Health effects of daily indoor nitrogen dioxide exposure in people with asthma

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ABSTRACT: Household gas appliances produce nitrogen dioxide (NO₂), which may be associated with an increase in symptoms in asthmatics. The relationship between indoor NO₂ exposure, and respiratory symptoms in people with asthma was evaluated.

Self-reported asthmatics (n=125) wore lapel badges that measured NO₂ daily over 6 weeks at home. Outdoor pollutants, spores and meteorological parameters were measured daily, in addition to smoking status and demographic factors. Seven asthma symptoms were recorded in diaries, for analysis by same day and also with 1 day lag exposures, using a generalized estimating equation.

Significant interactions were demonstrated between NO₂ at age ≤14 yrs, with respect to the symptoms of chest tightness on the same day (odds ratio (OR): 1.29, 95% confidence interval (CI): 1.16–1.43) and with a 1 day lag (OR: 1.29, 95% CI: 1.14–1.46), breathlessness on exertion with a 1 day lag (OR: 1.13, 95% CI: 1.00–1.28), daytime asthma attacks on the same day (OR: 1.13, 95% CI: 1.02–1.26) night asthma attacks on the same day (OR: 1.16, 95% CI: 1.03–1.30) and with a 1 day lag (OR: 1.15, 95% CI: 1.03–1.29) after adjustment for potential confounders. A significant interaction between NO₂ and age 35–49 yrs was demonstrated for coughs with a 1 day lag (OR: 1.15, 95% CI: 1.01–1.31).

Daily personal exposures to NO₂ are associated with asthmatic symptoms in children.

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Nitrogen dioxide (NO₂) is predominantly an indoor pollutant, and the major source of exposure is from household appliances fuelled by gas, particularly in households without flues for the gas appliances [1]. There is evidence that NO₂ is associated with an increase in respiratory symptoms among the general population, particularly in children, in a range of epidemiological studies that the authors have previously reviewed [2]. Studies under controlled conditions have indicated a relationship between NO₂ exposure and airway hyperresponsiveness in asthmatic children [3], and also with an enhanced bronchoconstrictor response to inhaled house dust mite and pollen antigens [4–8].

There are few community based studies on asthmatics, where patterns of exposure are more complex. A case-control study concerning the onset of asthma by INFANTE-RIVARD [9] demonstrated a dose-response relationship between asthma and a single personal NO₂ exposure over 24 hrs [9]. HOEK *et al.* [10] found no relationship in a further case-control study, but used a weekly residential NO₂ measurement. A cohort study of 164 asthmatic subjects by OSTRO *et al.* [11] demonstrated a significant relationship between daily recordings of gas appliance use and the incidence of repeated attacks of asthma symptoms, but they did not measure actual NO₂ levels. The effects of short-term personal NO₂ exposure, in a

cohort study, has never been measured on a daily basis in asthmatics. In view of the potential public health significance of even a small effect of NO₂ upon asthmatics, the aim was to perform a prospective study in asthmatics, in a residential household setting, to evaluate the relationship between asthma symptoms and short-term personal NO₂ exposure measurements during periods of household gas appliance use.

Methods

Asthmatic participants were identified from a cross-sectional health survey of Port Adelaide residents in South Australia [12], that utilized standard Australian Bureau of Statistics National Health Survey (NHS) sampling methodology and health related questions [13]. A high level of validity and reliability for self-reported asthma in the Australian setting has been previously recorded [14]. Criteria for selection to participate in the cohort study were based on the participant: 1) reporting asthma; and 2) having been symptomatic or taken preventative (maintenance inhaled or oral corticosteroids, disodium cromoglycate, or theophylline) or bronchodilator asthma medication within the last 12 months.

Information on preventative medication, smoking (for age ≥ 14 yrs), and types of household appliances were also recorded. Subjects were shown pictures of a range of cookers, and heaters with and without flues. Educational level was utilized as an indicator of socioeconomic status, and measured according to the completion of secondary schooling (in the childrens case, the household parents highest level of education).

