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Lucille Borlaza-Lacoste, Valeria Mardoñez, Anouk Marsal, Ian Hough, Vy Ngoc Thuy Dinh, et al.. Oxidative potential of particulate matter and its association to respiratory health endpoints in high-altitude cities in Bolivia. *Environmental Research*, 2024, 255, pp.119179. 10.1016/j.envres.2024.119179 . hal-04705771

HAL Id: hal-04705771

<https://hal.science/hal-04705771v1>

Submitted on 24 Sep 2024

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Oxidative potential of particulate matter and its association to respiratory health endpoints in high-altitude cities in Bolivia

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Highlights:

- Sources of PM₁₀ OP identified in Bolivia: mainly traffic and biomass burning.
- OP as a viable metric linked with respiratory health outcomes.
- OP_{DTT} associations found with hospital visits for pneumonia and acute respiratory diseases within first week of exposure.
- Traffic and dust sources also showed significant association with increased hospital visits, likely via distinct biological pathways (exogenous vs endogenous ROS).

Abstract.

Exposure to particulate matter (PM) pollution is a significant health risk, driving the search for innovative metrics that more accurately reflect the potential harm to human health. Among these, oxidative potential (OP) has emerged as a promising health-based metric, yet its application and relevance across different environments remain to be further explored. This study, set in two high-altitude Bolivian cities, aims to identify the most significant sources of PM-induced oxidation in the lungs and assess the utility of OP in assessing PM health impacts. Utilizing two distinct assays, OP_{DTT} and OP_{DCFH}, we

measured the OP of PM samples, while also examining the associations between PM mass, OP, and black carbon (BC) concentrations with hospital visits for acute respiratory infections (ARI) and pneumonia over a range of exposure lags (0-2 weeks) using a Poisson regression model adjusted for meteorological conditions. The analysis also leveraged Positive Matrix Factorization (PMF) to link these health outcomes to specific PM sources, building on a prior source apportionment study utilizing the same dataset. Our findings highlight anthropogenic combustion, particularly from traffic and biomass burning, as the primary contributors to OP in these urban sites. Significant correlations were observed between both OP_{DTT} and $PM_{2.5}$ concentration exposure and ARI hospital visits, alongside a notable association with pneumonia cases and OP_{DTT} levels. Furthermore, PMF analysis demonstrated a clear link between traffic-related pollution and increased hospital admissions for respiratory issues, affirming the health impact of these sources. These results underscore the potential of OP_{DTT} as a valuable metric for assessing the health risks associated with acute PM exposure, showcasing its broader application in environmental health studies.

Keywords : Particulate matter, oxidative potential, respiratory health, Bolivia, source apportionment, Positive matrix factorization, Poisson regression

1 Introduction

Ambient particulate matter (PM) air pollution has been linked to millions of premature deaths globally (Juginović et al., 2021) and remains a critical issue in many areas due to anthropogenic emissions from traffic, industry, and other sources (Borlaza et al., 2018, 2021a). Although the effects of PM pollution on human health have been extensively researched, studies addressing the unique context of high-altitude cities are limited. Cities, located over 2000 meters above sea level, face compounded risks due to factors such as limited oxygen availability affecting breath volume (Beall, 2007; Exposure Factors Handbook, 2022; Julian and Moore, 2019). Contrary to the reduction of PM concentrations due to emission control policies observed in some areas of the world (Aas et al., 2019; Collaud Coen et al., 2020; Borlaza et al., 2022a), several high-altitude cities in developing regions are experiencing worsening air quality due to industrial growth and increased traffic (Zalakeviciute et al., 2020; Ramírez et al., 2018).

Much work remains to elucidate the mechanism of PM exposure leading to adverse health effects. One of the well-recognized pathways is the capacity of certain PM components to induce oxidative stress in the lungs, leading to inflammatory responses that range from cell damage to cell death (Mudway et al., 2020; Ayres et al., 2008; Kaur et al., 2022). Some potential pathways of PM-induced oxidative stress arise from acute inflammatory responses, nucleic acid damage and repair, and energy perturbations (Tang et al., 2022). Hence, a growing number of studies have focused on assessing the oxidative potential (OP) of PM, defined as the capability of PM to generate reactive oxygen species (ROS) that deplete anti-oxidants in the lungs (Bates et al., 2019; Daellenbach et al., 2020; Park et al., 2018; Borlaza et al., 2018, 2021b).

Recent studies have begun to explore oxidative potential (OP) as an emerging health-based metric, highlighting its
70 significance in assessing the health impacts of particulate matter exposure (Borlaza et al., 2022b; Marsal et al., 2023;
Weichenthal et al., 2016, 2021). However, the comprehensive validation of OP as a robust health metric across diverse
environments remains an ongoing endeavor. This necessitates further research, especially in cities at high altitudes and in
developing countries, to fully understand its global applicability. Notably, Latin America is developing as a region for OP
research, with recent studies in Chile and Ecuador. Molina et al. (2023) investigated the OP of PM in two urban areas of
75 Chile, while Andrade et al. (2021) explored the oxidative potential and respiratory deposition of size-segregated PM within
the country. Additionally, research conducted in Ecuador has examined the chemical composition and OP of PM₁₀ near
flares in oil extraction and refining areas (Barraza et al., 2020). These studies underscore the critical importance of assessing
OP in varied geographical and environmental contexts to validate its use as a health metric.

An extensive study of ambient PM air pollution in two high-altitudes Bolivian cities, La Paz (approximately 3200-3600
80 meters above sea level (m.a.s.l.) and El Alto (4050 m a.s.l.), has been recently published (Mardoñez et al., 2023). This study
included a multisite Positive Matrix Factorization (PMF) modeling approach to discern the sources of particulate matter with
a diameter of 10 microns or less (PM₁₀) in the conurbation. Notably, an extensive array of organic markers, such as
levoglucosan, polycyclic aromatic hydrocarbons (PAHs), hopanes, and alkanes, was used in the analysis – a significant
expansion from traditional datasets commonly limited to ions, metals, and carbonaceous components. This methodology led
85 to the identification of 11 PM₁₀ sources, encompassing both natural and anthropogenic origins, including traffic-related
factors, non-exhaust emissions, and previously unresolved sources like lubricant oil and waste burning.

Building upon these foundational insights, the present study utilized an advanced PMF dataset (Mardoñez et al., 2023) and to
identified the main drivers of OP of PM₁₀ in the La Paz and El Alto conurbation. Furthermore, this study enhanced its
analysis of PM health impacts by incorporating a dataset on the PM_{2.5} fraction. Subsequently, a comprehensive investigation
90 was conducted using both PM₁₀ and PM_{2.5} datasets, alongside data on hospital visits for respiratory diseases. To the best of
our knowledge, this is the first study linking OP sources to respiratory health in high-altitude Andean cities, providing an
unprecedented perspective on the health impact of PM exposure.

