Environment International 185 (2024) 108530

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Who is more vulnerable to effects of long-term exposure to air pollution on COVID-19 hospitalisation?

Otavio Ranzani [a,b,c], Anna Alari [a,b,c], Sergio Olmos [a,b,c], Carles Milà [a,b,c], Alex Rico [a,b,c], Xavier Basagaña [a,b,c], Payam Dadvand [a,b,c], Talita Duarte-Salles [d,e], Francesco Forastiere [f,g], Mark Nieuwenhuijsen [a,b,c], Rosa M Vivanco-Hidalgo [h], Cathryn Tonne [a,b,c,*]

[a] Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[d] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
[e] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands
[f] National Research Council, IFT, Palermo, Italy
[g] Environmental Research Group, Imperial College London, London, UK
[h] Agency for Health Quality and Assessment of Catalonia (AquAS), Barcelona, Spain

ARTICLE INFO

Keywords:
COVID-19
Air pollution
Effect modification
Vulnerability

ABSTRACT

Objective: Factors that shape individuals' vulnerability to the effects of air pollution on COVID-19 severity remain poorly understood. We evaluated whether the association between long-term exposure to ambient NO_2, $PM_{2.5}$, and PM_{10} and COVID-19 hospitalisation differs by age, sex, individual income, area-level socioeconomic status, arterial hypertension, diabetes mellitus, and chronic obstructive pulmonary disease.

Methods: We analysed a population-based cohort of 4,639,184 adults in Catalonia, Spain, during 2020. We fitted Cox proportional hazard models adjusted for several potential confounding factors and evaluated the interaction effect between vulnerability indicators and the 2019 annual average of NO_2, $PM_{2.5}$, and PM_{10}. We evaluated interaction on both additive and multiplicative scales.

Results: Overall, the association was additive between air pollution and the vulnerable groups. Air pollution and vulnerability indicators had a synergistic (greater than additive) effect for males and individuals with low income or living in the most deprived neighbourhoods. The Relative Excess Risk due to Interaction (RERI) was 0.21, 95 % CI, 0.15 to 0.27 for NO_2 and 0.16, 95 % CI, 0.11 to 0.22 for $PM_{2.5}$ for males; 0.13, 95 % CI, 0.09 to 0.18 for NO_2 and 0.10, 95 % CI, 0.05 to 0.14 for $PM_{2.5}$ for lower individual income and 0.17, 95 % CI, 0.12 to 0.22 for NO_2 and 0.09, 95 % CI, 0.05 to 0.14 for $PM_{2.5}$ for lower area-level socioeconomic status. Results for PM_{10} were similar to $PM_{2.5}$. Results on multiplicative scale were inconsistent.

Conclusions: Long-term exposure to air pollution had a larger synergistic effect on COVID-19 hospitalisation for males and those with lower individual- and area-level socioeconomic status.

1. Introduction

The COVID-19 pandemic presented major challenges to societies and health systems worldwide (Bell et al., 2022). Several risk factors contributing to progression to severe COVID-19 have been identified, including age, male sex, chronic comorbidities and lower socioeconomic status (Burn et al., 2021; Du et al., 2021). In addition, long-term exposure to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) have been consistently associated with COVID-19 hospitalisation (Bowe et al., 2021; Chen et al., 2022a; Chen et al., 2022b; Ranzani et al., 2023; Sheppard et al., 2023; Sheridan et al., 2022). A 2023 systematic review reported a pooled odds ratio of 2.27 (95 % CI, 1.41–3.66, per 10 $\mu g/m^3$

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, disease caused by the Sars-CoV-2 infection; df, degrees of freedom; HR, hazard ratio; NO_2, nitrogen dioxide; PM_{10}, fraction of particles with an aerodynamic diameter smaller than 10 μm; $PM_{2.5}$, fraction of particles with an aerodynamic diameter smaller than 2.5 μm; RERI, relative excess risk due to interaction; RR, relative risk.

* Corresponding author at: Carrer del Dr. Aiguader 88, 08003 Barcelona, Spain.
E-mail address: cathryn.tonne@isglobal.org (C. Tonne).

https://doi.org/10.1016/j.envint.2024.108530
Received 6 September 2023; Received in revised form 23 January 2024; Accepted 22 February 2024
Available online 23 February 2024

increase in $PM_{2.5}$, n = 6 studies) for COVID-19 hospitalisation, intensive care admission or respiratory support (Sheppard et al., 2023). Additionally, four large population-based studies not included in the review analysing either the general population (Ranzani et al., 2023; Stafoggia et al., 2023; Zhang et al., 2023) or COVID-19 cases (Hyman et al., 2023) detected positive associations between air pollutants and severe COVID-19. Positive associations were reported for $PM_{2.5}$ and NO_2 and COVID-19 hospitalizations in three studies (Hyman et al., 2023; Ranzani et al., 2023; Zhang et al., 2023); for $PM_{2.5}$ and COVID-19 deaths in four studies (Hyman et al., 2023; Ranzani et al., 2023; Stafoggia et al., 2023; Zhang et al., 2023); and NO_2 and COVID-19 deaths in three (Ranzani et al., 2023; Stafoggia et al., 2023; Zhang et al., 2023).

However important gaps remain in our understanding of who is most vulnerable to developing air pollution related severe COVID-19 outcomes such as hospitalization or death. Overall, previous studies were not specifically designed to identify vulnerable groups, were limited by inadequate sample size and power, and did not provide a detailed evaluation of interaction on both additive and multiplicative scales (Knol and VanderWeele, 2012; VanderWeele and Knol, 2014). In addition to the multiplicative scale, evaluating interaction on the additive scale provides a more complete understanding of groups who would benefit most from reduced exposure, is more suitable when the baseline risk of outcome differs considerably between those with and without a vulnerability indicator, and is more informative regarding the public health significance of the evaluated interaction (Knol and VanderWeele, 2012; VanderWeele, 2019; VanderWeele and Knol, 2014). Additionally, some studies evaluated cohorts of COVID-19 cases rather than the general population, which may introduce bias in the effect modification estimates, particularly if the effect modifier is also associated with the risk of getting infected or diagnosed (Griffith et al., 2020; Millard et al., 2023).

Studies that evaluated effect modification for the association between ambient NO_2 and $PM_{2.5}$ and COVID-19 hospitalization yielded inconsistent results for age, sex and comorbidities. Zhang et al. observed effect modification on the multiplicative scale for NO_2 for those aged ≥65 years, but not for sex, and no modification for $PM_{2.5}$ for either age or sex in a general population-based cohort in Denmark (Zhang et al., 2023). Hyman et al. observed a multiplicative interaction for both NO_2 and $PM_{2.5}$ with age but not sex for COVID-19 hospitalization among a cohort of COVID-19 cases (Hyman et al., 2023). Chen et al. found no evidence of effect modification by age or sex for both pollutants (Chen et al., 2022b). Finally, Bowe et al. observed no evidence of effect modification for age or sex on the multiplicative scale, but a positive additive interaction for age for $PM_{2.5}$ and COVID-19 hospitalization (Bowe et al., 2021). Regarding comorbidities, Zhang et al. investigated multiplicative effect modification for several comorbidities and observed effect modification for COVID-19 hospitalization only for chronic obstructive pulmonary disease (COPD) and NO_2. The authors observed a decreased NO_2 hospitalization association for those with COPD compared with individuals without COPD (Zhang et al., 2023). In contrast, larger $PM_{2.5}$-hospitalization associations were observed among those with compared to those without chronic respiratory diseases in a cohort of selected COVID-19 cases (Mendy et al., 2021). Finally, Hyman et al. reported larger NO_2– and $PM_{2.5}$-associations with COVID-19 hospitalization with increasing body-mass index increases (Hyman et al., 2023).

