

# Distributed lag associations between respiratory illnesses and mortality with suspended particle concentration in Tula, a highly polluted industrial region in Central Mexico

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## Abstract

**Purpose** We aimed to evaluate the association between changes in airborne particulate matter concentration (PM) with changes in cases of mortality, acute respiratory infections (ARI) and asthma over 2004–2008 in an industrialized and polluted region in central Mexico.

**Methods** A generalized linear model with a Poisson distribution and a negative binomial analysis was used to evaluate the influence of PM and temperature on all-cause mortality (All-cause-M), cause-specific mortality (Cause-specific-M), ARI and asthma, using cubic spline functions and distributed lags of PM. Estimated changes in relative

risk were calculated for an exposure corresponding to each increase of  $10 \mu\text{g}/\text{m}^3$  in PM level.

**Results** Associations between PM and mortality and morbidity were statistically most consistent for total suspended particulate (TSP) than for particulate matter  $<10 \mu\text{m}$  aerodynamic diameter ( $\text{PM}_{10}$ ). The greatest effects in mortality were observed with a 3-week lag, and effects were greater for Cause-specific-M. We also found a displacement effect up to 4-week lag for Cause-specific-M and TSP. The greatest effects in morbidity were observed at 0-week lag, yet they were statistically marginal and were greater for asthma. We found a displacement effect at 4–5–6-week lag for asthma and TSP. All associations of mortality and morbidity, expressed as change in relative risk, were greater with  $\text{PM}_{10}$ ; however, all of them were statistically marginal.

**Conclusions** Increased respiratory morbidity and mortality is associated with weekly changes of PM air pollution in the region. A reduction in air pollutants from industrial sources would benefit life quality and health of the exposed population.

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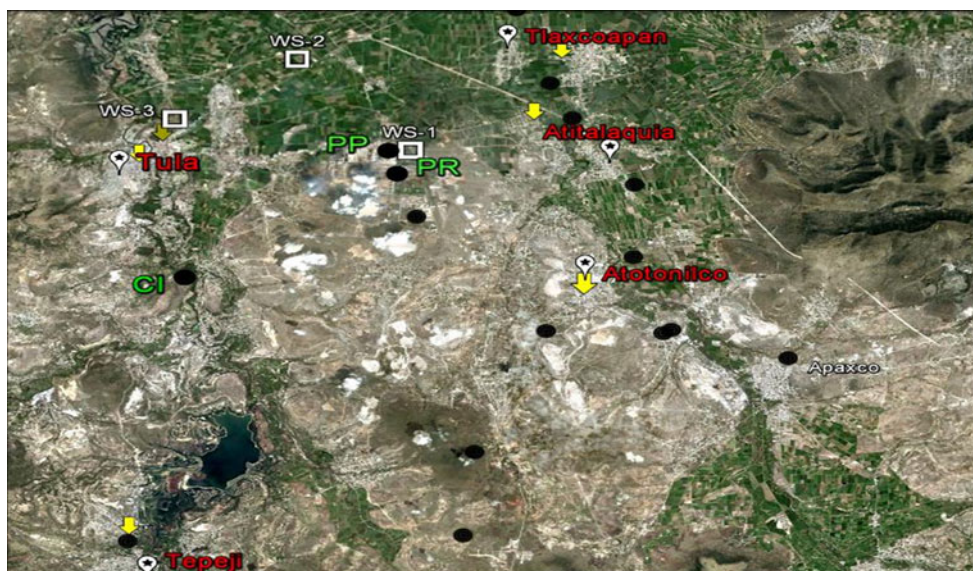
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## Introduction

Tula–Tepeji is a major industrial region located in the state of Hidalgo, northwest of Mexico City's Metropolitan Area, where power plants, an oil refinery and cement factories are located and release large amounts of pollutants into the air. This region is composed of 10 municipalities, of which four, Tula de Allende, Tepeji del Rio, Atotonilco de Tula

**Fig. 1** Tula–Tepeji region. Source Google Earth. Image © 2012. Yellow arrows: air quality monitoring sites (located in each one of the five cities); black circles: industries (energy sector “PP”, oil sector “PR” and cement “CI” and lime sector); white squares: weather stations (WS-1: CFE station, WS-2: National Institute for Forestry, Agriculture and Livestock Station, and WS-3: COEDE Station) and black stars: cities—residential areas (Tula, Tepeji, Tlaxcoapan, Atitalaquia and Atotonilco) (color figure online)



and Atitalaquia, are notable for their major industrial activity (Fig. 1).

In accordance with Mexican environmental regulations, this region is considered critically polluted (NOM-085-SEMARNAT-1994). According to the 2005 Emissions Inventory published by federal environmental authority, the industrial sectors of food and beverage; power generation; iron and steel; cement and lime; and petroleum and petrochemical generated, nationally and globally, account for more than 90 % of annual national emissions of PM<sub>10</sub>, PM<sub>2.5</sub>, SO<sub>2</sub>, CO, NO<sub>x</sub> and NH<sub>3</sub>. In the same year in the Tula–Tepeji region, 272 kttons per year (ktpy) of SO<sub>2</sub>, 35.5 ktty of particulate matter (PM) and 30.8 ktty of NO<sub>x</sub> were released (SEMARNAT 2009), reporting the town of Tula as the second municipality nationwide where the highest amount of pollutants are released, specifically PM and SO<sub>2</sub>, the latter attributed to oil processing (INEM 2005). When comparing the emissions (PM<sub>10</sub>, PM<sub>2.5</sub>, SO<sub>2</sub> and NO<sub>x</sub>) between Hidalgo state industrial area versus Mexico City urban area, important differences among air pollutants can be observed (Fig. 2); higher emissions of PM<sub>10</sub>, PM<sub>2.5</sub> and SO<sub>2</sub> are reported for Hidalgo state due mainly to the power generation, cement and lime and petroleum and petrochemical industries prevailing in the region, whereas in the Mexico City urban area the highest emitted pollutant was NO<sub>x</sub> attributable to mobile sources. The difference in pollutants and sources between a megapolis like Mexico City and the highly industrialized region around Tula less than 100 km from Mexico City emphasizes the importance of conducting studies in the Tula region.

