory level of precision, with a 5–10% percentage difference between duplicates at ~15 ppbv and excellent agreement with active NO₂ samplers [10]. A school sampler was also placed in the classrooms of participating children for two days to obtain cumulative exposure in the school environment during school hours. On the days when non-school sampling was conducted, classroom samplers were only open during normal school hours. In addition, parental questionnaire data were obtained on current home heating, gas cooking, parental smoking, child exposure to active smoking in the same room, child bedroom ventilation and other factors. In this paper, personal NO₂ exposure refers to the non-school sampling by personal badge and total NO₂ exposure refers to the combination of personal and school classroom exposure, weighted by the time of cumulative sampling.

Outcome measurements

Respiratory and allergic disease using the questionnaire set developed by the International Study of Asthma and Allergy in Childhood [11] was used to obtain data on rhinitis, hay fever, eczema and asthma and recent (in the past 12 months) wheeze. Skin prick testing (SPT) was used to assess the cutaneous reaction to exposure to the house dust mites *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1), cat, dog, alternaria, ryegrass, birch, plantain, paspalum and wattle (Hollister-Stier purified allergen extracts supplied by Bayer, Australia) and positive (histamine 6 mg/mL) and negative (glycerine) controls. For aeroallergens, weal allergen reactions of 3 mm or greater at 15 min were classified as positive [12].

Lung function

Baseline lung function measures were obtained as follows: the children were asked to perform forced expiratory manoeuvres standing without a nose clip following a standard protocol [13] using an Alpha compact spirometer (Alpha Vitalograph, Buckingham, UK) which was calibrated at the beginning of every session and hourly thereafter. In addition, lung function measures after four minutes of cold (-10 to -15 °C) air challenge [14] (Jaeger cold air provocation system, Germany) were also obtained. Children with a forced expiratory volume in one second (FEV₁) of less than 75% of that predicted for height at baseline were excluded from the cold air challenge.

Given that the effect of NO₂ on allergen-induced bronchial hyper-responsiveness has been shown to be maximal 48 h after NO₂ exposure, our protocol aimed to collect NO₂ exposure over a relatively narrow time period (48 h) and then time-lag the lung function tests two days after NO₂ measurement commenced. We initially examined the relationship between respiratory history and multiple lung function measures as possible indicators of airway obstruction, including the percentage predicted FEV₁ at baseline and post-challenge compared to an Australian child nomogram [15], the percentage drop of FEV₁ from pre- to post-challenge and also FEV₁/forced vital capacity (FVC) ratio at baseline and after cold air challenge. Children with a history of wheeze in the past year were more likely to have a lower FEV₁/FVC ratio at baseline ($P = 0.008$) or post-challenge ($P = 0.007$) but did not have a greater percentage drop in FEV₁ ($P = 0.3$). Other studies have also used the FEV₁/FVC ratio as an outcome [16,17]. For these reasons, we took the ratio of FEV₁ to FVC as the main measure of airway obstruction but also examined the effect of NO₂-related exposures on the other lung measures.

Statistical methods

Due to the skewness of the distribution of the measured personal exposure to NO₂ comparisons with respect to heating types and gas appliances were conducted after a natural log transformation. Relative risk estimates for respiratory symptoms were calculated using the method of Mantel and Haenszel with test-based 95% confidence intervals [18]. To control simultaneously for multiple confounders and to obtain confidence intervals for relative risk estimates, a generalized linear model with a log link function and binomial error structure was used [19]. The significance value for differences in effect by HDM sensitization status was assessed by the likelihood ratio test obtained when comparing model deviance with and without the relevant interaction terms. Multiple linear regression models were used to examine the associations

between exposure on and continuous outcomes such as the lung function measures of FEV₁, FVC and the ratio of FEV₁ to FVC with adjustment for relevant covariates. For the models involving total exposure (weighted average of school and non-school NO₂ levels) possible within-classroom correlation was accounted for using a generalized estimating equation approach. We conducted the analyses using STATA 6 [20].

Results

The study sample

Of eligible children, 78.6% (346/440) participated in the study and had NO₂ exposure recorded. Two of these children did not have lung function tested due to refusal and injury (a prior broken rib). Of the remaining 344 (78.2% of eligible) 337 also participated in the skin prick assessment of the concurrent allergy survey. Six children had baseline lung function measured but were excluded from cold air challenge because of low FEV₁ reading (less than 75% of that predicted for height) and one child refused the cold air component. The study characteristics of the study sample are shown in Table 1. Eighty-eight percent (301/344) of the children had lung function measurements two or three days after NO₂ measurement commenced.

