

# Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children

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<b>Background</b>	We enrolled a cohort of primary schoolchildren with a history of wheeze (n = 148) in an 11-month longitudinal study to examine the relationship between ambient ozone concentrations and peak expiratory flow rate.
<b>Methods</b>	Enrolled children recorded peak expiratory flow rates (PEFR) twice daily. We obtained air pollution, meteorological and pollen data. In all, 125 children remained in the final analysis.
<b>Results</b>	We found a significant negative association between daily mean deviation in PEFR and same-day mean daytime ozone concentration ( $\beta$ -coefficient = 0.88; $P = 0.04$ ) after adjusting for co-pollutants, time trend, meteorological variables, pollen count and <i>Alternaria</i> count. The association was stronger in a subgroup of children with bronchial hyperreactivity and a doctor diagnosis of asthma ( $\beta$ -coefficient = -2.61; $P = 0.001$ ). There was no significant association between PEFR and same-day daily daytime maximum ozone concentration. We also demonstrated a dose-response relationship with mean daytime ozone concentration.
<b>Conclusions</b>	Moderate levels of ambient ozone have an adverse health effect on children with a history of wheezing, and this effect is larger in children with bronchial hyperreactivity and a doctor diagnosis of asthma.
<b>Keywords</b>	Asthma, air pollution, ambient ozone, children, lung function, peak expiratory flow rate, bronchial hyperresponsiveness
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There is increasing evidence of associations between air pollution and morbidity and mortality.<sup>1–6</sup> The relationship between air pollution and lung function is mostly consistent, despite differences in definitions of exposure and outcome measurements

and the statistical methods used to model the relationship between air pollution and health outcomes.<sup>7–11</sup>

Asthma in children is a priority health issue in Australia. The prevalence of childhood asthma in Australia is already among the highest in the world with reported prevalence between 24% and 40%.<sup>12,13</sup> Further, the prevalence has increased over the past decade.<sup>13,14</sup> The cost of asthma to the community is considerable—it has been estimated that the total direct and indirect cost of asthma in Australia in 1991 was between \$600 and \$700 million Australian dollars.<sup>15</sup>

Despite the substantial financial and morbidity burden on the community and the known associations between air pollution and asthma morbidity, as far as we know, there are no reported longitudinal studies on air pollution and lung function in children with asthma and/or bronchial hyperresponsiveness.

We examined the relationship between air pollution and asthma morbidity in three groups of children in western and southwestern Sydney where the local geography and air flows combine to produce higher levels of air pollution than in other

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regions of Sydney.<sup>16</sup> We studied children with: recent wheeze, doctor diagnosis of asthma and bronchial hyperresponsiveness; recent wheeze and doctor diagnosis of asthma; and, recent wheeze only. In this paper we report on the association between ambient ozone and peak expiratory flow rates (PEFR) in these three groups of children.

## Methods

### Subject selection

We obtained ethics approval from all relevant institutional ethics committees prior to commencement of the study. In August 1993, a cross-sectional study was conducted of children in school, years 3–5, in six primary schools in western and southwestern Sydney. Each selected primary school was the closest to, and within 2 km, of a New South Wales Environment Protection Authority (EPA) ambient air quality monitoring station. The cross-sectional study included a parent-completed asthma questionnaire and measurement of childrens' airway responsiveness by histamine challenge. Children were classified as having airway hyperresponsiveness if their forced expiratory volume in one second (FEV<sub>1</sub>) fell by >20% from the post-saline value.

Children with a history of wheezing in the previous 12 months from the parent-completed questionnaire were then enrolled in the longitudinal study commencing in January 1994. Each child completed an asthma diary twice a day (on waking and before bed). The asthma diary requested information about PEFR, number of hours spent outdoors and whether the child was in Sydney. Each child recorded three PEFR measured in the standing position. We instructed children to leave the diary blank if they forgot to complete their diary.

Research assistants visited all children in the study at least once every 8 weeks and made telephone contact in between each home visit. At the first visit, the children and parents were instructed in the use of a mini-Wright peak flow meter (Clement Clarke International Ltd, UK) and the asthma diary. Parents supervised their child's diary keeping and PEFR measurements. At subsequent home visits we observed, and corrected if necessary, the child's PEFR measurement technique and recorded PEFR. Completed diaries were returned to us in self-addressed stamped envelopes or collected by the research assistants.

### Air pollution, meteorological and pollen data

We obtained daily air pollution and meteorological data for 1994 from six ambient air quality monitoring stations in western and southwestern Sydney. The monitoring stations continuously measured ambient ozone (Monitor Lab Ozone Analyzer Model 8810), particles <10 µm (PM<sub>10</sub>) (TEOM® Series 1400A, Rupprecht & Pataschnick Co., Inc., USA) and nitrogen dioxide (NO<sub>2</sub>) and other oxides of nitrogen (Monitor Lab Nitrogen Oxides Analyzer Model 8840). The EPA also provided us with daily temperature and humidity data.

