Interactive effects of long-term exposure to PM_{10}, NO_2 and O_3 on SARS-CoV-2 infection and severity: a population-based cohort study in northern Italy

Abstract (word count: 264)

Background. We examined the interactive effects, not yet explored, between long-term exposures to particulate matter (PM_{10}) with nitrogen dioxide (NO_2) and ozone (O_3) on SARS-CoV-2 infectivity and severity.

Methods. We followed 709,864 adult residents in the Varese Province from February 1st 2020 until the first positive test, COVID-19 hospitalization or death, up to December 31st, 2020. We estimated residential annual mean PM_{10}, NO_2 and O_3 in 2019 from chemical-transport and random-forest models. ~~, and~~We assessed the interactive effects of air pollutants and urbanicity ~~in urban and in non-urban areas, and by levels of co-pollutants, from~~ on SARS-CoV-2 infectivity, hospitalization and mortality endpoints using Cox regression models adjusting for socio-demographic factors and comorbidities. Additional cases due to interactions were estimated using Poisson models.

Results. 41,065 individuals were infected, 5,203 were hospitalized and 1,543 died from COVID-19 during follow-up. PM_{10} and NO_2 means were 1.6 and 2.6 times higher than the latest WHO limits, respectively, with wide gradients between urban and non-urban areas. PM_{10} and NO_2 were positively associated with SARS-CoV-2 infectivity and mortality, and PM_{10} with hospitalizations in urban areas. Interaction analyses revealed that the effect of PM_{10} (per 3.5 $\mu g/m^3$) on infectivity was the strongest in urban areas (HR=1.12, 95%CI: 1.09-1.16), corresponding to 854 additional cases per 100,000 person-years, and in areas at high NO_2 co-exposure (HR=1.15, 1.08-1.22). Moreover, at higher levels of PM_{10} co-exposure the protective effect of ozone reversed (HR=1.32, 1.17-1.49), yielding to 278 additional cases per $\mu g/m^3$ increase in O_3. Similar interactive effects were observed for COVID-19 severity endpoints.

Conclusions. Interactive effects between PM_{10}, NO_2 and O_3 exacerbated the burden of SARS-CoV-2 pandemic, the most detrimental co-exposures being in highly-conglomerated urban areas.

Keywords: long-term exposure, air pollution, SARS-CoV-2, interactive, cohort, Italy, urban

Introduction

In 2023, the detrimental effects of long-term exposure to outdoor airborne pollutants on health was on the agenda at the Conference of the Parties 28 agenda for the first time[1]. Latest estimates for Europe indicate that 94% of the population live at airborne particulate matter (PM) concentrations above the 2021 WHO guideline levels[2], resulting in 117,000 premature deaths[3]. Over the years, an extensive body of research has suggested that there is a causal link between air pollution and chronic, non-communicable diseases morbidity and mortality[4,5].

Less established is the link between long-term exposure to $PM_{2.5}$ and PM_{10} (e.g. particulate matter with aerodynamic diameter less than 2.5 and 10 µm, respectively), nitrogen dioxide (NO_2) and ozone (O_3) with infectious diseases, including the SARS-CoV-2 threats. A number of mechanisms support the biological plausibility of the association, including the well-established role of airborne pollutants on prolonged inflammation, down-regulation of the immune system, and over-expression of ACE-2 receptors in the lungs with impairment of alveoli macrophages to regulate the inflammation response[6–8].

Nonetheless, prospective epidemiological studies with individual-level data have been so far insufficient to fully elucidate the relationships of air pollution with SARS-CoV-2 infectivity and severity[9]. One nationwide study in Denmark[10] on a population at very low exposure levels showed a consistent, increased risk of infection, hospitalization and mortality for increased exposure to $PM_{2.5}$ and NO_2; whereas the associations for O_3 were protective, remaining negative also in bi-pollutant models. In the same pandemic period but at higher exposures, two distinct UK-biobank studies[11,12] and one in the northern Italian city of Varese[13] found positive associations between particulate matters and NO_2 for infectivity only; while two studies in Catalonia[14,15] and one in the city of Rome[16] confirmed positive associations for severity endpoints only. Some of these studies also reported negative associations of ozone with SARS-CoV-2 endpoints[13,15] in single-pollutant analyses, the estimates becoming positive after controlling for particulate matter[13] and NO_2[15].

The heterogeneity in estimates at different exposure levels, and in single-city vs. country-wide studies, may suggest the presence of interactive effects of air pollutants with SARS-CoV-2 infectivity and severity. Synergistic interactions between acute exposure to $PM_{2.5}$ and O_3 with total, respiratory and cardiovascular mortality were recently reported by Liu and colleagues in pooled analyses of 372 cities[17], while interactive effects of long-term exposures on the SARS-CoV-2

pandemic have not been formally investigated so far.

In the present prospective cohort study with individual-level data, we expand to the entire Varese Province – comprising of both urban and rural areas - our previous analysis limited to the city of Varese[13], and we further add COVID-19 hospitalizations and mortality to SARS-CoV-2 infection as endpoints. In particular, we aim to investigate the presence of interactive effects of long-term exposures to PM_{10}, NO_2 and O_3 with the study endpoints in urban and non-urban areas, with different levels of exposures.

Methods

Study population and study period

The target population was comprised of adults (≥18 years old) residents both on January 1st, 2019 and on December 31st, 2019 in the Province of Varese (Lombardia region, northern Italy) registered with the Regional Health Service (n=725,443). The province of Varese covers 1200 square kilometers, comprising 138 municipalities, most of which are medium to small in size. Individuals' residential addresses as of December 31st 2019 were geocoded.

Geocoding quality was high, with only 1.7% of individuals allocated to the centroid of the residential municipality. Regional healthcare databases were accessed to collect information on COVID-19, hospital discharge records, and outpatient drug prescriptions through a unique, anonymized identification code. The study period was antecedent to the opening of the vaccination season in the region, as well as to the circulation of the first variant of concern (alpha)[18], to avoid such sources of heterogeneity in study endpoints. We excluded n=5,562 individuals living in residential nursing homes, and n=10,017 individuals without active regional assistance as of February 1, 2020 (start date of follow-up), leaving a final sample of 709,864 individuals.

