HETEROGENEITY OF DAILY PULMONARY FUNCTION IN RESPONSE TO AIR POLLUTION AMONG ASTHMATIC CHILDREN

Wichai Aekplakorn[1], Dana Loomis[2], Nuntavarn Vichit-Vadakan[3] and Shrikant Bangdiwala[4]

[1]Community Medicine Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [2]Department of Epidemiology, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA; [3]College of Public Health, Chulalongkorn University, Bangkok, Thailand; [4]Department of Biostatistics, School of Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

Abstract. Several epidemiological studies have demonstrated the association of short-term exposure to air pollution with transient declines in pulmonary function. Although the magnitudes of declines in pulmonary function found in these studies are relatively small, the effects vary among children. This study examined whether the variation is evidence of biological heterogeneity or due to random variation by analyzing data from a panel study of 83 asthmatic school children exposed to SO_2 and PM_{10} in the Mae Moh district of Thailand. Daily pulmonary function testing was performed on the children for 61 days. General linear mixed models were used to examine and test for the null hypothesis of no variation in the subject-specific slopes of pulmonary functions in response to the air pollutants. The individual daily pulmonary functions measured were FVC, FEV1, PEFR, and $FEF_{25-75\%}$. These were used as an outcome to compare with air pollutant concentrations as random effects, adjusting for height, gender, time, and temperature. The results indicate evidence of inter-individual variation for subject-specific changes in FVC, FEV_1, and PEFR due to the effects of SO_2 and PM_{10} on children. In conclusion, even at low concentrations of daily SO_2 and PM_{10} in the study area, there is evidence of a heterogeneous response to short-term exposure to SO_2 and PM_{10} in children.

INTRODUCTION

Many epidemiological studies of the acute effects of ambient air pollution on respiratory health using repeated measurements of pulmonary function have been reported (Pope *et al*, 1991; 1992; Braun-Fahrlander *et al*, 1992; Roemer *et al*, 1993; Neas *et al*, 1995). These studies demonstrated that daily increases in air pollution, especially particulate air pollution, are negatively associated with pulmonary function. Many studies have also documented that some children are more sensitive to air pollution than others (Pope *et al*, 1992; Roemer *et al*, 1993; Neas *et al*, 1995; Vedal *et al*, 1998). Children who have a history of symptomatic asthma or chronic lung diseases screened by questionnaire, or clinical cases of asthma, have been reported to be more susceptible to air pollution than asymptomatic children.

Correspndence: Dr Wichai Aekplakorn, Community Medicine Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.

Although previous studies suggested differences in susceptibility to air pollution among children who have underlying health conditions, it is still not clear whether there are heterogeneous responses within this group of children. Dockery and Pope (1994) reviewed studies of the acute respiratory effects of particulate air pollution. They found the observed health effects on pulmonary function changes were modest, approximately 0.15% decrease in FEV_1 or $FEV_{0.75}$ and a 0.08% decrease in peak flow per 10 $\mu g/m^3$. Although the magnitude of the lung function change estimates were relatively small, there might be persons with responses much larger than average. Brunekreef *et al* (1991) analyzed data from three studies of children exposed to air pollution and pulmonary function responses to investigate whether the observed variability in pulmonary function indicates a difference in sensitivity or is due to random inter-occasion variability among

subjects. After statistical analyses comparing between-child variation to within-child variation, this study found evidence of a heterogeneous response to ozone but not to total suspended particles.

It would be interesting to reinvestigate whether there is evidence of heterogeneity in response to air pollution among affected children as opposed to random errors. If there is systematic biological variation in response to air pollution, some children would be more susceptible and some less susceptible to air pollution, as measured by pulmonary function. The identification of the existence of a more sensitive subgroup is of importance in terms of control and prevention measures. For the less susceptible group, further studies of underlying factors related to their lower susceptibility are also of importance.

Using data from a panel study on the acute effects of exposure to air pollution on pulmonary function in schoolchildren in Mae Moh, Thailand (Aekplakorn *et al*, 2003a), we investigated the hypothesis that there is no substantial difference between subjects in the slopes of pulmonary function in relation to daily changes in SO_2 or particulate air pollution (PM_{10}).

