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# Association between long-term exposure to air pollutants with breakthrough SARS-CoV-2 infections and antibody responses among COVID-19 vaccinated older adults in Northern Italy

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ABSTRACT

*Aims:* To investigate the association between long-term exposure to $PM_{2.5}$, $PM_{10}$, $NO_2$ and $O_3$ with SARS-CoV-2 breakthrough infections and COVID-19 vaccine-induced antibody responses in a northern Italian population-based sample of older adults.

*Methods:* Within an ongoing prospective population-based study, we followed-up 1326 vaccinated individuals aged 65–83 years, with no prior SARS-CoV-2 infection, for their first positive SARS-CoV-2 swab until December 31st, 2022. We assessed spike IgG antibody levels in most participants (n = 1206). The 2019 annual mean levels of air pollutants derived from combined use of chemical-transport and random-Forest models (spatial resolution: 1Kmq) were individually assigned based on the latest residence address. We estimated multivariable-adjusted associations (per 1 interquartile range increase, IQR) of air pollutants with breakthrough infections using Cox models with time-dependent vaccine exposure; and with percent change in the IgG geometric mean using generalized additive models.

*Results:* The mean (SD) age was 74.9 ± 4.1 years, and 50% were women. An IQR (1.2 $\mu g/m^3$) increase in long-term $PM_{2.5}$ exposure was associated with a 52% increase in breakthrough infection risk following a second vaccine and a 26% increase following a third vaccine. The effect vanished with the further increment of vaccination doses. Associations for $NO_2$ were inconsistent. Ozone was negatively associated with breakthrough infection risk, but this association reversed in bi-pollutant models adjusting for $PM_{2.5}$. $PM_{2.5}$ was associated with a −7.3% (−13.9% to −0.2%) reduction in vaccine-induced IgG levels. The reduction became more pronounced as the time delay from vaccination increased, and with adjustment for $NO_2$ co-exposure.

*Conclusion:* In our population of vaccinated older adults, fine particulate matter exposure was independently associated with a higher risk of SARS-CoV-2 breakthrough infection and a lower antibody response, both effects being influenced by timely and repeated vaccination schedule.

## 1. Introduction

Long-term exposure to ambient air pollution is an emerging risk factor for infectious diseases (Feng et al., 2024). Several prospective cohort studies elucidated the link between particulate matter (PM), nitrogen dioxides ($NO_2$) and ozone ($O_3$) with SARS-CoV-2 infectivity and severity (Zhang et al., 2023; Sheridan et al., 2022; Veronesi et al., 2022; Kogevinas et al., 2021; Ranzani et al., 2023; Zorn et al., 2024 Veronesi et al., 2025) through increased inflammation and down-regulation of the immune system (Andersen et al., 2021). The

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majority of evidence derives from studies conducted at the early phases of the pandemic, and sparse data exist on whether air pollution can determine the effectiveness of COVID-19 vaccines. Indirect evidence comes from a population-based study in Spain, showing lower antibody responses following vaccination (up to 2 doses) in SARS-CoV-2 naïve individuals who were exposed to higher pre-pandemic levels of air pollutants (Kogevinas et al., 2023). In another study in California among SARS-CoV-2 infected individuals, two doses of the COVID-19 vaccine did not mitigate the risk of severe COVID-19 associated with 1-year exposure to air pollution (Chen et al., 2023). No study has evaluated whether the effect of air pollution on COVID-19 vaccine response changes across the pandemic as populations receive more vaccine doses and different variants become dominant. From a public health perspective, the population of older adults (aged 65 or more) is of particular importance as they are at high risk for COVID-19 (Kerr et al., 2024), they present impaired vaccine efficacy (Dalla Gasperina et al., 2023), and the effects of long-term exposure to inhaled pollutants on their immune system are likely to be more pronounced due to accumulation (Ural et al., 2022). Vaccination-induced protection is mediated through a complex interplay between innate, humoral, and cell-mediated immunity (Pulendran and Ahmed, 2011), and it can be affected by a number of factors, including environmental ones (Zimmermann and Curtis, 2019). Air pollution may have a direct interaction with the immune system through oxidative stress and chronic inflammation, resulting in an alteration of immune signaling pathways (Frontera et al., 2020; Bayram et al. 2024). In addition, in experimental studies $PM_{2.5}$ has been associated with imbalance in the expression of the different immune pathways, such as the Th1/Th2 ratio necessary for an adequate vaccine response (Piao et al., 2023; Wu et al., 2023). Older adults are often characterized by a chronic low-grade inflammation status ("inflammaging"), mainly driven by adaptive immunity, which can disrupt the normal homeostasis of the immune system, potentially resulting in a major susceptibility to infections and a poorer response to vaccinations (Cianci et al., 2020). Chronic inflammation has been linked with initially-higher antibody levels in response to vaccination (Sheridan et al., 2012; Gianfagna et al., 2022), followed by a steeper decline resulting in an overall impaired ability to mount a protective immune response (Sheridan et al., 2012). The extent to which air pollution can affect SARS-CoV-2 infectivity risk in the vaccinated older adults, as well as the vaccine-induced antibody levels, remains to be ascertained. The aim of this study is to investigate the relationship between long-term exposure to outdoor air pollution and COVID-19 vaccine response in older adults receiving up to 5 vaccine doses and SARS-CoV-2 naïve. We considered two endpoints: i) breakthrough infections after first vaccine dose and ii) IgG levels against SARS-CoV-2 spike antigen post-vaccination.

