ORIGINAL ARTICLE

european journal
of neurology
the official journal of the european academy of neurology

The effect of air pollution on COVID-19 severity in a sample of patients with multiple sclerosis

Roberto Bergamaschi[1] | Marta Ponzano[2] | Irene Schiavetti[2] | Luca Carmisciano[2] | Cinzia Cordioli[3] | Massimo Filippi[4,5,6,7,8] | Marta Radaelli[9] | Paolo Immovilli[10] | Marco Capobianco[11] | Nicola De Rossi[3] | Giampaolo Brichetto[12] | Eleonora Cocco[13,14] | Cinzia Scandellari[15] | Paola Cavalla[16] | Ilaria Pesci[17] | Antonio Zito[18] | Paolo Confalonieri[19] | Girolama Alessandra Marfia[20] | Paola Perini[21] | Matilde Inglese[22,23] | Maria Trojano[24] | Vincenzo Brescia Morra[25] | Enrico Pisoni[26] | Gioacchino Tedeschi[27] | Giancarlo Comi[28] | Mario Alberto Battaglia[29,30] | Francesco Patti[31,32] | Marco Salvetti[33,34] | Maria Pia Sormani[2,23] | MuSC-19 study group[35]

[1]Multiple Sclerosis Research Center, IRCCS Mondino Foundation, Pavia, Italy

[2]Department of Health Sciences, University of Genova, Genova, Italy

[3]Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Montichiari, Italy

[4]Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

[5]Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

[6]Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

[7]Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

[8]Vita-Salute San Raffaele University, Milan, Italy

[9]Department of Neurology and Multiple Sclerosis Center, ASST 'Papa Giovanni XXIII', Bergamo, Italy

[10]Multiple Sclerosis Center, Ospedale Guglielmo da Saliceto, Piacenza, Italy

[11]Regional Referral Multiple Sclerosis Centre, Department of Neurology, University Hospital San Luigi, Orbassano (Torino), Italy

[12]AISM Rehabilitation Center, Italian MS Society, Genoa, Italy

[13]Centro Sclerosi Multipla, ATS Sardegna, Cagliari, Italy

[14]Dipartimento Scienze Mediche e Sanità Pubblica, Università di Cagliari, Cagliari, Italy

[15]IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla, Bologna, Italy

[16]MS Center, Department of Neuroscience, City of Health and Science University Hospital of Turin, Turin, Italy

[17]Centro SM UOC Neurologia, Fidenza, AUSL PR, Fidenza, Italy

[18]Multiple Sclerosis Research Center, IRCCS Mondino Foundation, Pavia, Italy

[19]Multiple Sclerosis Centre, Neuroimmunology Department 'Carlo Besta' Neurological Institute, Milan, Italy

[20]Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, Rome, Italy

[21]Department of Neurology Multiple Sclerosis Center, University of Padua, Padova, Italy

[22]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy

[23]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[24]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy

[25]Federico II University of Naples, Naples, Italy

[26]European Commission, Joint Research Centre (JRC), Ispra, Italy

[27]Department of Advanced Medical and Surgical Sciences, University of Campania, Napoli, Italy

[28]Università Vita Salute San Raffaele, Casa di Cura Privata del Policlinico, Milan, Italy

[29]Research Department, Italian Multiple Sclerosis Foundation, Genoa, Italy

[30]Department of Life Sciences, University of Siena, Siena, Italy

[31]Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, University of Catania, Catania, Italy

[32]Centro Sclerosi Multipla, Policlinico Catania, University of Catania, Catania, Italy

[33]Department of Neuroscience, Mental Health and Sensory Organs, Sapienza University of Rome, Rome, Italy

[34]Unit of Neurology, IRCCS Neuromed, Pozzilli, Italy

[35]See details of MuSC-19 study group in Supporting information

Correspondence
Maria Pia Sormani, Department of Health Sciences, University of Genova, Genova, Italy.
Email: mariapia.sormani@unige.it

Abstract

Background and purpose: Some studies have shown that air pollution, often assessed by thin particulate matter with diameter below 2.5 $\mu g/m^3$ (PM2.5), may contribute to severe COVID-19 courses, as well as play a role in the onset and evolution of multiple sclerosis (MS). However, the impact of air pollution on COVID-19 has never been explored specifically amongst patients with MS (PwMS). This retrospective observational study aims to explore associations between PM2.5 and COVID-19 severity amongst PwMS.