MATERIALS AND METHODS

Data from an epidemiological study conducted in the winter of 1997 in Mae Moh, Thailand was used. Population selection, exposure assessment and pulmonary function measurement methods were described previously (Aekplakorn *et al*, 2003b). Briefly, asthmatic children and non-asthmatic children identified by a cross-sectional survey of asthmatic children were recruited from 706 schoolchildren aged 6-14 years old living in a suburban area in the Mae Moh district, Lampang Province, Thailand. In a previous cross-sectional study, the parents of these children were asked to complete a respiratory symptom questionnaire modified from the World Health Organization (WHO) questionnaire for children (Florey, 1982). The children were considered as suspected cases of asthma if they reported a positive response to the following question: 'Has your child had attacks of shortness of breath while wheezing during the past year?' The suspected asthmatic children were then physically examined by a local physician. The children were considered as asthmatics and eligible for the study when they reported to the physician that the asthmatic symptom was diminished by taking bronchodilator medicine. This analysis includes only asthmatic children, because the previous study did not find adverse effects of exposure to air pollution on pulmonary function among non-asthmatic children. Of the 98 asthmatic children identified from the above criteria, 88 participated in the study.

Pulmonary function

Pulmonary function testing on each child was obtained on a daily basis for 61 days. The spirometry maneuver was performed while standing, without a nose clip, using a pneumotach spirometer (S&M instrument, USA), coupled with automatic data acquisition software in a laptop computer based on the recommendation of standardization of spirometry by the American Thoracic Society (ATS 1994). The acceptable values of forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), peak expiratory flow (PEF), and mean forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$) were obtained from the children under study in accordance with ATS criteria.

Air pollution

Air pollution was concurrently measured at three outdoor monitoring stations in the villages. Daily 24 hours measurements of SO_2 and PM_{10} were obtained from the Electricity Generating Authority of Thailand. During the study period, the level of SO_2 was relatively low, except for a few days. Mean SO_2 concentrations of 10 (maximum 99), 16.9 (maximum 128), and 26.5 $\mu g/m^3$ (maximum 109) were measured at the Sob Pad, Sob Moh and Hau Fai stations respectively, which were lower than the Thai (300 $\mu g/m^3$) and WHO (125 $\mu g/m^3$) ambient standards. PM_{10} had a mean concentration of 36 $\mu g/m^3$ (maximum 113.3). The mean temperature in the study area was 25ºC, and no extreme low or high temperatures occurred during the study period.

Data analysis

We performed analyses designed to evaluate the evidence for heterogeneity in response to air pollution. The analysis was based on regression models that examined the variation in sub-

ject-specific regression slopes describing the relationship of daily pulmonary function with daily variation in air pollution concentrations. Because the repeated measurements resulted in correlated outcomes for each subject, general linear mixed models were used. Each of the individual daily pulmonary function measures of FVC, FEV_1, PEFR, and $FEF_{25-75\%}$ were used as an outcome to compare with air pollutants and other explanatory variables. The general mixed models method was used to examine the subject-specific coefficients through a random effect component and take into account the correlated data.

Mixed models have the general formula:

$$Y_i = X_i\beta + Z_i b_i + e_i$$

in which Y is an outcome variable for the i^{th} individual, X_i and Z_i are n_i x p and n_i x q, (n=number of observations for each subject, p and q are the number of parameters) design matrices, β and b_i are unknown coefficients, and e_i is a n_i x 1 vector representing measurement error. The parameters in β are common for all subjects, and parameters b_i are subject-specific. It is assumed that the components of e_i are normally distributed with mean zero and common variance σ^2.

The model building strategy included the following steps. First, the base models were created using each pulmonary function parameter (FVC, FEV_1, PEFR, $FEF_{25-75\%}$) as an outcome variable to control for the effect of time trends, temperature, weekday, personal characteristics of height, and gender. These explanatory variables were included in the models as fixed effects. A final base model for each lung function parameter was chosen from several models that included time and weather variables in various forms based on biological plausibility and Akaike's information criterion (AIC) values. After the base models were created, the air pollutant variables were added to the models. The two pollutant models were evaluated, in which the effect of one pollutant was examined while controlling for the effect of another pollutant and the effects of the other covariates. In the two-pollutant models, random effect terms of deviation of intercept, SO_2, and PM_{10} were also included in the models as full models. Next, we evaluated the reduced model, which included all fixed effects but excluded the random effects of air pollutants.

