


# Long-Term Exposure to Air Pollution and COVID-19 Vaccine Antibody Response in a General Population Cohort (COVICAT Study, Catalonia)

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**BACKGROUND:** Ambient air pollution has been associated with COVID-19 disease severity and antibody response induced by infection.

**OBJECTIVES:** We examined the association between long-term exposure to air pollution and vaccine-induced antibody response.

**METHODS:** This study was nested in an ongoing population-based cohort, COVICAT, the GCAT-Genomes for Life cohort, in Catalonia, Spain, with multiple follow-ups. We drew blood samples in 2021 from 1,090 participants of 2,404 who provided samples in 2020, and we included 927 participants in this analysis. We measured immunoglobulin M (IgM), IgG, and IgA antibodies against five viral-target antigens, including receptor-binding domain (RBD), spike-protein (S), and segment spike-protein (S2) triggered by vaccines available in Spain. We estimated prepandemic (2018–2019) exposure to fine particulate matter [ $PM_{\leq 2.5}$   $\mu m$  in aerodynamic diameter ( $PM_{2.5}$ )], nitrogen dioxide ( $NO_2$ ), black carbon (BC), and ozone ( $O_3$ ) using Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) models. We adjusted estimates for individual- and area-level covariates, time since vaccination, and vaccine doses and type and stratified by infection status. We used generalized additive models to explore the relationship between air pollution and antibodies according to days since vaccination.

**RESULTS:** Among vaccinated persons not infected by SARS-CoV-2 ( $n = 632$ ), higher prepandemic air pollution levels were associated with a lower vaccine antibody response for IgM (1 month post vaccination) and IgG. Percentage change in geometric mean IgG levels per interquartile range of  $PM_{2.5}$  ( $1.7 \mu g/m^3$ ) were  $-8.1$  (95% CI:  $-15.9, 0.4$ ) for RBD,  $-9.9$  ( $-16.2, -3.1$ ) for S, and  $-8.4$  ( $-13.5, -3.0$ ) for S2. We observed a similar pattern for  $NO_2$  and BC and an inverse pattern for  $O_3$ . Differences in IgG levels by air pollution levels persisted with time since vaccination. We did not observe an association of air pollution with vaccine antibody response among participants with prior infection ( $n = 295$ ).

**DISCUSSION:** Exposure to air pollution was associated with lower COVID-19 vaccine antibody response. The implications of this association on the risk of breakthrough infections require further investigation. <https://doi.org/10.1289/EHP11989>

## Introduction

Air pollution has been associated with COVID-19 disease initially in ecological studies and later in cohort studies using individual data.<sup>1–6</sup> There are some differences between findings of individual-based studies concerning specific pollutants<sup>7</sup> and association with clinical disease,<sup>8</sup> but overall results are consistent in showing that long-term exposure to air pollution is associated with COVID-19 disease and severity of the disease. We have previously shown that prepandemic exposure to air pollution in Catalonia was associated with a 20%–50% increased risk of

COVID-19 disease and with higher risk for severe COVID-19.<sup>9</sup> Even though potential biases, particularly selection bias and confounding, were important concerns in early studies,<sup>10</sup> the most recent evidence, including populations evaluated when SARS-CoV-2 testing became massively available, indicates a positive association between long-term exposure to air pollution and COVID-19 hospitalizations and severity. Biases identified in early studies may still be present in more recent studies, but they are likely less important. In the study in Catalonia, we also observed positive associations between air pollution and immunoglobulin G (IgG) and IgA levels to specific viral antigens induced by SARS-CoV-2 infection.<sup>9</sup>

Air pollution has been associated with multiple health outcomes, including lung cancer, cardiovascular and respiratory diseases, metabolic diseases and diabetes, and mental health, as well as increased risk of several respiratory viral and bacterial infections, including influenza and respiratory syncytial virus.<sup>11</sup> Air pollutants have been shown to impair immune responses, induce oxidative stress, and stimulate proinflammatory cytokine release, thereby favoring multiple diseases.<sup>12–14</sup> The negative impact of chronic inflammation on vaccines efficacy has been seen mainly in the elderly and in chronic inflammatory conditions.<sup>15</sup> In relation to COVID-19, air pollutants may alter several immune pathways also mediated by epigenetic regulation<sup>16</sup> that are involved in the development and severity of the disease and could also affect vaccine efficacy.

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There exists evidence, not always consistent, on the association of post-vaccination antibody levels to exposure to immunotoxicants, such as polychlorinated biphenyls (PCBs), per- and polyfluoroalkyl substances (PFAS), and metals,<sup>17–19</sup> although studies on the effects of exposure to air pollutants on post-vaccination antibody levels in children or adults are largely lacking. A study in sera of 6-y-old children in Germany<sup>20</sup> identified lower antibody IgG titers against tetanus toxoid in children living in higher air pollution areas. There is previous evidence that air pollutants, such as polycyclic aromatic hydrocarbons and second-hand smoke, affect vaccine response in humans and animals.<sup>21</sup> To our knowledge, a single, fairly small study in China evaluated COVID-19 vaccine antibody response in relation to air pollution and identified lower neutralizing antibody titers of an inactivated SARS-CoV-2 vaccine among participants with higher air pollution levels; they also found higher levels of markers of chronic inflammation in the same participants.<sup>22</sup>

A number of factors have been associated with the COVID-19 vaccine response, predominantly previous infection and type of vaccine, but also age, sex, chronic disease, and smoking.<sup>23–25</sup> Several other factors have been associated with other vaccines in children and adults, including diet, predominantly in relation to malnutrition, mental health, and some lifestyle factors.<sup>26</sup> SARS-CoV-2 elicits robust humoral immune responses, including production of virus-specific IgM, IgA, and IgG. IgM and IgA isotypes dominate the early antibody response to SARS-CoV-2, and IgA contributes to virus neutralization at mucosal sites.<sup>27–29</sup> In serum, the three isotypes display neutralizing activity, with IgM and IgG1 (the predominant subclass of IgG) being the most important contributors.<sup>30</sup>

In this study, we examined the COVID-19 vaccine antibody response in a general population cohort in Catalonia in relation to pre-pandemic air pollution levels. By late spring 2021, the majority of the Catalan population had received a first vaccine dose and some had received a second. We measured IgM, IgA, and IgG antibodies against viral antigens elicited by vaccines administered in Spain. Our primary outcome was based on levels of IgG to spike proteins in noninfected vaccinated persons.