Methods: Data were retrieved from an Italian web-based platform (MuSC-19) which includes PwMS with COVID-19. PM2.5 2016–2018 average concentrations were provided by the Copernicus Atmospheric Monitoring Service. Italian patients inserted in the platform from 15 January 2020 to 9 April 2021 with a COVID-19 positive test were included. Ordered logistic regression models were used to study associations between PM2.5 and COVID-19 severity.

Results: In all, 1087 patients, of whom 13% required hospitalization and 2% were admitted to an intensive care unit or died, were included. Based on the multivariate analysis, higher concentrations of PM2.5 increased the risk of worse COVID-19 course (odds ratio 1.90; $p = 0.009$).

Conclusions: Even if several other factors explain the unfavourable course of COVID-19 in PwMS, the role of air pollutants must be considered and further investigated.

KEYWORDS
air pollution, coronavirus, multiple sclerosis

INTRODUCTION

The first cases of SARS-CoV-2 infections were identified in Wuhan, China, in December 2019, and in February 2020 the disease caused by this novel coronavirus was officially named coronavirus disease 2019 (COVID-19) [1,2]. This virus rapidly spread all over the world and in March 2020 the World Health Organization declared a pandemic [3]. In Italy, the first cases of COVID-19 were reported in January 2020; clusters of infected individuals were shortly found in Veneto and Lombardy and in March 2020 the virus had already spread throughout Italy, reaching 105,792 cases at the end of the month [4,5]. In May 2021, Italy counted more than 4.1 million confirmed cases and more than 120,000 deaths [6]. However, the spread and severity of COVID-19 was not uniform amongst Italian regions [6,7] and air pollution has been identified as a possible co-factor to explain the highest lethality rates in north Italy [8]. Many studies have pointed out that air pollution may play a role in the severity of SARS-CoV-2 infections: exposure to particulate matter (PM), including PM2.5 (thin particulate matter with diameter below 2.5 $\mu g/m^3$),

is linked to higher rates of COVID-19 mortality, hospitalization and intensive care unit (ICU) admission [9–13]. Although air pollution has been widely studied in the field of autoimmune diseases [14] and air pollutants have been identified as possible risk factors for MS onset and relapses [15–17], the impact of air pollution on COVID-19 severity has never been explored specifically amongst individuals with MS. The aim of this work consists in exploring the association between air pollution and COVID-19 severity specifically amongst MS patients, assessing air pollution by long-term exposures to PM2.5, which is the principal pollutant that impacts on human health.

METHODS

Demographic and clinical characteristics about COVID-19 severity were extracted from an Italian web-based platform (MuSC-19 project) containing clinician-reported data from 118 Italian MS centres. Details about data sharing agreements and ethical committee approval as well as about the variables collected in the platform and the

imputation methodology used to account for missing baseline characteristics have already been explained elsewhere [18]. Concerning environmental data, PM2.5 ground-level concentrations were derived from air quality model results, as provided by the Copernicus Atmospheric Monitoring Service [19], in correspondence with the place of exposure to SARS-CoV-2 reported by the patients. In particular, it is mainly the long-term exposure to bad air quality that can cause damage and weaken the cardiovascular and respiratory systems [20]. As such, in this study the PM2.5 yearly average for the 3-year period ending in 2018, which consists of the last year with available validated data, was considered. Adult MS patients with available PM2.5 concentrations and with a positive test (reverse transcription polymerase chain reaction on nasal and pharyngeal swabs) for SARS-CoV-2 or a positive serological test obtained at any point during the observation period (15 January 2020 to 9 April 2021) were included. Demographic and MS characteristics were presented as mean with standard deviation (SD), median with interquartile range (IQR = Q3–Q1) and number and percentage, depending on the nature of the variables. COVID-19 severity was defined on three levels as mild course, hospitalization and ICU admission or death. Ordered logistic regression models were used to study the association between PM2.5 and COVID-19 severity, running univariate models as well as a multivariate model controlling for the most relevant variables, also adjusting for geographical area (north, centre and south Italy) as a sensitivity analysis. Additionally, as a sensitivity analysis, ordered logistic regression models (univariate and multivariate) were also run using tertiles of PM2.5 concentrations, and interactions of PM2.5 with body mass index and with the presence of at least one comorbidity were investigated. In order to perform the ordered logistic regression models, the assumption of proportional odds was first checked for.

