

Original research

# Long-term exposure to air pollution and COVID-19 incidence: a prospective study of residents in the city of Varese, Northern Italy

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## ABSTRACT

**Objectives** To investigate the association between long-term exposure to airborne pollutants and the incidence of SARS-CoV-2 up to March 2021 in a prospective study of residents in Varese city.

**Methods** Citizens of Varese aged  $\geq 18$  years as of 31 December 2019 were linked by residential address to 2018 average annual exposure to outdoor concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, NO and ozone modelled using the Flexible Air quality Regional Model (FARM) chemical transport model. Citizens were further linked to regional datasets for COVID-19 case ascertainment (positive nasopharyngeal swab specimens) and to define age, sex, living in a residential care home, population density and comorbidities. We estimated rate ratios and additional numbers of cases per  $1 \mu\text{g}/\text{m}^3$  increase in air pollutants from single- and bi-pollutant Poisson regression models.

**Results** The 62 848 residents generated 4408 cases. Yearly average PM<sub>2.5</sub> exposure was  $12.5 \mu\text{g}/\text{m}^3$ . Age, living in a residential care home, history of stroke and medications for diabetes, hypertension and obstructive airway diseases were independently associated with COVID-19. In single-pollutant multivariate models, PM<sub>2.5</sub> was associated with a 5.1% increase in the rate of COVID-19 (95% CI 2.7% to 7.5%), corresponding to 294 additional cases per 100 000 person-years. The association was confirmed in bi-pollutant models; excluding subjects in residential care homes; and further adjusting for area-based indicators of socioeconomic level and use of public transportation. Similar findings were observed for PM<sub>10</sub>, NO<sub>2</sub> and NO. Ozone was associated with a 2% decrease in disease rate, the association being reversed in bi-pollutant models.

**Conclusions** Long-term exposure to low levels of air pollutants, especially PM<sub>2.5</sub>, increased the incidence of COVID-19. The causality warrants confirmation in future studies; meanwhile, government efforts to further reduce air pollution should continue.

## INTRODUCTION

In December 2019 a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) emerged in China causing a pneumonia outbreak called COVID-19 disease. The disease outbreak rapidly spread globally with an official pandemic announcement on 11 March 2020. As of late March 2021, the total number of cases was above 127 million worldwide, with more than 2.7 million

## Key messages

### What is already known about this subject?

► Although ecological studies found a correlation between air pollution and COVID-19, associations should be confirmed in prospective studies with individual-level data on airborne pollutant exposure, COVID-19 and comorbidities.

### What are the new findings?

► In our prospective study of adult residents in the city of Varese in northern Italy we found that an increase of  $1 \mu\text{g}/\text{m}^3$  in the annual average exposure to PM<sub>2.5</sub> was associated with a 5.1% increase in the rate of COVID-19 independently of covariates, corresponding to 294 additional cases per 100 000 person-years.

► The association was confirmed by a number of sensitivity analyses, including bi-pollutant models, seasonal versus annual average exposure, pandemic period and after excluding individuals living in residential homes.

### How might this impact on policy or clinical practice in the foreseeable future?

► Our findings provide the first solid empirical evidence for the hypothesised pathway linking long-term exposure to air pollution with the incidence of COVID-19 and deserve future generalisation in different contexts. Meanwhile, government efforts to further reduce air pollution levels can help to mitigate the public health burden of COVID-19.

deaths.<sup>1</sup> At the same date, Italy ranked seventh with more than 3.5 million cases, roughly corresponding to 6% of the population, and 108 000 deaths, corresponding to a case fatality of 3.1%.<sup>1</sup> From March to September 2021, cases and deaths increased by 1.5 million and 22 000, respectively. Four out of the first five Italian regions for numbers of cases are located in the north of the country in the Po valley, with the Lombardy region being the worst affected by the COVID-19 pandemic both in terms of cases and deaths (21% and 28% of national counts, respectively). Since the early phases of the epidemic, several reasons have been advocated to explain territorial heterogeneity in the number of

cases and deaths, including different testing strategies and population age structure.<sup>2</sup>

The Po valley is also one of the most polluted areas in Europe. According to recent estimates by the EU Environmental Agency, about 95% of the 3.9 million people in Europe living in areas where the limits of the main air pollutants are exceeded live in Northern Italy.<sup>3</sup> In the early phases of the epidemic outbreak, a joint position paper by the Italian Society of Environmental Medicine observed the presence of a correlation between air quality and COVID-19 cases.<sup>4</sup> A recent review included 19 papers investigating the role of airborne particulate matter (PM) and nitrogen dioxide (NO<sub>2</sub>) in COVID-19 infectivity and lethality, covering sub-national as well as country-wide areas from China, Italy, Spain, France, Germany, the USA and Peru.<sup>5</sup> In UK Biobank participants, long-term exposure to PM<sub>2.5</sub> and NO<sub>2</sub> was associated with a 12% and 5% increase in COVID-19 cases per single unit increase in pollutant, respectively.<sup>6</sup>

