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TITLE PAGE

Title

Carbon monoxide pollution is associated with decreased lung function in asthmatic adults.

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Running Title

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Abstract

The aim of this study was to test the effects of exposure to air pollutants on lung function in a panel of 19 adult asthmatics living in Padova followed for five 30-day periods during two consecutive years (1492 morning and 1434 evening analyzed measures). Peak expiratory flow (PEF) and forced expiratory volume in one second (FEV1) were measured by a pocket electronic meter. Daily levels of air pollutants and meteorological variables were collected at city outdoor monitoring sites. We observed inverse statistically significant associations between morning and evening PEF and CO (p=0.01-0.03) without clear differences between lags (0-3 days). An increment of 1 mg/m³ of CO was associated to a PEF variation which ranged from -2.6% to -2.8%. All effect estimates on PEF for CO remained significant and even increased after controlling for PM10, NO2 and SO2 in single and multi-pollutant models. A similar trend was observed for FEV1, but the associations were not statistically significant. A not statistically significant inverse relationship between evening PEF and SO_2 was also detected. PEF and FEV1 were not related to PM_{10} and NO_2 concentrations. Our results indicate that in this panel of adult asthmatics the worsening of lung function is associated with the exposure to gaseous pollutants and it occurs at levels of CO and SO_2 lower than current European standards.

Key words: air pollution; asthma; carbon monoxide; lung function; peak expiratory flow.

Introduction

There is an evidence that exposure to short-term levels of gaseous air pollutants and particulate matter (PM) is associated with mortality and morbidity in particular for cardiopulmonary diseases [1-3].

Epidemiological and clinical data suggest adverse health effects of air pollution especially in populations with pre-existing respiratory disease, such as asthmatics [4-7]. Since asthma exacerbations are associated with bronchocostriction, monitoring of lung function is a way to assess the course of the disease. There is substantial evidence that lung function in asthmatic children is decreased by exposure to air pollution [8-15], while fewer studies are available in adult asthmatics and the results are often controversial [16, 19, 20, 21, 22, 24, 25].

Peak expiratory flow (PEF) measurements are widely used in epidemiological studies to assess the effects of air pollutants on pulmonary function. Although it has been established that forced expiratory volume in one second (FEV1) is an independent predictor of respiratory and cardiovascular mortality [26], this parameter was less investigated in its relationship with air pollutants [11, 12, 14, 22, 24]. Moreover, most of the studies have focused on the relation between lung function and particulate matter [11-17, 21, 22], while several further gasses may be involved in the adverse effects of air pollution.

The present study was conducted within the framework of a longitudinal study funded by the local Environmental Protection Agency (Agenzia Regionale per la Prevenzione e Protezione Ambientale del Veneto – ARPAV) on the effects of personal PM_{10} exposure. The aim was to test the effects of exposure to different outdoor air pollutants (PM_{10}, NO_2, SO_2, CO) on lung function assessed by PEF and FEV1 in adult subjects with bronchial asthma living in Padova and followed up for two years.

Materials and methods

Study design

In order to identify the cohort of asthmatics, the prescriptions of inhaled β2 agonists, alone or in combination with corticosteroids (ACT R03A), during the period 1999-2003 were considered. The total number of prescriptions of anti-asthmatic drugs was 118,025, from which 23,207 subjects with at least one prescription/year were identified. In order to identify subjects with chronic asthma we applied the criterion of at least one R03A prescription per year for three consecutive years. As we wanted to study young adult asthmatics with a moderate to severe degree of disease, we considered subjects aged from 15 to 44 with the highest number of bronchodilator prescriptions. Patients with at least one prescription a year for three consecutive years, aged 15 to 44 at the recruitment (June 2004), and belonging to the quartile with the highest number of drug prescriptions (average prescriptions/year for 3 years >6) were selected (n=158). After the linkage to the population archive, in order to confirm that the subjects were alive and lived in Padova, the cohort resulted of 138 (87.3%) subjects. From this cohort, a panel of 40 subjects has been randomly sampled with an implicit stratification method and followed for five 30-days periods during two consecutive years, at times corresponding to different seasons: summer 2004, autumn 2004, winter 2005, summer 2005, autumn 2005.