## Materials and Methods

### Study Design and Participants

The COVID-19 cohort in Catalonia (the COVICAT study) evaluates the health impact of the COVID-19 pandemic on the population in Catalonia, Spain, and builds on five preexisting adult cohort studies.<sup>9</sup> We limited this analysis to the vaccine response in the largest cohort within COVICAT, the GCAT-Genomes for Life cohort.<sup>31</sup> The GCAT cohort started participant recruitment in 2015 and includes middle-aged (40–65 years of age at baseline) residents of Catalonia. Most enrolled participants were blood donors invited through a public agency, the Blood and Tissue Bank (BST). The last pre-pandemic follow-up was done in 2018–2019 ( $n=9,308$ ). In early summer 2020 post-lockdown, participants completed an online COVICAT questionnaire or responded to a computer-assisted telephone questionnaire; a random sample of participants also provided blood samples up to mid-November 2020.<sup>9,32</sup> Residential address at the time of the pre-pandemic questionnaire was geocoded.

We recontacted eligible participants a year later in spring 2021 after COVID-19 vaccine administration began in Spain (Figure S1). Participants were asked to respond to a questionnaire (online or via telephone) and provide a blood sample. Blood sampling in 2021 was offered to 2,404 participants, including all participants with a seropositive or undetermined serostatus in 2020 (response rate,  $N=507$ , 44.0%) and to a random sample of

seronegative participants in 2020 (response rate,  $N=575$ , 46.2%). People were aware of their 2020 serology results. A total of 1,090 participants provided blood samples and completed the questionnaire. We excluded from this analysis individuals who were not vaccinated ( $n=120$ ), those vaccinated with Janssen COVID-19 vaccine due to the small number of people receiving this (one dose) vaccine ( $n=16$ ), one participant <40 years of age, and 26 participants with incomplete information (questionnaire 2021, serology 2020, or air pollution data). This left 927 participants for this analysis.

Ethical approval was obtained by the ethics committees at the Hospital Universitari Germans Trias i Pujol (CEI no. PI-20-182) and the Parc de Salut Mar (CEIM-PS MAR, no. 2020/9,307/I). All participants provided informed consent and had consented to be recontacted during the first follow-up.

### Air Pollution Exposure

We linked participants' pre-pandemic addresses to estimates of long-term exposure to the following air pollutants: particulate matter with an aerodynamic diameter of  $\leq 2.5$   $\mu\text{m}$  (PM<sub>2.5</sub>), black carbon (BC), nitrogen dioxide (NO<sub>2</sub>), and ozone (O<sub>3</sub>). Air pollution estimates for the period 2018–2019 were based on models developed by the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (<http://www.elapseproject.eu/>), which have been described in detail.<sup>33</sup> We applied Europe-wide hybrid land-use regression models incorporating air pollution monitoring data, satellite observations, dispersion model estimates, land use, and traffic variables as predictors. We based the models for PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> (warm season) on 2010 measurements in the AirBase database that is maintained by the European Environmental Agency. We used European Study of Cohorts for Air Pollution Effects (ESCAPE) monitoring data to develop models of BC.<sup>34</sup> The model was evaluated using 5-fold hold-out validation in random subsets of the monitoring data stratified by type of measurement and region of Europe. Models explained 66% of measured spatial variation for PM<sub>2.5</sub> in annual average concentrations in hold-out validation; the corresponding fraction for BC was 52%; for NO<sub>2</sub>, 58%; and for O<sub>3</sub>, 63%. Participants were assigned the annual average 2010 concentration based on predicted surfaces (100 × 100 m) from the ELAPSE model. We then applied a temporal correction to estimate exposures for the years 2018 and 2019 following protocols for temporal extrapolation developed in the ESCAPE project. Although 2010 models have been validated, we did not have validation against measurement data from 2018–2019. We used daily time-series data from the official routine monitoring network and calculated the ratios between the 2018–2019 period and 2010 for NO<sub>2</sub>, nitrogen oxides (NO<sub>x</sub>), PM<sub>2.5</sub>, and O<sub>3</sub>. Because BC is not measured at routine monitoring stations, we used NO<sub>x</sub> to temporally adjust for BC values given that it is a primary combustion pollutant from traffic emissions with similar pollutant behavior. We used the average of 2018–2019 levels for each pollutant as our main exposure metrics.

### Samples and Serology

Blood samples collected at both follow-up periods (2020 and 2021) were processed within 24 h of collection and frozen, and anti-SARS-CoV-2 antibody levels in plasma were analyzed in one batch at the ISGlobal Immunology laboratory in Barcelona. The levels [median fluorescence intensity (MFI)] of IgG, IgM, and IgA were assessed by high-throughput multiplex quantitative suspension array technology against a panel of five SARS-CoV-2 antigens: the spike full length protein (S) and the receptor-binding domain (RBD) (both fused with C-terminal 6xHis and StrepTag purification sequences and purified from supernatant of lentiviral-

transduced CHO-S cells cultured under a fed-batch system<sup>35</sup>), the subregion S2 (purchased from SinoBiological), the nucleocapsid (N) full length (FL), and the specific C-terminal (Ct) region (both expressed in *E. coli* and His tag-purified).<sup>36</sup> Assay performance was previously established as 100% specificity and 95.78% sensitivity for seropositivity 14 d after symptoms onset (15). Antigen-coupled microspheres were added to a 384-well  $\mu$ Clear flat bottom plate (Greiner Bio-One) in multiplex (2,000 microspheres per analyte per well) in a volume of 90  $\mu$ L of Luminex buffer [1% bovine serum albumin (BSA), 0.05% Tween 20, 0.05% sodium azide in phosphate-buffered saline (PBS)] using the 384 channels Integra Viaflo semi-automatic device (96/384, 384 channel pipette). Hyperimmune pools were used as positive controls prepared at 2-fold, eight serial dilutions from 1:12.5. Prepandemic samples were used as negative controls to estimate the cutoff of seropositivity. Ten microliters of each dilution of the positive control, negative controls, and test samples (prediluted 1:50 in 96 round-bottom well plates), were added to a 384-well plate using an Assist Plus Integra device with a 12-channel Voyager pipette (final test sample dilution of 1:500 for all isotypes, and a second dilution at 1:5,000 for IgG to assess the response to S proteins in vaccinated participants, avoiding signal saturation). To quantify IgM and IgA, test samples and controls were pretreated with antihuman IgG (GullSorb) at 1:10 dilution, to avoid IgG interferences. Technical blanks consisting of Luminex buffer and microspheres without samples were added in 4 wells to control for nonspecific signals. Plates were incubated for 1 h at room temperature in agitation (Titramax 1000) at 900 rpm and protected from light. Then, the plates were washed three times with 200  $\mu$ L/well of PBS-T (0.05% Tween 20 in PBS), using BioTek 405 TS (384-well format). Twenty-five microliters of goat antihuman IgG-phycoerythrin (PE) (GTIG-001; Moss Bio) diluted 1:400, goat antihuman IgA-PE (GTIA-001; Moss Bio) 1:200, or goat antihuman IgM-PE (GTIM-001; Moss Bio) 1:200 in Luminex buffer were added to each well and incubated for 30 min as before. Plates were washed and microspheres resuspended with 80  $\mu$ L of Luminex buffer, covered with an adhesive film, and sonicated 20 s on a sonicator bath platform before acquisition on the Flexmap three-dimensional reader. At least 50 microspheres per analyte and per well were acquired, and MFIs were reported for each isotype–antigen combination. Assay positivity cutoffs specific for each isotype–antigen combination were calculated as 10 to the mean plus 3 standard deviations (SDs) of  $\log_{10}$ -transformed MFI of 128 prepandemic controls. Results were defined as undetermined when the MFI levels for a given isotype–antigen combination were between the positivity threshold and an upper limit at 10 to the mean plus 4.5 SD of the  $\log_{10}$ -transformed MFIs of prepandemic samples, and no other isotype–antigen combination was above the positivity cutoff. We defined overall serostatus by isotype and by antigen. Results for IgM are informative for the evaluation of short-term effects in antibody response and although measured in the whole study population are shown only for those participants having one dose at the time of the 2021 study visit, sampled within 1 month post vaccination.