2 Materials and methods

This section describes the methodologies used in the study, from the sampling and measurements (section 2.1 and section
95 2.2) to the mathematical and statistical tools used to deconvolute the pollution sources that contribute degrading the air
quality in the metropolitan area La Paz-El Alto (section 2.3 and section 2.4). Furthermore, section 2.5 describes the
methodologies used to unveil the existing associations between the air quality parameters considered in the present study,
and two respiratory health outcomes. A schematic diagram that outlines the research workflow and processes described in
sections 2.4 and 2.5 can be found in the supplementary information, to provide a coherent overview of the complex
100 methodologies employed in our study (Figure S1).

2.1 Study area and sampling parameters

The study area consists of two adjacent high-altitude cities in Bolivia, La Paz (LP, 16.50°S, 68.13°W, 3600 m.a.s.l.) and El Alto (EA, 16.51° S, 68.13° W, 4025 m.a.s.l.). The sampling locations were chosen to minimize direct interference from local sources such as vehicular traffic and pedestrian activities, as well as the distortion caused by buildings and other structures that can affect ground-level air quality measurements. At the same time, the selection of the sampling locations aimed to obtain a more representative sample of a wider urban background levels of PM, which are more reflective of the average exposure experienced by the urban population over time.

The sampling site in LP lies on the rooftop of a four-story building of the Museum Pipiripi (Espacio Interactivo Memoria y Futuro Pipiripi), located on a steep hill downtown, surrounded by residential areas. The EA sampling site is located on the Altiplano plateau, in the meteorological observatory of the El Alto International Airport, surrounded by a few industrial sites and a large vehicle fleet servicing regional and international connections for the metropolis. Both sites are considered an urban background site. Due to the topographical differences between the LP and EA sites, the meteorological conditions can vary greatly despite their separation of only 7 km (horizontal distance) and 0.5 km (vertical distance).

The sampling campaign was conducted between April 2016 and June 2018, with high-volume samplers (MCV CAV-A/Mb, 30 m³h⁻¹) to collect 24-hr PM₁₀ (April 2016- June 2017) and PM_{2.5} (June 2017- July 2018) samples onto quartz fiber filters (150 mm-diameter, Pallflex QAT and Whatman) once every three days, for a total of 182 filters in LP and 177 filters in EA. All filters were preheated at 500°C for 8 hours before sampling. After sample collection, all filters were safely stored in a low temperature-controlled environment until analysis.

Daily mass concentrations (μg m⁻³) were measured by gravimetric analysis of the filters. All filters were strategically fractionated to be sufficient for all the chemical analyses considered. The chemical characterizations were: elemental carbon (EC), organic carbon (OC), sugar anhydrides (Levogluconan, Mannosan), sugar alcohols (Arabitol, Mannitol), water-soluble ions (SO₄²⁻, NO₃⁻, Cl⁻, MSA, NH₄⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺), metals (Al, Ca, K, Na, Mg, Fe, Ti, V, Mn, Cu, Zn, Rb, Sn, Sb, Pb, among others), polycyclic aromatic hydrocarbons (PAHs: Fla (Fluoranthene), Pyr (Pyrene), Tri (Triphenylene), BaA (Benz[a]anthracene), Chr (Chrysene), BaP (Benzo[a]pyrene), BghiP (Benzo[ghi]perylene), IP (Indeno[1,2,3-cd]pyrene), BbF (Benzo[b]fluoranthene), Cor (Coronene)), alkanes (C21-C26), methyl PAHs, thiophens, hopanes (HP3 to HP4), alkane methoxyphenols, and methylnitrocatechols. Field blank samples (*n*=52) were also collected and used to calculate the limits of quantification, which were subtracted from the samples before calculating atmospheric concentrations. An intensive characterization study on the PM chemistry and sources in the area has been reported elsewhere (Mardoñez et al., 2023).

Equivalent black carbon (BC) mass concentrations were also measured during the same period at both sites using an aethalometer model AE33 in EA and an aethalometer model AE31 in LP (April 2016 - June 2018). However, due to the intermittence of data availability resulting from technical problems in EA, only the period of data collection from May 2016-Aug 2017 was considered in the present analysis.

Wind speed and direction were measured at both sites with a 15-min time resolution using wind monitors (YOUNG 05103) placed on the sites. Other meteorological variables were provided by the Airport air navigation administration (Administración de Aeropuertos y Servicios Auxiliares a la Navegación Aérea, AASANA) with 1-hour time resolution and corrected for standard temperature and pressure, for El Alto, and from the National Meteorology and Hydrology Service (Servicio Nacional de Meteorología e Hidrología, SENAMHI) for La Paz on a daily time resolution. The meteorological variables were aggregated to match our health outcome data by averaging all measures in each week.

2.2 Oxidative potential (OP) analysis

The OP of PM₁₀ and PM_{2.5} were assessed by two acellular assays (using dithiothreitol (DTT) and dichlorofluorescein probes (DCFH)) with filter extraction using a simulated lung fluid (SLF) solution at 37°C and at 25 µg mL⁻¹ iso-mass concentration based on the protocol proposed by Calas et al. (2018). The SLF (mixture of salts and lung surfactant 1,2-dipalmitoylphosphatidylcholine) is designed to mimic the lung's extracellular fluid, providing a relevant medium for extracting PM in a manner that closely approximates human lung exposure. This approach ensures that our OP measurements are reflective of potential biological responses to PM exposure.

In the DTT assay, the probe is an antioxidant surrogate representing the reaction between PM and biological reducing agents. The consumption of DTT in the reaction corresponds to the capacity of PM to generate reactive oxygen species (ROS) (Cho et al., 2005). The remaining DTT is reacted with 5,5-dithio-bis-(2-nitrobenzoic acid) to produce 5-mercapto-2-nitrobenzoic acid. This solution is then analysed under a spectrometer (absorbance at 412 nm wavelength using a TECAN spectrophotometer Infinite M200 Pro plate-reader) in 96-well multiwall plate (Greiner-Bio) for a total of 30 minutes of analysis time with a 10-minute interval. In the DCFH assay, a particle-bound ROS method is based on the reaction of the ROS in PM with DCFH, a non-fluorescent reagent, with horseradish peroxidase. This reaction produces a fluorescent compound, 2,7-dichlorofluorescein (DCF). The DCF formation is also analysed under a spectrometer (excitation at 485 nm, emission at 530 nm wavelength using the same plate-reader as the DTT-assay) in a black 96-well multiwell plate for a total of 30 minutes of analysis time with a 2-minute interval under constant agitation at 37°C. To ensure the stability of the OP analyses, a positive control was analysed in duplicates in every experiment using a 1,4-naphthoquinone (1,4-NQ) solution for DTT (40 µl of 24.7 µM stock solution) and DCFH (80 µl of 24.7 µM 1,4-NQ solution) assays. There is a ≤3% coefficient of variation (CV) in the positive control analysis for both assays.

Finally, the OP activity of PM is calculated based on a volume-normalized metric (OP_v) representing the OP consumption (nmol min⁻¹) of PM normalized by the air volume (m³) during sampling. All samples were analysed in triplicate with a CV between 0 and 10% for each assay. We aggregated the OP measures to match our health outcome data by averaging all measures in each week.