Although correlation does not imply causation, a number of clues indicate air pollution among the factors that may contribute to the spreading of COVID-19 infection and worsening of prognosis at a population level.<sup>7,8</sup> First, there have been several reports in the literature of links between air pollution and the spreading velocity of viruses<sup>9,10</sup> and case fatalities,<sup>11</sup> this latter evidence coming from an ecological study relative to the previous SARS epidemic. Second, from a mechanistic point of view, air pollution has a well-recognised role in prolonged inflammation and downregulation of the immune system.<sup>7,8</sup> Through this pathway, short-term and long-term exposures to increased levels of airborne PM<sub>10</sub>, PM<sub>2.5</sub>, ozone (O<sub>3</sub>), nitrogen oxides (NO) and NO<sub>2</sub> have been causally linked to adverse respiratory and cardiovascular outcomes.<sup>12</sup> It is worth noting that coronary heart disease, chronic obstructive pulmonary disease (COPD) and stroke are present in one of every 3, 5 and 10 COVID-19 deaths, respectively.<sup>13</sup> In addition, long-term PM<sub>2.5</sub> exposure could play a role in pulmonary immunity<sup>14</sup> by impairing the capacity of pulmonary macrophages to regulate the inflammation response, resulting in an increased death rate following influenza infection.<sup>15</sup> Therefore, air pollution may have a direct effect on COVID-19 susceptibility and severity by exacerbating the effects of the viral load on the respiratory system, and an indirect effect by increasing the prevalence of frail individuals (ie, those living with cardiovascular and respiratory comorbidities) in the population.<sup>7</sup> Finally, researchers have also hypothesised that air pollutants can serve as carriers and vehiculate the virus, favouring its survival in the air.<sup>8</sup>

Despite the large number of contributions, the current literature suffers from two major flaws, with most of the evidence coming from studies of ecological design<sup>5</sup> and no study extending the surveillance period beyond June 2020. In the present study we aim to investigate the association between long-term exposure to airborne pollutants and the COVID-19 epidemic spread as susceptibility increased from disease outbreak to March 2021 among residents in the city of Varese, the eighth largest city in the Lombardy region, accounting for major demographic, residential and clinical features measured at an individual level.

## METHODS

### Study population and data sources

Residents in the city of Varese who were beneficiaries of the Regional Health Service formed the target population. We identified 81 543 residents in the city of Varese as of 31 December 2017, 97.4% of which were successfully linked to the 2018 annual average level of exposure to the most relevant air

pollutants based on geocoding of their residency address. We further selected individuals still at risk of COVID-19 and residents in Varese at 31 December 2019 and restricted the study sample to individuals aged ≥18 years. Finally, these were further linked to regional healthcare databases collecting information on COVID-19 cases, hospital discharge records and outpatient drug prescriptions through a unique anonymised individual identification code. Sample selection criteria and number of excluded individuals are shown in online supplemental table S1.

### Environmental exposure

Estimates of annual and seasonal average ground level for five airborne pollutants (PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, NO and O<sub>3</sub>) were available for the year 2018 over an area 40 km wide at a spatial resolution of 1 km × 1 km. Concentrations were modelled using FARM (Flexible Air quality Regional Model), an open-source three-dimensional Eulerian chemical transport model for urban and regional scales.<sup>16,17</sup> FARM simulates the atmospheric dispersion and deposition of pollutants released by all known anthropogenic and biogenic emission sources over a given area and the subsequent formation of secondary pollutants due to atmospheric chemical reactions in gas and aerosol phases on the basis of current meteorological conditions. Input data were: the latest release of INEMAR (INventario EMISSIONI ARia Lombardia 2014), a regional inventory of measured atmosphere emissions from all anthropometric activities by the Regional Agency for Environmental Protection; and three-dimensional hourly meteorological (wind, temperature, humidity, cloud cover, precipitation) and chemical conditions for the year 2018. The model was run for the whole of the year 2018 and the exposure was assigned to each study participant based on the nearest grid centroid to her/his residential address on 31 December 2017. Summary statistics for the airborne pollutants are shown in online supplemental table S2.

