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Short-term exposure to $PM_{2.5}$ and 1.5 million deaths: a time-stratified case-crossover analysis in the Mexico City Metropolitan Area

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Abstract

Background Satellite-based $PM_{2.5}$ predictions are being used to advance exposure science and air-pollution epidemiology in developed countries; including emerging evidence about the impacts of $PM_{2.5}$ on acute health outcomes beyond the cardiovascular and respiratory systems, and the potential modifying effects from individual-level factors in these associations. Research on these topics is lacking in low and middle income countries. We aimed to explore the association between short-term exposure to $PM_{2.5}$ with broad-category and cause-specific mortality outcomes in the Mexico City Metropolitan Area (MCMA), and potential effect modification by age, sex, and SES characteristics in such associations.

Methods We used a time-stratified case-crossover study design with 1,479,950 non-accidental deaths from the MCMA for the period of 2004–2019. Daily 1 × 1 km $PM_{2.5}$ (median = 23.4 μg/m^3; IQR = 13.6 μg/m^3) estimates from our satellite-based regional model were employed for exposure assessment at the sub-municipality level. Associations between $PM_{2.5}$ with broad-category (organ-system) and cause-specific mortality outcomes were estimated with distributed lag conditional logistic models. We also fit models stratifying by potential individual-level effect modifiers including; age, sex, and individual SES-related characteristics namely: education, health insurance coverage, and job categories. Odds ratios were converted into percent increase for ease of interpretation.

Results $PM_{2.5}$ exposure was associated with broad-category mortality outcomes, including all non-accidental, cardiovascular, cerebrovascular, respiratory, and digestive mortality. A 10-μg/m^3 $PM_{2.5}$ higher cumulative exposure over one week (lag_{06}) was associated with higher cause-specific mortality outcomes including hypertensive disease [2.28% (95%CI: 0.26%–4.33%)], acute ischemic heart disease [1.61% (95%CI: 0.59%–2.64%)], other forms of heart disease [2.39% (95%CI: -0.35%–5.20%)], hemorrhagic stroke [3.63% (95%CI: 0.79%–6.55%)], influenza and pneumonia [4.91% (95%CI: 2.84%–7.02%)], chronic respiratory disease [2.49% (95%CI: 0.71%–4.31%)], diseases of the liver [1.85% (95%CI: 0.31%–3.41%)], and renal failure [3.48% (95%CI: 0.79%–6.24%)]. No differences in effect size of associations were observed between age, sex and SES strata.

Conclusions Exposure to $PM_{2.5}$ was associated with non-accidental, broad-category and cause-specific mortality outcomes beyond the cardiovascular and respiratory systems, including specific death-causes from the digestive and genitourinary systems, with no indication of effect modification by individual-level characteristics.

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Keywords $PM_{2.5}$, Cause-specific mortality, Short-term exposure, Case-crossover study

Introduction

Human exposure to fine particulate matter ($PM_{2.5}$) is a well-documented risk factor for non-accidental, cardiovascular and respiratory mortality [15]. Therefore, quantification of mortality burden from $PM_{2.5}$ exposure has been mostly estimated for such broad-category outcomes. New studies suggest that the $PM_{2.5}$-mortality relation largely varies among specific death causes (e.g. death-spectrum wide association study (DWAS) approach); then, the use of concentration–response associations from non-accidental mortality and broad-categories of death (e.g. all cardiovascular and all respiratory death causes) may lead to biased quantification of mortality burden from $PM_{2.5}$ [36]. Since exposure to $PM_{2.5}$ can affect nearly every organ system through different mechanisms of damage, including oxidative stress, systemic inflammation, and immune dysregulation [29], recent epidemiologic studies have reported associations between $PM_{2.5}$ exposure with mental, behavioral, nervous, cerebrovascular, metabolic, digestive, and genitourinary outcomes, mostly in the US and Asia [8, 34, 52, 63]. Little evidence on short-term exposure to $PM_{2.5}$ with acute mortality outcomes beyond the cardiovascular and respiratory death categories has been reported in low- and middle-income countries, including those from Latin America. In this world region, 80% of the population lives in urban areas where policies to improve ambient air quality have been insufficient, and millions of its residents are at high risk of adverse health effects from widespread exposure to $PM_{2.5}$ [44]. The Mexico City Metropolitan Area, the largest urban area in North America that is also part of Latin America, remains as one of the world's megacities that has not made large gains in air quality despite the enactment of several regulations, some of them similar to those from high-income countries [37]. Over the past few decades, the Mexico City Metropolitan Area has been successful at reducing emissions of primary pollutants, however it faces the challenge to do so with secondary pollutants including $PM_{2.5}$ [47]. Regardless of its numerous measures to improve local air quality, this megacity lacks the resources to implement all control measures and the tools for quantitative analyses required to identify strategies that would work the best [64]. The current challenge in many of the rapidly growing megacities with moderate to high $PM_{2.5}$ concentrations like the Mexico City Metropolitan Area, is to find the resources to support new air quality policy in a context of rapid population growth, large inequalities in terms of income and accessibility to services (i.e., health, law enforcement, public transit, education, etc.), and the presence of heterogeneous formal and informal settlements and economic activities [21]. In this regard, results from research focused on under-studied mortality outcomes linked to exposure to air pollutants could be highly informative for health protection and also needed to properly quantify the benefits of improving air quality in these world regions [36]. In the public-policy framework, omission of some health impacts may lead to underestimation of the benefits from interventions aimed to reduce the burden of disease from $PM_{2.5}$ relative to their costs [57]. Tailored epidemiologic evidence aimed to identify subgroups of the population at higher risk of adverse health effects from $PM_{2.5}$ is needed to advance environmental policy and public health in megacities from middle-income regions like the Mexico City Metropolitan Area.

The development of highly spatially-resolved $PM_{2.5}$ models (1×1-km $PM_{2.5}$ predictions) based on satellite data, has facilitated the assessment of human exposure at fine spatial scales, even in regions with low to moderate $PM_{2.5}$ monitoring, such as Latin America [21]. Also, the employment of satellite-based $PM_{2.5}$ models, and the combinations of different methods to estimate $PM_{2.5}$ for epidemiologic research, may reduce exposure measurement error, compared to the use of city-wide averages from small ground monitoring networks [1, 45, 53]. The use of highly spatially-resolved $PM_{2.5}$ estimates for exposure assessment along with individual-level health records could be leveraged by the case-crossover study design, which allows exploration of effect modification by stratifying on individual (or area-level shared) characteristics which are difficult to consider when using aggregated count data, like in traditional city-wide time-series studies [54, 62]. Age, sex, socio-economic status (SES), and race, are among the factors that seem to modify vulnerability to $PM_{2.5}$ exposure in high-income countries [16, 25, 43, 52]. Such characteristics are of interest for identification of vulnerable populations, science-based policy and targeted public-health interventions [60]. However, little has been reported about the potential modifying effects of these factors in middle-income countries like Mexico, where their distribution may differ compared to other regions.

In this study, we analyzed all ~ 1.5 million adult mortality records from the Mexico City Metropolitan Area for the period from 2004 to 2019, and estimated the

daily percent increase in non-accidental, broad-category, and cause-specific mortality outcomes associated with a 10-μg/m^3 higher $PM_{2.5}$ concentration; as well as potential effect modification in the $PM_{2.5}$-mortality relations by age-group (adults and the elderly), sex, and SES-related indicators (education, health-insurance and job-category).

