Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome: a longitudinal study

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To the Editor:

Chronic exposure to ambient air pollution has been related to increased mortality in the general population [1]. After the outbreak of the SARS-CoV-2 pandemic in 2019, there has been a fast proliferation of epidemiological studies linking ambient air pollution to coronavirus disease 2019 (COVID-19) incidence or adverse prognosis [2]. It has been hypothesised that ambient air pollution might increase human vulnerability to viruses by reducing immune defences, promoting a low-level chronic inflammatory state, or leading to chronic diseases [3]. Most studies have applied ecological designs, and failed to account for key individual-level or area-level determinants of COVID-19 spread or severity, such as demographic characteristics of the studied populations, socioeconomic or clinical susceptibility, and area-level proxies of disease spread such as mobility or population density [4].

In this study we aimed to investigate the association between chronic exposure to air pollution and SARS-CoV-2 incidence and COVID-19 mortality, independent from age, sex, individual-level and area-level socioeconomic deprivation, clinical history and neighbourhood characteristics.

All subjects aged ⩾30 years resident in Rome, Italy, at 1 January 2020 were followed-up until 15 April 2021 through record linkage between the different administrative archives of the Lazio Region Health Information System: population and mortality registries, 2011 Census data, and COVID-19 surveillance system. The COVID-19 integrated surveillance system collects all the new confirmed SARS-CoV-2 infections reported to the Regional Service for Surveillance of Infectious Diseases throughout the Lazio Region. Each subject entered at baseline and was observed until death, emigration out of the study area or end of follow-up, whichever came first. For each subject, baseline information was available on demographic characteristics (age, sex, marital status, place of birth), socioeconomic indicators (education level, occupational status, census block-level deprivation), clinical history (a list of 67 prevalent conditions based on past 5-year hospitalisations and drug prescriptions), neighbourhood characteristics (housing prices, unemployment rate, education level), and geographical coordinates of the residential address. Three study outcomes were defined: incidence of SARS-CoV-2 infection (newly identified cases based on a positive test through RT-PCR), COVID-19 mortality (deaths within 30 days from infection), and non-COVID-19 mortality (deaths among non-cases, or after 30 days since infection). Annual average concentrations of particulate matter smaller than 2.5 µm ($PM_{2.5}$) and nitrogen dioxide (NO_2) were estimated for 2019 at 1-km^2 spatial resolution for the entire Italian territory, using a machine learning spatiotemporal model which incorporated data from existing air quality monitoring networks, satellite images, atmospheric models, land-use and population characteristics [5].

We applied Cox proportional hazard models with adjustment for individual- and area-level covariates. These include: calendar time (as time axis); demographic variables (age in five classes: 30–54, 55–64, 65–74, 75–84, ⩾85 years; sex; marital status; place of birth; nationality); socioeconomic indicators (education level, occupational status and census block-level deprivation index); pre-existing chronic conditions (number of any conditions out of a list of 67 diseases, and six specific diseases); and neighbourhood-level characteristics. The latter were adjusted differently for incidence (a strata term for the 155 districts in Rome) or mortality outcomes (housing prices, unemployment rate and % university degree at the district level). We operated this choice because we assumed that factors related to viral spread in the general

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Long-term exposure to air pollution ($PM_{2.5}$ and NO_2) was associated with COVID-19 mortality, but not with SARS-CoV-2 incidence, in a large observational population-based cohort of >1.5 million subjects in Rome, Italy https://bit.ly/3zZjjSC

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population (person-to-person contacts, individual mobility, *etc*.) were better accounted for by assuming different baseline rates for each neighbourhood. Instead, socioeconomic characteristics of the residential neighbourhood could adequately adjust for spatially heterogenous susceptibility of the study population. Next, we added each exposure in turn ($PM_{2.5}$ or NO_2) as a linear term, and expressed all estimates as hazard ratios and 95% confidence intervals, of the study outcomes, per increments in the exposures equal to their interquartile ranges (IQRs).