### Vaccination and SARS-CoV-2 Infection

We retrieved data on the number of doses, date of administration, and trade names of vaccines for each participant from the electronic health records of the Epidemiological Surveillance Emergency Service of Catalonia of the Department of Health. Participants had received the following vaccines: Comirnaty (BNT162b2, mRNA; BioNTech-Pfizer), Spikevax (mRNA-1273; Moderna), and Vaxzevria (ChAdOx1 nCoV-19; AstraZeneca).

We detected a heterologous prime-boost approach in 11 people (Vaxzevria as a first shot followed by Comirnaty). Thus, participants' vaccine type is categorized according to the type of their first dose.

We used a two-part strategy to identify participants infected with SARS-CoV-2 prior to the 2021 study visit *a*) positive viral detection test (polymerase chain reaction or antigen test) prior to sample collection in 2021, self-reported in study questionnaires, or identified through record linkage with the SARS-CoV-2 test registry from the Epidemiological Surveillance Emergency Service of Catalonia of the Department of Health,<sup>37</sup> and *b*) seropositivity based on our antibody data using the following criteria: seropositivity in the prevaccination 2020 serology sample, or seropositivity to N-antigen in 2021 sample, given that the available vaccines do not contain or produce N-antigen.

### Covariates

Information on basic characteristics (age, sex, and educational level) was available from earlier contacts and verified in the COVICAT questionnaire (available in Spanish at <http://www.gcatbiobank.org/media/upload/arxiu/COVICAT/encuesta%20COVICAT.pdf>). In this analysis, we used self-reported information on several variables, including educational level, smoking, alcohol consumption, medical history diet, symptoms related to COVID-19, height, and weight. Medical history included prior diagnosis of any chronic disease, asking for a list of several major diseases that required a visit to the doctor or medical treatment in the last 6 months, such as cardiovascular (hypertension, heart attack, angina pectoris), respiratory (asthma, chronic obstructive pulmonary disease), diabetes, kidney, immune-related (autoimmune diseases, HIV, or other immunodeficiency), digestive, or gynecological diseases, as well as cancer, mental health diseases (anxiety, depression, or other diseases), and addictions, along with an open question on any other disease. Diet was assessed with the 14-point Mediterranean Diet Adherence Screener (MEDAS) used in the Prevención con Dieta Mediterránea (PREDIMED) study that has been validated against a classic food frequency questionnaire.<sup>38</sup> Self-reported symptoms related to COVID-19 included fever, cough, dyspnea, fatigue, headache, muscle/joint pain, loss of odor/taste, nausea, vomiting, and rash. We collected changes in residential address from the prepandemic period through the 2021 follow-up. We linked prepandemic residential addresses to census tract-level deprivation index based on the 2011 census<sup>39</sup>; the index uses six indicators, specifically, unemployment, manual work, temporary employment, insufficient education at >16 years of age, young age, and dwellings without access to internet. We also linked residential address with population density and degree of urbanization of the census tract of residence using information from the 2011 census.<sup>40</sup>

### Statistical Analysis

In all analyses, we used antibody levels that were  $\log_{10}$  transformed due to their skewed distribution. We applied linear regression models to assess the association between air pollution levels and the  $\log_{10}$ -transformed antibody levels, and results were expressed as percentage change in the geometric mean and 95% confidence intervals (CIs). Air pollutants were modeled continuously and estimates per interquartile range (IQR) of each pollutant were reported. Antibody responses to vaccination measured through IgM levels included only participants sampled within 1 month post first dose vaccination, whereas analyses on IgG/IgA levels included all participants irrespective of sampling time post vaccination. We considered the following variables as potential confounders: age (continuous), sex (male, female), highest attained educational level (primary or less, secondary, university), and socioeconomic status according to area of residency (in quantiles). Time since last vaccination (<31, 31–60, 61–90, 91–120, >120 d), type of vaccine and number of doses are strongly related to vaccine



**Table 1.** Description of the study population, COVICAT study, Catalonia, Spain ( $n = 927$ ).

Characteristic	Mean $\pm$ SD or $n$ (%)
Age (y)	57.5 $\pm$ 6.9
Sex	
Male	389 (42.0)
Female	538 (58.0)
Quintiles of deprivation index <sup>a</sup>	
1 (least deprived)	185 (20.0)
2	181 (19.5)
3	192 (20.7)
4	190 (20.5)
5 (most deprived)	179 (19.3)
Educational level	
University	453 (48.9)
Secondary	382 (41.2)
Primary or less	92 (9.9)
Type of vaccine	
Comirnaty–Pfizer/BioNTech	422 (45.5)
Spikevax–Moderna	113 (12.2)
Vaxzevria–AstraZeneca	392 (42.3)
Doses ( $n$ )	
1	319 (34.4)
2	608 (65.6)
Evidence of previous infection at time of serology	
No	632 (68.2)
Yes	295 (31.8)
Seropositivity 2021	
No	19 (2.0)
Yes	908 (98)

Note: COVICAT, COVID-19 cohort in Catalonia; SD, standard deviation.  
<sup>a</sup>1 (–2.27, –1.44), 2 (–1.44, –1.09), 3 (–1.09, –0.81), 4 (–0.81, –0.28), 5 (–0.28, 1.81).