Air pollution and meteorological data were provided as daily maximum, daily maximum for daytime period (0600–2100 h), daily arithmetic average and daily arithmetic average for daytime period. The maximum reading for a given period was the highest of the hourly readings whereas the mean for a given period was the arithmetic average of the hourly readings for that period of time.

We obtained daily total pollen and *Alternaria* counts from two sites in the study area using Burkard 7-day spore traps. Total pollen and *Alternaria* counts were averaged across the two sites and log transformed prior to analyses.

### Statistical methods

Our analysis period was from 1 February 1994 to 31 December 1994. We used the evening recorded PEFR as the outcome variable and included in the analyses only children who had more than 30 PEFR observations for the analyses period. We excluded the first two weeks of diary data for each child to compensate for any learning effect and diary records for when children were out of metropolitan Sydney.

### Air quality and meteorological data

We used the maximum one-hour and mean daytime values for air pollution and meteorological variables in our analyses. These values were only calculated if ≥80% of hourly values were present. For the population regression analyses, we used values for air pollutants and meteorological variables that were averaged across all six monitoring stations. In the generalized estimating equation (GEE) models, each child's air pollution and meteorological exposures were derived from the monitoring station closest to that child's school. Data from two monitoring stations were not utilized because of incomplete data collection.

### Peak expiratory flow rate measurements

The highest of the three evening PEFR readings was used in all analyses. For the population regression model, we calculated the daily mean deviation in PEFR (ΔPEFR). For each child, we calculated the ΔPEFR by subtracting the child's mean evening PEFR over the entire study period from the highest evening PEFR for that day. We normalized the child-specific deviations by dividing by the child's mean PEFR and then multiplying by 300. These normalized child-specific ΔPEFR were then averaged over each day of the study to determine the mean normalized daily ΔPEFR. In the GEE models, the dependent variable was the highest evening PEFR reading.

### Statistical modelling

We used the methods of Pope *et al.*<sup>17</sup> and Neas *et al.*<sup>7</sup> to develop population regression models<sup>18,19</sup> to determine associations between normalized ΔPEFR and explanatory variables. We also used GEE techniques,<sup>20,21</sup> which accounted for within-subject correlation, to examine the associations between PEFR and explanatory variables. Exposure variables were also lagged between one and 4 days and averaged over 2 and 5 days.

All population regression and GEE models included linear and quadratic terms for time trend (number of days since the start of the study), mean daytime PM<sub>10</sub> concentration, mean daytime NO<sub>2</sub> concentration, mean daytime temperature and humidity, number of hours spent outdoors, total pollen and *Alternaria* count, and season as covariates. Seasons were categorized as late summer–autumn (February–April), winter (May–September) and summer (October–December). The population regression model controlled for first order autocorrelation whereas the GEE models included a first order autoregression correlation structure. Higher order terms for all other covariates and interaction terms did not contribute to the final model. All analyses were performed using SAS statistical software.<sup>18,19,22</sup>

**Table 1** Demographic and risk factor characteristics of children included in analysis, Western Sydney Children's Asthma Study, February 1994–December 1994

	Children included in analysis <sup>a</sup>		
	Group 1 (n = 45)	Group 2 (n = 60)	Group 3 (n = 20)
Mean age ± SD <sup>b</sup> (years)	9.6 ± 0.99	9.7 ± 0.91	9.6 ± 0.89
Boys n (%)	30 (67)	35 (58)	8 (40)
Born in Australia n (%)	45 (100)	52 (87)	19 (95)*
Any atopy n (%)	44 (98)	34 (57)	8 (40)**
Dustmite atopy n (%)	40 (89)	28 (47)	7 (35)**
Age when first wheezed, mean age ± SD (years)	2.5 ± 1.22	3.0 ± 1.36	3.7 ± 1.56**
≥4 episodes of acute asthma in past 12 months n (%)	25 (56)	23 (38)	3 (15)*
Visited local doctor for asthma in past 12 months n (%)	14 (31)	15 (25)	0 (0)*
Mother smoked during pregnancy n (%)	7 (16)	20 (33)	8 (40)
One parent smoked in the home in the first 2 years of life n (%)	21 (47)	32 (53)	15 (75)
One parent with asthma n (%)	18 (41)	24 (41)	9 (45)

<sup>a</sup> Group 1 = Wheeze in past 12 months + positive histamine challenge + doctor diagnosis of asthma (three children did not have a doctor diagnosis of asthma); Group 2 = Wheeze in past 12 months + doctor diagnosis of asthma; Group 3 = Wheeze in past 12 months.

<sup>b</sup> Standard deviation.