We conducted a number of additional/sensitivity analyses: we defined three pandemic waves consistent with the viral spread in Rome (February–September 2020, October–December 2020, January–April 2021) and estimated wave-specific effects of air pollutants using time-varying models; we replaced the strata term for districts with population density in the adjustment model for SARS-CoV-2 incidence; we dropped the pre-existing conditions from the adjusted model, under the assumption that these might act as mediators, rather than confounders, of the studied associations; we adjusted for district-level rates of diabetes, COPD and lung cancer as proxies for BMI and smoking; we analysed COVID-19 hospitalisations and intensive care units as alternative outcomes of COVID-19 severity; finally, we estimated the exposure–response functions between the air pollutants and the study outcomes by modelling air pollutants with natural splines.

Descriptive statistics and results are displayed in table 1. We enrolled 1 594 308 subjects, with a mean±SD follow up of 461±48 days. Of these, 79 976 individuals were infected with SARS-CoV-2, 2656 died within 30 days from infection, and 1002 died after 30 days from infection. 31 563 individuals died without ever being diagnosed with COVID-19 during the follow-up. The average air pollution exposures at the baseline were: 14.63 $\mu g \cdot m^{-3}$ for $PM_{2.5}$ (IQR 0.92 $\mu g \cdot m^{-3}$) and 31.45 $\mu g \cdot m^{-3}$ for NO_2 (IQR 9.22 $\mu g \cdot m^{-3}$). Infection incidence rates, and hazard ratios from the fully adjusted model, were highest among younger subjects, students or employed people, those with higher socioeconomic deprivation and in neighbourhoods with lowest housing prices. COVID-19 mortality rates and hazard ratios substantially increased with age and number of pre-existing chronic conditions, and were higher among males, subjects with poor education and highest deprivation, or among patients with pre-existing renal failure, heart failure, ischaemic heart disease, COPD, type 2 diabetes or cancer. Similar patterns emerged for non-COVID-19 mortality, although with reduced differentials by sex and socioeconomic deprivation.

Table 1 reports the results of the association between $PM_{2.5}$ and NO_2 with the three study outcomes in the fully adjusted model. We found no association between air pollution and SARS-CoV-2 incidence: IQR increments in $PM_{2.5}$ and NO_2 were associated with hazard ratios of 1.01 (95% CI 0.99–1.03) and 1.00 (95% CI 0.98–1.02), respectively. In contrast, we estimated strong associations between the two air pollutants and COVID-19 mortality: IQR increments in $PM_{2.5}$ and NO_2 were associated with hazard ratios of 1.08 (95% CI 1.03–1.13) and 1.09 (95% CI 1.02–1.16). The association between air pollutants and non-COVID-19 mortality was comparatively smaller than the one with COVID-19 mortality: we estimated hazard ratios of 1.01 (95% CI 1.00–1.02) and 1.02 (95% CI 1.00–1.04) per IQR increments in $PM_{2.5}$ and NO_2, respectively. The results of the additional/sensitivity analyses confirm the main findings: associations were unaffected by alternative adjustment models, they did not differ substantially by pandemic wave, and were significant with hospital admissions but not with accesses to intensive care units. Finally, the exposure–response functions were consistent with flat associations between the two air pollutants and SARS-CoV-2 incidence, while associations with mortality outcomes were approximately linear, and much steeper for COVID-19 mortality (data not shown).To date, few studies have investigated the relationship between air pollution and COVID-19-related outcomes in population-based longitudinal studies. Chadeau-Hyam *et al*. [6] and Elliott *et al*. [7] linked COVID-19 data and mortality records to the UK Biobank and found no association between residential $PM_{2.5}$ exposure and either positive testing to SARS-CoV-2 or COVID-19 mortality, after multivariate adjustment for individual and area-level risk factors. Similarly, no association between air pollutants and SARS-CoV-2 positive testing was detected in the COVICAT cohort of Catalonia, Spain, although a statistically significant association was estimated with severe COVID-19 disease among infected patients [8]. No association between $PM_{2.5}$ or NO_2 and mortality was found in a prospective longitudinal study conducted in Ontario, Canada, while significant associations were estimated with hospitalisations and accesses to intensive care units [9]. In contrast, positive associations between $PM_{2.5}$ exposure and COVID-19 incidence were estimated in northern Italy [10] and southern California [11].

