Studi epidemiologici sugli effetti dell'inquinamento atmosferico sulla pandemia da SARS-CoV-2 in provincia di Varese

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Introduzione

Studi **prospettici con dati individuali** su associazione tra **esposizione di lungo-periodo** ad **inquinamento atmosferico** *outdoor* e **SARS-CoV-2**

Paese	Setting	Periodo	Esposizione annua $PM_{2.5}$, μg/m^3 [media±DS]	Infettività			Severità		
				$PM_{2.5}$	NO_2	O_3	$PM_{2.5}$	NO_2	O_3
Denmark	Nation-wide	Mar2020-Apr2021	7.4±0.5	**+**	**+**	**-**	**+**	**+**	**-**
UK	Nation-wide	Mar-Dic 2020	9.99±1.05	**+**	**+**	NI	+	+	NI
Netherlands	Nation-wide	Feb2020-Feb 2021	11.07±1.35	**+**	**+**	NI	**+**	**+**	NI
Italy (Varese)	Singola città	Mar2020-Mar2021	12.5±1.3	**+**	**+**	**-**	NI		
Spain (Catalonia)	Region-wide	Feb-Dic 2020	13.9±2.2	NI			**+**	**+**	**-**
Italy (Rome)	Singola città	Mar2020-Apr2021	14.6	+	+	NI	**+**	**+**	NI
Spain (Catalonia)	Region-wide	Giu-Nov2020	16.3±1.5	+	+	-	NI		

+: associazione positiva; -: association negativa; **grassetto=**significatività statistica.
Risultati da modelli single-pollutant. NI=Non Indagato. Severità: ospedalizzazioni e/o decessi

Studio sulla città di Varese, Centro EPIMED

Domande aperte

1. Effetti di interazione tra inquinanti non indagati

- Riportati per effetti acuti di PM & O_3 sulla mortalità giornaliera [Liu et al, *BMJ* 2023]
- Potrebbero spiegare eterogeneità delle stime a diversi livelli di esposizione

2. Studi su popolazioni di non-vaccinati condotti nella prima parte della pandemia (2020-primavera 2021) quando la vaccinazione di popolazione era agli esordi

- Quale effetto di inquinamento al crescere della copertura vaccinale?
- In popolazione di anziani?

Studio 1 - scopo e popolazione

Stimare la presenza di interazioni (su scala relativa e assoluta) nell'effetto di ciascun inquinante con SARS-CoV-2 endpoints

- **in aree urbane and non-urbane** [ben caratterizzate in termini di esposizione]
- **per quartili di co-esposizione ad un altro inquinante**. Coppie di interesse particolato con gas [PM_{10} & NO_2; PM_{10} & O_3]

Materiali e metodi

Coorte di tutti gli adulti (n=709,864) residenti in **provincia** di **Varese** con **dati individuali** su:

a. **Casi di SARS-CoV-2 cases, ospedalizzazioni & decessi per COVID-19** da marzo a dicembre 2020
b. **Medie annue pre-pandemia (2019)** di PM_{10}, NO_2, O_3 da FARM & random forest models – 1 Kmq di risoluzione spaziale, link tramite geo-coding dell'indirizzo di residenza
c. **Caratteristiche demografiche**, **comorbidità & trattamenti**

Deprivation index (Italian National Institute for Statistics) e **degree of urbanization (EUROSTAT classification)** disponibile a livello aggregato