Home determinants of personal non-school NO₂ exposure

The distribution of relevant characteristics in the child sample is shown in Table 1. The levels of NO₂ exposure were low. Only 8.7% (30/346) of the total daily NO₂ exposures and 10.7% (37/346) of the non-school NO₂ exposures were greater than 15 ppb. We then examined which factors in the home related to NO₂ levels. Table 2 shows that home heating type was a significant determinant of children's personal non-school NO₂ exposure. Higher NO₂ exposure relative to specific electric heating was most marked for unflued gas heaters but was also significantly associated with the use of flued gas heaters and gas central heating with an outside unit. Cooking with gas was also associated with higher NO₂ levels (ratio of geometric mean 1.35 (1.22–1.50) ($P < 0.0001$)) but maternal smoking or paternal smoking was not. Exposure to any active smoking in the same room also did not relate to NO₂ levels (mean ratio 0.94 (0.85–1.05)). These results were not altered after taking into account how the parents ventilated the child's room with regard to windows and door. After taking into consideration the effect of gas heaters (flued or unflued) (mean ratio 1.37 (1.21, 1.54)) and gas cooking (mean ratio 1.20 (1.07, 1.35)) on non-school NO₂, the use of other gas appliances was not strongly associated with non-school NO₂ levels (1.12 (0.98, 1.26) ($P = 0.09$)). Thus, gas

Table 1. The distribution of selected characteristics in the child sample

Characteristic	<i>n</i>	Mean	SD
Child age (years)	346	9.1	1.0
Child height (cm)	345	138.17	7.0
Child maximum FEV ₁ (litres)	344	1.89	0.32
Child maximum FVC (litres)	344	2.18	0.36
Child FEV ₁ /FVC ratio (%)	344	86.9	5.8
School NO ₂ exposure (ppb)	346	10.1	4.9
Non-school personal NO ₂ exposure (ppb)	346	10.4*	11.1
Total NO ₂ exposure (ppb)	346	10.1	8.6
	<i>n</i>	%	(<i>n</i> /total <i>n</i>)
History of asthma	344	39.0%	(134/344)
Recent wheeze in past 12 months	343	28.0%	(96/343)
Gas used for cooking	343	31.8%	(109/343)
Gas used for heating	343	61.2%	(210/343)
Maternal smoking	341	22.9%	(78/341)
Paternal smoking	334	18.3%	(61/334)
House dust mite sensitization	339	26.0%	(88/339)
Aeroallergen† sensitization	339	42.8%	(145/339)

* Median 8.3, interquartile range 6.8, 11.1.

†A positive skin prick test of 3 mm or greater to any one of the allergens tested.

Table 2. Non-school personal nitrogen dioxide exposure by home heating

Home heating type (<i>n</i> = any use of this heating)	Geometric mean NO ₂ for exposed	Geometric mean NO ₂ for specific electric heating only (<i>n</i> = 58 with only this heating)	Ratio in geometric mean NO ₂ (95% CI) (exposed/electric)	<i>P</i> -value
Gas heater unflued (<i>n</i> = 30)	14.53	7.92	1.83 (1.37–2.45)	0.0002
Other (including kerosene) (<i>n</i> = 4)	10.44	7.92	1.32 (0.29–5.94)	0.6
Gas heater flued (<i>n</i> = 63)	11.19	7.92	1.41 (1.23–1.61)	< 0.0001
Open fire (<i>n</i> = 9)	10.67	7.92	1.35 (1.01–1.79)	0.04
Gas central heating unit inside (<i>n</i> = 2)	11.61	7.92	1.41 (0.27–7.33)	0.3
No heating (<i>n</i> = 4)	9.66	7.92	1.22 (0.52–2.87)	0.5
Gas central heating outside unit (<i>n</i> = 53)	9.86	7.92	1.24 (1.10–1.41)	0.0006
Gas central heating unit in roof (<i>n</i> = 65)	7.89	7.92	1.00 (0.89–1.11)	0.9
Wood heater (<i>n</i> = 46)	6.96	7.92	0.88 (0.72–1.07)	0.2
Electrical heat pump (<i>n</i> = 30)	6.82	7.92	0.86 (0.74–0.99)	0.04
Oil (<i>n</i> = 3)	6.65	7.92	0.84 (0.41–1.72)	0.4

Table 3. The relationship between nitrogen dioxide exposure, home gas appliance type and child respiratory outcomes

