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ORIGINAL RESEARCH

Reducing Early-Life Smoke Exposure as a Preventive Strategy for Pediatric Multiple Sclerosis: Results from the PEDIGREE Study

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ABSTRACT

***Introduction*:** Assessing the environmental impact on multiple sclerosis (MS) is complex because of long disease latency and potential recall bias, especially for perinatal exposures. This study aimed to investigate the association between parental smoking and the development of pediatric MS (PedMS).

***Methods*:** As part of the Italian multicenter PEDIGREE study, the PEQ-IT questionnaire was used for prospective data collection. We enrolled subjects under 18 years with PedMS (2013 Krupp criteria) and disease duration ≤ 5 years from onset, along with matched controls.

***Results*:** The study included 114 PedMS cases and 121 controls. Female participants represented 77.2% of cases and 54.4% of controls,

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with a mean (SD) age of 16.8 (2.7) and 13.5 (4.9) years, respectively. The mean (SD) age at MS onset was 14.2 (2.6) years, and the median EDSS score was 1.0 (range 0–4.0). PedMS risk was higher in subjects with fathers who were current smokers (crude OR 1.94, 95% CI 1.10–3.40) or who smoked 3 months' pre-pregnancy (crude OR 1.79, 95% CI 1.03–3.11). The risk increased when both parents smoked (crude OR 2.03, 95% CI 1.12–3.68) and was highest when both smoked 3 months before pregnancy (crude OR 10.79, 95% CI 1.30–89.54), even after adjustments. No significant association was found with maternal smoking.

***Conclusion*:** Parental smoking, particularly paternal smoking current habit and before pregnancy, may increase the risk of PedMS. Promoting smoke-free behaviors among parents could therefore represent a feasible preventive approach to limit early-life environmental factors involved in disease susceptibility.

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Key Summary Points

Why carry out this study?

Pediatric multiple sclerosis (PedMS) represents 3–10% of total MS cases and carries a significant lifelong disease burden. Environmental factors, including cigarette smoke exposure, are suspected to influence disease risk, but evidence in pediatric populations remains limited.

Understanding whether parental smoking—before or during pregnancy or in early childhood—affects PedMS risk could identify a modifiable environmental factor and guide prevention strategies.

The study investigated whether exposure to parental cigarette smoking increases the risk of developing PedMS, hypothesizing that both maternal and paternal smoking, particularly pre-pregnancy exposure, contribute to disease susceptibility.

What was learned from the study?

In a multicenter Italian case–control cohort (114 cases, 121 controls), parental smoking—especially when both parents smoked or when smoking occurred in the 3 months prior to pregnancy—was associated with a higher risk of PedMS (adjusted OR up to 11.60, 95% CI 1.36–98.96).

Paternal smoking habits appeared to have a stronger influence than maternal smoking, suggesting potential paternal-specific biological or environmental mechanisms.

Even though some associations lost significance after adjustment, these findings highlight parental smoking as a potentially modifiable environmental risk factor. Promoting smoke-free environments before and during pregnancy may represent a cost-effective preventive measure for reducing PedMS risk.

INTRODUCTION

Multiple sclerosis (MS) is a chronic neurologic disorder characterized by demyelination and axonal loss in the central nervous system (CNS). Pediatric multiple sclerosis (PedMS) is a relatively rare condition, accounting for 3–10% of total MS cases [1, 2]. The etiology of MS is multifactorial, involving complex interactions between genetic predispositions and environmental exposures. Environmental factors, particularly those encountered early in life, are increasingly recognized for their role in influencing risk and disease progression in both adult and pediatric populations [3]. Low vitamin D serum levels [4], reduced sunlight exposure [5, 6], EBV infection during childhood and adolescence [7], and obesity [8] are significant risk factors in both age groups. Limited evidence suggests that also reduced infant breastfeeding [9] and household chemical exposures [10] may play a role in influencing PedMS risk. From a preventive standpoint, limiting children's exposure to cigarette smoke may contribute to reducing the risk of MS onset. Promoting smoke-free environments therefore represents a potential avenue for primary prevention in susceptible pediatric populations.