Participants were divided into 3 groups according to their geographical area. Daily personal NO₂ and symptom monitoring was rotated weekly across the 3 groups, whereby, results were recorded in group 1 for 1 week, group 2 the next, followed by group 3 the week after. This cycle was repeated 6 times, extending the cohort over 18 weeks including winter.

Passive diffusion lapel badge monitors were used to measure personal NO₂ exposure. These can be stored for up to 90 days under sealed conditions, without any reported interferences, to the assays according to previously described methods [15]. In the present study, the limit of detection for NO₂ measurements, for a 2-h sampling period, was 19 parts per billion (ppb). The mean coefficient of variation, determined for quadruplicate 2-h samples at 40, 80 and 120 ppb, was 10%. Samples that were less than the limit of detection were given a value of 1 half the limit of detection for the purpose of subsequent data analysis.

Badges were delivered twice weekly to panellists in an air-sealed bag, which included a control (blank) badge and a scavenger badge. Participants were instructed to attach a new lapel badge each day when arriving home from daily activities, and remove the cover of the badge in order to include potential indoor NO₂ exposure during periods of domestic cooking and heating activity. Participants were asked to replace the badge cover at bedtime each day, to record the time at first exposure of the badge and also the time of replacement into the airtight bag at bedtime later the same day. They were also instructed to replace the cover during periods of absence from the home. Batches of personal monitors were retrieved and analyzed in the week following exposure. A time-weighted average NO₂ exposure was calculated, with adjustment for values of the control badge. Badge NO₂ assays were performed by blinded independent analysts. Participants were informed only that the lapel badges were designed to monitor "air quality in the home".

Monitoring of daily ambient gas levels was also rotated each week across the three geographically distinct areas, concurrently with indoor NO₂ sampling, using an Environmental Protection Authority (EPA) van which contained a chemiluminescence monitor (for ambient NO₂) (Monitor Laboratories Pty Ltd, San Diego, CA, USA), Thermo-electron Model 43 Pulsed Fluorescence Analyzers (for sulphur dioxide (SO₂)) (Thermo Instruments Pty Ltd, Hopkinton, MA, USA) and Thermo-electron Model 48 Ultraviolet Analyzers (for ozone (O₃)) (Thermo Instruments Pty, Ltd, Hopkinton, MA, USA) to provide 24 h mean levels. Three regional High Volume EPA Samplers provided 24h measures every sixth day for total suspended particulates (TSP), and also particles with a 50% cut-off aerodynamic diameter of 10 μ m (PM₁₀) in two of the areas. A Burkhardt spore trap was positioned adjacent to the monitoring van, and provided daily spore and pollens measurements [16]. Daily temperature, humidity, wind

direction and wind speed were provided by the South Australian Bureau of Meteorology.

Concurrently with daily personal NO₂ monitoring, subjects were asked to indicate "yes" or "no", each day, according to whether they were bothered by chest wheezing, breathlessness, chest tightness, cough, breathlessness during physical activity, asthma attacks in the daytime and asthma attacks in the night by completion of an asthma diary, which utilized a previously reported tabulated layout and asthma attack definition; ("any asthma episode involving breathlessness and/or wheezing and/or chest tightness and/or coughing that interrupts ongoing activities or requires some procedures, such as resting or using a nebulizer to resume normal and comfortable breathing") [17]. Parental diary completion, when considered necessary by field workers, was carried out as described in previous reports [18]. The twice-weekly visits by the field-worker encouraged accurate diary completion, and subjects were asked to complete any missing days according to recall. The protocol was approved by the institutional ethics committee for human studies.

