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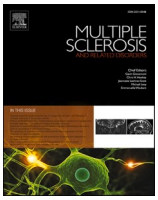

The impact of PM2.5, PM10 and NO2 on Covid-19 severity in a sample of patients with multiple sclerosis: A case-control study

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ABSTRACT

Background: Many studies investigated the association between air pollution and Covid-19 severity but the only study focusing on patients with Multiple Sclerosis (MS) exclusively evaluated exposure to PM2.5. We aim to study, in a sample of MS patients, the impact of long-term exposure to PM2.5, PM10 and NO2 on Covid-19 severity, described as occurrence of pneumonia.
Methods: A 1:2 ratio case-control study was designed, differentiating cases and controls based on Covid-19 pneumonia. Associations between pollutants and outcome were studied using logistic regression. Weighted quantile sum (WQS) logistic regression was used to identify the individual contribution of each pollutant within the mixture; Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression was performed to confirm the variable selection from WQS. All the analyses were adjusted for confounders selected a priori.
Results: Of the 615 eligible patients, 491 patients provided detailed place of exposure and were included in the principal analysis. Higher concentrations of air pollutants were associated with increased odds of developing Covid-19 pneumonia (PM2.5: 3rd vs 1st tercile OR(95% CI)=2.26(1.29;3.96); PM10: 3rd vs 1st tercile OR(95% CI)=2.12(1.22;3.68); NO2: 3rd vs 1st tercile OR(95% CI)=2.12(1.21;3.69)). Pollutants were highly correlated with each other; WQS index was associated to an increased risk of pneumonia (β=0.44; p-value=0.004) and the main contributors to this association were NO2 (41%) and PM2.5 (34%). Consistently, Lasso method selected PM2.5 and NO2.
Conclusions: Higher long-term exposure to PM2.5, PM10 and NO2 increased the odds of Covid-19 pneumonia among MS patients and the most dangerous pollutants were NO2 and PM2.5.

1. Introduction

Many studies have pointed out that air pollution may play a role in the severity of SARS- CoV-2 infections, leading to higher risk of common Covid-19 complications (Zang et al., 2022; Bourdrel et al., 2021). Pneumonia is the most common complication in severe Covid-19 patients (Williams et al., 2022) and presence of this condition is sufficient to differentiate Covid-19 cases between mild and moderate or severe (World Health Organization 2021). Air pollutants have also been associated to the occurrence and development of autoimmune diseases including Multiple Sclerosis (MS) (Zhao et al., 2019). In particular, higher pollutants concentrations have been identified as possible risk factors for MS onset and relapses (Bergamaschi et al., 2021; Tateo et al., 2019; Noorimotlagh et al., 2021). However, to the best of our knowledge, only one study explored the impact of air pollution on Covid-19 severity among patients with MS (Bergamaschi et al., 2022). This study revealed that higher concentrations of PM2.5 increase the risk of severe Covid-19 course among patients with MS, but there were some limitations. Firstly, PM2.5 long-term exposure was measured in correspondence to the patient-reported place of infection to Covid-19 even if they may have spent more time somewhere else in the more recent years. Secondly, it only focused on PM2.5 exposure without evaluating several pollutants simultaneously. Thus, our aim is to explore the association between air pollution and Covid-19 severity among patients with MS evaluating other pollutants at the same time (i.e. PM2.5, PM10 and NO2) and based on more precise information on the geographical area of exposure. Addressing and thoroughly evaluating this association among MS patients will provide critical information for identifying the effective role of the main air pollutants in worsening the course of Covid-19 infection. Since Covid-19 infection may carry additional reasons for concern among vulnerable individuals such as MS patients, increasing the knowledge of risk factors for severe outcomes within this specific group of patients can surely help to better protect them.

2. Methods

2.1. Study population

We designed a case-control study on MS patients living in Italy who got infected with Covid-19 differentiating cases of severe Covid-19 and controls based on the occurrence of documented pneumonia. All the data were retrieved from the MuSC-19 platform, an Italian web-based platform containing clinician-reported data on MS patients with Covid-19. Information on data sharing agreement and ethical committee approval as well as details on the data stored in the platform have been already reported (Sormani et al., 2021). We excluded patients with suspected Covid-19 infections not confirmed by a positive Covid-19 test and those who got infected after having received at least one dose of Covid-19 vaccination in order to avoid bias. On 28 January 2022, data of 205 patients with Covid-19 related pneumonia were collected from the platform. To calculate the required number of controls, we conducted a sample size calculation fixing the odds ratio of severe Covid-19 to 1.79 based on the data of our pilot study (Bergamaschi et al., 2022) and alpha level to 0.05. To achieve a power of 0.90, two controls per case were required and thus 410 controls were randomly selected among patients without pneumonia.

