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## **Effects of short- and long-term exposure to particulate matter on inflammatory marker levels in the general population**

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## **Abstract**

**Background:** The effect of particulate matter (PM) on health increase with exposure duration but the change from short to longer term is not well studied.

**Objectives:** We examined exposure to PM smaller 10  $\mu\text{m}$  ( $\text{PM}_{10}$ ) from short to longer duration and their associations with levels of inflammatory markers in the population-based CoLaus cohort in Lausanne, Switzerland.

**Methods:** Baseline and follow-up CoLaus data were used to study the associations between  $\text{PM}_{10}$  exposure and inflammatory markers, including the high-sensitivity C-reactive protein (CRP), as well as interleukin 1-beta ( $\text{IL-1}\beta$ ), interleukin 6 ( $\text{IL-6}$ ), and tumor-necrosis-factor alpha ( $\text{TNF-}\alpha$ ) using mixed models. Exposure was determined for each participant's home address from hourly air-quality simulations at 5-meter resolution. Short-term exposure intervals were one day, one week, and one month prior to the hospital visit (blood withdrawal); long-term exposure intervals were three and six months prior to the visit.

**Results:** In most time-windows,  $\text{IL-6}$ ,  $\text{IL-1}\beta$  and  $\text{TNF-}\alpha$  were positively associated with  $\text{PM}_{10}$ . No significant associations were identified for CRP. Adjusted associations with long-term exposures were stronger and more significant than those for short-term exposures. In stratified models, gender, age, smoking status and hypertension only led to small modifications in effect estimates, though a few of the estimates for  $\text{IL-6}$  and  $\text{TNF-}\alpha$  became non-significant.

**Conclusion:** In this general adult cohort exposed to relatively low average  $\text{PM}_{10}$  levels, clear associations with markers of systemic inflammation were observed. Longer duration

of elevated exposure was associated with an exacerbated inflammatory response. This may partially explain the elevated disease risk observed with chronic PM<sub>10</sub> exposure. It also suggests that reducing prolonged episodes of high PM exposure may be a strategy to reduce inflammatory risk.

**Keywords:** Particulate matter, Inflammation, Short-term, Long-term, modeling, air pollution

## Introduction

Air pollution is a widely-acknowledged environmental risk factor globally, estimated to cause 3.3 million premature deaths per year worldwide (Lelieveld et al., 2015). Several studies have shown that exposure to particulate matter (PM) is associated with adverse cardiovascular effects (Brook et al. 2010). Moreover, PM-induced inflammation has been postulated to be one of the mechanisms behind cardiovascular disease (Brook et al., 2010, Pope and Dockery, 2006). Inflammatory markers are known to be associated with increased risk of developing cardiovascular disease (Kaptoge et al. 2014 ; Kofler et al. 2005). Levels of inflammatory markers can also be mediated by lifestyle factors, such as smoking, or physical activity (Bermudez et al. 2002; Colbert et al. 2004).

A series of epidemiologic studies have documented associations between short-term exposure to PM and inflammatory markers (Hassanvand et al. 2017; Hertel et al. 2010; Steinvil et al. 2008; Tsai et al. 2012), while long-term exposure also appears to play an important role. In one study in the United Kingdom (UK), an association was detected between long-term exposure to PM having aerodynamic diameter of 10  $\mu\text{m}$  or smaller ( $\text{PM}_{10}$ ) and inflammatory markers in the general population (Forbes et al. 2009). Meanwhile, investigators in the United States (US) reported one year exposure to  $\text{PM}_{2.5}$  to be associated with high-sensitivity CRP among midlife women (Green et al. 2016; Ostro et al. 2014). In a German study, an association was identified between 365-day  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$  ( $\text{PM} < 2.5 \mu\text{m}$ ) and number of particles, and CRP in the general population (Hennig et al. 2014). Fewer studies have evaluated the consequences of PM exposure on inflammation markers, after both short- and long-term exposure, in the same population.

The upper thresholds for PM<sub>10</sub> recommended by the World Health Organization are 50  $\mu\text{g}/\text{m}^3$  for a 24-hour mean and 20  $\mu\text{g}/\text{m}^3$  for an annual mean (WHO, 2018). In Switzerland, the air quality is mostly below these values, which provides an opportunity for the health effects of relatively-low concentrations of PM to be studied in the general population.

Assessing exposure is a critical step in epidemiological studies. Many studies focusing on short-term and acute effects have relied on data extracted from air monitoring stations, taking advantage of the fact that day-to-day variations in pollutant concentrations generally are much smaller than spatial variations within a given region. For long-term studies, however, data on spatial distribution is necessary, and this requires the use of models. Our objective was to examine for associations between both short-term and long-term exposure to PM<sub>10</sub>, and several circulating inflammatory markers: C-reactive protein (CRP), interleukin 1-beta (IL-1 $\beta$ ), interleukin 6 (IL-6), and tumor-necrosis-factor alpha (TNF- $\alpha$ ).

## **Materials and Methods**

### **Study population**

The CoLaus study is a large, longitudinal, population-based cohort survey that includes residents, ages 35 to 75 years old, of Lausanne, Switzerland, a city of 117,161 inhabitants (data for 2003 from city of Lausanne population registry). The study's focus has been on cardiovascular and metabolic risk factors, as described elsewhere (Firmann et al. 2008). The Institutional Ethics Committee of the Faculty of Medicine of the University of Lausanne approved the CoLaus study. The informed written consent was obtained from all the participants.

A non-stratified random sample of 35% of the overall population was drawn. Recruitment was done between 2003 and 2006. The sample of 8,121 subjects who agreed to participate represented 41% of the initially-sampled population (“CoLaus 1”). Participants were asked to attend a specific outpatient clinic in the morning after an overnight fast. Between 2009 and 2012, all CoLaus participants (n=6,183) were invited for a first follow-up (“CoLaus 2”), amongst whom 4,679 (75.7%) accepted. Both CoLaus 1 and CoLaus 2 included standardized questionnaires (as well as questions on medications), a physical examination, and blood exams. The final sample size were 3860 subjects, who had modeling estimates of exposure levels for both waves.

### **Health data**

During both examinations, study participants reported, for their health examination, to the outpatient clinic at University Hospital of Lausanne (CHUV), always between 7 am and noon. Fasting blood samples were analyzed for the high-sensitively inflammatory marker C-reactive protein (CRP), as well as for interleukin 1-beta (IL-1 $\beta$ ), interleukin 6 (IL-6), and tumor-necrosis-factor alpha (TNF- $\alpha$ ). The laboratory equipment, analysis methods used, the lower detection limit and the method to substitute values below the lower detection limit were identical in CoLaus 1 and CoLaus 2, as described earlier (Tsai et al., 2012). On follow-up (CoLaus 2), 1139, 197, and 21 values for IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were below the lower detection limit.