antibody response, and we also included those variables in all models. We finally adjusted for factors that have been associated with response to COVID-19 or other vaccines, including smoking, diet, prior chronic diseases, and mental health.<sup>23–26</sup> We expected an attenuated effect among those with previous SARS-CoV-2 infection and therefore defined *a priori* stratified analysis by infection status. Evaluation of effect modification by infection status through likelihood ratio tests indicated  $p_{\text{Interaction}} < 0.1$  for all air pollutants and the S and S2 spike antigens. In the infected strata, we adjusted models for severity of the infection based on self-reported symptoms and from hospital records (0 symptoms, 1–3 symptoms,  $\geq 4$  symptoms, hospitalized). Participants with missing covariates were excluded from the complete-case analysis models. We used generalized additive models to explore the relationship between days since vaccination and IgG antibody levels among participants without prior infection according to air pollution levels (with low defined as below the median vs. high defined as above the median of the distribution for each pollutant). We performed all statistical analyses using Stata/SE (version 16; StataCorp LLC).

## Results

### Study Population

The flow chart in Figure S1 shows the participants contacted, those recruited, and those excluded. Of the 1,090 participants

**Table 2.** Spearman correlations of air pollution concentrations (2018–2019 average) at residence ( $n = 927$ ), COVICAT study, Catalonia, Spain.

	NO <sub>2</sub>	PM <sub>2.5</sub>	BC	O <sub>3</sub>
NO <sub>2</sub>	1			
PM <sub>2.5</sub>	0.799	1		
BC	0.789	0.739	1	
O <sub>3</sub>	–0.808	–0.780	–0.686	1

Note: BC, black carbon; COVICAT, COVID-19 cohort in Catalonia; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter.

**Table 3.** Distribution of air pollution concentrations (2018–2019 average) by type of vaccine, COVICAT cohort study, Catalonia, Spain.

Pollutant ( $\mu\text{g}/\text{m}^3$ )	Mean $\pm$ SD	Geometric mean (95% CI)	50th percentile	25th–75th percentile
All vaccines ( $n = 927$ )				
NO <sub>2</sub>	35.1 $\pm$ 8.9	33.7 (33.0, 34.4)	36.7	30.0–40.7
PM <sub>2.5</sub>	16.4 $\pm$ 1.4	16.3 (16.2, 16.4)	16.6	15.7–17.3
BC	1.8 $\pm$ 0.4	1.8 (1.8, 1.8)	1.9	1.7–2.1
O <sub>3</sub>	64.2 $\pm$ 6.6	63.9 (63.5, 64.3)	62.5	60.4–66.1
Pfizer ( $n = 422$ )				
NO <sub>2</sub>	34.9 $\pm$ 9.0	33.5 (32.5, 34.5)	36.5	29.6–40.5
PM <sub>2.5</sub>	16.3 $\pm$ 1.5	16.2 (16.1, 16.4)	16.6	15.5–17.3
BC	1.8 $\pm$ 0.4	1.8 (1.8, 1.8)	1.9	1.7–2.1
O <sub>3</sub>	64.5 $\pm$ 6.9	64.2 (63.5, 64.8)	62.6	60.7–66.1
Moderna ( $n = 113$ )				
NO <sub>2</sub>	34.3 $\pm$ 8.9	32.6 (30.5, 34.9)	35.5	29.5–40.5
PM <sub>2.5</sub>	16.2 $\pm$ 1.3	16.2 (15.9, 16.4)	16.1	15.5–17.2
BC	1.8 $\pm$ 0.4	1.7 (1.6, 1.8)	1.8	1.6–2.1
O <sub>3</sub>	64.9 $\pm$ 6.7	64.6 (63.4, 65.8)	63.3	60.4–69.4
AstraZeneca ( $n = 392$ )				
NO <sub>2</sub>	35.6 $\pm$ 8.7	34.3 (33.3, 35.3)	37.5	31.7–40.9
PM <sub>2.5</sub>	16.5 $\pm$ 1.3	16.4 (16.3, 16.6)	16.7	15.8–17.4
BC	1.9 $\pm$ 0.4	1.8 (1.8, 1.8)	1.9	1.7–2.1
O <sub>3</sub>	63.8 $\pm$ 6.3	63.5 (62.9, 64.1)	62.4	60.1–65.2

Note: BC, black carbon; CI, confidence interval; COVICAT, COVID-19 cohort in Catalonia; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter; SD, standard deviation.

recruited who gave blood samples, 927 participants were included in this analysis (Figure S1). The mean age was 57 y (range: 44–72 y), and 58% were female (Table 1). We evaluated differences in air pollution exposure, sociodemographic, and clinical variables between the 1,090 persons who gave blood samples in 2021 (participants) and the 1,314 who were contacted but did

**Table 4.** Association of air pollution with antibody levels induced after vaccination for IgM, IgA, and IgG among COVICAT cohort participants without prior infection ( $n = 632$ ).

Pollutants/ Spike Antigens <sup>a</sup>	IgM $n = 357$ (one dose only) <sup>b</sup>	IgA $n = 632$	IgG $n = 632$
	% change (95% CI) <sup>c</sup>	% change (95% CI) <sup>c</sup>	% change (95% CI) <sup>c</sup>
NO <sub>2</sub>			
RBD	–10.8 (–19.3, –1.4)	3.2 (–6.0, 13.3)	–1.8 (–10.2, 7.4)
S	–12.2 (–22.9, 0.0)	1.6 (–9.9, 14.5)	–7.3 (–13.9, –0.2)
S2	–5.3 (–14.2, 4.4)	3.0 (–7.8, 15.1)	–6.7 (–11.9, –1.1)
PM <sub>2.5</sub>			
RBD	–10.8 (–19.6, –1.0)	2.4 (–6.7, 12.3)	–8.1 (–15.9, 0.4)
S	–14.3 (–25.1, –1.9)	1.5 (–9.9, 14.4)	–9.9 (–16.2, –3.1)
S2	–6.0 (–15.1, 4.0)	3.0 (–7.8, 15.0)	–8.4 (–13.5, –3.0)
BC			
RBD	–5.6 (–13.8, 3.3)	1.0 (–7.2, 10.0)	–7.6 (–14.8, 0.3)
S	–7.8 (–18.1, 3.7)	0.3 (–10.1, 11.9)	–10.0 (–15.8, –3.7)
S2	–4.1 (–12.2, 4.7)	5.9 (–4.3, 17.2)	–8.0 (–12.7, –3.1)
O <sub>3</sub>			
RBD	6.3 (–1.1, 14.3)	–2.8 (–9.3, 4.1)	4.6 (–2.1, 11.7)
S	7.6 (–2.0, 18.2)	0.9 (–7.6, 10.2)	6.9 (1.2, 12.8)
S2	2.1 (–4.8, 9.5)	0.1 (–7.7, 8.6)	4.6 (0.3, 9.1)