2.2. Outcome assessment

A specific section of the platform was dedicated to radiological data, including information on the presence of documented pneumonia. This data were already available at the beginning of the study since clinicians had already completed this section.

2.3. Exposure assessment

To retrieve a precise information on the geographical area of exposure, the 615 eligible patients were contacted by investigators of their MS center and were asked the following question (in their mother tongue): “Where did you spend most of the active day (excluding

sleeping hours) in the last five years?". In case of severe health conditions preventing the patient to reply to our question or in case of patient death, the caregiver was contacted instead of the patient. A new section of the Musc-19 platform was created, where the investigators could insert the zip codes of the geographical area provided by the patients. When this information was missing, the address of the MS center was used as a proxy in sensitivity analysis. Air quality was assessed as 2018 annual average particulate matter (PM2.5 and PM10) and Nitrogen Dioxide (NO2) ground-level concentrations derived from air quality model results as provided by the 'Copernicus Atmospheric Monitoring Service' (CAMS). In particular, the 'reanalysis' product (the most accurate in the CAMS ones, created through assimilation of modeling results and observations at ground-level), has been used. Concentrations were referred to 2018 since we evaluated long-term exposure related to the last five years (2018–2022) and 'Copernicus Atmospheric Monitoring Service' most recent available data (in terms of reanalysis) were available indeed at 2018 (Wagner et al., 2021).

2.4. Statistical analyses

Descriptive characteristics of the study population were presented as mean with standard deviation, median with interquartile range or absolute frequency and percentage, depending on the nature of the variables. Characteristics of cases and controls were compared performing Chi-squared test and T-test as appropriate.

The association between each pollutant and Covid-19 pneumonia was investigated using univariable logistic regression models as well as multivariable models adjusted for potential confounders selected a priori (age, sex, BMI, comorbidities, EDSS, MS type, disease duration and treatments). Correlations between pollutants concentrations were calculated using Pearson correlation coefficients.

We next evaluated the joint exposure to the three pollutants as an environmental mixture. Weighted quantile sum (WQS) logistic regression was used to create a pollution index based on PM2.5, PM10 and NO2 concentrations, to study associations of the index with the risk of pneumonia, and to identify the individual contribution of each pollutant within the mixture (Carrico et al., 2015; Czarnota et al., 2015). For WQS modeling, we categorized each exposure into terciles and used the entire sample for weights estimation, generating 300 bootstrap samples to evaluate the positive mixture index (Czarnota et al., 2015; Renzetti et al., 2021). Finally, to confirm the variable selection from WQS, the pollutants mixture was also evaluated using Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression analysis, determining the optimal value of the penalty parameter using 10-fold cross validation (Tibshirani, 1996). Both the WQS and Lasso models were adjusted for the same set of confounders included in the multivariable logistic regression models. All statistical analyses were performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA) and R version 3.6.0. All tests were two-sided and P-values < 0.05 were conventionally regarded to as statistically significant.

3. Results

Of the 615 eligible patients, 491 patients (80%) provided detailed place of exposure and were thus included in the principal analysis. For the remaining 124 patients, the zip code of their referred MS center was used as a proxy for the exposure and they were only included in the sensitivity analysis (Fig. 1). Average observed concentrations of PM2.5, PM10 and NO2 are shown for each province in Fig. 2, together with the observed proportion of cases. Pneumonia was reported as a complication of Covid-19 for 169 patients (34%) (Table 1). Average exposures to pollutants concentrations were higher in cases compared to patients without pneumonia (PM2.5: $p = 0.020$; PM10: $p = 0.092$; NO2: $p = 0.009$). Median age was 46 years (IQR=36–55) but MS patients with pneumonia were significantly older than the ones without pneumonia ($p<0.001$). MS patients with pneumonia had a worse profile in terms of MS course and more frequently reported comorbidities compared to controls. At the time of Covid-19 infection, 414 patients (84%) were on