Methods

Mortality data

We obtained mortality records from the National Institute of Statistics and Geography of Mexico (INEGI) for the period spanning February 1st 2004 to December 31st, 2019. We excluded the month of January 2004 in order to keep only case-days and control-days with complete exposure histories of $PM_{2.5}$ and temperature, i.e. up to one week (lag 6) before the date of event. All mortality records included information on date of death, geographic identifiers for place of residence, underlying cause of death classified according to the International Classification of Diseases Tenth Revision (ICD-10), sex, age, education, healthcare affiliation, and job category. We restricted our analysis to non-accidental causes of death excluding most ICD-10 codes from the blocks V–Y (i.e. various accidents and side effects of treatments), and deaths in people ≥ 18 years-old. ICD-10 codes X6-Y0 were retained based on the evidence that $PM_{2.5}$ can trigger intentional self-harm and aggressive behavior [6, 13]. We organized individual ICD-10 coded death records into mutually exclusive broad-category (organ-system) and cause-specific mortality outcomes within the broad-categories. The selected ICD-10 codes included in our research were chosen to facilitate comparison with recently-published studies focused on under-studied associations between short-term exposure to $PM_{2.5}$ with mortality and morbidity outcomes [34, 63].

Environmental data

We utilized daily mean $PM_{2.5}$ estimates with spatial resolution of 1 × 1 km from our recently developed model based on extreme gradient boosting (XGBoost), and inverse-distance weighting (IDW) that uses aerosol optical depth data, meteorology, and land-use variables to assess short-term exposure to $PM_{2.5}$ at the sub-municipality level in the Mexico City Metropolitan Area [22]. Daily mean air temperature estimates with the same 1 × 1 km resolution came from our satellite-based land surface temperature model for Central Mexico [23]. We restricted our analyses to the spatial domain with available data for both $PM_{2.5}$ and temperature exposures over the Mexico City Metropolitan Area (~ 6650 km^2), as shown in Fig. 1. The study area was composed of 667 sub-municipal geographic areas defined as "localities" by the Instituto Nacional de Estadistica y Geografia. Localities correspond to the third level of subnational division in Mexico, after states and municipalities [27]. The total population in the Mexico City Metropolitan Area in 2010 was 20,116,842 [46]. For the same year, the population living in the localities included in our study region was 19,711,516 inhabitants, ~ 96% of the total Mexico City Metropolitan Area. Urban localities had a population of 19,346,527 (median of 8,523 inhabitants; range of 910 to 1,815,786) inhabitants, and rural localities had a total population of 364,989 (median of 582 inhabitants; range 1 to 5,135) inhabitants. We assigned exposures to $PM_{2.5}$ and temperature for all mortality records at the locality level. For 255 urban localities with census-provided polygons (median land area of 2.9 km^2; range 0.2 to 129.4 km^2), we estimated daily exposures using population-weighted aggregation with population density from the Gridded Population of the World (GPWv4) ~ 1-km raster cells [10], which utilizes data from the 2010 Mexican Census, and the R package *exactextractr* [5]. For 412 rural localities, we used the census only assigned points (rather than enclosing polygons), and for this subset of rural localities we assigned exposure to $PM_{2.5}$ and temperature using the 1 × 1 km grid cell containing the corresponding census-assigned points.

Statistical analysis

We estimated the association between short-term exposure to $PM_{2.5}$ with all mortality outcomes using a time-stratified case-crossover design [33]. Case days were defined as the date of death, and control days (3 to 4 days per month) were chosen on the same day of week as the case day within the same month, year and location. This approach controls for potential confounding effects by day of week, seasonal patterns and long-term time trends,therefore, variables indicating the long-term trend and seasonality are not necessary to be included in the model [28, 59]. Time-invariant covariates are controlled by design (within-person matching), and are not considered to be confounders,thus, daily variations in exposure to $PM_{2.5}$ and temperature on the case day are compared to exposures on control days within the same stratum (i), in order to estimate short-term associations between $PM_{2.5}$ with each mortality outcome. Equation 1 describes this approach:

$$\text{logit}(P(\text{case} = 1 \text{ in stratum } i \mid \text{expo}, \textit{covariates})) = \alpha_{\text{stratum } i} + \beta_0 \times \text{expo} + \beta^T \times \text{covariates} \quad (1)$$

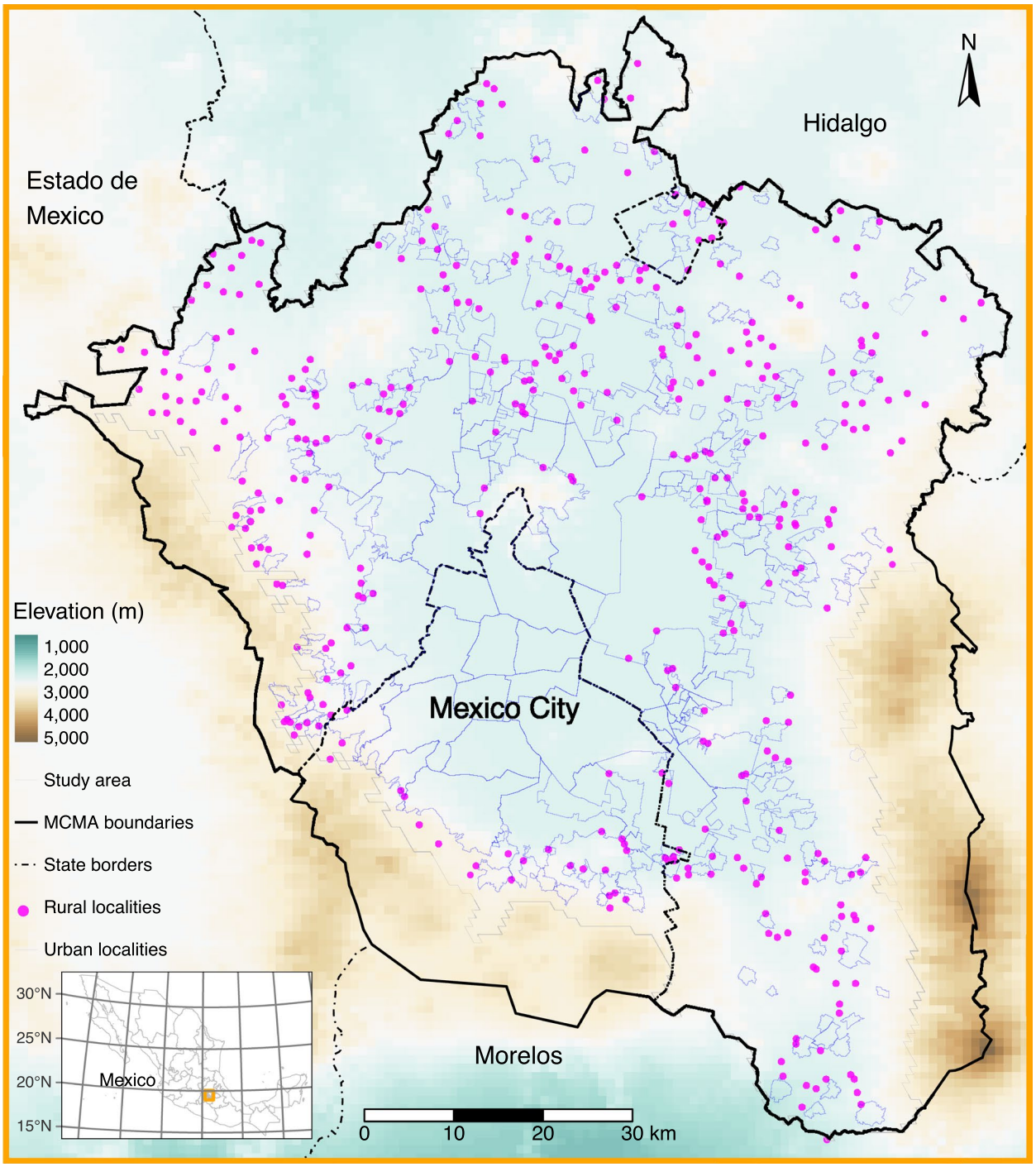

Fig. 1 Spatial distribution of rural and urban localities in the Mexico City Metropolitan Area (MCMA) included in our study. The study area was restricted to the spatial domain with available exposures estimates of $PM_{2.5}$ and temperature

