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Trade-offs between short-term mortality attributable to NO₂ and O₃ changes during the COVID-19 lockdown across major Spanish cities[☆]

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ABSTRACT

The emergence of the COVID-19 pandemic forced most countries to put in place lockdown measures to slow down the transmission of the virus. These lockdowns have led to temporal improvements in air quality. Here, we evaluate the changes in NO₂ and O₃ levels along with the associated impact upon premature mortality during the COVID-19 lockdown and deconfinement periods along the first epidemic wave across the provincial capital cities of Spain. We first quantify the change in pollutants solely due to the lockdown as the difference between business-as-usual (BAU) pollution levels, estimated with a machine learning-based meteorological normalization technique, and observed concentrations. Second, instead of using exposure-response functions between the pollutants and mortality reported in the literature, we fit conditional quasi-Poisson regression models to estimate city-specific associations between daily pollutant levels and non-accidental mortality during the period 2010–2018. Significant relative risk values are observed at lag 1 for NO₂ (1.0047 [95% CI: 1.0014 to 1.0081]) and at lag 0 for O₃ (1.0039 [1.0013 to 1.0065]). On average NO₂ changed by –51% (intercity range –65.7 to –30.9%) and –36.4% (–53.7 to –11.6%), and O₃ by –1.1% (–20.2 to 23.8%) and 0.6% (–12.4 to 23.0%), during the lockdown (57 days) and deconfinement (42 days) periods, respectively. We obtain a reduction in attributable mortality associated with NO₂ changes of –119 (95% CI: –273 to –24) deaths over the lockdown, and of –53 (–114 to –10) deaths over the deconfinement. This was partially compensated by an increase in the attributable number of deaths, 14 (–72 to 99) during the lockdown, and 8 (–27 to 50) during the deconfinement, associated with the rise in O₃ levels in the most populous cities during the analysed period, despite the overall small average reductions. Our study shows that the potential trade-offs between multiple air pollutants should be taken into account when evaluating the health impacts of environmental exposures.

1. Introduction

Exposure to outdoor air pollution is a major environmental risk factor contributing to a range of adverse health outcomes (Kampa and Castanas, 2008; Shah and Balkhair, 2011), with millions of premature annual deaths across the globe (Cohen et al., 2017; European Environment Agen, 2019). The emergence of the COVID-19 pandemic has forced societies to put in place lockdown measures to slow down the transmission of the virus. Lockdowns have severely impacted the activity of key socio-economic sectors (e.g., aviation, road transport, energy,

industry, tourism), leading to substantial reductions in anthropogenic emissions of air pollutants (Guevara et al., 2021) and temporal improvements in air quality, at least for some pollutants (Bauwens et al., 2020), which is expected to have an immediate public health benefit (Isaifan, 2020).

In Europe, given the large contribution of road transport to NO_x emissions, and its short lifetime, the COVID-19 lockdowns have led to unprecedented reductions in ambient NO₂ concentrations, reaching up to about –50% in urban areas (Petetin et al., 2020; Barré et al., 2020; Grange et al., 2020). The magnitude and sign of the changes in

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secondary pollutants such as O₃, as well as a large fraction of PM_{2.5}, are more heterogeneous partly due to the highly nonlinear atmospheric chemistry involved. In the case of O₃, the changes depend upon local factors including the amount of NO_x, the amount and reactivity of the VOCs, oxidant levels, and meteorology (Kroll et al., 2020) along with variations in imported O₃ from other regions. Generally, O₃ decreases when reducing NO_x in VOC-rich environments like rural areas. In contrast, O₃ can increase in NO_x-saturated environments such as large urban areas when reducing NO_x due to a reduced titration by NO. An increase of 20%–30% in the daily O₃ levels has been reported on average across a selection of the main European cities between February and July 2020 (Grange et al., 2020). Another study including most of the available European measurement stations (Ordóñez et al., 2020), showed either enhancements or reductions of the daily maximum 8-h running average O₃ in urban background and traffic sites and reductions in rural sites between March and April.