## 2. Materials and methods

### 2.1. Study population

This study is based on a re-examination of participants of the RoCAV (Risk Of Cardiovascular diseases and abdominal aortic Aneurysm in Varese) cohort which initially recruited a random sample of 50–74 years old residents (n = 3777) in the city of Varese between 2013 and 2016 (Gianfagna et al., 2016). The city of Varese (55 $km^2$ of surface, about 80,000 inhabitants) is located in a highly-urbanized and industrialized area north of Milan and close to the Alps, and it is characterized by a continental climate. In spring 2021, we contacted 2394 alive individuals ≥60 years old to undergo a comprehensive re-examination; of these, 1505 subjects (62.9% of the re-contacted) agreed to participate. Follow-up visits took place between May 12th, 2021 and April 13th, 2022 (Fig. S1), and consisted of a medical interview and a blood sample drawing at hospital settings. Furthermore, participants were invited to complete a web-based questionnaire investigating lifestyle habits, from which for these analyses we derived the information on the smoking status. Most of participants completed the questionnaires before the blood drawing for the serology test. Those who did not (18%) were contacted within the following month to complete it through a phone interview by trained physicians. The baseline and the re-examination surveys were conducted according to the guidelines set out in the Declaration of Helsinki, received approval by the local Ethics Committee (Azienda Socio Sanitaria Territoriale Sette Laghi, approval IDs 66/2011 and 69/2020), and participants completed written consent forms at both instances. In the present analyses we focus on vaccinated individuals aged 65 years or more without evidence of SARS-CoV-2 infection before the index date, e.g. date of first vaccine dose for the breakthrough infections endpoint (n = 1326), and date of serology for post-vaccination antibody level analyses (n = 1206; Fig. 1). We defined previous SARS-CoV-2 infection as the presence of positive swabs and on anti-nucleocapsid (anti-N) IgG antibody titer of SARS-CoV-2 measured at serology (immunoassay with chemiluminescent microparticles on Alinity i Abbott Laboratories, cut-off value: 1.4 in the default unit of the test), since anti-N IgG levels are not induced by COVID-19 vaccination. Subjects with previous SARS-CoV-2 infection were excluded since we expected an attenuated effect among them (Kogevinas et al., 2023).

COVID-19 vaccine date and type were retrieved through record linkage with the dedicated database held by the Local Health Agency. In Italy, the COVID-19 vaccine was offered to all individuals for free, starting from January 2021; a detailed overview of the vaccination strategy in our study population is reported in the Supplementary Appendix A. The earliest occurrence of dose 1 vaccine in our sample was on January 8th, 2021; we observed up to 5 doses (Fig. S1), and both mRNA (Pfizer-BioNTech, Moderna) and non-mRNA (Oxford-AstraZeneca, Janssen) vaccine types. For doses 4 and 5, observations were truncated on Dec 18th, 2022, as the end of the follow-up for the breakthrough infections endpoint was on Dec 31st, 2022. For the serology analyses, we defined a vaccination strategy variable combining the dose number (1, 2 or 3) with the vaccine type, and considering a "mixed" strategy when at least one of the first two vaccine doses was a non-mRNA vaccine, resulting in an 8-class study variable.

### 2.2. Study endpoints

The first outcome was a confirmed SARS-CoV-2 infection (first positive swab, either molecular-PCR or antigen test) following vaccination up to December 31st, 2022. Positive swabs were collected in a dedicated dataset by the Local Health Agency, linked to the study participants using a unique national identifier as a key. The severity of breakthrough infections was not consistently reported in the swab data, and we did not use it. The pandemic emergency in Italy ended on March 31st, 2022, some measures including the "green pass" (based upon evidence of vaccination, healing or negative testing) remained in force until the end of the study follow-up period (Law n.24, March 24th 2022).

The second outcome was IgG antibody titer against the SARS-CoV-2 spike antigen as measured in blood samples collected during the 2021–2022 follow-up visit. The IgG antibody titer testing against the SARS-CoV-2 spike glycoprotein in serum samples was performed using an indirect chemiluminescence (CLIA) immunoassay that detects IgG against the trimeric form of the spike glycoprotein (SARS-CoV-2 Trimeric S IgG-LIAISON- DiaSorin Inc., Stillwater, MN, USA).

### 2.3. Air pollution exposure

Study exposures are the 2019 annual mean values of $PM_{2.5}$, $PM_{10}$, $NO_2$, and $O_3$ estimated at a spatial resolution of 1 $Km^2$ from the combined use of chemical-transport and random-forest models, a methodology already used in the context of large epidemiological studies (Silibello et al., 2014; Gariazzo et al., 2020). The choice of a pre-pandemic year was consistent with the literature (Veronesi et al., 2022; Kogevinas et al., 2023; Chen et al., 2023). Briefly, for each pollutant the chemical-transport model combined data from emission