Where each stratum consists of 1 case (case = 1) and 3 or 4 controls (case = 0); P(case = 1 in stratum i | exposure, covariates) is the conditional probability of being a case in the i^{th} stratum given the value of exposure variable and other covariates, $a_{\text{stratum } i}$ represents the constant or intercept of stratum i, expo stands for the exposure variable of interest in the study ($PM_{2.5}$) with its coefficient β_0, covariates stand for variables adjusted in the model

(e.g. temperature), and β^T denotes the coefficients of covariates [59].

All models were adjusted for non-linear effects of temperature with quadratic b-splines (4 degrees of freedom), and equally-spaced knots in the space of this predictor [17]. The odds ratios for all dependent variables associated with short-term exposure to $PM_{2.5}$ were estimated with linear terms in stratified Cox proportional hazards models, equivalent to conditional logistic regression. We explored non-linearities in the concentration–response relationships between $PM_{2.5}$ for all broad-category mortality outcomes by comparing the fit of generalized additive models (GAMs) including parsimonious non-linear (penalized thin-plate splines) $PM_{2.5}$ terms (lag_0 to lag_6) with the fit of linear $PM_{2.5}$ terms using likelihood ratio tests. To address the delayed effects of exposure to $PM_{2.5}$ on all mortality outcomes we included distributed lag terms up to 6 days before the case day (seven terms for lags 0 to 6) to estimate mortality risks [19].

We explored potential effect modification in the associations between short-term exposure to $PM_{2.5}$ with broad-category mortality outcomes (i.e. non-accidental mortality, and deaths classified according to chapters F, G, I, J, K, N, and X from the ICD-10) with stratified analyses (subgroup analyses) by age-group (adults: 18–64 years-old, and elderly: + 65 years-old) and sex (males and females). We also explored effect modification by age-group (adults and the elderly), and SES related variables including degree of education (basic and more than basic education level), type of healthcare affiliation (having health social security affiliation or not), and employment status (based on job categories) in the associations between $PM_{2.5}$ with non-accidental mortality. We used health social security affiliation rather than health insurance alone, since it is related to formal employment and other individual social benefits that differ from specific healthcare programs aimed to provide health services to the most vulnerable populations in Mexico. Employment status was defined from the original job category variable in the mortality records that included the categories "Does not work" and "Looking for a job", which were combined into one single category “Not employed”. However, this categorization does not rule out the possibility that part of the category "Does not work" can also include retired people, with a higher SES compared with those who are actually unemployed. The rest of the job categories were combined into the category “Employed”. We also explored education-specific and job-specific associations. For the latter, given that the Mexican classification of occupations was updated in 2012, and specific occupations coded before 2012 were redistributed into new job categories in the most recent version, it was not possible to homogenize all job categories for the whole period of study. Thus, analyses of specific job categories were restricted to the period from 2013 to 2019. Our test of effect modification was performed by comparing if effect sizes of the associations between $PM_{2.5}$ exposure with broad-category mortality outcomes differed by sex and age group; as well as by education, healthcare affiliation, and employment status for the association between $PM_{2.5}$ with non-external mortality, by following the methods by [2]. Briefly, the statistical analysis of the difference between two strata of the potential effect modifier (i.e. sex, age, and SES related characteristics) was assessed by calculating the 95% CI of their difference in the log odds scale as shown in Eq. 2:

$$95\%\ \mathrm{CI} = (\mathrm{E}_1 - \mathrm{E}_2) \pm 1.96\sqrt{\sigma_1^2 + \sigma_2^2} \quad (2)$$

Where E_1 and E_2 are the coefficients of the association for strata 1 and 2, and σ_1 and σ_2 are the respective standard errors of these two groups.

For ease of interpretation, all odds ratios were converted into percent increase per 10 $\mu g/m^3$ higher $PM_{2.5}$. All analyses were performed in R version 4.2.1 [42] with packages: *data.table* [14], *survival* [50], *dlnm* [18], *and mgcv* [55]. Because the records used in all analyses were publicly available, the PI previously received a determination of exempt human research: 45 CFR 46. 101(b) (Category 4) from the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

Results

The total number of non-accidental deaths (≥ 18 years-old) analyzed from 2004 to 2019 in the Mexico City Metropolitan Area was 1,479,950.

Table 1 describes the demographic characteristics of the study population. There were slightly more deaths in men than women, and deaths in the elderly (≥ 65 years-old) accounted for ~ 63% of all deaths. Around 50% of the decedents attended only elementary school, 63% had health social security affiliation, and 32% were not working at the time of death. The five most common job categories in the mortality records for the period 2013–2019 were: not-employed or not working at the time of death, sales, unspecified occupations, craft and related trades, and professionals and technicians. Over the study period, the mean population-weighted exposure to $PM_{2.5}$ and temperature in the study region were 24.6 $\mu g/m^3$, and 16.6° C, respectively.

Table 2 shows the total number of broad-category (organ-system), and cause-specific deaths (≥ 18 years-old) analyzed over the study period. Circulatory system diseases were the most common death causes, accounting for almost 30% of the total, followed by digestive (12%) and respiratory (10%) diseases.

Table 1 Demographic characteristics of the analyzed deaths in people ≥ 18 years-old in the Mexico City Metropolitan Area from 2004–2019

Characteristic	Frequency
All non-accidental deaths	1,479,950 (100%)
Age group	
Elderly 65 +	927,795 (62.7%)
Adults 18–64	552,155 (37.3%)
Sex	
Men	751,804 (50.8%)
Women	728,146 (49.2%)
Education level	
Primary School	731,468 (49.4%)
Mid-High School	340,172 (23%)
No education	191,426 (12.9%)
College	153,100 (10.3%)
Unspecified	63,784 (4.3%)
Health insurance affiliation	
Health social security affiliation	928,678 (62.8%)
No health social security affiliation	496,491 (33.5%)
Unspecified	54,781 (3.7%)
Job category	
Does not apply before 2013	738,294 (49.9%)
Not employed	477,573 (32.3%)
Sales workers	53,918 (3.6%)
Unspecified	48,332 (3.3%)
Craft and related trades workers	47,834 (3.2%)
Professionals and technicians	44,423 (3%)
Plant and machine operators	21,727 (1.5%)
Agricultural, forestry and fishery	12,926 (0.9%)
Personal services	11,337 (0.8%)
Clerical support	9,581 (0.6%)
Elementary occupations	9,475 (0.6%)
Managers	4,530 (0.3%)
$PM_{2.5}$ ($\mu g/m^3$)	
Mean (SD)	24.6 (10.8)
Median [Min, Max]	23.4 [0.200, 202]
Ambient temperature (°C)	
Mean (SD)	16.6 (2.58)
Median [Min, Max]	16.8 [3.30, 24.1]