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

## Results

### Composition of cohort

In all, 148 children were enrolled in the longitudinal study. Forty children withdrew (27.3%) from the study. Most ( $n = 25$ ; 62.5%) withdrew within the first 3 months. Twenty-three children were excluded from the analyses because they had  $\leq 30$  observations for the 11-month study period. The remaining 125 children comprised three groups: Group 1 ( $n = 45$ ): history of wheeze in the past 12 months AND positive histamine challenge AND doctor-diagnosed asthma (including three children with a history of wheeze and positive histamine challenge but without a doctor diagnosis of asthma); Group 2 ( $n = 60$ ): history of wheeze in the past 12 months AND doctor-diagnosed asthma; and Group 3 ( $n = 20$ ): history of wheeze in the past 12 months only. The doctor diagnosis of asthma could have been made at any time in the child's life.

Group 1 children were younger when they had their first episode of wheeze, had more frequent episodes of wheeze, and were more likely to have positive skin testing to any allergen, but particularly for house dust mites (Table 1).

### Air quality, meteorological and pollen data

Univariate statistical and time series plots for selected air pollution and meteorological variables are presented in Table 2 and Figure 1. During the study period, mean daily daytime ozone concentration exceeded 4 parts per hundred million (pphm) only once. Daily maximum daytime ozone concentration did not exceed 10 pphm (range: 0.2–9.1 pphm), and only on two occasions did the daily maximum ozone concentration exceed 8 pphm. Ozone concentrations were higher in the summer months (December–February). The average daytime  $PM_{10}$  concentration was  $22.8 \mu g/m^3$  and the mean daytime  $NO_2$  concentration did not exceed 5 pphm.

There was a negative correlation between ozone and humidity, and a positive correlation between ozone and temperature (Table 3). All correlation coefficients were significant, except

those between temperature and  $PM_{10}$  ( $P = 0.44$ ), and temperature and humidity ( $P = 0.39$ ). Maximum daytime ozone had a similar positive correlation with mean temperature ( $r = 0.64$ ;  $P = 0.0001$ ) and a weaker correlation with mean daytime humidity ( $r = -0.31$ ;  $P = 0.0001$ ). The correlation coefficients among the six monitoring stations ranged from 0.80 to 0.97 for mean daytime ozone, 0.20 to 0.95 for mean daytime  $PM_{10}$  and 0.59 to 0.83 for mean daytime  $NO_2$ .

Averaged across the two monitoring stations, mean daily total pollen count was 36 (range: 3–165; SD: 30.0; median: 28), while mean daily *Alternaria* spore count was 36 (range: 0–350; SD: 53.0; median: 18).

### Evening PEFR and $\Delta$ PEFR

Children were in metropolitan Sydney for 36 956 child-days (88.5%) and evening PEFR was recorded for 31 209 child-days (75%) over the study period. The median number of daily evening PEFR observations was 95 (range = 55–117 PEFR observations; mode = 95 PEFR observations). The mean evening PEFR was 323.5 litres/min (range = 60–630 litres/min; SD = 54.9 litres/min; coefficient of variation = 17%). The mean evening PEFR for individual children ranged from 212 to 446 litres/min. The median within-child standard deviation was 23.5 litres/min.

For group 1, group 2 and group 3 children the mean evening PEFR was 314 litres/min (range: 212–446 litres/min; SD = 52.6 litres/min), 333 litres/min (range: 242–436 litres/min; SD = 44.9 litres/min) and 322 litres/min (range: 244–415 litre/min; SD = 45.0 litres/min), respectively. The median within-child standard deviations for groups 1, 2 and 3 were 26.3, 22.7 and 18.0 litres/min, respectively. The normalized evening  $\Delta$ PEFR ranged from –12.4 litres/min to 17.8 litres/min (mean = 0.55 litres/min; SD = 6.89 litres/min).

### Population regression and GEE models

We controlled for co-pollutants, meteorological variables, time trends, seasonality, and total pollen and *Alternaria* counts in all

**Table 2** Daily daytime<sup>a</sup> mean and maximum concentrations for ozone, PM<sub>10</sub>, NO<sub>2</sub>, temperature and humidity across the six monitoring stations, Western Sydney Children's Asthma Study, February 1994–December 1994