While observational studies have consistently shown an association between active smoking habit and increased MS risk and progression in adults [11–14] the role of cigarette smoke exposure in influencing the disease risk in the pediatric population is less studied. However, initial evidence focused on parental smoke exposure seems to point to the same conclusion also in the youngest patients. A case–control study conducted on the French KIDSEP neuropediatric cohort found a two-fold increased exposure and dose–response effect of smoking in PedMS [15]. Additionally, secondhand smoking was reported to be 3.7-fold more common in PedMS cases compared to monophasic acquired demyelinating syndrome when associated with *HLA-DRB1*15* [16].

Here, we aim to assess whether exposure to parental cigarette smoking is associated to an increased risk in patients with PedMS, benefitting from data from the PEDiatric Italian Genetic and enviRonment ExposurE (PEDIGREE) study. Cigarette smoke exposure may represent a modifiable protective factor in pediatric populations, reinforcing the importance of early-life prevention strategies aimed at reducing environmental risks for MS.

METHODS

Study Population

This research is part of the PEDIGREE study, a multicenter case–control study designed to investigate the genetic and environmental factors associated with PedMS in an Italian population and across 29 participating MS centers [17] (Supplementary material). Genetic and environmental data were collected between August 2020 and December 2023. Cases were subjects diagnosed with PedMS according to the diagnostic criteria in use at the time (Krupp et al., 2013 [18]), before 18 years of age and with a disease duration of 5 years or less. This time window was chosen to increase the number of eligible participants, given the rarity of PedMS, while still ensuring that cases were enrolled relatively close to disease onset. This approach allowed for more accurate reporting of early-life exposures and helped minimize recall bias in both patients and their parents. Controls were primarily recruited from Italian child neuropsychiatry units, with some additional participants drawn from the general population. They had no history of inflammatory disorders of the central nervous system. The study protocol initially aimed for a 1:2 case-to-control matching ratio based on age and sex. Recruitment began following this plan, but challenges in enrolling enough controls resulted in a final ratio of roughly 1:1. Despite the lack of perfect matching at recruitment, exposure information for all participants referred to the same early-life period.

Data Collection and Exposure Assessment

Environmental, prenatal, and perinatal exposure data were obtained using the PEQ-IT questionnaire, adapted from a USA-based tool and validated through a pilot study, whose methodology is reported in detail elsewhere [19]. The full version of the questionnaire, in Italian, is also fully available in that publication. Briefly, the development of the PEQ-IT involved translating and adapting the existing US tool, ensuring cultural relevance, acceptability, feasibility, and reliability through a pilot study. The questionnaire includes detailed questions on perinatal events and lifestyle exposures of the parents and of the children, tailored specifically to the Italian context.

The primary exposure of interest was parental smoking status, including smoking habits of both the father and the mother before, during, and after pregnancy, as well as smoking habits of the children participating in the study. The questionnaire included a series of questions aimed at gathering detailed information on the smoking habits of the biological parents and, for older children, their own smoking habits. It was completed by parents and by children when aged 10 years or older. Participants were first asked about the biological mother's smoking history. They were questioned whether the mother currently smoked, had smoked in the past, or had never smoked. If she smoked in the past, participants were asked to specify the month and year she last smoked. Next, participants were asked if the biological mother smoked during various critical periods: during pregnancy, in the 3 months before pregnancy, between the child's birth and their first birthday, and when the child was aged 1–5 years, 6–10 years, 11–15 years, and 16 years or older. For each period, the possible responses were "Yes," "No," or "I don't know." Information about the biological father's smoking habits was also collected. Participants were asked if the father had ever smoked at least one hundred cigarettes, pipes, or cigars in his lifetime and, if so, at what age he started smoking. They were also asked if the biological father or the primary father figure/guardian currently smokes and, if so, when he last smoked. Furthermore,

participants were asked whether the father smoked in the 3 months before the biological mother's pregnancy. Again, responses included "Yes," "No," or "I don't know." For pediatric subjects aged 10–17 years, additional questions were asked regarding their own smoking habits to be completed by themselves in order to avoid bias. They were asked if they currently smoked, had smoked in the past, or had never smoked. If they had smoked in the past, they were requested to indicate the month and year they last smoked. Demographic and clinical characteristics (date of birth, sex, year of onset, duration of follow-up, treatment exposure, EDSS) were recorded by clinicians in a separate case report form (CRF).