Table 2 Underlying broad-category and cause-specific mortality (≥ 18 years-old) in the Mexico City Metropolitan Area from 2004–2019

Mortality outcomes	ICD code	Frequency
All non-accidental deaths		1,479,950
Broad-category		
Circulatory System	I00-I99	427,420
Digestive system	K00-K93	172,906
Respiratory system	J00-J99	142,866
Genitourinary	N00-N99	57,372
Nervous system	G00-G99	22,735
Intentional self-harm	X60-X84	10,021
Mental and behavioral	F00-F99	9,577
Cause-specific		
Acute ischemic heart disease	I20-I22, I24	212,201
Diseases of the liver	K70-K77	92,562
Chronic respiratory disease	J40-J47	67,062
Hypertensive diseases	I10-I15	53,675
Influenza and Pneumonia	J09-J18	52,972
Renal failure	N17-N19	30,787
Other forms of heart disease	I30-I52	29,516
Stroke hemorrhagic	I60-I62	28,412
Chronic ischemic heart disease	I25	21,313
Disorders of gallbladder, biliary tract, and pancreas	K80-K87	16,266
Diseases of esophagus, stomach and duodenum	K20-K31	12,322
Stroke ischemic	I63	10,684
Suicides	X6-X84	9,954
Pulmonary heart disease	I26-I28	6,792
Diseases of the arteries	I70-I79	6,299
Chronic rheumatic heart diseases	I05-I09	4,314
Extrapyramidal and movement disorders	G20-G26	3,531

Among the specific death causes, acute ischemic heart disease and hypertensive disease were the leading causes from the circulatory system. Diseases of the liver were the leading death causes from the digestive system, and chronic respiratory disease, influenza and pneumonia were the most common causes of death from the respiratory system (Table 2).

Results from our assessment of linearity in the concentration–response functions between short-term exposure to $PM_{2.5}$ with all broad-category mortality outcomes showed no significant differences in model's fit when including non-linear $PM_{2.5}$ exposures (Table S1); therefore all our further results are based on linear concentration–response functions. Figure 2 shows associations between $PM_{2.5}$ exposure with the broad-category mortality outcomes analyzed over the study period stratified by age-group and sex. For consistency with previous studies, two-days ($lag_0 + lag_1$) and one-week (sum from lag_0 to lag_6) cumulative associations with $PM_{2.5}$ are shown. Among the broad-category death causes, two-days exposure to $PM_{2.5}$ (lag_{01}) was associated with total higher non-accidental mortality [adults = 0.72% (95%CI: 0.26%–1.19%), elderly = 1.04% (95%CI: 0.68%–1.40%)], with sex-specific associations for men of 0.84% (95%CI: 0.44%–1.24%) and women of 1.00% (95%CI: 0.60%–1.41%), cardiovascular mortality [adults = 1.03% (95%CI: -0.3%–2.10%), elderly = 1.01% (95%CI: 0.41%–1.62%)],

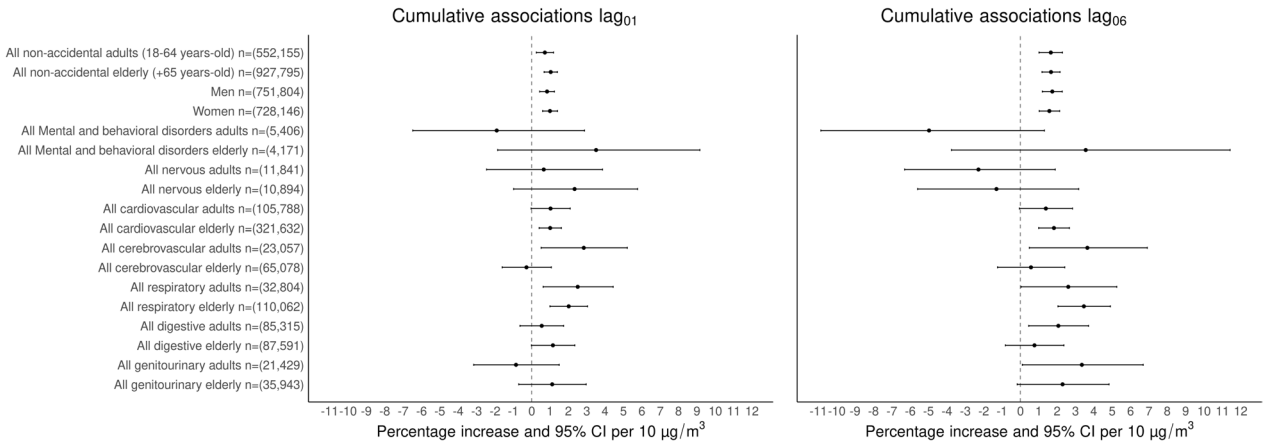

Fig. 2 Cumulative percentage increase (%) and 95% CI for broad-category death causes by age group (adults ≥ 18–64 years-old and elderly ≥ 65 years-old) per 10 µg/m^3 increase of $PM_{2.5}$ over two days (lag_{01}) and one week (lag_{06}) in the Mexico City Metropolitan Area for 2004–2019

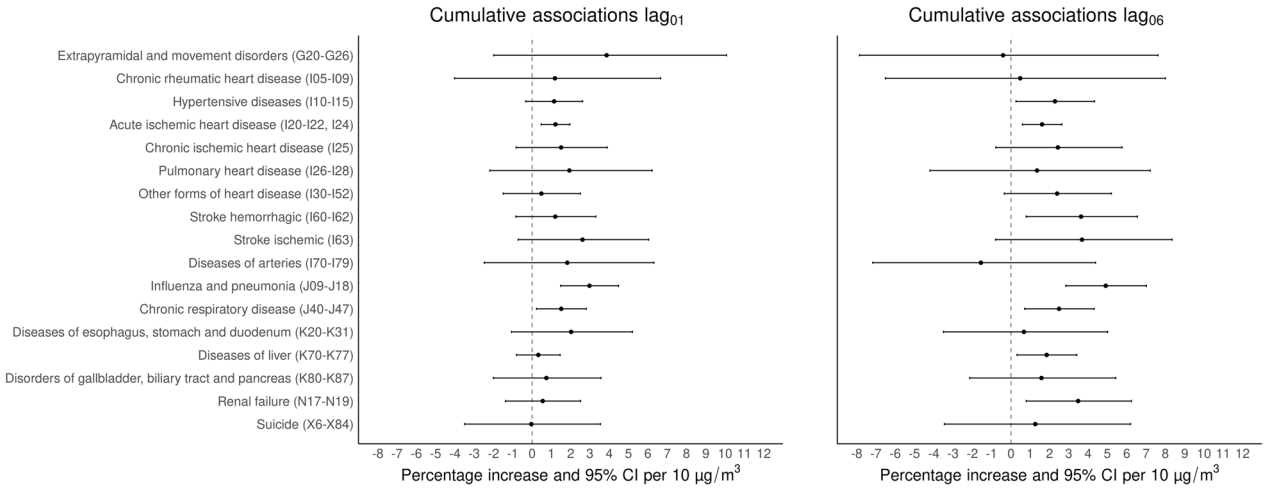

Fig. 3 Cumulative percentage increase (%) and 95% CI for cause-specific mortality by age group (adults ≥ 18 years-old and elderly ≥ 65 years-old) per 10 µg/m^3 increase of $PM_{2.5}$ over two (lag_{01}) days and one week (lag_{06}) in the Mexico City Metropolitan Area for 2004–2019