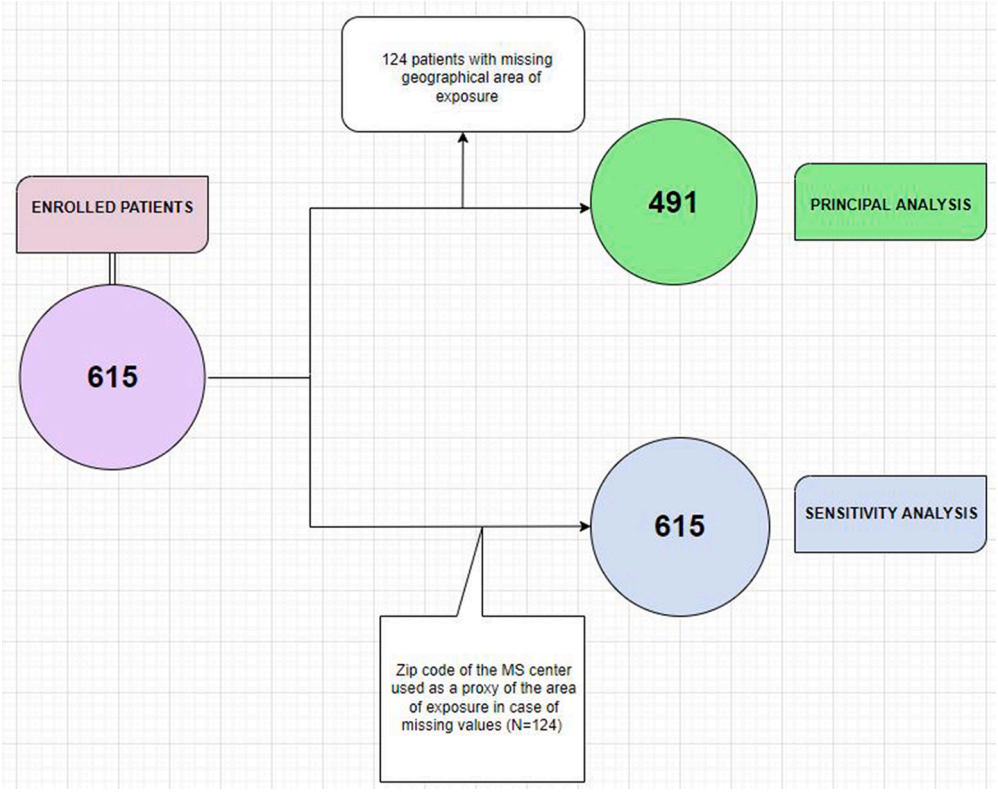

Fig. 1. Flowchart describing the patients included in the principal analysis and in the sensitivity analysis.