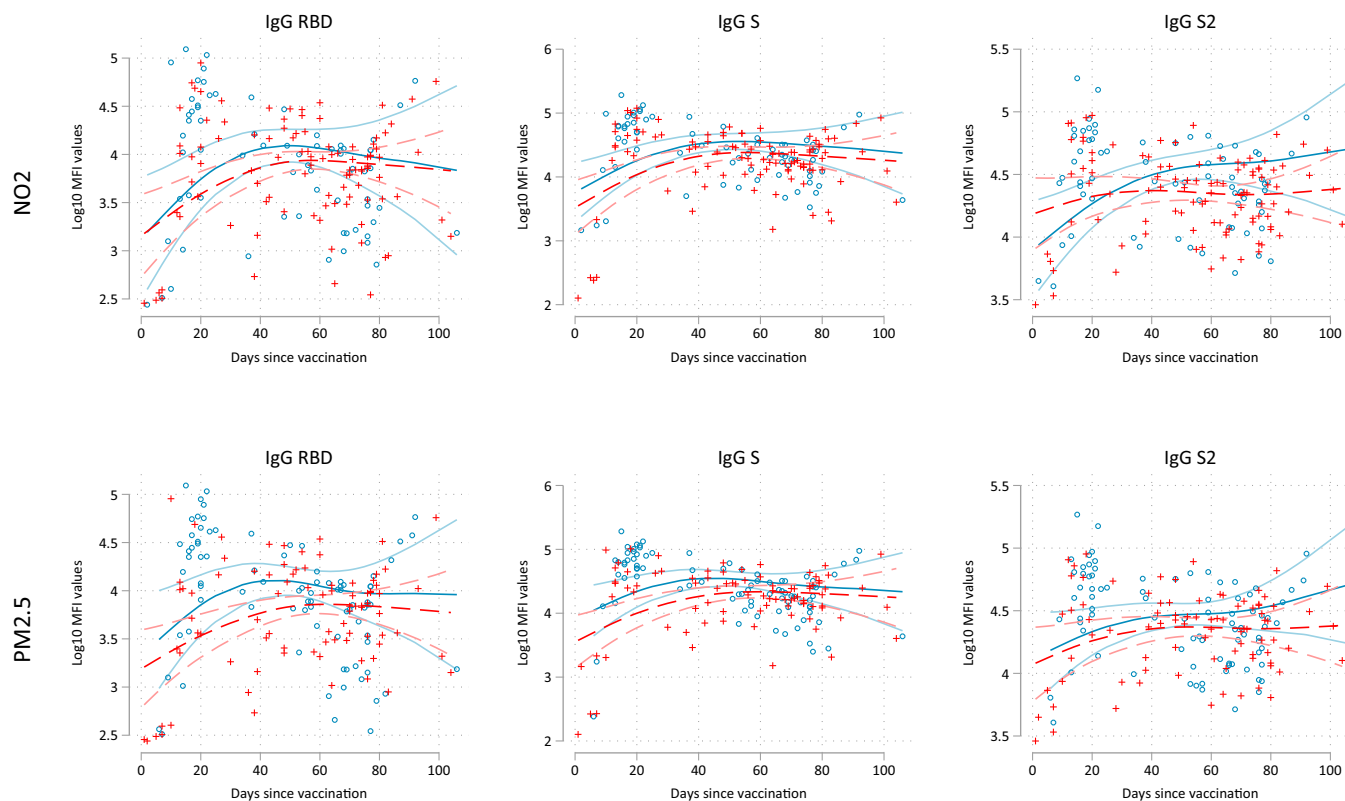
Note: Percentage change (95% CI) per IQR of air pollutants from linear regression for the log<sub>10</sub> MFI. %, percentage; BC, black carbon; CI, confidence interval; COVICAT, COVID-19 cohort in Catalonia; Ig, immunoglobulin; IQR, interquartile range; MFI, median fluorescence intensity; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter; RBD, receptor-binding domain; S, spike-protein; S2, segment spike-protein.

<sup>a</sup>Pollutants: NO<sub>2</sub> (IQR: 10.7), PM<sub>2.5</sub> (IQR: 1.7), BC (IQR: 0.4), and O<sub>3</sub> (IQR: 5.7); viral-target antigens: RBD, S, and S2.

<sup>b</sup>Restricted to 357 persons sampled within 1 month post first dose vaccination.

<sup>c</sup>Adjusted for age (continuous), sex, educational level (university, secondary, primary or less), quintiles of deprivation index, type of vaccine (Comirnaty, Spikevax, Vaxzevria), number of doses and time since last vaccine (<31, 31–60, 61–90, 91–120, >120 days). Adjustment for IgM does not include time since last vaccine.

## Participants with 1 dose and no prior infection



**Figure 1.** Vaccine responses in time since first vaccination by exposure to high or low air pollution levels among participants in the COVICAT study without prior infection and one vaccine dose ( $n=319$ ). Generalized additive models exploring the relationship between days since vaccination and antibody IgG levels induced after vaccination, by high (red, plus) or low (blue, circle)  $\text{NO}_2$  and  $\text{PM}_{2.5}$  air pollution levels. High and low air pollutant levels were defined as above or below the median ( $\text{NO}_2$ : 36.7;  $\text{PM}_{2.5}$ : 16.6). IgG levels were determined for three viral-target antigens: RBD, S, and S2. Data used in the figure are available in Excel Tables S1 and S2. Note: COVICAT, COVID-19 cohort in Catalonia; Ig, immunoglobulin; MFI, median fluorescence intensity;  $\text{NO}_2$ , nitrogen dioxide;  $\text{PM}_{2.5}$ , particulate matter  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter; RBD, receptor-binding domain; S, spike-protein; S2, segment spike-protein.

not attend the study visit in 2021 (nonparticipants). The average  $\text{NO}_2$  levels for participants and nonparticipants was similar ( $36.8 \mu\text{g}/\text{m}^3$  vs.  $36.6 \mu\text{g}/\text{m}^3$ , respectively) and for  $\text{PM}_{2.5}$  were nearly identical ( $16.6 \mu\text{g}/\text{m}^3$ ) (Table S1). Participants were slightly older (55.8 years of age) than nonparticipants (55.3 years of age). There were minor, nonstatistically significant differences for socioeconomic status/education, sex, and prior infection based on serological tests in 2020 (Table S1).