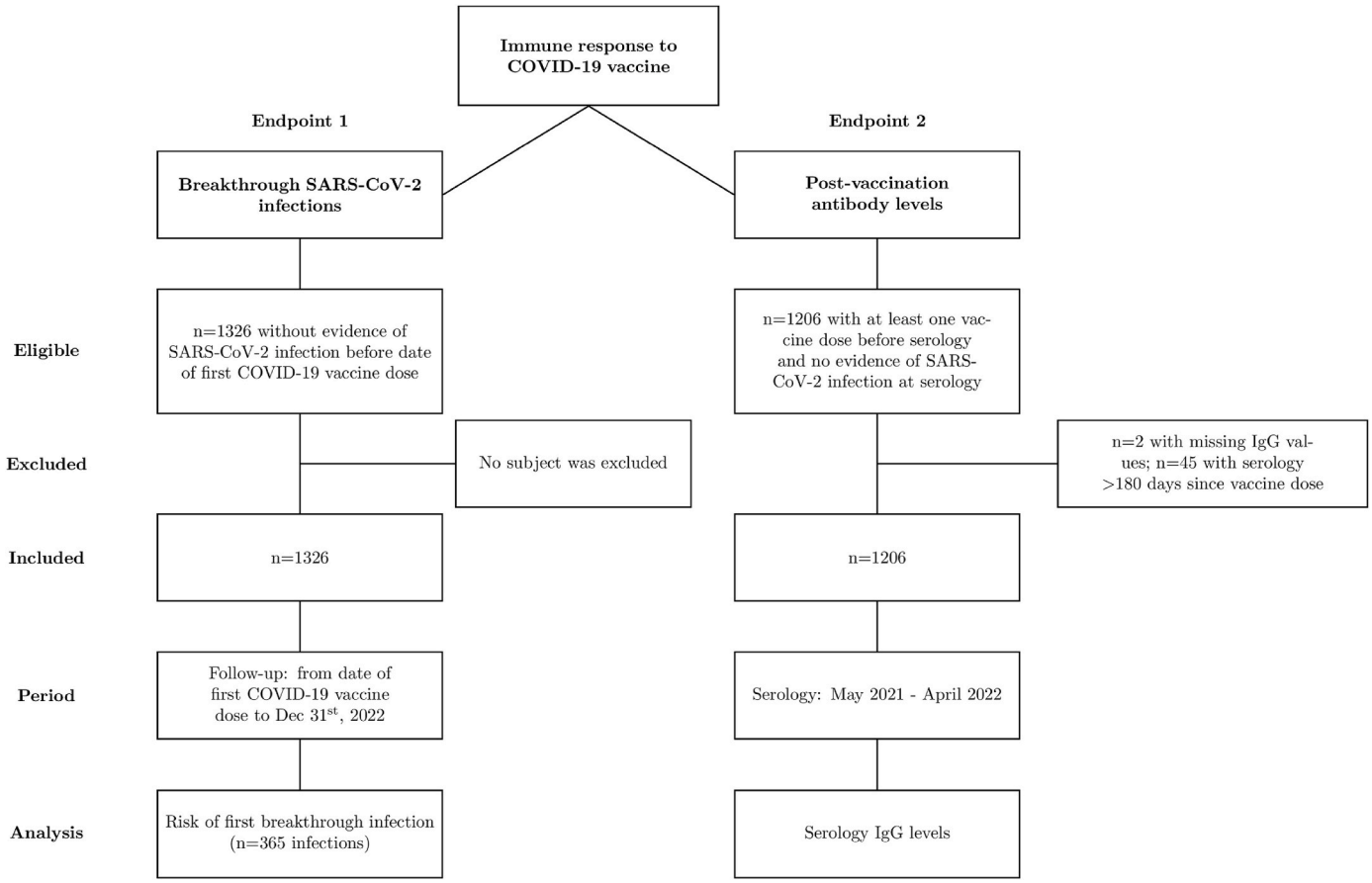


**Fig. 1.** Study flowchart for the two endpoints.

inventories and meteorological conditions to produce concentration fields that were further integrated with observed ground levels from monitoring stations using data fusion techniques (Silibello et al., 2014). 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 (Gariazzo et al., 2020). The overall performance of the random-forest model on the studied domain was satisfactory (percent of explained variability, $R^2$, of 0.85, 0.86, 0.77 and 0.93 for $PM_{2.5}$, $PM_{10}$, $NO_2$, and $O_3$). The average annual individual exposures for 2019 were calculated based on the georeferencing of the residential address as of June 30th, 2017, the latest available.

### 2.4. Covariates

Smoking habits were self-reported in the re-examination web questionnaire, and subjects were classified as current vs. non-current smokers. Age (in continuous) was defined at the index date for the two endpoints. Sex, educational attainment (categorized as university, high school and less than high school) and body mass index (BMI; in three classes, using 25 and 30 $kg/m^2$ as threshold values) were retained from the baseline visit in 2013–2016, the latter from measured height and weight. Positive history of comorbidities and use of drug treatments was based on available information from the baseline visit, the re-examination medical interview, and record linkage with drug prescription data from the Local Health Agency (full details in Appendix A).

### 2.5. Statistical analysis

Characteristics of the study sample were summarized as counts and percentage for categorical variables; mean and standard deviation (SD) for continuous variables; and median and interquartile range for skewed, continuous distributions.

For the occurrence of the first SARS-CoV-2 infection following COVID-19 vaccination (index date) to December 31st, 2022 (end of follow-up), we adopted single-pollutant Cox regression models, with time-dependent COVID-19 vaccine exposure variable and further adjusting for age, sex, current smoking status, positive history of autoimmune diseases and use of immunosuppressive treatments in the six months before first vaccine dose. Deaths during follow-up (n = 11) were accounted for as censored observations at death date. Educational class, BMI and other comorbidities were not independently associated with the endpoint, and were not considered further. For every individual, the time-dependent vaccine exposure could change from (1) <14 days after the second dose, to (2) ≥14 days after the second dose and <7 days after the third dose, to (3) ≥7 days after the third dose and <7 days after the fourth dose, to (4) ≥7 days after the fourth dose (periods adapted from Atiquzzaman M. et al. (Atiquzzaman et al., 2023). Due to sample size considerations (only 7 events in period (1) above), we did not consider a lag-time for the 1st dose. We then formally tested the null hypothesis of homogeneity of the effect of air pollution on breakthrough infections across vaccine exposures by adding an interaction term (Wald chi-square test with 1 df). We also ran sex-stratified models, to look at consistency across sex groups; and bi-pollutant models. As sensitivity analyses, we incorporated the monthly number of SARS-CoV-2 cases in the Varese Province (source: national COVID-19 count data) as time-dependent covariate, to consider the pandemic dynamics in the underlying, overall population (no age restrictions). In addition, to account for the possible loss of positive swabs in administrative healthcare datasets, we truncated the follow-up at the end of the emergency period, on March 31st, 2022. For the IgG spike level analyses, we first applied a log transformation to account for a skewed distribution. We used

single-pollutant, generalized additive regression models (GAMs) with natural cubic spline to model time since the last vaccination (in days). Estimates are expressed as percent change from the geometric mean for one interquartile range increase of each pollutant. Model 1 included age, sex, and the 8-class vaccination strategy variable (1 dose of AstraZeneca as reference); in model 2 we further added current smoking, positive history of autoimmune diseases and use of immunosuppressive drugs in the six months before serology, as potential mediators. As above, no other covariate was associated with the endpoint. Based on previous findings which identified that antibody levels peak after SARS-CoV-2 vaccination at 9 and 2–3 weeks after the first and the second/third dose, respectively (Cheetham et al., 2023), we also stratified the analyses according to time since the last vaccination, using 30, 60 and 90 days as thresholds. Results from bi-pollutant models are also reported. Finally, we formally tested the homogeneity of the effects of the air pollutants by sex and vaccine type (dichotomized as all doses with mRNA vaccines vs. at least one dose with a non-mRNA vaccine) by adding relevant interaction terms to the models (other covariates as in Model 2 above). We used the SAS software 9.4 release (SAS Institute Inc., Cary, NC, USA; Proc PHREG for time-to-event and Proc GLIMMIX for the GAMs) for the analyses, and R for drawing plots ("ggplot2" package).