Statistical methods

Epi info (Version 6; Centers for Disease Control and Prevention, Atlanta, GA, USA), SAS (Version 6.11 for Windows; SAS Institute Inc., NY, USA) and STATA (Version 6; Stata Statistical Software, Stata Corporation, College Station, TX, USA) were used for data entry and statistical analysis. The relationship between daily personal NO₂ exposure and daily asthma symptoms was analyzed using the Generalized Estimating Equation Approach (GEE) as given by LIANG and ZEGER [19], in order to account for the clustering of subjects within households and repeated measures over time for each subject. This analysis was carried out for symptoms on the same day as personal NO₂ exposure measurement, and also with a one day lag. Relationships between age and frequency of the 7 respiratory symptoms may occur due to the increasing prevalence of chronic obstructive pulmonary disease (COPD) with age. Therefore, age group (≤ 14 , 15–34, 35–49, 50+) interactions with NO₂ were examined in the GEE modelling in order to test for the influence of age group upon the relationship between NO₂ exposure and symptoms. These age groups are consistent with those used in both the NHS and the preliminary survey of Port Adelaide respiratory disease [12]. Age groups ≥ 15 were collapsed to provide equitable numbers of participants in these categories. Sex and smoking interactions were also examined.

Age, sex, smoking, area of residence, preventative medication use, highest level of education in each household, SO₂, NO₂, O₃, wind, relative humidity, minimum temperature, total fungal spore counts, cladosporium, and alternaria were all adjusted for. All items were included as a common set of study factors, for analysis with all 7 asthma symptom outcomes. Missing data occurred for both daily asthma symptoms and also the indoor NO₂ measurements, and these data were not missing at random [20, 21]. There was a tendency for those subjects with more incomplete data to be more likely to have symptoms on other days when symptoms were recorded. The method of multiple imputation [22] was therefore, used to account for

possible bias in the analysis based on all the available data, as follows: within subject regression equations were fitted to both the daily symptom and NO₂ data in order to generate predicted values, these predicted values were then used to calculate similarity measures between subjects, which in turn were used to calculate probabilities for selection; these probabilities were then used to select a complete subject from whom to impute the missing data for the incomplete subject. Ten complete datasets were created and analyzed in this process. All continuous variables were standardized (mean=0, standard deviation=1) prior to analysis.

Results

Study participants

Of the 1,946 randomly selected subjects interviewed in the cross-sectional survey, 239 (12.3%) reported a diagnosis of asthma. Of these, 212 subjects met the asthma panel cohort selection criteria, of whom 129 subjects (60.8%) in 104 households, then agreed to participate. Compared to 83 nonparticipants, the 129 cohort participants were not significantly different with respect to smoking (25% for each), no current reliever or preventer medication use at baseline (41% for each) age distribution and gender. Participants (in the childrens case, the household parents highest level of education) were equally likely to have completed secondary school (50.8% and 48.1% for participants and nonparticipants respectively).

Participants included 71 (55%) male and 58 (45%) female. In relation to age groups: ≤14, 15–34, 35–49, and >50 yrs, the distribution of males was 44%, 18%, 15% and 23%, and the distribution of females was 31%, 26%, 28% and 15%. Of the total number of subjects, 76% of males and 81% of females lived in gas households and other subjects lived in all-electric households. Of the 81 participants who were aged ≥14 yrs, 11 (28%) of males and 10 (24%) of females were current smokers. In relation to the above age groups, medication use at baseline (over 2 weeks prior to the commencement of the cohort) was 22%, 29%, 41%, and 52% respectively for regular inhaled corticosteroid use; 47%, 61%, 56% and 64% for relieving medications; and 2%, 0%, 11%, and 16% for oral corticosteroids. The characteristics of the 129 subjects in terms of symptoms burden during the cohort are described in tables 1 and 2.

Following commencement of the study, 4 of the 129 subjects (2 females aged 27 and 38, 2 males aged 2 and 35) failed to proceed with personal NO₂ exposures, (<5 badges

utilized). Therefore, they could not be included in further analyses relating to NO₂ exposure (table 3). Of these subjects none were current smokers. In the remaining 125 participants, aged 2–84, 3,255 out of a possible 5,250 NO₂ measurements were made over the study period (62%), and the rate of successful recording of symptoms was 80%.

Nitrogen dioxide results

The mean time±standard deviation (SD) for self-reported badge exposure was 4.5 h·day⁻¹ (±2.4). Personal time weighted average levels of NO₂ exposure ranged 0–1,760 ppb. The range of the median indoor NO₂ levels for each individual was 3.70–146.66 ppb. The within subject interquartile ranged 0.60–153.50 ppb.

