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Sensitive Subgroups and Normal Variation in Pulmonary Function Response to Air Pollution Episodes

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The Clean Air Act requires that sensitive subgroups of exposed populations be protected from adverse health effects of air pollution exposure. Hence, data suggesting the existence of sensitive subgroups can have an important impact on regulatory decisions. Some investigators have interpreted differences among individuals in observed pulmonary function response to air pollution episodes as evidence that individuals differ in their sensitivity. An alternative explanation is that the differences are due entirely to normal variation in repeated pulmonary function measurements. This paper investigates this question by reanalyzing data from three studies of children exposed to air pollution episodes to determine whether the observed variability in pulmonary function response indicates differences in sensitivity or natural interoccasion variability . One study investigated exposures to total suspended particulates (TSP), the other two investigated exposure to ozone. In all studies, each child's response to air pollution exposures was summarized by regressing that child's set of pulmonary function measurements on the air pollution concentrations on the day or days before measurement. The within-child and between-child variances of these slopes were used to test the hypothesis of variable sensitivity. Regression slopes did not vary significantly among children exposed to episodes of high TSP concentration, but there was evidence of heterogeneity in both studies of ozone exposures. The finding of heterogeneous response to ozone exposure is consistent with the epidemiologic and chamber studies of ozone exposures, but the lack of evidence for heterogeneous response to TSP exposures implies that observed variation in response can be explained by sampling variability rather than the presence of sensitive subgroup.

Introduction

A growing literature indicates that children experience short-term declines in pulmonary function level during and shortly after episodes of high outdoor air pollution (*1–7*). The evidence has been gathered by performing repeated pulmonary function measurements in cohorts of children exposed to episodes of elevated air pollution to determine whether pulmonary function levels vary inversely with air pollutant concentration. Such studies produce a natural measure of response for each participant: the coefficient of regression of the child's pulmonary function measurements on the air pollution concentrations on the day or days preceding the examinations.

Stebbings et al. (*1*) studied 224 children over a period of 6 days immediately after an episode of high concentrations of total suspended particulates (TSP) and sulfur dioxide (SO_2). that pulmonary function was depressed during the air pollution episode. Dockery et al. (*2*) obtained pulmonary function measurements at weekly intervals for 6 to 8 weeks in four different studies involving a total of 331 children. These examinations spanned several episodes of high TSP and SO_2 concentrations. In these studies, the majority of children had negative regression slopes of pulmonary function level on both TSP and SO_2 concentrations. Kinney et al. (*3*) studied the association between weekly measurements of pulmonary function and exposure to ozone (O_3) in a group of 154 school children in Kingston, Tennessee. In the majority of these children, pulmonary function level was negatively associated with O_3 concentration. The association between O_3 exposure and pulmonary function level has also been investigated in a number of summer camp studies (*4–7*). In these studies, pulmonary function was measured daily over periods of 1 to 4 weeks. Spektor et al. (*4*) studied a sample of 91 children who had at least seven daily pulmonary function measurements while resident at a summer camp in Fairview Lake, New Jersey. In the majority of children, O_3 was negatively associated with pulmonary function.

In all of these studies, the estimated regression coefficient of pulmonary function level on air pollution concentration varied among children. It is tempting to identify the children with the

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most negative slopes, or with significantly negative slopes, as a susceptible subgroup (*1*). If a susceptible subgroup exists, however, one would expect children in this group to show increased susceptibility to air pollutants repeatedly when exposed to several air pollution episodes. Equivalently, the existence of a sensitive subgroup implies that the expected response to an air pollution episode varies significantly among children.

This paper investigates the issue of heterogeneity of response. We reanalyze the data from three published studies; the Steubenville study of TSP effects (*2*), the Kingston study of O_3 (*3*), and the Fairview Lake, New Jersey, camp study of ozone (*4*), to determine whether the estimated slopes of individual regressions of pulmonary function level against air pollution concentration vary significantly more than sampling variability would predict. The basic feature of these studies is that regression analyses of pulmonary function on air pollution (or time) were performed for each child. The within-child or error variance of the regression slopes can be estimated from the deviations of the observed pulmonary function values around the individual regression lines. This error variance can be compared to the total variance of the child-specific regression slopes to see if there is evidence of response heterogeneity.