Evidence regarding modification of air pollution COVID-19 hospitalization associations by socioeconomic indicators are more consistent showing increased associations for those with lower socioeconomic status. Analysing representative cohorts of COVID-19 cases in the US, Bowe et al. observed a larger association for $PM_{2.5}$ and COVID-19 hospitalization among those living in more deprived areas both on multiplicative and additive scales (Bowe et al., 2021). In a population-based cohort of the general Danish population, Zhang et al. observed increased association for both NO_2 and $PM_{2.5}$ and COVID-19 hospitalization among those with lower compared to higher education on the multiplicative scale. Similar trends were observed for income, employment and wealth status, but interactions were not statistically significant (Zhang et al., 2023). Evidence from the US indicates modification on the multiplicative scale of air pollution and COVID-19 hospitalizations by race/ethnicity, with stronger associations among Black individuals (Bowe et al., 2021; Chen et al., 2022b).

We previously observed a positive association between long-term ambient $PM_{2.5}$ and NO_2 and COVID-19 hospitalisation in a large, population-based cohort in Catalonia, Spain (Ranzani et al., 2023). We now extend these results to evaluate whether demographic (age, sex), chronic comorbidities (arterial hypertension, diabetes mellitus, COPD) and socioeconomic (individual-level income and area-level socioeconomic index) characteristics confer vulnerability to the association of long-term air pollution exposure with COVID-19 hospitalisation. We selected vulnerability indicators that: 1) were risk factors for COVID-19 progression to severity (Burn et al., 2021; Dessie and Zewotir, 2021; Du et al., 2021); 2) had little missing data; and 3) in case of comorbidities, were prevalent across different age ranges (i.e., above and below 65 years). Potential mechanisms underlying increased vulnerability to air pollution of these indicators include: impaired response to oxidative stress and inflammation with increasing age and presence of comorbidities (Chistiakov et al., 2014; Liguori et al., 2018), different immune response by sex during acute COVID-19 infection (Takahashi et al., 2020), and low socioeconomic status having different occupational exposure resulting on high virus load during acute infection (Wachtler et al., 2020).

2. Methods

2.1. Study design and population

We analysed a population-based cohort of the adult population of Catalonia (northeast of Spain) constructed through record-linkage of data collected in the public health administration databases of Catalonia (Avellaneda-Gómez et al., 2022; Ranzani et al., 2023), whose system covers nearly its entire population (98.8 % of the 7.4 million in 2015) (Ranzani et al., 2023).

The original cohort included 5,127,059 adults (≥18 years) residing in Catalonia in January 2015. Our analysis included all individuals from the original cohort who were alive and residing in Catalonia in March 1st 2020 (n = 4,669,011).

The cohort design, definitions, and analysis plan were pre-specified in a protocol before any data extraction. Any deviance from the initial plan was labelled as post-hoc. The sample size was pragmatic based on the population-based cohort. We received ethics approval from the Parc de Salut Mar Ethics Committee (CEIM-PS MAR, no.2020/9610) to conduct this study.

2.2. Outcome

We defined COVID-19 related hospitalisation as hospital admission within 30-days of COVID-19 diagnosis (Chen et al., 2022b; Nobile et al., 2022; Ranzani et al., 2023). COVID-19 diagnosis was defined as positive RT-qPCR or rapid antigen test or clinical diagnosis of COVID-19 (defined by respective ICD-10 codes recorded in the administrative healthcare databases). We considered only the first COVID-19 diagnosis since the start of the cohort and excluded diagnoses at nursing homes (Chen et al., 2022a; Ranzani et al., 2023). To account for individuals who were first hospitalized and had a subsequent COVID-19 diagnosis, particularly during the first wave of the pandemic in Spain, we also included hospitalisations that occurred during ten days prior to first COVID-19 diagnosis.

2.3. Exposure assessment

We assigned annual average (2019) NO_2, $PM_{2.5}$ and PM_{10} at

participant's residential address using spatiotemporal machine learning models developed in the COVAIR-CAT project. Details of the model have been published elsewhere (Milà et al., 2023). The estimated performance of the models in terms of R^2 was 0.77 for NO_2, 0.61 for $PM_{2.5}$, and 0.64 for PM_{10}. We used residential address at the start of 2021 or the last available since address data collection for 2020 was disrupted by the pandemic. Exposure distributions are shown in the supplementary material.

2.4. Covariates

We obtained age, sex, individual-level income and health risk group in 2015 from the Central Registry of Insured Persons. Individual income group was based on the co-payment system for drug dispensations, which largely depends on income (Avellaneda-Gómez et al., 2022; Ranzani et al., 2023). Individual health risk group was based on a validated ordinal index which encompasses multimorbidity and levels of patient complexity, accounting for acute, chronic or oncological morbidities, single or multimorbidity, medications and demand of the health system (Monterde et al., 2020; Vivanco-Hidalgo et al., 2021).

Tobacco smoking status (non-smoker, former-smoker or active smoker) and arterial hypertension, diabetes mellitus, and COPD were obtained from the primary care database. Selected chronic comorbidities were also obtained from the hospital admissions database (e.g., COPD) (Avellaneda-Gómez et al., 2022; Ranzani et al., 2023). We considered a missing value for tobacco smoking as a non-smoker because the value is most often omitted for non-smokers in the primary care. Previous analysis using different approaches (e.g., multiple imputation) yielded similar results (Ranzani et al., 2023). Nursing home status for those with COVID-19 diagnosis was obtained from the COVID-19 surveillance system. We adjusted for the four area-level indicators: the Small Area Socioeconomic Index (Avellaneda-Gómez et al., 2022; Idescat. Small Area Socioeconomic Index, n.d); the distance from the residence to the closest primary care unit, as a proxy for the public healthcare system accessibility; the weekly test-positive proportion of RT-qPCR and rapid antigen tests as a proxy of the pandemic dynamics (Hitchings et al., 2021); and a residential urban/rural area binary indicator (Ranzani et al., 2023).

Further details of the cohort are in the supplementary material and published elsewhere (Avellaneda-Gómez et al., 2022; Ranzani et al., 2023).

2.5. Statistical analysis

We fitted Cox proportional hazards models to estimate the association between long-term exposure to air pollution and COVID-19 hospitalisation. Follow-up started on March 1st 2020, coinciding with the start of the pandemic in Catalonia in early March 2020, and finished if COVID-19 hospitalization occurred, or right-censoring at the first instance of (1) death; (2) 30 days after the first COVID-19 diagnosis among individuals who were not hospitalized in the 30 day window (Chen et al., 2022b; Nobile et al., 2022; Ranzani et al., 2023); (3) emigration outside the study area (we set July 1st 2020 as date of censoring, n = 39,241, 0.8 %, due to lack of exact date of emigration in 2020 due to pandemic disruption); and (4) the end of the study period (December 31st 2020).

We used time from March 1st 2020 in days as the time scale. We assessed the proportional hazards assumption by visual inspection of score residuals plotted against time. Associations were reported as Hazard Ratios (HR) with their 95 % Confidence Intervals (CI).

We used two approaches to evaluate effect modification on the additive scale. First, we created a 10-level category for each exposure and vulnerable group by combining quintiles of exposure and a binary indicator of vulnerability (Wang et al., 2023). We used quintiles to optimize the trade-off between preserving exposure variability and ensuring adequate sample size within each group. Second, we created a 4-level category using binary exposure above or below the median and a binary indicator of vulnerability to estimate the Relative Excess Risk due to Interaction (RERI) (Knol and VanderWeele, 2012; VanderWeele and Knol, 2014; Wang et al., 2023), a measure of departure from additivity, as defined below:

$$RERI = RR_{11} - RR_{10} - RR_{01} + 1$$

where RR_{11} is the risk when both conditions are present and RR_{10} and RR_{01} are the risks when only one of the conditions is present. RERI was estimated with the resulting HRs from the 4-level category. RERI tests whether the combined effect of exposure and vulnerability is greater (positive), smaller (negative) or equal (0 value) to the sum of their effects. Confidence intervals for RERI were estimated using the delta-method (Assmann et al., 1996).