### COVID-19 data

The Regional Health Authority collected information on patients with a diagnosis of COVID-19 from several sources: public and private hospitals (persons seen in the first aid service for an acute respiratory infection and infected inpatients, including those who received assisted ventilation); administrative healthcare data from Local Health Agencies (symptomatic outpatients receiving only home care, COVID-19 death); and laboratories accredited by the Regional Health Authority. Diagnosis was based on positive nasopharyngeal swab specimens tested with real-time reverse transcriptase/polymerase chain reaction assays targeting different genes (E, RdRp and M) of SARS-CoV-2. In the Lombardy region both symptomatic patients and asymptomatic individuals identified through contact tracing were tested. In the current study we considered all COVID-19 cases with onset date between 25 February 2020 and 13 March 2021 in the study sample, as described above. According to official statistics (<https://vaccinocovid.wired.it/vaccinazioni-per-regione.html>, last accessed on 23 September 2021), only 3.5% of the population in the entire region were fully vaccinated by the end of the observation period.

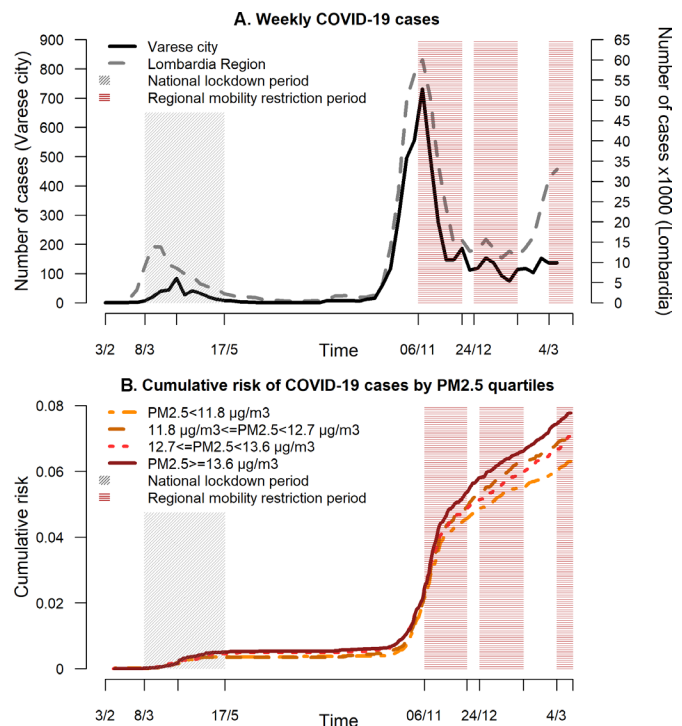
### Demographic, residential and clinical characteristics

Information on demographic, residential and clinical characteristics were derived from relevant regional databases and referred to 31 December 2019 as the index date. These included age, gender, living in a residential care home and population density in four classes with cut-off points of 736 (city average/2), 1470

(city average) and 2940 ( $2\times$ city average) inhabitants/km<sup>2</sup>. Drug medications were traced from the relevant regional healthcare database, with use defined as at least one prescription during the year 2019. We defined the following major treatment categories using the Anatomical Therapeutic Chemical classification (ATC) code: diabetes (including oral antidiabetic drugs and insulin; ATC A10); antihypertensives (ATC: C02, C03, C07, C08 e C09); lipid-lowering drugs (ATC C10); and drugs for respiratory diseases (including long-acting and short-acting bronchodilator inhalers, inhaled corticosteroids and other medications; ATC R03). A history of comorbidities was defined as at least one hospital discharge record between 2015 and 2019 with the following discharge diagnosis (any field out of available six, ICD-9 code): coronary heart disease (410.x–414.x), stroke (430.x–438.x), cancer (140.x–208.x) and COPD and allied conditions (490.x–496.x).