Extreme outliers were defined as those that were 10-fold more than the corresponding measurement’s 99<sup>th</sup> percentile (p99) value; all such outliers were excluded from further analysis. The extreme outliers in CoLaus 1 were described earlier (Tsai et al. 2012). In CoLaus2, no extreme outliers were detected for IL-1 $\beta$  (p99=74.8 pg/mL). For IL-6, there

was one extreme outlier at 2281 pg/mL (p99=222 pg/mL); and for TNF- $\alpha$ , two outliers, of 3242 and 3793 pg/mL (p99=93.8 pg/mL).

## **Exposure data**

***Assigning exposure to participants:*** Hourly PM<sub>10</sub> concentrations at the home addresses of individuals living in Lausanne were simulated with the GRAMM/GRAL model (see below). We assigned to each participant home exposure data for one day, seven days (1-week), 30 days (1-month), 90 days (3-months) and 180 days (6-months) before their health assessment. The model was validated by comparing its output with measurements conducted at a central monitoring station in the city of Lausanne (see below). The daily modeled and measured concentrations were correlated with an R<sup>2</sup> coefficient of 0.83 (Berchet et al., 2017). We calculated central monitoring site-time windows that corresponded to the modeled time windows for each of the participants, to understand gains in the population's exposure gradient, by using the model instead of central-site monitoring. As not all subjects lived within the GRAMM/GRAL model coverage area at both examinations, modeling data could only be assigned to 3860 participants who participated in both CoLaus 1 and CoLaus 2.

***GRAMM/GRAL exposure model:*** A coupled mesoscale-microscale model system — GRAMM/GRAL with 5-meter grid-resolution — was set up to simulate PM<sub>10</sub> concentrations in Lausanne. Briefly, computational fluid dynamic simulations were computed to simulate 1008 different typical weather situations that influence the three-dimensional wind and concentration fields in and around the city. To generate long-term series from pre-computed reference simulations, the catalogue of simulations was “matched to observations” (i.e., situations were selected from the catalogue of 1008



situations for which the simulated winds best matched observed winds at five different sites around Lausanne). Once the situations were identified, the simulated source-specific concentrations were scaled by characteristic time functions describing diurnal, day-of-week, and seasonal variability of the emissions from different source types (traffic, industry, residential heating, etc.) and added together to obtain the total concentration field of PM<sub>10</sub> (Berchet et al., 2017). This modeling did not require any local pollution measurements.

**Study area and central monitoring:** Lausanne covers an area of 70 x 15 km<sup>2</sup> and is built on the ridges and valleys of the northern shore of Lake Geneva. The highest point of the city is 600 m above lake level. One of the Swiss National air monitoring network (NABEL) stations is located in central Lausanne at César-Roux. A detailed description of the station can be found from NABEL website. We downloaded and averaged PM10 data into 24-hour means (0:00-23:59). NABEL had missing data only during CoLaus 1. There were 15% of hourly PM10 data missing, most of the gaps were one or two hours of missing data. This affected 27 (0.7%) of the subjects' daily averages. In case of one or two hours of missing data, we replaced the missing hourly data by the weighted average of the two hours before and after the gap. Longer gaps were replaced by the average of the corresponding three daytime hours of the day before and after the gap. Outdoor air temperature and air pressure data was obtained from MeteoSwiss, Switzerland's Federal Office for Meteorology and Climatology, which provides quality-assured weather and climate services for the protection and benefit of Switzerland.

**Analytic framework:** to investigate the short-term effects of PM exposure, we were able to use data from both the central monitoring station and the models. For assessing effects

of exposures longer than one month, however, only modeled data provided the necessary degree of variation related to the spatial variation between homes.

### **Statistical analysis**

Stata 14.1 (StataCorp, College Station, TX) was used for all statistical analyses. Log-transformation was performed to approximate a normal distribution of skewed variables (CRP, IL-1 $\beta$ , 1L-6, and TNF- $\alpha$ ). Descriptive results were expressed as number of participants, percentage for categorical variables and as mean (95% Confidence Interval) or median (Interquartile range) for continuous variables. Bivariate analyses were performed using chi-square test for qualitative variables and Student's t-test for quantitative variables between the two waves.

In a prior study reported by Tsai et al., a positive association between PM<sub>10</sub> exposure and pulse pressure and systolic blood pressure was evident only when the outdoor temperature was above 5°C (Tsai et al. 2015). Therefore, we created a covariate 'cold-day ratio', corresponding to the percentage of days within a given exposure period when the outdoor daily average temperature was below 5°C.

Linear mixed-effect regression models were used to examine the associations between the inflammatory markers and PM<sub>10</sub>. The outcome variables were CRP, IL-1 $\beta$ , 1L-6, and TNF- $\alpha$ , and the exposure variable was the PM<sub>10</sub> level from modeling and monitoring stations. Each regression model included fixed effects for age, sex, BMI, smoking status, diabetes, hypertension, cold-day ratio, outdoor air pressure, and CoLaus time period. The participants were fitted as random effects in the mixed-effects models.

Estimated effects for both long- and short-term exposure were presented as unit change per 1  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ . Short-term exposure interval means were 1-day, 1-week, and 1-month averages of  $\text{PM}_{10}$  level prior to the hospital visit (blood withdraw); while long-term exposure interval means were calculated for three and six months prior to the visit.

## Results

Characteristics of the CoLaus 1 and CoLaus 2 participants are summarized in **Table 1**. Only participants with health and environmental data available for both data-collection waves were included in this analysis. Body mass index was lower at baseline than at follow-up. Smoking rate dropped at follow-up, while diabetes and hypertension prevalence rates increased. Except for  $\text{IL-1}\beta$ , the inflammatory marker levels increased from baseline to follow-up. Table 1 also shows the distribution of  $\text{PM}_{10}$  and temperature. In general, concentrations in CoLaus 1 were higher than in CoLaus 2. The distributions of inflammatory markers were similar in the two waves (**Supplementary Figure S1**).