2.3 Source apportionment of PM₁₀

Source apportionment of PM₁₀ was performed using the Positive Matrix Factor (PMF 5.0) model, developed by the U.S. Environmental Protection Agency (EPA). The improved multi-site approach for the PMF analysis is detailed in (Mardoñez et al., 2023). Briefly, the PMF applies a weighted least-squares fit algorithm as described in Eq. 1:

$$x_{ij} = \sum_{k=1}^p g_{ik} f_{kj} + e_{ij} \quad [\text{Eq. 1}]$$

where x_{ij} represents the j th measured chemical species in the i th PM sample, p is the number of sources, g_{ik} is the contribution of the k th source to the i th sample, f_{kj} is the contribution of the k th source to the j th chemical species (obtained source chemical profiles), e_{ij} are the model residual for the j th chemical species in the i th sample. The final solution selected with good statistical indicators and sound geochemical properties resulted in 11 resolved sources: dust, secondary sulfate, secondary nitrate, primary biogenic aerosols (PBA), MSA-rich, biomass burning (BB), traffic 1 (gasoline traffic), traffic 2 (diesel traffic), lubricant, non-exhaust emissions, and waste burning. A complete description of each PM₁₀ source is presented in Mardoñez et al. (2023). Due to the timing of data preparation and analysis, the PM_{2.5} dataset was not included in the PMF analysis at the time of progression.

2.4 Source apportionment of OP

The OP contribution of each PM₁₀ source was apportioned using multiple linear regression (MLR) based on the procedure proposed by Weber et al. (2021). Briefly, the OP activity measured in each PM sample was used as the dependent variable while the mass contributions of each PMF-resolved source ($\mu\text{g m}^{-3}$) were used as the independent variables, as shown in Eq. 2:

$$OP_{obs} = (G \times \beta) + \varepsilon \quad [\text{Eq. 2}]$$

where OP_{obs} are the observed OP_v measured either by DTT or DCFH assay ($\text{nmol min}^{-1} \text{m}^{-3}$), G are the source contributions ($\mu\text{g m}^{-3}$) obtained from the PMF model, β are the regression coefficients representing the mass-normalized (“intrinsic”) OP (OP_m) ($\text{nmol min}^{-1} \mu\text{g}^{-1}$) of each source, and ε are the model residuals. The uncertainties of β were estimated by a bootstrapping method ($n=500$) using the random selection of samples to account for outliers and seasonal variation in each source specific OP_m . The OP contribution of each source ($\text{nmol min}^{-1} \text{m}^{-3}$) was calculated by multiplying β of each source by the mass contribution of the source (G).

190 2.5 Linking OP of PM to respiratory health endpoints

Weekly numbers of hospital visits at all health care centers in La Paz and El Alto due to either (1) pneumonia (Pneu) or (2) acute respiratory infections (ARI) other than pneumonia during the sampling campaign were obtained from the Bolivian Ministry of Health and Sports. Pneumonia is an inflammation of deep lung tissues including alveoli, in response to an infection caused by bacteria, viruses, fungi, or other chemical irritants. Acute respiratory infections are infections of the
195 airways, that can occur in the upper (from the nostrils to the larynx) or the lower respiratory tracts (from the trachea to the bronchioles), such as laryngitis or bronchitis. Pneumonia is classified under ICD-10 codes J12 to J18, encompassing various etiologies and types of pneumonia. Acute respiratory infections are broadly categorized under ICD-10 codes J00 to J06 for upper respiratory tract infections and J20 to J22 for lower respiratory tract infections, which include conditions such as laryngitis and bronchitis among others.

200 The adjusted associations of observed exposures (PM, OP_{DTT} , OP_{DCFH} , -BC), normalized by their respective interquartile range (IQR), with the health outcomes (Pneu and ARI) were estimated using single-exposure (mono-pollutant) quasi-Poisson regression models, in each size fraction (i.e., PM_{10} and $PM_{2.5}$). Baseline unadjusted associations were also computed for reference and are available in the supplementary information (SI) (Figure S2). To assess the potential impact of age on these associations, a stratified analysis by age group was conducted (Figure S3). Additionally, multipollutant models were
205 evaluated to investigate the combined effects of different pollutants (Figures S4-S7). However, the subsequent sections will focus on the main analysis, as both age stratification and multipollutant models showed minimal effects. The adjustment factors considered in the models were chosen based on the literature: temporal variable (time), meteorological conditions (temperature, relative humidity, wind speed), and a random effect representing the city (El Alto and La Paz).

The temporal variable representing time was modelled as a natural spline with 6 degrees of freedom per year, representing
210 time-varying unmeasured confounders having a period of two months or more. Each meteorological variable was modelled as a natural spline with three degrees of freedom to capture potentially non-linear associations with the health outcomes. A separate model was fit for each of exposure lags 0, 1, and 2 weeks where lag 0 is the week of the hospital visit count, lag 1 is the previous week, and lag 2 is the week before that. This approach was driven by the possibility that there may be a time lag between exposure, the manifestation of biological effects, and an individual seeking medical care. A similar analysis was
215 also applied to the sources of PM using a multi-pollutant approach, i.e. the linearly independent contributions of each source to PM_{10} (PMF-resolved sources) were simultaneously included as additive terms in the model.

Associations were reported as a percentage increase in the probability of hospital visits. All statistical analyses were performed using *R* (R Core Team, 2021); adjusted analyses used the *glmmPQL* function from the MASS package (Venables and Ripley, 2002).