The null hypothesis is that the slopes of pulmonary function on SO_2 and PM_{10} did not differ across subjects. If the null hypothesis is true then there is no variability in the subject-specific slope of pulmonary function on air pollutants (SO_2, PM_{10}) across subjects.

A comparison was made between (full) models with the random effects of air pollutants (SO_2 and particulate air pollution) to the (reduced) models without the random effects of air pollutants.

The full model has the following formula:

$$Y = \beta_0 + \beta_1(ht) + \beta_2(gender) + \beta_3(time) + \beta_4(temp) + \beta_5(SO_2) + \beta_6(PM_{10}) + b_{0j} + b_{1j}(SO_2) + b_{2j}(PM_{10}) + e$$

where $\begin{bmatrix} b_{0j} \\ b_{1j} \\ b_{2j} \end{bmatrix} \sim N \begin{bmatrix} 0, & d_{00}\ d_{01}\ d_{02} \\ 0, & d_{10}\ d_{11}\ d_{12} \\ 0, & d_{20}\ d_{21}\ d_{22} \end{bmatrix}$

The reduced model is:

$$Y = \beta_0 + \beta_1(ht) + \beta_2(gender) + \beta_3(time) + \beta_4(temp) + \beta_5(SO_2) + \beta_6(PM_{10}) + b_{0j} + e$$

In the full model, the fixed effects include intercept (β_0), height, gender, time, temperature, SO_2, and PM_{10}, and the random effects are random intercept (b_{0j}), random slope deviation on SO_2 (b_{1j}) and on PM_{10} (b_{2j}), and within-subject residual (e). The covariance parameters (d_{00}, d_{11}, d_{22}) for the intercept and slopes indicate how much variation there is across subjects. In a general linear mixed model, to test whether there is variability in pulmonary function for the effects of SO_2 and PM_{10} among children, the variability is tested by the null hypotheses: $d_{11} = d_{22} = 0$. The test is based on the covariance estimated, its standard error providing Z-statistics and p-value. These are based on asymptotic properties and are not reliable if the degree of freedom to estimate the covariance component is small (Little and Rubin, 1987).

Another test was to use likelihood ratio test statistics, since the reduced model is a special case

of the full model when $b_{1j}=b_{2j}=0$. Similarly, this is to test that the population-average slopes (β_5, β_6) provided by the fixed effects parameters adequately describe the relationship between air pollutants and pulmonary function. In other words, there is no real variation in subject-specific slopes across children. We used the likelihood ratio test to address the H_0: $b_{1j}=b_{2j}=0$. We computed the difference of restrictive maximum log likelihood (REML) between the two models. The difference of -2REML was then compared to a chi-square distribution with the degrees of freedom equal to the different number of covariance parameters between the two models (Littel *et al*, 1999).

In the preliminary analysis, we fitted the full models with the unstructured covariance matrix and the results showed that the covariance between the random intercept and slopes deviation (d_{01}, d_{02}) and covariance between the random slope deviations of pulmonary function for the effects of SO_2 and PM_{10} (d_{12}) were not different from zero. This indicates that there is no evidence that the effect of SO_2 on pulmonary function depends on the effect of PM_{10} and vice versa. In addition, the –2REML log likelihood test also indicated that $d_{01}=d_{02}=d_{12}=0$. As a result, our final random coefficients models (full models) were fitted assuming the covariance $d_{01}=d_{02}=d_{12}=0$.

In mixed model analysis, the within-child variation is controlled through the covariance parameters of the residual error. However, to exclude the influence of observations that have extreme values, a predictive and residual value for each observation was calculated to identify those observations. An additional analysis to test the null hypothesis that the variance of the random slope deviation of pulmonary function on SO_2 and PM_{10} is equal to zero was performed with the data, excluding the extreme values.