We investigated interaction on the multiplicative scale using two approaches. First, multiplicative interaction was estimated from the model used to calculated the RERI (Knol and VanderWeele, 2012; VanderWeele and Knol, 2014). Second, we added an interaction term between the air pollutant (continuous term) and each vulnerability indicator.

We adopted the terminology from VanderWeele to assess where on the interaction continuum (11 states ranked according to strength of positive interaction) our RERI results were located (VanderWeele, 2019). Where two exposures have positive associations with the outcome, the probability of the outcome in the doubly exposured group determines the location of the continuum (VanderWeele, 2019).

We adjusted models based on *a priori* assumptions about the relationships between exposures, covariates and the outcome (Fig. S1) (Ranzani et al., 2023). Models for the 10- and 4-level categories were adjusted by age (2 categories) + sex (2 categories) + smoking (3 categories) + health risk group (4 categories) + Small Area Socioeconomic Index (2 categories) + distance to the closest primary care unit (continuous) + urbanicity (2 categories) + average weekly test-positive proportion (continuous) + health region (strata of 7 categories). Models investigating multiplicative interaction with continuous exposure differed only by including continuous terms for age (penalized spline with 6 df) and Small Area Socioeconomic Index (main model in previous analysis (Ranzani et al., 2023)). In the models of the 4- and 10-level categories, continuous age and Small Area Socioeconomic Index would have resulted in high collinearity with dichotomous vulnerability indicators (e.g. age $\geq$65 years).

In *post-hoc* analysis to illustrate the phenomena observed in the multiplicative scale models with continuous exposures, we predicted the probability of COVID-19 hospitalisation from the Cox model using two vulnerable groups: diabetes mellitus and low individual income as examples of variables with strong (diabetes) and modest (individual income) associations with COVID-19 hospitalisation (Fig. 1).

All analyses were conducted in R (R Core Team, 2020) software (version 4.1.2). Cox proportional hazards model were conducted using the "survival" package (Thermeau, 2021), and RERI was estimated with the "interaction" package (Alli, 2021).

3. Results

3.1. Population characteristics

On March 1st 2020, there were 4,669,011 adults residing in Catalonia, of which we excluded 998 (<0.1 %) because of inconsistent or loss to follow-up information, 1512 (<0.1 %) missing residential address, 5999 (0.1 %) missing air pollution exposure, and 21,318 (0.4 %) COVID-19 cases from nursing-homes, resulting in the analysed population of 4,639,184 individuals (Fig. S2).

Table 1 presents the general characteristics of the full population and vulnerable groups, including their crude COVID-19 hospitalisation rates. The mean age was 54 (SD = 17) years, with 27 % of the population aged

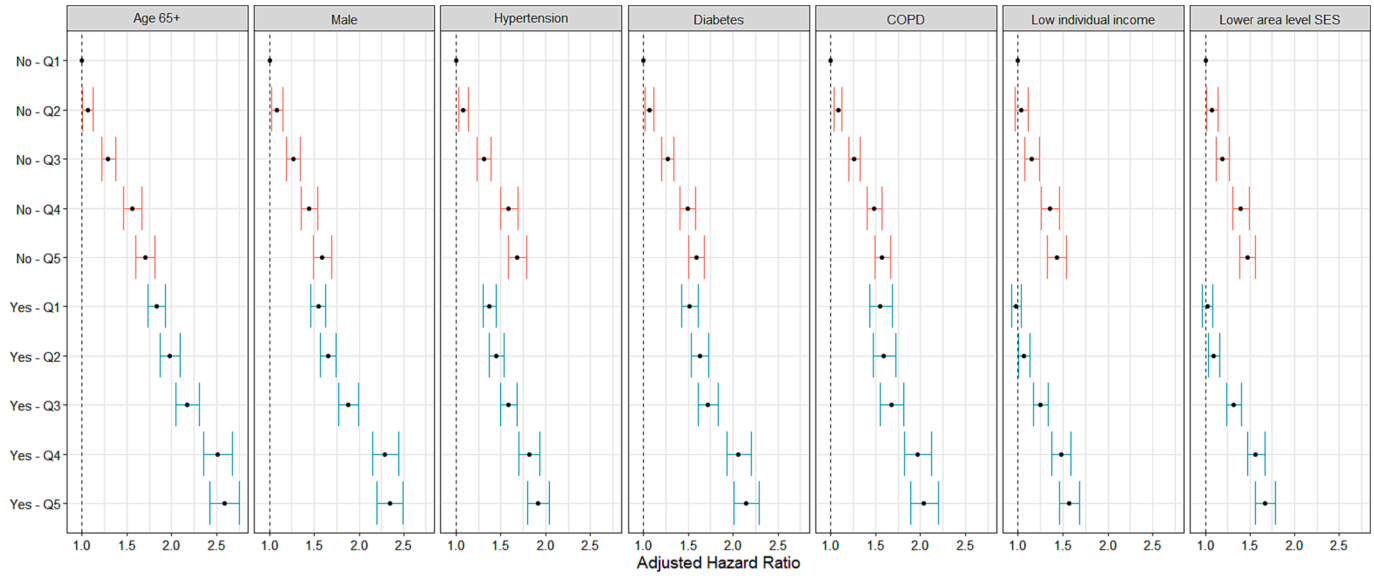

Fig. 1. Combined adjusted hazard ratios of long-term NO_2 and vulnerability indicators on the risk of COVID-19 hospitalisation. The ten category levels were created by combining the presence or absence of the vulnerable group and the quintiles of the long-term ambient NO_2. The hazard ratio was estimated with a Cox Proportional Hazards model, adjusted by age (factor, 2 categories) + sex (factor, 2 categories) + smoking (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (factor, 2 categories) + distance to the closest primary care unit (continuous term) + urbanicity (factor, 2 categories) + average weekly test-positive proportion (continuous term) + health region (strata, 7 categories). The reference group was always the group with absence of the vulnerable group indicator and the first quintile of the long-term ambient NO_2. The black circle refers to the point estimated hazard ratio and the stickers refers to the 95 % confidence interval.

Table 1
Characteristics and crude COVID-19 hospitalisation rates of the full population and vulnerable groups.

Variable	Category	Full population	Crude COVID-19 Hospitalisation rate, n (%)
n	n	4,639,184	42,741 (0.92)
Age categories, n (%)	23–64 years	3,390,376 (73.1)	20,407 (0.60)
	65 + years	1,248,808 (26.9)	22,334 (1.79)
Male, n (%)	No	2,431,299 (52.4)	19,470 (0.80)
	Yes	2,207,885 (47.6)	23,271 (1.05)
Hypertension, n (%)	No	3,469,940 (74.8)	22,956 (0.66)
	Yes	1,169,244 (25.2)	19,785 (1.69)
Diabetes mellitus, n (%)	No	4,173,175 (90.0)	32,186 (0.77)
	Yes	466,009 (10.0)	10,555 (2.26)
Chronic Obstructive Pulmonary Disease, n (%)	No	4,448,766 (95.9)	37,927 (0.85)
	Yes	190,418 (4.1)	4,814 (2.53)
Low individual income, n (%)	No	1,417,397 (30.6)	12,433 (0.88)
	Yes	3,221,787 (69.4)	30,308 (0.94)
Lower area-level SES, n (%)	No	2,333,456 (50.3)	20,300 (0.87)
	Yes	2,305,728 (49.7)	22,441 (0.97)

SES: socioeconomic status.

≥65 years. The prevalence of arterial hypertension was 25 %, followed by 10 % for diabetes mellitus and 4 % for COPD. About two thirds of the population had low income (<18,000 euros per year). The characteristics of those excluded (n = 29,827) are shown in Table S1. Excluded individuals were older, more likely to be female, with more comorbidities, and more likely to have low individual-level socioeconomic status compared to included individuals.