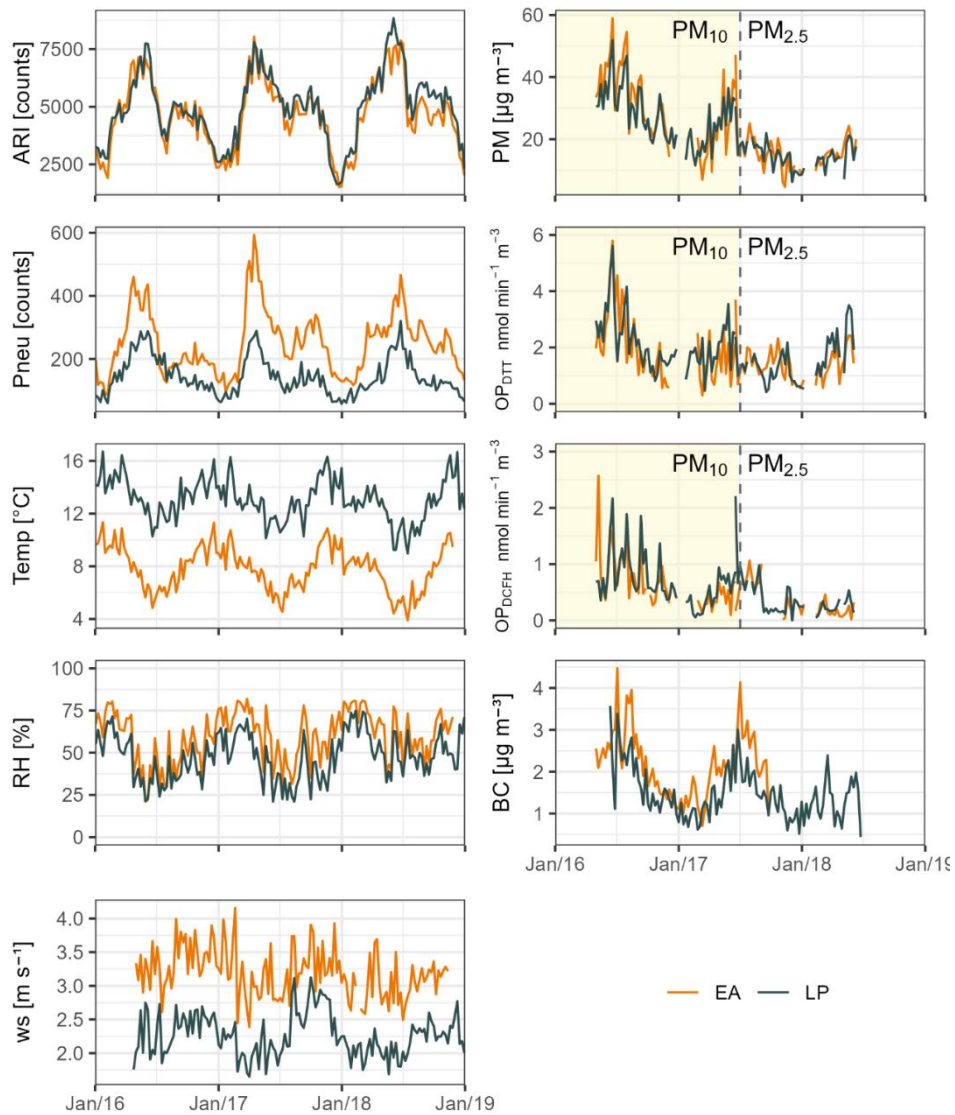


Figure 1: Temporal variation of the weekly number of hospital visits due to acute respiratory infection (ARI) and pneumonia (Pneu); meteorological variables: mean temperature (Temp), relative humidity (RH), and wind speed (ws); and exposures: particulate matter (PM), oxidative potential (OP_{DTT} & OP_{DCFH}), black carbon (BC) in La Paz (LP) and El Alto (EA) during the measurements campaign. Note: Difference in shades (yellow: PM_{10} , white: $PM_{2.5}$) refer to the period of measurements for each PM fraction.

225

3 Results and discussion

3.1 Study population and the characteristics of particulate matter (PM) and its oxidative potential (OP)

230 El Alto and La Paz have a surface area of 370 and 475 km², respectively, and a projected population of 1,030,151 and 912,960 inhabitants in 2018, respectively (Red MoniCA, 2021). The highest number of hospital visits occurred during the dry months of the year, April to June (average temperatures of 6.8°C in EA and 12.3°C in LP), highlighting the potential influence of meteorological conditions, with a second smaller mode between September and November for both health endpoints (Figure 1).

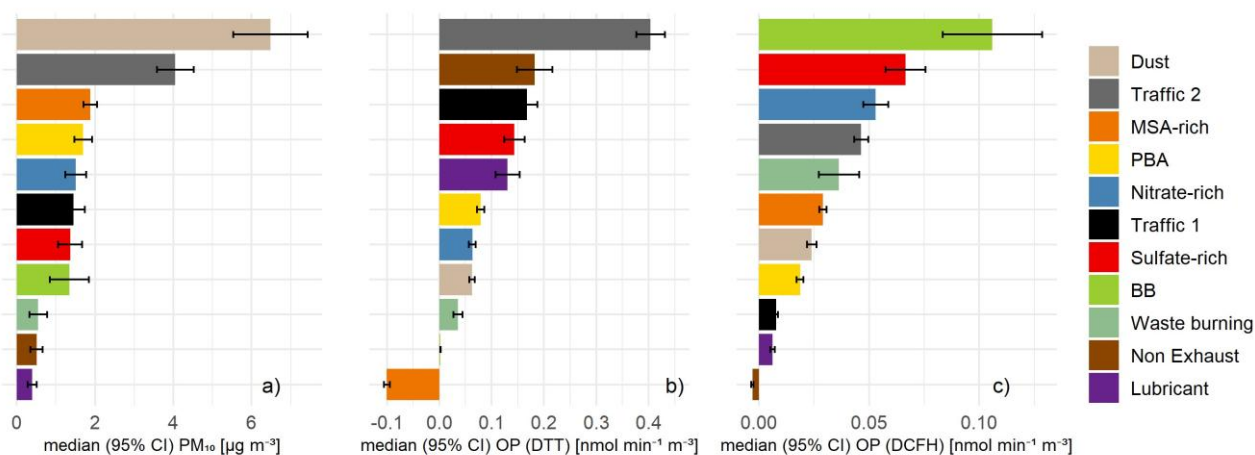
235 The median (25th – 75th percentile) mass concentrations of PM₁₀ and PM_{2.5} during the period of the study were 28.9 (21.2 – 39.3) and 15.5 (11.8–19.1) µg m⁻³, respectively, in El Alto and 27.1 (20.4 – 33.7) and 14.8 (12.1 – 17.4) µg m⁻³, respectively, in La Paz. A distinct seasonal variability was found, particularly high during dry season (colder months with minimum precipitation, May to August) and low during the wet season (December to March) (Figure 1). During the study period, 13% of the sampled days in EA and 4% of the sampled days in LP exceeded the 2021 WHO 24-hour air quality guideline level for PM₁₀ of 45 µg m⁻³. All exceedances occurred during the dry season, which overlaps with the austral winter months. In contrast, roughly 50% of the sampled days in both cities exceeded the 2021 WHO 24-hour AQ guideline level for PM_{2.5} of 15 µg m⁻³. It is important to note that these exceedances found in the sampling sites represent those of an urban background site. It is possible that the pollution level varies above these concentrations across the cities, especially closer to local sources of traffic, dust, or industrial emissions, highly likely reaching the local air quality regulatory levels (150 µg m⁻³). The annual median (25th – 75th percentile) of BC mass concentration was 1.0 (0.5 – 2.0) and 0.7 (0.4 – 1.3) µg m⁻³ in El Alto and La Paz, respectively, with a similar seasonality as PM (Figure 1).

245 The median (25th – 75th percentile) OP_{DTT} was 1.77 (1.3 – 2.6; average: 2.01) nmol min⁻¹ m⁻³ for PM₁₀ and 1.29 (0.9 – 1.9; average: 1.40) nmol min⁻¹ m⁻³ for PM_{2.5}; for OP_{DCFH} it was 0.54 (0.4 – 0.9; average: 0.65) nmol min⁻¹ m⁻³ for PM₁₀ and 0.26 (0.1 – 0.5; average: 0.35) nmol min⁻¹ m⁻³ for PM_{2.5}, following the same seasonality as PM mass concentration (Figure 1). In comparison to similar studies by the group using the same OP_{DTT} protocol, this work found a lower average OP_{DTT} of 2.0 nmol min⁻¹ m⁻³, contrasted from the average levels in France at 2.7 nmol min⁻¹ m⁻³ (Weber et al., 2021), India at 10 nmol min⁻¹ m⁻³ (Bhattu et al., 2024), and Barcelona at 2.5 nmol min⁻¹ m⁻³ (In 'T Veld et al., 2023).