	Mean daytime values	Maximum daytime values
<b>Ozone (pphm)<sup>b</sup> n = 333</b>		
Mean ± SD <sup>c</sup>	1.2 ± 0.68	2.6 ± 1.44
Maximum	4.3	9.1
Interquartile range	0.83	1.37
<b>PM<sub>10</sub> (µg/m<sup>3</sup>) n = 333</b>		
Mean ± SD	22.8 ± 13.89	44.9 ± 28.93
Maximum	122.8	250
Interquartile range	12.00	26.5
<b>NO<sub>2</sub> (pphm) n = 333</b>		
Mean ± SD	1.5 ± 0.60	2.9 ± 1.09
Maximum	4.7	7.9
Interquartile range	0.82	1.37
<b>Temperature (°C) n = 332</b>		
Mean ± SD	17.7 ± 4.82	22.3 ± 5.23
Maximum	36.5	43.5
Interquartile range	7.04	7.24
<b>Humidity (%) n = 332</b>		
Mean ± SD	65.1 ± 14.85	89.3 ± 11.69
Maximum	99.4	99.5
Interquartile range	20.26	14.54
<b>Daily values</b>		
<b>Total pollen (grains/m<sup>3</sup>) n = 334</b>		
Mean ± SD	35.5 ± 30.04	
Maximum	165	
Interquartile range	36.35	
<b>Total <i>Alternaria</i> (spores/m<sup>3</sup>) n = 334</b>		
Mean ± SD	35.5 ± 53.03	
Maximum	350	
Interquartile range	33.75	
<b>Hours spent outdoors n = 334</b>		
Mean ± SD	3.81 ± 0.83	
Maximum	5.98	
Interquartile range	1.43	

<sup>a</sup> Daytime readings for between 6 am and 9 pm.

<sup>b</sup> Parts per hundred million.

<sup>c</sup> Standard deviation.

regression models. In the population regression model, although the addition of mean daytime PM<sub>10</sub> and NO<sub>2</sub> did not significantly contribute to the model (Table 4), they were retained in the final model as the aim of the modelling was to determine the effect of ambient ozone on lung function after adjusting for co-pollutants.

Associations between normalised evening ΔPEFR and daily daytime ozone concentration in the population regression models are presented in Table 5. For all children in the study (n = 125), there was a significant negative association between ΔPEFR and mean daytime ozone (β coefficient = 0.88; P = 0.04). Group 1 children had a larger negative association (β-coefficient = 2.61; P = 0.001), whereas children without bronchial hyperreactivity

showed smaller associations between ΔPEFR and mean daytime ozone. Group 2 children demonstrated a non-significant negative association, whilst group 3 children had a positive association between ΔPEFR and mean daytime ozone. All three groups of children demonstrated smaller associations between ΔPEFR and maximum daytime ozone concentration (Table 5).

Group 1 children demonstrated a dose-response relationship between ΔPEFR and quartiles for mean daytime ozone (Figure 2). The β-coefficient for the association between ΔPEFR and second, third and fourth quartiles for mean daytime ozone were -0.78, -1.04 and -2.93, respectively. Such a relationship was not observed for children in groups 2 and 3.

Similar dose-response relationships were observed for the associations between ΔPEFR and quartiles for maximum daytime ozone (Figure 2). Group 1 children again demonstrated a clear dose-response relationship (β-coefficients of -0.114, -1.25 and -2.21 for second, third and fourth quartiles, respectively).