In this paper, we evaluate the changes in NO₂ and O₃ levels due to the COVID-19 lockdown and the associated predicted impact upon premature mortality across the provincial capital cities of Spain, which is among the countries most severely affected by COVID-19. We focus on the first epidemic wave, discriminating among three distinct phases of the lockdown between 15 March and 10 May 2020 (57 days), and the deconfinement between 11 May and 21 June (42 days). Recent studies have assessed the potential reduction in mortality due to improved air quality during the lockdown periods in China (Chen et al., 2020; Giani et al., 2020; Nie et al., 2021) and Europe (Giani et al., 2020), showing a substantial number of avoided predicted fatalities from PM_{2.5} and NO₂ that, in case of China, could have surpassed the number of reported deaths from COVID-19 (Chen et al., 2020).

Our methodological framework attempts to overcome some of the simplifications and assumptions that may be partly biasing some estimates provided in previous studies (Achebak et al., 2020). On the one side, quantifying the magnitude and the sign of the change in pollutants solely due to the lockdown in each location is challenging, in particular for O₃ due its strong sensitivity to meteorological variability. We effectively cancel out the effects of meteorological variability upon the changes in pollutant concentrations during the lockdown based on a machine learning meteorological normalization technique (Petetin et al., 2020; Barré et al., 2020; Grange et al., 2020). On the other side, we purposely avoid the use of the exposure-response functions between air pollutants and mortality reported in the literature to transform changes in the pollution levels into changes in mortality. Such an approach can lead to biases due to the lack of consistency in the periods, locations and sources of data between the calibration of the exposure-response models in the former studies and the estimation of pollution reductions in the latter ones. Instead, we fit epidemiological models based on historical health and air pollution data in each major Spanish city, and then we estimate the meteorology-normalized reduction in pollutant concentrations at the same locations to consistently compute the change in attributable deaths during the lockdown and deconfinement periods.

2. Data and methods

2.1. Data collection

We collected health and environmental data for 47 provincial capital cities in mainland Spain and the Balearic Islands. We obtained daily counts of death from the Spanish National Institute of Statistics (INE), and daily mean observations of temperature (°C) and relative humidity (%) from weather stations data available through the European Climate Assessment and Dataset (ECA&D) (Royal Netherlands Meteorology, 2020), both covering the period from 2010 to 2018. Mortality data had no missing values, whereas temperature and relative humidity were missing in 1.6% and 4.5% of days on average, respectively. We also obtained hourly quality-assured NO₂ and O₃ observations from the EEA Air Quality eReporting (European Environment Agency, 2020) urban

stations between 1 January 2010 and 21 June 2020. We computed 24-hr mean pollutant concentrations only if at least 75% of the hourly data were available. When more than one air quality station was available for a city, the daily values were averaged across stations. NO₂ and O₃ data were respectively missing in 4.3% and 5.3% of days on average.

2.2. Association between daily NO₂, O₃ and mortality

A two-stage analysis approach was developed to assess the short-term effects of NO₂ and O₃ on mortality. In the first stage, a time-stratified case-crossover design with conditional quasi-Poisson regression model (Armstrong et al., 2014) was applied to estimate the city-specific associations between daily NO₂ and O₃ levels and non-accidental mortality (ICD-10: A00-R99) during the period 2010–2018, summarized as relative risk (RR). These associations were characterized by using an unconstrained distributed lag model (DLM) with lags up to 3 days, which allows the description of the delayed effects of air pollutants on mortality. The regression model also included a stratum defined by a three-way interaction term of year, calendar month, and day of the week to control for the seasonal and long-term trends and the weekly cycle of mortality; a linear term to adjust for relative humidity; and a distributed lag non-linear model (DLNM) (Gasparrini et al., 2010) to account for the non-linear and delayed effects of temperature. The DLNM is based on the definition of a cross-basis, a bi-dimensional space of functions describing simultaneously the shape of the relationship along the exposure range (exposure-response function) and its distributed lag effects (lag-response function). Specifically, the exposure-response function was modelled through a quadratic B-spline, with one internal knot placed at the 75th percentile of the daily temperature distribution (Achebak et al., 2019), and the lag-response function was modelled through a natural cubic B-spline, with an intercept and three internal knots placed at equally spaced values in the log scale of the lag period 0–14. The quasi-Poisson regression model was as follows:

$$\text{Log(mortality)} = \text{intercept} + \text{stratum} + \text{dlm}(\text{pollution}, \text{lag} = 0-3) + \text{dlnm}(\text{temperature}, \text{lag} = 0-14) + \text{humidity}.$$