Nitrogen dioxide and type of domestic appliances

Figure 1 demonstrates the distribution of time weighted average personal levels of NO₂ for all the participants in relation to type of household appliances, and also includes the GEE means and confidence intervals for 21 all-electric households (779 observations) and 83 gas households (2,711 observations). Of the 83 gas households, 35 (959 observations) used gas for cooking and heating, 15 (506 observations) households used gas for heating only, and 33 (1,246) households used gas for cooking only. Of the gas heating households, 6 had gas heaters (212 observations) without flues and 44 households had flues (1,253 observations).

Regional ambient air quality

The mean±SD for the daily maximal 10 min outdoor averages were 9.8±1.1 ppb for NO₂, 2.7±1.9 ppb for SO₂, and 17.5±7.8 ppb for O₃, these were well within the current guidelines. The United States EPA TSP guideline (260 mg·m⁻³·24 h⁻¹), but not for PM₁₀, was exceeded on 3 occasions.

Relationship between indoor nitrogen dioxide and daily (same day and 1 day lag) respiratory symptoms

For all the subjects, indoor NO₂ levels were not significantly associated with any outcome symptoms on the same day, or with 1 day lag (table 3). Significant positive interactions were demonstrated between NO₂ and age ≤14 yrs, with respect to symptoms on the same day and with 1 day lag and for age 35–49 yrs with 1 day lag (table

Table 1. – Percentage of subjects with at least one symptom day from the 42 diary days over the study period

Symptom	Age				Gender		Smoker		IC	
	≤14	15–34	35–49	≥50	Male	Female	Yes	No	Yes	No
Subjects n	49	28	27	25	71	58	21	63	43	86
Wheeze	55	61	70	80	65	64	71	68	72	60
Breathlessness	53	64	74	96	66	71	71	78	74	65
Chest tightness	37	48	67	56	43	57	60	54	54	47
Cough	90	75	85	92	83	90	90	83	86	86
Breathlessness on exertion	61	67	78	92	69	76	65	81	68	79
Daytime asthma attacks	35	37	41	44	41	34	40	41	53	31
Night asthma attacks	27	30	41	40	33	33	50	29	49	25

IC: inhaled corticosteroids.

Table 2. – Mean number of symptom days from the 42 diary days over the study period

Symptom	Age				Gender		Smoker		IC	
	≤14	15–34	35–49	≥50	Male	Female	Yes	No	Yes	No
Subjects n	49	28	27	25	71	58	21	63	43	86
Wheeze	2	7	8	11	7	5	14	6	7	6
Breathlessness	2	6	21	16	8	6	12	8	10	5
Chest tightness	2	8	10	8	6	7	14	6	10	4
Cough	13	10	11	16	12	13	19	10	11	9
Breathlessness on exertion	3	7	9	17	8	6	11	9	12	5
Daytime asthma attacks	2	3	4	4	3	2	7	3	5	2
Night asthma attacks	1	3	4	4	3	2	8	2	4	2

IC: inhaled corticosteroids.

3). On repeating the analysis with the available data, without imputation, the results remained similar for the ≤14 yrs age group, with OR (and 95% CI) for same day symptoms of 1.09 (0.93–1.27) for wheeze, 1.01 (0.69–1.47) for breathlessness, 1.58 (1.32–1.88, $p<0.001$) for chest tightness, 1.09 (0.89–1.32) for cough, 1.21 (1.08–1.34, $p<0.001$) for breathlessness on exertion, 1.21 (1.06–1.35, $p<0.01$) for daytime asthma attacks, and 1.23 (1.03–1.47, $p<0.05$) for night asthma attacks. For 1 day lag symptoms, with available data, OR were 1.27 (1.11–1.45 $p<0.001$) for wheeze, 1.11 (0.92–1.35) for breathlessness, 1.60 (1.31–1.95, $p<0.001$) for chest tightness, 1.02 (0.83–1.26) for cough, 1.24 (1.09–1.42, $p<0.001$) for breathlessness on exertion 1.13 (0.90–1.42) for daytime asthma attacks, and 1.23 (1.07–1.43, $p<0.01$) for night attacks.