Environmental exposure

Study exposures are the 2019 annual mean values of PM_{10}, NO_2, and O_3 estimated at a spatial resolution of 1 Km^2 from combined use of chemical-transport and random-forest models, a methodology already used in the context of large epidemiological studies[19,20]. The choice of a pre-pandemic year was consistent with literature[10–16], to avoid modifications in pollutants' levels due to lockdown and to mobility restriction periods occurring in 2020. Briefly, for each pollutant the chemical-transport model combined data from emission inventories and meteorological conditions to produce concentration fields that were further integrated with observed ground levels from monitoring stations using data fusion techniques[19]. Then, random-forest algorithms downscaled the

"data fused" fields at the spatial resolution of 1 Km^2 using spatial-temporal predictors such as population density, traffic, land-use and surface greenness[20]. Based on considerations on the scanty availability of data monitoring stations in the study area resulting in unexpected weak correlations with the other pollutants, we excluded $PM_{2.5}$ from the present analyses. Full details, including some metrics of models' performance, are reported in the Supplementary Digital Content eAppendix 1. ~~The individual exposure was then assigned based on the nearest grid centroid to subject's address of residency as of December 31, 2019.~~ Individual exposures were then assigned based on the grid cell centroid closest to the subject's geocoded address.

Endpoints

The Regional Health Authority collected information on COVID-19 from several sources, including public and private hospitals, Local Health Agencies and accredited laboratories[13]. In Lombardia Region, both symptomatic patients and asymptomatic individuals identified through contact tracing were tested. The infectivity endpoint was defined as the occurrence of the first positive nasopharyngeal swab specimens tested with real-time reverse-transcriptase–polymerase-chain-reaction assays targeting different genes (E, RdRp, and M) of SARS-CoV-2 before 31/12/2020. In agreement with the literature[10,15], the COVID-19 hospitalization endpoint was defined as a

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hospital admission (including admission to the emergency departments) for any reason within 28 days from the detection of the first positive swab, or within 48 hours before the swab to account for minor discrepancies in dates. Finally, COVID-19 mortality was defined as a death for any cause within 30 days of the first positive swab[10,15].

Demographic, socio-economic and clinical characteristics

Age and gender were available in the regional healthcare databases. We used an area-based deprivation index developed and validated in Italy for epidemiological studies[21], available at census section level. The index uses individual data of the latest general population and housing census of 2011, and it considers 5 dimensions of social and material deprivation: low education, unemployment, renting, household crowding, and living in a single-parent family. The index is categorized into fifths using regional-specific quintiles. As a measure of population density, we used the Eurostat[22] classification of the degree of urbanization ("cities", "towns and suburbs", "rural areas"), available at a municipality level. Drug medications (one prescription during the year 2019) and history of comorbidities (at least one hospital discharge between 2015 and 2019) were defined

for each individual from relevant regional healthcare databases as in our previous research[13], specific codes being reported in the eAppendix 1.

Statistical analysis

Starting February 1st 2020, for each of the three endpoints the subjects contributed to follow-up
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February 1st 2020, for each of the three endpoints the subjects contributed to follow-up until the date of the event, or censoring due to death for any cause, residency change outside the Varese Province, or December 31st, 2020, whichever came first.

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effect of each pollutant on the endpoints from single-pollutant Cox regression models. Potential confounders and mediators from literature[6–8] were identified using directed acyclic graphs (DAGs), we report in eFigure 2 an exemplification for the infectivity endpoint. The associations between the potential confounders with the exposure and the endpoints were estimated using linear and Cox regression models, respectively. According to these, the analyses were adjusted for age, sex, degree of urbanization, deprivation index, selected comorbidities and active treatments. We accounted for non-linear effects of age on the infectivity and the mortality endpoints using polynomials of degree 3 and 2, respectively. Due to the low number of individuals and events in rural areas, we dichotomised the degree of urbanization as urban and non-urban, the latter comprising towns, suburbs and rural areas. The hazard ratios (HR) are reported for 1 interquartile range increase in the exposures.

To assess the presence of interactive effects, we adopted a stratified approach[17,23] consisting of regression models with one pollutant, one stratification variable indicating co-exposure, and their interaction terms. We used Cox models to formally test for interactions on the relative scale, and

Poisson models (SAS Proc NLMIXED; https://support.sas.com/kb/37/344.html) to further estimate the additional number of events due to interaction at the sample mean values for pollutants and covariates. Since our previous study investigated one single city[13], we first tested the homogeneity of air pollutant effects on the endpoints in urban and non-urban areas., Urbanicity represents not only different pollutant exposures but also factors potentially related to the pandemic such as population density ~~representing different levels of exposures~~. To favor the comparison with previous literature, we also report the hazard ratios for the first pandemic wave only (from March to May 2020) in urban and non-urban areas. In sensitivity analyses of the interactive effects by urbanization, we report the results from bi-pollutant Cox regression models.

Then, to better characterize the nature of the interactions overall, we looked at the association of each pollutant by levels of the other, classified according to the lowest (≤25%), middle (26-74%), and the highest (≥75%) quartile. In these analyses, NO_2 and O_3 were not considered together since nitrogen oxides are in the formation pathway of ozone[24,25]. We formally tested the homogeneity of effect by strata in Cox regression models with interaction terms between the pollutant and the co-pollutant levels (2 df Wald chi-square test), again using Poisson modelling for interaction on the additive scale.

Furthermore, since interactive effects so far have been investigated in urban settings only[17], we assessed associations of each pollutant and study endpoints by urbanization-specific strata of co-pollutant exposures (in fifths). For these analyses, the hazard ratios are reported for 1 $\mu g/m^3$ increase in pollutants, as fifths intervals were most of the times narrower that the overall interquartile range.

We conducted the statistical analyses using SAS (9.4 release) and R (version 4.1.2) for figures.

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Results

We observed 41,065 cases of first SARS-CoV-2 infection, corresponding to a rate of 6,424 per 100,000 person-years. Of these, 78% were symptomatic and 22% were identified through screening/contact tracing; while 97% and 3% of cases were confirmed though molecular and

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antigenic swabs, respectively. N=5,203 cases (rate: 747 per 100,000 py) were hospitalized, 58.8% of which required admission in Intensive Care Unit (ICU) or mechanical ventilation (n=3,061, rate: 439 per 100,000 py; eTable 3); and 1,543 (rate: 220 per 100,000 py) died. The completeness of case-ascertainment in our sample compared to official counts of cases (source: https://github.com/CSSEGISandData/COVID-19) is presented as eFigure 1 in the eAppendix 1. The independent associations between demographic and clinical characteristics of the study sample with the endpoints are reported in eTable 1. Age and male sex were negatively associated with infectivity, and positively with the severity endpoints. Urbanization was associated with SARS-CoV-2 infection, the risk being lower in towns and rural areas rather than cities; but not with COVID-19 hospitalization or mortality. Treatments and comorbidities were consistently associated with the endpoints, except for the lipid lowering treatments variable which was no longer considered in the analyses.