Methods

Populations

Study populations and methods of data collection have been described elsewhere (*2–4*). In Steubenville, Ohio, children participating in the Six Cities Study of Air Pollution and Health (*2*) were selected from four schools, by classroom, to participate in the alert study. A baseline measurement of pulmonary function was obtained in early fall or spring, before anticipated air pollution episodes. A second measurement was obtained at or immediately following an alert, and the children were then restudied on three subsequent occasions 1 week apart. The alert was triggered by a 24-hr period of elevated TSP or SO_2 or by a sham alert, intended to investigate temporal variation in pulmonary function level when an alert had not occurred (*2*).

In Kingston, Tennessee, children were selected from one school (*3*). All but 30 of these children were participants in the Six Cities Study. Pulmonary function was measured on six occasions over a 2-month period.

The Fairview Lake study was conducted at a summer camp in which the 91 participating children were resident for 2 to 4 weeks (*4*). Pulmonary function was measured daily between 11:30 AM. and 6:30 PM. Each child had at least 7 measurement days.

All spirometric measurements in all three studies were obtained in a uniform manner by trained technicians using Collins Survey Spirometers (Warren E. Collins, Braintree, MA). In this analysis we will consider the forced vital capacity (FVC) measurements reported in all three studies and the forced expired volume in three-quarters of a second ($FEV_{.75}$) reported from Steubenville and Kingston, and the similar forced expired volume in 1 sec (FEV_1) reported from Fairview Lake.

Air Pollution Exposure

In the original report on the Steubenville study, each child's pulmonary function measurements were regressed on average SO_2, TSP, and temperature for the 24 hr immediately preceding the pulmonary function measurements. This paper focuses on TSP, with averaging times of 1 and 5 days preceding the pulmonary function measurement, to permit analysis of delayed and/or persistent effects. The number of averaging days is indicated as follows: TSP-1 denotes the average TSP concentration during the 1-day period preceding examination and TSP-5 denotes TSP averaged over 5 days. TSP-1 values ranged from 11 to 292 $\mu g/m^3$ and TSP-5 from 38 to 205 $\mu g/m^3$ during the Steubenville alert studies.

Regression analyses of FVC and $FEV_{.75}$ on the two measures of TSP exposure were performed for each child, taking pulmonary function growth between studies into account by using indicator variables for year of study. The regression analyses were restricted to children who participated in 3 or 4 studies, to ensure that the individual slopes were calculated from reasonable numbers of observations. (In this group, the number of observations per individual ranged from 11 to 20.) The 165 children who participated in 3 or 4 studies contributed 558 (74%) of the total of 750 observations in the original analysis.

The Kingston report discussed exposure to O_3, fine sulfates (FSO_4), and fine particulate matter (FP). This paper focuses on exposure to O_3, defined as the maximum 1-hr O_3 concentration in the 24-hr period ending in the hour of lung function measurement. The Fairview Lake report presented results for O_3 exposure expressed as the mean of the hour before the pulmonary function test, plus the means of the previous 2 and 4 hr.

Statistical Analysis

The variance of the individual slopes is composed of two components: random or error variation due to interoccasion variability in the pulmonary function measurements of individual children, and systematic differences in slope between individual children. The hypothesis of no heterogeneity of regression coefficients among children can be tested by calculating a variance ratio of the form

$$\frac{\Sigma[SSX_i(\hat{b}_i - \hat{b}^*)^2]/(n-1)}{(\Sigma SSE_i)/(\Sigma EDF_i)} \tag{1}$$

where SSX_i = sum of squares of the X variable (TSP or O_3) for subject i;
n = number of subjects;
$\hat{b}_i$ = estimated regression coefficient for subject i;
$\hat{b}^*$ = weighted mean regression coefficient

$$= \frac{\Sigma(SSX_i * \hat{b}_i)}{\Sigma(SSX_i)}$$

SSE_i = error sum of squares for subject i
EDF_i = error degrees of freedom for subject i (2)

The variance ratio [Eq. (1)] follows an F-distribution with n-1 and $\Sigma(EDF_i)$ degrees of freedom when there is no between-subject variability of regression slopes and will otherwise tend to be large.