### Statistical analysis

A total of 79 462 (97.4%) of the 81543 residents in the city of Varese on 31 December 2017 were linked to average yearly aerial pollutant exposure data during 2018. We further excluded 6944 subjects who were no longer residents in Varese on 31 December 2019, considered the index date for the beginning of the COVID-19 at-risk period; 227 subjects living in residential care home settings outside Varese; and 9443 residents aged <18 years, leaving a final sample size of 62848 adults. Each individual contributed to follow-up until the onset date of confirmed COVID-19, death due to any cause, residency change outside Varese or 13 March 2021, whichever came first. To assess completeness of case ascertainment in our sample we compared the trend in the weekly number of COVID-19 cases in our data with the weekly number of cases in the Lombardy region, as available on the data repository operated by the Johns Hopkins University Centre for Systems Science and Engineering (JHU CSSE; <https://github.com/CSSEGISandData/COVID-19>). We first investigated the association between demographic and clinical features with the COVID-19 incidence rate using a Poisson regression model to select potential confounders. Then, in single- and bi-pollutant Poisson regression models with follow-up time as the offset variable, we estimated the rate ratio (RR) (with robust SE estimates for the 95% confidence intervals) due to an increase in 1 µg/m<sup>3</sup> in the investigated pollutants adjusting for age, gender and living in a residential care home (Model 1), and further adding a positive history of stroke and medications for diabetes, hypertension and obstructive airway diseases (Model 2). From Model 2 we also estimated the additional number of COVID-19 cases (per 100 000 person-years) above the average rate due to an increase in 1 µg/m<sup>3</sup> in airborne pollutants.<sup>18</sup> To address residual confounding due to socioeconomic conditions and mobility, in sensitivity analyses we added area-based census indicators of low socioeconomic status and use of public transportation for daily commuting to Model 2. The details and results are reported in the online supplemental material. We also performed computation of the E-value as a measure of the strength a hypothetical unmeasured confounder should have on both the exposure and the outcome to nullify the observed point estimate of the association of interest.<sup>19</sup> In further analysis, we excluded individuals living in residential care homes. We also estimated the cumulative incidence risk of COVID-19 by PM<sub>2.5</sub> exposure quartiles (11.8, 12.7 and 13.6 µg/m<sup>3</sup> for 25th, 50th and 75th percentiles, respectively) using a Kaplan–Meier test to describe the time dynamic of the effect of airborne pollutants on the progression of the epidemic. We further explored seasonality



**Figure 1** (A) Weekly number of COVID-19 cases in the city of Varese and in the Lombardy region and (B) cumulative incidence curves of COVID-19 cases in the city of Varese according to annual mean quartiles of PM<sub>2.5</sub>. National lockdown and regional mobility restriction periods are indicated as shaded areas. The national lockdown period lasted from 8 March to 17 May 2020. There were no mobility restrictions from May to October 2020. Thereafter, intermittent periods at different levels of mobility restrictions were in place from November 2020 to March 2021 in the Lombardy region, but these were not as stringent as during the national lockdown.

by replacing the annual with the seasonal average exposure to airborne pollutants, and tested the heterogeneity of the effect of the pollutants using I<sup>2</sup> and Cochran's Q test statistics as estimated from a random-effect meta-analysis model. Poisson regression models were repeated by cumulative pandemic periods, identifying a first wave up to 11 June 2020 for comparison with the literature and a second wave up to 31 December 2020. Finally, we investigated the effect of each pollutant in sensitive population subgroups, including age (<55, 55–64, 65–74 and ≥75 years) and gender groups and the presence of chronic conditions and use of medications. We formally tested the null hypothesis of homogeneity of effect across subgroups by adding appropriate subgroup × pollutant interaction terms to the Poisson models. We used SAS 9.4 release for the analyses and R version 3.6.3 for pictures.

### RESULTS

In the current study the 2018 annual mean PM<sub>2.5</sub> and NO<sub>2</sub> values were 12.5 and 20.1 µg/m<sup>3</sup>, respectively. The corresponding population-weighted average annual mean exposures in Italy in the same year were 15.5 and 20.1 µg/m<sup>3</sup>, respectively.<sup>3</sup> We observed 4408 COVID-19 cases, corresponding to a rate of 6005 cases per 100 000 person-years. The weekly number of cases in the city of Varese closely followed the regional trends (figure 1A), except for a delay in the first outbreak of the disease in March 2020. Of note, the first Italian case was observed in a different area of the Lombardy region on 21 February 2020. The steep rise in regional cases during February 2021, which led

**Table 1** Association of demographic and clinical characteristics of the study sample with COVID-19 case status

	Non-COVID-19 case	COVID-19 case	RR* (95% CI)
N	58440	4408	–
Person-years	69491.3	3909.1	–
Age, years	54.6 (19.4)	53.2 (20.0)	0.92 (0.91 to 0.94)†
Men, n (%)	27355 (46.8%)	2011 (45.6%)	0.96 (0.91 to 1.02)
Living in a residential care home, n (%)	247 (0.4%)	160 (3.6%)	10.6 (9.0 to 12.4)
Population density, persons/km <sup>2</sup> , n (%)			
<735 persons/km <sup>2</sup>	6494 (11.1%)	472 (10.7%)	Reference
736–1739 persons/km <sup>2</sup>	4650 (8.0%)	333 (7.8%)	0.99 (0.86 to 1.14)
1740–2939 persons/km <sup>2</sup>	11925 (20.4%)	940 (21.3%)	1.06 (0.95 to 1.19)
>2940 persons/km <sup>2</sup>	35371 (60.5%)	2663 (60.4%)	1.00 (0.91 to 1.11)
History of drug treatment, n (%)‡			
Diabetes	3238 (5.6%)	257 (5.8%)	1.17 (1.03 to 1.34)
Antihypertensive	17358 (29.7%)	1231 (27.9%)	1.12 (1.03 to 1.21)
Lipid-lowering	8432 (14.4%)	568 (12.9%)	0.94 (0.84 to 1.04)
Treatment for obstructive airway diseases	4816 (8.2%)	402 (9.1%)	1.17 (1.05 to 1.30)
Positive history, n (%)§			
Coronary heart disease	1105 (1.9%)	88 (2.0%)	1.07 (0.86 to 1.33)
Stroke	1017 (1.7%)	118 (2.7%)	1.29 (1.07 to 1.56)
Cancer	1771 (3.0%)	130 (3.0%)	1.07 (0.90 to 1.27)
COPD	591 (1.0%)	57 (1.3%)	1.05 (0.81 to 1.36)