There were 319,290 (6.9 %) COVID-19 cases identified during the study period, of whom 42,741 (13 %) were hospitalized. The mean follow-up time was 293 (SD = 48) days. The overall crude hospitalisation rate was 0.92 %, and varied according to vulnerability group: 1.79 % for those aged 65 + and 1.96 % (hypertension) to 2.53 % (COPD) for those with chronic comorbidities (Table 1).

3.2. *Additive effects of air pollution exposure and vulnerability indicators*

Overall, there was an additive effect when evaluating the combined effects of NO_2 (Fig. 1, Table S2), $PM_{2.5}$ (Fig. S3, Table S2) and PM_{10} (Fig. S4, Table S2) and vulnerability indicators. Relative to the least exposed quintile without vulnerability, the risk of COVID-19 hospitalisation was highest in the most exposed quintile for each vulnerability indicator for the three pollutants. For age, sex, and most comorbidities, the increase in risk of COVID-19 hospitalisation was close to monotonic across the ten categories. However, a distinct, non-monotonic pattern was observed for individual and area-level SES indicators, for which the effect of the vulnerability indicator on risk of COVID-19 hospital admission alone (e.g. comparison of with and without vulnerability in the first quintile of exposure) was modest.

3.3. *Additive interactions between air pollution and vulnerability indicators*

Broadly similar patterns were observed with dichotomous exposure (two categories using the median value) for $PM_{2.5}$, PM_{10}, and NO_2 (Tables 2 and 3, Table S3). Based on the RERI, there was evidence for a joint effect larger than the sum of effects (positive additive) of air pollution exposure and the vulnerability indicator for sex and the SES

Table 2
Association between NO_2 and COVID-19 hospitalisation by vulnerability indicators and their interaction on additive and multiplicative scales.

	NO_2*		Interaction on additive scale	Interaction on multiplicative scale	Type of interaction (VanderWeele, 2019)
	Low	High	RERI (95 % CI)	HR (95 % CI)	
Age, years					
23–64	1.00 (Reference)	1.49 (1.44 to 1.55)	0.06 (-0.01 to 0.12)	0.87 (0.84 to 0.91)	Zero additive
65+	1.81 (1.75 to 1.87)	2.36 (2.26 to 2.45)			Negative multiplicative
Male					
No	1.00 (Reference)	1.39 (1.34 to 1.45)	0.21 (0.15 to 0.27)	1.00 (0.96 to 1.04)	Positive additive
Yes	1.52 (1.47 to 1.57)	2.12 (2.03 to 2.20)			No multiplicative
Hypertension					
No	1.00 (Reference)	1.49 (1.43 to 1.54)	−0.10 (-0.16 to −0.05)	0.87 (0.84 to 0.90)	Negative additive
Yes	1.32 (1.28 to 1.37)	1.71 (1.64 to 1.78)			Negative multiplicative
Diabetes					
No	1.00 (Reference)	1.43 (1.38 to 1.48)	0.01 (-0.06 to 0.09)	0.91 (0.87 to 0.95)	Zero additive
Yes	1.49 (1.44 to 1.55)	1.94 (1.86 to 2.02)			Negative multiplicative
Chronic Obstructive Pulmonary Disease					
No	1.00 (Reference)	1.41 (1.36 to 1.46)	0.00 (-0.10 to 0.10)	0.91 (0.85 to 0.97)	Zero additive
Yes	1.45 (1.38 to 1.53)	1.86 (1.77 to 1.95)			Negative multiplicative
Low individual income					
No	1.00 (Reference)	1.30 (1.25 to 1.36)	0.13 (0.09 to 0.18)	1.10 (1.05 to 1.15)	Positive additive
Yes	1.00 (0.97 to 1.04)	1.44 (1.38 to 1.50)			Positive multiplicative
Lower area-level SES					
No	1.00 (Reference)	1.34 (1.29 to 1.39)	0.17 (0.12 to 0.22)	1.10 (1.06 to 1.15)	Positive additive
Yes	1.07 (1.04 to 1.11)	1.59 (1.53 to 1.65)			Positive multiplicative

RERI stands for relative excess risk due to interaction.
* NO_2 categories were defined by the median value (28.3), the low category has a mean of 17.4 (SD = 6) while the high category has a mean of 35.0 (SD = 5).

indicators. The RERI for the joint effect of NO_2 and vulnerability indicators was positive and statistically significant for: male sex (0.21 (95 % CI 0.15, 0.27)), low individual income (0.13 (95 % CI, 0.09, 0.18)) and higher area-level deprivation (0.17 (95 % CI, 0.12, 0.22)). For age, RERI was 0.06 (95 % CI, −0.01 to 0.12). There was no evidence of additive synergistic effects for chronic comorbidities. For hypertension, the RERI was negative (negative additive) indicating that their combined effect was less than the sum of their individual effects. Broadly similar patterns were observed for $PM_{2.5}$ and PM_{10}.

3.4. Interaction on the multiplicative scale

When evaluating multiplicative interaction between high air pollution exposure and vulnerability indicators, we observed a negative multiplicative interaction for older age and chronic comorbidities, no interaction for sex, and a positive multiplicative interaction for low individual-level income for all pollutants (Tables 2 and 3, Table S3).

A similar pattern was observed when evaluating the multiplicative interaction between continuous air pollutants and vulnerability indicators (Fig. S5). For instance, the hazard ratio per IQR increase in NO_2 among those aged 23–64 years was 1.42 (95 % CI, 1.37 to 1.47) while among those aged 65+ was 1.24 (95 % CI, 1.20 to 1.28), $p_{interaction} < 0.001$ (Table S4).

To illustrate the multiplicative interaction on a different scale than the hazard ratio, we plotted the probability of COVID-19 hospitalisation for the average individual with and without diabetes mellitus and low individual-level income. The probability of hospitalisation increased with increasing pollution levels (Fig. 2). However, those with diabetes consistently had higher risk of hospital admission, with the gap between the two groups slightly smaller at the highest pollutant levels consistent with a multiplicative interaction effect estimate less than one (negative multiplicative). In contrast, risk of hospital admission was similar among those with and without low income at low pollution levels; however, the difference in risk between those with and without low income increased with increasing pollution, with low income individuals having higher risk of hospital admission consistent with a multiplicative interaction effect estimate greater than one (positive multiplicative).

4. Discussion

In a large population-based cohort study of adults in Catalonia during the first year of the COVID-19 pandemic, the combined effects of air pollution and vulnerability indicators were, overall, additive and the risk of COVID-19 hospitalisation was highest in the most exposed quintile for each vulnerability indicator compared to the least exposed quintile without vulnerability. There was evidence for a joint effect greater than the sum of effects of air pollution and male sex and lower individual- and area-level socioeconomic status. Results regarding vulnerable groups were considerably different depending on whether interaction was evaluated on the additive versus multiplicative scale.

We found that the effect of air pollution on COVID-19 hospitalisation

Table 3
Association between $PM_{2.5}$ and COVID-19 hospitalisation by vulnerability indicators and their interaction on additive and multiplicative scales.