Table 1. Stem and leaf displays of regression slopes of FVC and $FEV_{.75}$ on TSP-1 for participants in the Steubenville alert studies.*

Stem	leaf	Number
FVC, mL/0.1/m³		
22	1	1
20		
18		
16		
14	9	1
12		
10	3	1
8	69	2
6	125	3
4	1334668256	10
2	02233566779002222235	20
0	12334455889911233344555588	27
− 0	766644433322111099887776544333000	33
− 2	87775553333220666554444331110 0	30
− 4	8766438654311110	16
− 6	81988777444331	14
− 8	241	3
− 10		
− 12	22	2
− 14		
− 16		
− 18		
− 20	9	1
− 22		
− 24	4	1
$FEV_{.75}$		
20	1	1
18		
16		
14	01	2
12	0	1
10	1	1
8	14	2
6	3684	4
4	046279	6
2	011133445567703479	18
0	22333345577788899022233445569	30
− 0	9888776555544431008887755554432211 1000	38
− 2	998765221110000999998665444 2000	31
− 4	87520875430	11
− 6	7543521111	10
− 8	83241	5
− 10	76	2
− 12	1	1
− 14	8	1
− 16		
− 18		
− 20	3	1

*Slopes of children with highly variable pulmonary function measurements are underlined.

Table 2. Mean slopes, averaged over studies, of FVC and $FEV_{.75}$ on TSP, full and restricted samples, Steubenville, Ohio, 1978–1980.

Exposure	Pulmonary variable	Mean slope (SE) Full sample	Restricted sample
TSP-1	FVC	− 0.099 (0.040)*	− 0.119 (0.034)†
TSP-5		− 0.192 (0.054)‡	− 0.167 (0.049)†
		n = 165	n = 154
TSP-1	$FEV_{.75}$	− 0.086 (0.040)*	− 0.104 (0.042)†
TSP-5		− 0.201 (0.059)†	− 1.74 (0.043)‡
		n = 165	n = 151

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

Because F-tests based on approximately normally distributed observations are sensitive to observations resulting from children with highly variable pulmonary function readings, an outlier criterion was developed, and the calculations were repeated after removal of children with highly variable pulmonary function readings. Outliers were identified by calculating the pooled estimate of within-child (error) variance

$$s^2 = (\Sigma SSE_i)/(\Sigma EDF_i) \quad (3)$$

where SSE_i = sum of squares of pulmonary function values for subject i. Then, the estimated error variance for the ith child, SSE_i/EDF_i, was compared to the quantity s^2*(chisq $_{.99}$/ EDF_i), where chisq $_{.99}$ is the 99th percentage point of the chi-square distribution with (EDF_i) degrees of freedom. If the within-child pulmonary function variance was larger than this quantity, the child was identified as an outlier for this analysis.

Statistical analyses were performed using PC/SAS Software (*8*) on a Compaq Deskpro 286 personal computer.

Results

Table 1 gives a stem-and-leaf display (*9*) of the distributions of the regression coefficients of FVC and $FEV_{.75}$ on TSP-1 for children participating in the Steubenville alert studies. The distributions show both positive and negative outlying values. All of the extremely positive and negative slopes met the criterion for large interoccasion variability. For FVC, 11 (7%) of the 165 children were found to be unacceptably variable; for $FEV_{.75}$, 14 (8%) of the 165 children were unacceptably variable. In Kingston, 8 (5%) children of a total of 154 were outliers for FVC and 13 (8%) for $FEV_{.75}$. In Fairview Lake, 7 (8%) of 91 children were outliers for FVC and 3 (3%) for FEV_1. The percentage of outliers is similar in all three studies.

Table 2 gives the mean slopes for Steubenville, both for the full sample and for the reduced sample after removing outliers. All mean slopes are negative and significantly different from zero. Removal of children with highly variable pulmonary function did not change the mean slopes much, but the standard errors of the mean slopes were generally smaller in the restricted population.

Table 3 shows the mean slopes for the Kingston data, again for the full sample and for the restricted sample. As in the Steubenville data, all mean slopes were negative and significantly different from zero. The mean slopes in the restricted sample were similar to those for the full sample, but smaller standard errors tended to make the mean slopes in the restricted sample more significant than those in the full sample, indicating increased sensitivity of the analysis after removal of children with highly variable pulmonary function.