\*Rate ratio (RR) from Poisson regression model.

†Rate ratio (RR) for 10-year increase in age.

‡At least one prescription during the year 2019. ATC classes: diabetes (A10); antihypertensive (C02, C03, C07, C08, C09); lipid-lowering (C10); treatment for obstructive airway diseases (R03).

§At least one hospital discharge record between 1 January 2015 and 31 December 2019. ICD-9 codes: coronary heart disease (410–414); stroke (430–438); cancer (140–208); chronic obstructive pulmonary disease (490–496).

to a regional lockdown beginning on 4 March 2021, was mainly due to the Brescia and Como Provinces rather than to the Varese area.

The association between demographic and clinical characteristics of individuals with the incidence of COVID-19 is shown in table 1. The median age at COVID-19 onset was 53 years, varying from a peak of 83 years in early April 2020 to a low of 22 years in early September 2020, in line with national trends. Overall, age was associated with a lower rate of infectivity. Living in a residential care home was associated with an increased incidence (RR 10.6, 95% CI 9.0 to 12.4). Use of medication for diabetes, hypertension and obstructive airway diseases as well as a history of stroke were associated with a 17%, 12%, 17% and 29% increase in the COVID-19 rate, respectively. Of note, population density was not associated with infectivity, as in other studies.<sup>6</sup>

After adjustment for age, gender and living in a residential care home, both PM<sub>2.5</sub> (RR for 1 µg/m<sup>3</sup> increase 1.051, 95% CI 1.027 to 1.076) and PM<sub>10</sub> (RR 1.040, 95% CI 1.021 to 1.060) were significantly associated with increased COVID-19 rate (table 2). Inspection of the cumulative risk curve for PM<sub>2.5</sub> (figure 1B) suggested an increased risk for one interquartile range (delta cumulative risk for PM<sub>2.5</sub><11.8 vs PM<sub>2.5</sub>>13.6 µg/m<sup>3</sup>: 1.5%), corresponding with downward trend periods in the pandemic curve represented by the weekly number of cases (figure 1A) and during restricted mobility periods due to national or regional regulations. The association was only slightly weaker for nitrogen oxides (NO<sub>2</sub>: RR 1.020, 95% CI 1.009 to 1.030; NO: RR 1.041, 95% CI 1.014 to 1.068). An increase in O<sub>3</sub> was associated with a 2% decrease in the rate of COVID-19. Further adjustments for medication use and chronic conditions did not substantially modify these figures. Finally, when adding

**Table 2** Association between annual mean levels of air pollutants and COVID-19 incidence rate, and estimated number of additional COVID-19 cases due to air pollution, in single-pollutant models

Air pollutant	Model 1		Model 2		Cases*	95% CI
	RR	95% CI	RR	95% CI		
PM <sub>2.5</sub>	1.051	1.027 to 1.076	1.051	1.027 to 1.075	294.1	152.7 to 435.5
PM <sub>10</sub>	1.040	1.021 to 1.060	1.040	1.020 to 1.060	230.9	115.6 to 346.1
NO <sub>2</sub>	1.020	1.009 to 1.030	1.020	1.009 to 1.030	113.1	51.7 to 174.5
NO	1.041	1.014 to 1.068	1.040	1.013 to 1.068	235.5	70.6 to 400.4
O <sub>3</sub>	0.980	0.970 to 0.990	0.980	0.970 to 0.990	–115.0	–174.0 to –57.0

Rate ratios (RRs) per 1 µg/m<sup>3</sup> increase in the annual average exposure to each pollutant estimated from Poisson regression models.

Model 1: single pollutants, adjusting for age, sex and living in a residential care home.

Model 2: Model 1 + positive history of stroke, treatment for diabetes, antihypertensive treatment and treatment for obstructive airway diseases.

\*Number of cases per 100 000 person-years due to 1 µg/m<sup>3</sup> increase in the pollutant above its mean value, estimated at the mean values of the confounders.