In Tula–Tepeji region in Hidalgo state, the main emitters are the Miguel Hidalgo oil refinery and Francisco Perez Rios power plant. The oil refinery, the largest in

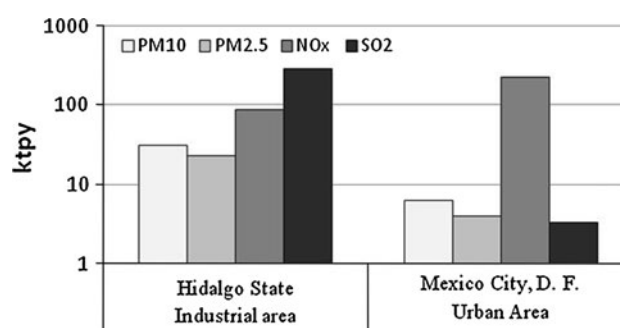


**Fig. 2** Comparison of the emissions in 2005 (ktpy: kilotons per year in logarithmic scale) between Hidalgo State (include Tula–Tepeji region) and the urban area of Mexico City (a highly polluted city)

Mexico (PEMEX 2010), processes 289.5 thousand barrels per day (TBD) of crude oil representing 22 % of the total refining capacity in the country, and this refinery will expand its capacity with additional 300 TBD in 2015. Francisco Perez Rios power plant is the second biggest power plant in the country with a capacity of 2095 Megawatts distributed in nine units combining vapor (fuel oil-based) and combined cycle (based on diesel and natural gas) technologies (CFE 2010). The air quality is poor and pollution sometimes exceeds Mexican Air Quality Standards. Reported evidence suggests that the incidence of respiratory illness (acute respiratory infections and asthma) in the Tula–Tepeji region is higher than in the rest of Hidalgo; in the case of acute respiratory infections, the incidence in the region is higher than in the rest of the country (Secretaría de Salud 2008) and the main municipalities affected are Tula de Allende, Tepeji del Rio, Atotonilco de Tula and Atitalaquia. The population of the Tula–Tepeji region is about 335,000 inhabitants (2005); the largest city in this region is Tula de Allende, which is

located approximately 100 km to the north-northwest of Mexico City. It is also the most populated municipality with a population of 93,296 inhabitants (2005), corresponding to 28.2 % of the population in the region. Tula de Allende also has the largest emissions of criteria pollutants in the region (Beltrán et al. 2008).

The impact of air pollution on human health has been widely studied and reported around the world. The evidence shows that exposure to ambient air pollution as well as short-term weather conditions may cause respiratory illnesses in the general population (Schwartz and Dockery 1992a, b; Schwartz and Marcus 1990). Some studies have also shown positive associations of air pollution with mortality, using distributed lag models with an effect noted through 40 days after exposure (Goodman et al. 2004; Zanobetti et al. 2003) and those that use single lags between 1 and 5 days (Cakmak et al. 2007; Welty and Zeger 2005).

In the 1990s, several studies evaluated the association between air pollutants and health effects, stimulated by findings of an annual increase in the number of days that exceeded the maximum permissible limits established by International and Mexican Air Quality Standards (Sánchez et al. 1991).

Population studies of mortality in adults and children (general, cardiovascular and respiratory illnesses) (Borja-Aburto et al. 1997a, b; Loomis et al. 1999), adverse effects on children's respiratory systems (Romieu et al. 1992), asthmatic children (acute inflammation) and school-age children (Barraza-Villarreal et al. 2008; Carbajal-Arroyo et al. 2011; Hernandez-Cadena et al. 2007; Rojas-Martinez et al. 2007; Romieu et al. 1995, 1996) found an association between mortality, morbidity and the concentration of ozone and particulate matter  $<10 \mu\text{M}$  aerodynamic diameter ( $\text{PM}_{10}$ ) and particulate matter  $<2.5 \mu\text{M}$  aerodynamic diameter ( $\text{PM}_{2.5}$ ) in Mexico City and in the border city of Ciudad Juarez, Chihuahua, Mexico. Most of the studies conducted in Mexico have focused primarily on health problems and air pollution in major metropolitan areas, either in the metropolitan area of Mexico City or the border city of Ciudad Juarez. No epidemiological or scientific studies of the impact of air pollutants in exposed populations have been published for other regions of the country, especially those considered to have critically high amounts of emissions from industrial activities or for regions where there are oil refineries and power plants, such as the Tula–Tepeji region. In addition, most of the previous studies have only considered health effects on the same day or a few days after the high air pollution event, while in this study, we report effects several weeks after exposure.

The goal of this study was to examine the associations between changes in total suspended particulate (TSP) and  $\text{PM}_{10}$  levels in the air and changes in weekly cases of

all-cause mortality (All-cause-M) and mortality related to the sum of respiratory illnesses, ischemic heart disease and cerebrovascular diseases (Cause-specific-M) as well as changes in weekly cases of acute respiratory infections (ARI) and asthma during the 2004–2008 period in the Tula–Tepeji region. We used generalized linear models with Poisson and negative binomial distributions to evaluate the influence of weekly PM concentrations and minimum temperature on All-cause-M, Cause-specific-M, ARI and asthma. We analyzed PM time series with a fast fourier transformation (FFT) to plot the frequency power spectrum in the series used in the models in order to explain the displacement effects due to results indicating that the estimated associations were two or three times larger for the extended 6-week follow-up period than for the acute effects as would be measured with daily PM measurements and daily mortality and morbidity.

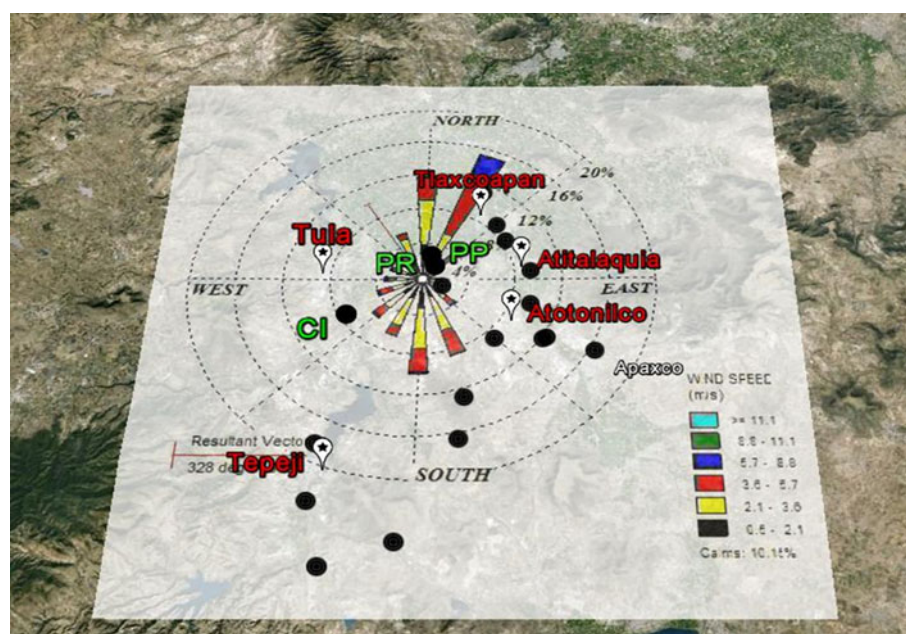
Results are expressed as the percentage of change in relative risk (% increase RR) in the outcome associated with each  $10 \mu\text{g}/\text{m}^3$  increase in PM pollution over the weekly lag periods.