For short-term exposure,  $\text{PM}_{10}$  levels derived from the NABEL station, averaged over the 1-day, 1-week, and 1-month intervals, were positively (directly) associated with  $\text{IL-1}\beta$ ,  $\text{IL-6}$  and  $\text{TNF-}\alpha$  (**Figure 1**). Similar results were obtained when using short-term exposure data extracted from the GRAMM-GRAL models. Long-term modeled  $\text{PM}_{10}$  exposure (3-month and 6-month) exerted more profound effects on these inflammatory markers. For long-term analyses (3-month and 6-month), only modeled data were used, due to the small variations in long-term pollutant levels at the single, central site. No association was found for CRP with either short or long-term exposure. The  $\text{PM}_{10}$  levels also were associated with  $\text{IL-1}\beta$ ,  $\text{IL-6}$ , and  $\text{TNF-}\alpha$  after dichotomizing these cytokines into high

(higher quartile) versus low (quartiles 1 to 3) levels, which suggests that the associations between PM<sub>10</sub> with the continuous cytokine were very robust to any distributional assumption, and to potential outlier values (**Supplementary Table S1**).

Associations between 6-month PM<sub>10</sub> exposure levels and inflammatory markers are provided for different subject subgroups in **Table 2**. Six-month exposure to PM<sub>10</sub> was significantly associated with IL-1 $\beta$  and IL-6 in men, in younger participants, and in normotensive participants; but with IL-1 $\beta$  and TNF- $\alpha$  in women and older participants. Associations with IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were more significant in non-smokers. However, the interactions between PM<sub>10</sub> exposure and the selected subgroups were not statistically significant for the various inflammatory cytokines.

In general, PM<sub>10</sub> concentrations decreased significantly from 2003 to 2012, covering both examinations (**Supplementary Figure S2**). The variability in PM<sub>10</sub> levels was greater for modeled than for NABEL data (**Supplementary Figures S3 and S4**).

## **Discussion**

In the current study, short-term and long-term exposures to PM<sub>10</sub> were associated with elevated levels of IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , but not of CRP. The short-term effects obtained with modeled air pollution exposures were consistent with our previous findings that used only NABEL data (Tsai et al. 2012). The long-term effects found in the current analysis also were much stronger than the short-term effects.

To date, only a few studies have assessed the association between long-term exposure to PM and CRP, IL-1 $\beta$ , IL-6 and TNF- $\alpha$  in general population. In a Swedish study, IL-6, TNF- $\alpha$ , and CRP were not significantly associated with one-year, five-year or 30-year

exposure to PM<sub>10</sub> (Panasevich et al. 2009). In the US MESA study, long-term exposure (one-year) to PM<sub>2.5</sub> was associated positively with IL-6, but not with CRP (Hajat et al. 2015). Meanwhile, in the US SWAN study, one-year exposure to PM<sub>2.5</sub> was associated with increased CRP in women, but IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were not included in the investigators' analysis (Green et al. 2016).

The possible pathophysiological mechanism underlying the link between PM and systemic inflammation could be the increased production of the pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 by alveolar macrophages in response to PM (Panasevich et al. 2009 ; van Eeden et al. 2001). Prolonged exposure to PM will result in more oxidative stress and prolonged activation of cell- and cytokine-mediated pathways including apoptosis, which can progress into a chronic inflammatory response with insufficient clearance of apoptotic cells (Grabiec and Hussell 2016; Robb et al. 2016).

Interleukin 6 is an acute phase reactant released by T-cells and macrophages. *In vitro* studies have revealed increased production of the proinflammatory cytokines, TNF- $\alpha$  and IL-6, by alveolar macrophages in response to PM (Becker et al. 2005; Imrich et al. 2007; van Eeden et al. 2001). The stronger effects that we observed with prolonged exposure levels suggest that there is no adaptation to such exposure over time; instead, there appears to be propagation of the inflammatory process by air pollutants. This may explain the increased rates of chronic inflammatory diseases associated with living in polluted areas (Chen and Schwartz 2008). In a cross-sectional study conducted in a representative sample of elderly Taiwan residents, long-term PM<sub>10</sub>, PM<sub>2.5</sub> and NO<sub>2</sub> concentrations were all linked to IL-6 levels (Chuang et al. 2011).

We identified no association between exposure to PM<sub>10</sub> and circulating CRP levels, with either long-term or short-term exposure, which is consistent with most prior population-based studies. In the US MESA study, circulating CRP levels were weakly, positively associated with exposure to 30-day and 60-day mean PM<sub>2.5</sub> exposures, but not to shorter term (one-day, two-day) exposures (Diez Roux et al. 2006). No association between short-term exposure to PM<sub>10</sub> and CRP was found in the Tel-Aviv Sourasky Medical Center Inflammation Survey (Steinvil et al. 2008). Similarly, no association between long-term exposure to PM<sub>10</sub> and circulating CRP levels was detected in 17'000 adults who participated in the Health Survey for England (Forbes et al. 2009). The absence of an association between PM<sub>10</sub> and CRP does not imply the absence of an inflammatory response to PM. Rather, CRP, as a ubiquitous inflammatory marker, just might not be ideal to detect the low-grade, chronic, respiratory inflammation that can result from relatively-low levels of air pollution. One of the results identified in the European Study of Cohorts for Air Pollution Effects (ESCAPE) was that elevated PM<sub>10</sub> levels were not associated with elevated CRP; however, living close to busy traffic was (Lanki et al. 2015).

Assessment of subgroups showed no significant interaction terms and the effect estimates were also in a similar range for most explored strata. Estimates across the various strata lied mostly well within the confidence intervals. A significant positive association of PM<sub>10</sub> exposure with TNF- $\alpha$  levels was observed in women, but not in men, whereas similar significant positive associations with IL-1 $\beta$  and IL-6 were observed in both men and women. Participants younger than 55 years tended to have a weaker association with IL-1 $\beta$  and a stronger one with IL-6 than older participants. A significant positive association of PM<sub>10</sub> exposure with TNF- $\alpha$  levels was observed in non-smokers, but not in smokers,

possibly the result of the pro-inflammatory action of smoking (McEvoy et al. 2015). Normotensive participants showed a stronger positive association of CRP with exposure to PM<sub>10</sub> than hypertensive participants, which could reflect the anti-inflammatory property of statins used by many hypertensive people (Miyata et al. 2013).