cerebrovascular mortality [adults = 2.84% (95%CI: 0.52%–5.21%)], respiratory mortality [adults = 2.51% (95%CI: 0.63%–4.44%), elderly = 2.02% (95%CI: 1.00%–3.04%)] and digestive mortality [elderly = 1.16% (95%CI: -0.01%–2.35%)]. Cumulative associations over one week (lag_{06}) were in general larger compared with associations for lag_{01} for most mortality outcomes; with the largest associations observed for cerebrovascular [adults = 3.65% (95%CI: 0.49%–6.91%)], respiratory [adults = 2.61% (95%CI: 0.04%–5.25%), elderly = 3.46% (95%CI: 2.05%–4.90%)], and genitourinary [adults = 3.35% (95%CI: 0.11%–6.69%), elderly = 2.30% (95%CI: -0.17%–4.83%)] mortality. However, our test to identify differences in the effect sizes of associations between $PM_{2.5}$ with broad-categories of death by age-group and sex did not suggest effect modification. Results for all single lag (lag_0 … lag_6) and cumulative (lag_{01} … lag_{06}) associations between $PM_{2.5}$ with broad-category death causes are reported in Table S2.

Associations between $PM_{2.5}$ exposure and cause-specific mortality for lag_{01} and lag_{06} are shown in Fig. 3. Cumulative exposure to $PM_{2.5}$ over two days (lag_{01}) was associated with mortality from hypertensive disease [1.14% (95%CI: -0.33%–2.62%)], acute ischemic heart disease [1.21% (95%CI: 0.47%–1.96%)], influenza and pneumonia [2.97% (95%CI: 1.48%–4.48%)], and chronic respiratory disease [1.51% (95%CI: 0.23%–2.81%)]. Associations for cumulative exposure to $PM_{2.5}$ over one week

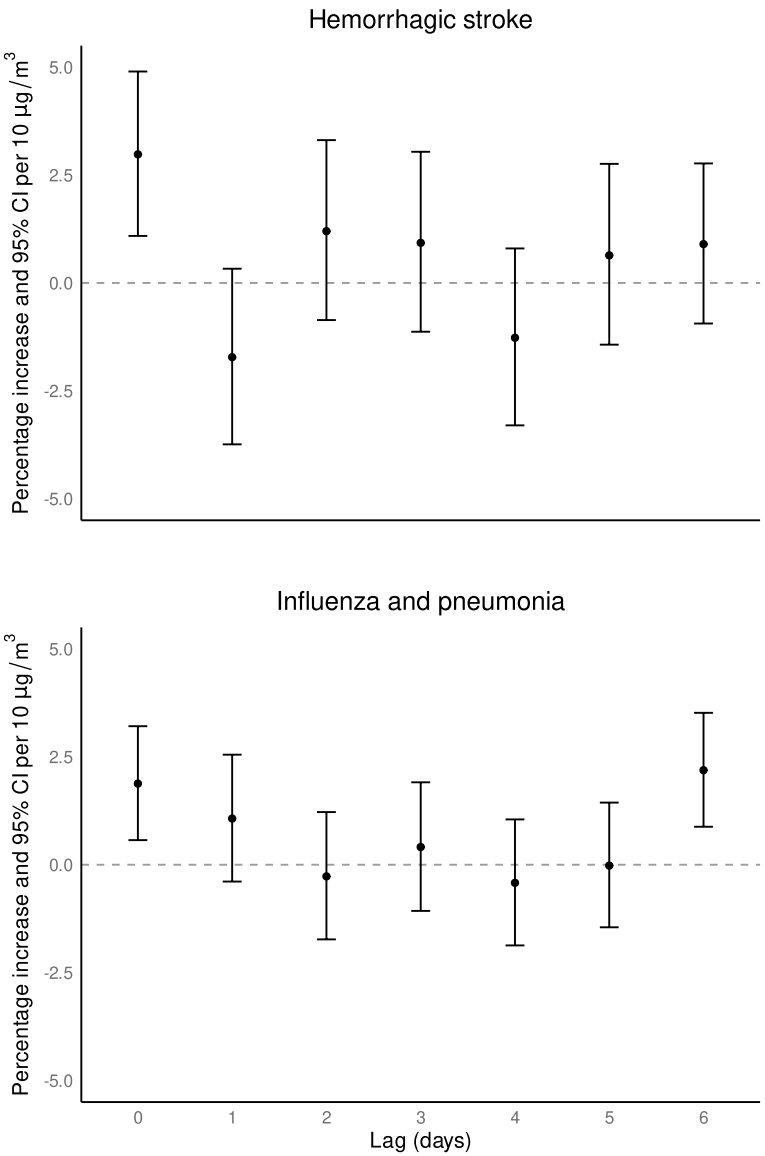

Fig. 4 Single-day lag associations as percent increase (%) and 95% CI for hemorrhagic-stroke and influenza and pneumonia per 10 µg/m^3 increase of $PM_{2.5}$

(lag_{06}) were observed for hypertensive disease [2.28% (95%CI: 0.26%–4.33%)], acute ischemic heart disease [1.61% (95%CI: 0.59%–2.64%)], other forms of heart disease [2.39% (95%CI: -0.35%–5.20%)], hemorrhagic stroke [3.63% (95%CI: 0.79%–6.55%)], influenza and pneumonia [4.91% (95%CI: 2.84%–7.02%)], chronic respiratory disease [2.49% (95%CI: 0.71%–4.31%)], diseases of the liver [1.85% (95%CI: 0.31%–3.41%)], and renal failure [3.48% (95%CI: 0.79%–6.24%)].

Same-day exposure to $PM_{2.5}$ (lag_0) showed the largest single lag associations with diseases of the arteries [4.62% (95%CI: 0.73%–8.67%)], hemorrhagic stroke [2.98% (95%CI: 1.09%–4.90%)], hypertensive disease [1.34% (95%CI: 0.02%–2.68%)], and acute ischemic heart disease [0.64% (95%CI: -0.02%–1.31%)]. Lag_1 showed the largest association with diseases of the esophagus, stomach and duodenum [3.40% (95%CI: 0.26%–6.64%)], and chronic respiratory disease [1.72% (95%CI: 0.44%–3.02%)]. Lag_4 had the largest effects for chronic ischemic heart disease [3.74% (95%CI: 1.37%–6.16%)], and ischemic stroke [3.08% (95%CI: -0.22%–6.50%)], and lag_6 for influenza and pneumonia [2.19% (95%CI: 0.88%–3.52%)]. Figure 4 shows the lag-response plots for two cause-specific mortality outcomes (hemorrhagic stroke and influenza and

