Acute Respiratory Health Effects in Asthmatic and Nonasthmatic Children Associated with Short-Term Exposure to Air Pollutants
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Acute respiratory health effects in asthmatic and nonasthmatic children associated with short-term exposure to air pollutants

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1. METHODS

Two methods were employed in analyzing this data set. A curve-fitting technique for repeated measurements was used to model changes in lung function with respect to changes in air-pollutant contents. Second, by invoking the quasilikelihood models described in Wei and Stram (1988), the relationship between self-reported symptoms and lung function was examined.

1.1. Curve Fitting for Repeated Measurements.

A standard growth-curve analysis is employed to examine repeated measurements with time-varying covariates that are constant across subjects on any given time point. For each subject, the vector of responses obtained at the different test periods is assumed to be normally distributed, with the mean response vector being modelled by some linear function of the covariates. Using the growth-curve analysis, the differences between subgroups of the subjects can also be examained.

1.2. Quasilikelihood Models.

In a recent article, Wei and Stram (1988) suggested the following method for analyzing repeated measurements with time-dependent covariates and with possibly missing observations. The distribution of the response at each time point is assumed to belong to the family of quasilikelihood models described in McCullagh and Nelder (1983). The time-specific regression coefficients are then estimated by solving the time-specific quasilikelihood equations.

Estimates of the time-specific regression coefficients are asymptotically jointly normal, with the covariance matrix estimable from the data. Thus, when there are no missing data, the tests performed on the quasilikelihood estimates are equivalent to simple t-tests, given that the natural link and normally distributed errors are assumed. Wei and Stram also proposed methods for assessing the effect of individual covariates over time, as well as a lack-of-fit test to examine the adequacy of the hypothesized model used for each test period. We refer the readers to the article for further detail. Analysis using this method was performed using software provided by Wei and Stram.

1.3. Comparison of the Two Methods.

The two methods described are different in several regards. The curve-fitting method is restricted to normally distributed responses, while the method described in Wei and Stram (1988) allows for responses with a distribution from the exponential family (which also includes the normal distribution). Secondly, the curve-fitting technique models responses with time-varying covariates that are independent of the subjects, whereas the quasilikelihood method is more appropriate for modelling responses with time-varying covariates that are subject-specific.

2. ANALYSIS

Several serious concerns were raised during a meeting with 11 local pulmonary-function experts after some preliminary analyses were performed on the data set. In particular, the lung functions of some nonasthmatic children indicated possible respiratory problems. Thus, the two groups of children might not be as distinct as the recorded disease status might suggest. Further, the possible use of bronchodilators by the asthmatic children would most likely mask any potential responses due to the atmospheric changes. Although all children were asked whether they had taken any medication, there was no information on what was taken or the dosage taken. Lastly, lung-function measurements depend strongly on the subject's gender, age, and height. Thus, comparisons based on the actual lung-function measurements for children of different gender, age, and height are not recommended. However, the pulmonary-function experts indicated that a 5–10% variation in lung function from one period to another would be considered normal. This remark has provided a guideline for determining the presence of an effect beyond the normal variation.

2.1. Relationship between Lung Function and Air Pollutants.

The relationship between lung function and air pollutants was examined using the curve-fitting method described earlier. Seven atmospheric variables were considered: fine particulate matter, average sulphate, average ozone, average sulphuric acid, average sulphur dioxide, temperature, and relative humidity. The objective was to determine whether changes in lung function of asthmatic and nonasthmatic children are sensitive to short-term changes in air-pollutant levels.

The missing values in the responses have been estimated using an *ad hoc* iterative method discussed in Montgomery (1984). This method takes into account the average response for the given subject, as well as the average response for the given time point. There were no missing atmospheric measurements.

Two simple models were considered. The first model (model A) assumes that the percentage change in lung function in one period depends linearly on the percentage changes in atmospheric measurements of the same period. The second model (model B)

TABLE 1: Maximum-likelihood estimates for model A, reported as percentage change in lung function per percent change in the corresponding environmental factor.

Lung function	FVC		FEV_1		PEF	
Asthmatic	Yes	No	Yes	No	Yes	No
Fine particle	.02	.02	.02	.01	.05	$-.03^a$
Sulphate	$-.05^a$	$.02^a$	$-.04$	.01	$-.02$	$.13^b$
Ozone	$.04^a$	$-.02^a$	.00	$-.01$	$-.04$	$-.04^a$
Sulphuric acid	.01	.01	.01	.01	.01	$.05^a$
Sulphur dioxide	.00	.00	$-.00$	.00	−,01	.01
Temperature	$-.03$	.02	$.16^a$	$.02^a$	.00	$.29^b$
Rel. Humidity	.02	.00	$.10^a$	$.03^a$	$.09^b$	$.06^b$

[a]Significant at 10% level.
[b]Significant at 5% level.

assumes that the percentage change in lung function over two periods depends linearly on the percentage changes in atmopsheric measurements during the first of the two periods.

The normality assumption seems appropriate for most time periods from the normal probability plots. Unfortunately, the estimated covariance matrices for the asthmatic and nonasthmatic children appear to be quite different. Thus, the two groups of children were examined separately. Results of the maximum-likelihood estimation for model A (Table 1) indicate that some of the atmospheric variables may affect lung function. However, the estimated changes in lung function corresponding to the median absolute changes in atmospheric variables are all less than 6%, well within the normal variation of lung function as indicated by the pulmonary-function experts we have consulted with. Similar results were obtained for model B.