## Materials and methods

### Particulate matter data

Air pollution data were obtained from the State Council of Ecology (COEDE, Spanish acronym) of Hidalgo, and data were validated by the National Center of Environmental Research and Training (CENICA, Spanish acronym) from the National Institute of Ecology (INE, Spanish acronym). In this region, as in many others in economically developing countries, the manual monitoring network measures TSP and  $\text{PM}_{10}$  1 day every 6 days. For this study, the data were obtained over the years from 2004 to 2008 (a total of 260 weeks). TSP and  $\text{PM}_{10}$  were measured using reference methods for HiVol Particulate Collection Systems (NOM-CCAM-002-ECOL 1993; USEPA 1990), as designated by the United States Environmental Protection Agency. The TSP and  $\text{PM}_{10}$  data from 6-day intervals were transformed to weekly-average (arithmetic mean) concentrations in those weeks where two measurements were recorded. The COEDE site is located at  $20^{\circ}3'38.90''$  North and  $99^{\circ}20'12.26''$  West, 6 km to the west of the main industries (an oil refinery and power plants). Meteorological data for year 2005 were considered for this study. Since winds at Tula predominantly blew from the N (12 %) and NNE (15 %), toward rather than from the primary sources of particulates, particulate exposure in Tula may represent a lower conservative bound to exposure in other cities of the region, where predominant winds favor particulate transport from the sources to those cities. The TSP monitors

**Fig. 3** Wind Rose for Tula–Tepeji region, 2005. WRPLOT View<sup>®</sup> *Black circles:* industries (energy sector “PP”, oil sector “PR” and cement “CI” and lime sector); and *black stars:* cities—residential areas (Tula, Tepeji, Tlaxcoapan, Atitalaquia and Atotonilco)



located in Tlaxcoapan, Atitalaquia and Atotonilco measured the highest TSP levels with winds blowing from the S and W, unfortunately the TSP and  $PM_{10}$  records for these three cities were sparse and not sufficient to be considered in the analysis of this study (Fig. 3).

#### Temperature data

The weather station of the Federal Commission of Electricity (CFE, Spanish acronym) located in Tula, Hidalgo, provided daily (24 h average) temperature data for the same period (2004–2008). We arranged the daily data into maximum and minimum weekly temperatures to match epidemiological weeks (Sunday to Saturday) for respiratory illness and mortality reports. Missing temperature values from the CFE site ( $20^{\circ}2'9.48''$  North and  $99^{\circ}17'2.30''$  West) were supplemented with data from the weather station located at the COEDE site, and from the weather station of the National Institute for Forestry, Agriculture and Livestock (INIFAP, Spanish acronym) located at  $20^{\circ}5'27.00''$  North and  $99^{\circ}18'2.00''$  West, which is located 6.3 km from the CFE site. CFE site is located in the power plant facility and very close to the oil refinery. In this analysis, we did not include relative humidity data because data were sparse.

#### Health data

The Ministry of Health of the State of Hidalgo and the Federal Commission for Protection against Health Risks (COFEPRIS, Spanish acronym) provided epidemiological respiratory illness records. The respiratory illness data were

obtained from the clinical records of different public health centers belonging to the health jurisdiction of Tula and were coded using the International Classification of Diseases version 10 (ICD-10).

Data were obtained from the Single Automated System for Monitoring Epidemiological (SUAVE, Spanish acronym), which is software to gather, validate and analyze the morbidity subject to epidemiological surveillance within the new-cases notification weekly subsystem. SUAVE currently provides total coverage of the medical units of the health sector in the country, since SUAVE includes data from SSA, IMSS, ISSSTE, PEMEX, DIF, INI, SEDENA and SEMAR (all government medical facilities) as well as some private medical services (SS 2008). The epidemiological data consisted of weekly number of new cases (counts of illness in outpatients and emergency room visits at health centers and regional hospitals) of acute respiratory infections (ICD-10: J00–J06, J20, J21, except J02.0 and J03.0), and asthma (ICD-10: J45, J46), covering a period of 5 years (2004–2008). Subsequently, non-acute cases are not taken into account for registration in weekly reporting (SINAVE 2006). Mortality data were obtained from the National Health Information website (<http://www.sinais.salud.gob.mx/>). We considered two types of mortality data, (a) all-cause mortality and (b) the sum of mortality events (cause-specific mortality), related to respiratory illnesses (ICD-10: A-15, A-16, H65.0–H65.1, J02.0, J03.0, J00–J06, J20, J21 except J02.0 and J03.0, J12–J18 except J18.2, J45 and J46), ischemic heart diseases (ICD-10: I20–I25) and cerebrovascular diseases (ICD-10: I60–I67, I69) combined, over the years from 2004 to 2008 in Tula. We summed those three diseases because the occurrence of each disease was

low. We chose those types of illnesses because they are related to air pollution, although the mechanisms by which these illnesses affect humans are different.

### Statistical methods

Generalized linear models (GLM) with parametric splines (e.g., natural cubic splines) (McCullagh and Nelder 1989) were used to estimate the effects associated with exposure to air pollution while accounting for smooth seasonal fluctuations in morbidity or mortality that may confound estimates of the pollution effect. Taking into account that the natural stochastic model for counts is a Poisson point process for the occurrence of the event of interest, which implies a Poisson distribution for the number of occurrences of the event, we used GLM with a Poisson distribution and a negative binomial regression model when the variance was significantly larger than the mean (overdispersion). A typical issue considered in time-series data analysis is the autocorrelation of the series residuals; we used the cubic spline functions to account for the seasonal variations of the count data (morbidity and mortality), which in turn solved the problem of residual autocorrelation.