	$PM_{2.5}$*		Interaction on additive scale	Interaction on multiplicative scale	Type of interaction (VanderWeele, 2019)
	Low	High	RERI (95 % CI)	HR (95 % CI)	
Age, years					
23–64	1.00 (Reference)	1.40 (1.35 to 1.45)	0.04 (-0.02 to 0.11)	0.89 (0.86 to 0.93)	Zero additive
65+	1.78 (1.72 to 1.84)	2.22 (2.14 to 2.30)			Negative multiplicative
Male					
No	1.00 (Reference)	1.32 (1.27 to 1.36)	0.16 (0.11 to 0.22)	1.00 (0.96 to 1.04)	Positive additive
Yes	1.52 (1.47 to 1.57)	2.00 (1.94 to 2.07)			No multiplicative
Hypertension					
No	1.00 (Reference)	1.37 (1.33 to 1.42)	−0.05 (-0.11 to 0.00)	0.91 (0.87 to 0.95)	Zero additive
Yes	1.29 (1.24 to 1.33)	1.61 (1.55 to 1.67)			Negative multiplicative
Diabetes					
No	1.00 (Reference)	1.34 (1.30 to 1.38)	0.02 (-0.05 to 0.09)	0.93 (0.89 to 0.97)	Zero additive
Yes	1.47 (1.42 to 1.53)	1.83 (1.77 to 1.90)			Negative multiplicative
Chronic Obstructive Pulmonary Disease					
No	1.00 (Reference)	1.33 (1.29 to 1.36)	0.01 (-0.09 to 0.10)	0.93 (0.87 to 0.99)	Zero additive
Yes	1.43 (1.36 to 1.51)	1.77 (1.69 to 1.85)			Negative multiplicative
Low individual income					
No	1.00 (Reference)	1.26 (1.21 to 1.31)	0.10 (0.05 to 0.14)	1.07 (1.03 to 1.12)	Positive additive
Yes	1.02 (0.99 to 1.06)	1.37 (1.32 to 1.43)			Positive multiplicative
Lower area-level SES					
No	1.00 (Reference)	1.29 (1.25 to 1.33)	0.09 (0.05 to 0.14)	1.04 (1.00 to 1.09)	Positive additive
Yes	1.11 (1.07 to 1.14)	1.49 (1.44 to 1.54)			Positive multiplicative

RERI stands for relative excess risk due to interaction.
* $PM_{2.5}$ categories were defined by the median value (13.9), the low category has a mean of 12.1 (SD = 1) while the high category has a mean of 15.6 (SD = 1).

was higher among individuals with lower income and higher area-level deprivation on both additive and multiplicative scales (positive multiplicative positive additive) and for the three pollutants. This is consistent with findings from a cohort of COVID-19 cases (n = 169,102) from the US Department of Veterans Affairs healthcare databases where the risk of hospitalisation was higher for those living in more deprived areas compared with those in low deprived areas on the multiplicative (RR 1.15, 95 % CI, 1.12 to 1.18, for high deprivation versus RR 1.08, 95 % CI, 1.05 to 1.11 for low deprivation, per 1.9 $\mu g/m^3$ increase of $PM_{2.5}$, $p_{interaction} = <0.001$) and additive scales (RERI 0.04, 95 % CI, 0.02 to 0.06) (Bowe et al., 2021). A similar pattern was observed for race, with higher risk of hospitalisation for Black compared to White on both scales (Bowe et al., 2021). Additionally, in a population-based cohort of the general Danish population, increased risk for COVID-19 hospitalization was found for low compared to high education level on a multiplicative scale (Zhang et al., 2023). However, other studies did not observe a clear pattern of effect modification of air pollution and COVID-19 severity by education level or race/ethnicity on the multiplicative scale (Bozack et al., 2022; Chen et al., 2022b; Kogevinas et al., 2021). Inconsistent results across studies may reflect the large sample size needed to detect modification of the association between long-term air pollution and COVID-19 hospitalization.

While age has been consistently identified as a main predictor of COVID-19 severity (Burn et al., 2021; Du et al., 2021; Ranzani et al., 2021), our results based on the multiplicative scale indicated that the effect of air pollution was lower for those above compared to under 65 years (negative multiplicative), whereas the effect of air pollution exposure combined with older age was clearly associated with higher risk of hospital admission compared to younger age on an additive scale (Tables 2 and 3, Fig. 1, Figs. S2 and S3) with a positive, non-statistically significant RERI (0.06, 95 % CI, −0.01 to 0.12 for NO_2). This can be explained by the large difference in baseline risk of severe COVID-19 across the two age groups (Table S5). The literature regarding vulnerability according to age has been inconsistent, likely because most studies have evaluated interaction on a multiplicative scale and across different age ranges. Some studies observed a U-shaped risk, with higher risks of severe COVID-19 in the young and elderly groups (Chen et al., 2022b), while others observed a higher risk among the elderly (Hyman et al., 2023; Zhang et al., 2023) or found no evidence for interaction in the multiplicative scale, but a positive association in the additive scale (Bowe et al., 2021).

We observed a positive additive interaction but no multiplicative interaction for male sex. Other studies found no associations on either scales or when stratifying analyses by sex (Bowe et al., 2021; Chen et al., 2022b; Hyman et al., 2023; Kogevinas et al., 2021; Stafoggia et al., 2023; Zhang et al., 2023). Results from many previous studies are challenging to interpret regarding vulnerability by sex since they were not population-based and were often based on a cohort of COVID-19 cases with notably different sex distributions from what would be expected in the general population (Bowe et al., 2021).

A pattern similar to that for age was observed for chronic comorbidities, in which the combined effect of air pollution and comorbid