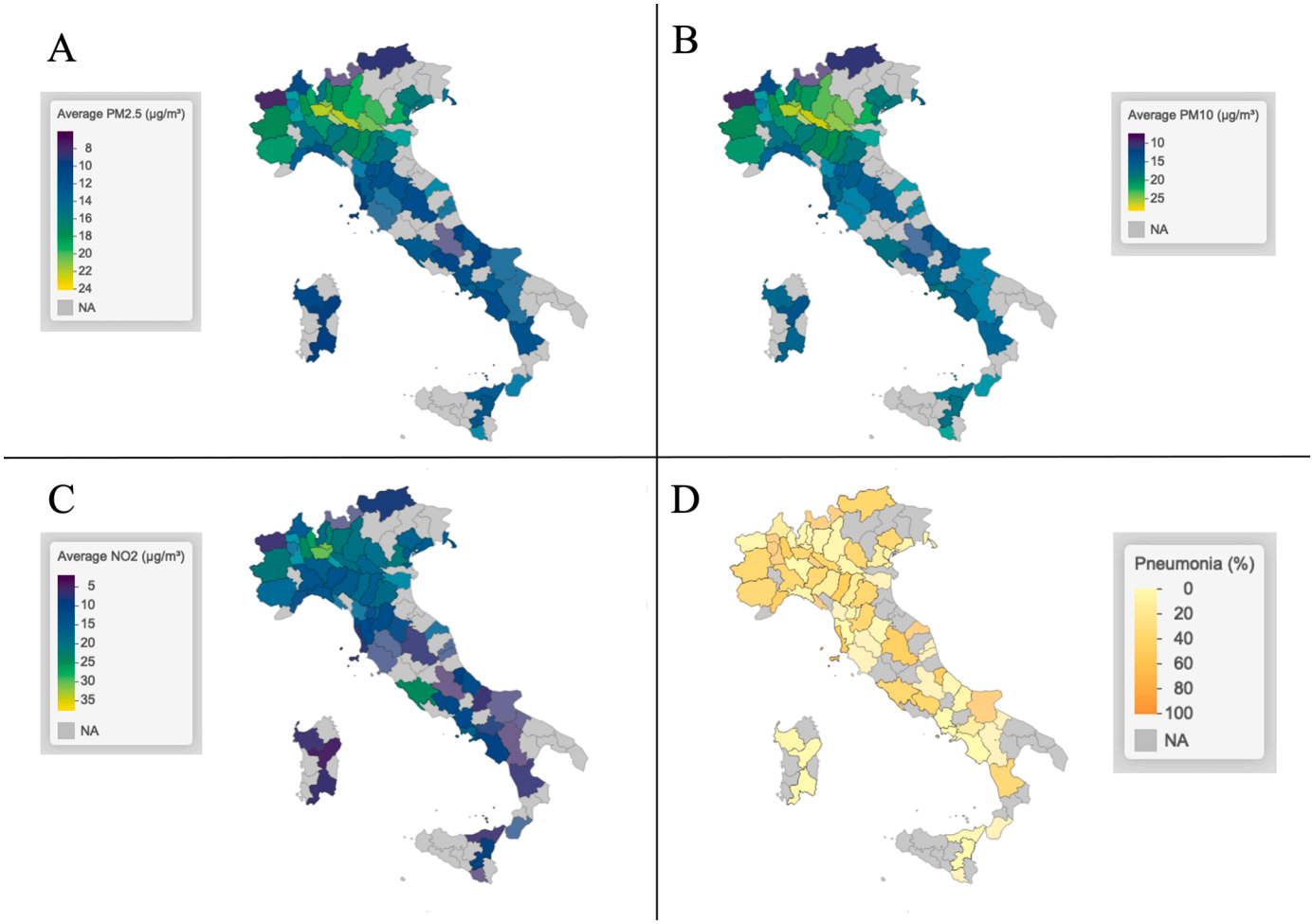

Fig. 2. Average observed annual concentrations of PM2.5 (Panel A), PM10 (Panel B), NO2 (Panel C) and proportion of cases of Covid-19 pneumonia occurred (Panel D). Observed averages and proportions refer to the 491 patients included in the principal analysis and areas where no patients were included are in gray.

Table 1
Characteristics of the patients included in the principal analysis, overall and based on the presence of Covid-19- related pneumonia.

	Overall*N* = 491	No Pneumonia*N* = 322(66%)	Pneumonia*N* = 169(34%)	p-value
PM2.5, median (IQR)	14.45(11.87; 19.61)	13.57(11.61; 19.28)	15.86(12.59; 19.91)	**0.0199**
PM10, median (IQR)	18.89(16.27; 22.87)	18.81(16.14; 22.71)	19.10(16.64; 23.77)	0.0921
NO2, median (IQR)	17.17(10.24; 22.69)	16.53(9.28; 22.07)	18.69(11.43; 23.47)	**0.0091**
Age, mean (SD)	46.12(13.12)	42.19(11.67)	53.60(12.48)	**<0.001**
Female sex, N (%)	324(66%)	220(68%)	104(62%)	0.1320
BMI, mean (SD)	24.74(6.01)	24.05(5.23)	26.06(7.11)	**0.0004**
Presence of comorbidities, N (%)	110(22%)	41(13%)	69(41%)	**<0.001**
MS phenotype, N (%)				
Relapsing–remitting	395(80%)	284(88%)	111(66%)	**<0.001**
Primary progressive	28(6%)	10(3%)	18(11%)	
Secondary progressive	68(14%)	28(9%)	40(24%)	
MS disease duration, median (IQR)	9.08(3.49–16.00)	7.69(2.77; 13.97)	13.25(5.80; 19.79)	**<0.001**
EDSS, median (IQR)	2(1;4)	2(1;3.5)	3.5(2;6)	**<0.001**
MS treatment, N (%)				
None	77(16%)	39(12%)	38(22%)	**<0.001**
Other	299(61%)	216(67%)	83(49%)	
Interferon	40(8%)	31(10%)	9(5%)	
Anti-CD20	75(15%)	36(11%)	39(23%)	
Previous methylprednisolone, N (%)	38(8%)	20(6%)	18(11%)	0.080