Statistical Analysis

Frequencies (percent) were reported for categorical variables and mean [standard deviation (SD)] for continuous variables. Fisher exact test and Mann–Whitney *U* test were used to calculate significance after comparison of categorical and continuous non-parametric variables, respectively. The association between parental smoking and the risk of PedMS was assessed using logistic regression models, adjusting for potential confounders (sex, mother's education at participants' birth). Results were expressed as crude (ORs) and adjusted (adjORs) odds ratios with 95% confidence intervals (CIs), indicating the risk of PedMS associated with various smoking exposures. Participants with missing information for a given exposure variable (classified as "Unknown") were excluded from the corresponding regression analyses. The Statistical Package for the Social Sciences (SPSS) versions 20 and 27 for Windows (SPSS Inc., IBM, Somers, New York, USA) [20, 21] was used for statistical analysis.

Statement of Ethics

The study protocol was approved by the ethics committees of all participating centers and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians prior to study enrollment.

RESULTS

The demographic and clinical characteristics of the study population, comprising 114 cases and 121 controls, are summarized in Table 1. The cases had a mean (SD) age of 16.8 (2.7) years as compared to controls with a mean age of 13.5 (4.9) years ($p<0.001$). A higher proportion of cases were female (77.2%) compared to controls (54.4%) ($p<0.001$). The mean (SD) age at disease onset was 14.2 (2.6) years, with an average disease duration of 28.5 months.

The association between exposure to parental cigarette smoking habits among MS cases and controls as the crude and adjusted ORs is reported in Table 2. For participants aged 10–17 years, being an ever smoker was not significantly associated with MS in crude analysis (OR 1.49, 95% CI 0.74–2.99, $p=0.295$), and this association remained non-significant after adjustment (adjOR 1.40, 95% CI 0.63–3.08, $p=0.405$).

For parental smoking habits, a history of smoking in both parents was significantly associated with MS in crude analysis (OR 2.03, 95% CI 1.12–3.68, $p=0.024$), but this association decreased after adjustment (adjOR 1.79, 95% CI 0.92–3.47, $p=0.085$). When considering smoking 3 months prior to pregnancy, both parents smoking showed a significant crude association with MS (OR 10.79, 95% CI 1.30–89.54, $p=0.028$), which remained significant after adjustment (adjOR 11.60, 95% CI 1.36–98.96, $p=0.025$).

For mothers, a history of smoking was not significantly associated with MS in crude analysis (OR 1.59, 95% CI 0.92–2.76, $p=0.098$), and after adjustment (adjOR 1.60, 95% CI 0.87–2.93, $p=0.128$). Similarly, smoking during pregnancy showed no significant association with MS, both before and after adjustment. Smoking habit over the 3 months prior to

Table 1 Demographic and clinical characteristics of the study population

	Cases ($n = 114$)	Controls ($n = 121$)	p
Age at time of study, mean (SD), years	16.8 (2.7)	13.5 (4.9)	< 0.001
Female sex (%)	88 (77.2)	67 (54.4)	< 0.001
Age at disease onset, mean (SD), years	14.2 (2.6)	–	–
Disease duration, mean (SD), years	28.5 (23.1)	–	–
EDSS mean (range)[b]	1.4 (0–4.0)	–	–
Education of the mother at pregnancy, *N* (%)			
None/elementary degree	1 (0.9)	1 (0.8)	< 0.001
Junior high degree	32 (28.1)	7 (5.8)	
Secondary degree	38 (33.3)	45 (37.2)	
University degree	30 (26.3)	53 (43.8)	
Unknown	13 (11.4)	15 (12.4)	
Participant's active smoking habit[a], *N* (%)			
Never smokers	72 (63.2)	73 (60.3)	0.067
Ever smokers	25 (21.9)	17 (14.1)	
Unknown	17 (14.9)	31 (25.6)	
Maternal smoking habit, *N* (%)			
Never smoker	61 (53.5)	80 (66.1)	0.107
Ever smoker	45 (39.5)	37 (30.6)	
Unknown	8 (7.0)	4 (3.3)	
Maternal smoking habit during pregnancy, *N* (%)			
Non-smoker	90 (78.9)	97 (80.2)	0.824
Smoker	11 (9.6)	13 (10.7)	
Unknown	13 (11.4)	11 (9.1)	
Maternal smoking habit 3 months pre-pregnancy, *N* (%)			
Non-smoker	92 (80.7)	98 (81.0)	0.107
Smoker	9 (7.9)	3 (2.5)	
Unknown	13 (11.4)	20 (16.5)	
Maternal smoking habit when participant is aged < 1 year, *N* (%)			
Non-smoker	84 (73.3)	97 (80.2)	0.323
Smoker	10 (8.8)	11 (9.1)	
Unknown	20 (17.5)	13 (10.7)	