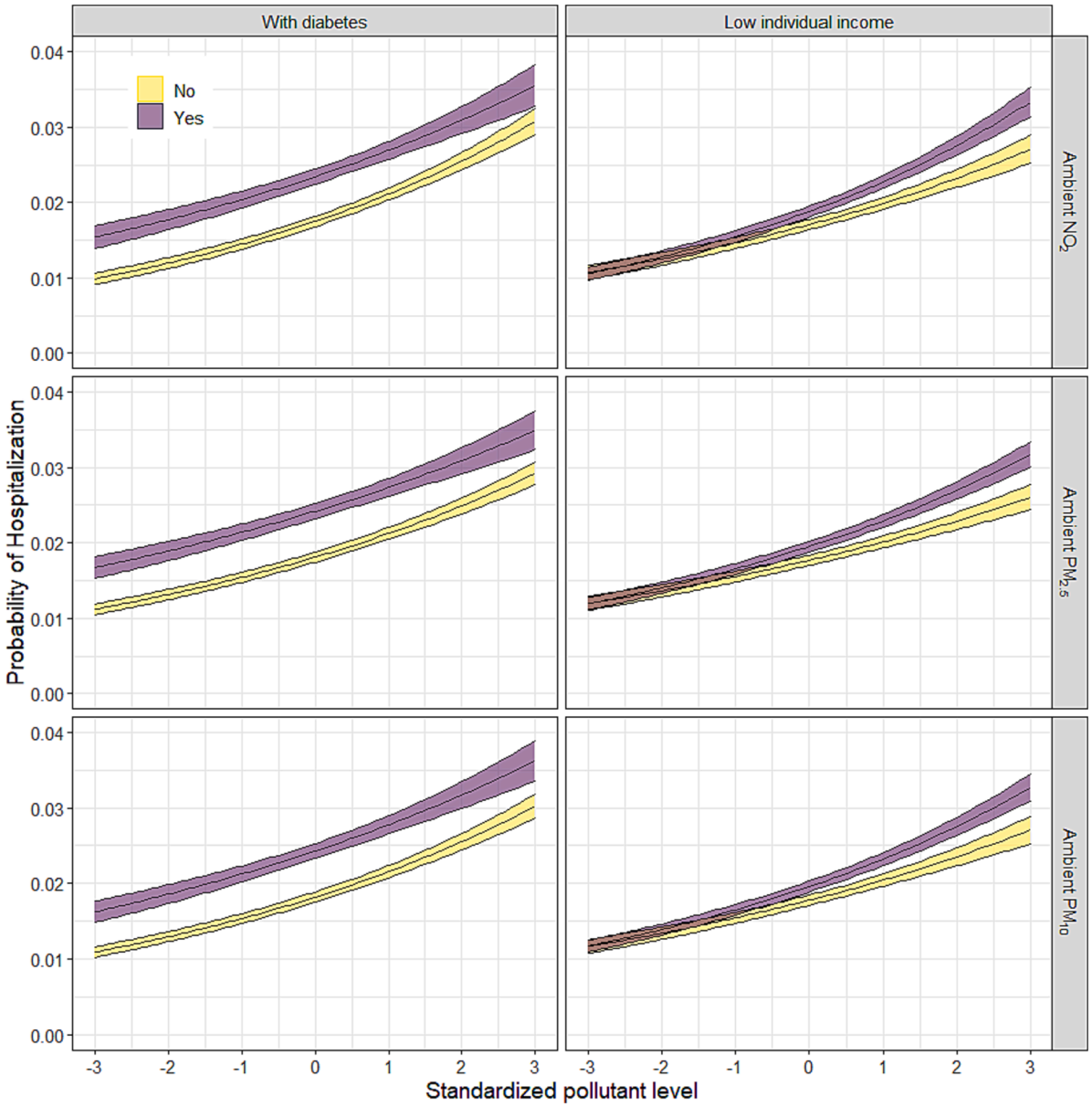

Fig. 2. Cumulative probability of COVID-19 hospitalisation according to air pollution exposure and diabetes mellitus and individual income status. Illustrative cumulative probability and 95 % confidence interval of COVID-19 hospitalisation at 305 days of follow-up (maximum follow up time in the cohort) representing individuals with average age, male, non-smoker, low individual income status (for the diabetes plot), moderate health risk group, average small area socioeconomic index, average distance to the nearest primary health care unit, residence in urban municipality, average test positive proportion and health region of Barcelona. These cumulative probabilities are from the main model of analysis which included an interaction term between the pollutant and diabetes mellitus (left plots) and between the pollutant and individual income status (right plots).

conditions were additive and air pollution had a smaller effect on COVID-19 hospital admission among those with comorbidities on a multiplicative scale. Few studies have evaluated effect modification for chronic comorbidities, and most found no evidence for effect modification on the multiplicative scale. One cohort study (n = 1128) with selected COVID-19 patients reported higher association between 10-year average $PM_{2.5}$ and the risk of hospitalisation among those with chronic respiratory diseases (Mendy et al., 2021). Another cohort study of COVID-19 patients showed an increased risk of hospitalisation for increases in NO_2 and $PM_{2.5}$ and several chronic comorbidities on the multiplicative scale (Hyman et al., 2023), and a population-based cohort from Denmark showed decreased risk of hospitalisation in relation to NO_2 among those with COPD (Zhang et al., 2023).

For vulnerability indicators that are strong predictors (i.e., have high baseline risk) of COVID-19 hospital admission (e.g., age, male sex, and comorbidities; Table S5), we observed that multiplicative interactions based on Cox proportional hazards models could be difficult to interpret and that additive scale provided more consistent, biologically plausible results. For instance, diabetes has been consistently identified as a main predictor of COVID-19 severity. In our model, the HR for COVID-19 hospitalization was 1.37 (1.33–1.40) for those with diabetes compared with those without diabetes. However, when evaluating diabetes and air pollution interaction on the multiplicative scale, we observed that the effect of air pollution was lower for those with diabetes compared with those without diabetes (negative multiplicative). In contrast, the risk of hospital admission among the most exposed quintile, was higher among those with compared to those without diabetes (Fig. 1) and when transforming the relative risk to probability, which adds the additional risk of air pollution to the baseline risk of those with and without diabetes (Fig. 2). Other factors beyond the baseline risk could also result in

different results between scales, such as the measure of effect estimated (e.g., relative risk vs. odds ratio) and the prevalence of the vulnerable indicator in the population, likely influencing the power to detect interactions.

The biological and social mechanisms underpinning patterns of effect modification of associations between air pollution and COVID-19 hospitalisation are not well understood. Some, such as older age and chronic comorbidities, likely reflect reduced capacity to manage oxidative stress and inflammation (Bajaj et al., 2021; Chistiakov et al., 2014; Liguori et al., 2018; Rebelo-Marques et al., 2018). However, the mechanisms involved in the synergistic additive effect between air pollution and sex and low socioeconomic status are less clear. We hypothesize that sex-specific differences in innate and adaptive immunity could play a role (Chaturvedi et al., 2022; Takahashi et al., 2020) as could non-biological sex-differences such as health self-awareness and occupation (Chaturvedi et al., 2022; Vahidy et al., 2021) which may result in higher exposure to the virus. Individuals with low individual- and area-level SES were identified as being vulnerable to air pollution for COVID-19 hospitalisation. Our results suggest these patterns do not operate through comorbidities and instead may be related to occupational exposure to high viral loads (Mena et al., 2021; Wachtler et al., 2020) or differences in health care access or utilization (Riou et al., 2021).

Strengths of this study include the combination of population representativeness spanning large urban and rural areas, with detailed individual-level data for exposures and confounding adjustment in a country heavily affected by the pandemic during 2020, yielding good statistical power to evaluate interaction effects (Ranzani et al., 2023). Analysing the general population helped us to better control the potential selection bias present in studies that evaluated cohorts of COVID-19 patients, given that potential effect modifiers are also those associated with the likelihood of being tested, such as sex, age, chronic comorbidities and socioeconomic status (Griffith et al., 2020; Millard et al., 2023). A major strength is that we evaluated interaction effects on both multiplicative and additive scales (Knol and VanderWeele, 2012; VanderWeele and Knol, 2014), where departure from additive interactions can inform the potential for interventions to reduce the absolute risk of hospitalisation (VanderWeele and Knol, 2014).

Some limitations need to be acknowledged. First, we evaluated the first year of the pandemic, thus our analysis does not shed light on the role of COVID-19 vaccines in shaping vulnerability (Chen et al., 2022a). Second, to estimate the additive joint effect – RERI – we categorized exposures and some continuous variables (e.g. age) to create vulnerability indicators, which may have resulted in loss of precision and cut-offs for categories may not be generalizable to other populations. Third, we did not have data on race/ethnicity, which has been shown to confer vulnerability to COVID-19 outcomes. Fourth, we took an additional post-hoc decision that has not an impact on the interpretation of the results and was only an illustration of the interaction in the probability scale.

5. Conclusions

In conclusion, the combined effect of long-term air pollution with male sex and low individual- and area-level socioeconomic status on the risk of COVID-19 hospitalisation was synergistic (greater than the sum of effects), indicating that these population subgroups may benefit most from air pollution reductions as part of pandemic preparedness and public health protection.

Funding

This work was supported by Health Effects Institute (HEI) research agreement (grant No 4980-RFA20-1B/21-3). Research described in this article was conducted under contract to the HEI, an organisation jointly funded by the US Environmental Protection Agency (EPA) (assistance award No R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers. OTR acknowledges support by a Sara Borrell fellowship from the Instituto de Salud Carlos III (CD19/00110). We acknowledge support from the grant CEX2018-000806-S funded by MCIN/AEI/ 10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program.

CRediT authorship contribution statement

Otavio Ranzani: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft. **Anna Alari:** Methodology, Writing – review & editing. **Sergio Olmos:** Data curation, Methodology, Writing – review & editing. **Carles Milà:** Data curation, Methodology, Writing – review & editing. **Alex Rico:** Data curation, Writing – review & editing. **Xavier Basagaña:** Conceptualization, Methodology, Writing – review & editing. **Payam Dadvand:** Conceptualization, Writing – review & editing. **Talita Duarte-Salles:** Conceptualization, Writing – review & editing. **Francesco Forastiere:** Conceptualization, Writing – review & editing. **Mark Nieuwenhuijsen:** Conceptualization, Writing – review & editing. **Rosa M Vivanco-Hidalgo:** Conceptualization, Writing – review & editing. **Cathryn Tonne:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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.

Data availability

The authors do not have permission to share data.

Acknowledgments

The authors would like to acknowledge the efforts of all public healthcare workers involved in the management of the COVID-19 pandemic during these challenging times in Catalonia. We would also like to thank all healthcare professionals of Catalonia who daily register information in the populations' electronic health records. The authors also acknowledge the Public Data Analysis for Health Research and Innovation Program of Catalonia for providing the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108530.