disease modifying treatment; Ocrelizumab or Rituximab were more commonly used among cases (23% vs 11%). Results remained consistent in the sensitivity analysis (Supplementary Table 1).

Univariable and multivariable analyses evaluating factors associated with the odds of severe Covid-19 course are reported in Table 2. The results confirmed previous findings (Bergamaschi et al., 2022; Schiavetti et al., 2022) indicating higher PM2.5 concentrations, older age, higher BMI, presence of comorbidities, and anti-CD20 treatment as risk factors and identifying Interferon therapy as a protective factor. Concerning the other pollutants under study, higher concentrations of PM10 and NO2 were significantly associated with increased odds of developing pneumonia (PM10: 2nd vs 1st tercile OR(95% CI)=1.83

Table 2
Logistic regression models for risk of pneumonia: univariable models and multivariable models including one single pollutant at a time (PM2.5, PM10 and NO2).

	Univariable Analysis		Multivariable AnalysisPM2.5		Multivariable AnalysisPM10		Multivariable AnalysisNO2	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
PM2.5								
1st Tercile	1.00(ref)	—	1.00(ref)	—	—	—	—	—
2nd tercile	1.71(1.07;2.74)	**0.025**	2.09(1.20;3.65)	**0.010**	—	—	—	—
3rd tercile	1.82 (1.14;2.91)	**0.012**	2.26(1.29;3.96)	**0.004**	—	—	—	—
PM10								
1st Tercile	1.00(ref)	—	—	—	1.00(ref)	—	—	—
2nd tercile	1.32(0.83;2.11)	0.240	—	—	1.83(1.05;3.20)	**0.033**	—	—
3rd tercile	1.64(1.04;2.60)	**0.034**	—	—	2.12(1.22;3.68)	**0.008**	—	—
NO2								
1st Tercile	1.00(ref)	—	—	—	—	—	1.00(ref)	—
2nd tercile	1.23(0.77;1.96)	0.389	—	—	—	—	1.22(0.70;2.12)	0.485
3rd tercile	1.58(1.00;2.50)	**0.049**	—	—	—	—	2.12(1.21;3.69)	**0.008**
Age (10-unit)	2.22(1.84;2.68)	**<0.001**	2.16(1.66;2.80)	**<0.001**	2.16(1.67;2.80)	**<0.001**	2.15(1.66;2.78)	**<0.001**
Sex: Male vs Female	1.35(0.91;1.99)	0.132	1.18(0.74;1.88)	0.481	1.21(0.76;1.92)	0.425	1.20(0.75;1.91)	0.442
BMI	1.06(1.02;1.09)	**0.001**	1.06(1.02;1.10)	**0.004**	1.06(1.02;1.10)	**0.004**	1.06(1.02;1.10)	**0.004**
Comorbidities: yes vs no	4.73(3.02;7.41)	**<0.001**	2.24(1.30;3.86)	**0.004**	2.23(1.30;3.84)	**0.004**	2.22(1.30;3.81)	**0.004**
MS type: Progressive vs Relapsing	3.91(2.46;6.21)	**<0.001**	0.94(0.42;2.13)	0.883	1.03(0.45;2.32)	0.951	1.04(0.46;2.34)	0.931
MS disease duration	1.06(1.03;1.08)	**<0.001**	1.01(0.98;1.04)	0.631	1.01(0.98;1.04)	0.647	1.01(0.98;1.04)	0.451
EDSS	1.35(1.24;1.47)	**<0.001**	0.99(0.85;1.17)	0.936	0.98(0.83;1.15)	0.808	0.98(0.83;1.15)	0.772
MS Treatment								
None	1.00(ref)	—	1.00(ref)	—	1.00(ref)	—	1.00(ref)	—
Other	0.39(0.24–0.66)	**<0.001**	0.76(0.40–1.47)	0.420	0.75(0.39–1.44)	0.390	0.78(0.40–1.50)	0.450
Interferon	0.30(0.13–0.71)	**0.006**	0.35(0.13–0.96)	**0.042**	0.36(0.13–0.98)	**0.046**	0.38(0.14–1.06)	0.064
Anti-CD20	1.11(0.59–2.10)	0.744	2.93(1.33–6.48)	**0.008**	2.89(1.31–6.38)	**0.008**	2.91(1.32–6.39)	**0.008**
Methylprednisolone: yes vs no	1.80(0.92;3.50)	0.084	1.92(0.88;4.20)	0.100	1.99(0.91;4.35)	0.085	1.91(0.87;4.18)	0.105