Table 1 continued

	Cases ($n = 114$)	Controls ($n = 121$)	p
Maternal smoking habit when participant is aged 2–5 years, N (%)			
Non-smoker	81 (71.1)	86 (71.1)	0.909
Smoker	20 (17.5)	23 (19.0)	
Unknown	13 (11.4)	12 (9.9)	
Maternal smoking habit when participant is aged 6–10 years, N (%)			
Non-smoker	75 (65.8)	84 (69.4)	0.808
Smoker	22 (19.3)	22 (18.2)	
Unknown	17 (14.9)	15 (12.4)	
Paternal smoking habit, N (%)			
Never smoker	56 (49.1)	83 (68.6)	0.007
Ever smoker	38 (33.3)	28 (23.1)	
Unknown	20 (17.5)	10 (8.3)	
Paternal smoking habit 3 months pre-pregnancy, N (%)			
Non-smoker	49 (43.0)	73 (60.3)	0.014
Smoker	48 (42.1)	40 (33.1)	
Unknown	17 (14.9)	8 (6.6)	

[a]Investigated in subject aged 10–17 years old

[b]Calculated on 107/114 available EDSS score

pregnancy also did not show a significant association, though an almost significant result was observed after adjustment (adjOR 3.75, 95% CI 0.95–14.76, $p = 0.059$). No significant associations were found between mother's smoking habit at different age range of the child and PedMS (Data not shown).

For fathers, a history of smoking was significantly associated with MS in crude analysis (OR 1.94, 95% CI 1.10–3.40, $p = 0.024$), but this association became non-significant after adjustment (adjOR 1.46, 95% CI 0.79–2.73, $p = 0.231$). Similarly, smoking 3 months prior to pregnancy showed a significant crude association with MS (OR 1.79, 95% CI 1.03–3.11, $p = 0.039$), but this was not significant after adjustment (adjOR 1.59, 95% CI 0.86–2.93, $p = 0.142$).

DISCUSSION

In this study, we examined whether parental smoking exposure contributes to the risk of pediatric multiple sclerosis (PedMS). Overall, our adjusted analyses did not reveal consistent independent associations between either paternal or maternal smoking and disease risk. However, crude analyses suggested a potentially stronger influence of paternal smoking compared with maternal smoking. Thus, the potential role of paternal smoking should be considered exploratory rather than conclusive. In addition, a possible signal emerged for combined parental smoking during the 3 months preceding pregnancy. Despite the limitations outlined below, these findings may indicate a potential contribution of very early-life or preconceptional smoking exposure to PedMS susceptibility.

Table 2 Crude and adjusted odds ratios (95% CIs) for the association between parental or active cigarette smoking habit and MS status (cases vs. controls)