RESULTS

On 9 April 2021, 1087 PwMS with confirmed COVID-19 infection and with available PM2.5 exposure levels had completed their follow-up (full recovery or death) and were thus included. Baseline demographic and clinical characteristics of the cohort are presented in Table 1. The median age was 45 years (IQR 35–53), 68.7% of the patients were females and 14.6% were in a progressive phase. 934 (85.9%) patients were treated at the time of COVID-19 onset and the most used disease modifying therapy was dimethyl fumarate (17.9%). Most of the patients had a mild COVID-19 course (84.7%), 13.2% required hospitalization and 23 (2.1%) were admitted to the ICU or died (Table 1). Concentrations of PM2.5 were quite heterogeneous and are shown in Figure 1. The highest levels are clearly concentrated in the north of Italy (Po valley). Univariate and multivariate analysis evaluating factors associated with a risk of a severe COVID-19 are reported in Table 2. The results confirmed previous findings [18], indicating older age, higher Expanded Disability Status Scale, male sex and the presence of comorbidities as risk factors with a significant effect on the risk of severe COVID-19. Additionally, patients with progressive MS were at higher risk of severe COVID-19

TABLE 1 Baseline demographic and clinical characteristics of included patients

	Confirmed COVID-19 N = 1087
Age, mean (SD)	44.14 (12.20)
Female sex, N (%)	747 (68.7%)
BMI, mean (SD)	24.19 (5.22)
Presence of comorbidities, N (%)	213 (19.6%)
MS phenotype, N (%)	
Primary progressive	55 (5.1%)
Relapsing–remitting	929 (85.5%)
Secondary progressive	103 (9.5%)
MS disease duration, median (IQR)	8.57 (3.42–15.32)
EDSS, median (IQR)	2 (1–3.5)
MS treatment, N (%)	
Untreated	153 (14.1%)
Interferon	108 (9.9%)
Glatiramer-acetate	90 (8.3%)
Teriflunomide	71 (6.5%)
Dimethyl-fumarate	194 (17.9%)
Natalizumab	138 (12.7%)
Fingolimod	126 (11.6%)
Anti-CD20	148 (13.6%)
Other	59 (5.4%)
Previous methylprednisolone, N (%)	30 (2.8%)
COVID-19 course, N (%)	
Mild	921 (84.7%)
Hospitalization	143 (13.2%)
ICU or death	23 (2.1%)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; ICU, intensive care unit; IQR, interquartile range; MS, multiple sclerosis.