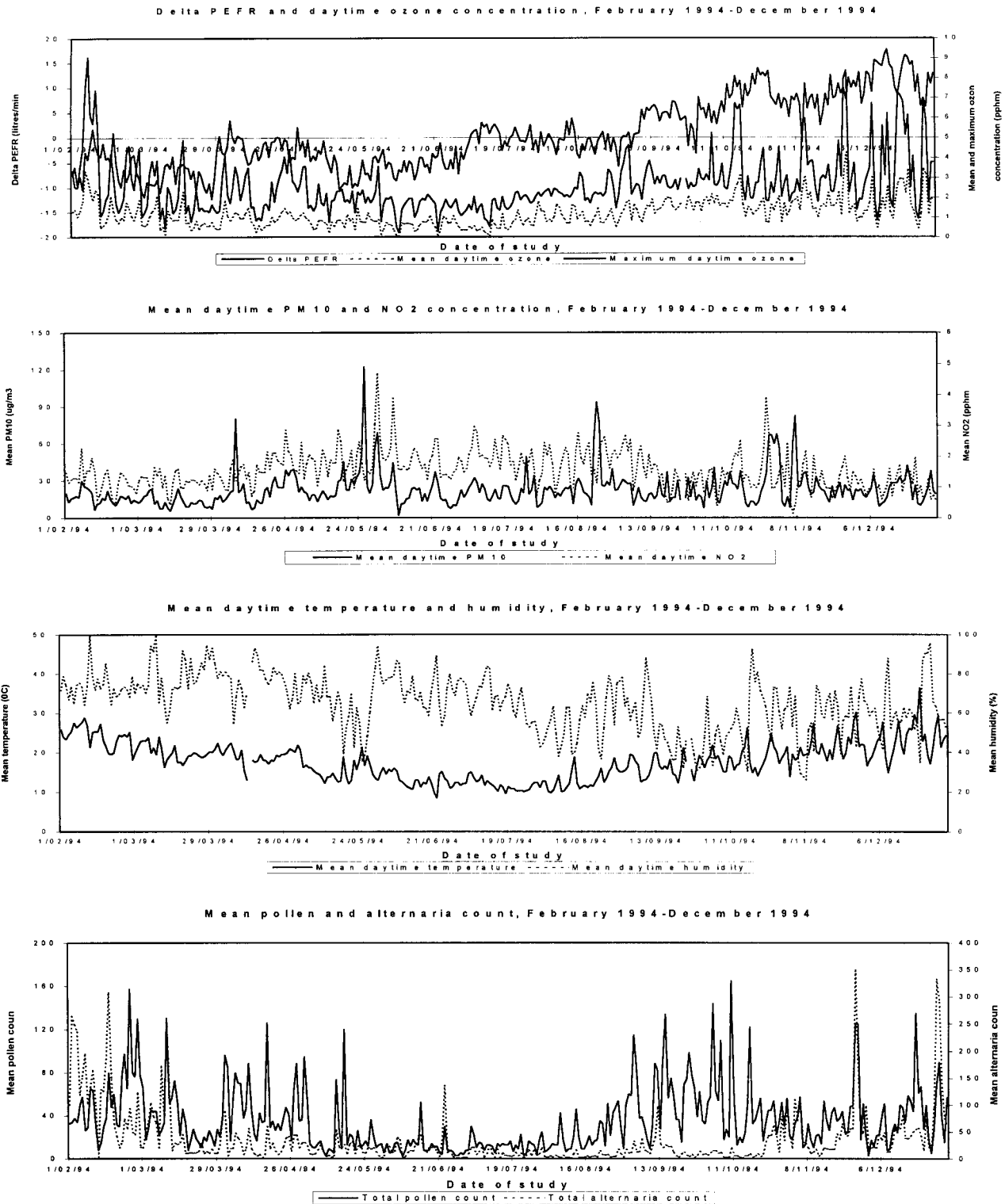
Results from regression analyses comparing the GEE and population regression models for group 1 children with lagged and averaged values for daytime ozone are presented in Table 6. In the GEE model, for both same-day mean and maximum daytime ozone concentrations, there was a negative association with evening PEFR, however neither of the associations was statistically significant. Lagging by up to 4 days or averaging ozone concentrations over 2- and 5-day periods did not result in any significant associations between mean daytime ozone and evening PEFR. Results were similar for maximum daytime ozone, except that for at lag 2 days there was a positive and significant association between maximum daytime ozone and evening PEFR (GEE model: β-coefficient = 0.33, P = 0.01; Population regression model: β-coefficient = 0.58, P = 0.02).

## Discussion

This study, one of the largest longitudinal studies of its kind in Australia, found a significant negative association between ΔPEFR and same-day mean daytime ozone concentration in a group of children who had wheezed in the 12 months prior to enrolment in the study. This association between ΔPEFR and same-day mean daytime ozone was found for moderately low levels of ambient ozone concentrations and was most evident in a subgroup of children who had bronchial hyperreactivity to histamine challenge and a doctor diagnosis of asthma. Further, for ozone exposure, there was also a suggestion of a dose-response relationship in this subgroup of children.

We categorized the children in our study into three groups based on presence or absence of bronchial hyperreactivity to histamine challenge and presence or absence of a doctor diagnosis of asthma. We hypothesized, *a priori*, that children with bronchial hyperreactivity and a doctor diagnosis of asthma (Group 1) would possibly be more sensitive to the effects of air pollution than children without bronchial hyperreactivity but with a doctor diagnosis of asthma (Group 2), and children with wheeze only (Group 3). The results confirmed our hypothesis. Group 1 children demonstrated the greatest reductions in ΔPEFR when exposed to ambient ozone compared to children in the other two groups.

In this group of children, although the population regression models and the GEE models (Table 6) gave slightly different



**Figure 1** Daily air pollution, meteorological, pollen and *Alternaria* readings, Western Sydney Children's Asthma Study, February 1994–December 1994

results, the  $\beta$ -coefficients were generally in the same direction particularly in the case of mean daytime ozone. The GEE models were more likely to produce negative coefficients compared to the population regression models. With so many tests and so

few significant associations it is possible that these may be chance findings. However, in view of the consistency of findings for both mean and maximum daytime ozone, we have more likely demonstrated a real effect. Interestingly, for maximum

**Table 3** Correlation coefficients for daily mean daytime<sup>a</sup> values for ozone, PM<sub>10</sub>, NO<sub>2</sub>, temperature, humidity, total pollens and *Alternaria* across the six monitoring stations, Western Sydney Children's Asthma Study, February 1994–December 1994

	Ozone (pphm) <sup>b</sup>	PM <sub>10</sub> (mg/m <sup>3</sup> )	NO <sub>2</sub> (pphm)	Temperature (°C)	Humidity (%)	Total pollen <sup>c</sup>
Ozone	1.00					
PM <sub>10</sub>	0.13*	1.00				
NO <sub>2</sub>	-0.31**	0.26**	1.00			
Temperature	0.63**	0.04	-0.31**	1.00		
Humidity	-0.52**	-0.29**	0.23**	-0.05	1.00	
Total pollen	0.48**	0.04	-0.17*	0.58**	-0.20*	1.00
<i>Alternaria</i>	0.33**	0.04	-0.19*	0.67**	0.03	0.52**

<sup>a</sup> Daytime readings are for between 6 am and 9 pm.