One important strength of the current study is that it is representative of the general adult population of a city. Many previously-published studies focused on specific population groups, like women (Green et al. 2016; Ostro et al. 2014), the elderly (Rioux et al. 2010) or patients. Our study also included several inflammatory cytokines, while previous general population studies only included CRP (Diez Roux et al. 2006; Hertel et al. 2010; Hoffmann et al. 2009; Rioux et al. 2010; Steinvil et al. 2008). Our longitudinal design included repeated measurements at baseline and 5-year follow-up, which reinforces the robustness of the results. A final important strength of the current study are the accurate estimates of PM<sub>10</sub> exposure (Berchet et al. 2017), since we estimated exposures for 5-meter grid-lengths at hourly intervals, using air dispersion models, also taking into account both meteorological data and emission inventories.

Some limitations exist. First, for particles, only modeled and measured data on PM<sub>10</sub> was available in Lausanne, thus this study does not provide granularity on how much of the inflammatory response may be attributable to the size fractions PM<sub>2.5</sub> and ultrafine particles. Second, gaseous pollutants such as nitrogen dioxide and ozone are also known to influence inflammatory processes. Third, Lausanne is a comparably clean city, thus caution should be applied when translating these findings to other, more polluted regions of the world. Fourth, exposure estimates were based on home addresses. However, we did not have the information on when the participants moved to their current addresses.

While they are usually fairly well correlated with personal exposure (Culyba et al. 2018; Shafran-Nathan et al. 2017), they are associated with an error, which increases the uncertainty of the effect estimates. Finally, our analysis focused on PM<sub>10</sub>, but further work should extend the analysis to other air pollutants, such as NO<sub>2</sub> or O<sub>3</sub>.

## **Conclusions**

Our results indicate that long-term exposure to high PM<sub>10</sub> levels is associated with elevated markers of systemic inflammation in the general adult population, when PM levels generally are low. Prolonged elevated exposure to PM<sub>10</sub> seems to exacerbate systemic inflammatory response, which may contribute to the elevated disease risk generally observed with chronic PM<sub>10</sub> exposure. A clear increase in effect estimates started after one month of high exposure, which suggests that reducing elevated exposures to less than one month may be helpful to reduce negative long-term effects.

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**Table 1. Characteristics of participants, that had participated in both waves and that had the addresses within the pollution map (N=3860). The data indicates categorical data (% of total), and continuous data (mean, 95% CI or median, 25%-75%).**

	CoLaus 1	CoLaus 2		Data type
<b>Age</b>	53.2 (52.9-53.5)	58.8 (58.5-59.1)	***	Mean (95% CI)
<b>Female, %</b>	1765, 45.7%	1765, 45.7%	---	Count, % of total
<b>BMI</b>	25.6 (25.5-25.8)	26.2 (26.0-26.3)	***	Mean (95% CI)
<b>Diabetes</b>	241, 6.3%	430, 11.2%	***	Count, % of total
<b>Hypertension</b>	1327, 34.4%	1686, 43.8%	***	Count, % of total
<b>CRP (µg /mL)</b>	1.3 (0.6-2.7)	1.4 (0.7-2.8)	***	Median (25%-75%)
<b>IL-1β (pg/mL)</b>	1.2 (0.5-3.9)	0.6 (0.1-2.3)	***	Median (25%-75%)
<b>IL-6 (pg/mL)</b>	1.4 (0.7-3.4)	2.5 (1.0-7.8)	***	Median (25%-75%)
<b>TNF-α (pg/mL)</b>	2.8 (1.8-4.4)	4.8 (2.7-8.5)	***	Median (25%-75%)
<b>Current smoker</b>	1015, 26.3%	833, 21.8%	***	Count, % of total
<b>1-day PM10 (NABEL)</b>	31.8 (31.2-32.4)	21.5 (21.1-21.9)	***	Mean (95% CI)
<b>1-week PM10 (NABEL)</b>	29.8 (29.3-30.2)	21.1 (20.8-21.4)	***	Mean (95% CI)
<b>1-month PM10 (NABEL)</b>	29.5 (29.2-29.8)	21.1 (20.9-21.4)	***	Mean (95% CI)
<b>1-day PM10</b>	22.3 (21.8-22.7)	17.6 (17.2-17.9)	***	Mean (95% CI)
<b>1-week PM10</b>	24.5 (24.1-24.9)	18.0 (17.7-18.2)	***	Mean (95% CI)
<b>1-month PM10</b>	24.8 (24.5-25.0)	18.0 (17.8-18.2)	***	Mean (95% CI)
<b>3-month PM10</b>	23.4 (23.2-23.5)	18.1 (18.0-18.3)	***	Mean (95% CI)
<b>6-month PM10</b>	21.8 (21.7-21.9)	18.3 (18.2-18.4)	***	Mean (95% CI)
<b>Pressure</b>	956.1 (955.9-956.3)	954.3 (954.1-954.6)	***	Mean (95% CI)
<b>Cold days (&lt;5°C)</b>	1293, 33.5%	691, 17.9%	***	Count, % of total

\*\*\* p-value <0.001. Bivariate analyses were performed using chi-square test for qualitative variables and Student's t-test for quantitative variables between the two waves.



**Table 2. Association of long-term exposure to 6-month average PM10 with inflammatory markers (unit change in cytokine per 1 ug/m<sup>3</sup> increase in PM10) by selected strata.**