compared to patients with relapsing–remitting MS ($p < 0.001$) based on the univariate analysis (results not shown). Amongst the disease modifying therapies, the effect of anti-CD20 that emerged in previous analyses [18] is also confirmed (odds ratio [OR] 1.84, $p = 0.038$) versus no treatment. A strong protective effect of interferon [21] is now confirmed (OR 0.30, $p = 0.016$) and a protective role of teriflunomide is also emerging (OR 0.36, $p = 0.041$) in this larger dataset. In the univariate analysis PM2.5 concentrations were not significantly associated with COVID-19 severity ($p = 0.09$), but after controlling for the other relevant variables higher concentrations of PM2.5 were significantly associated with increased odds of developing a worse COVID-19 prognosis (OR 1.90; $p = 0.009$). Results remained consistent when third versus first tertiles of PM2.5 concentrations were compared (Table 3). Also when geographical area was additionally adjusted for, a significant difference comparing third versus first tertiles of PM2.5 concentrations was found (OR 1.85; p value 0.017). No significant interactions of PM2.5 with body mass index or with the presence of comorbidities were found.
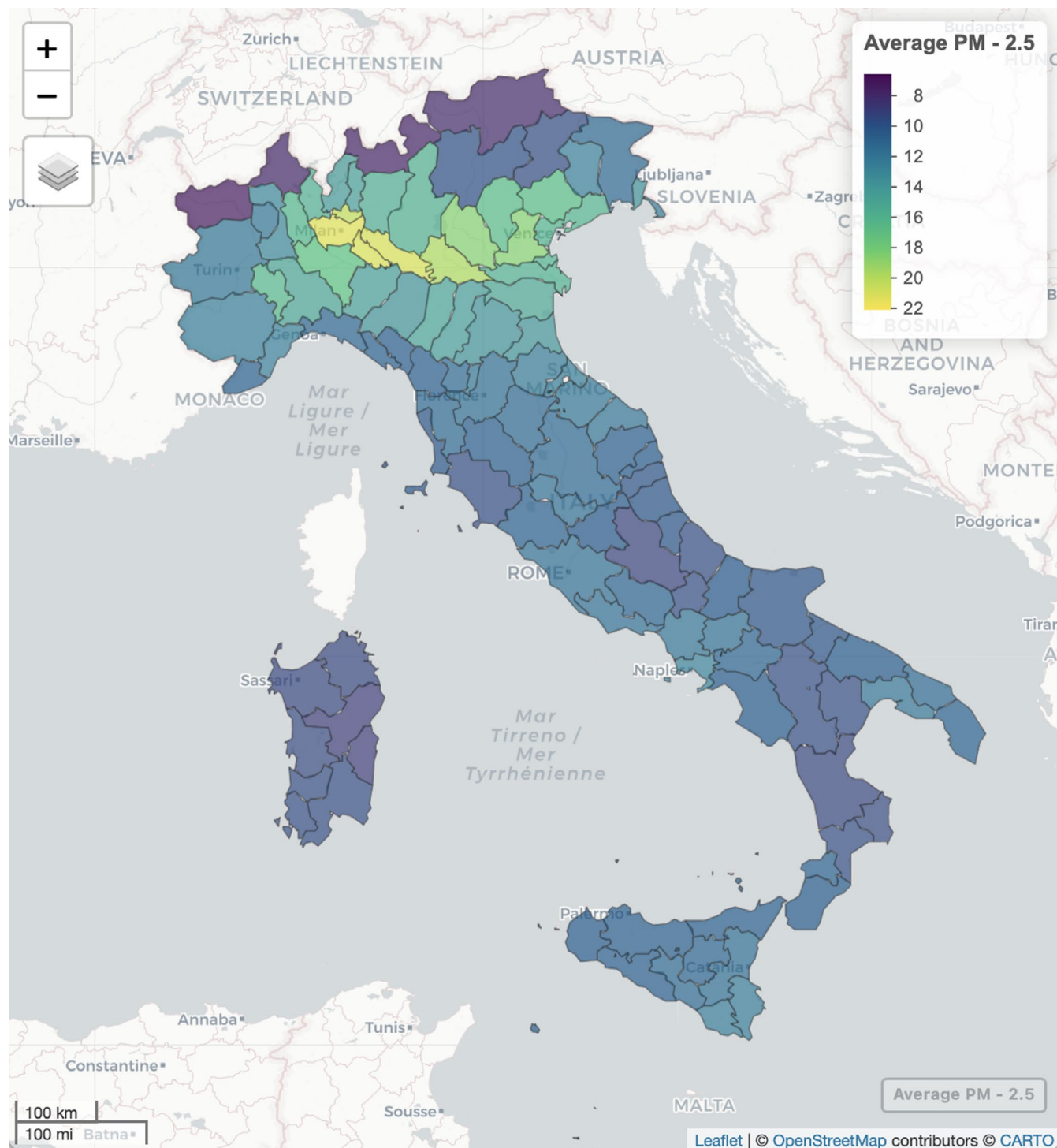
FIGURE 1 PM2.5 2016–2018 average concentrations in Italy [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

Air pollution is a major environmental cause of morbidity and mortality worldwide. Being a serious risk factor of respiratory infections and/or aggravation of existing pulmonary and cardiac diseases, it is responsible for about 4 million deaths each year [22]. In the past, during the 2003 SARS outbreak in the Republic of China, SARS patients from regions with high air pollution levels had a significantly higher risk of dying compared to those from regions with low air pollution [23]. The new SARS (SARS-CoV-2) can result in a self-limiting disease in about 80% of patients, but the remaining 20% get complicated by serious pneumonia with acute respiratory distress syndrome [24,25] possibly leading to death [26]. The rapid pandemic spread has involved all world countries [27], and Italy has emerged as one of the most affected countries with a very high number of deaths, the majority of which are in northern regions