## 3. Results

### 3.1. Sample characteristics and distribution of air pollutants

From the 1505 individuals who gave their informed consent, we excluded 47 non-vaccinated individuals, 41 aged less than 65 at first vaccine dose, and 91 with a positive SARS-CoV-2 swab before first vaccine dose, leaving a sample size of 1326. The mean age (±SD) was 74.9 ± 4.1 years (age range: 65–83), 50% were women, 11.7% current smokers and 17.5% had a university degree (Table 1). The descriptive statistics for the air pollutants, and the Spearman correlation coefficients, are reported in Table S1. Annual mean values (±SD) for $PM_{2.5}$, $PM_{10}$, $NO_2$ and $O_3$ were 17.9 ± 1.3, 23.6 ± 1.2, 26.7 ± 3.4 and 55.8 ± 2.2 μg/m$^3$, respectively. The observed mean values for $PM_{2.5}$ and $NO_2$ are 80% and 34% larger than the new European Union Ambient Air Quality Directive limit of 10 and 20 μg/m$^3$, respectively. Correlation coefficients between particulate matter and $NO_2$ were positive; while ozone was negatively associated with the other pollutants, and in particular with $PM_{2.5}$ (Spearman coefficient: −0.859). Annual mean values of pollutants were not associated with the number of vaccine doses at the time of serology (Table S2).

### 3.2. Association of air pollution with SARS-CoV-2 infectivity after vaccination

During a median follow-up of 610 days, we observed 365 breakthrough infections (rate: 5 cases per 10000 person-days). Individuals with SARS-CoV-2 breakthrough infections were less likely to be smokers (8.5% vs 12.9%) and had lower anti-spike IgG responses (331 vs. 431 BAU/ml; Table 1) than those not experiencing the infection during follow-up. Overall, increased exposure to particulate matter was not associated with risk of breakthrough infectivity (Table 2A). $PM_{2.5}$ and $PM_{10}$ were associated with higher risk of breakthrough infections in individuals with a complete primary vaccine cycle with the hazard ratios being as high as 1.52 (1.08–2.15) and 1.26 (1.04–1.52). Their detrimental effect on infectivity decreased with the incremental number of vaccine doses (Wald chi-square test for interaction p-value = 0.03): we observed no risk excess from 7 days after dose 3 on, and in individuals with dose 4 and 5. We observed a similar pattern for $NO_2$. Ozone was found to be protective on SARS-CoV-2 infection in individuals up to the second dose. When we truncated the follow-up at the end of the emergency period (Table 2B), the above reported associations for the entire investigated period were confirmed. Results were robust to further adjustment for the time-dependent monthly infection count in the underlying population (Table S3), and were consistent in men and women (Table S4).

**Table 1**
Characteristics of the study sample, overall and by occurrence of breakthrough infection during follow-up. Individuals with no SARS-CoV-2 infection before vaccine (n = 1326).

| | All sample | SARS-CoV-2 infection post vaccination (breakthrough infection) | |
|---|---|---|---|
| | | No | Yes |
| No of. subjects | 1326 | 961 | 365 |
| Age (years) | 74.9 ± 4.1 | 75.0 ± 4.1 | 74.6 ± 3.9 |
| Men | 668 (50.4%) | 476 (49.5%) | 192 (52.6%) |
| Current smokers | 155 (11.7%) | 124 (12.9%) | 31 (8.5%) |
| Educational level[a] | | | |
| University | 231 (17.5%) | 169 (17.7%) | 62 (17.0%) |
| High school | 474 (35.9%) | 338 (35.4%) | 136 (37.4%) |
| Less than high school | 615 (46.6%) | 449 (46.9%) | 166 (45.6%) |
| Body mass index (kg/m$^2$) | | | |
| Normal/underweight (<25 kg/m$^2$) | 478 (36.1%) | 353 (36.7%) | 125 (34.2%) |
| Overweight (25–29.9 kg/m$^2$) | 603 (45.5%) | 440 (45.8%) | 163 (44.7%) |
| Obese (≥30 kg/m$^2$) | 245 (18.5%) | 168 (17.5%) | 77 (21.1%) |
| Presence of comorbidities, n (%) | | | |
| Cardiovascular disease[b] | 150 (11.3%) | 102 (10.6%) | 48 (13.2%) |
| Cancer | 211 (15.9%) | 153 (15.9%) | 58 (15.9%) |
| Diabetes^ | 155 (11.7%) | 110 (11.5%) | 45 (12.3%) |
| Hypertension^ | 831 (62.7%) | 609 (63.4%) | 222 (60.8%) |
| Hypercholesterolemia^ | 730 (55.1%) | 534 (55.6%) | 196 (53.7%) |
| Autoimmune disease | 32 (2.4%) | 20 (2.1%) | 12 (3.3%) |
| Use of immunosuppressant treatment[c] | 55 (4.2%) | 37 (3.9%) | 18 (4.9%) |
| Serum IgG spike response°, BAU/ml | 390 (101; 1620) | 431 (108; 1640) | 331 (82; 1560) |

In the table: mean ± standard deviation for age, n (%) for categorical variables, median (25th; 75th percentiles) for IgG levels.
^: Anamnestic or use of drug treatments.
°: in individuals still negative at the time of serology (n = 1,159, 299 SARS-CoV-2 infections).
[a] Data not available for n = 6 individuals.
[b] Cardiovascular diseases: coronary heart disease or stroke.
[c] Including chemotherapy and cortisone therapy, in the 6 months before vaccination.

**Table 2**
Association of air pollution with risk of SARS-CoV-2 infection after vaccination, in the overall sample and by time-dependent vaccine exposure until December 31st, 2022 (end of study follow-up) and March 31st, 2022 (end of pandemic emergency in Italy). N = 1326 subjects, n = 365 first SARS-CoV-2 infections.