Air pollutants distributions

Over the year 2019, the annual mean±SD levels of PM_{10}, NO_2, and O_3 were 24.3±3.0 µg/m^3, 26.1±5.4 µg/m^3 and 52.1±5.8 µg/m^3, respectively (eTable ~~1~~ 2 in eAppendix 1). Notably, in the entire Province the exposure ranges were 13.4-28.2 µg/m^3 for PM_{10} and 8.3-37.0 µg/m^3 for NO_2, indicating a wide variation in exposures. Air pollutant distributions had a clear gradient according to the degree of urbanization (Table 1). In contrast to the rural areas mainly located in the north, the southern part of the Province is constituted by a cluster of closely situated cities, collectively forming a densely populated conurbation, with exceptionally high annual mean levels of PM_{10} (26.2 µg/m^3) and NO_2 (30.5 µg/m^3), and low levels of O_3 (48.2 µg/m^3; eTable ~~1~~ 2 and eFigures 3-5 in eAppendix 1). PM_{10} and NO_2 were positively correlated each other (Spearman correlation coefficient: 0.84) and negatively with ozone (-0.87 and -0.89, respectively; eTable ~~1~~2). We observed no consistent gradient in air pollutant distributions by deprivation index, nor by demographic and clinical characteristics of the individuals (Table 1).

Interactive effects by urbanization

~~Urbanization was associated with SARS-CoV-2 infection, the risk being lower in towns and rural areas rather than cities; but not with COVID-19 hospitalization or mortality (eTable 2).~~

The hazard ratios (with 95% confidence intervals) for the association of air pollutants with the study endpoints, in the entire Province and by urban vs. non-urban areas are reported in Table 2. In the entire Province, after the adjustment for covariates, PM_{10} and NO_2 were associated with an increased risk of SARS-CoV-2 infection and COVID-19 mortality. The associations with COVID-19 hospitalization, and with hospitalizations requiring ICU or mechanical ventilation, were also generally positive for PM_{10} and NO_2, ~~, but not statistically significant.~~ Conversely, O_3 was

negatively associated with all endpoints. ~~infectivity.~~ These associations were confirmed in sensitivity analyses excluding individuals with exposure attributed at the centroid of their municipality of residency (1.7%; eTable 4).

We observed a spatial heterogeneity in the effect of PM_{10} on SARS-CoV-2 infection and hospitalization (urban area*pollutant interaction test p-value<0.001), the associations being stronger in urban rather than non-urban areas (Table 2). On the additive scale, due to the interactions, in urban areas we estimated 854 (95%CI: 600-1,107), 174 (86-261) and 74 (13-134) additional SARS-CoV-2 cases, hospitalizations, and hospitalizations requiring ICU/mechanical ventilation (per 100,000 py), corresponding to 13%, 23% and 17% of the event rates, respectively. Finally, we also observed a higher protective effect of ozone in urban areas. The restriction to the first pandemic wave did not modify the associations for PM_{10}, NO_2 and O_3 with the study endpoints in urban and non-urban areas (eTable 5). Results from sensitivity analyses using bi-pollutant models (eTables ~~5~~6-~~7~~8) support the independent role of PM_{10} and NO_2 in urban and in non-urban setting, respectively. In addition, the associations between ozone and the study endpoints reversed when adjusting for PM_{10} in urban areas.

Interactive effects by co-pollutant levels

The stratified associations of PM_{10}, NO_2 and O_3 with the study endpoints by levels of co-pollutant are reported in Table 3. The associations of PM_{10} with SARS-CoV-2 infectivity increased in higher ~~centiles~~ quartiles of NO_2 (interaction test p-value <.0001; the HR in the highest fourth being 1.15, 95%CI: 1.08-1.22); and in lower quartiles ~~centiles~~ of ozone (p-value<.0001, the HR in the lowest fourth being 1.15, 1.06-1.25). Conversely, the effect of NO_2 was the strongest at low levels of PM_{10} (HR=1.09; 1.03-1.16; interaction test p-value <.0001). Finally, in the highest fourth of particulate matter exposure, the effect of O_3 on SARS-CoV-2 on infectivity became positive and statistically significant (HR=1.32, 1.17-1.49; interaction test p<.0001). On the additive scale, we estimated 278 (95%CI: 184-372) additional cases per 100,000 py per each $\mu g/m^3$ increase in O_3 due to the interaction.

When we further looked at the stratified associations by considering co-pollutant levels by degree of urbanization (Figure 1), we mostly observed consistent effects in urban and non-urban areas characterized by the same co-pollutant exposure level. The progressive increase of O_3 HRs with infectivity by quintile levels of PM_{10} is shown in Figure 1d. The stratified analyses for COVID-19 hospitalizations and mortality confirmed the presence of interactive effects of PM_{10} by levels of NO_2 and ozone; and of NO_2 and ozone by levels of PM_{10}, but the estimates have lower precision (Table 3 and eFigures 6-7 in eAppendix 1). ~~Results from sensitivity analyses using bi-pollutant models (eTables 5-7) support the independent role of PM_{10} and NO_2 in urban and in non-urban~~

~~setting, respectively. In addition, the associations between ozone and the study endpoints reversed when adjusting for PM_{10} in urban areas.~~

~~*Interactive effects by pandemic waves*~~

~~The associations between air pollutants and the study endpoint, in urban and non-urban areas, stratified by pandemic waves are described in Table 4. In urban areas, we observed heterogeneity in the effects of PM10 with COVID-19 hospitalizations (time*pollutant interaction test p-value: 0.003). Although the association was stronger in the first rather than the second wave, with HRs of 1.56 and 1.11, it remained statistically significant also in the latter period. Conversely, the associations between NO2 with SARS-CoV-2 infection and COVID-19 hospitalizations were statistically significant in the first pandemic wave only. In non-urban areas we detected no heterogeneity of effects by pandemic waves.~~

Discussion

In this large prospective study of adult residents in the Varese Province, we found associations between increasing PM_{10} and NO_2 exposure levels with increased risks of SARS-CoV-2 infection and mortality, and between PM_{10} and COVID-19 hospitalizations in urban areas. Associations were the strongest in urban settings, particularly so for PM_{10}. Annual mean PM_{10} and NO_2 were 1.6 and 2.6 times higher than the latest WHO limits[2], respectively. Thus, we generalized at higher exposure levels the associations detected in Denmark[10], where about 40% of the population was instead exposed to NO_2 levels below the limit of 10 $\mu g/m^3$.