TABLE 2 Univariate and multivariate ordinal logistic regression models evaluating risk factors for severe coronavirus disease 2019

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
PM2.5 (10-unit)	1.44 (0.94–2.21)	0.09	1.90 (1.18–3.06)	0.009
Age (10-years increase)	2.14 (1.83–2.51)	<0.001	1.66 (1.36–2.03)	<0.001
Sex: male vs. female	1.60 (1.13–2.24)	0.007	1.47 (1.01–2.14)	0.045
EDSS	1.44 (1.33–1.55)	<0.001	1.17 (1.06–1.29)	0.002
MS treatment				
Untreated	1.00 (ref)	—	1.00 (ref)	—
Interferon	0.15 (0.06–0.38)	<0.001	0.30 (0.12–0.80)	0.016
Glatiramer-acetate	0.41 (0.20–0.83)	0.013	0.79 (0.36–1.73)	0.56
Teriflunomide	0.24 (0.10–0.60)	0.002	0.36 (0.14–0.96)	0.041
Dimethyl-fumarate	0.28 (0.16–0.51)	<0.001	0.75 (0.38–1.49)	0.41
Natalizumab	0.23 (0.11–0.47)	<0.001	0.74 (0.33–1.67)	0.47
Fingolimod	0.46 (0.25–0.84)	0.012	0.82 (0.41–1.61)	0.56
Anti-CD20	1.03 (0.62–1.71)	0.90	1.84 (1.03–3.26)	0.038
Other	0.55 (0.25–1.18)	0.12	0.59 (0.25–1.38)	0.23
Comorbidities: yes vs. no	4.29 (3.01–6.12)	<0.001	2.55 (1.70–3.82)	<0.001
Methylprednisolone: yes vs. no	2.40 (1.09–5.30)	0.030	2.05 (0.86–4.91)	0.11

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OR, odds ratio; PM2.5, particulate matter with diameter below 2.5 µg/m^3.

TABLE 3 Univariate and multivariate ordinal logistic regression models evaluating PM2.5 tertiles concentrations and the risk of severe COVID-19

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
PM2.5 <11.57	1.00 (ref)	—	1.00 (ref)	—
PM2.5 11.57–15.55	0.92 (0.60–1.39)	0.68	1.09 (0.69–1.73)	0.71
PM2.5 ≥15.72	1.43 (0.97–2.10)	0.07	1.92 (1.24–2.97)	0.003

Note: Multivariate analysis included age, sex, EDSS, MS treatment, presence of at least one comorbidity and methylprednisolone use.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OR, odds ratio; PM2.5, particulate matter with diameter below 2.5 µg/m^3.

where air quality is a major concern. In the Po valley in northern Italy, PM concentrations are elevated due to high anthropogenic emissions, peculiar geographical features (the natural barrier of the Alps extending north) and low wind speed, which favour the accumulation of air pollutants. Recent studies indicated that acute and chronic exposure to air pollution is related to the incidence, prevalence, severity and mortality of COVID-19 [28]. Amongst air pollutants, PM2.5 is more toxic since it is easily respirable and can deposit more deeply in the lungs than larger particles [29]. The exposure to high levels of PM2.5 was associated with the risk of having autoimmune inflammatory diseases [14], as well as with the risk of MS developing [15] and exacerbations [30]. Taking into account