	Adjusted* difference (95% CI) in baseline FEV ₁ /FVC ratio (%)	P-value	Adjusted* difference in post-cold air challenge FEV ₁ /FVC ratio (%)	P-value	Adjusted† relative risk estimate (95% CI) for recent wheeze	P-value	Adjusted† relative risk estimate (95% CI) for asthma ever	P-value
Total NO ₂ exposure (per 1 ppb increase)	-0.001 (-0.12-0.12)	0.9	-0.13 (-0.27-0.01)	0.07	0.99 (0.95-1.03)	0.6	0.99 (0.96-1.02)	0.4
Personal NO ₂ exposure (per 1 ppb increase)	-0.02 (-0.12-0.07)	0.7	-0.12 (-0.23 to -0.01)	0.04	1.00 (0.97-1.02)	0.8	0.99 (0.97-1.02)	0.7
Gas heater use (per 1 ppb increase)	-0.76 (-2.15-0.64)	0.3	-1.50 (-3.16-0.17)	0.08	0.97 (0.66-1.43)	0.8	0.93 (0.69-1.26)	0.7
Gas cooking	0.12 (-1.23-1.48)	0.9	-0.68 (-2.30-0.93)	0.4	1.08 (0.75-1.55)	0.7	1.20 (0.91-1.58)	0.2

*Adjusted for child height, sex, research technician, child exposure to active smoking in the same room and number of days between NO₂ measurement and spirometry. Total NO₂ also adjusted for clustering by classroom. †Adjusted for child exposure to active smoking in the same room, number of siblings, sex and breastfeeding.

heaters, rather than gas central heating appeared to be the stronger indicator of high personal NO₂ levels.

Relationship between NO₂ or gas appliance exposure and respiratory health

Respiratory outcomes Characteristics associated with lower FEV₁/FVC ratios at baseline were HDM sensitization (Adjusted difference: -1.5% (-0.1% to -3.0%)) and recent wheeze (Adjusted difference: -2.1% (-3.5% to -0.81%)). Children who had ever had asthma tended to have lower baseline FEV₁/FVC ratios (-0.9% (-2.2% to 0.4%)). A history of recent wheeze was also significantly associated with a reduction in this ratio post-cold air challenge (Adjusted difference: -2.2% (-3.8% to -0.6%)) but a history of ever having asthma or mite sensitization was not significantly associated with *P*-values of 0.1 and 0.5, respectively.

There was no evidence of a relationship between total or personal NO₂ exposure, gas heater use or gas cooking and baseline lung function indices (FEV₁, FVC and FEV₁/FVC). However, higher personal NO₂ exposure was associated with a linear decrease in the FEV₁/FVC ratio after cold air challenge (Table 3). The FEV₁ reduction post-cold air associated with gas heater use was -22.1 mL (-52.4 mL to 8.1 mL). Similar patterns but of borderline significance were found for daily NO₂ exposure or gas heater use and the post-challenge ratio (Table 3). The association between gas heater use and the post-cold air ratio was reduced after adjustment for personal NO₂ (adjusted difference -1.0% (-2.8% to 0.7%)). Personal NO₂ exposure greater than 15 ppb compared to lower exposure was also associated with a reduction in the post-challenge ratio of -1.8% (-4.2% to -0.6%). Personal or daily NO₂ exposure, gas heater use and gas cooking did not appear associated with asthma or wheeze (Table 3). Further adjustment for parental history of asthma did not alter the results in Table 3. Exclusion of the seven children with no post-cold air results did not alter the associations in Table 3 for baseline FEV₁/FVC ratio. In this cross-sectional survey, the parents of 33 children reported a change in home heating arrangements due to asthma, with six children residing in homes which had changed to gas heating and two where the type of gas heating had changed to flued central heating. The comment section concerning the type of home heating change was not completed in four cases. Exclusion of these 33 children from the analyses did not alter the results reported in Table 3, but the lower post-challenge FEV₁/FVC ratio associated with gas heater use was more evident (adjusted difference -2.0% (-3.7% to 0.2%)) (*P* = 0.03)). We also examined the associations reported in Table 3 for other subgroups such as children with an FEV₁ < 90% of predicted, children with total NO₂

exposure greater than 10 ppb, and children with asthma. Similar patterns were observed. Among children with an FEV₁ at baseline < 90% of predicted, gas heater use was strongly associated with a lower post-challenge FEV₁ to FVC ratio (Adjusted difference = - 5.14%, $P = 0.006$).