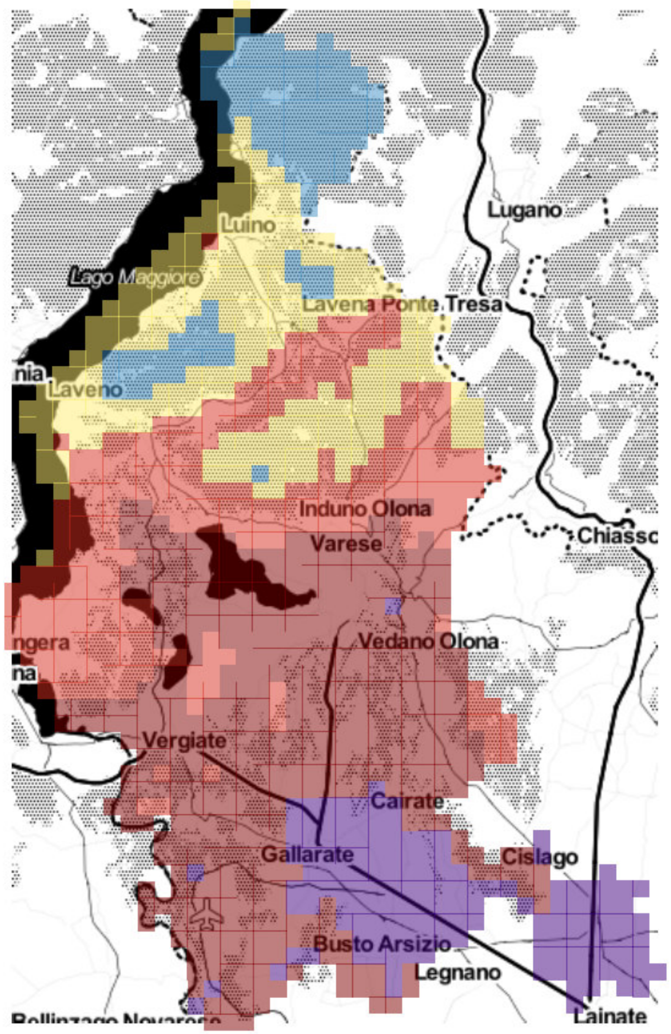
Modellizzazione delle interazioni

Single-pollutant Cox (scala relativa) o Poisson (scala additiva) regression models, aggiustati per le covariate, con termini di **interazione** tra ciascun inquinante e:

a. **Urbanizzazione** (urban vs. non-urban)
b. **per quartili di co-esposizione ad un altro inquinante**.
   Coppie di interesse: particolato con gas [PM_{10} & NO_2; PM_{10} & O_3]