The modelling choices were thoroughly tested in sensitivity analyses and, in addition to the model described above, two-pollutant models were also fitted to test the robustness of the associations between NO₂ and O₃ and mortality (Supplementary Information, pp 3–4).

In a second stage, a multivariate random-effects meta-analysis was performed to estimate the average association between air pollutants and mortality across cities, and to derive the best linear unbiased predictions of the pollutant-mortality relationship in each location.

2.3. Business-as-usual NO₂ and O₃ levels during the lockdown and deconfinement periods

Quantifying the impact of the lockdown on air pollution requires estimating the business-as-usual (BAU) pollutant concentrations that would have been observed in the absence of the mobility restrictions. Given the strong influence of meteorology upon the variability of pollutant concentrations, the use of climatological concentrations obtained from historical data may provide biased BAU concentrations, especially if specific meteorological anomalies prevail locally. Here, we implemented machine learning (ML) models following the methodology described and validated in Petetin et al., 2020 to obtain the daily BAU NO₂ and O₃ concentrations and their associated uncertainties during the lockdown and deconfinement. ML models fed with ERA5 reanalysis meteorological data (daily minimum, mean and maximum 2-m temperature, surface wind speed, normalized 10-m zonal and meridional wind speed components, surface pressure, total cloud cover, net solar radiation at the surface, downward solar radiation at the surface, downward UV radiation at the surface, and the boundary layer height) and time variables (date index, Julian date, day of the week) were trained with historical 2017–2019 data and used to predict NO₂ and O₃

daily concentrations in 2020. As demonstrated in Petetin [Petetin et al., 2020](#), these models successfully estimate weather-normalized changes in pollutant concentrations during the COVID-19 lockdown. We evaluated the ML-based predictions in all cities during 2020 and before the COVID-19 lockdown, considering the normalized mean bias (nMB), the normalized root mean square error (nRMSE) and the Pearson correlation coefficient (PCC). Although the predictive skills show some variability from one city to another ([Tables S1 and S2](#) in Supplementary Material), an overall good performance is found for both NO₂ and O₃, with nMB/nRMSE/PCC of +5%/28%/0.86 (N = 3463 points) and +6%/22%/0.86 (N = 3625 points), respectively.

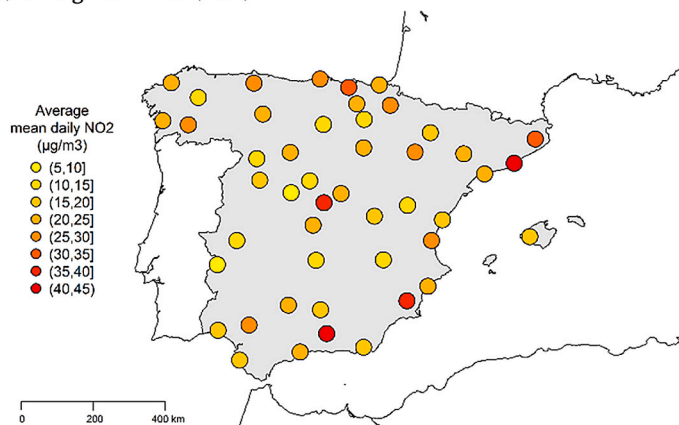
2.4. Quantification of the changes in mortality attributable to NO₂ and O₃ during the lockdown and deconfinement periods