**Table 3** Association between annual mean levels of air pollutants and COVID-19 incidence rate by cumulative infection waves in single-pollutant models

Air pollutant	First wave		Second wave		Third wave	
	RR	95% CI	RR	95% CI	RR	95% CI
PM <sub>2.5</sub>	1.074	0.978 to 1.179	1.029	1.002 to 1.056	1.051	1.027 to 1.075
PM <sub>10</sub>	1.064	0.985 to 1.149	1.023	1.001 to 1.045	1.040	1.020 to 1.060
NO <sub>2</sub>	1.034	0.991 to 1.080	1.010	0.999 to 1.022	1.020	1.009 to 1.030
NO	1.094	0.980 to 1.221	1.022	0.991 to 1.053	1.040	1.013 to 1.068
O <sub>3</sub>	0.974	0.935 to 1.016	0.990	0.978 to 1.001	0.980	0.970 to 0.990

Rate ratios (RR) per 1 µg/m<sup>3</sup> increase in the annual average exposure to each pollutant estimated from Poisson regression model. Covariates in the model are: age, sex, living in a residential care home, positive history of stroke, treatment for diabetes, antihypertensive treatment and treatment for obstructive airway diseases.

First wave from COVID-19 outbreak to 11 June 2020; second wave from COVID-19 outbreak to 31 December 2020; third wave from COVID-19 outbreak to 13 March 2021 (end of observational period).

area-based census indicators of socioeconomic condition and use of public transportation for daily commuting (see online supplemental tables S3–S5 for description), the point estimate for PM<sub>2.5</sub> was attenuated to 1.036 (95% CI 1.009 to 1.064; online supplemental table S6). The E-value suggested that the PM<sub>2.5</sub> model was the most robust to unmeasured confounding. Any unmeasured confounder should have an association of 1.23 and 1.11 (on a multiplicative scale) with both exposure and the outcome to nullify the observed RR point estimate and lower bound of the 95% CI, respectively.

The estimated RRs were consistent when we considered seasonal rather than annual averages of exposure, with p values for the Cochran's Q test statistics >0.05 for all the investigated pollutants (see online supplemental table S7). In bi-pollutant models, the association between PM<sub>2.5</sub> and COVID-19 persisted independently of nitrogen (di)oxide or O<sub>3</sub> (online supplemental table S8). Conversely, the negative association between O<sub>3</sub> and COVID-19 reversed its sign when either PM<sub>2.5</sub> or PM<sub>10</sub> were included in the model.

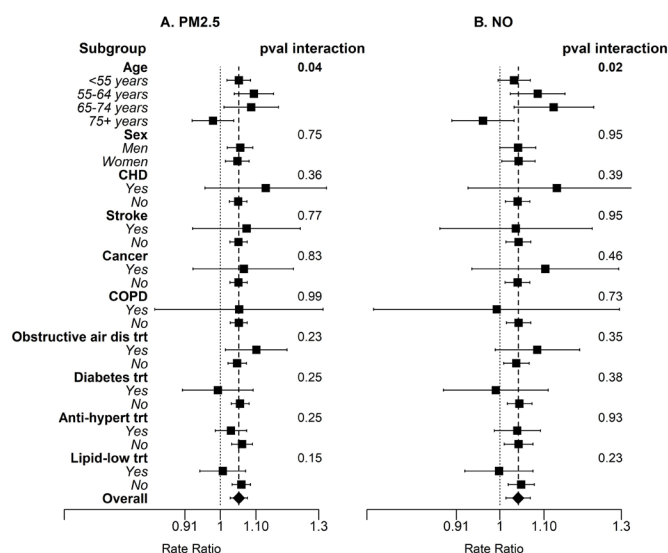
On an absolute scale, the additional number of COVID-19 cases per 100 000 person-years attributed to an increase of 1 µg/m<sup>3</sup> in airborne pollutants ranged between 231 and 294 for PM<sub>10</sub> and PM<sub>2.5</sub>, respectively, and from 113 and 236 for NO<sub>2</sub> and NO, respectively (table 2). In sensitivity analyses, after the exclusion of residents of long-term care facilities, RRs and rate differences were substantially confirmed and remained statistically significant (online supplemental table S9).

RRs across different pandemic waves (table 3) suggested that the association between airborne pollutants and the incidence of COVID-19 was quite consistent over time. For example, for PM<sub>2.5</sub> the RRs were 1.074, 1.029 and 1.051 for the first, second and third pandemic periods, respectively, with overlapping confidence intervals to suggest homogeneity of effects over time. Similar figures were observed for the remaining pollutants.