For cough with 1 day lag in the 35–49 yr age group, analysis with the available data remained significant (OR: 1.11, 95% CI: 1.03–1.19). Each ratio reported in table 3 reflects the increase in each symptom when there is a 1 sd increase in indoor personal NO₂ exposure, which was 43.8 ppb for daily symptoms with imputation and 50.6 ppb with available data.

Smoking and gender

In children aged <14, there was no evidence of confounding by household environmental tobacco smoke. Mean NO₂ levels in nonsmoking households (39.8 ppb, 95% CI: 34.2–45.4 ppb, in 23 households) was higher than in households with parental smoking (22.7 ppb, 95% CI: 20.2–25.3 ppb in 26) and there were no significant relationships between parental smoking and symptoms.

No significant interactions were demonstrated between smoking or sex and NO₂ levels in relation to same day symptoms or 1 day lag symptoms, with respect to both available data and imputed data.

Discussion

When all the subjects were analysed, there was no evidence of a positive relationship for same day or 1 day lag symptoms. However, significant interactions between NO₂ and age ≤14 were demonstrated for 3 of the 7 symptom outcomes measured for both same day and 1 day lag. The consistency between these findings with imputation, and also when analysing only the available data (4 significant symptom associations for both same day and

also 1 day lag), in age group ≤14 as well as other age groups, indicates the robustness of these associations. An increase in the same day symptoms in the 14 age group of up to 29% (table 3) (58% based upon available data) is associated with a sd increase in NO₂ exposure (43.8 ppb) and is of clinical significance, as it occurs at NO₂ level increments that are readily attained by the use of domestic gas appliances (fig. 1). Adults in this study did not demonstrate such relationships, other than for 1 of the 7 symptoms in the 35–49 yr-old age group, and only with a 1 day lag. This single positive finding in subjects ≥15 yrs-of-age may have been by chance alone. Interpretation of the relative lack of significant interactions in older age groups is limited by a lack of power relative to the ≤14 age group. However, children may be more sensitive to the effects of air pollutants including NO₂. A recent study of respiratory symptoms and air pollution including outdoor NO₂, demonstrated that children with bronchial hyperresponsiveness and relatively high total immunoglobulin-E (IgE) levels are more susceptible to air pollution [23]. The relatively higher ratio of "airway surface area" to "volume contained" in the airways of children, will result in a greater relative exposure for a given change in the badge NO₂ measurements, and may explain the lack of positive findings in adults compared to children in this study.

Although the evidence available indicates a relationship between environmental tobacco smoke and respiratory disease in children [24], no association between parental smoking and respiratory symptoms was present in the sample of subjects in the present study ≤14, NO₂ levels were also not higher in households with parental smokers. Confounding by parental smoking in this group is therefore unlikely to explain the relationships demonstrated in table 3, although daily measures of environmental tobacco smoking in the presence of children, were not performed.

Education is a socioeconomic indicator, which might be associated with the use of ageing gas appliances, as well as greater respiratory illness and symptoms due to less access to health care services, and thus may act as a potential confounder of relationships between personal NO₂ exposure and asthma symptoms. However, a common set of potential demographic and environmental founders, including education, for all 7 symptom outcomes were adjusted for. Incomplete response rates to daily personal exposure measurements and symptom records occurred in this community based study, despite twice-weekly home visits by field workers.