the above separately analysed relationships between air pollution exposure, MS and mortality from COVID-19, studying the different severities of COVID-19 infection in a large cohort of MS patients in relation to their previous exposure to air pollutants was considered. Our findings do not reveal a higher occurrence of severe COVID-19 infection in MS patients living in highly polluted areas but suggest that a high concentration of air pollutants might be a relevant co-factor of risk of unfavourable COVID-19 evolution when associated with the other already known risk factors, indicating that air pollutants could exert an additional impact on patients suffering from MS. This could occur through various mechanisms related not only to respiratory impairment but also to the inflammatory up-stimulation leading to the dreaded cytokine storm syndrome [31]. Air pollutants inhaled in the lower respiratory tract may stimulate lung resident dendritic cells (DCs) and, after migration to bronchial associated lymphoid tissue, induce a pro-inflammatory response with generation of Th17 cells and enhance their migratory properties, ultimately leading to inflammatory exacerbations [32]. This observation parallels previous evidence in experimental autoimmune encephalomyelitis, the animal model of MS, of a primary role of the lung in licensing auto-reactive lymphocytes to enter the central nervous system by boosting their migratory properties [33]. PM could increase interleukin 1beta (IL1beta), IL6 and IL23 production by DCs and enhance DC-dependent generation of IL17-producing T cells [32]. Finally, air pollution might trigger epigenetic changes, especially DNA methylation alterations, resulting in pro-inflammatory cytokine production [33]. In this regard and remembering that one of the factors associated with a severe evolution of COVID-19 is being overweight, it is interesting to note that the effects of PM exposure on the methylation of clock genes is particularly enhanced in subjects with obesity [34]. To conclude, chronic exposure to nanoparticles such as PM2.5, that are smaller than cells and their organelles, can contribute to the damage of lungs, heart and other organs and make them more vulnerable to viral attack, especially in elderly and fragile individuals [29]. Furthermore, the exposure to atmospheric pollution could induce modifications of the immune system, favouring pro-inflammatory and auto-aggressive responses leading to severe evolution of COVID-19, until death. Even if several other factors (comorbidities, genotype, gender–age composition, population density and mobility, socioeconomic status, different communities' behaviours, ICU availability) [35] may explain the unfavourable course of COVID-19, the role of air pollutants deserves to be taken into consideration and further investigated. Future research should surely take into consideration more pollutants than just PM2.5, in order to evaluate the complex nature of pollution as an environmental mixture. Additionally, this research can be improved by retrieving more details on the place of exposure of the patients: patient-reported place of infection to COVID-19 has been collected, but retrieving data about where they lived for the longest time would certainly be more appropriate for assessing their long-term exposure since it is possible that in the last few years some patients have moved or changed habits concerning regularly frequented places.

AUTHOR CONTRIBUTIONS

Roberto Bergamaschi: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review and editing (equal). Marta Ponzano: Conceptualization (equal); data curation (equal); methodology (equal); writing—original draft (equal); writing—review and editing (equal). Irene Schiavetti: Conceptualization (equal); data curation (equal); methodology (equal); writing—review and editing (equal). Luca Carmisciano: Conceptualization (equal); data curation (equal); writing—review and editing (equal). Cinzia Cordioli: Conceptualization (equal); writing—review and editing (equal). Massimo Filippi: Conceptualization (equal); writing—review and editing (equal). Marta Radaelli: Conceptualization (equal); writing—review and editing (equal). Paolo Immovilli: Conceptualization (equal); writing—review and editing (equal). Marco Capobianco: Conceptualization (equal); writing—review and editing (equal). Nicola De Rossi: Conceptualization (equal); writing—review and editing (equal). Giampaolo Brichetto: Conceptualization (equal); writing—review and editing (equal). Eleonora Cocco: Conceptualization (equal); writing—review and editing (equal). Cinzia Scandellari: Conceptualization (equal); writing—review and editing (equal). Paola Cavalla: Conceptualization (equal); writing—review and editing (equal). Ilaria Pesci: Conceptualization (equal); writing—review and editing (equal). Antonio Zito: Conceptualization (equal); writing—review and editing (equal). Paolo Confalonieri: Conceptualization (equal); writing—review and editing (equal). Girolama Alessandra Marfia: Conceptualization (equal); writing—review and editing (equal). Paola Perini: Conceptualization (equal); writing—review and editing (equal). Matilde Inglese: Conceptualization (equal); writing—review and editing (equal). Maria Trojano: Conceptualization (equal); writing—review and editing (equal). Vincenzo Brescia Morra: Conceptualization (equal); writing—review and editing (equal). Enrico Pisoni: Conceptualization (equal); writing—review and editing (equal). Gioacchino Tedeschi: Conceptualization (equal); writing—review and editing (equal). Giancarlo Comi: Conceptualization (equal); writing—review and editing (equal). Mario Alberto Battaglia: Conceptualization (equal); writing—review and editing (equal). Francesco Patti: Conceptualization (equal); writing—review and editing (equal). Marco Salvetti: Conceptualization (equal); writing—review and editing (equal). Maria Pia Sormani: Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review and editing (equal). Study MuSC-19: Conceptualization (equal); writing—review and editing (equal).