Finally, figure 2 reports the RRs for a 1 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> and NO across population subgroups (age and gender groups) and presence of clinical conditions. We observed a significant interaction with age (Wald  $\chi^2$  test p=0.04 and p=0.02 for PM<sub>2.5</sub> and NO, respectively), indicating a stronger effect of pollutants on the COVID-19 rate in the 55–64 and 65–74 year age groups. RRs were homogeneous for use of medications or presence of chronic conditions (all p values for interaction tests >0.05), although the low statistical power (illustrated by the wide confidence intervals) due to the reduced number of individuals with chronic conditions should be acknowledged.

## DISCUSSION

The current literature on outdoor air pollution and COVID-19 is characterised by both an increased number of studies<sup>5 20</sup> and by serious concerns on sources of substantial bias, including the ecological study design, misclassification of air pollution exposure and lack of appropriate control of potential confounders.<sup>21</sup> In addition, all evidence comes from the first pandemic wave up to June 2020.<sup>5 20</sup> Our study, based on individual-level data for ambient air pollution exposure, COVID-19 diagnosis up to March 2021 and demographic and clinical confounders, overcomes most of these methodological concerns. Among adult residents in the city of Varese we observed a 5.1% increase in the incidence rate of COVID-19 for an increase of 1 µg/m<sup>3</sup> in long-term exposure to PM<sub>2.5</sub>, corresponding on an absolute scale to 294 additional cases per 100 000 person-years, adjusting for relevant demographic and clinical characteristics. The increased RR of PM<sub>2.5</sub> was confirmed by a number of sensitivity analyses, including bi-pollutant models and using seasonal rather than annual average, and after excluding potential case clusters



**Figure 2** Association between 1 µg/m<sup>3</sup> increase in (A) PM<sub>2.5</sub> and (B) NO with COVID-19 incidence rate by population subgroups and p value testing the interaction between PM<sub>2.5</sub> and NO with the subgroup. The rate ratios and 95% CIs in the Forest plot were estimated from Poisson regression model per 1 µg/m<sup>3</sup> increase in the annual average exposure to each pollutant, including the interaction terms between subgroup and air pollution and adjusting for the covariates as in Model 2 (table 2). The overall estimate (diamond) is the same as reported in Model 2 (table 2).

among individuals living in residential care structures. Our point estimate is slightly weaker than the 12% increased odds of COVID-19 infectivity observed by another individual-level analysis in England,<sup>6</sup> although this figure refers to the first pandemic period up to April 2020. Of note, we observed a reduction in our estimates from 7.4% to 5.1% when extending the observational period from June 2020 to March 2021, thus suggesting that the different timing on the pandemic curve should be taken into account in between-study comparisons.<sup>21</sup> We further observed a 2–4% increased rate of COVID-19 attributed to an increase of  $1 \mu\text{g}/\text{m}^3$  in  $\text{PM}_{10}$ , NO and  $\text{NO}_2$ . Conversely,  $\text{O}_3$  was associated with a 2% decrease in disease rate. This finding is in agreement with previous observations<sup>6</sup> and it aligns with the notion of a reduced NO conversion to  $\text{O}_3$  in urban areas at heavy traffic,<sup>22</sup> the setting of our study. Actually, bi-pollutant models including NO and PM reduced or even reversed the  $\text{O}_3$  association with the disease, respectively. In addition, NO conversion to  $\text{O}_3$  needs solar radiation, which itself has a negative impact on the SARS-CoV-2 virus.<sup>23</sup> A recent review suggested the potential role of  $\text{O}_3$  in inactivating seasonal influenza viruses<sup>24</sup> and also the SARS-CoV-2 virus.<sup>25</sup> These observations, together with the results of cohort studies conducted in Belgium and Sweden,<sup>26,27</sup> support the notion that the detrimental role of  $\text{O}_3$  exposure on health might be less established than for other airborne pollutants.

Several factors combined with air pollution, including socioeconomic deprivation and urban mobility through public transportation, may play a role in increasing the incidence of COVID-19<sup>28,29</sup> and offer alternative explanations to a causal exposure–outcome relationship. In our study the addition in sensitivity models of two area-based indicators of low socioeconomic level and use of public transportation for daily commuting accounted for about 29% of the observed association between  $\text{PM}_{2.5}$  and the incidence of COVID-19 which, however, remained statistically significant. We cannot rule out residual confounding due to lack of socioeconomic and mobility information at an individual level or due to modifications during the pandemic period in social behaviours, workplace conditions and use of private over public transportation, differential to socioeconomic class and hence to air pollution exposure. We computed the E-value as a measure of the strength a hypothetical unmeasured confounder should have with both the exposure and the outcome—in addition to covariates already included in the model—to fully account for the results we report.