References

Alli, B.Y., 2021. InteractionR: an R package for full reporting of effect modification and interaction. Software Impacts 10, 100147. https://doi.org/10.1016/j.simpa.2021.100147.

Assmann, S.F., Hosmer, D.W., Lemeshow, S., Mundt, K.A., 1996. Confidence intervals for measures of interaction. Epidemiology 7, 286–290. https://doi.org/10.1097/00001648-199605000-00012.

Avellaneda-Gómez, C., Vivanco-Hidalgo, R.M., Olmos, S., Lazcano, U., Valentin, A., Milà, C., Ambrós, A., Roquer, J., Tonne, C., 2022. Air pollution and surrounding greenness in relation to ischemic stroke: a population-based cohort study. Environ. Int. 161, 107147 https://doi.org/10.1016/j.envint.2022.107147.

Bajaj, V., Gadi, N., Spihlman, A.P., Wu, S.C., Choi, C.H., Moulton, V.R., 2021. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections? Front. Physiol. 11, 571416 https://doi.org/10.3389/fphys.2020.571416.

Bell, E., Brassel, S., Oliver, E., Schirrmacher, H., Arnetorp, S., Berg, K., Darroch-Thompson, D., Pohja-Hutchison, P., Mungall, B., Carroll, S., Postma, M., Steuten, L., 2022. Estimates of the global burden of COVID-19 and the value of broad and equitable access to COVID-19 vaccines. Vaccines 10, 1320. https://doi.org/10.3390/vaccines10081320.

Bowe, B., Xie, Y., Gibson, A.K., Cai, M., van Donkelaar, A., Martin, R.V., Burnett, R., Al-Aly, Z., 2021. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. Environ. Int. 154, 106564 https://doi.org/10.1016/j.envint.2021.106564.

Bozack, A., Pierre, S., DeFelice, N., Colicino, E., Jack, D., Chillrud, S.N., Rundle, A., Astua, A., Quinn, J.W., McGuinn, L., Yang, Q., Johnson, K., Masci, J., Lukban, L., Maru, D., Lee, A.G., 2022. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. Am. J. Respir. Crit. Care Med. 205, 651–662. https://doi.org/10.1164/rccm.202104-0845OC.

Burn, E., Tebé, C., Fernandez-Bertolin, S., Aragon, M., Recalde, M., Roel, E., Prats-Uribe, A., Prieto-Alhambra, D., Duarte-Salles, T., 2021. The natural history of symptomatic COVID-19 during the first wave in Catalonia. Nat. Commun. 12, 777. https://doi.org/10.1038/s41467-021-21100-y.

Chaturvedi, R., Lui, B., Aaronson, J.A., White, R.S., Samuels, J.D., 2022. COVID-19 complications in males and females: recent developments. J. Comp. Eff. Res. 11, 689–698. https://doi.org/10.2217/cer-2022-0027.

Chen, Z., Sidell, M.A., Huang, B.Z., Chow, T., Eckel, S.P., Martinez, M.P., Gheissari, R., Lurmann, F., Thomas, D.C., Gilliland, F.D., Xiang, A.H., 2022b. Ambient air pollutant exposures and COVID-19 severity and mortality in a cohort of COVID-19 patients in Southern California. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.202108-1909OC rccm.202108-1909OC.

Chen, C., Wang, J., Kwong, J., Kim, J., van Donkelaar, A., Martin, R.V., Hystad, P., Su, Y., Lavigne, E., Kirby-McGregor, M., Kaufman, J.S., Benmarhnia, T., Chen, H., 2022a. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. CMAJ 194, E693–E700. https://doi.org/10.1503/cmaj.220068.

Chistiakov, D.A., Sobenin, I.A., Revin, V.V., Orekhov, A.N., Bobryshev, Y.V., 2014. Mitochondrial aging and age-related dysfunction of mitochondria. Biomed. Res. Int. 2014, 1–7. https://doi.org/10.1155/2014/238463.

Dessie, Z.G., Zewotir, T., 2021. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect. Dis. 21, 855. https://doi.org/10.1186/s12879-021-06536-3.

Du, P., Li, D., Wang, A., Shen, S., Ma, Z., Li, X., 2021. A systematic review and meta-analysis of risk factors associated with severity and death in COVID-19 patients. Can. J. Infect. Dis. Med. Microbiol. 2021, 1–12. https://doi.org/10.1155/2021/6660930.

Griffith, G.J., Morris, T.T., Tudball, M.J., Herbert, A., Mancano, G., Pike, L., Sharp, G.C., Sterne, J., Palmer, T.M., Davey Smith, G., Tilling, K., Zuccolo, L., Davies, N.M., Hemani, G., 2020. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nat. Commun. 11, 5749. https://doi.org/10.1038/s41467-020-19478-2.

Hitchings, M.D.T., Dean, N.E., García-Carreras, B., Hladish, T.J., Huang, A.T., Yang, B., Cummings, D.A.T., 2021. The usefulness of the test-positive proportion of severe acute respiratory syndrome coronavirus 2 as a surveillance tool. Am. J. Epidemiol. 190, 1396–1405. https://doi.org/10.1093/aje/kwab023.

Hyman, S., Zhang, J., Andersen, Z.J., Cruickshank, S., Møller, P., Daras, K., Williams, R., Topping, D., Lim, Y.-H., 2023. Long-term exposure to air pollution and COVID-19 severity: a cohort study in Greater Manchester, United Kingdom. Environ. Pollut. 327, 121594 https://doi.org/10.1016/j.envpol.2023.121594.

Idescat. Small Area Socioeconomic Index [WWW Document], n.d. URL: https://www.idescat.cat/pub/?id=ist&lang=en (accessed 11.2.22).

Knol, M.J., VanderWeele, T.J., 2012. Recommendations for presenting analyses of effect modification and interaction. Int. J. Epidemiol. 41, 514–520. https://doi.org/10.1093/ije/dyr218.

Kogevinas, M., Castaño-Vinyals, G., Karachaliou, M., Espinosa, A., de Cid, R., Garcia-Aymerich, J., Carreras, A., Cortés, B., Pleguezuelos, V., Jiménez, A., Vidal, M., O'Callaghan-Gordo, C., Cirach, M., Santano, R., Barrios, D., Puyol, L., Rubio, R., Izquierdo, L., Nieuwenhuijsen, M., Dadvand, P., Aguilar, R., Moncunill, G., Dobaño, C., Tonne, C., 2021. 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. 129, 117003 https://doi.org/10.1289/EHP9726.

Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., Gargiulo, G., Testa, G., Cacciatore, F., Bonaduce, D., Abete, P., 2018. Oxidative stress, aging, and diseases. CIA 13, 757–772. https://doi.org/10.2147/CIA.S158513.

Mena, G.E., Martinez, P.P., Mahmud, A.S., Marquet, P.A., Buckee, C.O., Santillana, M., 2021. Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile. Science 372, eabg5298. https://doi.org/10.1126/science.abg5298.

Mendy, A., Wu, X., Keller, J.L., Fassler, C.S., Apewokin, S., Mersha, T.B., Xie, C., Pinney, S.M., 2021. Long-term exposure to fine particulate matter and hospitalization in COVID-19 patients. Respir. Med. 178, 106313 https://doi.org/10.1016/j.rmed.2021.106313.

Milà, C., Ballester, J., Basagaña, X., Nieuwenhuijsen, M.J., Tonne, C., 2023. Estimating daily air temperature and pollution in Catalonia: a comprehensive spatiotemporal modelling of multiple exposures. Environ. Pollut. 337, 122501 https://doi.org/10.1016/j.envpol.2023.122501.