Lung function and outdoor air pollution were measured for about one month in each period for a total of 156 days.

The diagnosis of asthma was confirmed in all subjects by their history and lung function tests according to GINA Guidelines [27] prior to the start of the study. This selection method from the drug prescriptions population database identified a cohort of patients with asthma resulting with an high percentage (81%) of moderate-severe disease, higher than the 31% estimated in the overall population of asthmatics in Italy [28].

Atopy was assessed by skin-prick testing to a panel of aeroallergens (house dust mite, moulds, cat and dog dander, tree and grass pollens) [29].

Current drug treatment was recorded at the beginning of each monitoring period. At inclusion, the subjects received a detailed explanation of the study and a written consent was obtained. The study design was approved by the local ethical committee.

Lung function measurements

PEF and FEV1 were measured by a pocket electronic meter (Piko 1, QUBYSoft S.r.l., Italy). The Piko-1 stored up to 96 readings which can be downloaded to a computer. Each participant was trained for the use of Piko-1, including breathing technique, proper positioning, and maintenance of the instrument. Subjects were instructed to perform a forced vital capacity (FVC) three times in the morning and three times in the evening in standing position before taking any respiratory medication. The highest of the PEF and FEV_1 readings performed on each session were selected as results of the test by Piko1. The device included a software to check acceptability of forced expiratory manoeuvre and not acceptable FVC were discharged.

Air-pollution measurements

Outdoor concentrations of air particulate matter ≤ 10 μm (PM_{10}), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and carbon monoxide (CO) were measured continuously at two fixed sites within the city of Padova by the Regional Agency of Health Prevention and Environmental Protection in Veneto. PM_{10} were collected on glass fibre filters using sampling heads CEN (UNI 12341) connected to pumps (Explorer plus, Zambelli) at a flow rate of 38.3 l/min. NO_2, SO_2, and CO were measured according to national regulations with Thermo Environmental Instruments (K50312, K50313, K50314, K50315, Philips, The Netherlands). Ambient $PM_{2.5}$ was not measured at the time of the study. Temperature, humidity and pressure values were provided by the Meteorological Centre of ARPAV.

Daily 24-h average PM_{10}, NO_2, SO_2 and 8-h maximum moving average CO were considered for data analysis.

Data analysis

We considered for the analyses all the 40 recruited subjects and those with at least one third of the expected measures (50/156).

The data were analyzed via unpaired *t*-tests together with chi-square tests as appropriate to compare the characteristics of the subjects with at least one third of expected measures and the other ones.

The association between air pollutants and health outcomes, were examined using marginal linear models for continuous variables, based on the Generalized Estimating Equations (GEE) proposed by Liang and Zeger [30]. This method generates robust estimators regardless of the specification of the covariance matrix, and as autocorrelation is included in the covariance, coefficients can be interpreted as usual. The models were tested using the Stata XTGEE procedure (with the option "robust" which produces valid standard errors even if the correlations within group are not as hypothesized by the specified correlation structure).

Separate regression models were run using morning and evening PEF and FEV1 as the dependent variables. All the models included average of 24-h temperature, humidity, and atmospheric pressure along with current use of corticosteroids (yes/no) and smoking habit (yes/no) as confounders. The associations were examined with respect to the mean pollutant concentrations of the 24h period ending on the noon of the day when the PEF and FEV1 were measured (lag0), the previous day (lag1), 2 days before (lag2), three days before (lag3) and to the cumulative exposures over the previous 0-1 days (lag 0-1) and 0-3 days (lag 0-3). Results from the analyses were reported as absolute changes of PEF and FEV1 per 10 $\mu g/m^3$ increase in pollutant concentrations (except for CO where the unit increase was 10 mg/m^3). Finally, bi-pollutant and multi-pollutant models were conducted in which CO and PM10 levels or NO2 levels or SO2 levels or all pollutants were correlated with lung function. The same lag (lag1) was evaluated simultaneously for each pollutant.

All tests were two-sided, and a p-value below 0.05 was considered to be statistically significant.

All analyses were performed using the statistical package Stata (Stata software version 8; Stata Corp, college Station, TX).