GLM with Poisson distributions were applied to assess the quantitative association between mortality (All-cause-M and Cause-specific-M) and pollutant concentration levels, and negative binomials were used to assess the quantitative association between disease incidence (ARI and asthma) and pollutant concentration levels, according to the model diagnostic indications. We considered minimum temperature to be a confounding variable, and we additionally adjusted the models with the estimated exposed population week by week. We used a polynomial regression to interpolate the population of the study area during the period of interest (2004–2008) to take into account historical population trends based on population data from 1990 to 2005, from the every 5-year points given by the national census of the region, the population size was 91,539 inhabitants (at week 1, 2004) at the start of the mortality series and 103,768 inhabitants (at week 52, 2008) at the end of the series, smoothly increasing over the interval. We estimated the average exposed population to be 96,381.89 (95 % CI 95977.44, 96786.35) inhabitants per week. In addition, we took into account different model assumptions and controlled for the following: (a) the use of cubic spline functions, for mortality and morbidity data, in the regression analysis to smooth and seasonally adjust the model (Royston and Sauerbrei 2007; Sasieni 1994), fitting the spline function to the original mortality and morbidity series, models effectively measure the effect of particulates on departures from these seasonal influences (b) the use of orthogonal distributed lag models to verify the influence of exposure over many previous weeks on outcomes, avoiding

multi-collinearity or correlated covariates (Dear et al. 2005) with orthogonal third-degree polynomials with up to 6 weeks of lag, allowing weekly mortality and morbidity to be influenced by air pollution and temperature over the previous 40 days (Goodman et al. 2004; Zanobetti et al. 2003). This approach is based on the concept that exposure to air pollution may produce an increased risk of mortality/morbidity on the day of exposure, for subsequent days or possibly many days after exposure. (c) We first tested a GLM with a Poisson distribution for goodness of fit; failure of goodness of fit was followed up with a negative binomial model with verification that the  $\ln(\alpha)$  parameter was significantly above 0 (score test) to confirm overdispersion. (d) We diagnosed possible serial correlations of model residuals with the autocorrelation function. (e) We used robust standard errors to adjust for residual heterogeneity in the model. (f) We plotted histograms of the residuals showing a symmetrical distribution around zero. (g) We analyzed the association of PM with mortality and morbidity using both linear and logarithmic particulates while controlling for both linear and logarithmic minimum temperature and compared model results with the Akaike Information Criterion (AIC) to select the best-fitting characterizations of these variables (detailed results not shown). (h) We used a FFT analysis to plot the frequency histogram of power in the PM series used in the models.

### Sensitivity testing

To date, the assessment of public health consequences of air pollution focuses on a multi-pollutant approach aimed to estimate the increased risk of adverse health outcomes associated with the exposure to several air pollutants and incorporate the chemical composition of fine and coarse particles into the analysis. We were unable to use measures of ozone ( $O_3$ ),  $SO_2$  and  $NO_x$  in this study since there was an excess of missing data for those measures for the 2004–2008 period. However, to assess the influence of these pollutant gases, we used a short period from week 23 of 2006 to week 34 of 2007 (64 weeks in total with the most complete gas pollutant data) in sensitivity testing in order to evaluate the association between multi-pollutants (TSP or  $PM_{10}$  with  $O_3$  and  $NO_x$ ) and mortality and morbidity using a distributed lag model and a GLM with a Poisson distribution. The inclusion of both gases ( $NO_x$  and  $O_3$ ) in the models did not substantially change the results of the % RR. However, there were insufficient observations to model  $PM_{10}$  and the two gases for mortality (All-cause-M and Cause-specific-M), ARI and asthma. Though the power of the models with gases was very low because of incomplete data, the same temporal patterns of the association of morbidity and mortality with PM alone and PM

with gases suggest that the inclusion of gases, while possibly affecting the size of the morbidity and mortality effects, did not materially affect the main body of the results with PM, as described in the PM-alone minimum temperature models.

We expressed the effect as the percentage of change in relative risk (% increase in RR) in the outcome associated with each  $10 \mu\text{g}/\text{m}^3$  increase in PM pollution over the lag period. Data management and statistical procedures were performed with Stata version 11.1 (StataCorp, College Station, TX, USA).

## Results

### Descriptive statistics

Table 1 shows descriptive statistics for all variables included in the analysis. Of the total number of cases recorded for the entire period of analysis (2004–2008), there were 267,911 cases of ARI, 2,672 cases of asthma, 5,120 cases of All-cause-M and 933 cases of Cause-specific-M. From the total number of Cause-specific-M, we found 14 % for respiratory illnesses, 51 % for ischemic heart disease and 35 % for cerebrovascular diseases. The table also shows the weekly minimum, maximum, mean and standard deviation for each outcome.

We plotted the observations (disease incidence, mortality data, and minimum temperature and air pollution concentration levels) against time to visualize variable changes over time (Fig. 4). The data appeared to fluctuate over time in a pattern. For that analysis, we assumed that the main sources of variation were the trend, seasonality, outliers, discontinuous and shorter cyclic changes in the series (Chatfield 2004). We noted the yearly variations for

each of the variables analyzed (ARI, asthma, All-cause-M, Cause-specific-M, TSP,  $\text{PM}_{10}$  and temperature).

Particulate emissions in the Tula–Tepeji region increased over the period of 2002–2005 from 17.16 ktpy in 2002 (SEMARNAT 2006) to 35.5 ktpy in 2005 (SEMARNAT 2009). In 2002, we observed 5,449 cases of ARI per 10,000 inhabitants and a weekly average of 927 cases of ARI, while in 2005, the number of annual cases of ARI was 6,334 cases per 10,000 inhabitants with a weekly average of 1,136 cases, representing an increase of 16.24 % in population-adjusted cases. In accordance with the Mexican emission inventory (SEMARNAT 2009), the main contributions to PM emissions in the region were the power generation industry and the petroleum and petrochemical industry, followed by the cement and lime industries.

### Mortality models

Figure 5 presents the results from the Poisson regression model for estimating the relationship between All-cause-M and Cause-specific-M and changes in the TSP and  $\text{PM}_{10}$  concentrations. The results show (Fig. 5) that All-cause-M increased 0.4 % RR (95 % CI 0.0, 0.9) with a 3-week lag with an increasing trend from 0- to 2-week lag, although not statistically significant and that Cause-specific-M increased 1.3 % RR (95 % CI 0.2, 2.5) with a 3-week lag and 1.4 % RR (95 % CI 0.2, 2.7) with a 4-week lag, per each increase of  $10 \mu\text{g}/\text{m}^3$  in TSP levels. The Cause-specific-M trend increased from 0 to 4-week lag and then decreased.