ETHICAL APPROVAL

The study was approved by the Regional Ethics Committee of Liguria (University of Genoa) (n 130/2020 – DB id 10433) and at a national level by Agenzia Italiana del Farmaco (AIFA).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Marta Ponzano https://orcid.org/0000-0003-4091-4686
Irene Schiavetti https://orcid.org/0000-0002-5460-2977
Luca Carmisciano https://orcid.org/0000-0001-6263-3864
Massimo Filippi https://orcid.org/0000-0002-5485-0479
Marco Capobianco https://orcid.org/0000-0003-2501-2932
Giampaolo Brichetto https://orcid.org/0000-0003-2026-3572
Antonio Zito https://orcid.org/0000-0001-8720-1742
Giancarlo Comi https://orcid.org/0000-0002-6989-1054
Francesco Patti https://orcid.org/0000-0002-6923-0846

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. https://doi.org/10.1056/NEJMoa2001017
2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it; 2020 (accessed 5 July 2021).
3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020; 2020. Accessed July 5, 2021.
4. Giovanetti M, Benvenuto D, Angeletti S, et al. The first two cases of 2019-nCoV in Italy: where they come from? *J Med Virol*. 2020;92(5):518-521. https://doi.org/10.1002/jmv.25699
5. La Maestra S, Abbondandolo A, De Flora S. Epidemiological trends of COVID-19 epidemic in Italy over March 2020: from 1000 to 100 000 cases. *J Med Virol*. 2020;92(10):1956-1961. https://doi.org/10.1002/jmv.25908
6. Lab 24: Coronavirus in Italia, i dati e la mappa. https://lab24.ilsole24ore.com/coronavirus/; 2020. Accessed July 5, 2021.
7. Azzolina D, Lorenzoni G, Silvestri L, et al. Regional differences in mortality rates during the COVID-19 epidemic in Italy. *Disaster Med Public Health Prep*. 2020;14:1-7. https://doi.org/10.1017/dmp.2020.486
8. Conticini E, Frediani B, Caro D. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in northern Italy? *Environ Pollut*. 2020;261:114465.

9. Pozzer A, Dominici F, Haines A, et al. Regional and global contributions of air pollution to risk of death from COVID-19. *Cardiovasc Res*. 2020;116(14):2247-2253. https://doi.org/10.1093/cvr/cvaa288

10. Frontera A, Cianfanelli L, Vlachos K, et al. Severe air pollution links to higher mortality in COVID-19 patients: the 'double-hit' hypothesis. *J Infect*. 2020;81(2):255-259. https://doi.org/10.1016/j.jinf.2020.05.031

11. Magazzino C, Mele M, Schneider N. The relationship between air pollution and COVID-19-related deaths: an application to three French cities. *Appl Energy*. 2020;279:115835. https://doi.org/10.1016/j.apenergy.2020.115835

12. Yao Y, Pan J, Liu Z, et al. Temporal association between particulate matter pollution and case fatality rate of COVID-19 in Wuhan. *Environ Res*. 2020;189:109941.

13. Bowe B, Xie Y, Gibson AK, et al. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. *Environ Int*. 2021;154:106564. https://doi.org/10.1016/j.envint.2021.106564

14. Zhao CN, Xu Z, Wu GC, et al. Emerging role of air pollution in autoimmune diseases. *Autoimmun Rev*. 2019;18(6):607-614. https://doi.org/10.1016/j.autrev.2018.12.010

15. Bergamaschi R, Monti MC, Trivelli L, et al. PM2.5 exposure as a risk factor for multiple sclerosis. An ecological study with a Bayesian mapping approach. *Environ Sci Pollut Res Int*. 2021;28(3):2804-2809. https://doi.org/10.1007/s11356-020-10595-5

16. Tateo F, Grassivaro F, Ermani M, et al. PM2.5 levels strongly associate with multiple sclerosis prevalence in the Province of Padua, Veneto Region, North-East Italy. *Mult Scler*. 2019;25(13):1719-1727. https://doi.org/10.1177/1352458518803273