Results

Baseline demographic data are presented in Table 1. No differences were observed between the subjects with more than one third of the measures (n=19) and the other ones (n=21) with regard to age (39 years on average), corticosteroid therapy (68%) and asthma severity (80% with moderate or severe persistent asthma), whereas we found differences with regard to sex (chi-square=4.9, p-value=0.027) and smoking status (chi-square=5.8, p-value=0.015). The following results referred only to the 19 subjects with at least one third of measures, in order to include people who attended consistently the longitudinal study.

The distribution of the outcome variables during the study is presented in Table 2. The number of satisfactory observations of morning PEF and FEV1 was 1492 (50.3% of expected) and 1434 (48.4% of expected) considering the evening measures. PEF and FEV1 were lower in the morning as expected in asthmatic subjects.

Mean air pollutant concentrations and meteorological measures during the study period, as well as Pearson correlation coefficients, are summarized in Table 3. Mean and median concentrations of PM_{10} and NO_2 were above the daily current European limits of 50 $\mu g/m^3$ and 40 $\mu g/m^3$ respectively. Conversely, none of the SO_2 and CO values exceeded the daily limits of 125 $\mu g/m^3$ for SO_2 and 10 mg/m^3 for CO [31]. We found significant correlations among all the four pollutants (r from 0.48 between CO and NO_2 and 0.68 between PM_{10} and NO_2).

Figures 1a-1d show the relationship between lung function parameters and air pollutants for the 19 subjects. We observed inverse statistically significant associations between outdoor CO and PEF in the morning (p-values between 0.01-0.02) and in the evening (p-values between 0.02-0.03),

whereas no statistically significant associations with FEV1 were observed (p-values 0.16-0.24). Increments of SO_2 were associated with decrements of PEF in the evening, but the associations didn't reach the statistical significance (p-values between 0.09-0.19). There were no associations between PEF or FEV1 measurements and PM_{10} or NO_2 concentrations. No substantial differences between lags were observed. An increment of 1 mg/m³ of CO contributed to a variation of PEF which ranged from -2.6% (lag2 morning PEF) to -2.8% (lag 0-3 evening PEF). An increment of 10 µg/m³ of SO_2 contributed to a variation of respiratory function which ranged from -1.8% (lag3 morning PEF) to -4.6% (lag 3 evening PEF).

We observed similar results considering all the 40 subjects although the associations were generally less statistically significant. An increase of outdoor CO was associated with a trend toward a decrease of PEF in the morning (p-values between 0.09-0.14) and with a statistically significant decrease of PEF in the evening (p-values between 0.05-0.06). An increment of 1 mg/m³ of CO contributed to a variation of evening PEF around 2.15%. Increments of SO_2 were associated with a trend toward decrements of PEF in the evening (p-values between 0.06-0.09). An increment of 10 µg/m³ of SO_2 contributed to a variation of evening PEF around 4.2%. No significant associations between PEF or FEV1 measurements and PM_{10} or NO_2 concentrations were detected.

Little differences were observed in the regression coefficients when the data of first and second year were considered separately (data not shown). However, this analysis was limited by the small number of data.

Tables 4 shows the results for bi-pollutant and multi-pollutant models that focused on CO levels at lag 1. Most effect estimates remained significant and some even grew larger after controlling for the other pollutants in particular for morning PEF, where the effect was the largest.

Discussion

The present study shows that in adult asthmatics living in Padova increments of outdoor levels of CO, and less clearly of SO_2, were associated with decreases in lung function. No associations between PEF and FEV1 measurements and PM_{10} and NO_2 concentrations were observed.

In our study, PEF resulted more sensitive than FEV1 in detecting relationship with air pollution. This may be surprising since both indexes derive from a single forced expiratory manoeuvre and FEV1 is generally more sensitive to detect bronchoconstriction in laboratory under supervised conditions [32]. Since optimal FEV1 measurement is more technically demanding than PEF, the latter index is probably more suitable in home monitoring of lung function. Since the meter was provided by quality control software capable to discard unsatisfactory expirations, we can reasonably be confident to have excluded wrong values in the data set.