An examination of the possible effect modification of the relationship between NO₂ or gas appliance exposure and respiratory outcomes by HDM sensitization status Gas heater use and gas cooking were not associated with an altered risk for mite sensitization. However, the relationship between these variables and respiratory outcomes tended to differ by whether a child was mite-sensitized or not. After adjustment for exposure to tobacco smoke and history of breastfeeding, the adjusted relative risk for gas heater use and recent wheeze was 1.47 (1.00–2.18) among mite-sensitized and 0.74 (0.40–1.38) among non-mite-sensitized children (difference in effect, $P = 0.1$). For gas cooking and wheeze the estimates were 0.76 (0.46–1.27), 1.63 (0.98–2.69) (difference in effect, $P = 0.02$). The stronger relationship between gas cooking and wheeze among non-mite-sensitized children persisted after further adjustment for gas heater use, asthma, asthma medication use in the past year, sibling number, parental asthma, rye or general aero-sensitization. We then examined the association between NO₂ and post-challenge FEV₁/FVC ratio by mite sensitization status. The negative association between personal NO₂ exposure and post-challenge ratio was evident among non-mite-sensitized children (Adjusted difference, - 0.17% (- 0.29% to - 0.05%) per 1 ppb increase). Among mite-sensitized children it was 1.02% (- 0.3% to 0.4%). Gas heater use was significantly ($P = 0.008$) associated with a post-challenge FEV₁/FVC ratio reduction (Adjusted difference - 2.6% (- 4.6% to - 0.7%)) among non-mite-sensitized children but not among mite-sensitized children (- 0.5% (- 4.3% to 3.3%)). Gas cooking was not associated with a significant reduction in the post-challenge FEV₁/FVC ratio in either group. These results were not altered substantially by using a 2-mm cutoff to define a positive skin prick test. There was no evidence that the relationships reported in Table 3 differed significantly by rye sensitization or general atopy (a positive reaction to any one of the aeroallergens tested).

Discussion

The levels of personal NO₂ exposure experienced by children in this study were low with a median concentration of 8.3 ppb. Low indoor NO₂ concentrations (median = 6.0 ppb (11.6 µg/m³)) have also been reported in a recent study from Latrobe, Australia [21]. These levels are considerably lower than those reported for Australian studies during the late 1980s or early 1990s [22,23].

Canberra is a city with a high proportion of modern housing, low outdoor pollution [24] and the proportion of homes using gas for space heating increased substantially from 5.7% in 1983 to 46.3% in 1994 [25], indicating that gas cookers and heating are more likely to be of modern design. Nevertheless, some forms of gas home heating were still associated with significantly higher personal NO₂ exposure. In particular, the use of separate gas heaters (flued or unflued), rather than gas central heating, was associated with higher personal NO₂ levels. Gas cooking was also associated with higher NO₂ levels. Interestingly, the use of an electric heat pump (reverse cycle) heating system was associated with lower NO₂ levels, suggest a potential benefit of air exchange heating systems in not only the non-generation but also expulsion of indoor pollutants, particularly in settings of low outdoor pollution. This study was not designed to fully investigate this issue but other studies, which also examine potential confounders such as differences in pollutant-related behaviours by heat pump use with a larger sample of heat pump users may be warranted. Exposure to smokers in the home has been previously related to child personal NO₂ exposure (26). The lack of association between parental smoking and child personal NO₂ exposure here may reflect unmeasured ventilation or good smoking hygiene practices in this study.

This study was designed to test the key hypothesis that personal NO₂ exposure a few days prior to testing relates to lung function. We also examined the association between personal NO₂ exposure and other outcomes such as asthma. However, for asthma, long-term NO₂ measures would be more appropriate. The lack of a significant association between either NO₂ exposure or gas appliance use and HDM sensitization or asthma could partially reflect methodological problems. Firstly, this is a cross-sectional design in a location with high residential mobility [27]. We have previously reported that the cross-sectional association between home gas cooking during infancy and asthma was stronger for children who had not changed postcode residence since birth in the Tasmanian cohort [8]. A second limitation when examining asthma is that the sample size here would only have allowed us to detect significant associations with a rate ratio greater than 1.5, thus the likelihood of type II error is high, particularly for respiratory reports which are likely to have more non-differential misclassification than a more precise measure such as spirometric lung function prospective cohort studies. Large studies of prospective cohort design are better able to address the issue of long-term NO₂ exposure and child asthma. Other limitations of the current study are the absence of peak NO₂ exposure and a lack of data on possible copollutants. We obtained some self-report measures of home ventilation practices and adjustment for these did not alter the findings. It is unlikely that

selective avoidance of home gas use among families of children with asthma explains the lack of association reported here, as a relatively small number of children had a positive report of alteration in home heating because of asthma. They did not change away from gas use, and exclusion of these children did not alter the findings in Table 3 with regard to asthma or wheeze history.