Each pulmonary function parameter (FVC, FEV_1, PEFR, and $FEF_{25-75\%}$) was analyzed in the same manner as a separate outcome in the models with a specific set of best-fit base models. To eliminate the training effect, we excluded the first week of pulmonary function data from the analysis. Participants who performed pulmonary function tests for less than 15 days were excluded from the analysis (n=5), thus we had 83 children in the analysis. The statistical analyses procedures were performed using SAS (version 8.1).

RESULTS

Table 1 shows the percentile distribution of subject-specific slopes of pulmonary function parameters in relation to a 10 μg/m^3 increase in SO_2 and PM_{10}, after adjusting for height, gender, time trend, and temperature. The subject-specific slopes for each pulmonary function parameter ranged from negative to positive. The frequency distributions of these subject-specific slopes for FEV_1 are also shown in Figs 1-2.

Table 2 shows the covariance parameter es-

Table 1
Percentile distribution of subject-specific slopes of pulmonary function in relation to an increase of 10 μg/m^3 of SO_2 and PM_{10}, after adjusting for height, gender, time, and temperature.

	Min	5%	25%	50%	75%	90%	Max
SO_2 (n=84)							
FVC (ml)	-8.39	-4.68	-2.32	-0.57	1.21	2.81	6.33
FEV_1 (ml)	-8.55	-5.26	-2.25	-0.48	1.24	2.61	7.78
PEFR(ml.sec^{-1})	-21.69	-13.82	-6.87	-2.63	2.17	5.80	27.50
$FEF_{25-75\%}$ (ml.sec^{-1})	-9.08	-6.96	-3.81	-1.52	0.56	4.14	11.96
PM_{10} (n=84)							
FVC (ml)	-23.37	-13.32	-8.31	-5.64	-2.48	0.43	5.23
FEV_1 (ml)	-31.47	-16.01	-8.38	-5.10	-0.04	4.41	8.53
PEFR (ml.sec^{-1})	-62.06	-42.19	-25.18	-16.71	-7.43	0.88	28.63
$FEF_{25-75\%}$ (ml.sec^{-1})	-18.87	-13.58	-5.64	-.98	3.12	6.51	23.16

Table 2
Covariance parameter estimates of the random effects in the full model for evaluation of SO_2 and PM_{10} on pulmonary function, adjusting for height, gender, time, and temperature.

Pulmonary function	Covariance parameter estimates	Standard error	p-value	-2REML
FVC (n=3,479)				11,516.6
- d_{00}	5.6351	0.9451	<0.0001	
- d_{11} (SO_2)	0.000027	0.000014	0.0282	
- d_{22} (PM_{10})	0.000056	0.000030	0.0310	
- σ^2 (residual)	1.3833	0.03437	<0.0001	
FEV_1 (n=3,479)				10,934.8
- d_{00}	5.5363	0.9863	<0.0001	
- d_{11} (SO_2)	0.000021	0.000013	0.0467	
- d_{22} (PM_{10})	0.000074	0.000040	0.0326	
- σ^2 (residual)	1.1632	0.02896	<0.0001	
PEFR (n=3,479)				18,447.0
- d_{00}	56.7950	10.0740	<0.0001	
- d_{11} (SO_2)	0.000175	0.000103	0.0443	
- d_{22} (PM_{10})	0.000591	0.000327	0.0353	
- σ^2 (residual)	10.1186	0.2520	<0.0001	
$FEF_{25-75\%}$ (n=3,479)				16,324.4
- d_{00}	53.7558	9.7030	<0.0001	
- d_{11} (SO_2)	0.000042	0.000048	0.1864	
- d_{22} (PM_{10})	0.000198	0.000160	0.1077	
- σ^2 (residual)	5.4481	0.1357	<0.0001	

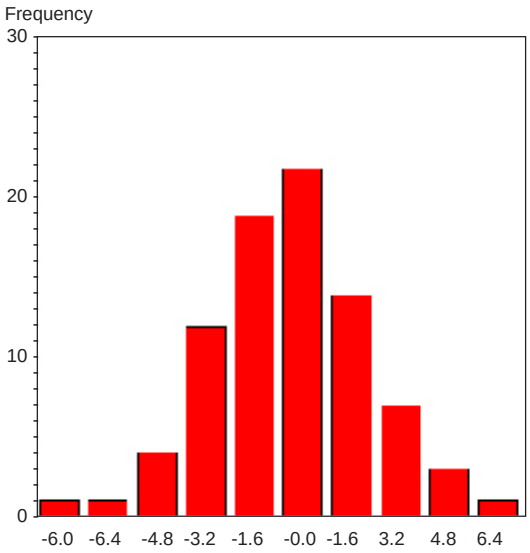

Fig 1–Distribution of individual slopes of FEV_1 on SO_2, asthmatic children, Mae Moh.