255 Several studies in South America have used different extraction procedures from those used in our research. As a result, their reported findings are generally lower than ours. For example, a study conducted at two sites in Chile, referred to as STG and CHI, reported distinct mean oxidative potential of dithiothreitol (OPDTT) values. In STG, the mean OP_{DTT} values for PM₁₀ were 0.53 nmol min⁻¹ m⁻³ (range: 0.15–1.52), and for PM_{2.5}, 0.38 nmol min⁻¹ m⁻³ (range: 0.07–0.979). In CHI, the corresponding values were 0.56 nmol min⁻¹ m⁻³ (range: 0.09–2.78) for PM₁₀ and 0.66 nmol min⁻¹ m⁻³ (range: 0.03–260 1.94) for PM_{2.5}. However, the difference in extraction procedures makes direct comparisons challenging. Notably, the studies in Chile did not use simulated lung fluid (SLF) for particulate matter extraction, a key component of our methodology.

3.2 Sources of OP of PM₁₀

Sources of PM₁₀ in terms of mass concentration were previously identified and apportioned using PMF (Mardoñez et al., 2023) (Figure 2). These PMF-resolved sources were matched to the available OP of PM₁₀ data and then used to apportion the corresponding OP of PM₁₀ using MLR. This analysis resulted in an OP deconvolution with an R^2 (coefficient of determination) of 0.48 for OP_{DTT} and 0.67 for OP_{DCFH}, respectively. Spearman correlation coefficients (r_s) for measured OP and the PMF-resolved sources were also calculated for each assay (see Table S1 in the SI). Generally, the reconstructed OP was well within the range of the observed OP. However, some local peaks of measured OP were not captured by the MLR model (see Figure S8). The two assays used in this study allowed a wider sensitivity towards various sources compared to the other existing OP assays (Dominutti et al., 2023), but ultimately focused on the impact of anthropogenic sources to OP of PM₁₀.



275 **Figure 2: Median source contribution to a) PM₁₀ mass concentrations (obtained from PMF), b) reconstructed volume-normalized OP_{DTT} of PM₁₀, and c) reconstructed volume-normalized OP_{DCFH} of PM₁₀ (right). The error bars represent the 95% confidence interval. Note: PBA – primary biogenic aerosols, BB – biomass burning.**

Key insights into the OP of PM₁₀, as indicated by the mass-normalized OP (OP_m , nmol min⁻¹ µg⁻¹) of each source, is presented in Figure S9. The PM₁₀ sources with higher OP_m contain more redox-active species. Notably, the daily median OP_{DTT} contribution was predominantly from traffic-related sources. Specifically, the leading contributors to OP_{DTT} include traffic 2 (0.42 ± 0.32 nmol min⁻¹ m⁻³; average: 0.47), non-exhaust (0.18 ± 0.38 nmol min⁻¹ m⁻³; average: 0.29), and traffic 1 (0.16 ± 0.22 nmol min⁻¹ m⁻³; average: 0.23), as shown in Figure 2. Based on the factor description of traffic 1 and traffic 2 (Mardoñez et al., 2023), it is highly probable that traffic 1 corresponds to emissions from gasoline-powered vehicles, while traffic 2 is predominantly associated with diesel-powered vehicles. These findings underscore the significant impact of vehicular emissions on the OP of PM₁₀.

In contrast, for OP_{DCFH} , the top contributors are biomass burning ($0.10 \pm 0.25 \text{ nmol min}^{-1} \text{ m}^{-3}$; average: 0.20), sulfate-rich ($0.07 \pm 0.10 \text{ nmol min}^{-1} \text{ m}^{-3}$; average: 0.10), and nitrate-rich sources ($0.05 \pm 0.06 \text{ nmol min}^{-1} \text{ m}^{-3}$; average: 0.07). The sulfate-rich source is predominantly associated with long-range transport of pollutants, while the nitrate-rich source is linked to the oxidation of nitrogen oxides from traffic emissions. Together, these sources account for approximately 58% of the total OP_{DCFH} , confirming the substantial role of anthropogenic emissions in influencing the oxidative potential of PM_{10} in the studied areas (Mardoñez et al., 2023).

Figure 2 illustrates the disparities in source impacts on PM_{10} mass concentration versus OP. The primary sources of PM_{10} , notably dust and traffic 2, contribute to 43% of the total PM_{10} mass. In terms of redox activity, traffic 2 emerges as a top contributor to OP_{DTT} , while also ranking fourth in OP_{DCFH} . Meanwhile, dust shows a substantially lower capacity to induce oxidative stress in both assays, with an intrinsic OP eight times lower than traffic 2 for OP_{DTT} . Conversely, sources such as non-exhaust (OP_{DTT} only), traffic 1, lubricant, sulfate-rich, and nitrate-rich, though contributing minimally to PM_{10} mass, were significant contributors to OP in both assays. These findings underscore the importance of considering these differences when assessing the potential health impacts of PM_{10} .

The varying source rankings between the two assays can be attributed to their different sensitivities to redox active species in PM (Dominutti et al., 2023). DTT, being a thiol, displays a balanced sensitivity to both organic (mainly OC and quinones) and inorganic (mainly metal traffic-related) PM components, while DCFH is sensitive to OC, total carbon, and secondary components like SO_4^{2-} and NO_3^- (Pietrogrande et al., 2019; Borlaza et al., 2021b), targeting particle-bound ROS and reactive nitrogen (Venkatachari et al., 2005; Crow, 1997). This sensitivity explains why the traffic 2 source significantly contributes to both mass and OP_{DTT} , underscoring the importance of mitigating diesel traffic emissions to alleviate the health impacts associated with PM_{10} exposure. Furthermore, in high-latitude areas where wood burning is less significant for domestic heating, biomass burning from agricultural burning stands out as a significant source of OP, as measured by OP_{DCFH} . Although anthropogenic sources are important drivers of OP of PM_{10} , there are also contributions from biogenic sources (MSA-rich and PBA). These sources, identified by organic tracers, can play an important role in the dynamics of OP in PM_{10} (Daellenbach et al., 2020; Borlaza et al., 2022b) based on their ability to modulate the redox-active species in PM (Samake et al., 2017). By recognizing seasonal emission variabilities, targeted mitigation efforts could effectively improve regional air quality.