With an increase of  $10 \mu\text{g}/\text{m}^3$  in  $\text{PM}_{10}$ , the Cause-specific-M increased marginally by 1.9 % RR (95 % CI –0.3, 4.2) with 3-week lag, and an increasing trend from 0- to 2-week lag, with the highest value at 2-week lag but

**Table 1** Descriptive statistics for all variables in the analysis, 2004–2008

| Variables                                 | Unit                     | Weeks | Min  | Max    | Mean    | SD    | Total cases | Exceed NOM 24 h <sup>b</sup> | Exceed NOM annual <sup>c</sup> |
|-------------------------------------------|--------------------------|-------|------|--------|---------|-------|-------------|------------------------------|--------------------------------|
| ARI                                       | Cases                    | 260   | 420  | 1,892  | 1,030.4 | 307.1 | 267,911     |                              |                                |
| Asthma                                    | Cases                    | 259   | 1    | 26     | 10.3    | 5     | 2,672       |                              |                                |
| All-cause mortality                       | Cases                    | 260   | 6    | 42     | 19.7    | 5.3   | 5,120       |                              |                                |
| Specific causes of mortality <sup>a</sup> | Cases                    | 260   | 0    | 10     | 3.6     | 1.8   | 933         |                              |                                |
| TSP                                       | $\mu\text{g}/\text{m}^3$ | 158   | 14.3 | 293.28 | 86.25   | 44.7  |             | 1 Time                       | (n.a.)                         |
| $\text{PM}_{10}$                          | $\mu\text{g}/\text{m}^3$ | 161   | 3.4  | 159.15 | 34.08   | 23.91 |             | 3 Times                      | 24 Times                       |
| $T_{\min}$                                | °C                       | 234   | –3.8 | 13.1   | 7.27    | 3.94  |             |                              |                                |

ARI acute respiratory infections, TSP total suspended particulate,  $\text{PM}_{10}$  particulate matter < 10  $\mu\text{M}$  aerodynamic diameter,  $T_{\min}$  minimum temperature, Weeks number of weekly records, Min minimum, Max maximum, SD Standard Deviation, NOM mexican air quality standard for TSP and  $\text{PM}_{10}$  (NOM-025-SSA1-1993 amended: 24 h average and annual), n.a. not applicable

<sup>a</sup> Sum of respiratory, cardiovascular and cerebrovascular diseases

<sup>b</sup> NOM-025-SSA1-1993 amended for  $\text{PM}_{10}$  24 h average:  $120 \mu\text{g}/\text{m}^3$  and NOM TSP 24 h average:  $210 \mu\text{g}/\text{m}^3$

<sup>c</sup> NOM-025-SSA1-1993 amended for  $\text{PM}_{10}$  annual:  $50 \mu\text{g}/\text{m}^3$

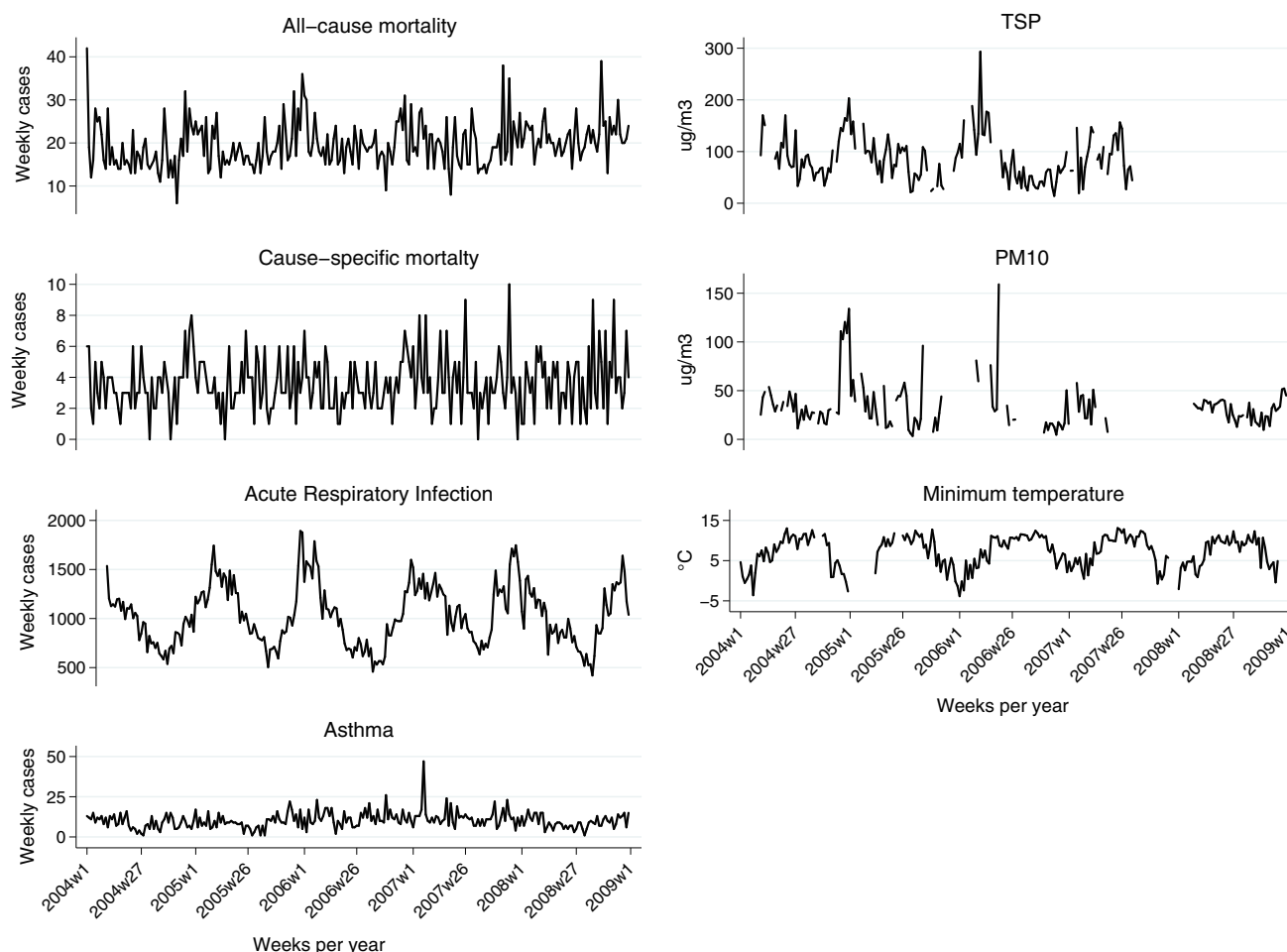


**Fig. 4** Time-series plot for mortality data (all-cause mortality and cause-specific mortality), disease incidence (acute respiratory infection and asthma), TSP (total suspended particulate), PM<sub>10</sub> (particulate

matter < 10 µm aerodynamic diameter) and minimum temperature in order to visualize variable changes over time

without statistical significance and then a subsequent decrease in relative risk; and the All-cause-M increased marginally by 1.0 % RR (95 % CI -0.4, 2.5), with a 3-week lag in both cases, with the trend behavior similar to the one presented for TSP.