Interactive effects of PM_{10} with NO_2 and O_3

With respect to existing literature[10–15], we added the notion of interactive effects of chronic exposure to PM_{10} with NO_2 and O_3 on SARS-CoV-2 risk, the former having an increased detrimental effect when combined with high levels of NO_2, and with lower levels of O_3. This mixture occurs in cities, characterized by elevated particulate matter and NOx emissions, the latter mainly represented by nitrogen oxide that reacts with ozone (ozone titration) leading to NO_2 formation[24,26]. The interactions then are consistent with each other, and support both the observed heterogeneity of PM_{10} effects by urbanization, and the independent effect of PM_{10} in urban settings as emerging from bi-pollutant models. Notably, in urban areas the interactive effects of pollutants substantially contributed to the total burden of pandemic by as much as 13%-23% of infectivity and hospitalization rates.

Conversely, the effect of NO_2 was the highest for lower levels of PM_{10}, as in non-urban areas characterized by lower levels of nitrogen oxide and particulate due to reduced level of traffic and of other anthropogenic sources. Since about 65% of the population in Italy lives in non-urban areas[27],

our finding corroborates the Italian nationwide EpiCovAir ecological study, which estimated a larger effect of NO_2 vs. particulate matter on SARS-CoV-2 infectivity[28].

Furthermore, our interaction analyses cast a new perspective on the role of O_3 in the SARS-CoV-2 pandemic. In single-pollutant analyses in the literature, O_3 was associated with a reduced risk of SARS-CoV-2 infectivity[10,13] and severity[10,15], as was observed in our study. The negative associations have been attributed to several reasons, including the photochemical origin of ozone that depends on solar radiation, which itself has a virucidal effect[29]; and to the ability of ozone to inactivate SARS-CoV-2 in indoor experimental studies[30]. On the other hand, ozone has detrimental health effects on the respiratory tract due to its pro-inflammatory capacity and oxidative activity[31]; pathways shared with particulate matter[6–8]. ~~However, i~~In bi-pollutant models, O_3 remained protective at low levels of PM_{10}, as in Denmark[10]; but the association reversed at higher levels of PM_{10}, as in the city of Varese[13] and in urban areas in the present paper. Although with some caution due to the different methodological approaches, in line with these observations, the findings we report in Table 3 and Figure 1d for the infectivity endpoint indicate that ozone maintains a protective effect only at low levels of particulate matter~~, suggesting that the putative advantage related to the mechanisms of virus inactivation are counterbalanced by the detrimental effects of a joint exposure to increasing levels of particulate matter~~. This suggests that in presence of elevated PM co-exposure, the detrimental effects of ozone through inflammatory and oxidative pathways may completely counterbalance and overcome the putative advantages due to the mechanisms of virus inactivation. Instead, in SARS-CoV-2 infected individuals, ozone increases the risk of severe disease and of adverse outcomes, in particular death, already at the lowest levels of particulate matter observed in our study (again Table 3 and eFigures 7). A synergic interaction between $PM_{2.5}$ and O_3 has been recently reported on other adverse health outcomes, including daily mortality for cardiovascular and respiratory diseases[17] and preterm birth for co-exposures occurring during the entire pregnancy period[31]. Liu and colleagues[17] in particular report small increases in all-cause and cardiovascular disease mortality risks associated with increasing ozone already at low levels of $PM_{2.5}$. These findings are supported by experimental studies investigating the biological plausibility of a combined effect of PM and O_3 through pathways involving inflammation, oxidative stress, macrophage activity, and endothelial dysfunction[32]. Most of these mechanisms are also invoked for the link between chronic exposure to air pollution and SARS-CoV-2[6–8]. In addition, sulfuric acid, related to ambient PM, enhances the severity of pulmonary lesions produced by ozone[33]. Finally, one study found a peculiar combination of high particulate matter with weather conditions favoring the accumulation of ozone beneath the worst pandemic wave in the Tokyo metropolitan area[34].

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Future studies looking at the specific chemical composition of particulate matter[35] may further elucidate the nature of the interactions we have detected.

Strengths and limitations

Study strengths include the design and the availability of a variety of individual-level data on exposure, outcomes, and potential confounders, in a large population residing in urban and rural areas, in one of the most polluted regions in Europe. We were able to investigate COVID-19 severity endpoints on the entire population potentially reducing collider biases[36]. Study weaknesses include the definition of long-term exposure based on a 1-year average of pollutants, but air quality reports from the Regional Agency for Environmental Protection indicate no substantial temporal trends from 2014 on in the study region. In order to minimize misclassification of long-term exposure, our study population is defined by individuals who stayed in the study area during the entire exposure year 2019. However, we have no further information on time since residency at the address used to attribute exposure. We were not able to investigate here the effects of $PM_{2.5}$. However, in our previous study in the city of Varese, the effects of $PM_{2.5}$ and PM_{10} on SARS-CoV-2 infectivity were overlapping[13]. As in many observational studies, our associations require a cautious interpretation in causal terms as they are exposed to residual confounding. We have no information on individual-level socio-economic status, but its effect as residual confounder on top of multi-dimensional area-based deprivation is not well established[10,11,15]. We were not able to take into account the potential role of mobility and social interactions on the pandemic dynamics, although mobility restrictions were in force during about a half of our study period. Although we considered a variety of potential confounders, we lack of data on obesity and on lifestyle habits, including smoking. The differential distributions of these factors across exposure levels have not been well documented. Furthermore, our results are adjusted for socio-economic status and for major non-communicable chronic diseases having obesity and smoking as causal factors.