| | Hazard ratios (95%CI) for 1 IQR increase in 2019 annual mean level | | | |
|---|---|---|---|---|
| | $PM_{2.5}$ | $PM_{10}$ | $NO_2$ | $O_3$ |
| **A – Entire follow-up period (end: December 31st, 2022)** | | | | |
| Overall effect^ | 1.05 (0.95; 1.16) | 1.07 (0.98; 1.17) | 0.96 (0.87; 1.07) | 0.97 (0.89; 1.06) |
| Effect by vaccine exposure[a] | | | | |
| Dose 1 to <14 days after dose 2 (n = 7 events) | 1.52 (1.08; 2.15) | 1.42 (1.07; 1.89) | 1.32 (0.93; 1.88) | 0.74 (0.54; 0.96) |
| ≥14 days after dose 2 to <7 days after dose 3 (n = 73 events) | 1.26 (1.04; 1.52) | 1.22 (1.05; 1.43) | 1.12 (0.92; 1.36) | 0.86 (0.74; 0.99) |
| ≥7 days after dose 3 to <7 days after dose 4 (n = 240 events) | 1.03 (0.93; 1.14) | 1.05 (0.96; 1.15) | 0.95 (0.85; 1.06) | 0.99 (0.91; 1.08) |
| From 8 days after dose 4 on (n = 45 events) | 0.85 (0.69; 1.04) | 0.90 (0.75; 1.08) | 0.80 (0.64; 1.00) | 1.15 (0.97; 1.36) |
| Trend test p-value[b] | 0.03 | 0.04 | 0.06 | 0.03 |
| **B – Restricted follow-up period (end: March 31st, 2022)** | | | | |
| Overall effect^ | 1.17 (0.97; 1.40) | 1.15 (0.98; 1.35) | 1.07 (0.89; 1.29) | 0.91 (0.78; 1.06) |
| Effect by vaccine exposure[a] | | | | |
| Dose 1 to <14 days after dose 2 (n = 7 events) | 1.73 (1.01; 2.95) | 1.64 (1.07; 2.51) | 1.40 (0.85; 2.32) | 0.70 (0.48; 1.04) |
| ≥14 days after dose 2 to <7 days after dose 3 (n = 51 events) | 1.33 (1.03; 1.73) | 1.29 (1.05; 1.60) | 1.17 (0.92; 1.49) | 0.84 (0.69; 1.01) |
| ≥7 days after dose 3 to <7 days after dose 4 (n = 67 events) | 1.03 (0.82; 1.30) | 1.02 (0.83; 1.25) | 0.98 (0.77; 1.25) | 0.99 (0.81; 1.22) |
| From 8 days after dose 4 on (n = 0 events) | ne | ne | ne | ne |
| Trend test p-value[b] | 0.11 | 0.07 | 0.26 | 0.16 |

IQR width values: $PM_{2.5}$ = 1.22 μg/m$^3$; $PM_{10}$ = 1.03 μg/m$^3$; $NO_2$ = 3.63 μg/m$^3$; ozone = 1.86 μg/m$^3$ ne = not estimable (no events).
^: single-pollutant Cox regression model, adjusting for age, sex, current smoking, autoimmune disease, use of immunosuppressant treatment in the six months before first vaccine dose, and time-dependent vaccine exposure periods.
[a] Single-pollutant Cox regression model, with vaccine exposure as time-dependent covariate and air pollutant*vaccine exposure interaction, further adjusting for age, sex, current smoking, autoimmune disease, use of immunosuppressant treatment in the six months before first vaccine dose.
[b] Wald chi-square test for the null hypothesis of no heterogeneity of effect for air pollutant by increasing vaccine exposure (1 df).

### 3.3. Association of air pollution with post-vaccination serology

From 1206 vaccinated individuals aged 65 or more and SARS-CoV-2 naïve at the time of serology, we excluded 2 with missing serology data, and 45 with serology taken more than 180 days since the last vaccination (max observed lag time for dose 3), leaving a sample size of 1159 (Fig. 1). The median time (25th to 75th percentiles) from last vaccination to serology was 82 days (39–126 days), ranging from 49 median days for individuals with only one dose, to 99 days for subjects with 2 doses (Table S5). Table 3 reports the % change in the anti-spike IgG geometric mean (with 95% confidence intervals) per an IQR increase in long-term exposure to air pollutants. In Model 1, every interquartile range increase in $PM_{2.5}$ exposure was associated with decreased antibody responses, the largest effect size being observed in the first 90 days post vaccination. Further adjustment for smoking, autoimmune disease and use of immunosuppressant treatment (Model 2) did not substantially modify the estimates, suggesting that most of $PM_{2.5}$ effect is not mediated by these factors. The effect was consistent by sex and vaccine type (interaction test p-values >0.05; Table S6). Individuals at low $PM_{2.5}$ exposure showed a faster rising phase in IgG spike antigen levels, in particular after dose 1 and dose 3, and a higher IgG level peak, followed by a steady waxing phase after doses 2 and 3 (Fig. 2). We estimated

**Table 3**
Association of air pollution with antibody levels induced after vaccination for IgG spike antigen, in vaccinated individuals with no evidence of SARS-CoV-2 infection at serology (n = 1159), by days since last vaccination.

| | N | Model 1 | Model 2 |
|---|---|---|---|
| | | % change (95%CI)^ | % change (95%CI)^ |
| **$PM_{2.5}$** | 1159 | −7.5% (−14.1%; −0.3%) | −7.3% (−13.9%; −0.2%) |
| *By days since last vaccination* | | | |
| *≤30 days* | 254 | −1.2% (−16.2%; 16.3%) | −2.2% (−17.2%; 15.6%) |
| *≤60 days* | 387 | −1.6% (−13.1%; 11.5%) | −1.9% (−13.5%; 11.1%) |
| *≤90 days* | 627 | −9.7% (−18.0%; −0.7%) | −9.6% (−17.9%; −0.5%) |
| **$PM_{10}$** | 1159 | −5.2% (−11.3%; 1.2%) | −5.3% (−11.3%; 1.1%) |
| *By days since last vaccination* | | | |
| *≤30 days* | 254 | −5.2% (−18.1%; 9.7%) | −5.6% (−18.6%; 9.5%) |
| *≤60 days* | 387 | −6.1% (−16.0%; 5.1%) | −6.2% (−16.2%; 5%) |
| *≤90 days* | 627 | −10.2% (−17.5%; −2.1%) | −10.0% (−17.4%; −1.9%) |
| **$NO_2$** | 1159 | −1.6% (−9.3%; 6.7%) | −1.3% (−8.9%; 6.9%) |
| *By days since last vaccination* | | | |
| *≤30 days* | 254 | 8.7% (−8.8%; 29.6%) | 8.2% (−9.6%; 29.4%) |
| *≤60 days* | 387 | 4.6% (−8.7%; 19.8%) | 4.1% (−9.2%; 19.3%) |
| *≤90 days* | 627 | −1.3% (−11.2%; 9.7%) | −1.3% (−11.2%; 9.8%) |
| **$O_3$** | 1159 | 3.4% (−3.2%; 10.4%) | 4.0% (−2.6%; 11%) |
| *By days since last vaccination* | | | |
| *≤30 days* | 254 | 1.7% (−12.9%; 18.7%) | 2.4% (−12.5%; 19.8%) |
| *≤60 days* | 387 | 1.8% (−9.2%; 14.1%) | 2.1% (−9.0%; 14.5%) |
| *≤90 days* | 627 | 6.9% (−2.1%; 16.7%) | 7.0% (−2.0%; 16.8%) |