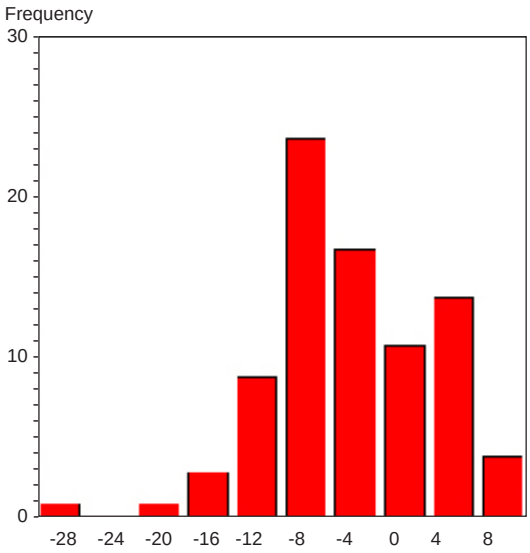

Fig 2–Distribution of individual slopes of FEV_1 on PM_2, asthmatic children, Mae Moh.

timates and standard errors of the random effects of intercept, SO_2 and PM_{10} in the full models. There are variations in the intercepts of pulmonary function parameters across subjects, as the tests of the null hypotheses for the variance component estimates of the intercept (d_{00}) of each

Table 3
The -2REML of models with and without the random-effect of SO_2 and PM_{10} after adjusting for height, gender, time, and temperature.

Models\ Pulmonary function (n=3,479)	-2REML			
	FVC	FEV_1	PEFR	$FEF_{25-75\%}$
Model 1 Fixed effects + Random effects of intercept, SO_2, PM_{10}	11,516.6	10,934.8	18,447.8	16,324.4
Model 2 Fixed effects + Random effects of intercept, SO_2	11,519.0	10,940.1	18,452.2	16,326.4
Model 3 Fixed effects + Random effects of intercept, PM_{10}	11,520.7	10,939.4	18,451.6	16,325.2
Model 4 Fixed effects + random intercept	11,526.9	10,948.1	18,457.8	16,328.1

Fixed effects: height, gender, time, and temperature.

pulmonary function parameter did reject that d_{00} is equal to zero. This suggests that the baselines of pulmonary function adjusting for height, gender, time, temperature, and air pollution vary across subjects.

The hypothesis testing presented in Table 2 also indicates that both variance component estimates of FVC, FEV_1, and PEFR slopes for the effects of SO_2 (d_{11}) and PM_{10} (d_{22}) are different from zero. However, for $FEF_{25-75\%}$, the test did not reject that the variance component estimates of the slopes on SO_2 (d_{11}) and PM_{10} (d_{22})= *0*. This suggests that the subject-specific slopes of FVC, FEV_1, and PEFR for the effects of either SO_2 or PM_{10} do differ across children except for the slopes of $FEF_{25-75\%.}$

The evidence of heterogeneity of subject-specific slopes was confirmed by the results of the log-likelihood ratio test comparing the full model with the reduced models. Table 3 shows the restrictive maximum likelihood of several models of random effects and fixed effects. The comparison of Models 1 and 4 suggests that the random slope deviation (b_{1j}, b_{2j}) of FVC, FEV_1, and PEFR differ from zero, and that the models that include both the random effects of SO_2 and PM_{10} fit better. For $FEF_{25-75\%}$, neither random slope deviation was different from zero. In addition, the model that includes both the random effects of SO_2 and PM_{10} also provides a better fit than the model including either SO_2, or PM_{10} only (models 2 and 3).