Risultati

Caratterizzazione dell’inquinamento atmosferico in aree **urbane e non-urbane**



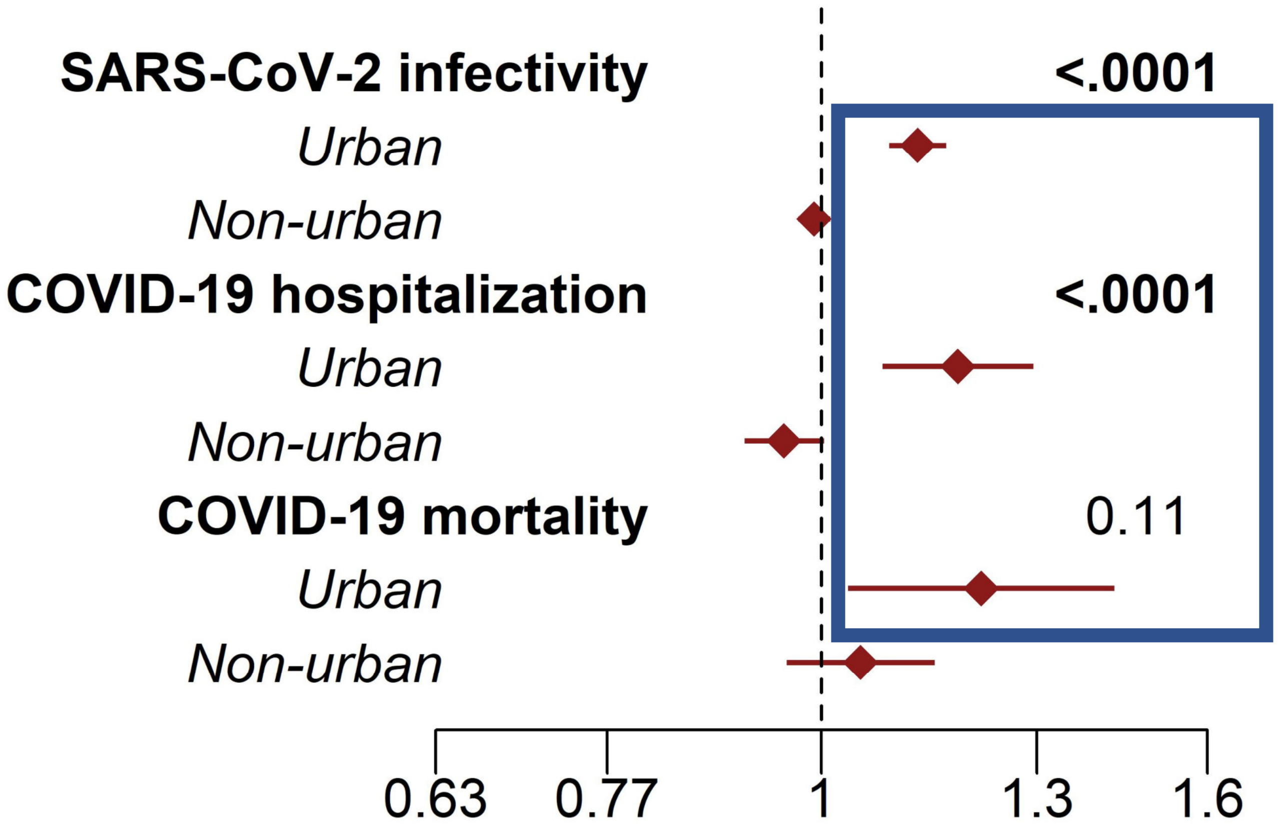
PM_{10}

Values (µg/m3)
- (10,15.5]
- (15.5,18.5]
- (18.5,23]
- (23,26]
- (26,31]

	PM_{10} [µg/m3]	**NO_2** [µg/m3]	**O_3** [µg/m3]
2019 annual mean (±SD)	24.3±3.0	26.1±5.4	52.1±5.8