17. Noorimotlagh Z, Azizi M, Pan HF, et al. Association between air pollution and multiple sclerosis: a systematic review. *Environ Res*. 2021;196:110386. https://doi.org/10.1016/j.envres.2020.110386

18. Sormani MP, De Rossi N, Schiavetti I, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol*. 2021;89(4):780-789. https://doi.org/10.1002/ana.26028

19. Inness A, Ades M, Agustì-Panareda A, et al. The CAMS reanalysis of atmospheric composition. *Atmos Chem Phys*. 2019;19(6):3515-3556. https://doi.org/10.5194/acp-19-3515-2019

20. Bu X, Xie Z, Liu J, et al. Global PM2.5-attributable health burden from 1990 to 2017: estimates from the Global Burden of Disease study 2017. *Environ Res*. 2021;197:111123. https://doi.org/10.1016/j.envres.2021.111123

21. Sormani MP, Salvetti M, Labauge P, et al. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. *Ann Clin Transl Neurol*. 2021;8(8):1738-1744. https://doi.org/10.1002/acn3.51408.

22. Landrigan PJ, Fuller R, Acosta NJR, et al. The Lancet Commission on pollution and health. *Lancet*. 2018;391(10119):462-512. https://doi.org/10.1016/S0140-6736(17)32345-0. Epub 2017 Oct 19. Erratum in: Lancet. 2018;391(10119):430.

23. Cui Y, Zhang ZF, Froines J, et al. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. *Environ Health*. 2003;2:15. https://doi.org/10.1186/1476-069X-2-15

24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648

25. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-848. https://doi.org/10.1007/s00134-020-05991-x. Epub 2020 Mar 3. Erratum in: Intensive Care Med. 2020 Apr 6: PMID: 32125452; PMCID: PMC7080116.

26. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020;323(18):1775-1776. https://doi.org/10.1001/jama.2020.4683. Erratum. In: JAMA. 2020 Apr 28;323(16):1619. PMID: 32203977.

27. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-76. https://doi.org/10.1016/j.ijsu.2020.02.034. Epub 2020 Feb 26. Erratum in: Int J Surg. 2020 May;77:217. PMID: 32112977; PMCID: PMC7105032.

28. Katoto PDMC, Brand AS, Bakan B, et al. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity and mortality of COVID-19: a rapid systematic review. *Environ Health*. 2021;20(1):41. https://doi.org/10.1186/s12940-021-00714-1

29. Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol*. 2007;19(14):1135-1146. https://doi.org/10.1080/08958370701665434

30. Bergamaschi R, Cortese A, Pichiecchio A, et al. Air pollution is associated to the multiple sclerosis inflammatory activity as measured by brain MRI. *Mult Scler*. 2018;24(12):1578-1584. https://doi.org/10.1177/1352458517726866

31. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34(2):327-331. https://doi.org/10.23812/CONTI-E

32. Cortese A, Lova L, Comoli P, et al. Air pollution as a contributor to the inflammatory activity of multiple sclerosis. *J Neuroinflammation*. 2020;17(1):334. https://doi.org/10.1186/s12974-020-01977-0

33. Odoardi F, Sie C, Streyl K, et al. T cells become licensed in the lung to enter the central nervous system. *Nature*. 2012;488(7413):675-679. https://doi.org/10.1038/nature11337

34. Monti P, Iodice S, Tarantini L, et al. Effects of PM exposure on the methylation of clock genes in a population of subjects with overweight or obesity. *Int J Environ Res Public Health*. 2021;18(3):1122. https://doi.org/10.3390/ijerph18031122

35. Du RH, Liu LM, Yin W, et al. Hospitalization and critical care of 109 decedents with COVID-19 pneumonia in Wuhan, China. *Ann Am Thorac Soc*. 2020;17(7):839-846. https://doi.org/10.1513/AnnalsATS.202003-225OC

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

[Correction added on 15 December 2021, after first online publication: Supporting information containing list of contributors in MuSC-19 study group has been added.]

How to cite this article: Bergamaschi R, Ponzano M, Schiavetti I, et al. The effect of air pollution on COVID-19 severity in a sample of patients with multiple sclerosis. *Eur J Neurol*. 2022;29:535–542. https://doi.org/10.1111/ene.15167