#### Morbidity models

We used the negative binomial model to evaluate the association between respiratory illnesses and pollution since the distribution of acute respiratory infections and asthma data displayed signs of overdispersion, measured by a significant dispersion coefficient (log-alpha). Results indicate that ARI increased 0.6 % RR (95 % CI -0.1, 1.3) with a 0-week lag and at lag-weeks 4, 5 and 6 [0.2 % RR (95 % CI -0.1, 0.6), 0.3 % RR (95 % CI 1.0, 0.6) and 0.1 % RR (95 % CI 0.0, 0.3), respectively] after TSP levels increased 10 µg/m<sup>3</sup>, with an increasing trend from 1- to 5-week lag, and the highest value at the 5-week lag and then the elevation in relative risk decreased. Asthma

increased marginally by 1.4 % RR (95 % CI -0.5, 3.3) at the 0-week lag and at lag-weeks 4, 5 and 6 [1.1 % RR (95 % CI 0.2, 2.0), 1.1 % RR (95 % CI 0.2, 1.9) and 0.5 % RR (95 % CI 0.1, 0.8), respectively] after each increase of 10 µg/m<sup>3</sup> in TSP levels and with the same time trend seen with TSP and ARI (Fig. 6). Both ARI and asthma increased marginally by 1.1 % RR (95 % CI -0.2, 2.4) and 3.0 % RR (95 % CI -1.0, 7.2), respectively, at the 0-week lag (Fig. 6) after each increase of 10 µg/m<sup>3</sup> in PM<sub>10</sub> levels. In the first case, trend behavior is similar to the one presented for TSP but without statistical significance. In the case of asthma and TSP the highest, though non-significant %RR was with 0-week lag, decreasing throughout lags 1 and 2 weeks and remained stable thereafter.

#### Fast fourier transformation (FFT) analysis

We used FFT analysis to plot a frequency power spectrum in the PM series used only in the morbidity models. We observed power frequency peaks between 4 and 8 weeks in

**Fig. 5** The effect of changes in the TSP and PM<sub>10</sub> concentrations on mortality (all-cause and cause-specific mortality), expressed as % increase in RR (95 % CI confidence interval). Fitted models were selected based on AIC values. All models were adjusted for natural log-minimum temperature (lnT)

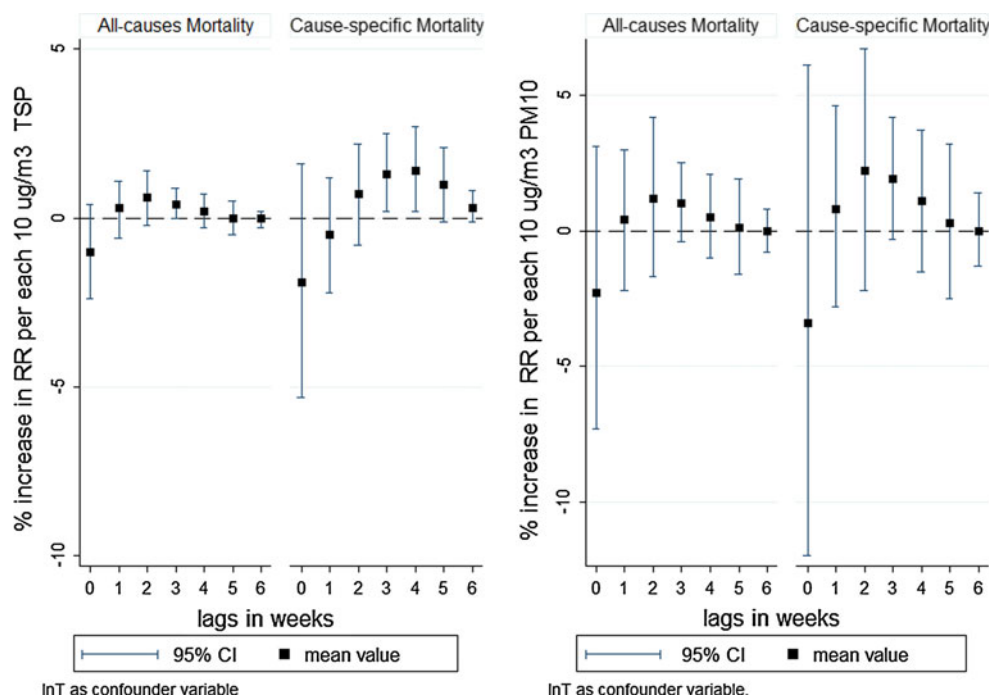
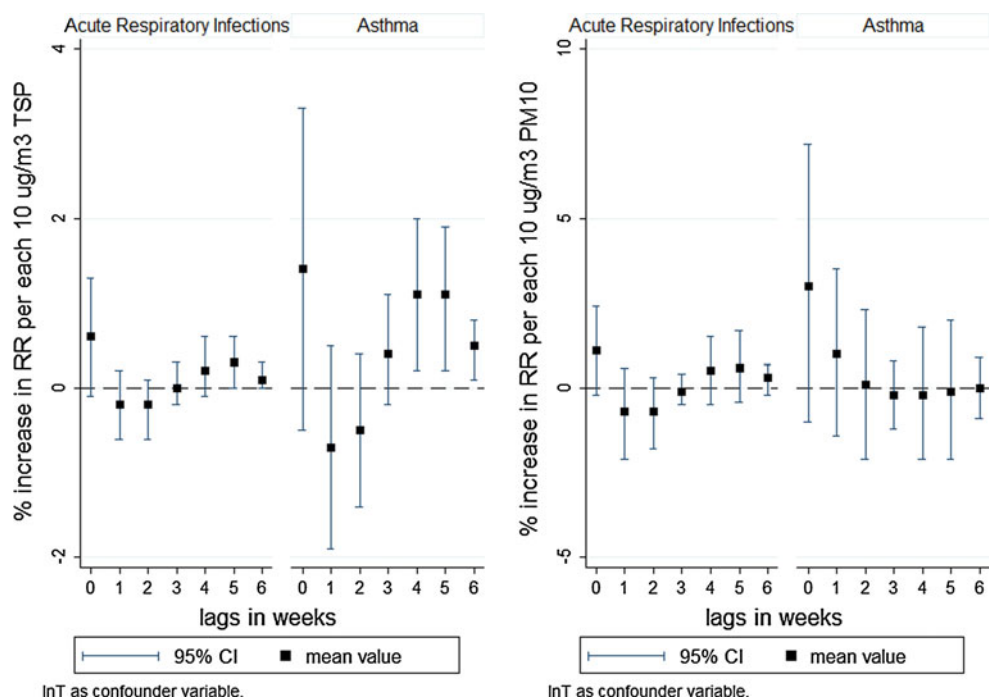


**Fig. 6** The effect of changes in the TSP and PM<sub>10</sub> concentrations on morbidity (ARI and asthma), expressed as % increase in RR (95 % CI confidence interval). Fitted models were selected based on AIC values. All models were adjusted for natural log-minimum temperature (lnT)



the PM<sub>10</sub> series (Fig. 7a) and 6–9 weeks in the TSP series (Fig. 7b).