By degree of urbanization			
Urban	**26.2±1.6**	**30.2±3.5**	**48.2±4.2**
Non-urban	22.5±2.9	22.4±4.0	55.7±4.7

Risultati – PM_{10}

Hazard ratios per 1 IQRw increase in PM_{10}
in aree **urbane e non-urbane**



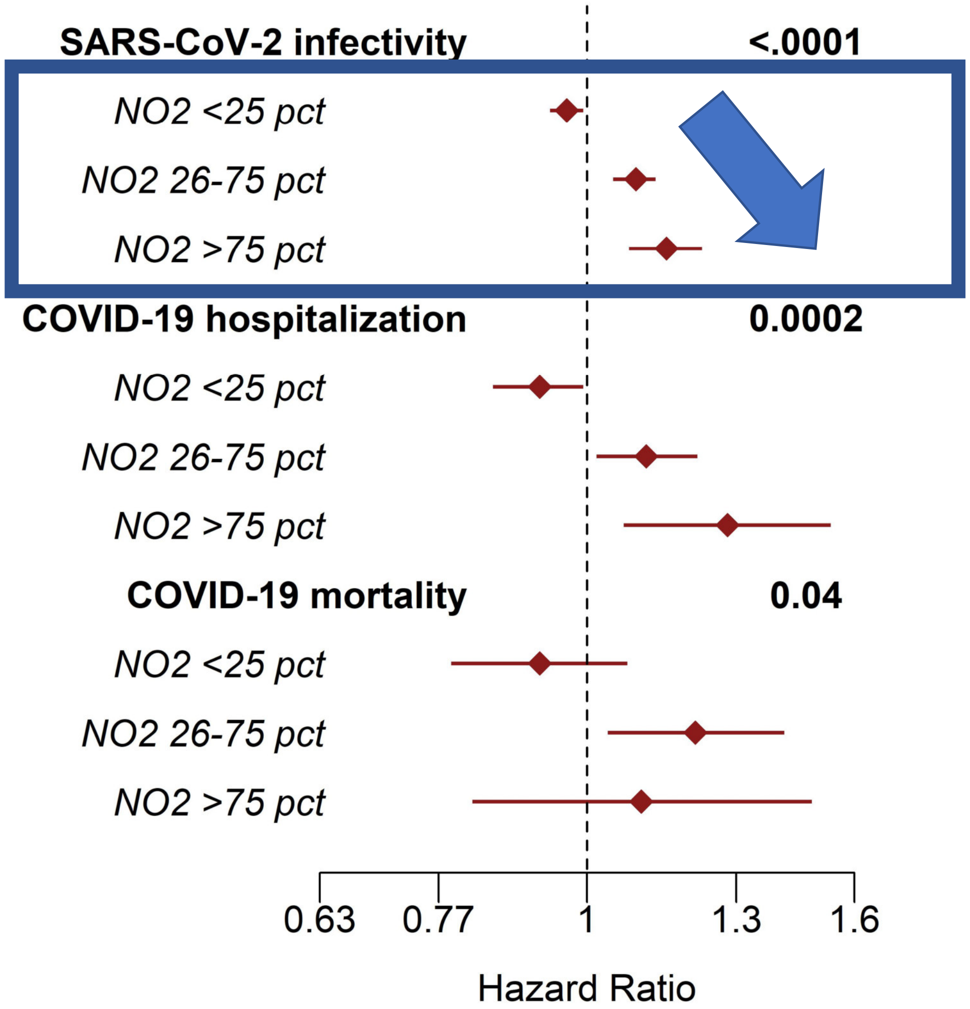
Casi aggiuntivi
(per 100000 py) in aree urbane **dovuti ad interazione**:

854 (600-1107)

174 (86-261)

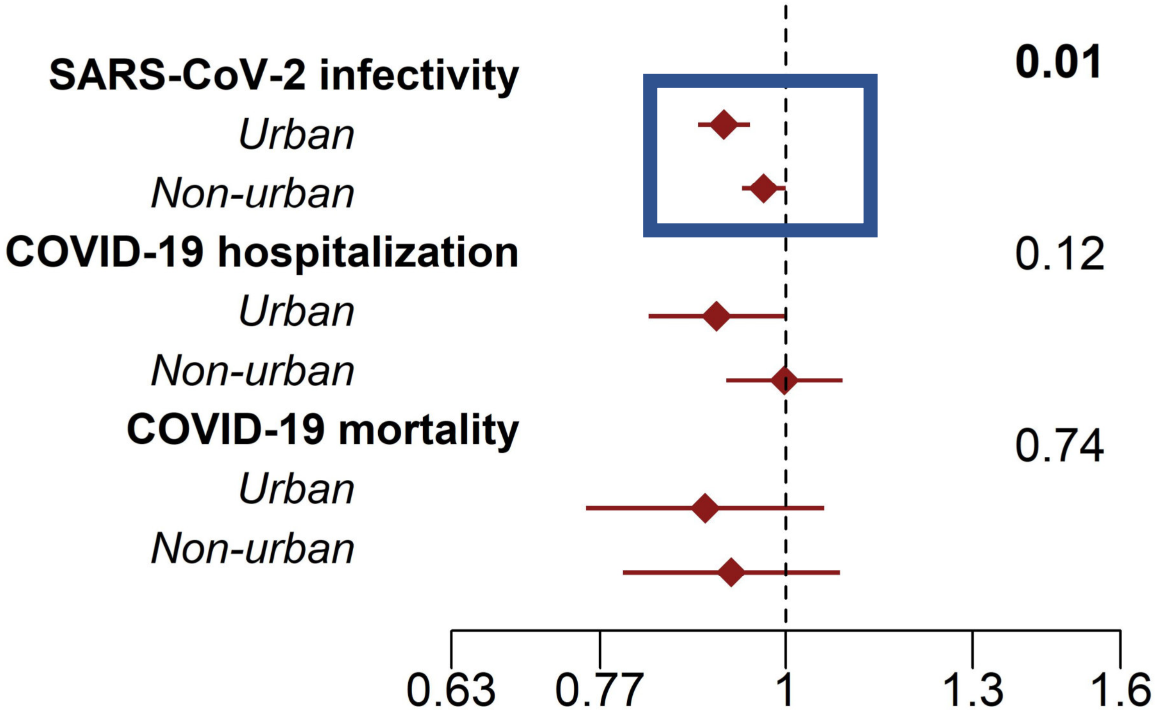
Risultati – PM_{10}

Hazard ratios per 1 IQRw increase in PM_{10}, **per quartili di NO_2**

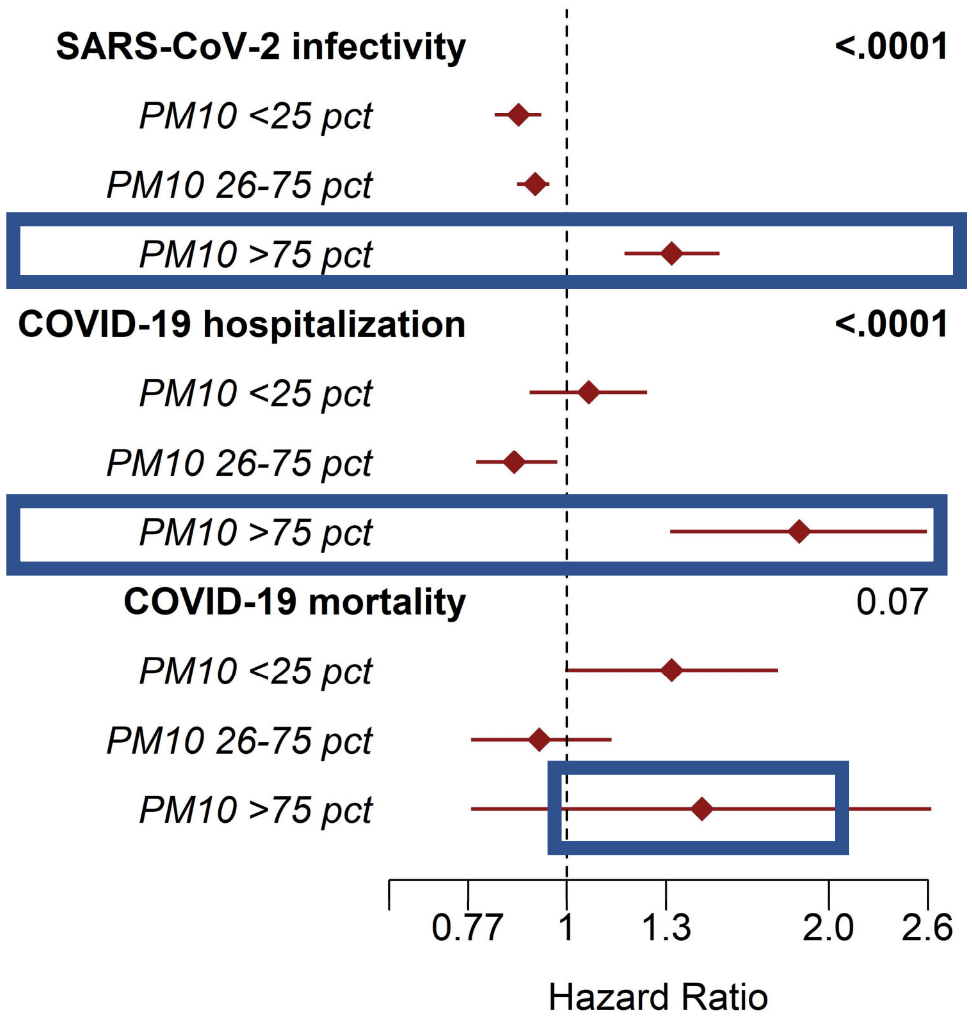


Risultati – HRs for 1 IQRw increase in O_3

a. Aree urbane e non-urbane



b. quartili di PM_{10}



Discussione & take-home

ORIGINAL ARTICLE

OPEN

Interactive Effects of Long-term Exposure to Air Pollutants on SARS-CoV-2 Infection and Severity

A Northern Italian Population-based Cohort Study

Giovanni Veronesi,[a] Sara De Matteis,[b] Camillo Silibello,[c] Emanuele M. Giusti,[a] Walter Ageno,[a] and Marco M. Ferrario[a]