3.3 Linking PM exposure to respiratory health endpoints

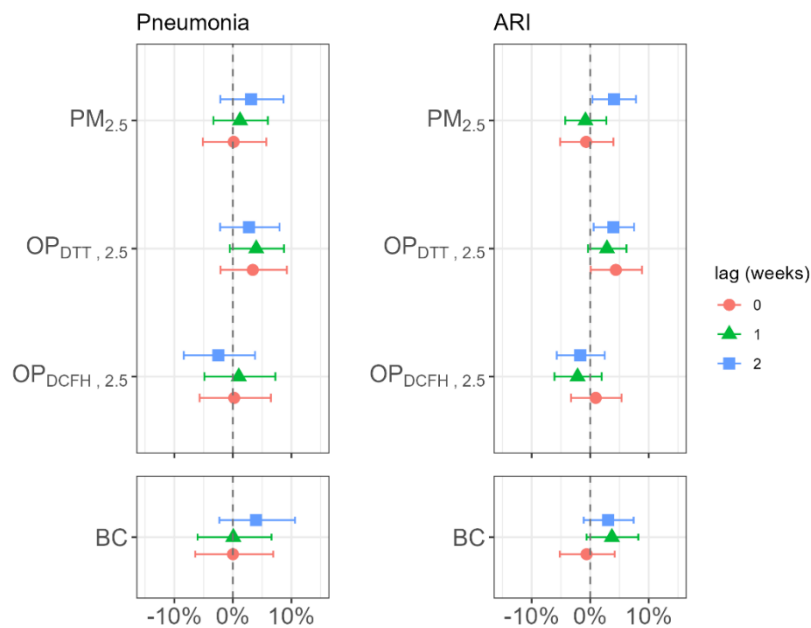
First, the adjusted associations between exposure metrics ($PM_{2.5}$, OP_{DTT} , OP_{DCFH} , and BC) and the number of weekly hospital visits for two respiratory outcomes (ARI and Pneu) are illustrated in Figure 3. The associations were presented over different time lags (0, 1, and 2 weeks).

For Pneu, an IQR increase in $PM_{2.5}$ mass concentration tends to show a positive association with a 3% (95% CI: -2% to 9%) increase in hospital visits at 2 weeks lag, which seems to weaken at 0- and 1-week lag (Figure 3). Very similar associations were found for BC mass concentration. An IQR increase in OP_{DTT} showed a positive association at all lags, with the

strongest association at 0-week lag (3% increase in hospital visits, 95% CI: -2% to 9%). OP_{DCFH} did not show any association with hospital visits due to Pneu (Table S2).

For ARI, an IQR increase in $PM_{2.5}$ mass concentration showed an association with increased hospital visits by 4% (95% CI: 0%–8%) at 2 weeks lag. An IQR increase in BC mass concentration showed a similar increase in hospital visits at both 1-week and 2 weeks lag. OP_{DTT} showed positive associations across all lags, with the strongest association at 2 weeks lag (4% increase in hospital visits, 95% CI: 1% to 8%). OP_{DCFH} did not tend to show any association with increased hospital visits due to ARI (Table S2).

The variation in the strength and direction of associations across metrics and time lags indicates that effects from PM exposure were more pronounced at a 2-week delay. This suggests that the physiological impact of exposure may take time to manifest as symptoms that lead to hospital consultations, or it could be that people only seek hospital care when symptoms become severe, rather than at their onset. Notably, the OP_{DTT} of $PM_{2.5}$ demonstrated a consistent positive association with respiratory health outcomes at all examined lags, highlighting its potential as a more sensitive indicator of health impact. Such insights into the temporal dynamics of pollution effects are crucial for informing public health strategies and shaping timely interventions in response to pollution events.



335 **Figure 3: Adjusted associations between weekly hospital visits for pneumonia (Pneu, left panel) and acute respiratory infection (ARI, right panel) with exposure metrics, including PM , OP_{DTT} , OP_{DCFH} in the $PM_{2.5}$ fraction, and BC. Note: All estimates are for an IQR increase in exposure, adjusted for time trend, temperature, relative humidity, wind speed, and with a random effect representing the city (El Alto and La Paz).**

340 In contrast, no clear associations were observed between PM_{10} mass concentration or its OP and increased hospital visits, as
illustrated in Figure S10 in the SI. Intriguingly, negative associations between Pneu and both PM_{10} mass concentration and
 OP_{DTT} were found, which contrasts with the findings in the $PM_{2.5}$ fraction. This disparity might be attributed to the different
sampling periods for PM_{10} (April 2016 to June 2017) and $PM_{2.5}$ (June 2017 to July 2018). Consistent with existing literature,
 $PM_{2.5}$ is typically associated more strongly with health outcomes than PM_{10} (Mebrahtu et al., 2023; Bodor et al., 2022;
345 Janssen et al., 2013). In fact, a few studies have reported an association of OP_{DTT} of $PM_{2.5}$ with increased risks of emergency
department visits for respiratory diseases (Fang et al., 2016), with stronger effect than $PM_{2.5}$ mass concentration (Abrams et
al., 2017; Bates et al., 2015). To further explore this, we analysed the specific PM_{10} sources identified through PMF.

3.4 Linking PM_{10} sources to respiratory health endpoints

Taking advantage of the previous study apportioning the sources of PM_{10} in the same sites (Mardoñez et al., 2023), the
350 associations of PM_{10} sources with hospital visits for Pneu and ARI were also examined and presented in Figure 4 (see Table
S3 for a tabulated summary). PM_{10} appears more suited for an exhaustive and comprehensive source apportionment,
especially when accounting for non-exhaust emissions that are mostly emitted in the coarse mode.