(1.05; 3.20) and 3rd vs 1st tercile OR(95% CI)=2.12(1.22; 3.68); NO2: 3rd vs 1st tercile OR=2.12(1.21; 3.69)). Results remained consistent in the sensitivity analysis (Supplementary Table 2).

Pollutants were highly correlated with each other, with the following correlation coefficients: 0.80, 0.83 and 0.97 (Fig. 3). Based on WQS regression, we found that higher levels of pollutants mixture were associated to increased odds of pneumonia (β=0.44; p-value=0.004) and results remained consistent in the sensitivity analysis. Significant contribution to the summary index was provided by NO2 (41%) and PM2.5 (34%), suggesting that these pollutants are the most important components of the mixture (Fig. 4). Consistently, Lasso method set PM10 coefficient to zero and selected PM2.5 and NO2 as important variables, either in the principal analysis or in the sensitivity analysis.

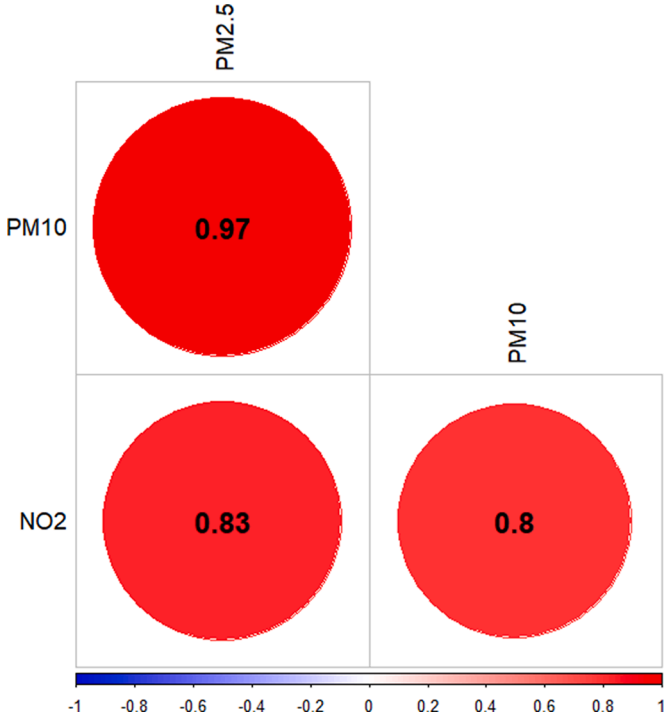

Fig. 3. Pearson correlation coefficients between the components of the mixture.

4. Discussion

In this study, long-term exposure to high concentrations of PM2.5 were found to increase the odds of Covid-19 pneumonia in a sample of patients with MS, confirming results from a previous study carried out on MS patients (Bergamaschi et al., 2022). Additionally, also PM10 and NO2 were found to be associated with increased odds of developing a severe Covid-19 course supporting the findings of other studies carried out on the general population (Zang et al., 2022; Karimi et al., 2022). Based on our results, we could thus infer that higher exposure to PM2.5, PM10 and NO2 can contribute to a worst Covid-19 course also among MS patients. Since a link between air pollutants, including PM2.5, PM10, NO2, and MS was already found (Bergamaschi et al., 2021; Tateo et al., 2019; Noorimotlagh et al., 2021; Bergamaschi et al., 2018; Cortese et al., 2020; Heydarpour et al., 2014; Gregory et al., 2008; Parolisi et al., 2021; Jeanjean et al., 2018), it was reasonable to expect that the effects of pollution, widely documented in the general population, would have been confirmed or even further enhanced among MS patients and thus our results are not surprising. Among MS patients, air pollution can thus additionally contribute to the risk of unfavorable Covid-19 course, being a co-factor together with other well known risk factors for the general population (older age, higher BMI and presence of comorbidities) and for patients with MS (higher EDSS, progressive MS phenotype, disease duration and Anti-CD20 treatment).