Table 4 shows that the results of the additional analyses excluding extreme values are similar to the analyses with full data. There is evidence of variation in the random slope of FVC, FEV_1, PEFR on SO_2 and PM_{10} across subjects after excluding observations with the extreme values of the pulmonary function. In addition, there is also evidence of variation of $FEF_{25-75\%}$ individual slopes for the effect of PM_{10} across subjects.

DISCUSSION

The present study evaluated whether there is evidence that the variation of pulmonary function response to air pollution across subjects is greater than expected from random variation alone. The analysis using the general mixed models method has the advantage of accommodating the correlation of repeated measures within subjects and in detecting the subject-specific effect through the random effect component.

We tested the null hypothesis that there was no variation in association of air pollution with pulmonary function across children. In models including SO_2 and PM_{10} as random effects, we

Table 4
Covariance parameter estimates of random effects in the full model for evaluation of effect of SO_2 and PM_{10} on pulmonary function adjusting for height, gender, time, and temperature. in data excluding extreme values.

Pulmonary function	Covariance parameter estimates	Standard error	p-value	-2REML
FVC (n=3,411)				10,320.8
- d_{00}	5.7475	0.9585	<0.0001	
- d_{11} (SO_2)	0.000029	0.000013	0.0119	
- d_{22} (PM_{10})	0.000076	0.000039	0.0253	
- σ^2 (residual)	1.0232	0.02574	<0.0001	
FEV_1 (n=3,424)				9,921.0
- d_{00}	5.9105	1.0435	<0.0001	
- d_{11} (SO_2)	0.000022	0.000011	0.0213	
- d_{22} (PM_{10})	0.000087	0.000037	0.0088	
- σ^2 (residual)	0.8960	0.02251	<0.0001	
PEFR (n=3,402)				16,904.6
- d_{00}	59.1329	10.3212	<0.0001	
- d_{11} (SO_2)	0.000177	0.000081	0.0141	
- d_{22} (PM_{10})	0.000861	0.000316	0.0032	
- σ^2 (residual)	7.0954	0.1789	<0.0001	
$FEF_{25-75\%}$ (n=3,426)				15,222.2
- d_{00}	56.4941	9.9878	<0.0001	
- d_{11} (SO_2)	0.000054	0.000040	0.0871	
- d_{22} (PM_{10})	0.000307	0.000153	0.0227	
- σ^2 (residual)	4.1768	0.1049	<0.0001	

evaluated whether there was evidence of variation in the covariance parameters of random slope deviation for FVC, FEV_1, PEFR, and $FEF_{25-75\%}$ for the effects of both SO_2 and PM_{10} (H_0: $d_{11} = d_{22} = 0$). A better test for the null hypothesis of no variation was provided by the likelihood ratio statistic, based on the REML log-likelihood ratio test comparing the full model with a reduced model excluding the random effects of air pollutants. The results of both tests show that there is evidence of a heterogeneous response of individual changes in FVC, FEV_1, and PEFR in response to exposure to both SO_2 and PM_{10} across the children in Mae Moh. The additional analyses of data excluding extreme values did not substantially change the results.

It should be noted that the variation of subject-specific slopes of FVC, FEV_1, and PEFR in response to SO_2 and PM_{10} across subjects was higher than those of $FEF_{25-75\%}$. This may suggest that FVC, FEV_1, and PEFR are more sensitive in detecting the variability of pulmonary function across subjects and/or that the air pollutants have a more homogeneous effect on small airways than on large airways across subjects. The variability across subjects being larger for FVC (reflecting large airway effects) than $FEF_{25-75\%}$ (reflecting effects on small airways) was also observed by Kinney *et al* (1989), although they studied the effects of short-term pulmonary change in association with ozone. They measured weekly the FVC, $FEV_{.75}$, $FEF_{25-75\%}$, and $Vmax_{75}$ of 154 school children in Kingston, Tennessee for a 2-month period. In that study, only FVC showed that there was variation in slopes across children.