	<b>CRP</b>	<b>p</b>	<b>IL-1<math>\beta</math></b>	<b>p</b>	<b>IL-6</b>	<b>p</b>	<b>TNF-<math>\alpha</math></b>	<b>p</b>
<b>Men</b>	0.0132 (-0.002, 0.028)	0.083	<b>0.103</b> (0.075, 0.131)	<b>&lt;0.001</b>	<b>0.056</b> (0.030, 0.083)	<b>&lt;0.001</b>	0.0067 (-0.009, 0.023)	0.410
<b>Women</b>	-0.017 (-0.018, 0.015)	0.839	<b>0.104</b> (0.074, 0.134)	<b>&lt;0.001</b>	<b>0.040</b> (0.011, 0.067)	<b>0.006</b>	<b>0.019</b> (0.001, 0.036)	<b>0.036</b>
<b>Pint<sup>a</sup></b>		Pint=0.066		Pint=0.405		Pint=0.595		Pint=0.429
<b>Age&lt;55</b>	0.0052 (-0.011, 0.021)	0.518	<b>0.091</b> (0.062, 0.120)	<b>&lt;0.001</b>	<b>0.062</b> (0.035, 0.089)	<b>&lt;0.001</b>	0.013 (-0.004, 0.029)	0.125
<b>Age<math>\geq</math>55</b>	0.012 (-0.003, 0.028)	0.125	<b>0.119</b> (0.090, 0.149)	<b>&lt;0.001</b>	<b>0.033</b> (0.006, 0.060)	<b>0.019</b>	0.011 (-0.006, 0.028)	0.206
<b>Pint<sup>a</sup></b>		Pint=0.544		Pint=0.215		Pint=0.189		Pint=0.575
<b>Nonsmoker</b>	0.003 (-0.009, 0.016)	0.594	<b>0.102</b> (0.078, 0.125)	<b>&lt;0.001</b>	<b>0.047</b> (0.025, 0.070)	<b>&lt;0.001</b>	<b>0.015</b> (0.001, 0.029)	<b>0.031</b>
<b>Current smoker</b>	0.017 (-0.005, 0.040)	0.131	<b>0.104</b> (0.062, 0.145)	<b>&lt;0.001</b>	<b>0.050</b> (0.012, 0.088)	<b>0.011</b>	0.006 (-0.017, 0.030)	0.596
<b>Pint<sup>a</sup></b>		Pint=0.743		Pint=0.472		Pint=0.465		Pint=0.348
<b>Normotensive</b>	<b>0.016</b> (0.002, 0.031)	<b>0.025</b>	<b>0.095</b> (0.068, 0.121)	<b>&lt;0.001</b>	<b>0.060</b> (0.035, 0.084)	<b>&lt;0.001</b>	0.010 (-0.005, 0.025)	0.177
<b>Hypertensive</b>	-0.005 (-0.023, 0.013)	0.567	<b>0.117</b> (0.084, 0.150)	<b>&lt;0.001</b>	<b>0.034</b> (0.003, 0.065)	<b>0.031</b>	0.014 (-0.006, 0.033)	0.166
<b>Pint<sup>a</sup></b>		Pint=0.342		Pint=0.242		Pint=0.169		Pint=0.102

<sup>a</sup> Pint=p-value for interaction term

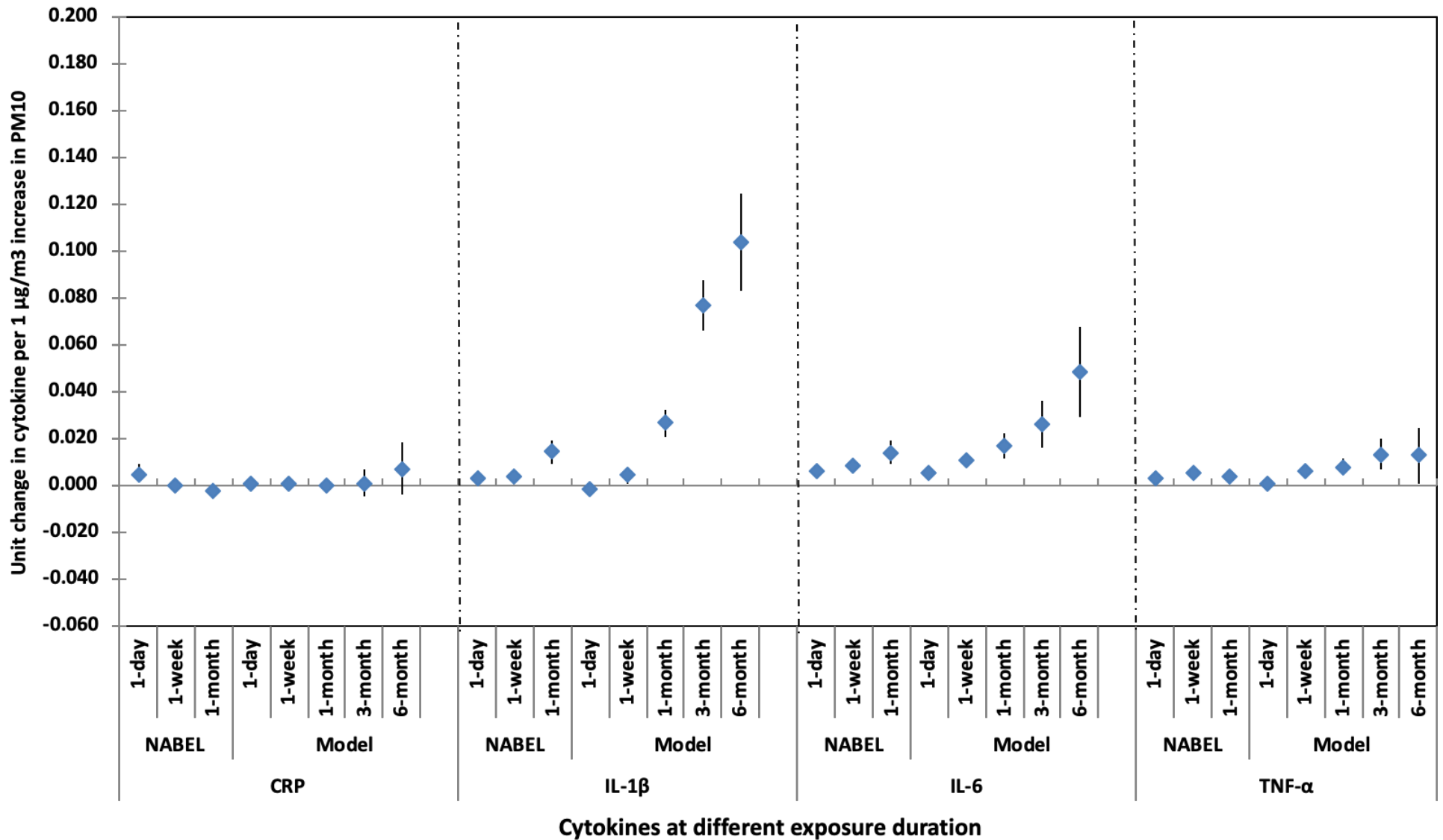


Figure1. Association between exposure to PM10 on short-term and long-term averages from NABEL monitoring stations and Model data. Data are regression coefficients and 95% confidence intervals of mixed models. Cytokine units are  $\mu\text{g}/\text{mL}$  for CRP,  $\text{pg}/\text{mL}$  for the other cytokines. All estimates are adjusted for age, sex, BMI, smoking status, diabetes, hypertension, cold-day ratio, outdoor air pressure, and CoLaus time period.