Concerning immunological and pro-inflammatory mechanisms that could aggravate Covid-19, it is hypothesized that the hasty aggression in course of respiratory illness is fostered by the massive release of pro-inflammatory cytokines, followed by lung inflammation (World Health Organization 2020). Therefore, the exposure to atmospheric pollution could induce modifications of the immune system (Tsai et al., 2019) favoring an auto-aggressive response in a typically inflammatory auto-immune disease such as multiple sclerosis. A severe evolution of Covid-19 in MS might be led by the cytokine storm syndrome, characterized by the increase of IL-2, IL-7, granulocyte- colony stimulating

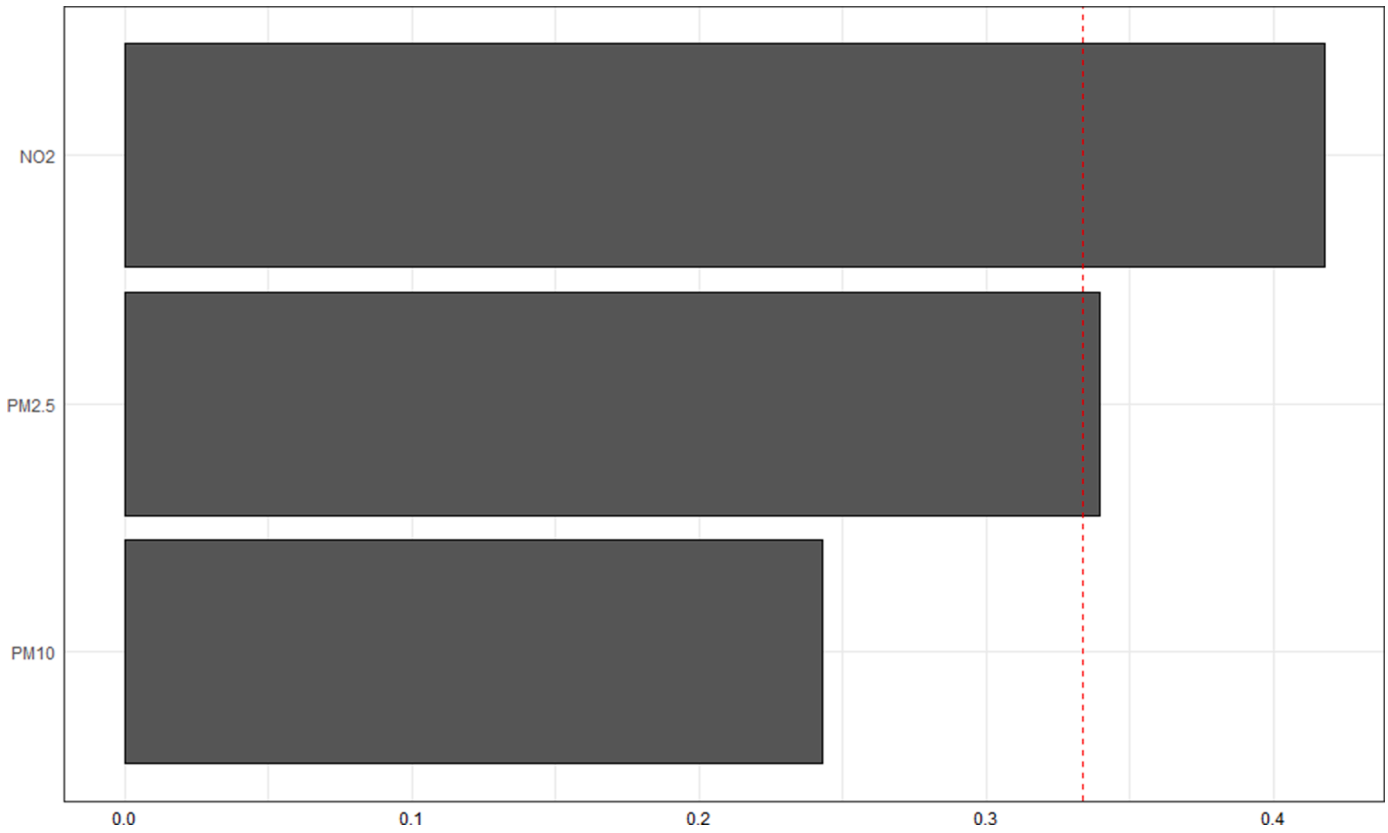

Fig. 4. WQS logistic covariates-adjusted models: WQS index weights for positive direction. The dashed line indicates the selection threshold.

factor, interferon-γ inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α) (Huang et al., 2020). In addition, the oxidative stress induced by PM2.5 in the lungs, resulting in cell damage, local/systemic inflammation and cytokine release, (Veldhoen et al., 2022) might enhance the inflammatory framework in Covid-19. As a counter-proof of this argument, we have the findings on effectiveness of therapeutic strategies based selective cytokine blockade (e.g., Tocilizumab) (Abidi et al., 2022).

A relevant strength of this study consists in the evaluation of the complex nature of pollutants as an environmental mixture, using WQS and Lasso approaches to take into account the high observed correlations between pollutants and to infer the overall mixture effect while assessing the specific contribution of each pollutant to the mixture (Dominici et al., 2010). Even if focusing on single exposures as if exposure occurs individually may lead to inadequate and misleading conclusions, this is what is most commonly done in practice (Braun et al., 2016) and in fact current studies on environmental factors and Covid-19 have generally focused on evaluating pollutants one at the time. An overall harmful effect of the pollutants was confirmed when accounting for the high correlation, and we consistently identified NO2 and PM2.5 as the main contributors of the mixture to Covid-19 pneumonia, thus leaving to PM10 a minor role in this association. The fact that PM2.5 is selected instead of PM10 is not surprising. PM2.5 is in fact more toxic than bigger particles since it is easily respirable and can deposit more deeply in the lungs than larger