A very limited number of epidemiological studies have examined the heterogeneity of response of pulmonary function changes in relation to exposure to SO_2 and particulate air pollution (Nowak *et al*, 1997; Roemer *et al*, 1999). The results of the present study are consistent with the results from an experimental study by Horstman *et al* (1986). They reported the distribution of individual bronchial sensitivity to sul-

fur dioxide on 27 nonsmoking asthmatics, metacholine reactive, but not on inhalation of corticosteroid or cromolyn sodium. The bronchial sensitivity to SO_2, defined as the concentration of SO_2, provoked an increase in specific airway resistance 100% greater than the response to clean air. Variability in sensitivity was observed for 23 subjects with bronchial sensitivity to SO_2 ranging between 800 and 5,434 $\mu g/m^3$, while for the other four subjects, the response to SO_2 was greater than 5,720 $\mu g/m^3$. The median for bronchial sensitivity was at 2,145 $\mu g/m^3$ SO_2, and 6 subjects had bronchial sensitivity at 800 to 1,430 $\mu g/m^3$. This experiment suggested heterogeneity in the response to SO_2 in asthmatics. Even though the concentrations of ambient SO_2 measured in the present study were much lower than those in the experimental studies, the present study also observed heterogeneous changes in pulmonary function following exposure to SO_2.

For particulate air pollution, Brunekreef *et al* (1991) analyzed data from a study of children exposed to air pollution in Steubenville, Ohio. This study also included non-asthmatic children; however, they reported a lack of evidence for a heterogeneous response to total suspended particles (TSP) and explained that the observed variability in the responses was due to sampling variability rather than the presence of a sensitive subgroup. Whittemore and Korn (1980) reported a study of asthmatics in Los Angeles in which asthma attack rates were positively associated with TSP concentration after controlling for temperature, relative humidity, day of week, day of study, and attacks on the previous day. They also found that the estimated coefficients for TSP did not vary among individuals. The inconsistent findings of the present study relative to the previous studies mentioned above may be due to the different indicators for particulate air pollution exposure. The previous studies used TSP rather than PM_{10} as measurement of exposure to particle air pollution. TSP is not as sensitive as PM_{10} in detecting adverse effects and heterogeneity of response (Brunekreef *et al*, 1991). The different results might also be due to the different statistical methods used in the analysis. Previous studies used the variance ratio method to compare between-subject variability to within-subject variability. The present study used a mixed models approach, which takes into account correlated data and allows us to examine subject-specific responses through random effects and may be more sensitive to variation across subjects. Another possibility is the different biologic effects of particles in different research locations due to the physical and chemical nature of the particles in the study area. Finally, the children in the present study included only asthmatics, and one would expect a relatively homogeneous response in this group of children. However, since the criteria for recruiting asthmatics were based on parental-reports, this process might constitute a study group with children who have only mild symptoms of clinical asthma which results in variation of susceptibility to air pollution.

Recently, the issue of heterogeneity in response to air pollution has been of interest. Roemer *et al* (1999) reported the results of a multicenter panel study of the acute effect of particles (PM_{10}), black smoke, SO_2, and NO_2 on respiratory health of children with chronic respiratory diseases in Europe. They evaluated whether the potentially more sensitive subgroups were associated with the variations in air pollution. The predefined potentially sensitive groups were the presence of chronic respiratory symptoms, the use of respiratory medication, atopy, sex, and baseline lung function. They did not find a strong association between respiratory morbidity and air pollution among these groups of children.

A potential limitation of the present study is the measurement of air pollution exposure, as it was based on outdoor monitoring to represent the exposure of the individual. However, the study area is relatively small and we expect that air pollution is relatively homogenous and that the problem of spatial variability is reduced. This study did not incorporate time spent by children outdoors and indoors. It is unlikely that we overestimated exposure, however, the study area had a moderate temperature and most of the houses and schools had open windows and were well ventilated with indoor air-quality not different from the ambient air. Therefore, using ambient air pollutant concentrations should be appropriate. All the potential limitations mentioned above might affect only the population-average associa-

tion of air pollution with pulmonary function. It is unlikely to influence the pattern of heterogeneous responses among children.