^: change in IgG geometric mean for 1 interquartile Range (IQR) increase in air pollutants.
IQR width values: $PM_{2.5}$ = 1.22 μg/m$^3$; $PM_{10}$ = 1.03 μg/m$^3$; $NO_2$ = 3.63 μg/m$^3$; $O_3$ = 1.86 μg/m.$^3$.
Model 1: adjusted for age, sex, 8-class vaccination strategy (combination of dose number – 1 to 3 – and of vaccine type (mRNA only or mixed strategy)), and a restricted cubic spline for time since last vaccine dose. Model 2: Model 1 + current smoker, history of autoimmune diseases, use of auto-immune drug treatment in the six months before serology date.

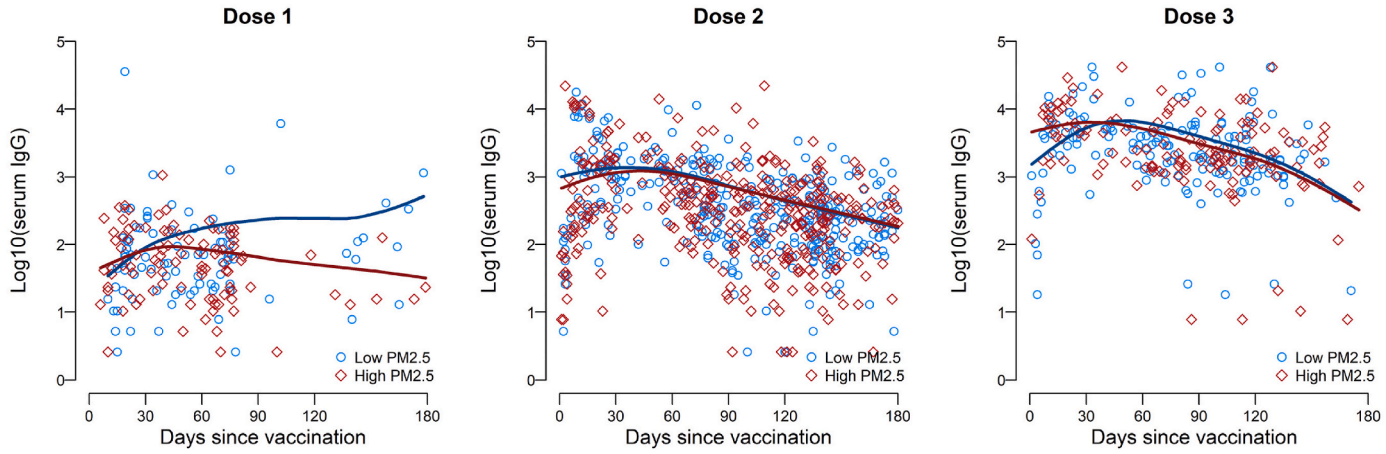


**Fig. 2.** Serum IgG spike response in days since last vaccination by exposure to high (≥median) or low (<median) $PM_{2.5}$ levels in vaccinated individuals with no evidence of SARS-CoV-2 infection at serology (n = 1159), after 1st, 2nd and 3rd vaccine dose.
Generalized additive models exploring the relationship between days since vaccination and antibody IgG levels induced after 1, 2 or 3 vaccine doses, by high (red, diamond) and low (blue, circle) $PM_{2.5}$ levels, defined according to the sample median (18.26 μg/m$^3$). Points are observed IgG values, lines are predicted from GAM model adjusting for age, sex and 8-class vaccination strategy (combination of dose number – 1 to 3 – and of vaccine type (mRNA only or mixed strategy)), with a spline for time since last vaccine dose, and expressed for 75 years old men undergoing Comirnaty (Pfizer) or Spikevax (Moderna) vaccination.

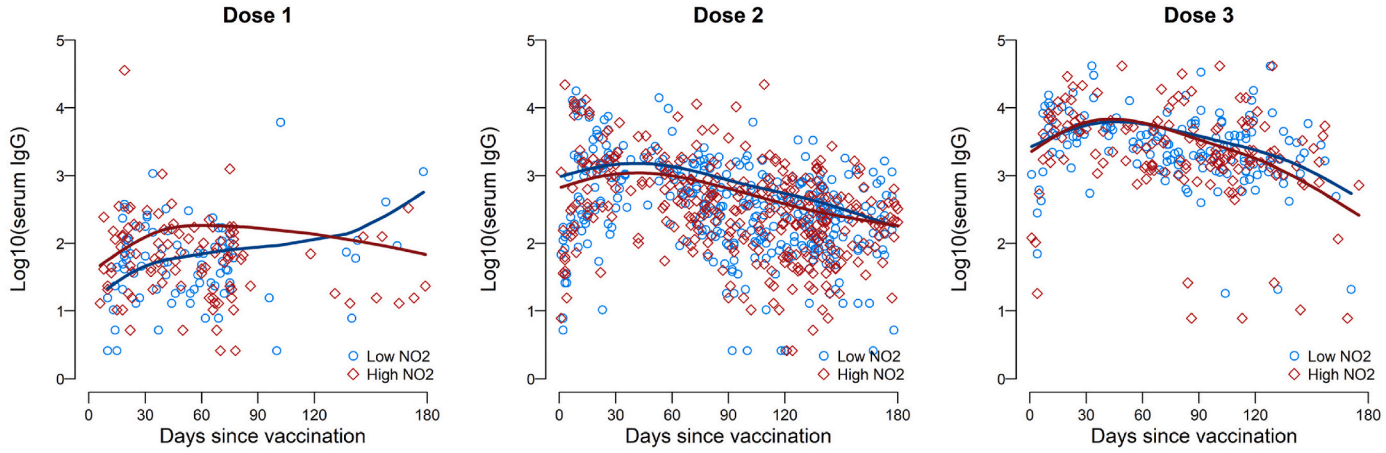


**Fig. 3.** Serum IgG spike response in time since last vaccination by exposure to high (≥median) or low (<median) $NO_2$ levels in vaccinated individuals with no evidence of SARS-CoV-2 infection at serology (n = 1159), after 1st, 2nd and 3rd vaccine dose.
Generalized additive models exploring the relationship between days since vaccination and antibody IgG levels induced after 1, 2 or 3 vaccine doses, by high (red, diamond) and low (blue, circle) $NO_2$ levels, defined according to the sample median (26.59 μg/m$^3$). Points are observed IgG values, lines are predicted from GAM model adjusting for age, sex and 8-class vaccination strategy (combination of dose number – 1 to 3 – and of vaccine type (mRNA only or mixed strategy)), with a spline for time since last vaccine dose, and expressed for 75 years old men undergoing Comirnaty (Pfizer) or Spikevax (Moderna) vaccination.