Although PM_{10} and NO_2 levels frequently exceeded the current European standards of 50 $\mu g/m^3$ and 40 $\mu g/m^3$ respectively throughout the study period, we were not able to show any inverse significant association of PM_{10} with PEF and FEV1 deviations. This may reflect the low within-season variation of particulate mass in Padova urban air. Our findings agree with those of Harre and coworkers in patients with COPD, who reported that PEF wasn't significantly affected by PM_{10} [33]. Similarly, Brauer and coworkers in a panel of COPD adults and Girardot and coworkers in a panel of healthy adults found only trends for decreases in FEV1 and PEF related to ambient air PM [34, 35]. Peters and colleagues found that the effects of SO_2 and PM on adults with an history of asthma were smaller and less consistent than on asthmatic children [16]. Penttinen and colleagues found that daily mean number concentration of particles, but not particle mass was negatively associated with daily PEF deviation [21]. In a recent study no effects of $PM_{2.5}$ were found among adult asthmatics [24].

To our knowledge, this is one of the few epidemiological studies to report a significant association between lung function in adult asthmatics and CO. A previous study demonstrated that FEV1 decreased significantly with CO at lag2 in the evening, among a panel of subjects with

advanced COPD in Denver [36]. Penttinen and colleagues found that CO was negatively associated with daily morning and evening PEF rates in adult asthmatics [21]. Park and colleagues showed that CO was significantly associated with PEF variability and with the mean daily PEF in a panel of 64 asthmatic adults [23]. Carbon monoxide is the product of incomplete combustion mainly produced by motor vehicles in urban areas. A direct association between CO and asthma lacks biologic plausibility. The primary effect of CO exposure at concentration largely above those we observed outdoor is indeed hypoxia, which results in confusion, headache and nausea. However, CO might be a marker for other noxious combustion products. In our study, air pollutants were highly correlated so that it was difficult to separate out the contributions of individual air pollutants. Anyway, all effects estimates on PEF for CO remained significant and even increased after controlling for PM_{10}, NO_2 and SO_2 in single and multi-pollutant models.

It is important to note that the adverse effects occurred at levels of CO and SO_2 lower than current European standards, whereas the daily mean and median concentration of PM_{10} and NO_2 were repeatedly above these standards. This may rise some concern that current ambient air quality standards might not be stringent enough to protect human subjects from adverse effects, considering that the real exposure is a mixture of several pollutants.

The validity of our findings relies on the long period of the study, the use of repeated measures of lung function on the same individuals, the method for selecting the study population from the database of drug prescriptions of the National Health System rather than from clinical series which might be affected by selection bias. Whereas few studies selected patients from the general population randomly [37], in most studies patients were selected by general practitioners or chest physicians, and by attendance to chest departments or out patient clinics, thus being not representative of the average asthmatic population [18, 19, 22, 24, 38]. The selection of patients with the highest rate of bronchodilator prescriptions allowed an identification of a cohort of asthmatics enriched in more severe disease. Moreover, the use of an electronic PEF/FEV1 meter

avoided inclusion of fabricated measurements and reduced the possibility of misreporting data. Just one study used the same methodology in adult asthmatics [25].

The study may be however affected by some limitations. The size of the study was limited by the small number of subjects, but the number of observations we collected is comparable to previous panel studies on adult asthmatics with similar longitudinal design [20, 24, 25]. We choose fewer subjects and longer period of monitoring because we wanted to maximize the difference in exposures to pollutants known to occur in different seasons. Other panel studies have generally been limited to shorter periods, whereas just few studies on adult asthmatics covered a period above one year [11, 16, 37, 38].

A study design involving five different monitoring sessions over two years increased the probability of loosing participants to follow-up. The number of subjects with less than one third of the measures may appear elevated. Anyway, among these 21 subjects, 9 (43%) had observations just in the first monitoring section and only 1 in more than three seasons. Moreover, the total number of observations obtained from these subjects is a minority of all available data (354/1856 morning; 301/1735 evening). For these reasons we decided to consider as more robust data those concerned the 19 subjects who consistently participated in the study. A total of 50 participation days (33% of possible days) was required for inclusion in the main analyses, in agreement with the majority of other similar studies [8, 16, 20, 21, 25, 37].

Since ambient $PM_{2.5}$ was not measured at the time of the study, we cannot exclude an effect of smaller particles.