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Conclusions

In conclusion, we found interactive effects between PM_{10} and NO_2, and between O_3 and PM_{10}, on SARS-CoV-2 incidence and on COVID-19 severity. The total burden on disease, and the overload of hospitalisations requiring intensive cares, due to long-term exposure to multiple pollutants may then exceed the sum of single exposures, thus sustaining the inclusion of environmental health amongst the key factors for public health preparedness to the next pandemic crisis[37]. Based upon our study, intervention priorities should be given to cities and highly-conglomerated urban areas in Europe, where residential and traffic emissions are amongst the main contributors to air pollution health effects[38].

Contributors: GV and MMF contributed to the conceptualisation and design of the study and writing the original draft. In addition, GV contributed to data acquisition, formal statistical analyses and is the study guarantor; and MMF supervised the statistical analyses and contributed to the interpretation of the results. SDM, WA and EMG contributed to interpretation of the results and to manuscript review and editing. CS contributed to exposure data modelling and acquisition, to interpretation of the results and to manuscript review and editing.

Ethical approval: This study, based on record-linkage of administrative healthcare data in which individuals are fully anonymized, received approval by the Regional Health Authority (approval ID: 54887/2021, date: 13/09/2021). No other approval was required. According to regional laws, the inclusion in the healthcare databases and the use of data for research purposes do not require written consent by the individuals.

References

1. Romanello M, Napoli C di, Green C, et al. The 2023 report of the Lancet Countdown on health and climate change: the imperative for a health-centred response in a world facing irreversible harms. *Lancet Lond Engl*. Published online November 13, 2023:S0140-6736(23)01859-7. doi:10.1016/S0140-6736(23)01859-7
2. *WHO Global Air Quality Guidelines. Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. Geneva: World Health Organization;2021*.
3. van Daalen KR, Romanello M, Rocklöv J, et al. The 2022 Europe report of the Lancet Countdown on health and climate change: towards a climate resilient future. *Lancet Public Health*. 2022;7(11):e942-e965. doi:10.1016/S2468-2667(22)00197-9
4. Holgate S. Air pollution is a public health emergency. *BMJ*. 2022;378:o1664. doi:10.1136/bmj.o1664
5. Thurston GD, Kipen H, Annesi-Maesano I, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J*. 2017;49(1):1600419. doi:10.1183/13993003.00419-2016
6. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017-1032. doi:10.1038/s41591-020-0968-3
7. Andersen ZJ, Hoffmann B, Morawska L, et al. Air pollution and COVID-19: clearing the air and charting a post-pandemic course: a joint workshop report of ERS, ISEE, HEI and WHO. *Eur Respir J*. 2021;58(2):2101063. doi:10.1183/13993003.01063-2021
8. Frontera A, Cianfanelli L, Vlachos K, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: The “double-hit” hypothesis. *J Infect*. 2020;81(2):255-259. doi:10.1016/j.jinf.2020.05.031
9. Weaver AK, Head JR, Gould CF, Carlton EJ, Remais JV. Environmental Factors Influencing COVID-19 Incidence and Severity. *Annu Rev Public Health*. 2022;43:271-291. doi:10.1146/annurev-publhealth-052120-101420
10. Zhang J, Lim YH, So R, et al. Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalisation or death: Danish nationwide cohort study. *Eur Respir J*. 2023;62(1). doi:10.1183/13993003.00280-2023
11. Sheridan C, Klompmaker J, Cummins S, James P, Fecht D, Roscoe C. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: Observational evidence from UK Biobank. *Environ Pollut Barking Essex 1987*. 2022;308:119686. doi:10.1016/j.envpol.2022.119686
12. Elliott J, Bodinier B, Whitaker M, et al. COVID-19 mortality in the UK Biobank cohort: revisiting and evaluating risk factors. *Eur J Epidemiol*. 2021;36(3):299-309. doi:10.1007/s10654-021-00722-y
13. Veronesi G, De Matteis S, Calori G, Pepe N, Ferrario MM. Long-term exposure to air pollution and COVID-19 incidence: a prospective study of residents in the city of Varese, Northern Italy. *Occup Environ Med*. 2022;79(3):192-199. doi:10.1136/oemed-2021-107833
14. Kogevinas M, Castaño-Vinyals G, Karachaliou M, et al. Ambient Air Pollution in Relation to SARS-CoV-2 Infection, Antibody Response, and COVID-19 Disease: A Cohort Study in Catalonia, Spain (COVICAT Study). *Environ Health Perspect*. 2021;129(11):117003. doi:10.1289/EHP9726

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15. Ranzani O, Alari A, Olmos S, et al. Long-term exposure to air pollution and severe COVID-19 in Catalonia: a population-based cohort study. *Nat Commun*. 2023;14(1):2916. doi:10.1038/s41467-023-38469-7

16. Nobile F, Michelozzi P, Ancona C, et al. Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome - a longitudinal study. *Eur Respir J*. 2022;60(3). doi:10.1183/13993003.00589-2022

17. Liu C, Chen R, Sera F, et al. Interactive effects of ambient fine particulate matter and ozone on daily mortality in 372 cities: two stage time series analysis. *BMJ*. 2023;383:e075203. doi:10.1136/bmj-2023-075203

18. Lai A, Bergna A, Menzo S, et al. Circulating SARS-CoV-2 variants in Italy, October 2020-March 2021. *Virol J*. 2021;18(1):168. doi:10.1186/s12985-021-01638-5

19. Silibello C, Bolignano A, Sozzi R, Gariazzo C. Application of a chemical transport model and optimized data assimilation methods to improve air quality assessment. *Air Qual Atmosphere Health*. 2014;7(3):283-296. doi:10.1007/s11869-014-0235-1

20. Gariazzo C, Carlino G, Silibello C, et al. A multi-city air pollution population exposure study: Combined use of chemical-transport and random-Forest models with dynamic population data. *Sci Total Environ*. 2020;724:138102. doi:10.1016/j.scitotenv.2020.138102

21. Rosano A, Pacelli B, Zengarini N, Costa G, Cislaghi C, Caranci N. Update and review of the 2011 Italian deprivation index calculated at the census section level. *Epidemiol Prev*. 2020;44(2-3):162-170. doi:10.19191/EP20.2-3.P162.039