similar effects for $PM_{10}$ (Table 4 and Fig. S2). Conversely, the associations for $NO_2$ were modest and inconsistent, especially after the first dose (Fig. 3) and in those receiving at least one non-mRNA vaccine dose (Table S6). $O_3$ was positively associated with IgG levels at all times, although not in a statistically significant fashion. Compared to their less exposed counterparts, individuals exposed at higher $O_3$ levels had a higher response after dose 1, and showed a steeper decline after doses 2 and 3 (Fig. S3).

### 3.4. Bi-pollutant models

In bi-pollutant models (Table 4), the associations of $PM_{2.5}$ and $PM_{10}$ with the study endpoints were confirmed, or even strengthened, when adjusting for either $NO_2$ or $O_3$. Conversely, when adjusting for $PM_{2.5}$, the protective effect for ozone on breakthrough infection risk reversed; and the point estimates were suggestive of a decrease in IgG levels for increasing $O_3$ exposure.

## 4. Discussion

To the best of our knowledge, ours is the first study assessing the role of chronic exposure to air pollution on COVID-19 vaccine response in a SARS-CoV-2 naïve older adults, across the pandemic and vaccination schemes. Our results suggest that every 1.2 μg/m$^3$ increase in $PM_{2.5}$ was associated with a 7.3% reduction in vaccine-induced IgG levels. In addition, the detrimental effect of $PM_{2.5}$ on breakthrough infectivity risk decreased with vaccine exposure, being as high as 52% and 26% in individuals with a complete primary cycle and one booster dose, respectively. Null associations were revealed for $NO_2$; while an inverse protective pattern was observed for $O_3$ that was diluted when considering PM in the same model. Our results were consistent by sex and vaccine type groups, as well as robust to the pandemic dynamics in the underlying population. Together these results suggest lower immune response following COVID-19 vaccine among older adults exposed to high fine particulate matter levels, as in urban settings.

No previous study has investigated the link between long-term

**Table 4**
Bi-pollutant associations of air pollution with the study endpoints in vaccinated individuals.

| | A - SARS-CoV-2 infection after vaccination^ | | B - Antibody levels after vaccination* | |
|---|---|---|---|---|
| | Single-pollutant | Bi-pollutant | Single-pollutant | Bi-pollutant |
| **$PM_{2.5}$** | 1.05 (0.95; 1.16) | – | −7.3% (−13.9%; −0.2%) | – |
| *Adjusting for*: | | | | |
| $NO_2$ | – | 1.13 (1.00; 1.28) | – | −11.4% (−19.6%; −2.2%) |
| $O_3$ | – | 1.08 (0.91; 1.29) | – | −11.6% (−22.4%; 0.8%) |
| **$PM_{10}$** | 1.07 (0.98; 1.17) | – | −5.3% (−11.3%; 1.1%) | – |
| *Adjusting for:* | | | | |
| $NO_2$ | – | 1.12 (1.01; 1.24) | – | −6.6% (−13.5%; 0.9%) |
| $O_3$ | – | 1.23 (1.01; 1.50) | – | −9.0% (−21.0%; 4.9%) |
| **$NO_2$** | 0.96 (0.87; 1.07) | – | −1.3% (−8.9%; 6.9%) | – |
| *Adjusting for:* | | | | |
| $PM_{2.5}$ | – | 0.88 (0.77; 1.02) | – | 7.6% (−3.3%; 19.7%) |
| $PM_{10}$ | | 0.90 (0.79; 1.02) | | 3.2% (−6.1%; 13.4%) |
| $O_3$ | – | 0.91 (0.80; 1.05) | – | 2.8% (−7.2%; 13.9%) |
| **Ozone** | 0.97 (0.89; 1.06) | – | 4.0% (−2.6%; 11%) | – |
| *Adjusting for:* | | | | |
| $PM_{2.5}$ | – | 1.03 (0.88; 1.21) | – | −4.9% (−15.3%; 6.7%) |
| $PM_{10}$ | | 1.17 (0.96; 1.42) | | −4.3% (−16.9%; 10.3%) |
| $NO_2$ | – | 0.93 (0.84; 1.04) | – | 5.5% (−3.0%; 14.6%) |

^: hazard ratios (with 95% CI) from Cox regression models, adjusting for age, sex, current smoking, autoimmune disease, use of immunosuppressant treatment in the six months before first vaccine dose, and time-dependent vaccine exposure periods.
°: % change in IgG spike antigen geometric mean (with 95%CI) for 1 interquartile Range (IQR) increase in air pollutants, from linear regression models adjusting for age, sex, 8-class vaccination strategy (combination of dose number – 1 to 3 – and of vaccine type (mRNA only or mixed strategy)), current smoker, history of auto-immune diseases, use of auto-immune drug treatment in the six months before serology date, and a restricted cubic spline for time since last vaccine dose.
Hazard ratios and %change in IgG levels are expressed for 1 IQR change in pollutants. IQR width values: $PM_{2.5} = 1.22\ \mu g/m^3$; $PM_{10} = 1.03\ \mu g/m^3$; $NO_2 = 3.63\ \mu g/m^3$; ozone = 1.86 μg/m.$^3$.

exposure to air pollution with breakthrough infections in a population-based study sample. Chen et al. observed an increased risk of COVID-19 hospitalization in fully vaccinated (2 doses) but infected individuals of 12% and 22% for $PM_{2.5}$ and $NO_2$, respectively (Chen et al., 2023). In a Spanish cohort of adults, long-term exposure to $PM_{2.5}$ and $NO_2$ was associated with decreased vaccine-induced antibody levels in SARS-CoV-2 naïve individuals after 1 or 2 vaccine doses (Kogevinas et al., 2023). Our results are consistent with these for particulate matter, but not for nitrogen dioxide. While $PM_{2.5}$ levels in our and the Spanish studies were similar, the mean exposure to $NO_2$ in our population was lower by about one-fourth (26.7 vs. 35.1 $\mu g/m^3$), possibly contributing to the observed differences.