	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	*p*	adjOR (95% CI)	*p*
Mother						
History of smoking habit						
Never smoker	61 (57.5)	80 (68.4)	1.0		1.0	
Ever smoker	45 (42.5)	37 (31.6)	1.59 (0.92, 2.76)	0.098[a]	1.60 (0.87, 2.93)	0.128[b]
Smoking during pregnancy						
Non-smoker	90 (89.1)	97 (88.2)	1.0		1.0	
Smoker	11 (10.9)	13 (11.8)	0.91 (0.39, 2.14)	0.832	1.31 (0.50, 3.43)	0.576[b]
Smoking 3 months pre-pregnancy						
Non-smoker	92 (91.1)	98 (97.0)	1.0		1.0	
Smoker	9 (8.9)	3 (3.0)	3.20 (0.84, 12.17)	0.089	3.75 (0.95, 14.76)	0.059[b]
Father						
History of smoking habit						
Never smoker	31 (31.3)	53 (46.9)	1.0		1.0	
Ever smoker	68 (68.7)	60 (53.1)	1.94 (1.10, 3.40)	0.024[a]	1.46 (0.79, 2.73)	0.231[b]
Smoking 3 months pre-pregnancy						
Non-smoker	49 (50.5)	73 (64.6)	1.0		1.0	
Smoker	48 (49.5)	40 (35.4)	1.79 (1.03, 3.11)	0.039	1.59 (0.86, 2.93)	0.142[b]
Smoking habit in both parents						
History of smoking habit						
Never smokers	59 (60.8)	85 (75.9)	1.0		1.0	
Ever smokers	38 (39.2)	27 (24.1)	2.03 (1.12, 3.68)	0.024[a]	1.79 (0.92, 3.47)	0.085[b]
Smoking 3 months pre-pregnancy						
Non-smokers	43 (47.8)	58 (59.2)	1.0[c]		1.0	
1 parent smoker	39 (43.3)	39 (39.8)	1.35 (0.75, 2.44)	0.323	1.15 (0.59, 2.24)	0.675[b]
Both smokers	8 (8.9)	1 (1.0)	10.79 (1.30, 89.54)	0.028	11.60 (1.36, 98.96)	0.025[b]
Study participants						
Active smoking habit[d]						
Never smokers	72 (74.2)	73 (81.1)	1.0		1.0	
Ever smokers	25 (25.8)	17 (18.9)	1.49 (0.74, 2.99)	0.295[a]	1.40 (0.63, 3.08)	0.405

[a]Fisher exact test

[b]Logistic regression: odds ratio (OR) adjusted for mother's education at participants' birth (adjOR)

[c]*p* trend = 0.025 (dose–response effect)

[d]Investigated in subjects aged 10–17 years old; logistic regression: odds ratio (OR) adjusted for sex and mother's education at participants' birth

Several hypotheses may explain a potentially greater influence of paternal compared to maternal smoking on PedMS risk. Men generally smoke more heavily than women [22], possibly leading to higher second-hand smoke exposure for the child. Mothers, instead, are more likely to reduce or stop smoking when planning a pregnancy, during gestation, and in early childcare, thereby limiting exposure in critical developmental periods. Differences in timing, intensity, and indoor smoking habits may also result in longer or more consistent exposure from fathers. Social and household factors, including smoking norms or socioeconomic conditions, could contribute as well. Interactions between paternal smoking and the child's genetic susceptibility may further play a role: smoking can promote lung inflammation and autoimmune responses through antigen cross-reactivity, and genetic factors such as *HLA-DRB1*15* may modulate this susceptibility [23]. Although evidence remains limited and inconsistent regarding prenatal exposure, paternal smoking has been associated with other pediatric outcomes, including asthma and respiratory infections [24], childhood cancers [25], and congenital anomalies [26], supporting the plausibility of biological effects.

In contrast, in our study maternal smoking habits, both during and before pregnancy, showed no significant association with the risk of PedMS, reinforcing the notion that maybe paternal factors might be more influential in this context. Nonetheless, a trend towards significance with maternal smoking habit suggests that with a larger sample size, these findings might reach statistical significance. Additionally, the increased risk from overall parental smoking suggests a multiplicative rather than additive interaction between maternal and paternal smoking habits before pregnancy.

The finding that parental smoking in the 3 months prior to pregnancy may be associated with PedMS susceptibility suggests that environmental factors acting during the preconceptional period warrant biological explanation. This timing is significant within the framework of the Developmental Origins of Health and Disease (DOHaD), which posits that environmental stressors, including tobacco smoke, can induce molecular alterations [27]. Potential mechanisms include epigenetic modifications, such as DNA methylation and histone marks, which control gene expression and can be transmitted via the germ line (spermatogenesis and oocyte maturation) or modulate the nascent uterine environment [27]. Exposure to tobacco smoke is well documented to cause systemic and persistent alterations in DNA methylation and gene expression in relevant pathways, including the upregulation of genes like *CYP1A1* [28, 29]. Epigenetic changes resulting from toxicant exposure during development may lead to functional changes in gene expression and increased disease risk later in life [27]. However, while this biological rationale supports the plausibility of these mechanisms, the evidence directly linking preconception smoking exposure to specific PedMS mechanisms remains limited and scarce [15, 16, 30].