<sup>b</sup> Parts per hundred million.

<sup>c</sup> Total pollen and *Alternaria* measured as natural logs.

\*  $P < 0.05$ , \*\*  $P = 0.0001$ .

**Table 4** Single and multi-pollutant population linear regression models<sup>a</sup> for associations between daily mean deviation in peak expiratory flow rate ( $\Delta$ PEFR) for all children ( $n = 125$ ) in the study, Western Sydney Children's Asthma Study, February 1994–December 1994

	Ozone		PM <sub>10</sub>		NO <sub>2</sub>	
	$\beta$ (SE)	$P$ -value	$\beta$ (SE)	$P$ -value	$\beta$ (SE)	$P$ -value
Mean daytime ozone only	-0.9178 (0.4192)	0.03	–	–	–	–
Mean daytime PM <sub>10</sub> only	–	–	0.0045 (0.0125)	0.72	–	–
Mean daytime NO <sub>2</sub> only	–	–	–	–	0.3646 (0.3473)	0.29
Mean daytime ozone + mean daytime PM <sub>10</sub>	-0.9195 (0.4199)	0.03	0.0051 (0.0124)	0.68	–	–
Mean daytime ozone + mean daytime NO <sub>2</sub>	-0.8825 (0.4212)	0.04	–	–	0.2954 (0.3468)	0.40
Mean daytime ozone + mean daytime PM <sub>10</sub> + mean daytime NO <sub>2</sub>	-0.8823 (0.4225)	0.04	-0.0031 (0.0127)	0.81	0.2797 (0.3544)	0.43

<sup>a</sup> Adjusted for time trend, time trend squared, mean daytime temperature, mean daytime humidity, daily pollen count, daily *Alternaria* count, number of hours spent outdoors and season.

<sup>b</sup> Standard error.

<sup>c</sup> Nitrogen dioxide.

**Table 5** Associations between daily mean deviation in peak expiratory flow rate ( $\Delta$ PEFR) and mean and maximum daytime ozone concentration from population regression models,<sup>a</sup> Western Sydney Children's Asthma Study, February 1994–December 1994

	Mean daytime ozone (pphm) <sup>b</sup>			Maximum daytime ozone (pphm)		
	$\beta$	SE <sup>c</sup>	$P$ -value	$\beta$	SE	$P$ -value
Group 1 children <sup>d</sup> ( $n = 45$ )	-2.6115	0.7766	0.001	-0.5477	0.3247	0.09
Group 2 children ( $n = 60$ )	-0.3569	0.4816	0.46	-0.0792	0.1983	0.69
Group 3 children ( $n = 20$ )	1.9090	0.9091	0.04	0.6123	0.3747	0.10
All children ( $n = 125$ )	-0.8823	0.4225	0.04	-0.1437	0.1753	0.41

<sup>a</sup> Adjusted for time trend, time trend squared, mean daytime PM<sub>10</sub>, mean daytime NO<sub>2</sub>, mean daytime temperature, mean daytime humidity, daily pollen count, daily *Alternaria* count, number of hours spent outdoors and season.

<sup>b</sup> Parts per hundred million.

<sup>c</sup> Standard error.

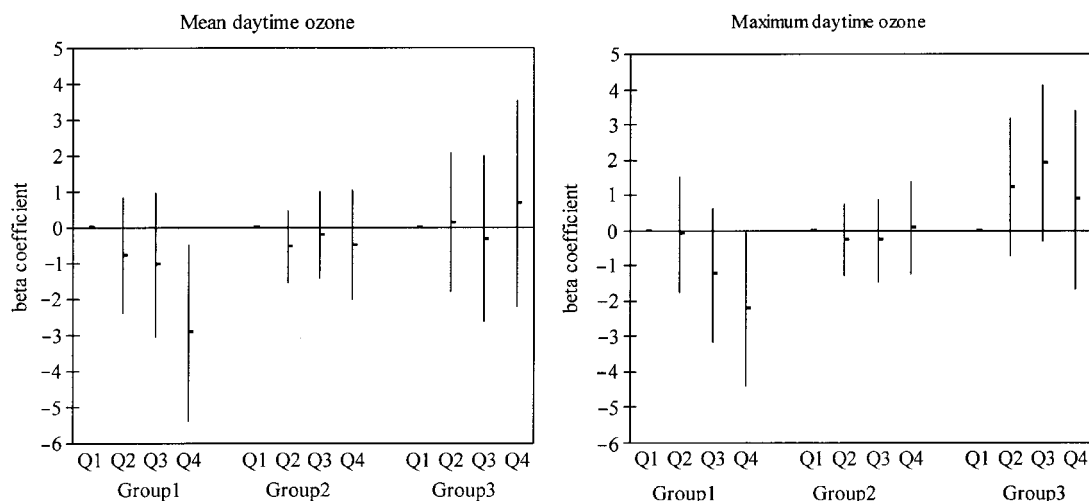
<sup>d</sup> Group 1 = Wheeze in past 12 months + positive histamine challenge + doctor diagnosis of asthma (three children did not have a doctor diagnosis of asthma); Group 2 = Wheeze in past 12 months + doctor diagnosis of asthma; Group 3 = Wheeze in past 12 months.