The RR of mortality associated with NO₂ and O₃ levels in each city was used to transform the daily (i) observed and (ii) BAU NO₂ and O₃ time-series during the lockdown and deconfinement periods into daily number of deaths attributable respectively to NO₂ and O₃, following a method described elsewhere ([Gasparrini and Leone, 2014](#)). Then, the change in mortality attributable to NO₂ and O₃ during the lockdown and deconfinement results from the sum of the difference between the number of deaths attributable to the observed NO₂ and O₃ and the number of deaths attributable to BAU NO₂ and O₃, respectively. The baseline mortality used to quantify attributable deaths was from the average annual cycle corresponding to the period 2010–2018. We provide 95% confidence intervals for the number of deaths that account for the uncertainties associated to both the fitted regression model and the

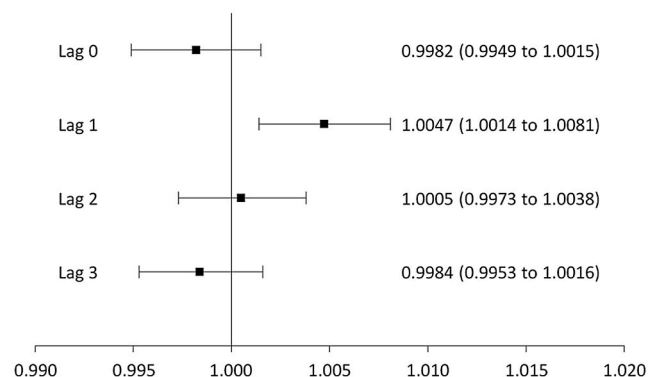
machine learning-based BAU pollution estimates, assuming random daily BAU level uncertainties across the reported periods. We note that our approach assumes no change in the risk of dying from air pollution when computing attributable deaths during the COVID-19 period, which may actually not be the case. For example, if COVID-19 killed the elderly, the population as a whole will become less vulnerable to air pollution, i.e. the RR will decrease. Moreover, “air pollution deaths” and “COVID-19 deaths” may at least partly overlap.

The changes in mortality are shown for the three distinct phases of the lockdown. During the first phase of the lockdown, from 15 March to 29 March, the citizens had to stay at home, except for purchasing essential goods (i.e., food and medicines), working or attending emergencies, and nonessential shops and businesses (including bars and restaurants) had to close. Due to the persistent rise in infections and hospitalisations, more severe restrictions were adopted by the authorities in a second phase of the lockdown from 30 March to 12 April (partially coinciding with Easter holidays), during which only essential activities such as food trade, healthcare services, and some industries were authorised. A third and last phase of the shutdown began on 13 April, when some nonessential economic sectors, including construction and industry, were allowed to return to work. The deconfinement period lasted from 11 May to 21 June, and it was also characterised by different stages that, unlike the lockdown period, were not homogeneously implemented across the country given that the evolution of the epidemic differed among territories.

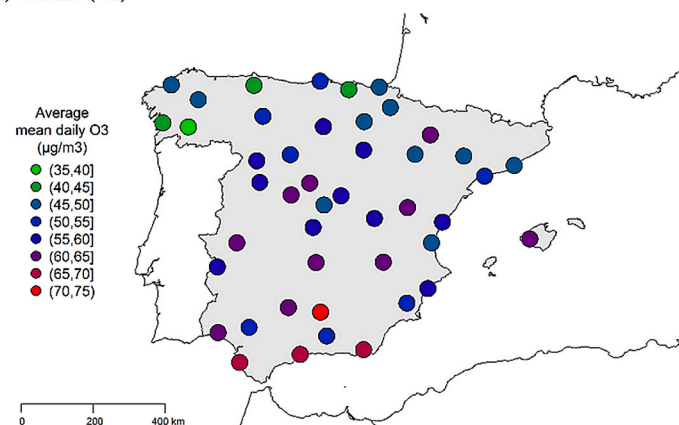
a) Nitrogen dioxide (NO₂)



b) Relative risk of death per 10 µg/m³ increase in daily NO₂



c) Ozone (O₃)