While the analyses were adjusted for several confounders, i.e. temperature, humidity, pressure, tobacco smoke, corticosteroid use, it was not possible to control for aeroallergens, which were not measured. To minimize the influence of grass pollen, the spring season was not included in the study periods. Thurston and colleagues considered pollens in their summer study and found no associations between PEF and pollen counts [39]. Hence, it is unlikely that pollen would be a significant confounder in this study as levels are lower in other seasons.

It might be argued that smoking could be a confounder in this study, although we adjusted for smoking. We deliberately did not exclude asthmatic smokers since the aim was the analysis of a panel representative of the current population of asthmatics in which smoking habit is present [40].

According with the design of the study, we tried to select asthmatics toward the severe end of the spectrum of the disease. In fact, only 20% of the patients had mild asthma. The need of corticosteroids is a component of the severity of the disease, as underlined in the last revision of GINA guidelines [27]. In addition, there is some evidence that corticosteroids treatment may attenuate the air pollutant effects [8, 11], although a consensus on this issue has not been established [19]. For this reasons, the use of corticosteroids was assessed when the patients were seen quarterly and this information was used as a covariate in the regression model. By design of the study, our data refer mainly to a moderate-severe population and the imbalance in degree of severity of our sample (together with the small size) prevents to make meaningful stratified analysis by steroid use.

In conclusion, our results indicate that lung function in this panel of adult asthmatics appears to be affected by the exposure to gaseous pollutants, in particular carbon monoxide, and less strongly by sulphur dioxide, whereas it doesn't correlate with the exposure to particulate matter. The adverse effects occurred at levels of CO and SO_2 lower than current European standards.

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Table 1 Characteristics of the study subjects

	All Subject (n=40)	**Subjects >50 measures (n=19)**	**Subjects <=50 measures (n=21)**
Female, n° (%)*	20 (50)	13 (68.42)	7 (33.33)
Age, mean (±SD)	39.2 (7.8)	40.9 (6.4)	37.6 (8.7)
Corticosteroid therapy, n (%)			
None	13 (32.50)	8 (42.11)	5 (23.81)
Low dose	9 (22.50)	3 (15.79)	6 (28.57)
Medium dose	10 (25.00)	6 (31.58)	4 (19.05)
High dose	8 (20.00)	2 (10.53)	6 (28.57)
Asthma severity [a], n (%)			
Intermittent	3 (7.50)	2 (10.53)	1 (4.76)
Mild Persistent	5 (12.50)	2 (10.53)	3 (14.29)
Moderate Persistent	13 (32.50)	6 (31.58)	7 (33.33)
Severe Persistent	19 (47.50)	9 (47.37)	10 (47.62)
Smokers, n (%)*	14 (35.00)	3 (15.79)	11 (52.38)

Notes:
[a] GINA Classification of Asthma Severity
* Chi-square test: $p<0.05$

Table 2 Descriptive statistics of PEF, FEV1

		Subjects >50 measures (n=19)
PEFm[a]	N	1492
	Mean (SD[e])	327.1 (107.4)
PEFe[b]	N	1434
	Mean (SD[e])	336.8 (115.3)
FEV1m[c]	N	1492
	Mean (SD[e])	2.3 (0.7)
FEV1e[d]	N	1434
	Mean (SD[e])	2.4 (0.7)

Notes:
[a] morning PEF
[b] evening PEF
[c] morning FEV1
[d] evening FEV1
[e] SD: standard deviation

Table 3a Summary and **3b** Pearson correlation coefficients of air pollutant concentrations and meteorologic parameters for the 156 studied days.