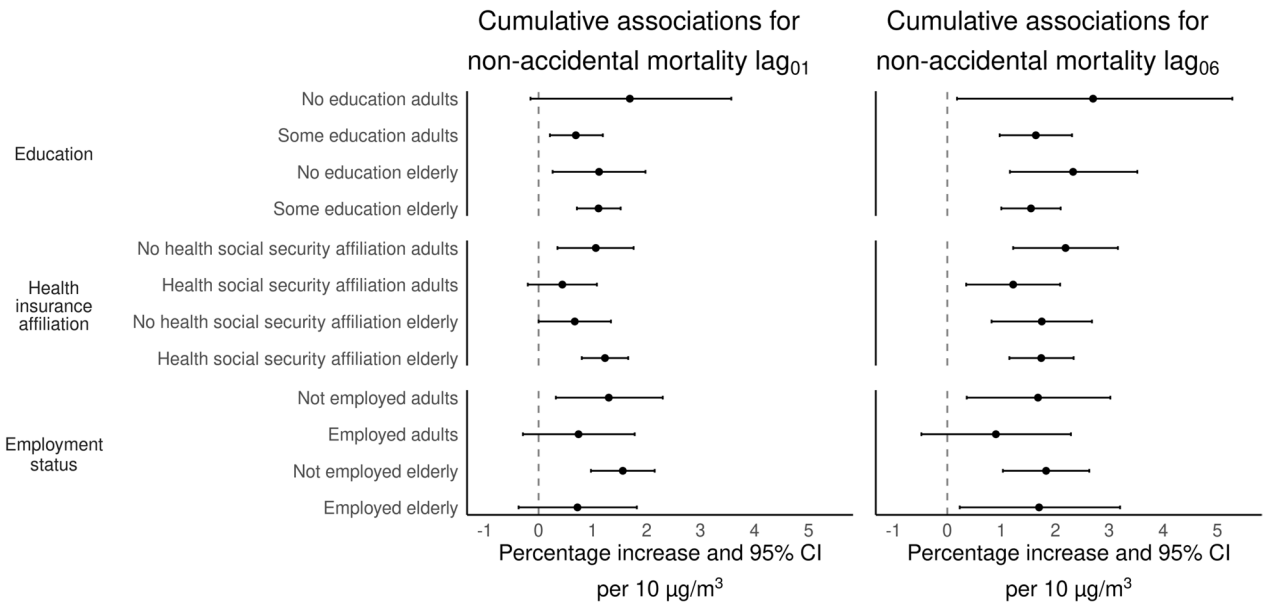

Fig. 5 Cumulative percentage increase (%) and 95% CI for non-accidental mortality by education, health insurance affiliation, and employment status (adults 18–64 years-old, elderly ≥ 65 years-old) per 10 µg/m^3 increase in $PM_{2.5}$ over two (lag_{01}) days and one week (lag_{06}) in the Mexico City Metropolitan Area for 2004–2019. Associations for employment status are for the period from 2013–2019

pneumonia); and to complement this information, results for all single lag and cumulative associations for all cause-specific mortality outcomes are reported in Table S3.

Figure 5 shows the associations between short-term exposure to $PM_{2.5}$ with non-accidental mortality in adults (≥ 18–64 years-old) and the elderly (≥ 65 years-old), further stratified by education level (having or not basic education), health insurance affiliation (having or not health social security affiliation), and employment status (either being working or not when the person died). Associations for lag_{06} in those with no education were 2.70% (95%CI: 0.18%–5.28%), and 2.33% (95%CI: 1.16%–3.52%) for adults and the elderly, respectively. While for those having at least basic education the associations were 1.64% (95%CI: 0.97%–2.31%) for adults, and 1.55% (95%CI: 1.00%–2.10%)], for the elderly. For the same exposure window, mortality risk in adults without health social security affiliation was 2.19% (95%CI: 1.22%–3.16%), and 1.75% (95%CI: 0.82%–2.68%) for the elderly. Adults with health insurance showed a 1.22% (95%CI: 0.35%–2.09%) mortality risk, and the elderly 1.74% (95%CI: 1.15%–2.34%). Results by employment status for the period from 2013–2019, showed that associations for adults not working at the time of death were 1.68% (95%CI: 0.36%–3.02%), and 1.83% (95%CI: 1.03%–2.63%) for the elderly; compared to those who were working with mortality risks of 0.90% (95%CI: -0.48%–2.29%) and 1.70% (95%CI: 0.23%–3.20%), for adults and the elderly, respectively. Our statistical test of the differences in effect sizes of associations between SES-related strata did not suggest effect modification in the association between $PM_{2.5}$ with non-accidental mortality. Figure S1, shows job-specific associations with $PM_{2.5}$ exposure for the same period of time.

Discussion

This study presents a detailed analysis on the associations between short-term exposure to $PM_{2.5}$ with non-external, broad-category (organ-system) and cause-specific mortality outcomes in the Mexico City Metropolitan Area, and the role that age-group, sex, and SES-related characteristics play in such associations. Our research involved the use of state-of-the-art methods to assess short-term exposure to $PM_{2.5}$, using highly spatially-resolved satellite-based $PM_{2.5}$ models. With our $PM_{2.5}$ estimates, we were able to assign daily $PM_{2.5}$ exposures at the sub-municipality level; leveraging the smallest geographic identifier for place of residence (i.e. localities) included in the Mexican mortality records. To our knowledge, this is one of the most comprehensive analyses in Latin America in terms of the amount of mortality outcomes analyzed, and assessment of potential effect modifiers in the $PM_{2.5}$-mortality associations using individual records.

Our results support previous evidence on the associations between exposure to $PM_{2.5}$ with increased risks of non-accidental, cardiovascular, cerebrovascular and respiratory mortality in the Mexico City region [7, 24]. We also found associations between $PM_{2.5}$ exposure

with causes of death not previously reported in the Mexico City Metropolitan Area, such as digestive and genitourinary mortality outcomes. Our results for non-accidental, cardiovascular and respiratory mortality in adults, the three most consistent broad-category mortality outcomes linked to $PM_{2.5}$ exposure for lag_{01}, were larger than the associations reported by Li et al. [34] for non-accidental [0.25% (95% CI: 0.11%–0.38%)], circulatory system [0.39% (95% CI: 0.21%–0.58%)], and respiratory [0.43%; 95% CI: 0.05%–0.78%)] mortality, and also larger than the results from Xu et al. [60] for all-cause [0.13% (95% CI: 0.01%–0.27%)], cardiovascular [0.02% (95% CI: -0.17%–0.21%)], and respiratory [0.81% (95% CI: 0.39%–0.96%)] mortality for Beijing. Our results for the same health outcomes were similar to those reported in the meta-analyzes of Atkinson et al. [4] for all-cause [1.04% (95% CI: 0.52%–1.56%)], cardiovascular [0.84% (95% CI: 0.41%–1.28%)], and respiratory [1.51% (95% CI: 1.01%–2.01%)] mortality [4]. Orellano et al. [40] also reported similar associations for all-cause [0.65% (95% CI: 0.44%–0.86%)] and cardiovascular [0.92% (95% CI: 0.61%–1.23%)] mortality, but their associations for respiratory [0.73% (95% CI: 0.29%–1.16%)] and cerebrovascular [0.72% (95% CI: 0.12%–1.32%)] mortality were lower compared to our results [40]. It is possible that the selection of heterogeneous effect estimates from different lags structures that were combined in the meta-analyzes of Atkinson et al. [4], and Orellano et al. [40] could have induced some biases, although to a greater degree in the study by Atkinson et al. [4], since the results of Orellano et al. [40] similar in a sensibility analysis including only associations for lags 0–1. Differential toxicity related to $PM_{2.5}$ composition, variation in the underlying health status between populations, and distribution of potential effect modifiers between study regions can also play a role in the differences between associations reported in the literature. Also, it has been suggested that at higher concentrations of $PM_{2.5}$ like those observed in Asian cities, the slopes in the concentration–response functions between $PM_{2.5}$ with cardiorespiratory mortality flattens out (supralinear exposure–response curve), which might also explain the differences in effect estimates between study regions [35]. Future research efforts exploring the shape of the concentration response functions for mortality outcomes other than cardiorespiratory outcomes could aid to understand the variation in mortality risks across study regions.