Our estimates of association between air pollutants and COVID-19 mortality are similar to those found in previous large ecological studies [2, 12], and much higher than those usually found with natural-cause mortality in the general population [1, 13]. Several mechanisms have been proposed as responsible for an enhanced severity of COVID-19 in combination with exposure to air pollution. First, air pollution-induced inflammation may amplify inflammation due to COVID-19 and lead to adverse health outcomes, including

TABLE 1 Population characteristics, study outcomes, and associations between individual covariates, exposure and the study outcomes in the fully adjusted model

	Study population (n=1 594 308)		Incident cases (n=79 976)				COVID-19 deaths (n=2656)				Non-COVID-19 deaths (n=32 565)			
	N	%	Rate per 1000 person-years	HR	95% CI		Rate per 1000 person-years	HR	95% CI		Rate per 1000 person-years	HR	95% CI	
Demographic variables														
Age (years)														
30–54	699 791	43.9	47.1	1.00	–	–	0.09	1.00	–	–	1.19	1.00	–	–
55–64	332 651	20.9	41.1	0.84	0.82	0.85	0.46	3.76	2.89	4.90	4.57	2.95	2.74	3.19
65–74	260 430	16.3	30.2	0.62	0.60	0.64	1.55	8.93	6.93	11.53	13.42	5.74	5.33	6.18
75–84	208 644	13.1	28.3	0.59	0.57	0.61	3.79	16.85	12.92	21.99	38.65	11.81	10.94	12.75
⩾85	92 792	5.8	31.3	0.67	0.64	0.71	8.05	34.94	26.61	45.90	136.02	37.51	34.71	40.54
Sex														
Male	715 610	44.9	42.3	1.00	–	–	1.76	1.00	–	–	16.56	1.00	–	–
Female	878 698	55.1	37.8	0.94	0.92	0.95	0.96	0.46	0.43	0.51	15.55	0.81	0.79	0.83
Marital status														
Single	724 491	45.4	39.6	1.00	–	–	1.32	1.00	–	–	16.15	1.00	–	–
Married	682 340	42.8	40.0	1.01	0.99	1.02	1.32	1.02	0.94	1.11	15.63	1.00	0.97	1.02
Separated/divorced	67 373	4.2	39.3	1.00	0.96	1.03	1.30	0.95	0.79	1.16	17.22	1.05	1.00	1.11
Widowed	120 104	7.5	39.8	1.00	0.98	1.03	1.29	0.96	0.82	1.12	16.58	1.02	0.97	1.06
Born in Rome														
Yes	940 690	59.0	39.7	1.00	–	–	1.29	1.00	–	–	15.67	1.00	–	–
No	653 618	41.0	40.0	0.99	0.97	1.00	1.35	0.99	0.91	1.08	16.49	1.00	0.98	1.03
Italian nationality														
Yes	1 380 875	86.6	39.8	1.00	–	–	1.31	1.00	–	–	15.83	1.00	–	–
No	213 433	13.4	39.8	1.00	0.98	1.02	1.37	1.04	0.92	1.18	17.18	1.01	0.98	1.05
Socioeconomic variables														
Level of education														
Primary or less	195 587	12.3	35.5	1.00	–	–	4.40	1.00	–	–	54.72	1.00	–	–
Middle school	350 961	22.0	42.1	0.95	0.93	0.98	1.49	0.85	0.77	0.94	17.12	0.93	0.91	0.96
High school	652 376	40.9	41.9	0.93	0.91	0.96	0.77	0.77	0.69	0.86	9.13	0.84	0.82	0.87
University or more	395 384	24.8	36.4	0.86	0.83	0.88	0.60	0.65	0.56	0.75	7.78	0.77	0.74	0.80
Employment status														
Employed	891 706	55.9	44.7	1.00	–	–	0.40	1.00	–	–	3.62	1.00	–	–
Searching for first employment	18 999	1.2	39.1	0.80	0.75	0.85	0.17	0.80	0.30	2.15	2.53	1.27	0.99	1.64
Unemployed	59 121	3.7	39.3	0.81	0.78	0.84	0.36	1.17	0.79	1.73	3.73	1.39	1.23	1.57
Retired	317 698	19.9	28.9	0.82	0.80	0.85	4.24	1.21	1.05	1.39	53.43	1.43	1.36	1.49
Student	40 097	2.5	42.7	0.94	0.90	0.98	0.10	0.86	0.35	2.09	1.10	0.77	0.59	1.00
Housewife	181 ,316	11.4	35.6	0.87	0.84	0.89	1.24	1.09	0.92	1.30	18.05	1.21	1.15	1.28
Other	85 371	5.4	35.7	0.82	0.79	0.84	1.95	1.42	1.18	1.69	24.85	1.71	1.62	1.80
Socioeconomic deprivation (of the census block)														
Low	338 918	21.3	34.4	1.00	–	–	1.10	1.00	–	–	16.39	1.00	–	–
Mid-low	424 703	26.6	37.0	1.01	0.99	1.03	1.30	1.16	1.03	1.30	15.92	1.02	0.99	1.05