## Supplementary material

Article title: Effects of short- and long-term exposure to particulate matter on inflammatory marker levels in the general population

Journal name: Environmental Science and Pollution Research

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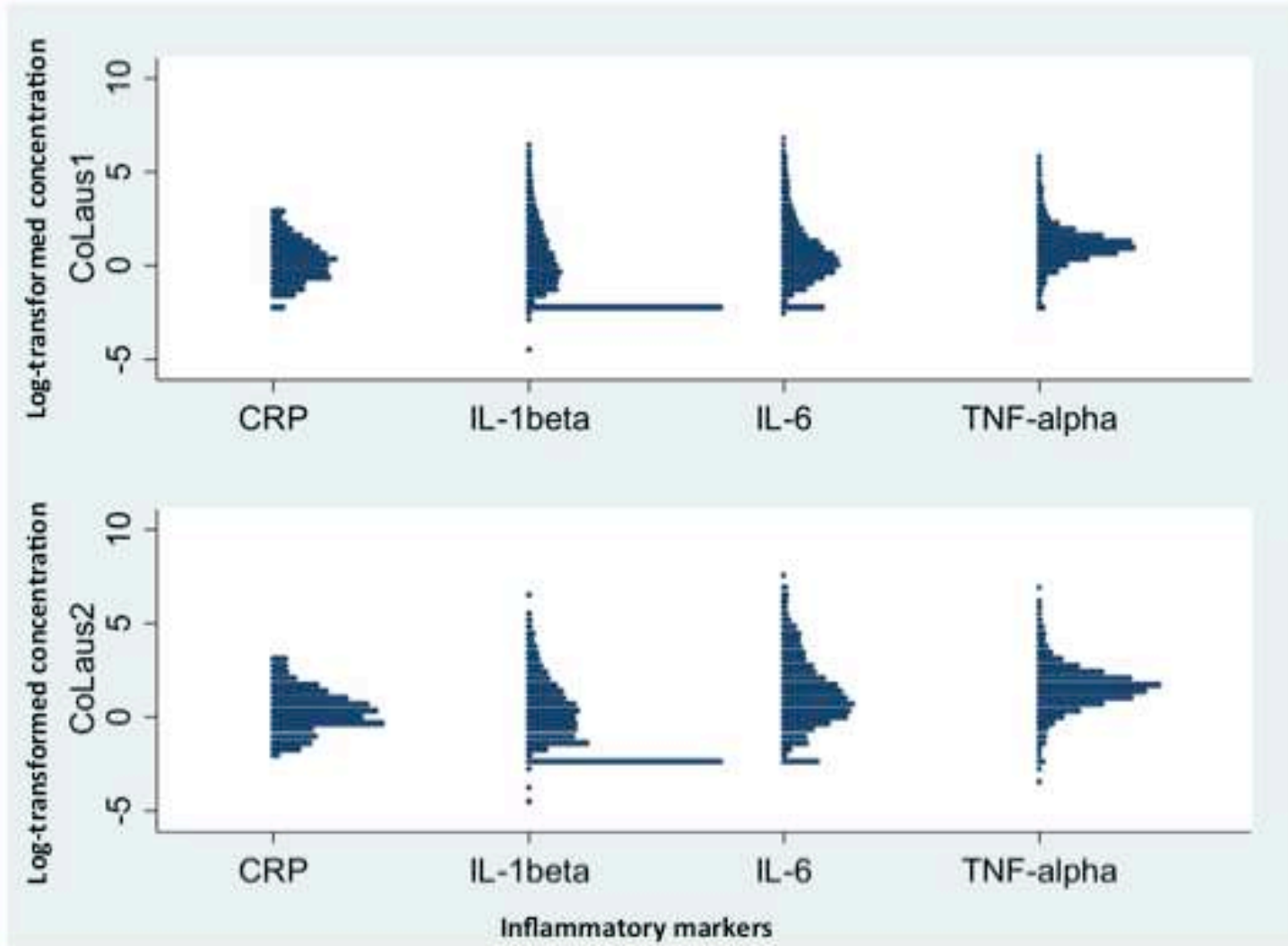


Figure S1. Dot plot of inflammatory markers in CoLaus 1 and CoLaus 2.