d) Relative risk of death per 10 µg/m³ increase in daily O₃

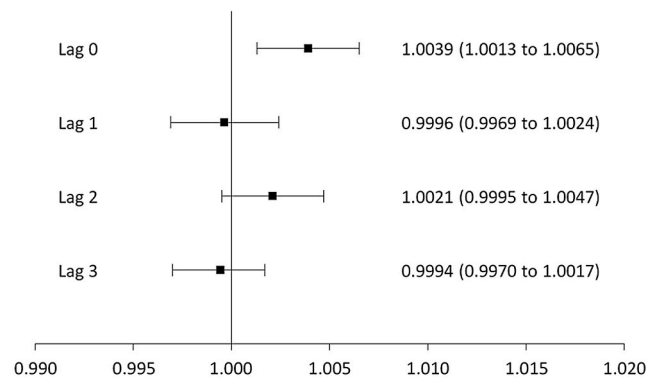


Fig. 1. Geographical distribution of study locations and the corresponding overall pollution-mortality association, 2010–2018. The study locations are represented with the corresponding average daily mean pollution level. Error bars are 95% CIs.

3. Results

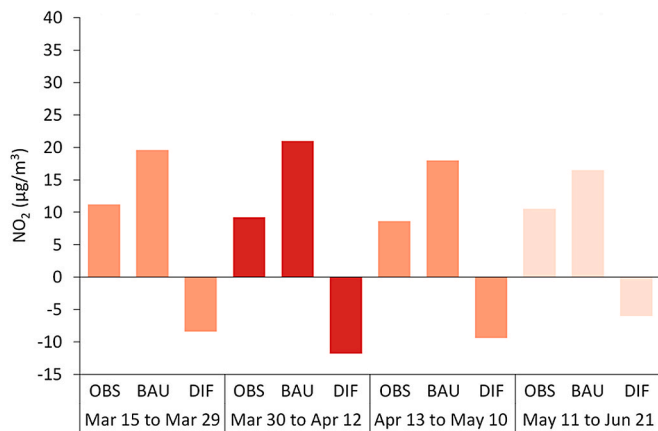
We analysed data from 47 major cities representing about 32% of the total Spanish population. During the period 2010–2018, the overall average concentrations of NO₂ and O₃ across the 47 cities (Fig. 1) were 22.0 µg/m³ (SD 13.5) and 55.3 µg/m³ (SD 21.8), respectively. As expected, the highest concentrations of NO₂ are observed in winter and the lowest ones in summer, whereas the opposite pattern is observed for O₃. Daily NO₂ concentrations are negatively correlated with temperature (PCC = -0.19) and O₃ (PCC = -0.53), but positively correlated with humidity (PCC = 0.10). By contrast, daily O₃ concentrations are positively correlated with temperature (PCC = 0.45) and negatively correlated with humidity (PCC = -0.50). The average mortality from non-external causes was 7 (SD 12.2) daily deaths, ranging from 1 in the rural city of Teruel to 74 in the largest city, Madrid.

Fig. 1 shows the pooled RR values of death at 10 µg/m³ of NO₂ and O₃ over lags 0–3 days. Significant RR values were observed at lag 1 for NO₂ (1.0047 [95% CI: 1.0014 to 1.0081]) and at lag 0 for O₃ (1.0039 [1.0013 to 1.0065]). These risk estimates were found to be robust across different modelling choices related to the control of the temperature and the humidity, but some degree of sensitivity was found if the model was adjusted for other pollutants (Figs. S1 and S2 in the Supplementary Material). However, results from two-pollutant models should be interpreted with particular caution because of multicollinearity issues