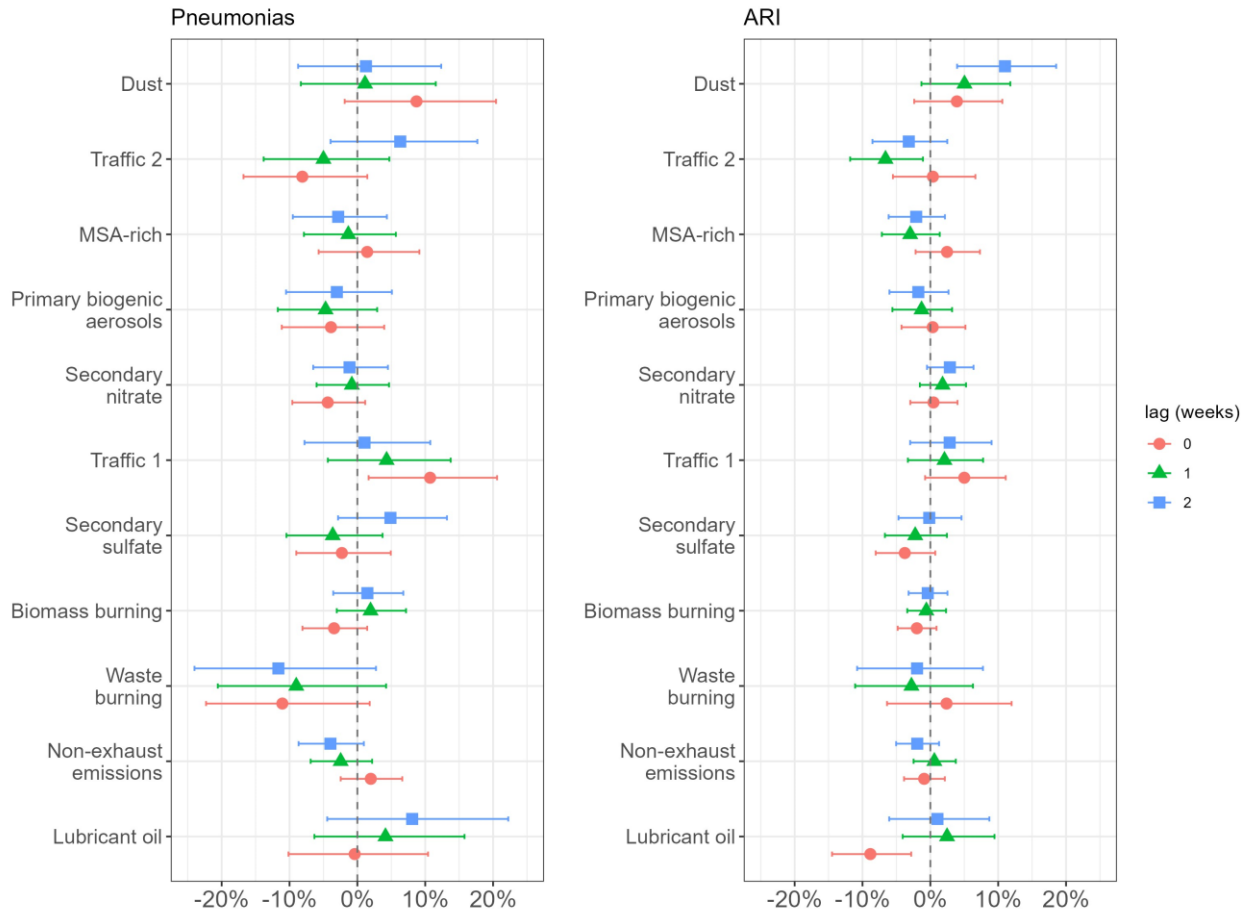
Specific PM_{10} sources were found to have stronger associations with hospital visits for both Pneu and ARI. Notably, dust and
traffic 1 factors demonstrated consistent positive correlations across all lags for both respiratory outcomes. Specifically, an
355 IQR increase in PM_{10} from traffic 1 was linked to an 11% rise (95% CI: 2%–21%) in Pneumonia-related hospital visits
within the week of exposure. Similarly, an IQR increase in PM_{10} from dust was associated with an 11% increase (95% CI:
4%–19%) in ARI-related visits, but with a 2-week delay. Conversely, most other PM_{10} sources did not exhibit a clear
connection with increased hospital visits.

An increase in PM_{10} from traffic 2 and lubricant oil factors was linked to a decrease in ARI hospital visits, with a 7%
360 reduction (95% CI: -12% to -1%) at a 1-week lag for traffic 2, and a 9% reduction (95% CI: -14% to -3%) with no lag for
lubricant oil. Similarly, waste burning factor was negatively associated with pneumonia across all lags, though these findings
did not significantly deviate from a null effect (see Table S3). These factors all had relevant contributions from specific
organic markers such as PAHs, alkanes, and hopanes (Mardoñez et al., 2023). PAHs can participate in photochemical
reactions, leading to ROS formation. It is important to note that while PAHs can exhibit redox activity, their primary
365 characteristic in the atmosphere are mainly related to their role as pollutants and carcinogens (Hrdina et al., 2022), rather
than their redox properties per se. The direct capacity to induce oxidative stress of PAHs is less pronounced compared to
other pollutants. This mechanism typically involves metabolic transformation into reactive intermediates that can generate
oxidative stress (Guarieiro et al., 2014). This highlights a key point: the mechanisms of toxicity of environmental pollutants
can vary significantly. Some, like certain PAHs, may have a more pronounced role in long-term health outcomes like cancer,
370 rather than immediate respiratory distress.

Another consideration on the inverse relationships of these factors may also reflect compensatory mechanisms (i.e.,
protective effect), such as upregulated antioxidant defenses or enhanced detoxification and repair systems, in response to

PAHs exposure (Låg et al., 2020). These physiological adaptations could alleviate the immediate impact of oxidative stress, potentially leading to fewer ARI hospital visits in the short-term. Such inverse relationships may seem biologically implausible, suggesting the possibility of residual confounding in these associations. Chemical interactions could also affect overall toxicity (antagonistic/synergistic effects), potentially reducing the toxicity of specific factors (Borlaza et al., 2021b) with contributions from organics. Accordingly, the interpretation of these findings necessitates caution, acknowledging the complex interplay of biological compensations, chemical interactions, and potential unmeasured confounding factors that may influence the observed associations.

380



385 **Figure 4: Associations between weekly hospital visits for Pneumonia (left panel) and acute respiratory infection (ARI, right panel) and the PMF-resolved sources of PM₁₀ in a multi-pollutant model. Note: All estimates are for an IQR increase in exposure, adjusted for time trend, temperature, relative humidity, wind speed, and with a random effect representing the city (El Alto and La Paz).**

Traffic-related emissions, especially those from traffic 1 (likely gasoline traffic emissions, (Mardoñez et al., 2023)), emerged as significant contributors to both Pneu- and ARI-related hospital visits and are also principal sources of OP_{DTT} in PM₁₀. Given that most traffic exhaust emissions are fine particles, they are likely captured in the PM_{2.5} fraction. Contrastingly, the impact of dust on respiratory health seems to operate through a mechanism distinct from oxidative stress, as it was a minor contributor to OP in PM₁₀. The physical characteristics of mineral dust particles, such as composition and shape (Fussell and Kelly, 2021), are known to be able to directly damage epithelial cells, leading to an inflammatory response characterized by cytokine release and a localized oxidative stress (which represent endogenous ROS), which could precipitate acute lung toxicity (Naota et al., 2010). This aligns with the findings of this study suggesting a different pathway for dust. Acellular OP assays primarily measure exogenous ROS, hence endogenous ROS cannot be assessed due to the absence of lung cells in the assay (He and Zhang, 2023). Additionally, the regional climatic conditions of the conurbation, notably its low humidity levels, could intensify the adverse health effects of high dust events (Deroubaix et al., 2013), analogous to the observed relationship between dust events and meningitis in Africa (Yarber et al., 2023). The differing lags in associations observed for Pneu versus ARI may reflect variations in the progression rates or symptom severity between these respiratory conditions. These findings underscore the need for pollution control policies that are responsive to the varying temporal patterns of health impacts associated with different PM sources.

3.5 Strengths and limitations of the study

This study evaluated the OP across fine (PM_{2.5}) and coarse (PM₁₀) fractions using DTT and DCFH assays, and apportioned OP of PM₁₀ sources identified by PMF analysis from prior research (Mardoñez et al., 2023). This study, by linking exposure metrics and PMF-resolved sources with respiratory health endpoints, offers pioneering research within the context of a Bolivian high-altitude urban background. It represents the first effort to associate these parameters, marking a critical step towards assessing OP as a viable health-based metric.