Background: We examined interactions, to our knowledge not yet explored, between long-term exposures to particulate matter (PM_{10}) with nitrogen dioxide (NO_2) and ozone (O_3) on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity and severity.
Methods: We followed 709,864 adult residents of Varese Province from 1 February 2020 until the first positive test, COVID-19 hospitalization, or death, up to 31 December 2020. We estimated residential annual means of PM_{10}, NO_2 and O_3 in 2019 from chemical transport and random-forest models. We estimated the interactive effects of pollutants with urbanicity on SARS-CoV-2 infectivity, hospitalization, and mortality endpoints using Cox regression models adjusted for socio-demographic factors and comorbidities, and additional cases due to interactions using Poisson models.
Results: In total 41,065 individuals were infected, 5203 were hospitalized and 1543 died from COVID-19 during follow-up. Mean PM_{10} was 1.6 times higher and NO_2 2.6 times higher than WHO limits, with wide gradients between urban and nonurban areas. PM_{10} and NO_2 were positively associated with SARS-CoV-2 infectivity and mortality, and PM_{10} with hospitalizations in urban areas. Interaction analyses estimated that the effect of PM_{10} (per 3.5 μg/m³) on infectivity was strongest in urban areas [hazard ratio (HR) = 1.12; 95% CI =1.09, 1.16], corresponding to 854 additional cases per 100,000 person-years, and in areas at high NO_2 co-exposure (HR = 1.15; 1.08, 1.22). At higher levels of PM_{10} co-exposure, the protective association of O_3 reversed (HR =1.32, 1.17, 1.49), yielding 278 additional cases per μg/m³ increase in O_3. We estimated similar interactive effects for severity endpoints.
Conclusions: We estimate that interactive effects between pollutants exacerbated the burden of the SARS-CoV-2 pandemic in urban areas.

Keywords: Air pollution; SARS-CoV-2; Cohort; Italy; Interactive effect; Long-term exposure; Urban

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G.V. and M.M.F. contributed to the conceptualization and design of the study and writing the original draft. In addition, G.V. contributed to data acquisition, formal statistical analyses and is the study guarantor; and M.M.F. supervised the statistical analyses and contributed to the interpretation of the results. S.D.M., W.A., and E.M.G. contributed to interpretation of the results and to manuscript review and editing. C.S. contributed to exposure data modeling and acquisition, to interpretation of the results and to manuscript review and editing.
The authors report no conflicts of interest.
Data are collected by the Regional Health Authority as part of its duties and cannot be made publicly available due to data protection constraints.
SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).
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This study, based on record-linkage of administrative healthcare data in which individuals are fully anonymized, received approval by the Regional Health Authority (approval ID: 54887/2021, date: 13 September 2021). No other approval was required. According to regional laws, the inclusion in the healthcare databases and the use of data for research purposes do not require written consent by the individuals.

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In 2023, the detrimental effects of long-term exposure to outdoor airborne pollutants on health were on the agenda at the Conference of the Parties 28 agenda for the first time.[1] Latest estimates for Europe indicate that 94% of the population live at airborne particulate matter (PM) concentrations above the 2021 WHO guideline levels,[2] resulting in 117,000 premature deaths.[3] Over the years, an extensive body of research has suggested that there is a causal link between air pollution and morbidity from chronic, noncommunicable diseases.[4,5]

Less established is the link between long-term exposure to $PM_{2.5}$ and PM_{10} (e.g., particulate matter with aerodynamic diameter less than 2.5 and 10 μm, respectively), nitrogen dioxide (NO_2), and ozone (O_3) with infectious diseases, including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) threats. A number of mechanisms support the biologic plausibility of the association, including the well-established role of airborne pollutants in prolonged inflammation, downregulation of the immune system, and over-expression of angiotensin-converting enzyme-2 receptors in the lungs with impairment of alveoli macrophages to regulate the inflammation response.[6–8]

Prima evidenza di effetti interattivi degli inquinanti (PM) su **rischio di malattie infettive**

Effetto "mistura" in aree urbane ha esacerbato il rischio legato alla pandemia in quelle aree – **approccio anche per altre patologie?**

In aree ad elevate co-esposizione a PM_{10} gli effetti detrimenti dell'**ozono** legati a processi infiammatori e di stress ossidativo **sovvertono** i vantaggi dovuti ai meccanismi di inattivazione virale

Epidemiology 2025;36(1):11-15

Studio 2 - scopo

Studi su popolazioni di non-vaccinati

La **maggior parte degli studi** su SARS-CoV-2 ed inquinamento è stato condotto nella prima parte della pandemia (2020-primavera 2021) quando la **vaccinazione di popolazione era agli esordi**