daytime ozone, there was a significant positive association at lag two in both the GEE and population regression models. We do not have a ready explanation for this phenomenon.

The above association that we found for group 1 children needs to be further clarified as a number of experimental studies have not demonstrated differences between asthmatics and non-asthmatic, healthy controls in their responses to inhaled ozone.<sup>23,24</sup> However, Boezen *et al.*<sup>25</sup> have demonstrated that

children with bronchial hyperreactivity and high serum IgE levels are susceptible to air pollution compared to children with bronchial hyperreactivity and low serum IgE levels. Therefore, in longitudinal studies such as ours, there may be unknown factors confounding the association between ambient ozone and lung function.

In the regression models we adjusted for important covariates such as time trend (day of study and its quadratic term),



**Figure 2** Associations between daily mean deviation in peak expiratory flow rate and quartiles for ozone, Western Sydney Children's Asthma Study, February 1994–December 1994

**Table 6** Associations between daytime ozone and peak expiratory flow rate (PEFR) derived from generalized estimating equation (GEE) and population regression models<sup>a</sup> for Group 1 children, Western Sydney Children's Asthma Study, February 1994–December 1994

	GEE model		Population regression model	
	$\beta$	SE <sup>b</sup>	$\beta$	SE
<b>Mean daytime ozone</b>				
Same day	-1.2114	0.6886	-2.6115*	0.7766
Lag 1	0.5952	0.4153	1.0667	0.5568
Lag 2	0.5665	0.5325	0.8304	0.5452
Lag 3	-0.4323	0.5410	-0.0869	0.5569
Lag 4	-0.2047	0.6739	0.0062	0.5575
2-day average <sup>c</sup>	-0.1498	0.6928	-0.2469	0.8848
5-day average <sup>d</sup>	-0.4063	2.0701	0.8107	1.4054
<b>Maximum daytime ozone</b>				
Same day	-0.3270	0.2687	-0.5477	0.3247
Lag 1	0.0358	0.1889	0.3469	0.2396
Lag 2	0.3257**	0.1326	0.5779***	0.2362
Lag 3	-0.0465	0.1889	0.1981	0.2411
Lag 4	-0.2049	0.2096	-0.0652	0.2409
2-day average	-0.3007	0.2803	0.0472	0.3856
5-day average	-0.3379	0.6451	0.9809	0.5865

<sup>a</sup> Adjusted for time trend, time trend squared, mean daytime PM<sub>10</sub>, mean daytime NO<sub>2</sub>, mean daytime temperature, mean daytime humidity, daily pollen count, daily *Alternaria* count, number of hours spent outdoors and season.

<sup>b</sup> Standard error.

<sup>c</sup> Same day and previous day values averaged.

<sup>d</sup> Same day and previous four days values averaged.

\*  $P = 0.001$ , \*\*  $P = 0.01$ , \*\*\*  $P = 0.02$ .

temperature, humidity, season, number of hours children spent outdoors, as well as pollen and *Alternaria* counts. Time trend adjusted for lung growth over time whereas temperature and season adjusted for long-term cyclical variations. The multi-pollutant model also accounted for co-pollutants such as PM<sub>10</sub> and NO<sub>2</sub>. In metropolitan Sydney, ambient ozone and PM<sub>10</sub> concentrations are poorly correlated, with ambient ozone concentrations higher in the summer months when PM<sub>10</sub> levels are

low. We were therefore able to examine the effects of ozone on lung function independent of PM<sub>10</sub> concentration.