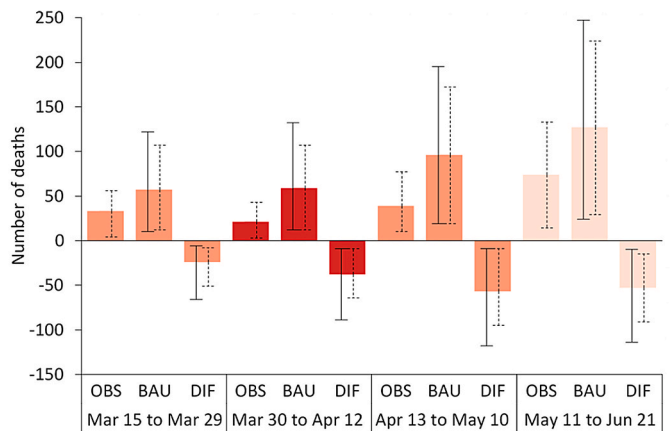
between pollutants and because the data used in this approach are limited to one or a few cities, which does not ensure sufficient statistical power to consistently characterise the associations. Note that the city-specific estimates of RR of mortality were not statistically significant for O₃ (Figs. S3 and S4 in the Supplementary Material), except for Madrid, which is, in turn, the most populous city in Spain and a major contributor to the total mortality burden due to air pollution in the country (Tables S3 and S4 in the Supplementary Material). The fractions of mortality attributable to NO₂ and O₃ over the period 2010–2018 were, respectively, 1.4% (95% CI: 0.4 to 2.5) and 1.9% (95% CI: -0.5 to 4.2), which translates into 1737 (95% CI: 451 to 3006) and 2281 (95% CI: -573 to 5056) premature annual deaths across the 47 cities.

Overall, applying the weather normalization technique, we found that the levels of NO₂ decreased on average by -51.0% (range across cities from -65.7 to -30.9) during the lockdown, and by -36.4% (range -53.7 to -11.6) during the deconfinement, which is equivalent to reductions of -9.8 µg/m³ (range -18.3 to -3.3) and -6.0 µg/m³ (range -16.9 to -1.3), respectively (Fig. 2a, and Table S5 in the Supplementary Material). These changes in air pollutants are consistent with the recent literature (Petetin et al., 2020; Barré et al., 2020; Grange et al., 2020; Ordóñez et al., 2020). At least part of the spatial variability in NO₂ reductions can be attributed to the differences in city size, which implies differences in the relative contribution of road transport to total NO_x emissions, which is typically higher in larger cities (Petetin et al., 2020;

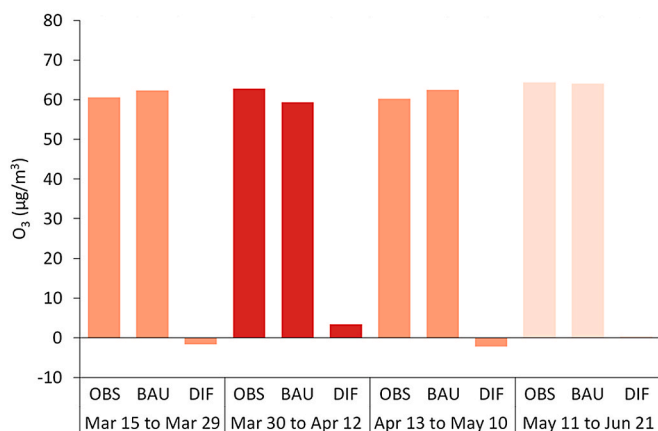
a) Nitrogen dioxide (NO₂)



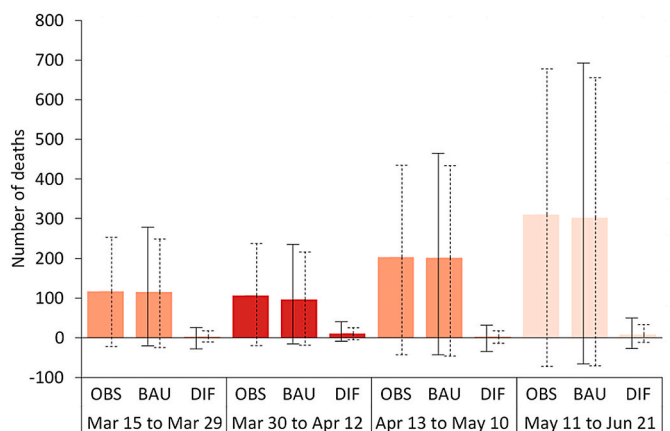
b) Mortality attributable to NO₂ (Lag 1)



c) Ozone (O₃)



d) Mortality attributable to O₃ (Lag 0)