The strength of this study lies in the integration of a range of air quality parameters and specific PM sources to establish their relationship with respiratory health in a high-altitude environment. The findings reveal a link between PM_{2.5} mass, its OP, and respiratory diseases, predominantly influenced by traffic-related emissions. We observed associations between OP of PM_{2.5} and health impacts within the exposure week, whereas the effects of PM_{2.5} mass were delayed, emerging two weeks post-exposure. This underscores the relevance of OP as a health-relevant metric for PM exposure, corroborating other research that has explored various health outcomes (Marsal et al., 2023; Borlaza et al., 2021b; Bates et al., 2019; Lavigne et al., 2018; Mataveli et al., 2021; Strak et al., 2017).

The PM₁₀ and PM_{2.5} sampling periods were not conducted simultaneously, as illustrated in Figure 1. While we anticipate minimal variation in PM composition or unmeasured confounders between 2016 and 2017, any such variations could potentially clarify why more distinct associations were observed with respiratory health for PM_{2.5} than for PM₁₀. The study was limited to adjustment for meteorological factors, but could not adjust for other potential confounders, and temporal

adjustments were applied for periods exceeding two months. Consequently, our analysis examines acute rather than chronic
420 effects of PM exposure. Furthermore, the weekly resolution of health data constrained our capacity to identify effects that
manifest over shorter timescales and may have caused exposure misclassification for patients admitted early in the week. PM
sampling every third day could also result in underestimating exposure by missing transient pollution spikes, and resulted in
weekly mean exposures that were alternatingly based on 2 or 3 measures. Additionally, estimating exposure based on PM
425 measurements from two sites may not accurately reflect individual exposures, leading to exposure misclassification. These
factors could attenuate our findings or reduce the statistical power to detect true associations (Zeger et al., 2000; Armstrong,
1998). Thus, conducting online observations of PM and OP for extended periods is crucial to disentangle the health
outcomes from PM exposure and refine epidemiological approaches.

We fully acknowledge the crucial role of PM_{2.5} as a key exposure metric for assessing health outcomes related to air
pollution and recognize the importance of incorporating PM_{2.5} results to mitigate reporting bias and enhance the robustness
430 of our findings. In our study, we delved into the associations between PM_{2.5} mass concentration and its OP, marking a
significant and novel contribution to the field. Despite this, we are aware of the limitation due to the unavailability of
apportioned sources of PM_{2.5} at the time of our analysis. Nevertheless, we assert that the absence of detailed source
apportionment for PM_{2.5} does not detract from the importance and innovation of our findings, particularly regarding the
associations of PM mass concentration and OP with respiratory outcomes. Such aspects have seldom been explored in
435 existing literature, positioning our study as a pioneering effort in this domain.

Our analysis prioritized PM₁₀ source contributions over source-specific OP due to the superior performance of the PM₁₀
source apportionment model ($R^2 = 0.99$) compared to the OP deconvolution models ($R^2 = 0.48$ for OP_{DTT} and $R^2 = 0.68$ for
OP_{DCFH}). Although a considerable number of associations ($n = 90$) were tested, formal corrections for multiple comparisons
were not applied, acknowledging that some reported associations might be due to chance findings.

440 Despite these caveats, this study contributes valuable insights into the health impacts of distinct PM sources and the viability
of OP as an air quality metric that is indicative of health risks. Our findings align with and extend prior research on the
detrimental health effects of anthropogenic emissions, especially those related to traffic. This work also provided novel
evidence of the association between OP of PM_{2.5} and respiratory health within the unique context of a high-altitude
environment, an area that has not yet been extensively explored.

445 **4 Conclusions**

This study takes advantage of a unique opportunity to assess the OP of PM in high-altitude cities of Bolivia, a region with
complex topography and meteorology, and to find the link between PM and OP sources with hospital visits for respiratory
outcomes, particularly pneumonia and acute respiratory infection. The primary sources of OP were anthropogenic, with
traffic-related emissions being the most significant contributors to OP in the region, while dust played a secondary role in
450 redox activity despite its substantial contribution to PM mass.

The epidemiological models evidenced that OP measured by DTT assay detected positive associations with both pneumonia and acute respiratory diseases within the first week of exposure. In contrast, associations for PM mass concentrations were detected with a 2-week lag.

455 The deconvolution of OP_{DTT} sources pinpoints traffic as a primary oxidizer, yet epidemiological evidence suggests dust and traffic both associate with increased hospital visits, likely via distinct biological pathways. OP measured by DTT acellular assay predominantly captures exogenous oxidative stress from reactive oxygen species present in or generated by PM. However, there could be endogenous effects driven by exposure to dust suggesting a complex interplay between various mechanisms of oxidative stress.

460 These insights are essential in guiding the efforts to mitigate traffic and dust emissions, which are key factors in controlling the health impacts of PM pollution, particularly in high-altitude environments. Moreover, this study has contributed significantly to advancing the validation of OP as an emerging health-based metric.

Acknowledgements

465 The authors would like to thank the Viceministerio de Promoción, Vigilancia Epidemiológica y Medicina Tradicional del Ministerio de Salud y Deportes (Vice ministry of Promotion, Epidemiologic surveillance, and Traditional Medicine, from the Ministry of Health and Sport) for providing the health endpoints data. The long-term observations are performed within the framework of GAW and ACTRIS, receiving support from the Universidad Mayor de San Andrés and from the international stakeholders. In France, support from the Centre National de la Recherche Scientifique (CNRS) through ACTRIS-FR/SNO CLAP as well as the Institut de Recherche et Développement (IRD) and Observatoire des Sciences de l'Univers de Grenoble (OSUG) through the French National Research Agency's Laboratories of Excellence in particular, is greatly acknowledged.

470 In Spain, financial support for filters and analysis of metals from the CSIC is acknowledged.

Financial support

475 The postdoc of Lucille Borlaza-Lacoste is funded by the Predict'air project (grant Fondation UGA-UGA 2022-16 and grant PR-PRE-2021 FUGA-Fondation Air Liquide). The PhD of Valeria Mardonez was supported by IRD/CNRS, ARTS Grant. The work on Oxidative Potential measurements is also supported by the French National Research Agency in the framework of the research programs, Get OP Stand OP (ANR-19-CE34-0002-01) and ACME (ANR-15-IDEX-02). Maintenance of measurements on site and chemical analysis on the Air-O-Sol facility at IGE was made possible with the funding of some of the equipment by the Labex OSUG@2020 (ANR10 LABX56) and with internal in-kind fundings from the Air Quality group at IGE.

Code availability

480 The software code could be made available upon request by contacting the corresponding author.

Data availability

The OP and health datasets could be made available upon request by contacting the corresponding author.

Author contributions

GU designed the study, developed the OP assays, and gathered health data. MA, PL, AA, JLB made the project and
485 sampling possible in Bolivia (High-volume sampler donation). IM performed the air sampling. JLJ, AA, JLB, GU produced
the air quality data. VM processed the data of the study. LB, VM, AM, IH developed the epidemiological models. LB
analysed and synthesized the results. LB wrote the manuscript draft. All authors reviewed and edited the manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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