### Air Pollution Exposure

Pollution levels at residence had the following correlations: 0.8 between  $\text{NO}_2$  and  $\text{PM}_{2.5}$ ,  $\sim 0.8$  for  $\text{NO}_2$  and BC and 0.7 for  $\text{PM}_{2.5}$  and BC, and  $\sim -0.8$  for  $\text{NO}_2$  and  $\text{PM}_{2.5}$  with  $\text{O}_3$  (Table 2). Mean exposure during 2018–2019 in the study population was  $35.1 \mu\text{g}/\text{m}^3$  for  $\text{NO}_2$  and  $16.4 \mu\text{g}/\text{m}^3$  for  $\text{PM}_{2.5}$  (Table 3).

### Vaccination and Association of Air Pollutants with Type of Vaccine

Among vaccinated participants, 319 (34.4%) had one dose and 605 (65.6%) had completed two doses (Table 1). The first dose was either Comirnaty–Pfizer/Biontech (45.5%) or Vaxzevria–AstraZeneca- (42.3%), and a smaller fraction of people were vaccinated with Spikevax–Moderna (12.2%). Vaxzevria was administered as a first dose followed by Comirnaty in 11 people. Median time since the last vaccination was 28 d (IQR: 14–54 d, minimum: 1 d, maximum: 160 d). Median time between the first

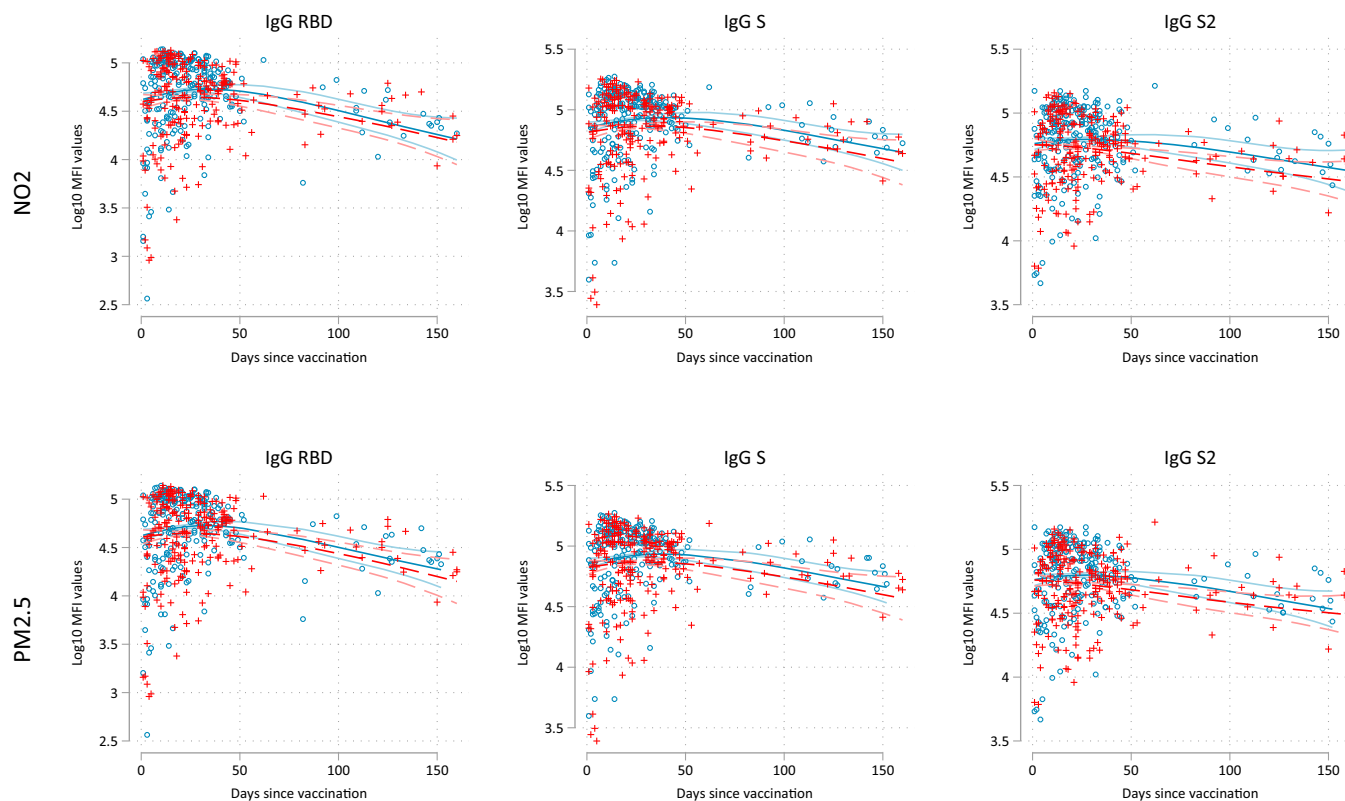
and second dose was 21 d for Comirnaty (IQR: 21–22 d, minimum: 14 d, maximum: 42 d), 28 d for Spikevax (IQR: 28–29 d, minimum: 27 d, maximum: 36 d), and 83 d for Vaxzevria (IQR: 78–95 d, minimum: 63 d, maximum: 121 d).

There was no clear association of air pollutant levels with the type of vaccine administered (Table 3). Recipients of the AstraZeneca vaccine had only slightly higher average exposure levels of  $\text{NO}_2$  ( $35.6 \mu\text{g}/\text{m}^3$ ) and  $\text{PM}_{2.5}$  ( $16.5 \mu\text{g}/\text{m}^3$ ) compared with those receiving the Pfizer ( $34.9 \mu\text{g}/\text{m}^3$  and  $16.3 \mu\text{g}/\text{m}^3$ , respectively) and Moderna vaccines ( $34.3 \mu\text{g}/\text{m}^3$  and  $16.2 \mu\text{g}/\text{m}^3$ , respectively).