3a

Variable	Mean	Median	SD[c]	Min	Max
PM_{10} ($\mu g/m^3$) [a]	56.98	50.65	32.25	12	188
NO_2 ($\mu g/m^3$) [a]	51.04	50.51	12.57	19.16	90.41
SO_2 ($\mu g/m^3$) [a]	3.57	2.64	2.86	0.46	12.78
CO (mg/m^3) [b]	1.72	1.3	1.00	0.6	5.2
Temperature (C°) [a]	15.12	15.18	8.29	-2.33	28.18
Relative humidity (%) [a]	74.11	72.51	15.21	40.85	98.44
Barometric pressure (hPa) [a]	1014.56	1014	4.88	1003	1029

Notes:

[a] Average of 24h concentrations measured at 2 locations

[b] Average of 8h maximum measured at 2 locations

[c] SD: standard deviation

3b

	PM_{10}	SO_2	NO_2	CO	Temp	Humidity	Pressure
PM_{10}	-	-	-	-	-	-	-
SO_2	0.509**	-	-	-	-	-	-
NO_2	0.684**	0.535**	-	-	-	-	-
CO	0.624**	0.499**	0.480**	-	-	-	-
Temp.	-0.529**	-0.564 **	-0.480**	-0.786**	-	-	-
Humidity	0.202*	-0.307*	0.077	0.209*	-0.185*	-	-
Pressure	0.408**	0.245*	0.469**	0.293*	-0.3462**	0.102	-

Notes:

* 0.5<p-value<=0.001

** p-value<0.001

Table 4. Relations between lung function and CO measured on the previous day (lag1), bi-pollutant and multi-pollutants models

	Other adjustment	Beta*	Standard error	p-value	% change per 1 mg/m^3
Morning PEF	**none**	-8.50	3.54	**0.02**	**-2.60**
	SO^2	-8.23	3.41	**0.02**	**-2.52**
	PM^{10}	-10.52	4.18	**0.01**	**-3.22**
	$N0^2$	-8.64	3.52	**0.01**	**-2.64**
	All pollutants	-10.70	4.15	**0.01**	**-3.27**
Evening PEF	**none**	-9.17	4.22	**0.03**	**-2.72**
	SO^2	-8.53	4.24	**0.04**	**-2.53**
	PM^{10}	-9.28	4.91	0.06	-2.76
	$N0^2$	-9.56	4.62	**0.04**	**-2.84**
	All pollutants	-9.18	4.89	0.06	-2.72
Morning FEV1	**none**	-0.03	0.02	0.22	-1.17
	SO^2	-0.03	0.02	0.25	-1.09
	PM^{10}	-0.03	0.03	0.34	-1.17
	$N0^2$	-0.03	0.02	0.21	-1.28
	All pollutants	-0.03	0.03	0.34	-1.18
Evening FEV1	**none**	-0.05	0.04	0.21	-1.98
	SO^2	-0.04	0.04	0.24	-1.77
	PM^{10}	-0.05	0.04	0.20	-2.24
	$N0^2$	-0.05	0.04	0.16	-2.22
	All pollutants	-0.05	0.04	0.22	-2.19

*Regression coefficient from GEE models for panel data controlling for temperature, relative humidity, atmospheric pressure, corticosteroid use and smoking habit. Changes for 1 mg/m³ increase in pollutant concentrations.

Figure 1a Relations between morning PEF and pollutants measured on the same day (lag 0), the previous day (lag1), average of 0-1 days (lag 0-1), 2 days before (lag2), 3 days before (lag3), and average of 0-3 days (lag 0-3). *Beta: Regression coefficient and C.I.: confidence intervals 95% from GEE models for panel data controlling for temperature, relative humidity, atmospheric pressure, corticosteroid use and smoking habit. Changes for 10 µg/m³ increase in pollutant concentrations (except for CO where the unit increase is 1 mg/m³).