Table 3. – Relationship (odds ratio (95% confidence interval)) between average personal nitrogen dioxide levels of exposure and daily symptoms or daily symptoms with a one day lag, over the 18 week study period according to age group

Symptom	≤14 yrs		15–34 yrs		35–49 yrs		≥50 yrs		All age groups	
	Same day	1 day lag	Same day	1 day lag	Same day	1 day lag	Same day	1 day lag	Same day	1 day lag
Subjects n	48		26		26		50			
Wheeze	1.04 (0.89–1.12)	1.13 (0.96–1.32)	1.12 (0.71–1.75)	1.30 (0.75–2.24)	0.66 (0.37–1.20)	0.75 (0.47–1.21)	0.99 (0.51–1.91)	1.04 (0.66–1.65)	0.94 (0.86–1.03)	1.02 (0.93–1.12)
Breathlessness	0.95 (0.70–1.31)	1.06 (0.85–1.32)	1.15 (0.71–1.88)	1.07 (0.67–1.69)	1.01 (0.94–1.07)	1.01 (0.94–1.08)	0.86 (0.47–1.56)	0.94 (0.57–1.56)	0.99 (0.92–1.85)	1.03 (0.93–1.13)
Chest tightness	1.29 (1.16–1.43)***	1.29 (1.14–1.46)***	1.08 (0.59–1.98)	0.91 (0.55–1.52)	0.99 (0.92–1.06)	1.02 (0.95–1.09)	0.84 (0.48–1.46)	0.80 (0.47–1.35)	1.09 (0.93–1.27)	1.14 (0.98–1.31)
Cough	1.07 (0.89–1.29)	0.99 (0.82–1.21)	0.79 (0.43–1.44)	0.85 (0.50–1.44)	1.06 (0.93–1.22)	1.15 (1.01–1.31)*	0.75 (0.48–1.18)	1.01 (0.59–1.74)	1.03 (0.94–1.13)	1.01 (0.93–1.18)
Breathlessness on exertion	1.09 (0.97–1.21)	1.13 (1.0–1.28)*	0.90 (0.44–1.83)	0.75 (0.33–1.73)	0.56 (0.25–1.24)	0.59 (0.27–1.28)	0.70 (0.43–1.12)	0.91 (0.55–1.50)	0.96 (0.83–1.12)	1.01 (0.91–1.12)
Daytime asthma attacks	1.13 (1.02–1.26)*	1.11 (0.94–1.31)	0.91 (0.37–2.23)	1.36 (0.59–3.14)	0.83 (0.53–1.30)	0.79 (0.40–1.57)	0.68 (0.32–1.42)	0.95 (0.33–2.74)	1.03 (0.94–1.12)	1.04 (0.94–1.15)
Night asthma attacks	1.16 (1.03–1.30)*	1.15 (1.03–1.29)*	1.70 (0.78–3.68)	0.60 (0.23–1.58)	0.83 (0.43–1.59)	0.74 (0.33–1.67)	0.67 (0.30–1.53)	0.78 (0.30–2.05)	1.06 (0.97–1.16)	1.03 (0.92–1.15)

OR: odds ratio; CI: confidence interval. OR and 95% CI by Generalized Estimating Equation analysis [19], with imputation [22], with adjustment for gender, education level, use of preventative medication, and area of residence, and with additional adjustment in the daily symptoms analysis for daily outdoor parameters of SO₂, NO₂, O₃, wind direction, relative humidity, minimum temperature, total fungal spore counts, cladosporium, and alternaria. *: p<0.05; **: p<0.01; ***: p<0.001; ns: not significant.

Fig. 1. – Box and whisker plots demonstrating median, interquartile range (IQR) and outliers (data points >15 IQR beyond the third quartile) of nitrogen dioxide (NO₂) levels according to household appliances. Five outlying values of NO₂ which exceeded 500 ppb were not included. Two of the outlying values were from households with gas cooking only, three from households with gas used for both cooking and heating, one household had heating with a flue and two were without. Horizontal line represents the World Health Organization guideline level of 110 ppb for nitrogen dioxide. Mean (95% confidence interval) ppb for each treatment in turn: gas cook+heat: 28.7 (21–40); gas heat: 20 (18–22); gas cook: 32 (24–44); all electric: 12 (11–15); unflued gas: 67 (27–165); flued gas heater: 23 (19–28).

There was limited explanatory information on the missing data, reasons for incomplete participation cited by study subjects included variations in domestic arrangements due to illness, school holidays, and irregularities in living arrangements due to custodial access in the case of single parent households.