The association between air pollutants and the incidence rate of COVID-19 was quite homogeneous across frail population subgroups. Several reasons may be advocated for this finding, including the homogeneity of exposure in an urban setting, the lack of statistical power due to a low number of people with a specific chronic condition and—for the oldest—a combination of social isolation, lower exposure to outdoor pollution and the earlier effects of the vaccination plan. Although not statistically significant, the larger than average excess COVID-19 infection rate we observed in people with previous chronic heart disease, cancer or receiving medication for obstructive airway diseases warrants future investigations in larger studies. Then, all considered, our study aligns well with the current epidemiological view linking long-term exposure to airborne pollutants with the incidence of SARS-CoV-2 through an increased susceptibility mechanism.<sup>30</sup>

Our assessment of the cumulative risk curve in conjunction with the temporal pandemic period adds new elements to the existing knowledge. The COVID-19 cumulative incidence risk connected to long-term exposure to airborne pollutants suggests that outdoor pollution can sustain the disease rate after its

temporal peak and irrespective of national or regional quarantine/lockdown periods. This implies a specific mechanism of action with respect to factors more directly involved during the acute rise of the pandemic curve. In support of this hypothesis, in a multi-city study in China population mobility had a 1-day lagged effect on COVID-19 spread, while particulate matter consistently increased the COVID-19 risk after an 8-day lag period.<sup>31</sup> Furthermore, quarantine/lockdown periods have a short-term and heterogeneous impact on reducing long-term pollutant levels in the urban settings.<sup>7,32</sup> In Milan, the largest city in the Po valley 60 km away from the study city of Varese, the 2020 average concentration of PM and  $\text{NO}_2$  did not decrease compared with the previous year, also due to an increased use of private over public transportation.<sup>33</sup> One study in the UK also concluded that  $\text{PM}_{2.5}$  concentrations were less affected by transportation changes during the lockdowns than the  $\text{NO}_2$  concentrations, partly due to the different emission sources between the two pollutants.<sup>34</sup> Although there is growing optimism on the future of the pandemic stage at least in most industrialised countries, the perspective under which SARS-CoV-2 becomes endemic in the population is considered as a ‘real’ one by scientists.<sup>35</sup> Under this scenario, our results imply a higher disease pressure in the most polluted areas, which already experience a higher burden of non-communicable diseases due to the same exposures.<sup>36–38</sup>

### Strengths and weaknesses

The strengths of this study are related to the study design and the availability of a variety of individual-level data on exposure, COVID-19 diagnosis and potential confounders. We acknowledge the following study weaknesses on exposure, outcome and residual confounding. The main findings are based on 1-year exposure and on single-pollutant models. Although we report bi-pollutant models in the online supplemental material, their interpretation requires caution due to collinearity in exposures. We lack data on indoor air pollution; however, during the lockdown periods some authors found a high indoor–outdoor correlation in Italy due to particle penetration from outside in conjunction with inadequate ventilation.<sup>39</sup> The diagnosis of COVID-19 cases followed the regional indications for being referred to a nasopharyngeal swab which were subject to modifications over time, especially during the first months after the pandemic outbreak.<sup>2</sup> However, we report consistent associations across different pandemic waves. We focused on the association between pollutants and COVID-19 cases only because the low number of COVID-19 deaths (resulting in non-precise estimates and low statistical power) and the limited clinical information on COVID-19 hospitalised cases that was available at the time of planning the analyses prevented us from considering further hypotheses on severity of disease. As many observational studies, our associations require a cautious interpretation in causal terms as they are exposed to residual confounding. Although we considered a variety of potential confounders, we were not able to take into account the potential role of mobility, social interaction, humidity and temperature on the pandemic dynamics. In addition, we did not consider some comorbidities (eg, renal diseases, mental health condition/substance abuse) as individuals with these conditions are more likely to receive outpatient care, and hence are poorly detectable from the available Regional Health System hospital records. Due to the specific features of SARS-CoV-2 infection in the paediatric population compared with adults,<sup>40</sup> we restricted the analysis to residents aged  $\geq 18$  years. Future studies are needed to investigate the role of air

pollution in disease susceptibility at younger ages. Finally, future studies are required to generalise our findings to wider non-urban settings.

## CONCLUSION

In the city of Varese an increase in exposure to long-term airborne pollutants of  $1\mu\text{g}/\text{m}^3$  is associated with a 2–5% increase in the rate of COVID-19 incidence up to March 2021 and after adjustment for demographic and clinical confounders measured at an individual level. Ambient pollutants may sustain the SARS-CoV-2 infectivity also after the pandemic period, thus exacerbating the already unfavourable health profile among the population living in more polluted areas. Causality warrants confirmation in future studies; meanwhile, government efforts to further reduce air pollution should continue.<sup>7</sup>

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