A study involving a French population and including 129 children with MS and 1038 matched controls found a significant association between parental smoking and an increased risk of childhood-onset MS [15]; that study highlighted that smoking during pregnancy and exposure to second-hand smoke were particularly influential. This is somewhat consistent with our finding of an initial significant association between paternal smoking and MS risk. However, unlike our study, Mikaeloff et al. maintained these significant associations even after adjusting for confounding factors, suggesting a more robust association in their population or possibly a larger sample size that could detect smaller effect sizes [15]. Lavery et al. (2019) conducted their study in Canada, including 216 children with monophasic acquired demyelinating syndrome (mono-ADS) and 81 children with PedMS. Their study focused on second-hand smoke exposure and its interaction with genetic factors such as *HLA-DRB1*15* alleles. They found that while second-hand smoke alone was not a significant risk factor, its combination with genetic predispositions significantly increased the risk of MS. This complements our findings by emphasizing the potential role of genetic and environmental interactions in MS risk [16].

However, existing evidence is scarce and conflicting. On the basis of the Swedish MS Registry data, Montgomery et al. analyzed maternal smoking during pregnancy and found no significant association with MS risk in offspring, indicating that prenatal exposure might not be a critical factor compared to postnatal exposures [30].

The observed association in our study derives from a very small subgroup (8 cases and 1 control) and is therefore characterized by wide uncertainty, underscoring the need for larger and adequately powered cohorts to determine whether a true preconception effect exists. Importantly, previous studies have not separately evaluated maternal and paternal smoking, and our results add preliminary, hypothesis-generating insight suggesting that these exposures may contribute differently to PedMS susceptibility. However, given the limited sample size and the instability of the estimates, these patterns should be interpreted cautiously and considered as exploratory signals that require confirmation in future research.

Finally, our findings indicate no significant association between active smoking in participants aged 10–17 years and PedMS risk, though this may be influenced by the small sample size. Parental smoking, particularly pre-pregnancy or in early life, may have a greater impact due to longer exposure during critical developmental phases. Since adolescents usually start smoking close to disease onset, the shorter exposure window may limit its effect. To our knowledge, no studies have specifically examined active smoking as a risk factor for MS in the pediatric population.

This study has some limitations. The sample size may be insufficient to detect smaller effect sizes, e.g., for maternal smoking habits. Because smoking exposures were reported retrospectively, recall bias is possible; parents of affected children may recall or report past smoking habits differently than parents of controls, potentially inflating observed associations, whereas no differential recall errors would instead bias results toward the null. Additionally, the study did not account for other environmental exposures or genetic factors that might interact with parental smoking and the significant rate of missing values ("Unknown") may present an additional potential bias. Despite thorough adjustments for confounders, residual confounding cannot be ruled out, indicating a need for more sophisticated statistical methods or longitudinal data. Despite shared etiological factors, the timing and impact of environmental exposures can vary between adults and children, but research on environmental exposures in PedMS offers benefits: closer exposure to symptom onset reduces recall bias, aids in understanding adult MS etiology, and higher exposure levels in children make detection easier, with parent input enhancing data accuracy.

This study highlights a potentially relevant role of parental smoking exposure in PedMS susceptibility, an area that remains understudied and of growing interest. While the associations—particularly those involving paternal and pre-pregnancy smoking—were not consistently significant after adjustment, they point to signals worthy of further investigation. The indication of a possible combined effect when both parents smoked, although based on small numbers, contributes to an emerging line of evidence on early-life environmental influences in PedMS. Larger, adequately powered studies will be essential to confirm these preliminary observations and to clarify the distinct contributions of maternal and paternal smoking within the etiopathogenic framework of the disease. From a public health perspective, the avoidance of parental smoke exposure before and during pregnancy, as well as throughout early childhood, may constitute an actionable and cost-effective preventive measure to reduce the burden of PedMS. Establishing and maintaining smoke-free environments within families could yield a dual benefit—directly limiting children's exposure to harmful neurotoxic and proinflammatory agents, and indirectly fostering healthier parental behaviors and greater awareness of environmental risk factors. Moreover, reducing parental smoke exposure in the preconceptional period may prevent potential epigenetic alterations in germ cells that could contribute to immune dysregulation in offspring. Integrating the promotion of smoke-free homes and parental cessation support into maternal–child health and educational programs may therefore