### Association of Air Pollutants with Vaccine Antibody Response

Among participants without prior infection, antibody responses to vaccination measured through IgM levels (participants within 1 month post first dose vaccination) and IgG levels (any time post vaccination, all participants) were negatively associated with long-term air pollution; no associations were observed for IgA (Table 4). The decrease in IgM levels was between 5% and 14% per IQR increase in  $\text{NO}_2$  and  $\text{PM}_{2.5}$ , and it was statistically significant for most antigens. The decrease in IgM was slightly smaller for BC, whereas no associations were observed for  $\text{O}_3$ . For IgG, IQR increases in  $\text{NO}_2$ ,  $\text{PM}_{2.5}$ , and BC were associated with statistically significant decreases of the S and S2 antigens. An IQR increase in  $\text{PM}_{2.5}$  was associated with an  $\sim 8\%$ – $10\%$

## Participants with 2 doses and no prior infection



**Figure 2.** Vaccine responses in time since second vaccination by exposure to high or low air pollution levels among participants in the COVICAT study without prior infection and two vaccine doses ( $n=608$ ). Generalized additive models exploring the relationship between days since vaccination and antibody IgG levels induced after vaccination, by high (red, plus) or low (blue, circle)  $\text{NO}_2$  and  $\text{PM}_{2.5}$  air pollution levels. High and low air pollutant levels were defined as above or below the median ( $\text{NO}_2$ : 36.7;  $\text{PM}_{2.5}$ : 16.6). IgG levels were determined for three viral-target antigens: RBD, S, and S2. Data used in the figure are available in Excel Tables S3 and S4. Note: COVICAT, COVID-19 cohort in Catalonia; Ig, immunoglobulin; MFI, median fluorescence intensity;  $\text{NO}_2$ , nitrogen dioxide;  $\text{PM}_{2.5}$ , particulate matter  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter; RBD, receptor-binding domain; S, spike-protein; S2, segment spike-protein.

decrease in IgG levels; for RBD, percentage change =  $-8.1$  (95% CI:  $-15.9, 0.4$ ); for S, percentage change =  $-9.9$  (95% CI:  $-16.2, -3.1$ ); and for S2, percentage change =  $-8.4$  (95% CI:  $-13.5, 3.0$ ). Similar associations were observed for BC, whereas for  $\text{NO}_2$  the decrease in IgG antibody response was slightly smaller (Table 4). An inverse association for IgG was observed for exposure to  $\text{O}_3$ . Estimates for IgG and air pollutants adjusted only for age and sex are shown in Table S2. Associations adjusted for the same variables as in the Table 4 models but also including lifestyle factors (smoking and alcohol consumption), the diet MEDAS score, prior mental health diseases, and prior medical history of chronic diseases gave similar estimates (Table S3) as those shown in Table 4 for more limited adjustments. The direction of the air pollution–antibody response associations was similar in women and men, but they were stronger in men (Table S4). There were no statistically significant interactions ( $p_{\text{Interaction}} < 0.1$ ) observed by sex for  $\text{NO}_2$ ,  $\text{PM}_{2.5}$ , or BC, although there were for  $\text{O}_3$  exposure. Finally, we evaluated whether the association of air pollution with vaccine response depended on type of vaccine (Table S5). Results were similar for the three main vaccines administered.

Among participants without prior infection, differences in IgG antibody response between high and low air pollution exposures (defined as above or below the median exposure for  $\text{NO}_2$  and  $\text{PM}_{2.5}$ ) were small but persisted over time since vaccination after both the first (Figure 1) and the second dose (Figure 2). After the first dose, the peak in IgG RBD and S responses occurred later, and

lower levels were observed in people exposed to high levels of  $\text{PM}_{2.5}$  and  $\text{NO}_2$  (Figure 1). After the second dose, we identified a faster decrease of IgG levels with time in noninfected participants with high air pollution exposure (Figure 2).

Among infected participants, there were no associations observed between air pollution and antibody response to vaccines for any of the air pollutants examined (Table 5). The largest decrease in IgG levels per IQR increase in  $\text{PM}_{2.5}$  was observed for RBD ( $-8.7\%$ ) but results were not statistically significant.

### Discussion

We examined whether long-term exposure to air pollution is associated with antibody responses to COVID-19 vaccines in a prospective cohort study. Our study resulted in several key findings. First, we identified that exposure to  $\text{PM}_{2.5}$ ,  $\text{NO}_2$ , and BC was associated with a 5%–10% decrease in vaccine antibody responses among individuals without prior infection after adjusting for confounders. The decrease was shown both for early responses measured through IgM and late responses measured through IgG. Second, lower antibody response among participants with air pollution exposure above the median persisted over several months following vaccination. In this study, we did not address whether the observed decrease in antibody responses was associated with risk of breakthrough infections and their severity.

Air pollutants have been shown to impair immune response, including effects on severe COVID-19, although there is very



**Table 5.** Association of air pollution with antibody levels induced after vaccination for IgM, IgA, and IgG among COVICAT cohort participants with prior infection ( $n = 295$ ).

Pollutants/ spike antigens <sup>a</sup>	IgM ( $n = 140$ ) (one dose only) <sup>b</sup>	IgA ( $n = 295$ )	IgG ( $n = 295$ )
	% change (95% CI) <sup>c</sup>	% change (95% CI) <sup>c</sup>	% change (95% CI) <sup>c</sup>
NO <sub>2</sub>			
RBD	2.3 (-11.8, 18.7)	-2.5 (-21.4, 20.9)	-1.0 (-17.9, 19.4)
S	-0.1 (-17.7, 21.4)	2.6 (-18.9, 29.9)	0.8 (-13.7, 17.7)
S2	-5.0 (-18.2, 10.3)	14.9 (-5.3, 39.5)	2.4 (-8.6, 14.7)
PM <sub>2.5</sub>			
RBD	6.1 (-8.2, 22.7)	-14.8 (-31.0, 5.2)	-8.7 (-24.1, 9.7)
S	-0.4 (-17.6, 20.5)	-10.9 (-29.3, 12.4)	-5.2 (-18.6, 10.5)
S2	-5.1 (-18.0, 9.8)	6.4 (-12.2, 28.8)	-1.8 (-12.1, 9.9)
BC			
RBD	-0.2 (-12.4, 13.8)	-10.4 (-25.7, 8.0)	-1.0 (-15.9, 16.5)
S	-3.9 (-19.0, 14.0)	-5.8 (-23.3, 15.7)	1.0 (-11.8, 15.6)
S2	-8.0 (-19.3, 4.8)	7.5 (-9.3, 27.3)	0.8 (-8.7, 11.3)
O <sub>3</sub>			
RBD	-3.9 (-14.4, 7.9)	8.0 (-7.6, 26.3)	1.8 (-11.2, 16.6)
S	-2.1 (-15.9, 13.9)	3.2 (-13.0, 22.5)	1.0 (-9.7, 13.1)
S2	2.2 (-9.0, 14.9)	-3.0 (-15.7, 11.8)	-0.5 (-8.3, 8.1)

Note: Percentage change (95% CI) per IQR of air pollutants from linear regression for the log<sub>10</sub> MFI. %, percentage; BC, black carbon; CI, confidence interval; COVICAT, COVID-19 cohort in Catalonia; Ig, immunoglobulin; IQR, interquartile range; MFI, median fluorescence intensity; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter ≤2.5 μm in aerodynamic diameter; RBD, receptor-binding domain; S, spike-protein; S2, segment spike-protein.