Among the cause-specific mortality associations with $PM_{2.5}$, those related to the circulatory system (e.g. diseases of the arteries, hypertensive disease, acute ischemic heart disease, and stroke) were the most clear, with the largest associations observed on the same day of exposure (lag_0 in Table S3). Li et al. [34] also reported consistent associations between $PM_{2.5}$ with mortality outcomes from the circulatory and respiratory systems in Beijing. However, we found larger associations compared to those reported by Li et al. [34] for ischemic heart disease (0.46%,95% CI: 0.19%–0.72%), influenza and pneumonia (0.35%; 95% CI: -0.32%–1.03%), and chronic respiratory disease (0.62%; 95% CI: 0.08%–1.16%). They also reported associations between $PM_{2.5}$ and subspecific causes of ischemic heart disease such as: acute ischemic heart disease (ICD-10 codes: I20-I22, I24), acute myocardial infarction (ICD-10 codes: I21-I22), and myocardial infarction (ICD-10 codes: I21-I23). We did not explore such subtypes of ischemic heart disease, as Li et al. [34] did, because the grouping of such health outcomes involves the overlap of several ICD-10 codes,while we only focused on reporting associations for mutually exclusive health outcomes. We found larger associations than those reported by Xu et al. [60] for ischemic heart disease (-0.06%,95% CI: -0.33%–0.22%), and chronic respiratory disease (0.96%; 95% CI: 0.35%–1.57%) also in Beijing. Our results for specific cardiovascular and cerebrovascular outcomes were larger than those reported by Chen et al. [11] for 30 Chinese counties [11]. Our results on larger effect estimates compared to those reported in Asian cities may suggest that not only non-accidental, and cardiorespiratory mortality associations with $PM_{2.5}$ might follow a supralinear concentration–response curve, but also risks for cause-specific mortality outcomes within those broad-categories. Intentional-self harm mortality was not associated with $PM_{2.5}$ exposure in our study, consistent with results of Astudillo-García et al. [3] for Mexico City, providing further evidence that short-term exposure to $PM_{2.5}$ is not associated with higher risk of suicide in the adult population from this study region [3]. However, emergent evidence assessing the $PM_{2.5}$-suicide relation in people with major depressive disorders and other mental health conditions, as well as people chronically exposed to high $PM_{2.5}$ concentrations justifies more research focused on vulnerable and highly exposed subgroups of the population [9, 26, 51].

Contrary to the results from Li et al. [34], we did not find associations between short-term exposure to $PM_{2.5}$ with acute mortality outcomes from the nervous system (e.g. extrapyramidal and movement disorders), however we observed positive associations between cumulative exposure to $PM_{2.5}$ with digestive (diseases of the liver) and genitourinary (renal failure) mortality. Exposure to $PM_{2.5}$ has been associated with increased serum levels of hepatic enzymes, such as γ-glutamyltranspeptidase (GTP), and alanine transaminase (ALT), which are biomarkers of liver damage. $PM_{2.5}$ can induce systemic oxidative stress and inflammation when deposited in the airways, and when swallowed $PM_{2.5}$ are removed from

the airways by mucociliary clearance leading to gastrointestinal exposure with the largest internal dose and adverse effects observed in the liver [30, 49]. On the other hand, recent evidence has shown that $PM_{2.5}$ is related to renal injury and increases the risk of nephropathy, as well as increased risk of first hospital admission from kidney and total urinary system diseases [32, 41]. $PM_{2.5}$ can unbalance the kidney function by accumulation in the kidney tissue, endothelial dysfunction, abnormal renin-angiotensin system, and immune complex deposition. The mechanisms of damage from $PM_{2.5}$ to the kidney involve inflammation, oxidative stress, apoptosis, DNA damage, and autophagy [61].

The EPA's Integrated Science Assessment (ISA) for Particulate Matter [15] defined the associations between short-term exposure to $PM_{2.5}$ with cardiovascular and respiratory mortality as causal and likely causal, respectively; but less evidence is available for making conclusions about other causes of death [15]. Although our results suggest that short-term exposure to $PM_{2.5}$ may trigger cause-specific mortality beyond the circulatory and respiratory systems, more epidemiological evidence is needed to understand the links between $PM_{2.5}$ exposure with the different specific death causes evaluated in our study. New studies about the adverse effects of $PM_{2.5}$ exposure on multiple prevalent but rarely studied causes of hospital admissions adds to the body of epidemiologic evidence that supports our findings, and it opens the possibility to replicate such results in different locations with ongoing or future health studies [54].

Cumulative associations from distributed lags can capture the impact of multiple days after initial exposure to $PM_{2.5}$ on mortality. In general, consistent associations between short-term exposure to $PM_{2.5}$ with all-cause (i.e. non-accidental) or broad-category mortality outcomes (mostly from cardiovascular and respiratory diseases) have been observed during the first week of exposure [15]. Therefore, communicating results of cumulative exposures from distributed lags for lag_{01} and lag_{06}, has become the standard, as the evidence shows immediate (lag_{01}) and more prolonged (lag_{06}) effects on cardiovascular, and respiratory mortality, respectively. That said, the onset and duration of the mechanisms of damage leading to death can vary for other health outcomes, with mortality from $PM_{2.5}$ exposure occurring with a delay of a few days [58]. Thus far, little has been documented about the timing when the largest single-day lag effects of $PM_{2.5}$ on cause-specific mortality occur, and these "peaks" in mortality can be missed when reporting cumulative effects only for lag_{01}, or lag_{06}. Such evidence could be used by health professionals with preventive aims. In general, information on the timing when health effects occur after initial exposure to $PM_{2.5}$, or any other air pollutant, is of importance for public health administrators and pollution control managers. Identifying the lag days over which health effects are observed can inform the development of air quality standards, risk communication tools (e.g. air quality indices), quantification of health impacts, mitigation strategies (e.g. planning and allocation of clinical resources), and the design of emission control measures. Our results are consistent with the epidemiologic evidence showing that short-term exposure to $PM_{2.5}$ has an immediate effect on non-accidental and cardiovascular mortality, and a more prolonged effect on respiratory mortality [15]. However, when considering specific death causes (Table S3) within the broad-category mortality outcomes, there seems to be more variability about the timing when the largest (single and cumulative) associations are observed. For instance, chronic ischemic heart disease and ischemic stroke showed the largest associations with $PM_{2.5}$ on lag_4, while the rest of the death causes from the circulatory system showed the largest association on lag_0 and lag_1. For respiratory mortality, our results are within the range of observed associations, with chronic respiratory disease showing the largest association with $PM_{2.5}$ on lag_1, while the association with influenza and pneumonia remained high at lag_6. On the other hand, it is known that the strength of the relationship between exposure to $PM_{2.5}$ and health effects varies depending on the exposure duration i.e., short- or long-term exposure, but less is known about the strength of this relationship for sub-daily exposures e.g. hourly peak exposures. Results from such investigations are inconclusive on whether sub-daily exposures pose a greater risk of mortality, or not, compared to daily averaged exposures [15]. Since we only focused on short-term exposures to daily mean $PM_{2.5}$ concentrations assuming that the same averaging time could have the same relevance for all mortality outcomes, we can not rule out the possibility that there might be averaging times (sub-daily, or sub-chronic exposures) that could be of greater relevance for the different death causes analyzed in our research. With the advent of new geostationary satellites (Zoogman et al. 2017), the capacity to estimate hourly concentrations of $PM_{2.5}$ will be augmented, along with the possibility to assess sub-daily exposures, and potential error reduction in the estimation of daily-mean $PM_{2.5}$ concentrations.