represent a feasible strategy to mitigate the environmental component of MS susceptibility. Future research should further investigate how reinforcing smoke-free lifestyles could translate into measurable reductions in disease incidence and provide valuable insights for preventive neurology.

CONCLUSION

This multicenter study adds novel evidence on the potential influence of parental smoking—especially pre-pregnancy exposure—on susceptibility to PedMS, using an Italian national cohort and a validated questionnaire for early-life environmental factors [17, 19]. Our findings support further investigation of maternal and paternal smoking in larger, well-powered studies and reinforce the relevance of promoting smoke-free environments before and during pregnancy. However, the observed associations should be interpreted with caution, as they remain exploratory and hypothesis-generating.

Author Contributions. Silvy Pilotto, Angelo Ghezzi, Martina Tosi, Nicola Pomella, Andrea Corona, Alen Zollo, Maria Pia Amato, Eleonora Cocco, Maria Trojano, Filippo Martinelli-Boneschi, Sandra D'Alfonso, Roberto Bergamaschi e Maura Pugliatti were responsible for the conceptualization, methodology, and overall coordination of the PEDIGREE study. Silvy Pilotto and Maura Pugliatti performed the formal analysis and wrote the first draft of the manuscript. Angelo Ghezzi, Maria Pia Amato, Eleonora Cocco, Maria Trojano, Filippo Martinelli-Boneschi, Sandra D'Alfonso, Roberto Bergamaschi and Maura Pugliatti supervised the work and contributed to the interpretation of results. Silvy Pilotto, Angelo Ghezzi, Stefania Maria Bova, Marzia Fronza, Pietro Annovazzi, Marta Simone, Antonio Gallo, Agnese Suppiej, Roberta Lanzillo, Sarah Rasia, Angela Berardinelli, Valentina Torri Clerici, Lucia Moiola, Maurizio Viri, Stefano Sotgiu, Simona Malucchi, Alessandra Protti, Carlotta Canavese, Giacomo Lus, Luigi Grimaldi, Marta Zaffira Conti, Giovanna Borriello, Giovanna De Luca, Valentina Tomassini, Alberto Priori, Martina Tosi, Nicola Pomella, Andrea Corona, Alen Zollo, Maria Pia Amato, Eleonora Cocco, Maria Trojano, Filippo Martinelli-Boneschi, Sandra D'Alfonso, Roberto Bergamaschi and Maura Pugliatti contributed to data collection and patient enrolment, critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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Data Availability Statement. The data supporting the findings of this study are available from the corresponding author upon reasonable request and with approval from the PEDIGREE Study Group Committee.

Declarations

Conflict of Interest. Angelo Ghezzi is an Editorial Board member of *Neurology and Therapy* was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Silvy Pilotto, Angelo Ghezzi, Stefania Maria Bova, Marzia Fronza, Pietro Annovazzi, Marta Simone, Antonio Gallo, Agnese Suppiej, Roberta Lanzillo, Sarah Rasia, Angela Berardinelli, Valentina Torri Clerici, Lucia Moiola, Maurizio Viri, Stefano Sotgiu, Simona Malucchi, Alessandra Protti, Carlotta Canavese, Giacomo Lus, Luigi Grimaldi, Marta Zaffira Conti, Giovanna Borriello, Giovanna De Luca, Valentina Tomassini, Alberto Priori, Martina Tosi, Nicola Pomella, Andrea Corona, Alen Zollo, Maria Pia Amato, Eleonora Cocco, Maria Trojano, Filippo Martinelli-Boneschi, Sandra D'Alfonso, Roberto Bergamaschi and Maura Pugliatti have nothing to disclose in relation to this study.

Ethical Approval. The study protocol was approved by the ethics committees of all participating centers and conducted in accordance

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