#### Temperature association

There were no differences in the analysis when temperature was included with its original values (T) or values

transformed to natural logarithm of temperature (lnT). The values of % RR are similar in both cases. In Figs. 5 and 6, we report the values of % RR resulting from the model that included lnT. When we analyzed the models (Poisson model and negative binomial model) between morbidity and mortality with particulate matter including maximum temperature as a confounder variable, no association was observed.

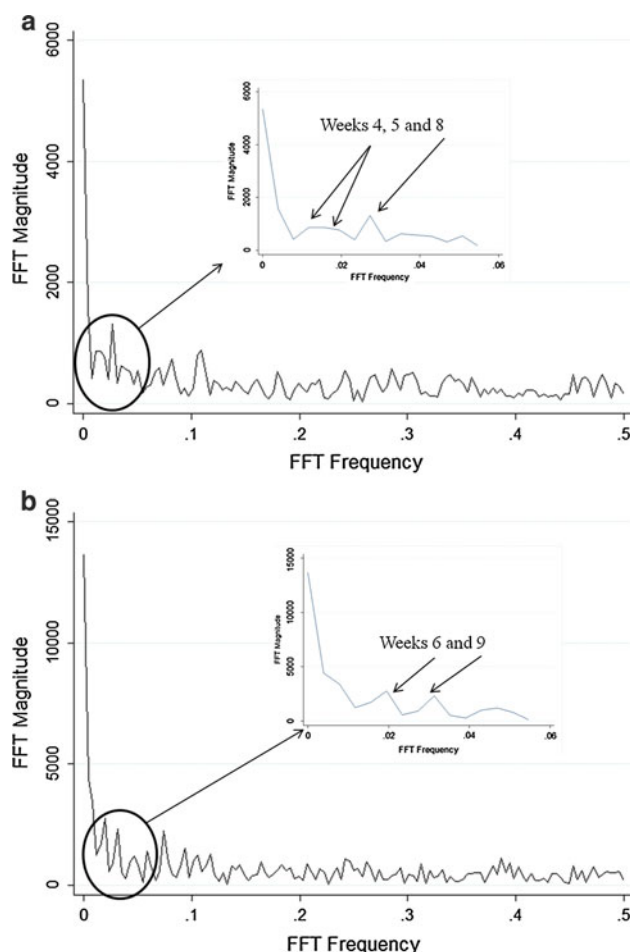


**Fig. 7** **a, b** Fast fourier transform (FFT) for the PM<sub>10</sub> and TSP series. Note the secondary peaks in spectral power between 4 and 9 weeks, suggesting that some part of the significant lag associations beyond 3 weeks found in this study may be due to the cyclical pattern of particulate emissions in this zone

## Discussion

This study shows that in Tula–Tepeji region, PM concentrations and morbidity and mortality were very likely to be higher during winter and in early spring over period 2004–2008. Moreover, there were statistically significant associations between PM and epidemiological variables, the maximum effect in mortality occurred 3 weeks after the PM concentration increase and for morbidity the maximum effect was at 0-week lag, but also re-appeared at 4-, 5- and 6-week lag.

We had to aggregate particulate data into weekly values or averages due to the 6-day measurement routine practiced in the Tula–Tepeji region, similar to particulate measurement schemes in many economically developing countries. In addition to forcing the aggregation of mortality and morbidity cases into weekly averages, thus not permitting analyses on the scale of days as in many recent studies, the

procedure left open the possibility that in some weeks the critical increases or decreases of measured PM actually occurred after most of the illnesses or deaths for that week had already occurred. In other words, this study was carried out considering 6-day interval data transformed to weekly average. Uncertainties of up to  $\pm 3$  days in the period in which atmospheric pollutants occurred and impacted morbidity and mortality were unavoidable. However, weekly analysis allowed the estimation of short-term effects since the effects were accounted for in the first week covered from day 0 to 7. Thus, it was possible to evaluate the short-term effects although we could not discern if the event occurred on the day of particulate measurement or within  $\pm 3$  days.

The statistical model applied in this study was not affected by weekly data, since the data complied with the model assumptions: there were count data and positive numbers, there was no autocorrelation of the series residuals, and the residuals showed a symmetrical distribution around zero, which also minimized heteroscedasticity of the residuals. Moreover, this study established the need to have daily records of diseases and daily records of criteria pollutants in the Tula–Tepeji region for a better understanding of the immediate impact of air pollutants on health for effective environmental management. Also, the advantage of conducting weekly studies is that it was possible to demonstrate that in long-term exposure analysis, we can detect positive and statistically significant effects on morbidity and mortality. Since previous daily studies (Goodman et al. 2004; Zanobetti et al. 2003) as well this weekly study demonstrated significant effects of particulates up to 40 days from the particulate event, subsequent studies should expand the search for delayed effects up to at least this range of lags.

The small number of weekly events limited statistical analysis, especially for asthma and specific cause of mortality and prevented a more detailed analysis by age or gender groups, by season or by each specific cause of mortality or other respiratory illnesses (pneumonia or bronchitis). Study power was also limited by the relatively small number of weeks available for analysis. The ability to detect small %RR as significant at any criterion level would increase if we had a larger number of time periods.