Several mechanisms could explain the negative impact of air pollution on immune response following COVID-19 vaccination. In the airways, particulate matter-dependent reduction of phagocytic antigen-presenting activity could be involved, due to either a reduced surfactant availability or to an antigen-masking mechanism (Rebuli et al., 2021; Bourdrel et al., 2021; Glencross et al., 2020). In addition, Ural et al. showed that air pollutants accumulate with age in lung-associated lymph nodes which are critical sites for adaptive immune responses particularly to respiratory pathogens such as SARS-CoV-2 (Ural et al., 2022). At these sites air pollutants accumulation was accompanied by a disruption in architecture and function which can lead to a decreased adaptive immune response including the production of antibody-secreting plasma cells and memory B cells. Beyond the lung, air pollutants can exert distal effects on the immune system (Rebuli et al., 2021) as they can be absorbed directly into the bloodstream through the pulmonary epithelium. Our study suggests that high air pollution levels interfere with the capacity to elicit B-cell memory post COVID-19 vaccination (Syeda et al., 2024), determining the differences in kinetics we observed between individuals at high vs. low $PM_{2.5}$ exposure, especially 60–90 days after the first vaccine dose. The paradoxical protective effect of $O_3$, observed also with COVID-19 in pre-vaccination era (Veronesi et al., 2022), may be due to its oxidizing activity during the infection time, which could counteract the detrimental effects due to its chronic exposure (Bourdrel et al., 2021). One recent study from our group suggested that the protective effect may reverse at high particulate matter co-exposure (Veronesi et al., 2025). Such interactive effects are in line with the observed change in the direction of estimates for $O_3$ in bi-pollutant models adjusting for particulate matter. Future studies may better elucidate the role of interactive effects and air pollution mixture on vaccine response.

The main strength of this study is that it was conducted in a sample of older adults from the general population, nested in an ongoing cohort study with high participation rates at baseline and at the re-examination visits, exposed to up to 5 vaccine doses, and with three different SARS-CoV-2 variants (Alpha, Delta and Omicron) being dominant in Italy during serology and follow-up (Marziano et al., 2023). Our estimates were robust to several potential confounders, including infectivity dynamics in the underlying population. Finally, the combined use of breakthrough infection and of IgG levels as endpoints allow a comprehensive evaluation of the interplay between air pollution and COVID-19 vaccine response. However, as we were not able to investigate cellular immune response, future studies are advocated to fully elucidate the biological pathways.

Amongst the study limitations, long-term exposure was defined based only on 1 year of exposure (2019), but air quality reports from the Regional Agency for Environmental Protection indicate no substantial temporal trends from 2014 to 2019 in the study region. Consistently with the literature (Zhang et al., 2023; Sheridan et al., 2022; Veronesi et al., 2022; Kogevinas et al., 2021, 2023; Ranzani et al., 2023; Zorn et al., 2024), the year 2019 was the latest pre-pandemic one, hence un-affected by lockdown and mobility restriction periods occurring in Italy mostly during 2020. Exposure was assessed based on the residential address in 2017, the latest available point in time. Change in residency is limited in our sample of older adults, only 7% moved from the original residency address at baseline. Our study setting is a single, medium-size city with air pollutant levels above the recommended threshold levels. Future research is advocated to generalize our findings to different settings. Another limitation is the availability of one blood sample, while longitudinal individual IgG data would have been needed to better investigate immunity stability over time. Nonetheless, we provide indirect evidence on the effects of air pollution on antibody kinetics by combining serological data at a single time point of different individuals. We lacked of reliable data on the severity of breakthrough infections, nonetheless our results are in the same direction as with studies using

severe COVID-19 as an outcome (Chen et al., 2023). Finally, according to simulation models, SARS-CoV-2 infections reported through the surveillance system may underestimate the true infections in Italy between January 2021 and March 2022 (Marziano et al., 2023). The shift of infection towards vaccinated individuals may have resulted in higher amount of asymptomatic or pauci-symptomatic infections, which are less likely to be detected by the surveillance system, especially so after the end of the emergency period. Air pollution has been repeatedly linked with case severity (Ranzani et al., 2023), also in the vaccinated population (Chen et al., 2023). Then, if differential underreporting occurred according to air pollution exposure (highly exposed being more likely to report positive cases because more severe), it could have led to an overestimation of the associations. We restricted the follow-up to the end of the emergency period, finding larger, and not lower, point estimates than for the entire follow-up period, when asymptomatic cases underreporting should have been more severe. Hence, in our older adult population underreporting of positive cases through surveillance systems is more likely to have been non-differential, likely leading to an underestimate of the true associations of air pollutants with breakthrough infections.

In conclusion, in our population-based cohort of vaccinated older adults, long-term exposure to fine particulate matter was associated with higher risk of SARS-CoV-2 breakthrough infections and with a reduced antibody response to vaccination independently on smoking, autoimmune disease and use of immunosuppressant treatments, suggesting that chronic exposure may impact vaccine-induced immunity. The periodic booster doses nullified the increased risk of more exposed individuals, thus supporting the current vaccination policy and recommendations in the older adult population (Ministero della Salute, 2024). Our findings have implications for understanding infectious disease susceptibility, vaccine development, and vaccine scheduling among older adults, for instance by reinforcing the vaccination campaign in populations at high air pollution exposure. To these extents, generalization in future studies and different settings are advocated.

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## CRediT authorship contribution statement

**Giovanni Veronesi:** Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Francesco Gianfagna:** Writing – review & editing, Project administration, Methodology. **Marianna Karachaliou:** Writing – review & editing, Methodology. **Luigina Guasti:** Writing – review & editing, Methodology. **Manolis Kogevinas:** Writing – review & editing, Supervision. **Marco M. Ferrario:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

## Declaration of competing interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120450.

## Data availability

The datasets generated and analyzed during the current study can be made available from the corresponding author on reasonable request.

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