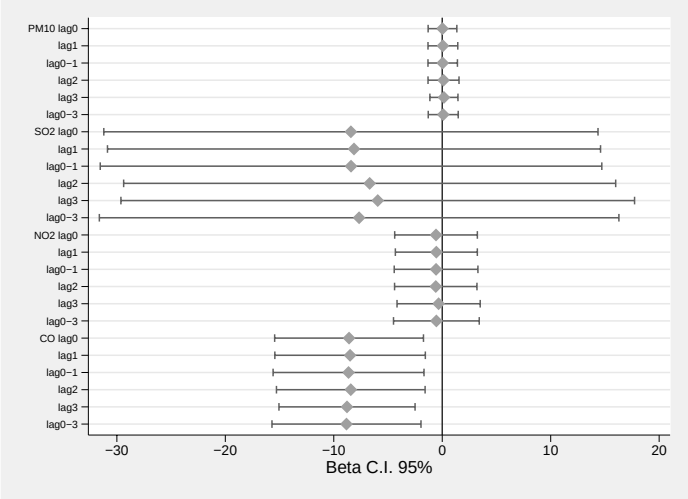

Figure 1b Relations between evening PEF and pollutants measured on the same day (lag 0), the previous day (lag1), average of 0-1 days (lag 0-1), 2 days before (lag2), 3 days before (lag3), and average of 0-3 days (lag 0-3). *Beta: Regression coefficient and C.I.: confidence intervals 95% from GEE models for panel data controlling for temperature, relative humidity, atmospheric pressure, corticosteroid use and smoking habit. Changes for 10 µg/m³ increase in pollutant concentrations (except for CO where the unit increase is 1 mg/m³).

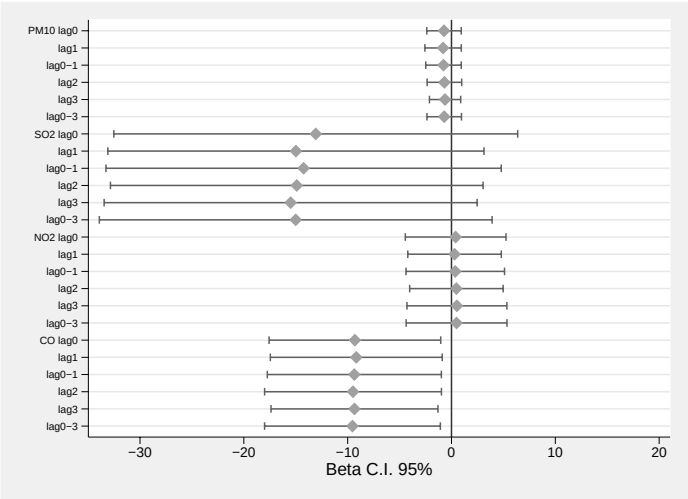

Figure 1c Relations between morning FEV1 and pollutants measured on the same day (lag 0), the previous day (lag1), average of 0-1 days (lag 0-1), 2 days before (lag2), 3 days before (lag3), and average of 0-3 days (lag 0-3). *Beta: Regression coefficient and C.I.: confidence intervals 95% from GEE models for panel data controlling for temperature, relative humidity, atmospheric pressure, corticosteroid use and smoking habit. Changes for 10 µg/m³ increase in pollutant concentrations (except for CO where the unit increase is 1 mg/m³).

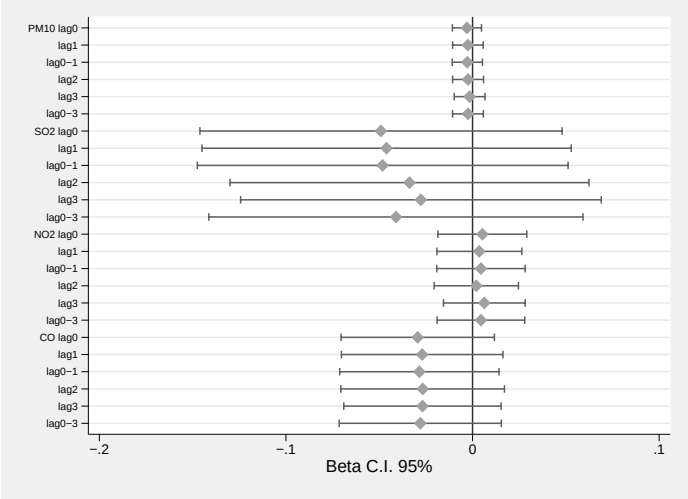

Figure 1d Relations between evening FEV1 and pollutants measured on the same day (lag 0), the previous day (lag1), average of 0-1 days (lag 0-1), 2 days before (lag2), 3 days before (lag3), and average of 0-3 days (lag 0-3). *Beta: Regression coefficient and C.I.: confidence intervals 95% from GEE models for panel data controlling for temperature, relative humidity, atmospheric pressure, corticosteroid use and smoking habit. Changes for 10 µg/m³ increase in pollutant concentrations (except for CO where the unit increase is 1 mg/m³).