Millard, L.A.C., Fernández-Sanlés, A., Carter, A.R., Hughes, R.A., Tilling, K., Morris, T.P., Major-Smith, D., Griffith, G.J., Clayton, G.L., Kawabata, E., Davey Smith, G., Lawlor, D.A., Borges, M.C., 2023. Exploring the impact of selection bias in observational studies of COVID-19: a simulation study. Int. J. Epidemiol. 52, 44–57. https://doi.org/10.1093/ije/dyac221.

Monterde, D., Vela, E., Clèries, M., Garcia-Eroles, L., Roca, J., Pérez-Sust, P., 2020. Multimorbidity as a predictor of health service utilization in primary care: a registry-based study of the Catalan population. BMC Fam. Pract. 21, 39. https://doi.org/10.1186/s12875-020-01104-1.

Nobile, F., Michelozzi, P., Ancona, C., Cappai, G., Cesaroni, G., Davoli, M., Di Martino, M., Nicastri, E., Girardi, E., Beccacece, A., Scognamiglio, P., Sorge, C., Vairo, F., Stafoggia, M., 2022. Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome – a longitudinal study. Eur. Respir. J., 2200589 https://doi.org/10.1183/13993003.00589-2022.

Ranzani, O., Alari, A., Olmos, S., Milà, C., Rico, A., Ballester, J., Basagaña, X., Chaccour, C., Dadvand, P., Duarte-Salles, T., Foraster, M., Nieuwenhuijsen, M., Sunyer, J., Valentín, A., Kogevinas, M., Lazcano, U., Avellaneda-Gómez, C., Vivanco, R., Tonne, C., 2023. Long-term exposure to air pollution and severe COVID-19 in Catalonia: a population-based cohort study. Nat. Commun. 14, 2916. https://doi.org/10.1038/s41467-023-38469-7.

Ranzani, O.T., Bastos, L.S.L., Gelli, J.G.M., Marchesi, J.F., Baião, F., Hamacher, S., Bozza, F.A., 2021. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir. Med. 9, 407–418. https://doi.org/10.1016/S2213-2600(20)30560-9.

Rebelo-Marques, A., De Sousa Lages, A., Andrade, R., Ribeiro, C.F., Mota-Pinto, A., Carrilho, F., Espregueira-Mendes, J., 2018. Aging hallmarks: the benefits of physical exercise. Front. Endocrinol. 9, 258. https://doi.org/10.3389/fendo.2018.00258.

Riou, J., Panczak, R., Althaus, C.L., Junker, C., Perisa, D., Schneider, K., Criscuolo, N.G., Low, N., Egger, M., 2021. Socioeconomic position and the COVID-19 care cascade from testing to mortality in Switzerland: a population-based analysis. Lancet Public Health 6, e683–e691. https://doi.org/10.1016/S2468-2667(21)00160-2.

Sheppard, N., Carroll, M., Gao, C., Lane, T., 2023. Particulate matter air pollution and COVID-19 infection, severity, and mortality: a systematic review and meta-analysis. Sci. Total Environ. 880, 163272 https://doi.org/10.1016/j.scitotenv.2023.163272.

Sheridan, C., Klompmaker, J., Cummins, S., James, P., Fecht, D., Roscoe, C., 2022. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: observational evidence from UK Biobank. Environ. Pollut. 308, 119686 https://doi.org/10.1016/j.envpol.2022.119686.

Stafoggia, M., Ranzi, A., Ancona, C., Bauleo, L., Bella, A., Cattani, G., Nobile, F., Pezzotti, P., Iavarone, I., the EpiCovAir Study Group, 2023. Long-term exposure to ambient air pollution and mortality among four million COVID-19 cases in Italy: the EpiCovAir study. Environ. Health Perspect. 131, 057004 https://doi.org/10.1289/EHP11882.

Takahashi, T., Ellingson, M.K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J.E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E.Y., Casanovas-Massana, A., Wyllie, A.L., Vogels, C.B.F., Earnest, R., Lapidus, S., Ott, I.M., Moore, A.J., Yale IMPACT Research Team, Anastasio, K., Askenase, M.H., Batsu, M., Beatty, H., Bermejo, S., Bickerton, S., Brower, K., Bucklin, M.L., Cahill, S., Campbell, M., Cao, Y., Courchaine, E., Datta, R., DeIuliis, G., Geng, B., Glick, L., Handoko, R., Kalinich, C., Khoury-Hanold, W., Kim, D., Knaggs, L., Kuang, M., Kudo, E., Lim, J., Linehan, M., Lu-Culligan, A., Malik, A.A., Martin, A., Matos, I., McDonald, D., Minasyan, M., Mohanty, S., Muenker, M.C., Naushad, N., Nelson, A., Nouws, J., Nunez-Smith, M., Obaid, A., Ott, I., Park, H.-J., Peng, X., Petrone, M., Prophet, S., Rahming, H., Rice, T., Rose, K.-A., Sewanan, L., Sharma, L., Shepard, D., Silva, E., Simonov, M., Smolgovsky, M., Song, E., Sonnert, N., Strong, Y., Todeasa, C., Valdez, J., Velazquez, S., Vijayakumar, P., Wang, H., Watkins, A., White, E.B., Yang, Y., Shaw, A., Fournier, J.B., Odio, C.D., Farhadian, S., Dela Cruz, C., Grubaugh, N.D., Schulz, W.L., Ring, A.M., Ko, A.I., Omer, S.B., Iwasaki, A., 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588, 315–320. https://doi.org/10.1038/s41586-020-2700-3.

Thermeau T, 2021. A Package for Survival Analysis in R. R package version 3.2-13, https://CRAN.R-project.org/package=survival.

Vahidy, F.S., Pan, A.P., Ahnstedt, H., Munshi, Y., Choi, H.A., Tiruneh, Y., Nasir, K., Kash, B.A., Andrieni, J.D., McCullough, L.D., 2021. Sex differences in susceptibility, severity, and outcomes of coronavirus disease 2019: cross-sectional analysis from a diverse US metropolitan area. PLoS One 16, e0245556. https://doi.org/10.1371/journal.pone.0245556.

VanderWeele, T.J., 2019. The interaction continuum. Epidemiology 30, 648–658. https://doi.org/10.1097/EDE.0000000000001054.

VanderWeele, T.J., Knol, M.J., 2014. A tutorial on interaction. Epidemiol. Methods 3, 33–72. https://doi.org/10.1515/em-2013-0005.

Vivanco-Hidalgo, R.M., Molina, I., Martinez, E., Roman-Viñas, R., Sánchez-Montalvá, A., Fibla, J., Pontes, C., Velasco Muñoz, C., Real World Data Working Group, 2021. Incidence of COVID-19 in patients exposed to chloroquine and hydroxychloroquine: results from a population-based prospective cohort in Catalonia, Spain, 2020. Euro Surveill. 26 https://doi.org/10.2807/1560-7917.ES.2021.26.9.2001202.

Wachtler, B., Michalski, N., Nowossadeck, E., Diercke, M., Wahrendorf, M., Santos-Hövener, C., Lampert, T., Hoebel, J., 2020. Socioeconomic inequalities in the risk of SARS-CoV-2 infection – first results from an analysis of surveillance data from Germany. 10.25646/7057.

Wang, J., Li, D., Ma, Y., Tang, L., Xie, J., Hu, Y., Tian, Y., 2023. Long-term exposure to ambient air pollutants and increased risk of pneumonia in the UK Biobank. Chest S0012369223002635. https://doi.org/10.1016/j.chest.2023.02.018.

Zhang, J., Lim, Y.-H., So, R., Jørgensen, J.T., Mortensen, L.H., Napolitano, G.M., Cole-Hunter, T., Loft, S., Bhatt, S., Hoek, G., Brunekreef, B., Westendorp, R., Ketzel, M., Brandt, J., Lange, T., Kølsen-Fisher, T., Andersen, Z.J., 2023. Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalization or death: Danish nationwide cohort study. Eur. Respir. J., 2300280 https://doi.org/10.1183/13993003.00280-2023.