A major strength of this study was the inclusion of a measure of lung function after a dynamic challenge as well as baseline spirometric lung function indices in a population-based setting. Randomised controlled trials indicating a potentiation effect of allergen-induced bronchial hyper-responsiveness have found that NO₂ exposure at 400 ppb [6] or 260 ppb NO₂ [28] or NO₂ (400 ppb) and sulphur dioxide (SO₂) (200 ppb) exposure [5] can enhance mite-allergen induced broncho-constriction in terms of the change in FEV₁. However, most population-based studies examining the effect of NO₂ exposure on respiratory health have not included an assessment of dynamic lung function with challenge tests to assess bronchial hyper-responsiveness. Moran et al. did assess lung function at baseline and after salbutamol inhalation. They found that the reduction in FEV₁/FVC in gas users compared to electricity users was slightly reduced after salbutamol [17]. Here, although NO₂ and NO₂ source exposures did not relate to baseline lung function, there was some evidence that the ratio of FEV₁ to FVC after cold air challenge was reduced with increasing NO₂ or gas heater use. These associations persisted after adjustment for relevant covariates and exclusion of children with asthma-related home heating change. However, the magnitude of the effects was small. Here, mite sensitization and recent wheeze were associated with a 1.5% and 2.1% respective reduction in the baseline FEV₁/FVC ratio. Gas heater use was associated here with a post-cold air ratio reduction of similar magnitude. This is the first population-based report of an association of NO₂ or NO₂ sources and airway function after cold air challenge with careful attention to the timing of exposure measures before lung function testing. The clinical significance of these findings is unclear. However, they do indicate that epidemiological investigations of the respiratory effects of NO₂ should include a dynamic measure of airway function, as it is possible that NO₂ may particularly influence airway reactivity.

In the study by Garrett et al. gas cooking remained associated with respiratory symptoms after adjustment for NO₂ exposure [21]. In this study however, the effect of gas heater use on the post-cold air ratio was reduced by adjustment for personal NO₂ exposure, suggesting that part of the adverse effect of gas heater use on the post-cold air FEV₁/FVC ratio was mediated through NO₂ or a closely related copollutant.

The potential interaction between gas combustion pollutant and allergen was highlighted as an area that warrants further investigation [7]. The randomised con-

trolled trials showing a potentiation between NO₂ exposure and mite allergen-induced airway obstruction were conducted on subjects who were sensitized to dust mite [5,6] or pollen [28]. Two population-based studies have shown a non-significant tendency for the relationship between NO₂ or gas cooking and respiratory symptoms to be stronger in atopic individuals [21,29]. Here, surprisingly, the adverse effect of personal NO₂ exposure on the post-cold air challenge FEV₁/FVC ratio or gas cooking and wheeze was more evident among non-mite-sensitized children. This difference in effect was not removed after adjustment for confounders or child asthma. If not due to chance or unmeasured biases, this difference in effect may be explained by a differing effect of NO₂ at lower than higher levels or the difference between irritant-induced vs. allergen-induced broncho-constriction. The NO₂ exposures used to demonstrate allergen-induced bronchial hyper-responsiveness or molecular biological changes have been much higher [30] than those studied here. The finding that mite sensitized children had lower FEV₁/FVC ratios at baseline but not after cold air challenge also raises the possibility that non-mite-sensitized children, with a lower level of baseline broncho-constriction compared to mite-sensitized children exhibit increased airway responses to cold air in conjunction with NO₂. We cannot resolve these issues here and agree with Jarvis that large longitudinal studies to assess the respiratory effects of NO₂ and allergen exposure in populations of known atopic status are required [7]. The findings from this indicate that the specific delineation of house dust mite-sensitized children as well as the general classification of 'atopic to one or more aeroallergens' may assist this task.

In conclusion, this study found generally low levels of child exposure to nitrogen dioxide. Gas heater use (flued or unflued) was associated with significantly higher NO₂ exposure. NO₂ levels or gas appliance use did not appear to be associated with baseline lung function, asthma or wheeze but, after cold air challenge, increasing levels of personal NO₂ or gas heater use were associated with a reduction in the FEV₁ to FVC ratio, suggesting that even at low levels, NO₂ exposure may increase non-specific bronchial reactivity. The ability to replicate or the clinical significance of this finding remains to be established. Future prospective epidemiological studies investigating the role of NO₂ in child respiratory illness should include measures on child sensitization to HDM and challenge lung function testing rather than only lung function at rest.

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