There was no association between  $\Delta$ PEFR and mean daytime PM<sub>10</sub> and NO<sub>2</sub> in either single pollutant or multi-pollutant models. We were also not able to demonstrate any association between  $\Delta$ PEFR and total pollen and *Alternaria* counts (All children: total pollen:  $\beta$ -coefficient = 0.18,  $P = 0.47$ ; *Alternaria*:  $\beta$ -coefficient = -0.08,  $P = 0.66$ ; Group 1 children: total pollen:

$\beta$ -coefficient =  $-0.05$ ,  $P = 0.92$ ; *Alternaria*:  $\beta$ -coefficient =  $-0.12$ ,  $P = 0.72$ ). Others have also not been able to demonstrate associations between pollen counts and lung function.<sup>26,27</sup> The effect of *Alternaria* on lung function, although only very small, is consistent with studies demonstrating fungal spore effects on both lung function<sup>27</sup> and asthma symptoms.<sup>28</sup>

The study location is an urbanized part of metropolitan Sydney and there are no point sources of air pollution, and most of the ambient ozone is secondary to motor vehicle exhaust.<sup>29</sup> The ambient daily maximum daytime ozone concentration for the study period did not exceed 12 pphm (Australian National Health and Medical Research Council's threshold for the protection of human health at the time of the study<sup>2</sup>), and only once did it exceed 9 pphm. The mean daytime concentration averaged only 1.2 pphm and did not exceed 4.3 pphm. The mean daytime concentration averaged for the summer months was only marginally higher (1.5 pphm).

Despite the low concentrations of daytime ambient ozone, we found significant negative associations between PEFR and mean daytime ozone concentration. Importantly, there also appears to be a dose-response relationship between lung function and ambient ozone concentration (for both daily mean and maximum ozone concentration), but this was not consistent across all three groups of children. Children with bronchial hyperreactivity and a doctor diagnosis of asthma had greater decreases in  $\Delta$ PEFR on days with the highest ozone concentrations with a suggestion of threshold effect for mean daytime ozone. Although, the dose-response relationship appears to be stronger with maximum ozone concentration, the overall association between maximum daytime ozone and lung function was not significant.

In our study there were greater effects for mean daytime ozone concentration than for maximum daytime ozone concentration. Similar patterns of results have been reported by others.<sup>30</sup> We estimate that in group 1 children, an increase in mean daytime ozone equivalent to the observed range of mean daytime ozone concentration (4.3 pphm) would result in a 4% decrease in PEFR. For a similar increase in maximum daytime ozone concentration (8.8 pphm), the estimated decrease in PEFR in group 1 children was about 1.6%.

Our findings of the associations between lung function and daily mean ozone concentrations are similar to those from other reported studies.<sup>7-10</sup> Neas *et al.*<sup>7</sup> studied symptomatic and asymptomatic children who kept asthma diaries for 3 months in summer. In their population regression model, a 1-pphm increment in mean daytime ozone resulted in a 0.74 litres/min decrease in  $\Delta$ PEFR. The summer daytime mean ozone concentration in their study was 5 pphm. Hoek *et al.*,<sup>8</sup> in a study of 533 Dutch schoolchildren over 3 months in spring and summer, demonstrated a decrease in PEFR of 2 litres/min for every 1-pphm increase in maximum ozone concentration in children with doctor-diagnosed asthma. In a study of 91 healthy children in a 4-week summer camp, Spektor *et al.*<sup>9</sup> also found a negative association between daily one-hour peak ozone concentration measured in pphm and PEFR ( $\beta$ -coefficient =  $-0.75$ ). In children with mild asthma in Mexico city, Romieu *et al.*<sup>10</sup> demonstrated significant decrements in evening PEFR ( $-1.81$  litres/min for ozone change of 5 pphm). The ambient ozone concentrations were high in this study (maximum daily one-hour concentration ranged from 4 to 39 pphm, with a mean of 19.6 pphm).

In our study, for a 4 pphm increase in mean daytime ozone concentration, the average decrease in PEFR was only about 1% and 4% for all children and children with bronchial hyperreactivity plus a doctor diagnosis of asthma, respectively. Even for such a large increase in ozone exposure, the decrements in lung function are small and unlikely to be clinically significant. However, in our data, an increase in daytime mean ozone concentration equivalent to the interquartile range was associated with about a 20% increase in the prevalence of PEFR greater than 20% below the median.

Hoek *et al.*<sup>31</sup> demonstrated a similar pattern in relation to ambient PM<sub>10</sub>. A 10  $\mu\text{g}/\text{m}^3$  increase in PM<sub>10</sub> was associated with only a 0.07% decrease in the population PEFR but with a 3% increase in the prevalence of PEFR greater than 20% below the median. The authors suggest there is a shift in the whole PEFR distribution. Therefore in population terms, even a small decrease in average lung function may have important effects at the extreme ends of the distribution.<sup>32</sup>

In conclusion, we suggest that current levels of ambient ozone in western Sydney may have an adverse health effect on children with a history of wheezing, and that the effect is greater in children with bronchial hyperreactivity and a doctor diagnosis of asthma.

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