Results suggested that an increase of 10  $\mu\text{g}/\text{m}^3$  in air PM levels increased the relative risk for mortality (All-cause-M and Cause-specific-M) with a substantial lag effect. The increase in relative risk was significantly associated with TSP and marginally associated with PM<sub>10</sub>. In both cases, the maximum elevation in mortality occurred 3 weeks after the PM concentration increase. We also found a different pattern of mortality risk over time because the magnitude of effects for mortality (All-cause-M and Cause-specific-M) and air pollution (PM<sub>10</sub> and TSP) increased from 1 to 3

weekly lags. It is likely that exposure to air pollution simultaneously increases the number of people who become frail or exacerbates pre-existing respiratory diseases, resulting in death several weeks later. These associations in the statistical models were not affected by the inclusion of minimum temperature data. Since the seasonal variation in mortality and morbidity tracked well with temperature, the inclusion of the spline function to track overall changes in mortality and morbidity likely reduced the impact of the temperature variable on outcomes. Zanobetti et al. (2003) used an unconstrained distributed lag in a Poisson regression to model the effect of  $PM_{10}$  exposure on deaths up to 40 days after the exposure. The results indicated that the size of health effect estimates for exposure to  $PM_{10}$  was twice as great when considering long-term effects for all causes of mortality. Several studies have confirmed that most of the adverse health effects, associated with air pollution, persist not only for a few days but also for more than a month after exposure (Goodman et al. 2004; Kelsall et al. 1997; Schwartz and Dockery 1992a, b; Schwartz and Marcus 1990; Zanobetti et al. 2003). Other studies have compared the association of adverse health effects with short-time effects (1–3 days mean) versus the cumulative associations over extended follow-up periods. The results indicated that the estimated associations were two or three times larger for the extended follow-up period than for the acute effects, because of short-time exposure (Dominici et al. 2003; Goodman et al. 2004). This effect is called “displacement effect or harvesting”.

Rosales-Castillo et al. (2001), in a meta-analysis, observed an increase of 0.96 % in respiratory mortality and 1.82 % in cardiovascular mortality when  $PM_{10}$  levels increased  $10 \mu g/m^3$ . Our effect-size estimates are higher than previous studies in Mexico City (O'Neill et al. 2004; Rosales-Castillo et al. 2001) and in other countries or multi-city studies (Chang et al. 2003; Dockery 2001; Lippmann et al. 2000; Samoli et al. 2001; Sunyer et al. 2000; Zanobetti and Schwartz 2009), although our study was performed in a smaller area, with intense industrial activity where the pollutant emissions from point sources are continuous and in large quantities.

Acute respiratory infections in Tula were associated with TSP air pollution, although PM levels are lower than the maximum permissible limits established by the Mexican Air Quality Standards. We observed a significant and positive association of acute respiratory infections with TSP in the statistical models. The adverse effects were observed in the same week that TSP level increased. We found positive and marginally significant associations with increased  $PM_{10}$  levels. Asthma and  $PM_{10}$  were marginally statistically significant for 0-week lag. We also found a marginally significant association between asthma and TSP

levels at lag 0, whereas at 4, 5 and 6-weeks of lags, the associations were significant.

Air pollution is convincingly associated with many signs of asthma aggravation. These include pulmonary function decrements, increased bronchial hyper-responsiveness, visits to emergency departments, hospital admissions, increased medication use and symptom reporting, inflammatory changes, interactions between air pollution and allergen challenges, and immune system changes (Koenig 1999). The main characteristic of asthma is inflammation of airways; this inflammatory state may be driven by exposure to inhaled allergens, such as house dust mites, pollens or mold spores, that is, there are specific stimuli generating an early response. The increased frequency of exposure both in quantity and frequency activates primary response in the bronchial mucosa defense repeatedly, and it triggers an antigen–antibody response, initiating immune-mediated phenomenon, which is not an immediate response (GINA 2011). However, the manifestation of the primary symptoms that occur at 0-week lag could be asthma-like symptoms, because response is not immune-mediated; in other words, there is no recognition of allergen.

When the stimuli are continuous as with prolonged exposure to air pollutants, these pollutants may act as inciters or triggers when the airways are hyper-responsive, resulting in transient airway narrowing.

Also, air pollution may act as an inducer to increase airway inflammation and therefore airway hyper-responsiveness, which may persist beyond the exposure time, affecting the immune system, resulting in sensitization or increased allergic responses in the airway and the inflammatory response tends to become chronic (Cruz Mena and Moreno Bolton 1999; LaDou 2005).

This could be the mechanism by which we find positive and statistically significant associations between TSP and asthma, even at 4-, 5- and 6-week lag. Abdo Arbex et al. (2007) carried out a study in Brazil, and they observed that TSP had an acute effect on asthma admissions, starting 1 day after TSP concentrations increased and remaining almost unchanged for the next 4 days.

Also, we observed peak power frequencies of 4–8 weeks in the  $PM_{10}$  series (Fig. 7a) and 6–9 weeks in the TSP series (Fig. 7b) in the FFT analysis. These periodicities might be caused by peak emissions from industrial activities such as startup and shutdown events for maintenance or emergencies, resulting in a lack of control in the discharge of pollutants into the atmosphere. This may partially explain the observed lags of several weeks in adverse health effects. This would be in addition to the inflammatory processes lasting up to several days after the pollution event because of cumulative exposure, which

would be reflected in the association of pollution and health effects until 4 or 5 weeks of lag.

Barraza-Villarreal, in 2008, observed that the effects on inflammatory markers were higher for  $PM \leq 2.5 \mu m$  and  $O_3$  than for  $NO_2$ . The effects appeared on the same day as the exposure and were cumulative over several days, resulting in lung function impairment after 4 or 5 days of cumulative exposure. In addition, the oxidative effects of PM can increase secretions of pro-inflammatory cytokines and other molecules and enhance allergic reactions in the airway (Behndig et al. 2006; Takizawa 2004).

Hernandez-Cadena et al. (2000) reported estimates similar to our findings, but in relation to increments in  $PM_{10}$  levels in association with increments in ozone levels. TSP concentrations were not included in that study. Most time-series analyses of the relationship between air pollution and respiratory diseases are associated with  $PM_{10}$  and  $PM_{2.5}$  and, more recently, with coarse particles. Most of those studies were performed in large cities or urban areas. There is little prior evidence of the relationship between air pollution and respiratory diseases in industrial areas rather than urban areas.

Finally, despite the prevailing winds blowing from the N and NNE, in a conservative scenario, there is the assumption that the measured concentrations of TSP and  $PM_{10}$  at the Tula monitoring station represent a lower bound of the exposure to which population are exposed in the entire region.

Considering TSP and  $PM_{10}$  concentrations was below those established by the NOM-025-SSA-1-1993 for most weeks of the study years, corresponding associations, positive and statistically significant, were found with mortality, acute respiratory infections and asthma.

This study provides evidence for the need to expand air quality monitoring network and the daily record of the criteria pollutants in the region.

## Conclusions

Increased respiratory morbidity and mortality is associated with weekly changes of PM air pollution in the region. A reduction in air pollutants from industrial sources would benefit life quality and health of the exposed population.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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