particles, irritate and corrode the alveolar wall, and thus affect lung function (Ciencewicki and Jaspers, 2007; Xing et al., 2016). Concerning limitations of this study, even if looking at the three pollutants simultaneously is a strength of this work, a future research evaluating other additional pollutants within the environmental mixture will guarantee a more complete overview. Another limitation of this study regards the exposure assessment. Specifically, some people with MS are quite active and thus it is not unlikely the long-distance commuting for work reasons. Even if the specification of the meaning of active time (exclusion of sleeping hours) may help the patients in deciding where they spend most of the active time, they may still find it difficult to consider whether they spend more time at home or at their job place. In this situation of indecision, patients could report only one place of exposure and thus a source of bias was introduced. In future studies, giving the opportunity to provide two places of exposure in case of indecision would surely result in a more complete and accurate view of the patient's profile. Finally, another limitation of this work consists in the unavailability of variables on the socioeconomic status, that may act as possible confounders.

In conclusion, even if several other factors may explain the unfavorable course of Covid-19 infection, also air pollution plays its role and since it is a modifiable exposure, urgent measures should be adopted especially to protect the most vulnerable population.

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CRediT authorship contribution statement

Marta Ponzano: Conceptualization, Methodology, Formal analysis, Writing - Original Draft; Irene Schiavetti: Conceptualization, Formal analysis, Writing - Review & Editing; Roberto Bergamaschi: Conceptualization, Writing - Review & Editing; Enrico Pisoni: Conceptualization, Methodology, Writing - Review & Editing; Andrea Bellavia: Conceptualization, Methodology, Writing - Review & Editing; Giulia Mallucci: Conceptualization, Writing - Review & Editing; Luca Carmisciano: Writing - Review & Editing, Visualization; Matilde Inglese: Writing - Review & Editing, Data Curation; Cinzia Cordioli: Writing - Review & Editing, Data Curation; Girolama Alessandra Marfia: Writing - Review & Editing, Data Curation; Eleonora Cocco: Writing - Review & Editing,

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104243.

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