The present study lacks information on certain personal characteristics that are potentially associated with response to air pollution, such as history of atopy, evidence of allergy, and severity of asthma. This information should be taken into account in future studies. A more detailed medical history of the subjects who had large negative slopes of pulmonary function in response to pollutants might help identify the underlying factors related to susceptibility to air pollution. Other known air pollutants (ozone and nitrogen oxides) in the study area, that could confound the association between pulmonary function and SO_2 and $PM_{10,}$ are at low concentration.

Conclusion

The results of this study suggest that, even with low concentrations of daily SO_2 and PM_{10} in the study area, there is evidence of a heterogeneous response of lung function changes due to short-term exposure to SO_2 and particulate air pollution (PM_{10}). This study only evaluated transient changes in pulmonary function from short-term exposure. The pattern of long term effects and the factors that relate to their variation in susceptibility should be further evaluated.

ACKNOWLEDGEMENTS

This study was supported by the Department of Health, Ministry of Public Health, Thailand.

REFERENCES

Aekplakorn W, Loomis D, Vichivadakan N, Shy C, Wongtim S, Vitayanon P. Acute effect of SO_2 from a power plant on pulmonary function of children, Thailand. *Int J Epidemiol* 2003a; 32: 854-61.

Aekplakorn W, Loomis D, Vichit-Vadakan, Shy C, Plungchuchon S. Acute effect of sulfur dioxide from a power plant on respiratory symptoms of children. *Southeast Asian J Trop Med Public Health* 2003b; 34: 906-14.

Braun-Fahrlander C, Ackermann-Liebrich U, Schwartz J, Gnehm HP, Rutishauser M, Wanner HU. Air pollution and respiratory symptoms in preschool children. *Am Rev Respir Dis* 1992; 145: 42-7.

Brunekreef B, Kinney PL, Ware JH, *et al*. Sensitivity subgroups and normal variation in pulmonary function response to air pollution episodes. *Environ Health Perspect* 1991; 90: 189-93.

Dockery DW, Pope CA. Acute respiratory effects of particulate air pollution. *Annu Rev Public Health* 1994; 15: 107-32.

Florey C du V, Leeder SR.. Method for cohort studies of chronical airflow limitation. Copenhagen: WHO Regional Publication, European Series. 1982: 12.

Horstman D, Roger LJ, Kehrl H, Hazucha M. Airway sensitivity of asthmatics to sulfur dioxide. *Toxicol Ind Health* 1986; 2: 289-98.

Kinney Pl, Spengler JD, Dockery DW, Speizer FE, Ferris BG Jr. Short-term pulmonary function association with ozone in Kingston, Tennessee. *Am Rev Respir Dis* 1989; 139: 56-61.

Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley and Son, 1987.

Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS System for mixed models. Cary, NC, USA: SAS Institute Book by Users, 1999.

Neas LM, Dockery DW, Koutrakis P, Tollerud DJ, Speizer FE. The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. *Am J Epidemiol* 1995; 141: 111-22.

Nowak D, Jorres R, Berger Jurgen, Claussen M, Magnussen H. Airway responsiveness to sulfur dioxide in an adult population sample. *Am J Respir Crit Care Med* 1997; 156: 1151-6.

Pope CA, Dockery DW, Spengler JD, Raizenne ME. Respiratory health and PM_{10} pollution: a daily time series analysis. *Am Rev Respir Dis* 1991; 144: 668-74.

Pope CA, Dockery DW. Acute health effects of PM_{10} pollution on symptomatic and asymptomatic children. *Am Rev Respir Dis* 1992; 145: 1123-8.

Hoek G, Brunekreef B. Effects of low-level winter air pollution concentrations on respiratory health of Dutch children. *Environ Res* 1994; 64: 136-50.

Roemer W, Hoek G, Brunekreef B. Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. *Am Rev Respir Dis* 1993; 147: 118-24.

Roemer W, Clench-Aas J, Englert N, *et al*. Inhomogeneity in response to air pollution in European children (PEACE project) *Occup Environ Med* 1999; 56: 86-92.

Vedal S, Petkau J, White R, Blair J. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. *Am J Resp Crit Care Med* 1998; 157: 1034-43.

Whittemore, AS, Korn EL. Asthma and air pollution in the Los Angeles area. *Am J Public Health* 1980; 70: 687-96.