Table 3. Mean slopes of pulmonary function on ozone, full and restricted samples, Kingston, Tennessee, 1981.

Pulmonary variable	Mean slope (SE) Full sample	Restricted sample
FVC	− 0.918 (0.356)*	− 1.291 (0.267)‡
	n = 154	n = 146
$FEV_{.75}$	− 0.994 (0.363)†	− 1.152 (0.300)‡
	n = 154	n = 141

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

Table 4. Mean slope of FVC and FEV_1 on ozone, full and restricted samples, Fairview Lake, New Jersey, 1984.

Exposure variable	Pulmonary variable	Mean slope (SE) Full sample	Restricted sample
O_3 (1 hr)[a]	FVC	− 1.291 (0.188)*	− 1.045 (0.154)*
(2 hr)		− 1.274 (0.182)*	− 1.031 (0.148)*
(4 hr)		− 1.264 (0.198)*	− 1.002 (0.160)*
		$n = 91$	$n = 84$
O_3 (1 hr)	FEV_1	− 1.401 (0.174)*	− 1.287 (0.166)*
(2 hr)		− 1.443 (0.175)*	− 1.332 (0.167)*
(4 hr)		− 1.497 (0.187)*	− 1.381 (0.177)*
		$n = 91$	$n = 88$

[a]Numbers in parentheses indicate number of averaging hours.
*$p < 0.001$.

The mean slopes of FVC and FEV_1 on O_3 for the Fairview Lake study are shown in Table 4, for the full and restricted sample. The mean slopes are all significantly less than zero. As with the other two studies, removing the most variable responses reduces the standard error, but does not substantially change the mean slopes. In fact, the estimated effect of ozone in the Fairview Lake study is very close to the Kingston estimate. The standard errors are less, due in part to the larger number of observations for each child.

The comparability of the mean slopes in the full and restricted samples in each of the studies suggests that the children with highly variable pulmonary function measurements were not more responsive to air pollution exposure. If more responsive children had tended to be removed, the mean slopes would have been smaller in the restricted samples.

The variance ratio calculations (Table 5) show little evidence of heterogeneity of response between individuals in the Steubenville data; all ratios are close to 1. In Kingston, all ratios are significantly larger than 1, although only the ratio for FVC is much larger, with a value of 2.62. In Fairview Lake, all ratios are also significantly larger than 1. (The F-ratios between the studies are not directly comparable because of the different number of children and observations producing different degrees of freedom for each study.)

As noted previously, 11 of 165 Steubenville children were declared outliers in the analysis of FVC, and 14 out of 165 were declared outliers in the analysis of $FEV_{.75}$. If the variances had followed the chi-square distribution, only one or two outliers would have been expected. In the Kingston data, 8 of 154 subjects were outliers in the FVC analysis and 13 in the $FEV_{.75}$ analysis, and in the Fairview Lake data, 7 anf 3 out of 91 subjects were outliers in the FVC and FEV_1 analyses, respectively. Removal of outliers decreased the significance of the F-ratios for FVC, but increased them slightly for the FEV measures (Table 6) from the Kingston and Fairview Lake studies. In the Steubenville data, all ratios are very close to 1; in the Kingston and Fairview Lake data, the ratios remain significantly larger than 1.

Table 5. Variance ratios testing variability between subjects in pulmonary function response to air pollution, Steubenville, Ohio, Kingston, Tennessee, and Fairview Lake, New Jersey.

Study location	F-ratios for regressions FVC	$FEV_{.75/1.0}$
Steubenville		
TSP-1	1.01	0.89
TSP-5	1.12	0.98
Kingston		
O_3 (max hr)	2.62‡	1.27*
Fairview lake		
O_3 (1 hr)	1.34*	1.53†
(2 hr)	1.32*	1.48†
(4 hr)	1.33*	1.45†

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

Discussion

In each of the studies considered, the distributions of the regression slopes tended to have heavy tails (Table 1). Most of the large negative and positive slopes were obtained in children with highly variable pulmonary function measurements. There was no indication that high variability of pulmonary function was associated with air pollution exposure. Children with highly variable pulmonary function had both extremely negative and extremely positive slopes. Removal of these children from the analysis resulted in distributions with less heavy tails and, consequently, smaller standard deviations (Tables 2–4). The percentage of children with highly variable pulmonary function measurements was larger than would have been expected, 3 to 8%, when the method would have generated only 1% if the between-occasion variability was constant across children. The origin of this apparent high variability of pulmonary function in some of the children is not obvious, but appears to be due to factors other than air pollution episodes.