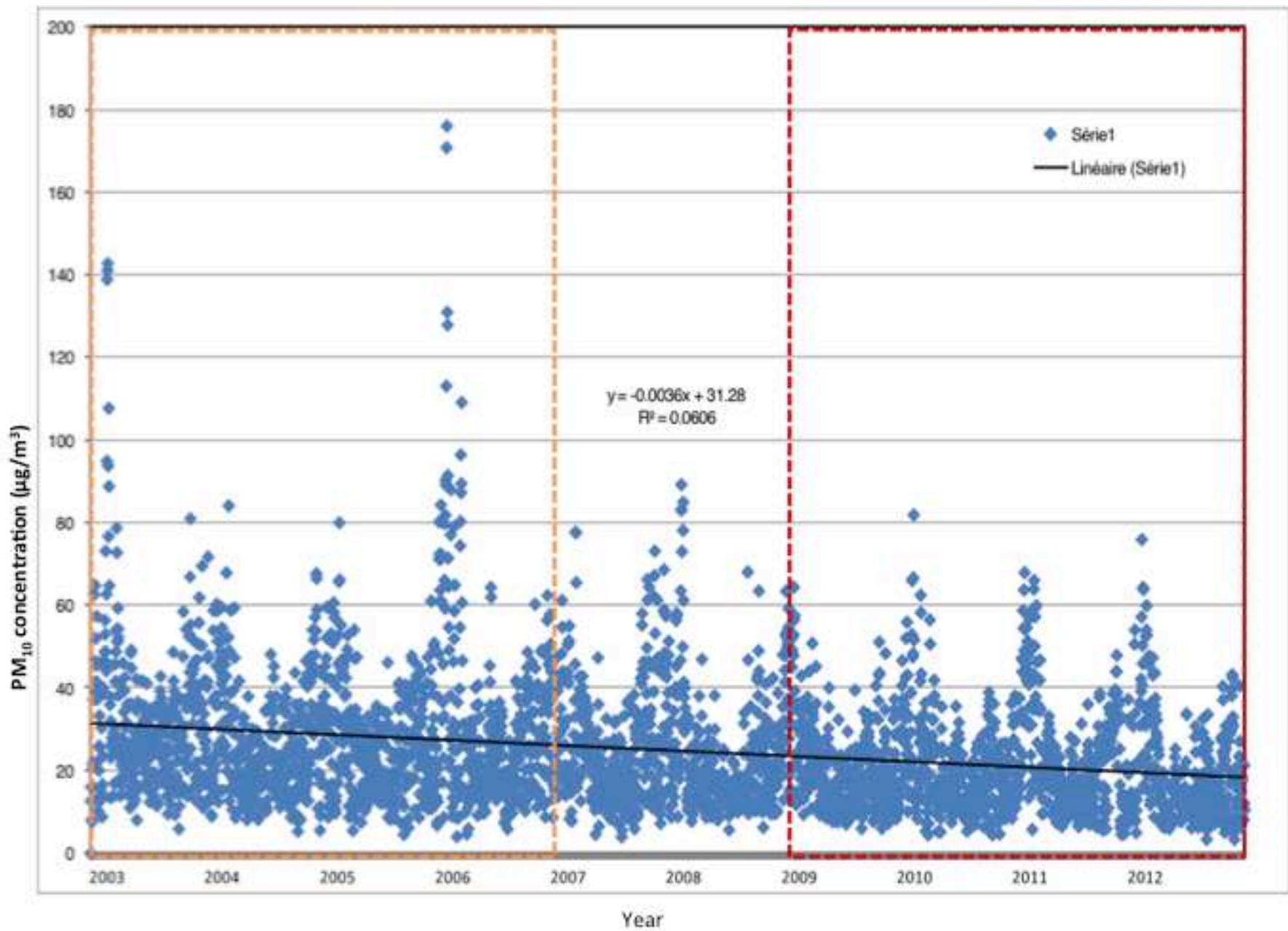


Figure S2. Daily concentrations of PM<sub>10</sub> at César-Roux Station from 2003 to 2012 (CoLaus1 : 2003-2006, CoLaus2 : 2009-2012).

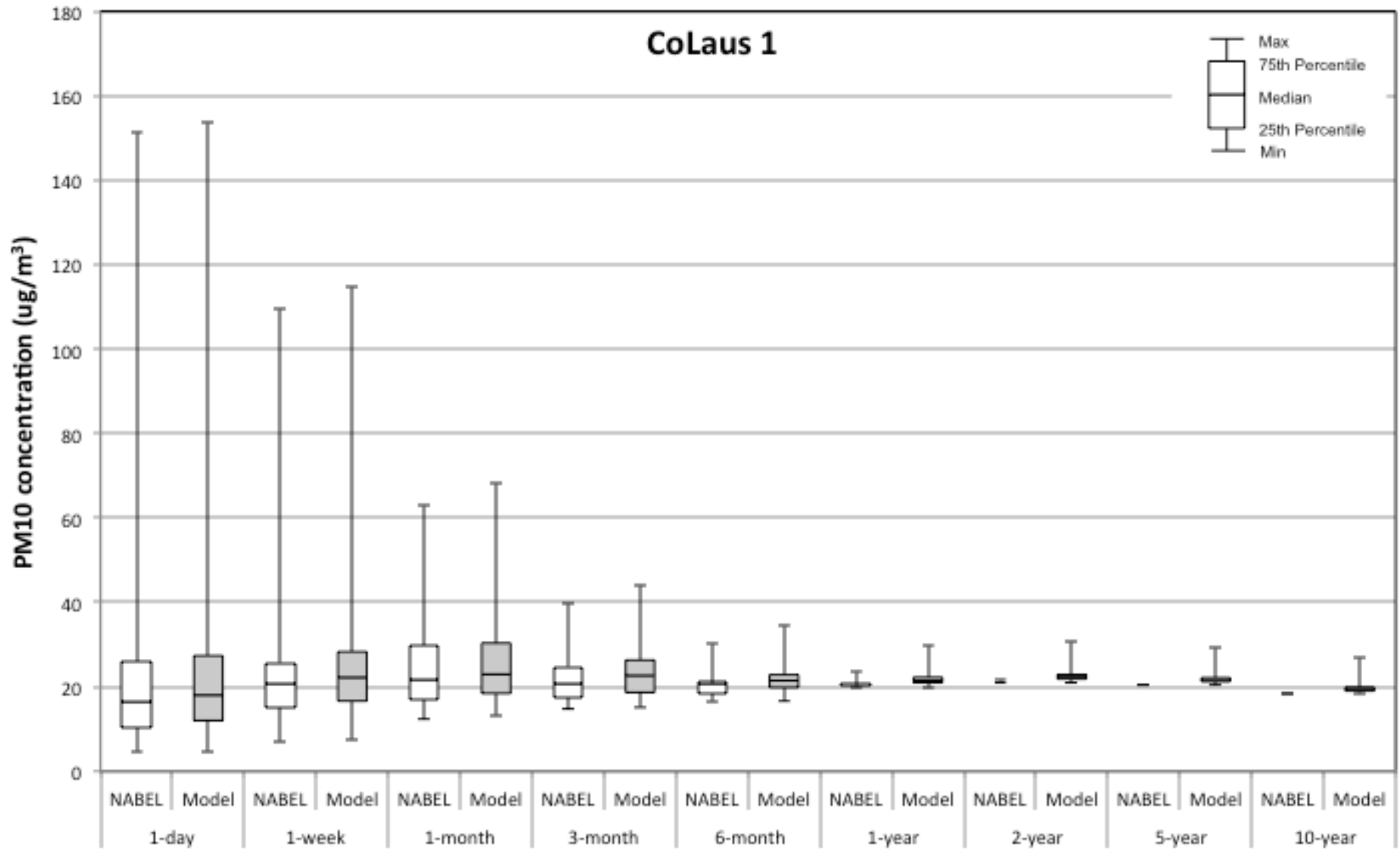


Figure S3. Box plot of different averaging PM10 concentrations of César Roux station and modeled data for CoLaus1.