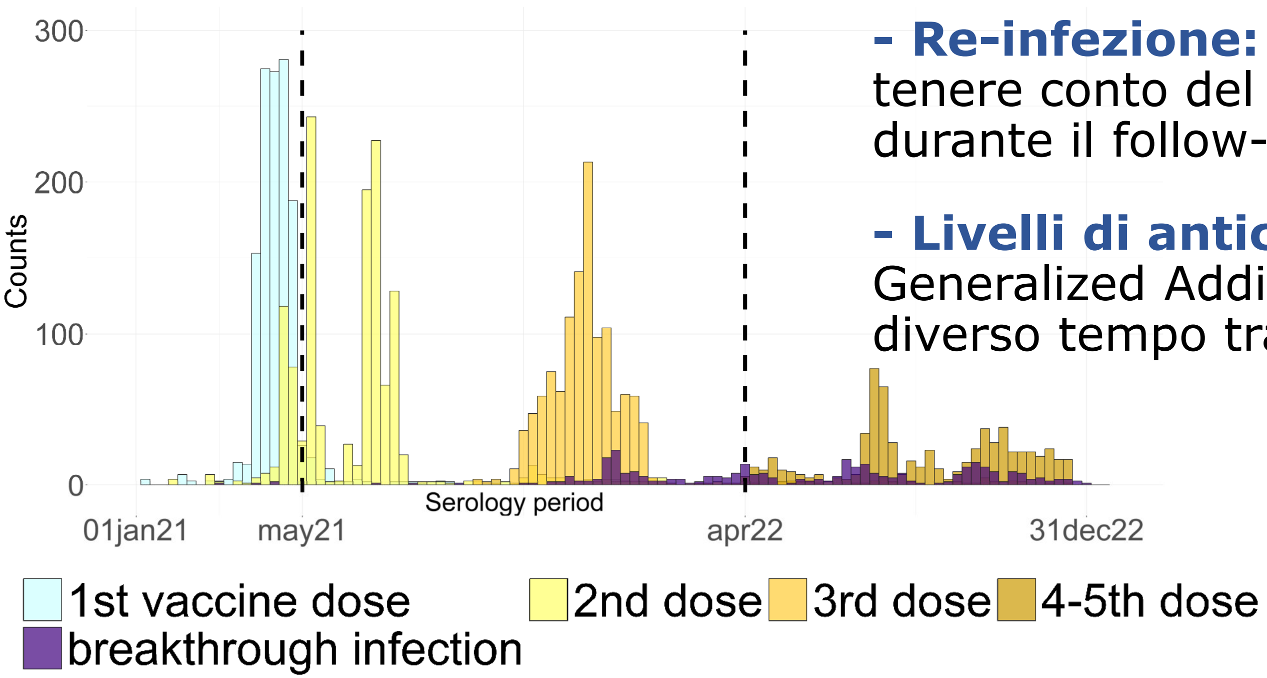
Open question(s)

L'esposizione di lungo-periodo ad inquinanti **incrementa il rischio di infezione da SARS-CoV-2 dopo la vaccinazione**? Come si modifica il rischio **all'aumentare della copertura vaccinale** (numero di dosi)? **Quale effetto sui livelli di anticorpi anti-IgG** dopo la vaccinazione?

- **Popolazione di anziani (65+):** target preferenziale

Popolazione – coorte RoCAV

- N=1326 individui **SARS-CoV-2 naïve** 65-83 anni, 50% donne
- **1-5 dosi di vaccino**
- **Outcome: infezione** da SARS-CoV-2 dopo la prima dose di vaccino (primo tampone positivo, dati ATS)
- **Medie annue 2019 di particolato ($PM_{2.5}$ e PM_{10}), NO_2, O_3** link ad indirizzo **residenza geo-referenziato**



- **Re-infezione: time-dependent Cox models** per tenere conto del crescente numero di dosi di vaccino durante il follow-up

- **Livelli di anticorpi IgG dopo la vaccinazione:** Generalized Additive Model (GAM)s per tenere conto del diverso tempo tra vaccinazione e prelievo

Risultati

Table 2

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

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

IQR width values: $PM_{2.5}$ = 1.22 µg/m^3; PM_{10} = 1.03 µg/m^3; NO_2 = 3.63 µg/m^3; ozone = 1.86 µg/m^3 ne = not estimable (no events).