22. Eurostat. *Methodological Manual on Territorial Typologies. 2018 Edition*. 2018th ed. Accessed December 2, 2023. doi:10.2785/22845

23. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Lond Engl*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7

24. Monks PS. Gas-phase radical chemistry in the troposphere. *Chem Soc Rev*. 2005;34(5):376. doi:10.1039/b307982c

25. Dominici F, Peng RD, Barr CD, Bell ML. Protecting Human Health from Air Pollution: Shifting from a Single-Pollutant to a Multi-pollutant Approach. *Epidemiol Camb Mass*. 2010;21(2):187-194. doi:10.1097/EDE.0b013e3181cc86e8

26. Hagenbjörk A, Malmqvist E, Mattisson K, Sommar NJ, Modig L. The spatial variation of O3, NO, NO2 and NOxand the relation between them in two Swedish cities. *Environ Monit Assess*. 2017;189(4):161. doi:10.1007/s10661-017-5872-z

27. ISTAT. *Annuario Statistico Italiano 2023. Capitolo 1: Territorio*.; 2023. Accessed February 1, 2024. https://www.istat.it/it/archivio/291790

28. Ranzi A, Stafoggia M, Giannini S, et al. [Long-term exposure to ambient air pollution and the incidence of SARS-CoV-2 infections in Italy: The EpiCovAir study]. *Epidemiol Prev*. 2023;47(3):125-136. doi:10.19191/EP23.3.A605.025

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ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

29. Belosi F, Conte M, Gianelle V, Santachiara G, Contini D. On the concentration of SARS-CoV-2 in outdoor air and the interaction with pre-existing atmospheric particles. *Environ Res*. 2021;193:110603. doi:10.1016/j.envres.2020.110603

30. Bayarri B, Cruz-Alcalde A, López-Vinent N, Micó MM, Sans C. Can ozone inactivate SARS-CoV-2? A review of mechanisms and performance on viruses. *J Hazard Mater*. 2021;415:125658. doi:10.1016/j.jhazmat.2021.125658

31. Siddika N, Rantala AK, Antikainen H, et al. Synergistic effects of prenatal exposure to fine particulate matter (PM2.5) and ozone (O3) on the risk of preterm birth: A population-based cohort study. *Environ Res*. 2019;176:108549. doi:10.1016/j.envres.2019.108549

32. Bouthillier L, Vincent R, Goegan P, et al. Acute effects of inhaled urban particles and ozone: lung morphology, macrophage activity, and plasma endothelin-1. *Am J Pathol*. 1998;153(6):1873-1884. doi:10.1016/S0002-9440(10)65701-X

33. US EPA O. Pulmonary Toxicity of Particulate Matter and Ozone | Research Project Database | Grantee Research Project | ORD | US EPA. Accessed May 10, 2024. https://cfpub.epa.gov/ncer_abstracts//index.cfm

34. Zoran MA, Savastru RS, Savastru DM, Tautan MN. Peculiar weather patterns effects on air pollution and COVID-19 spread in Tokyo metropolis. *Environ Res*. 2023;228:115907. doi:10.1016/j.envres.2023.115907

35. Huang H, Xie B, Liu Y, et al. Long-term exposure to PM2.5 compositions and O3 and their interactive effects on DNA methylation of peripheral brain-derived neurotrophic factor promoter. *Int J Environ Health Res*. Published online November 8, 2023:1-12. doi:10.1080/09603123.2023.2280157

36. Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun*. 2020;11(1):5749. doi:10.1038/s41467-020-19478-2

37. Lee JM, Jansen R, Sanderson KE, et al. Public health emergency preparedness for infectious disease emergencies: a scoping review of recent evidence. *BMC Public Health*. 2023;23(1):420. doi:10.1186/s12889-023-15313-7

38. Khomenko S, Pisoni E, Thunis P, et al. Spatial and sector-specific contributions of emissions to ambient air pollution and mortality in European cities: a health impact assessment. *Lancet Public Health*. 2023;8(7):e546-e558. doi:10.1016/S2468-2667(23)00106-8

Tables and figures

Table 1: Association between demographic and clinical characteristics of the study sample with annual mean values of air pollutant (year 2019).

	PM_{10} [µg/m^3] beta[a] (95%CI)	**NO_2 [µg/m^3] beta[a] (95%CI)**	**O_3 [µg/m^3] beta[a] (95%CI)**
Age, years	-0.045 (-0.018; -0.011)[b]	0.002 (-0.004; 0.007)[b]	0.03 (0.02; 0.03) [b]
Men vs. women	0.019 (0.008; 0.029)	-0.006 (-0.023; 0.011)	-0.03 (-0.05; -0.01)
Degree of urbanization			
Cities	REF	REF	REF
Towns and suburbs	-3.46 (-3.48; -3.45)	-7.45 (-7.47; -7.43)	7.14 (7.12; 7.16)
Rural	-8.54 (-8.58; -8.50)	-14.47 (-14.53; -14.42)	15.87 (15.78; 15.96)
Deprivation index - quintiles (regional)			
1 - Least deprived	REF	REF	REF
2	-0.09 (-0.11; -0.08)	-0.10 (-0.13; -0.08)	-0.52 (-0.55; -0.49)
3	-0.23 (-0.25; -0.21)	0.31 (0.29; 0.34)	-0.81 (-0.84; -0.78)
4	-0.68 (-0.70; -0.66)	0.10 (0.07; 0.13)	-0.42 (-0.45; -0.38)
5 - Most deprived	-0.62 (-0.64; -0.60)	0.11 (0.08; 0.14)	0.18 (0.15; 0.22)
History of drug treatment[c], yes vs. no[c]			
Diabetes	0.01 (-0.01; 0.04)	-0.02 (-0.06; 0.02)	-0.07 (-0.11; -0.02)
Anti-hypertensive	0.02 (0.01; 0.04)	0.0002 (-0.024; 0.024)	-0.07 (-0.10; -0.04)
Lipid-lowering	-0.02 (-0.04; 0.004)	-0.07 (-0.10; -0.04)	0.02 (-0.014; 0.05)
Treatment for obstructive airway diseases	0.05 (0.03; 0.06)	0.02 (-0.008; 0.05)	-0.04 (-0.07; 0.003)
Positive history of, yes vs. no[d]			
Coronary heart disease	0.021 (-0.02; 0.06)	0.06 (-0.01; 0.12)	-0.03 (-0.11; 0.05)
Stroke	-0.08 (-0.13; -0.04)	-0.10 (-0.17; -0.02)	0.20 (0.12; 0.29)
Cancer	0.023 (-0.009; 0.05)	0.07 (0.02; 0.12)	-0.09 (-0.15; -0.03)
COPD	-0.20 (-0.26; -0.13)	-0.26 (-0.36; -0.16)	0.58 (0.46; 0.70)