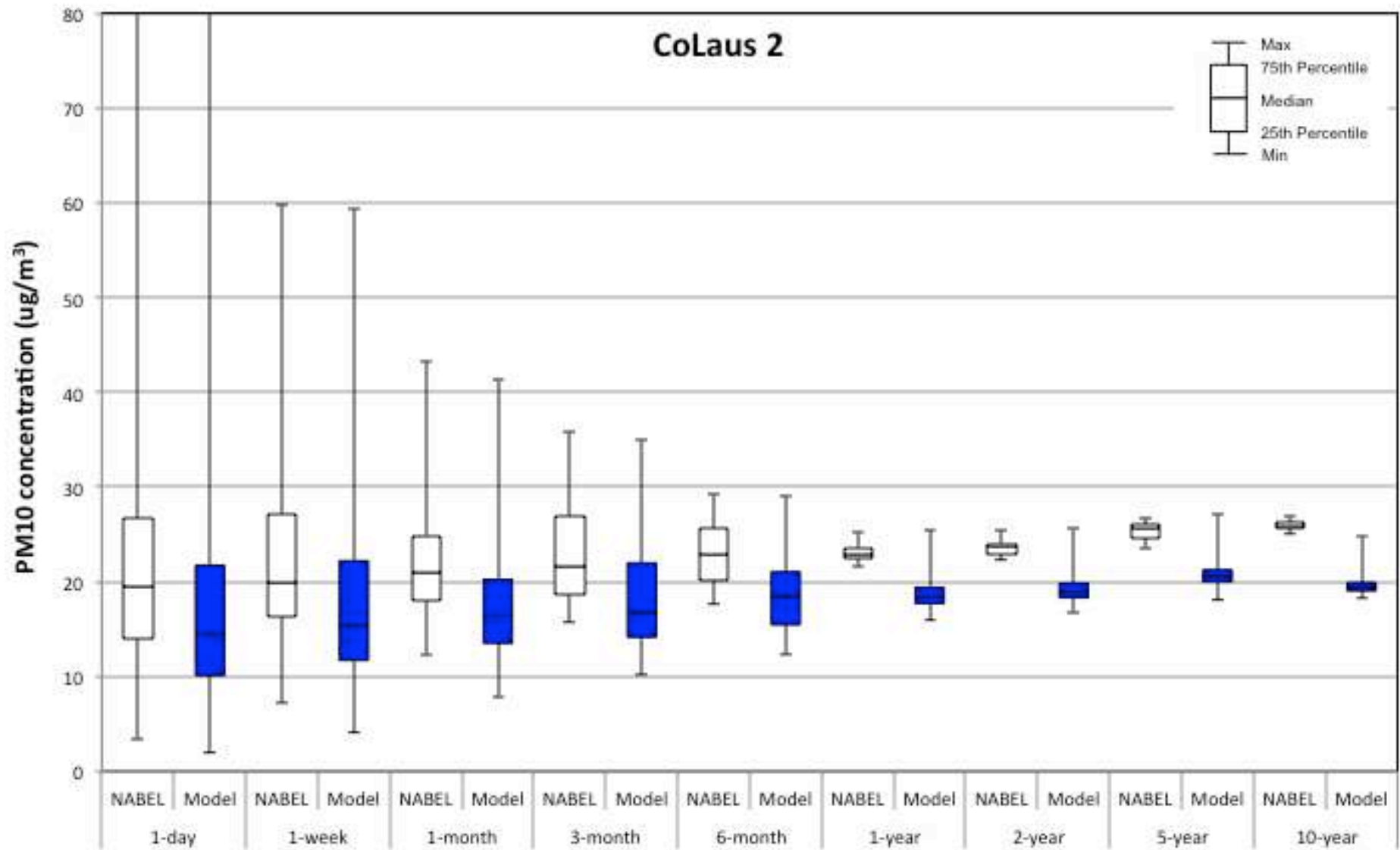


Figure S4. Box plot of different averaging PM10 concentrations of César Roux station and modeled data.

**Table S1. Association of particular matters with elevated inflammatory markers as binary outcomes ( $\geq P75$  vs.  $< P75$ ) (using 0.1 to replace ' $< 0.2$ '), Odds Ratios for every 1  $\mu\text{g}/\text{m}^3$  changes in  $\text{PM}_{10}$ .**

		CRP level $\geq P75^b$		IL-1 $\beta$ level $\geq P75^b$		IL-6 level $\geq P75^b$		TNF- $\alpha$ level $\geq P75^b$	
		Adjusted OR (95% CI)	p- value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<b>NABEL</b>	<b>PM10: daily average</b>	1.002 (0.997, 1.006)	0.426	<b>1.005</b> <b>(1.001, 1.009)</b>	<b>0.010</b>	1.004 (0.999, 1.007)	0.063	<b>1.004</b> <b>(1.001, 1.008)</b>	<b>0.023</b>
	<b>PM10: weekly average</b>	1.004 (0.998, 1.009)	0.178	<b>1.007</b> <b>(1.002, 1.011)</b>	<b>0.009</b>	<b>1.008</b> <b>(1.003, 1.013)</b>	<b>0.001</b>	<b>1.010</b> <b>(1.005, 1.015)</b>	<b>&lt;0.001</b>
	<b>PM10: monthly average</b>	0.999 (0.990, 1.008)	0.867	<b>1.011</b> <b>(1.002, 1.019)</b>	<b>0.011</b>	<b>1.015</b> <b>(1.007, 1.023)</b>	<b>&lt;0.001</b>	0.998 (0.989, 1.006)	0.574
<b>Model</b>	<b>PM10: daily average</b>	1.002 (0.997, 1.008)	0.365	0.997 (0.992, 1.003)	0.319	<b>1.005</b> <b>(1.000, 1.010)</b>	<b>0.043</b>	0.997 (0.992, 1.002)	0.273
	<b>PM10: weekly average</b>	1.005 (0.998, 1.012)	0.165	<b>1.009</b> <b>(1.002, 1.015)</b>	<b>0.007</b>	<b>1.008</b> <b>(1.002, 1.015)</b>	<b>0.010</b>	<b>1.011</b> <b>(1.005, 1.018)</b>	<b>&lt;0.001</b>
	<b>PM10: monthly average</b>	1.005 (0.994, 1.015)	0.357	<b>1.032</b> <b>(1.022, 1.042)</b>	<b>&lt;0.001</b>	<b>1.020</b> <b>(1.010, 1.030)</b>	<b>&lt;0.001</b>	1.010 (0.999, 1.020)	0.054
	<b>PM10: 3-month average</b>	1.003 (0.985, 1.023)	0.728	<b>1.076</b> <b>(1.057, 1.094)</b>	<b>&lt;0.001</b>	<b>1.046</b> <b>(1.028, 1.064)</b>	<b>&lt;0.001</b>	<b>1.049</b> <b>(1.032, 1.068)</b>	<b>&lt;0.001</b>
	<b>PM10: 6-month average</b>	1.003 (0.971, 1.035)	0.871	<b>1.091</b> <b>(1.060, 1.123)</b>	<b>&lt;0.001</b>	<b>1.064</b> <b>(1.033, 1.095)</b>	<b>&lt;0.001</b>	<b>1.066</b> <b>(1.036, 1.096)</b>	<b>&lt;0.001</b>

<sup>a</sup> Adjusted factors: gender, age, BMI, smoking status, diabetes, hypertension, outdoor air temperature, outdoor air pressure and season. <sup>b</sup> Cytokine levels equal to or above the 75<sup>th</sup> percentile were coded as 1, and as 0 otherwise.