^: single-pollutant Cox regression model, adjusting for age, sex, current smoking, autoimmune disease, use of immunosuppressant treatment in the six months before first vaccine dose, and time-dependent vaccine exposure periods.

[a] Single-pollutant Cox regression model, with vaccine exposure as time-dependent covariate and air pollutant*vaccine exposure interaction, further adjusting for age, sex, current smoking, autoimmune disease, use of immunosuppressant treatment in the six months before first vaccine dose.

[b] Wald chi-square test for the null hypothesis of no heterogeneity of effect for air pollutant by increasing vaccine exposure (1 df).

Risultati

Table 3

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

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

^: change in IgG geometric mean for 1 interquartile Range (IQR) increase in air pollutants.

IQR width values: $PM_{2.5}$ = 1.22 $\mu g/m^3$; PM_{10} = 1.03 $\mu g/m^3$; NO_2 = 3.63 $\mu g/m^3$; O_3 = 1.86 $\mu g/m.^3$.

Model 1: adjusted for age, sex, 8-class vaccination strategy (combination of dose number – 1 to 3 – and of vaccine type (mRNA only or mixed strategy)), and a restricted cubic spline for time since last vaccine dose. Model 2: Model 1 + current smoker, history of autoimmune diseases, use of auto-immune drug treatment in the six months before serology date.

Discussione

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

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A R T I C L E I N F O

Keywords:
Air pollution
COVID-19 vaccine
Older adults
Immune response
Breakthrough infection
Long-term exposure

A B S T R A C T

Aims: To investigate the association between long-term exposure to $PM_{2.5}$, PM_{10}, NO_2 and O_3 with SARS-CoV-2 breakthrough infections and COVID-19 vaccine-induced antibody responses in a northern Italian population-based sample of older adults.
Methods: Within an ongoing prospective population-based study, we followed-up 1326 vaccinated individuals aged 65–83 years, with no prior SARS-CoV-2 infection, for their first positive SARS-CoV-2 swab until December 31st, 2022. We assessed spike IgG antibody levels in most participants (n = 1206). The 2019 annual mean levels of air pollutants derived from combined use of chemical-transport and random-Forest models (spatial resolution: 1Kmq) were individually assigned based on the latest residence address. We estimated multivariable-adjusted associations (per 1 interquartile range increase, IQR) of air pollutants with breakthrough infections using Cox models with time-dependent vaccine exposure; and with percent change in the IgG geometric mean using generalized additive models.
Results: The mean (SD) age was 74.9 ± 4.1 years, and 50% were women. An IQR (1.2 μg/m^3) increase in long-term $PM_{2.5}$ exposure was associated with a 52% increase in breakthrough infection risk following a second vaccine and a 26% increase following a third vaccine. The effect vanished with the further increment of vaccination doses. Associations for NO_2 were inconsistent. Ozone was negatively associated with breakthrough infection risk, but this association reversed in bi-pollutant models adjusting for $PM_{2.5}$. $PM_{2.5}$ was associated with a −7.3% (−13.9% to −0.2%) reduction in vaccine-induced IgG levels. The reduction became more pronounced as the time delay from vaccination increased, and with adjustment for NO_2 co-exposure.
Conclusion: In our population of vaccinated older adults, fine particulate matter exposure was independently associated with a higher risk of SARS-CoV-2 breakthrough infection and a lower antibody response, both effects being influenced by timely and repeated vaccination schedule.

1. Introduction

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

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Nella popolazione anziana, l'esposizione di lungo-periodo a $PM_{2.5}$

- **incrementa il rischio di infezione** in soggetti vaccinati, l'effetto negativo **decresce all'aumentare della copertura vaccinale.**

- **riduce i livelli di IgG dopo la vaccinazione**

"Vaccination campaign in highly-exposed, older populations should be re-enforced".

Environ res 2025:120450

Progetti per il 2025

- **Studio AirClimact** su effetti congiunti di cambiamento climatico ed inquinamento atmosferico sulla salute [finanziato]

- **Studio PAPETHE** sugli effetti di lungo-periodo di picchi espositivi e variabilità nell'esposizione a PM2.5 [application *under-review*]

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