[a]: change in air pollutant annual mean, from linear regression models. [b]: beta for 10-year increase in age. [c]: At least one prescription during the year 2019. ATC classes: diabetes (A10); anti-hypertensive (C02, C03, C07, C08 and C09); lipid-lowering (C10); treatment for obstructive airway diseases (R03).~~ATC codes are reported in eAppendix 1.~~ [d]: at least one hospital discharge record between Jan, 1st 2015 and Dec, 31st 2019. ICD-IX codes: coronary heart disease (410-414); stroke (430-438); cancer (140-208); COPD (490-496).~~ICD-IX codes are reported in the eAppendix 1.~~

Table 2: Association between long-term exposure to air pollutants and the study endpoints, in the entire Province and in urban and non-urban areas.

	Province[a]			Urban[b]			Non-urban[b]			Urban*pollutant interaction p-value[b]
	HR	95%CI		HR	95%CI		HR	95%CI		
Infectivity										
PM_{10}	1.02	1.01	1.03	1.12	1.09	1.16	0.99	0.98	1.01	<0.001
NO_2	1.02	1.00	1.05	1.03	1.00	1.07	1.02	0.99	1.05	0.48
O_3	0.95	0.93	0.97	0.92	0.89	0.95	0.97	0.94	1.00	0.01
Hospitalization										
PM_{10}	1.00	0.96	1.04	1.18	1.08	1.29	0.96	0.91	1.00	<0.001
NO_2	1.02	0.95	1.08	1.06	0.96	1.17	0.99	0.91	1.07	0.28
O_3	0.96	0.90	1.02	0.91	0.83	1.00	1.00	0.92	1.08	0.12
of these: hospitalization requiring ICU/mechanical ventilation										
PM_{10}	0.99	0.94	1.05	1.13	1.01	1.27	0.96	0.90	1.02	0.01
NO_2	1.05	0.97	1.14	1.10	0.97	1.25	1.02	0.92	1.14	0.38
O_3	0.94	0.87	1.01	0.85	0.75	0.96	1.01	0.91	1.11	0.04
Mortality										
PM_{10}	1.09	1.01	1.17	1.22	1.04	1.42	1.05	0.96	1.14	0.11
NO_2	1.18	1.05	1.32	1.18	0.99	1.41	1.17	1.00	1.37	0.97
O_3	0.91	0.82	1.02	0.89	0.76	1.05	0.93	0.80	1.08	0.74

Abbreviations: ICU=Intensive Care Unit.

[a]: Single-pollutant Cox regression models, adjusting for age, sex, urbanization (urban vs. non-urban), deprivation index (quintiles), positive history of coronary heart disease, stroke, cancer, Chronic Obstructive Pulmonary Disease, treatment for diabetes, anti-hypertensive treatment, treatment for obstructive airway diseases. For the infectivity and the mortality endpoints, age was modelled as a polynomial of degree 3 and 2, respectively.

[b]: Single-pollutant Cox regression models, adjusting for age, sex, urbanization (urban vs. non-urban), deprivation index (quintiles), positive history of coronary heart disease, stroke, cancer, Chronic Obstructive Pulmonary Disease, treatment for diabetes, anti-hypertensive treatment, treatment for obstructive airway diseases + air pollutant*urbanization interaction term (1 df). For the infectivity and the mortality endpoints, age was modelled as a polynomial of degree 3 and 2, respectively.

HR: Hazard ratios for 1 interquartile range (IQR) increase in Province-wide air pollutants. ~~(2019 annual mean).~~ IQR values: PM_{10}=3.5 µg/m^3; NO_2=8.7 µg/m^3; O_3=9.7 µg/m^3

Table 3: Hazard ratios for SARS-CoV-2 infectivity, hospitalization and mortality associated with one interquartile range increase in PM_{10}, NO_2 and O_3, by levels of co-pollutants

	PM_{10} by NO_2 levels	**NO_2 by PM_{10} levels**	**PM_{10} by O_3 levels**	**O_3 by PM_{10} levels**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Infectivity				
≤25th pct	0.96 (0.94; 0.99)	1.09 (1.03; 1.16)	1.15 (1.06; 1.25)	0.88 (0.83; 0.93)
~~25~~26-75th pct	1.09 (1.05; 1.13)	1.06 (1.01; 1.10)	1.07 (1.04; 1.11)	0.92 (0.88; 0.95)
>75th pct	1.15 (1.08; 1.22)	0.87 (0.82; 0.93)	0.96 (0.94; 0.99)	1.32 (1.17; 1.49)
Heterogeneity p-value[a]	<.0001	<.0001	<.0001	<.0001
Hospitalization				
≤25th pct	0.92 (0.85; 0.99)	1.00 (0.85; 1.18)	1.09 (0.85; 1.38)	1.06 (0.91; 1.23)
~~25~~26-75th pct	1.11 (1.02; 1.21)	1.10 (0.98; 1.24)	1.17 (1.08; 1.27)	0.87 (0.79; 0.97)
>75th pct	1.28 (1.07; 1.53)	0.81 (0.68; 0.98)	0.88 (0.81; 0.95)	1.85 (1.32; 2.58)
Heterogeneity p-value[a]	0.0002	0.02	<.0001	<.0001
Mortality				
≤25th pct	0.92 (0.79; 1.07)	0.95 (0.69; 1.31)	1.27 (0.82; 1.97)	1.32 (1.00; 1.74)
~~25~~26-75th pct	1.21 (1.04; 1.41)	1.25 (1.01; 1.54)	1.31 (1.12; 1.52)	0.93 (0.78; 1.12)
>75th pct	1.10 (0.82; 1.48)	0.88 (0.64; 1.22)	0.99 (0.86; 1.15)	1.43 (0.78; 2.61)
Heterogeneity p-value[a]	0.04	0.10	0.03	0.07

HR: Hazard ratios for 1 interquartile range (IQR) increase in Province-wide air pollutants. IQR values: PM_{10}=3.5 µg/m^3; NO_2=8.7 µg/m^3; O_3=9.7 µg/m^3.
Hazard Ratios estimates from Cox models including age, sex, urbanization (urban vs. non-urban), deprivation index (quintiles), positive history of coronary heart disease, stroke, cancer, Chronic Obstructive Pulmonary Disease, treatment for diabetes, anti- hypertensive treatment, treatment for obstructive airway diseases, air pollutant, co-pollutant levels (in three classes) and air pollutant*co-pollutant levels interaction. For the infectivity and the mortality endpoints, age was modelled as a polynomial of degree 3 and 2, respectively.
[a]: 2df Wald chi-square test.