The daily asthma diary has not been validated against physiological parameters, however, elements of the diary methodology, including parental completion for children, are consistent with other epidemiological asthma studies [17, 18]. The diary approach offers an indication of discomfort and morbidity, and also enables cohort study members to serve as their own controls over time. Peak flow meters were not utilized in this study, as the primary outcome of interest was symptom burden. Time of badge exposure each day was also self reported. Future research could benefit from the addition of relevant objective measurements. Outdoor particulates (ambient TSP and PM₁₀) arise from outdoor sources, and would not be expected to confound the relationships demonstrated between indoor NO₂ and respiratory symptoms in residents, and only 3 readings exceeded United States EPA guidelines during the study period.

Relevant general population studies include the European Community Respiratory Health Survey (ECRHS) (which used proxy measures of NO₂ exposure in a study of adults) [25, 26], the Harvard 6 Cities Study [27] (which measured weekly indoor NO₂ in a study of children), and a cohort study of Australian school children [28] (which measured daily schoolroom NO₂). These studies demonstrated an association between the use of gas appliances and lung function reduction and subjective respiratory outcomes, including evidence of a dose-response relationship. However, prospective studies of children aged

0–5 in 2 cities in Switzerland [29] and of a birth cohort in North America [30] reported negative findings, although indoor mean NO₂ concentrations were low. The two-weekly NO₂ measurements in the latter study may also have been too insensitive to determine the effects of peak exposures. Studies such as the European Community Health Survey (ECHS) [25, 26] of general adult populations were limited by cross section design and the exposure misclassification risk due to questionnaire scoring of gas combustion exposure, rather than actual measures of NO₂. Participating ECHS centres varied considerably with respect to prevalence of gas appliances, symptoms, subject participation, and associations demonstrated. The ECHS found no associations in male subjects, but positive associations were present in females in some centres, possibly due to their greater proximity to gas cooking, and the ECHS's power to detect a relationship in such a large study of over 6,000 female adults. Domestic arrangements for cooking practices may vary between countries, and may help to explain the heterogeneity of the results in females. However, the adequacy of adjustment for potential confounders such as smoking and residential ventilation is uncertain, such that unmeasured confounding may also vary between centres, according to centre specific cultural practices and residential factors. General population studies such as these, as well as the 3 epidemiological studies specifically on asthmatics [9–11] have therefore, had inconsistent results which may be related to the use of proxy measures, prolonged NO₂ measures, and limited evaluation of potential confounders. None of the studies were designed to evaluate same day and 1-day lag respiratory effects in a domestic setting. The authors have reported the first study to measure daily symptoms and daily personal NO₂ exposures, in a cohort study specifically in asthmatics. Much of the previous research in this area has been limited by methodological problems which have been previously described in a systematic review [2]. In particular, the risk of NO₂ exposure misclassification which is inherent in studies which have used proxy measures, such as questionnaires, have been avoided by the use of daily personal NO₂ measures in the present study. The cohort design, with evaluation of same day and 1-day lag symptoms, also provides evidence of a temporal relationship which is lacking in cross-section studies. The repeated short-term personal exposure measurements in this cohort study of asthmatics, including children, increased the capability to detect day-to-day peak exposures to indoor NO₂, and associated symptoms. Peak levels of exposure are more pathogenic than long term average exposures in animal studies [31], true peak NO₂ exposures are likely to be even higher than those demonstrated by the time weighted averages in this study [28], and certain types of gas appliances are associated with greater levels of personal NO₂ exposure (fig. 1).

Port Adelaide has a Mediterranean climate and any generalization of the results should consider the slightly higher regional prevalence of smoking and gas stoves, compared to Australia-wide and South Australian data respectively, which has been previously reported [12].

To conclude, community based asthmatic children have a demonstrable association between increased respiratory symptoms and nitrogen dioxide at levels which are readily

encountered in domestic settings. As both asthma and gas appliances are common, the findings of this study have considerable clinical and public health implications.

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