Continued

TABLE 1 Continued

	Study population (n=1 594 308)		Incident cases (n=79 976)				COVID-19 deaths (n=2656)				Non-COVID-19 deaths (n=32 565)			
	N	%	Rate per 1000 person-years	HR	95% CI		Rate per 1000 person-years	HR	95% CI		Rate per 1000 person-years	HR	95% CI	
Medium	290 133	18.2	40.7	1.01	0.99	1.04	1.23	1.11	0.97	1.27	15.55	1.06	1.03	1.10
Mid-high	251 250	15.8	44.7	1.05	1.02	1.08	1.38	1.22	1.06	1.41	14.87	1.06	1.02	1.10
High	289 304	18.1	45.2	1.07	1.04	1.09	1.63	1.31	1.14	1.50	17.14	1.13	1.09	1.17
Pre-existing chronic conditions[#]														
Number														
0	763 781	47.9	41.6	1.00	–	–	0.24	1.00	–	–	2.80	1.00	–	–
1	348 492	21.9	39.0	1.07	1.05	1.09	1.00	1.62	1.37	1.91	11.26	1.44	1.37	1.51
2	209 386	13.1	37.0	1.12	1.09	1.15	1.70	1.74	1.47	2.06	22.37	1.65	1.57	1.73
3	121 952	7.6	35.8	1.13	1.10	1.17	2.82	2.15	1.80	2.56	34.47	1.84	1.74	1.93
⩾4	150 697	9.5	39.3	1.24	1.19	1.29	5.98	2.79	2.33	3.33	73.08	2.19	2.08	2.31
Specific conditions														
Cancer	41 985	2.6	37.9	1.06	1.01	1.11	4.13	1.47	1.27	1.70	97.84	3.47	3.37	3.58
Type 2 diabetes	101 874	6.4	40.3	1.08	1.05	1.12	4.16	1.13	1.02	1.25	43.72	1.06	1.03	1.09
Ischaemic heart disease	65 307	4.1	40.9	1.08	1.03	1.12	6.31	1.10	0.98	1.23	70.78	1.06	1.02	1.09
Heart failure	60 726	3.8	40.5	1.11	1.06	1.16	7.58	1.33	1.19	1.48	104.39	1.52	1.48	1.57
COPD	88 007	5.5	38.7	1.07	1.03	1.10	4.57	1.15	1.04	1.28	62.88	1.33	1.30	1.37
Renal failure	21 850	1.4	42.2	1.14	1.07	1.21	10.27	1.65	1.44	1.89	128.68	1.55	1.49	1.61
District-level covariates														
House prices (quintiles)														
1	338 871	21.3	49.5	–	–	–	1.23	0.85	0.66	1.10	12.14	0.94	0.87	1.01
2	330 823	20.8	43.3	–	–	–	1.45	0.79	0.63	0.98	16.24	0.94	0.89	1.00
3	300 216	18.8	38.3	–	–	–	1.47	0.86	0.70	1.05	17.65	0.98	0.93	1.04
4	314 726	19.7	34.8	–	–	–	1.24	0.84	0.72	0.98	17.18	0.99	0.94	1.03
5	309 672	19.4	31.9	–	–	–	1.20	1.00	–	–	17.21	1.00	–	–
Unemployment rate[¶] (mean, IQR)	6.5	1.8	–	–	–	–	–	1.04	0.93	1.16	–	1.02	0.99	1.05
Per cent with university degree or more[¶] (mean, IQR)	39.3	31.3	–	–	–	–	–	0.86	0.71	1.04	–	1.05	1.00	1.11
Exposures[¶]														
$PM_{2.5}$ ($\mu g \cdot m^{-3}$) (mean, IQR)	14.63	0.92	–	1.01	0.99	1.03	–	1.08	1.03	1.13	–	1.01	1.00	1.02
NO_2 ($\mu g \cdot m^{-3}$) (mean, IQR)	31.45	9.22	–	1.00	0.98	1.02	–	1.09	1.02	1.16	–	1.02	1.00	1.04