Table 4: Association between long-term exposure to air pollutants and the study endpoints, by pandemic waves, in urban and non-urban areas.

	Pandemic wave[a]	Infectivity HR (95%CI)	Hospitalization HR (95%CI)	Mortality HR (95%CI)
Urban				
PM_{10}	1st wave	1.24 (1.10; 1.41)	1.56 (1.28; 1.92)	1.56 (1.07; 2.26)
	2nd wave	1.12 (1.08; 1.16)	1.11 (1.00; 1.22)	1.16 (0.97; 1.39)
	p-value wavePM_{10} interaction*[b]	0.11	0.003	0.16
NO_2	1st wave	1.29 (1.12; 1.48)	1.38 (1.11; 1.71)	1.38 (0.93; 2.06)
	2nd wave	1.02 (0.98; 1.05)	1.00 (0.89; 1.11)	1.13 (0.92; 1.38)
	p-value waveNO_2 interaction*[b]	0.001	0.008	0.37
O_3	1st wave	0.89 (0.78; 1.01)	0.79 (0.64; 0.97)	0.72 (0.49; 1.06)
	2nd wave	0.91 (0.88; 0.95)	0.93 (0.84; 1.03)	0.92 (0.77; 1.11)
	p-value waveO_3 interaction*[b]	0.69	0.16	0.25
Non-urban				
PM_{10}	1st wave	0.98 (0.91; 1.04)	0.94 (0.84; 1.04)	1.04 (0.84; 1.29)
	2nd wave	0.99 (0.98; 1.01)	0.97 (0.92; 1.02)	1.06 (0.96; 1.16)
	p-value wavePM_{10} interaction*[b]	0.61	0.57	0.87
NO_2	1st wave	1.02 (0.90; 1.15)	0.91 (0.75; 1.10)	1.13 (0.76; 1.68)
	2nd wave	1.02 (0.99; 1.05)	1.01 (0.92; 1.11)	1.18 (1.00; 1.41)
	p-value waveNO_2 interaction*[b]	0.97	0.33	0.84
O_3	1st wave	0.93 (0.83; 1.04)	0.97 (0.81; 1.17)	0.86 (0.59; 1.25)
	2nd wave	0.97 (0.94; 1.00)	1.00 (0.92; 1.09)	0.94 (0.80; 1.11)
	p-value waveO_3 interaction*[b]	0.49	0.81	0.67

HR=Hazard ratios for 1 interquartile range increase in air pollutant (2019 annual mean). IQR values: PM_{10}=3.5 μg/m^3; NO_2=8.7 μg/m^3; O_3=9.7 μg/m^3. HR estimates from single-pollutant Cox models including age, sex, urbanization (urban vs. non-urban), deprivation index (quintiles), positive history of coronary heart disease, stroke, cancer, Chronic Obstructive Pulmonary Disease, treatment for diabetes, anti-hypertensive treatment, treatment for obstructive airway diseases, air pollutant and air pollutant*wave interaction. For the infectivity and the mortality endpoints, age was modelled as a polynomial of degree 3 and 2, respectively.

[a]: first wave: 01/02-31/05/20. Second wave: 01/06-31/12/20.

[b]: 1df Wald chi-square test.

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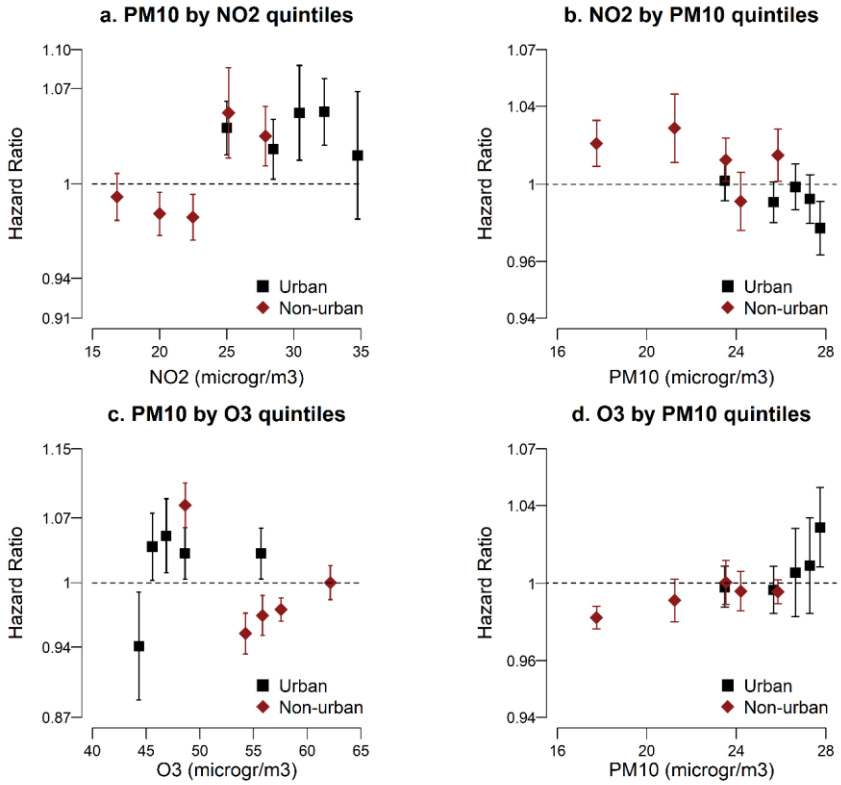
Figure 1: Modelling of SARS-CoV-2 infectivity risks due to 1 µg/m^3 increase in one pollutant by urban and non-urban specific quintiles of the co-pollutant.