Legend: ■ Lockdown ■ Lockdown (Only essential activities) ■ Deconfinement

Fig. 2. Air pollution levels and attributable mortality during the lockdown and deconfinement periods in Spain. OBS = Observed; BAU = Business-as-usual; DIF = Difference (OBS-BAU). Error bars are 95% CIs. Solid error bars represent CIs taking into account both the uncertainties of the fitted regression model and of the estimated BAU levels. For reference, dashed error bars represent CIs without considering the uncertainty in BAU levels.

[Ordóñez et al., 2020](#)). The strongest reductions in NO₂ occurred during the second phase of the lockdown, when the most stringent measures to lower the transmission of the virus were in place. The reduction in NO₂ concentrations was observed in all the cities included in the study ([Table S6](#) in the Supplementary Material), and it was associated with a significant decrease in the mortality attributable to NO₂ of −119 (95% CI: −273 to −24) deaths over the lockdown (57 days), and of −53 (−114 to −10) deaths over the deconfinement (42 days) ([Fig. 2b](#), and [Table S7](#) in the Supplementary Material).

By contrast, the changes in O₃ levels were much lower and quite variable across cities, including both increases and decreases during the analysed periods ([Table S8](#) in the Supplementary Material). The strongest relative changes in O₃ occurred during the most stringent lockdown period (first half of April) ([Fig. 2c](#), and [Table S9](#) in the Supplementary Material), when O₃ was found to substantially increase, although only in a subset of cities, including Madrid and Barcelona. On average, O₃ decreased by −1.1% (inter-city range of −20.2 to 23.8) during the lockdown and increased by 0.6% (range −12.4 to 23.0) during the deconfinement, which is equivalent to −0.7 µg/m³ (range −12.1 to 11.5) and 0.4 µg/m³ (range −8.9 to 10.5), respectively ([Fig. 2c](#), and [Table S9](#) in the Supplementary Material). These changes in O₃ concentrations were associated with an increase in premature mortality of 14 (−72 to 99) deaths during the lockdown, and of 8 (−27 to 50) deaths during the deconfinement ([Fig. 2d](#), and [Table S10](#) in the Supplementary Material).

4. Discussion

We applied a weather normalization technique to quantify the variation in NO₂ and O₃ during the lockdown and deconfinement periods, and fitted epidemiological models to estimate the corresponding predicted change in mortality across 47 provincial capital cities in Spain.

Overall, the ML-based weather normalization technique used in this study to estimate the BAU NO₂ and O₃ concentrations showed a good performance, despite several potential sources of uncertainty. This includes (1) the relatively coarse spatial resolution of the ERA5 meteorological data that may not always represent adequately the conditions prevailing at the urban level, (2) the presence of trends that are here taken into account in a simplified way, and (3) the influence of other drivers on pollutant concentrations, especially for O₃ (e.g. deposition, long-range transport, inter-annual variability of background O₃ levels).