The variability of the regression slopes appeared to be largely determined by within-child variability rather than between-child variability. In the Steubenville data, the F-ratios were close to 1 after removal of children with highly variable pulmonary function. In the two studies of ozone exposure, Kingston and Fairview Lake, there remained some evidence for heterogeneity after outlier removal, but the F-ratios were all smaller than 1.5, indicating that a large part of the observed variability was due to within-child variability and not to between-child variability. These results suggest that it is not possible to identify responders or susceptible subgroups by their position in the lower tail of an observed distribution of slopes, as has been suggested (*1*).

The observed variance of response is not much determined by real differences between subjects as by our inability to characterize individual response more exactly. One reason for this might be that the studies described here relied on central site monitoring for their assessment of exposure to air pollutants. It

Table 6. Variance ratios testing variability between subjects in pulmonary function response to air pollution, after removal of outliers.

Study location	F-ratios for regressions of FVC	$FEV_{.75/1.0}$
Steubenville		
TSP-1	0.91	0.86
TSP-5	1.07	0.89
Kingston		
O_3 (max hr)	1.45†	1.30*
Fairview Lake		
O_3 (1 hr)	1.20	1.57†
(2 hr)	1.16	1.54†
(4 hr)	1.17	1.46†

*$p > 0.05$.
†$p > 0.01$.

is well known that personal exposure may be quite different (*10*) from concentration measured at a central site. Variation among individuals in true air pollution exposure contribute to variability among individuals in estimated slopes. In the Steubenville and Kingston studies, which were school based, it is likely that children had very different air pollution exposures as they went about their daily activities. In the Fairview Lake study, these exposure differences were lessened by studying children in a resident camp such that the participants were always within a limited distance from the central ambient monitor.

Other studies do not suggest increased within-person variability of pulmonary function levels during air pollution episodes. Kanner et al. (*11*) report correlation coefficients of 0.943 (FVC) and 0.922 ($FEV_{.75}$) for pulmonary function measurements made 1 month apart in a group of 8- to 9-year-old children. Average correlations with baseline pulmonary function levels were 0.941 (FVC) and 0.892 ($FEV_{.75}$) in Steubenville, and 0.932 (FVC) and 0.915 ($FEV_{.75}$) in Kingston. Lower correlations would have been expected if there had been increased within-child variability due to differential response to air pollution.

McDonnel and co-workers (*12*) have shown that adults repeatedly exposed to ozone in a chamber had reproducible responses, but that these responses varied substantially among the individuals. Kulle and co-workers (*13*) also found that the dose-response curves of adults exposed to ozone in a chamber had substantially different slopes. Thus, controlled exposure studies have shown that ozone produces a reproducible pulmonary function response for individual subjects, while the size of the response varies among subjects.

The analysis of variance of the Kingston and Fairview Lake ozone studies suggests that the variance of the individual slopes is larger than would be expected based on the inherent variability of repeated pulmonary function measurements alone. This is consistent with the results from controlled exposure studies. For TSP concentrations, no evidence was found for clear interindividual differences in response. Thus, the results apparently differ for ozone and TSP. This may indicate a different mechanism for the effects of TSP (and associated pollutants) and ozone.

In a study of asthmatics in the Los Angeles area, Whittemore and Korn (*14*) found that asthma attack rates increased with oxidant and TSP concentrations after adjusting for temperature, relative humidity, day of the week, day of study, and attacks on the previous day. Interestingly, they found that the estimated TSP coefficients did not vary between individuals, but there was interindividual variability for the coefficients for ozone.

This analysis suggests that there is heterogeneity of response to ozone exposure, but not with exposure to particulate pollution episodes. Nevertheless, the component of variation in response due to random measurement error is still large, which implies that the actual range of response may be much smaller than in dicated by the histograms of individual regression slopes. It is therefore not appropriate to base risk estimates for susceptible individuals on the distribution of individual response without adjusting for measurement error.

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