It is known that subgroups of the population with lower SES indicators may have higher prevalence of health disorders and comorbidities, lower living standards, and higher exposure to air pollutants (e.g. living closer to a highway or lack of green spaces) [48, 60]. We used three indicators of SES, namely education, health social security affiliation, and employment status to assess their roles as potential effect modifiers in the $PM_{2.5}$-mortality relationship. Although in general point estimates for the

lower SES related strata (lower education level, not having health social security affiliation, and not being working at the time of death) seemed larger than those in the higher SES indicators; we did not find evidence of effect modification in the $PM_{2.5}$-mortality associations (analyzed on the log scale) between SES strata [2]. In Mexico there is limited evidence about the role of education in the association between short-term exposure to $PM_{2.5}$ and mortality, however O'Neill et al. [39] did not observe evidence of effect modification in the association between short-term exposure to PM_{10} and mortality across education levels [39]. Health insurance access can modify the susceptibility to detrimental effects of environmental stressors, including $PM_{2.5}$, by providing access to medications, supplements and overall preventive services [56]. Our results did not show significant effect modification between strata of health social security affiliation. Also, our results for employment status did not suggest greater risk of mortality for those in the not-employed strata compared with people in the employed category. The evidence on the effects of working status on health suggests that unemployment is related to poor health (e.g. greater risk of mental illness, physical complaints, and an increased risk for coronary heart diseases) and early mortality [31]. Although our models were further stratified by age group to address potential effect modification by this characteristic, our results should be carefully interpreted, since there was not a well-defined measure of unemployment excluding all the economically inactive [12]. We did not have information on the health status of those in the "non-working" group before death, so it is not possible to determine if a deteriorating health status led to a "non-working" condition (healthy worker effect). When evaluating the role of specific job categories in the association between short-term exposure to $PM_{2.5}$ and mortality, the lack of consistency in the codification of specific job categories throughout the period of study led us to evaluate these associations for a shorter time period (2013–2019), likely reducing power to identify associations by individual job categories (Figure S1). Two major problems with the use of death certificates for classifying employment include ambiguity about whether unemployed persons are actually retired or if a prior occupation is reported for retired decedents and thus may not represent their recent exposures.

Among the potential explanations on the lack of consistency in effect modification observed in our study compared with evidence on modifying effects from age, sex, and SES characteristics in high income regions are: different overall exposure patterns; higher prevalence in the use of air conditioning in high-income regions that reduces residential exposure in more affluent segments of the population; greater mortality risk from infectious diseases, road injuries, violence, etc. in low-SES populations, while those of high-SES are more vulnerable to $PM_{2.5}$ exposure due to lower absolute risks from other risk factors (i.e. competing risk factors) [20]. It is also possible that studies from high-income countries are less likely to experience exposure measurement error given the availability to assign exposure to air pollutants at the residential address of study subjects, instead of zip-code, county or municipality level; which are often large and socially heterogeneous. The reason why effect modifiers commonly observed in high-income regions might not be identified in low- and middle-income countries deserve further investigation.

Other limitations in our study could be related to the inaccurate classification of death causes for some diseases. In general, inaccurate classification of death causes in Mexico is considered low [38]. However, errors might exist in the classification of some mortality outcomes, including those from the circulatory system, which have been recognized among the most affected by the use of "garbage codes", namely, those that are not underlying causes of death (e.g. heart failure), but codes that define poorly-specified diagnoses not clearly identifying a death cause. For Mexico City, we have previously reported that the use of garbage codes tends to bias effect estimates of cardiovascular outcomes to the null, and that proportional redistribution of garbage codes into actual death causes may help to reduce such bias [24]. Also, there are contributions to exposure measurement error that accumulate from the combination of prediction model error and the use of locality of residence to represent all relevant time-activity, which may bias effect estimates (albeit less than the use of a single city-wide exposure time series). Although our models were adjusted by the potential confounding effect of ambient temperature, we did not control by humidity, either alone or combined with temperature into a heat index to better reflect the human-perceived temperature discomfort which could also trigger mortality. On the other hand, since holidays are time-varying and are not fully controlled by design, i.e. those are not matched on in control selection, there is possibility of residual confounding by their influence. Stratification by season of the year was not conducted in our analyses. Therefore, there might be potential seasonal variations related to changes in $PM_{2.5}$ toxicity, population behavior, and seasonal interactions with extreme temperatures that warrant further investigation. The study of effect modification by age group, sex, and SES indicators can be sensitive to analytic methods. Although our stratified analyses have been the standard in case-crossover and time-series studies, the sparse numbers in some of the strata could have reduced statistical power to detect associations. Finally, we presented cumulative

associations for up to six days and observed a trend of increasing mortality risks suggesting the absence of harvesting effects. However, the case-crossover approach has inherent limitations when examining associations over longer time periods than just a few days, including positive autocorrelation in the exposure series of case and control days, which could affect efficiency in effect estimation.

Conclusion

Our findings support the growing evidence that short-term exposure to $PM_{2.5}$ may trigger cause-specific mortality beyond cardiovascular and respiratory outcomes, including mortality from diseases of the digestive and genitourinary systems. This evidence can be used to inform and update local environmental health policies, and to more comprehensively assess the benefits of interventions aimed to reduce $PM_{2.5}$ pollution in the Mexico City Metropolitan Area. Our findings suggest that short-term exposure to $PM_{2.5}$ increases the risk of acute mortality in adults from the study region, regardless of age group, sex, and SES characteristics.

Abbreviations

$PM_{2.5}$	Particulate matter < 2.5 μm in aerodynamic diameter
CI	Confidence interval
IQR	Interquartile range
INEGI	National Institute of Statistics and Geography of Mexico
ICD-10	International Classification of Diseases Tenth Revision
XGBoost	Extreme gradient boosting
IDW	Inverse-distance weighting
GPWv4	Gridded Population of the World version 4
GAM	Generalized additive models

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-023-01024-4.

Additional file 1: Figure S1. Cumulative percentage increase (%) and 95% CI for non-accidental mortality by education, insurance type and job categories (adults ≥18 years-old) per 10 μg/m^3 increase in $PM_{2.5}$ over two days (lag_{01}) and one week (lag_{06}) in the Mexico City Metropolitan Area for 2004-2019. Job category associations are for the period from 2013-2019. **Table S1.** Linearity tests in the associations between short-term exposure to $PM_{2.5}$ and broad-group mortality outcomes. **Table S2.** Single lag and cumulative Odds Ratios and 95% confidence intervals for broad-group mortality outcomes associated with 10μg/m^3 increase in $PM_{2.5}$. **Table S3.** Single lag and cumulative Odds Ratios and 95% confidence intervals for cause-specific mortality outcomes associated with 10μg/m^3 increase in $PM_{2.5}$.

Authors' contributions

IGA: Conceptualization, Methodology, Data Curation, Software, Formal Analysis, Writing–Original Draft. HRR: Conceptualization, Writing–Review & Editing. EC: Methodology, Writing–Review & Editing. JR: Software, Formal Analysis, Writing–Review & Editing. MTO: Conceptualization, Writing–Review & Editing. VHBA: Conceptualization, Writing–Review & Editing. ACJ: Conceptualization, Methodology, Supervision, Writing–Original Draft, Project Administration, Resources. All authors reviewed the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Because the records used in all analyses were already publicly available, the senior author (ACJ) received a determination of exempt human research [45 CFR 46. 101(b) (Category 4)] from the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

Competing interests

The authors declare no competing interests.

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