<sup>a</sup>Pollutants: NO<sub>2</sub> (IQR: 10.7), PM<sub>2.5</sub> (IQR: 1.7), BC (IQR: 0.4), and O<sub>3</sub> (IQR: 5.7); viral-target antigens: RBD, S, and S2.

<sup>b</sup>Restricted to 140 persons sampled within 1 month post first dose vaccination.

<sup>c</sup>Adjusted for age (continuous), sex, educational level (university, secondary, primary or less), quintiles of deprivation index, type of vaccine (Comirnaty, Spikevax, Vaxzevria), number of doses and time since last vaccine (<31, 31–60, 61–90, 91–120, >120 d), disease severity (0 symptoms, 1–3 symptoms, ≥4 symptoms, hospitalized). Adjustment for IgM does not include time since last vaccine.

limited evidence evaluating the association of long-term exposure to air pollution on vaccine response.<sup>22</sup> Wider effects of air pollution indicate alterations across multiple classes of immune cells affecting various diseases, including respiratory infections, exacerbations of asthma and chronic obstructive pulmonary disease, and cardiovascular disease.<sup>12–14</sup> Chronic inflammation, such as induced by air pollution, has been associated with a negative effect on vaccine efficacy.<sup>15</sup> Finally, our findings on air pollution exposure are consistent with evidence regarding pollution more broadly, including evidence that persistent organic pollutants, such as PCBs, reduce vaccine response in children.<sup>17–19</sup>

We identified an association of exposure to air pollution with vaccine antibody response among participants without prior infection. Moreover, people exposed to air pollution had a later peak in antibody responses after the first dose and they had persistently lower levels of antibodies in time. The combination in the same multiplex assay of antigens only present in the virus (N) and in both the virus and the vaccines (S) allowed us to make a distinction between participants who were infected and those who were not along with data from viral detection tests and prior serology in the beginning of the pandemic. We had shown in an earlier analysis based on the COVICAT data<sup>9</sup> that higher levels of air pollution were associated with a higher risk of severe COVID-19 and a higher antibody response to the infection and that previous infections are associated with higher vaccine antibody responses.<sup>23</sup> Thus, the effect of pollutants on vaccine responses could differ and be masked among those infected. We therefore adjusted the models on the association of air pollution with vaccine antibody response among those infected for disease severity. As the pandemic and vaccination campaigns have evolved, a higher proportion of the population has immunity developed through a combination of infection and vaccine, and

further research should investigate the role of long-term exposure to air pollution on this hybrid immunity.

The identification of small differences in the response of the three S antigens are difficult to evaluate given that they are highly correlated. Decreases in antibody levels were consistent for NO<sub>2</sub>, PM<sub>2.5</sub>, and BC. Positive associations for O<sub>3</sub> are most likely due to the strong inverse correlation between O<sub>3</sub> and NO<sub>2</sub> levels.

For COVID-19 vaccines, similarly to influenza and other vaccines, research on immunological responses has largely focused on IgG responses while other isotypes are generally neglected. The inclusion of the three isotypes is a strength of this study. Virus-specific IgM are produced early following infection/vaccination, followed by IgA and IgG virus-specific antibody production.<sup>29</sup> The identification of differences in early responses measured through IgM reinforce our findings concerning IgG. We identified a negative effect of air pollution particularly on IgG and to a much lesser extent for IgA levels. We had hypothesized that air pollution would have a negative impact also for IgA. Unfortunately, we could not assess direct effects of air pollution on IgA production and distribution at mucosal sites, particularly in the respiratory tract. Systemic IgA and mucosal IgA may not necessarily correlate given that they are under different regulatory mechanisms. Recent studies, however, have identified IgA levels following intramuscular COVID-19 vaccination also in saliva,<sup>41,42</sup> as well as a correlation between serum and saliva IgA levels.<sup>42</sup> These data highlight the need for assessing antigen-specific mucosal IgA levels in future studies.

Key strengths of our study are the use of prospectively collected individual-level data through individual contact and electronic registers and the use of repeated serological testing for a wide range of antigens. Sources of bias that are concerns in previous studies linking air pollution and COVID-19 disease<sup>10</sup> are less relevant for the outcomes we studied. Detection bias that may affect studies on SARS-CoV-2, was not an issue in this study, which was based on complete serological testing of the study population. The availability of extensive individual information, both prepandemic and at two different post-pandemic time points, allows for extensive control of potential confounding by lifestyle factors (e.g., tobacco smoking) and contextual variables (e.g., socioeconomic status) and also for factors that have been shown in vaccine trials for other diseases to be associated with vaccine response (e.g., nutrition). In our study, the degree of confounding by these variables was minimal. The two main limitations of our study are the low response rates among participants providing blood samples for a second time and the lack of long-term clinical follow-up data to associate alterations in vaccine antibody response with clinical effects. Our main outcome is based on levels of IgG to S proteins, a biomarker, which eliminates the possibility of self-selection based on the outcome. Still, immune response could be a correlate of other factors associated with exposure to air pollution, such as socioeconomic status, and bias from nonresponse would occur if individuals with more symptoms were more likely to participate and if participation was related to prepandemic air pollution levels. We showed that participants were very similar to those not participating in terms of exposure, vaccination factors, and prior clinical symptoms, which probably eliminates or substantially diminishes the probability of this bias. In addition, we showed that the type of vaccine administered was also not associated with air pollution exposure. Finally, the population studied was mostly mid-age. Given well-known differences in vaccine response by age,<sup>26</sup> the generalization of these findings particularly to older ages may be limited.

## Conclusions and Potential Implications

Our study identifies an effect of air pollution on COVID-19 vaccine immune response. Participants exposed to higher levels of

fine particles (PM<sub>2.5</sub>), NO<sub>2</sub>, and BC had ~10% lower antibody responses to S antigens that are elicited by the vaccines. This finding strengthens the evidence on the multiple immune pathways through which air pollution affects multiple diseases, including infections and chronic diseases. Whether this decrease in antibody response has observable effects on future risk of COVID-19 risk should be evaluated with longer-term prospective data. Similarly, our findings open the possibility of air pollution affecting immunization for other diseases. Overall our findings add to the knowledge on the adverse effects of air pollution that are identified even in the relatively low levels observed in western Europe and urge for stricter control of exposure as recommended by the World Health Organization.

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