The effects of gender, age, and height were each investigated by changing the design matrices in the above models. As before, asthmatic and nonasthmatic subjects were examined separately. Since the sample sizes were small, only two age groups (<12 years and $\geq$12 years) and two height groups (<145 cm and $\geq$145 cm) were considered. Results of the simultaneous tests on the equalities of the coefficients show that the differences between the two gender, age, and height groups were not significant.

2.2. Relationship between Lung Function and Self-Reported Symptoms.

The relationship between lung function and self-reported symptoms was investigated using the quasilikelihood method described earlier. Since most of the self-reported symptoms were constant over time, only three of the symptoms were examined: runny nose, sneeze, and cough. Further, since the reliability of the children's recall on the number of sneezes and coughs is somewhat doubtful, only the absence or presence of the three self-reported symptoms was considered.

The percentage changes from the first recorded lung function were modelled as a repeated measure design with each of the above three covariates. At each time point, the percentage change in lung function was modelled as a linear function of a variable, indicating the absence or presence of the specific symptom. In all cases, the natural link function and normally distributed errors were used. As before, the analysis was performed separately for the asthmatic and the nonasthmatic subjects.

TABLE 2: Quasilikelihood estimates and standard errors for FEV_1, reported as percentage change in FEV_1 from the first test period in the presence of the cough system.

Trial	Change, % (standard error) Nonasthmatic	Asthmatic
2	4.43 (5.19)	−5.12 (3.09)
3	1.70 (2.30)	−2.18 (1.27)
4	−0.95 (3.66)	−3.06 (3.93)
5	−0.30 (2.79)	−0.02 (2.06)
6	0.83 (2.66)	−5.92 (5.30)
7	−1.37 (2.11)	1.83 (4.24)
8	1.66 (3.80)	−0.04 (6.51)
9	−5.47 (1.69)[a]	−7.35 (2.07)[a]
10	1.38 (3.14)	−14.71 (6.93)
11	−4.76 (2.23)[a]	0.81 (3.61)
12	−0.78 (4.80)	−0.99 (3.82)
13	−3.06 (2.76)	−2.96 (2.30)
14	5.97 (4.46)	−2.63 (6.70)
15	−3.79 (3.13)	−1.35 (5.91)
16	−1.29 (5.72)	3.98 (8.61)
17	0.45 (2.92)	−6.58 (3.93)
18	5.27 (5.19)	−9.33 (6.47)

[a]Estimate is beyond 2 standard errors.

The statistically significant quasilikelihood estimates are mostly negative, indicating that the presence of self-reported symptoms may have negative effect on the lung function. However, in most cases, as can be seen in the estimation results for the presence of the cough symptom (Table 2), the effect is not consistent over time. Thus, the general relationship between the self-reported symptoms and lung function was unclear, and so no further hypothesis testing was performed. Furthermore, the observed effects on the asthmatic children were generally similar to those on the nonasthmatic children.

3. DISCUSSION

Two methods were described for the analysis of repeated measurements with time-dependent covariates. Two types of covariates were of concern: one was time-varying and independent of the subjects, and the other was time-varying but specific to each subject. A curve-fitting method was suggested for modelling with the first type, while the quasilikelihood method described in Wei and Stram (1988) was suggested for the latter.

No significant relationship between the change in lung function and the change in air pollutants was detected using the growth-curve analysis. Although some of the estimated effects achieved *statistical significance*, they did not achieve *practical significance*. The estimated changes in lung function due to changes in the environment were well within the normal variation of lung function. Furthermore, no significant pattern was discovered between lung function and the selected self-reported symptoms. However, the results suggest possible negative effects on lung function in the presence of selected symptoms.

Since strong associations among the atmospheric variables may have accounted for the poorly determined individual coefficients in the modelling of changes in lung function, further analysis may be applied to some other functions of the atmospheric variables. Although the current data set did not reveal any sensible reduction of the number of parameters required to estimate the covariance matrices, future analysis of similar data sets should further explore this possibility.

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Analysis of the Lake Couchiching data

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1. INTRODUCTION

What is presented here is not intended to be a complete analysis but rather a way to approach such an analysis. Obviously, a more thorough analysis would involve more communication with the principal investigators regarding their intentions and the clinical meaning and relevance of the variables. For the sake of brevity, many graphs and tables have been excluded, although a sound graphical analysis was the basis of our work. We have chosen to concentrate on the relationship between lung function and environmental factors.

The approach taken to the analysis is that of ordinary least-squares regression (OLS). This was the method of our choice because, in addition to its being a familiar technique to nonstatisticians, quantification of *effects* is easily handled in a number of ways. For example, the direction and magnitude of regression coefficients, prediction and confidence intervals, and graphs may be used to convey conclusions and interpretations of the problem in question. In addition to OLS, analyses permitting correlation over time for each subject were undertaken and resulted in similar conclusions to those obtained using the uncorrelated models.

The remainder of the paper proceeds as follows. We begin by describing the rationale for the model employed in this paper. The primary purpose of the study was to detect the effect of low-level changes in the environment on lung function. For reasons to be presented in the subsequent section, we offer an "answer" in the form of a prediction interval for the change in lung function between a good and a bad day. We next discuss model validation, and in particular the effect on our conclusions of introducing correlation