Rates are computed as ratios between numbers of outcomes and person-years, multiplied by 1000. Hazard ratios are estimated from a Cox proportional hazards model adjusted for calendar time (time axis), age (five classes), sex, marital status (for classes), place of birth, Italian nationality, education level (four classes), employment status (seven classes), census-block-level socioeconomic deprivation index (five classes), number of pre-existing conditions (five classes), presence of six specific pre-existing conditions (cancer, type-2 diabetes, ischaemic heart disease, heart failure, COPD, renal failure), and district-level characteristics. The latter are adjusted with a "strata" term for the 155 Rome districts in incidence analysis, and with three district-level covariates (house prices in five classes, % university degree or more, unemployment rate) in the mortality analyses. $PM_{2.5}$: particulate matter smaller than 2.5 µm; NO_2: nitrogen dioxide; IQR: interquartile range. [#]: pre-existing chronic conditions include a list of 67 groups of diseases based on past 5-year hospital admissions or drug prescriptions; [¶]: associations between continuous covariates (unemployment rate, per cent with university degree or more) and air pollutants with the study outcomes are expressed as hazard ratios (and 95% confidence intervals) per IQR increments. Exposures are modelled one at a time (single-pollutant models).

premature death; second, air pollution may reduce the immune response against the virus by inhibiting phagocytic function of macrophages and decreasing the T-cell response; third, chronic exposure to air pollution may induce endothelial damage and microthrombi, thus increasing the risk of cerebral damage, pulmonary embolism, and cardiac dysfunction among COVID-19 patients [14].

This study has two main limitations. First, our cohort lacks data on relevant individual-level lifestyle characteristics, such as smoking, physical activity and dietary habits, or physiological parameters, such as body mass index and cholesterol levels. While these might confer greater susceptibility to the individuals, it is however not clear to what extent they should correlate with ambient air pollution, once area-specific covariates (*e.g.* socioeconomic deprivation) are accounted for. Secondly, our COVID-19 surveillance system, especially in the early stages of the pandemic, could only identify a selected sample of all infected individuals, *e.g.* those with severe symptoms or close contacts of primary cases. The testing policy was broadened to asymptomatic primary contacts and to various screening programmes (*e.g.* ahead of hospital admission for other causes) only after the first wave, when Italy entered the transition phase and a test–track–trace strategy was adopted. Therefore, our definition of SARS-CoV-2 incidence is only partial. Again, however, there are no *a priori* reasons to believe that included and excluded cases should be different with regard to air pollutant distributions.

In conclusion, in this large longitudinal study, long-term residential exposure to air pollution was associated with increased mortality among COVID-19 patients, but not with SARS-CoV-2 incidence in the general population. Our study supports the hypothesis that chronic exposure to air pollution might increase human vulnerability to viruses, thus worsening prognosis of COVID-19 cases, while they are unlikely to increase the spread of infection in the general population.

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Authors contribution: F. Nobile, P. Michelozzi and M. Stafoggia conceived and designed the study. G. Cappai, G. Cesaroni, M. Di Martino and C. Sorge collected the data. F. Nobile analysed the data, with input from M. Stafoggia, P. Michelozzi and C. Ancona. P. Michelozzi and C. Ancona helped interpret the results. F. Nobile and M. Stafoggia drafted the manuscript, and M. Davoli, E. Nicastri, E. Girardi, A. Beccacece, P. Scognamiglio and F. Vairo critically revised it for important intellectual content. All authors read and approved the final manuscript.

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