By fitting epidemiological models in each city, we found that, on average, an increase of 10 µg/m³ in daily NO₂ and O₃ were associated with a RR of death of 1.0047 (95% CI: 1.0014 to 1.0081) and 1.0039 (1.0013–1.0065), respectively. The magnitude of the association for NO₂ is much smaller than the one reported in a previous study in Spain (1.012 [95% CI: 1.010 to 1.014]) ([Linares et al., 2018](#)). This difference could be explained by the different modelling approach, as well as the possible measurement error in the latter study, arising from the use of air pollution data from air quality stations located in the provincial capital cities and mortality data aggregated for the whole provinces. This mismatch is likely to have biased the exposure-response associations because NO₂ shows high spatial variability, and therefore, measurements from air monitoring stations in the provincial capital city might not be representative of the exposure of the whole population in the province. The ideal approach would have been to restrict the analysis to the capital cities as we did here. On the other side, the estimation obtained for O₃ is higher than the one found by [Vicedo-Cabrera and colleagues for Spain](#) (1.0006 [95% CI: 0.9992 to 1.0019]) ([Vicedo-Cabrera et al., 2020](#)) in a multi-country analysis, which, in turn, could be explained by the differences in the definition of the exposure variable. In our study, the RR of mortality is given by the average of the 24 hourly values of O₃ at lag 0, while in the study by [Vicedo-Cabrera and colleagues](#) ([Vicedo-Cabrera et al., 2020](#)) is given by the daily maximum of the 8-h averages at lags 0–1. Our results are more in line with a recent systematic review and meta-analysis ([Orellano et al., 2020](#)) (1.0072

[95% CI: 1.0059 to 1.0085] for NO₂, and 1.0043 [95% CI: 1.0034–1.0052] for O₃) and a multilocation analysis in 398 cities ([Meng et al., 2021](#)) for NO₂ (1.0046 [95% CI: 1.0036 to 1.0057]).

During the lockdown and deconfinement periods we found a strong reduction in NO₂ levels (−45% on average) that was associated with a significant decrease in the number of deaths, although some of these deaths may have occurred anyway a few days, weeks or months later among the frailest individuals. This reduction in mortality from the NO₂ drop was however partially compensated by a small increase in the number of deaths associated with the rise in O₃ levels during the analysed period in the most populated cities (Madrid, Barcelona), despite the average reduction of −0.5% across all the cities. Our study shows that trade-offs between multiple air pollutants should be taken into account when evaluating the health impacts of environmental exposures. The overall positive impact on mortality from lower NO₂ levels will likely continue, although to a lesser extent, as lockdown measures are imposed again due to new peaks of the epidemic and/or due to the foreseen slowdown of the economy and the levels of social and industrial activity (e.g. transport). While NO₂ reductions will likely not be as intense, their duration could be relatively long. Anticipating the magnitude and even the sign of response of O₃ is more complex as it depends strongly not only on the location and chemical sensitivity regime, but also on seasonal weather variations. For example, our study period does not include the month of July 2020, when O₃ levels are typically at their maximum in Spain.

In this study, we focused only on NO₂ and O₃ because of the higher availability and density of data, both temporally (during the historical and the COVID-19 period) and spatially (covering almost all the capital cities of the Spanish provinces), compared to other pollutants such as PM₁₀, PM_{2.5}, SO₂ or CO. The number of missing values in the time series is particularly important when assessing the exposure-response association between air pollution and health outcomes. Indeed, one of the aspects that makes our study unique and robust is that we used data that is consistent between the historical period (2010–2018), used to describe the daily epidemiological associations, and the COVID-19 period, for which we predicted the reduction in attributable mortality. In future studies, we plan to consider air pollution data from sources other than monitoring stations (i.e., gridded data from satellite observations, simulation models), to extend the present analysis to the entire geographical domain of Spain, thus including both rural and urban areas.

5. Conclusion

Our findings provide useful insight on the potential short-term health benefits of reducing air pollutant emissions from road traffic and economic activities. With permanent reductions in emissions, the positive effects could be even greater on the long-term. This may even include less severe health impacts from epidemics causing respiratory infections such as COVID-19, as the diseases caused by long-term exposure to air pollution are in turn risk factors for COVID-19 severity and mortality.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2021.117220>.

Author contributions

HA designed the study, did the epidemiological analysis, interpreted the results, and wrote the original draft. HP contributed to the study design, implemented the machine-learning meteorology-normalization model for air pollution data and edited the manuscript. MQ-Z contributed to the study design and processed mortality and temperature data. DB contributed to the study design and processed air pollution data. CPG-P contributed to the study design and edited the manuscript. JB provided the mortality data, contributed to the study design and edited the manuscript. All authors contributed to the submitted version of the manuscript and approved the final version.

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