

Maternal smoking and multiple sclerosis risk in offspring: A further clue of prenatal environmental triggers

Emilio Portaccio  and Pietro Iaffaldano 

Date received: 1 December 2023; accepted: 16 December 2023

Multiple sclerosis (MS) is a complex, inflammatory, and neurodegenerative disease of the central nervous system, whose exact cause is not fully understood. Among potential risk factors, there is consistent evidence indicating that active and passive smoking increases the risk of both the development of MS and a more aggressive disease course after onset.¹ On the contrary, the potential effects of smoking during pregnancy on the risk of MS in offspring have not yet been clarified. Smoking during pregnancy has been shown to influence fetal development, including that of the nervous system and immune system,² and could therefore interfere with the normal immunological containment of other MS triggers, such as Epstein–Barr virus infection. A few previous studies on this topic obtained conflicting evidence of an association with higher risk of developing MS, mainly due to potential methodological limitations, such as small sample size and both recall and selection biases.³

With this background, in order to overcome these issues, Nielsen et al.³ explored the association between maternal smoking and the risk of MS in their children on data from Danish national registers. Using the Medical Birth Register (MBR) and the National Patient Register (NPR), they studied all Danish women, pregnant in the period 1991–2018, ($n=789,299$) and singletons from these pregnancies ($n=879,135$). The nationwide coverage of the registers, with virtually no losses to follow-up, allowed the recruitment of a very large sample, without influence by selection bias.

As a further strength of this study, information on smoking was prospectively included in the MBR for pregnancies since 1991, eliminating the possible influence of recall bias, while information on MS diagnoses among study participants was obtained

from the Danish NPR. Moreover, data on the following potential confounders were also retrieved and included in the statistical models: parental age, birth weight, maternal obesity, and history of maternal infectious mononucleosis (IM). The authors used Cox regression analysis to estimate hazard ratios (HRs) for the association between smoking and MS risk. They first compared the risk of developing MS in women who smoked during pregnancy and those who did not smoke: the former had a 42% increased risk of developing MS, in line with existing evidence in other non-pregnant populations.¹ In a second step, they compared the risk of MS among singletons of women who smoked during pregnancy versus singletons born to non-smoking women: being exposed to smoke during intrauterine life conferred a 38% higher risk of developing MS.

The study is not without limitations. The analysis did not allow determining whether the observed increased risk of MS in offspring exposed to maternal smoking during pregnancy was related to in utero exposure or to presumed passive smoking in childhood or both. Moreover, parental smoking is associated with an increased probability of offspring taking up smoking themselves, information that was lacking in the present analysis. Furthermore, there were no data on number of cigarettes smoked per day and other potential risk/protective factors such as vitamin D levels in the mother and lactation.

Despite these limitations, in this prospective register-based analysis, an association between smoking during pregnancy and MS risk in offspring clearly emerged. The implications of this finding are manifold. On one hand, it suggests that environmental factors act on the risk of developing MS very early in a person's life, maybe even in utero. This result is in line with a few previous studies indicating an in

Multiple Sclerosis Journal

2024, Vol. 30(2) 137–138

DOI: 10.1177/
13524585241224667

© The Author(s), 2024.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

E Portaccio
Department of
NEUROFARBA, University
of Florence, Viale G.
Pieraccini, 6, 50139 Florence,
Italy.

emilio.portaccio@unifi.it

Emilio Portaccio
Department of
NEUROFARBA, University
of Florence, Florence, Italy

Pietro Iaffaldano
Department of Translational
Biomedicine and
Neurosciences (DiBrain),
University of Bari Aldo
Moro, Bari, Italy

utero/neonatal effect of other potential risk factors, such as vitamin D deficiency⁴ and latitude effect.⁵ Importantly, these data bring the concept of exposome⁶ (i.e. an individual's cumulative lifelong exposure from the prenatal period onwards), recently applied in cancer and other neurodegenerative disease, in MS research, as well. On the other hand, it strengthens the detrimental role of smoking independently of exposure timing. Consistently with previous evidence in non-pregnant cohort,¹ smoking increased the risk of developing MS in both the mother and offspring, representing one of the more relevant modifiable risk factors for MS.

Overall, this study shed more light on the role of environmental factors, and smoking in particular, in MS pathogenesis. These findings are on the edge of contemporary MS research, which is focusing on the pre-clinical/prodromal phases of the disease, a time window in which acting on modifiable environmental triggers, including lifestyle habits, is of crucial importance.⁷ Together with a few previous evidence,^{4,5} they indicate that research on potential environmental MS risk factors, as well as interventions aimed at their modification, should be introduced much earlier than that believed in the past, even in the prenatal/neonatal period.


Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Emilio Portaccio  <https://orcid.org/0000-0002-9662-1762>

Pietro Iaffaldano  <https://orcid.org/0000-0003-2308-1731>

References

1. Zhang P, Wang R, Li Z, et al. The risk of smoking on multiple sclerosis: A meta-analysis based on 20,626 cases from case-control and cohort studies. *PeerJ* 2016; 4: e1797.
2. Ekblad M, Korkeila J and Lehtonen L. Smoking during pregnancy affects foetal brain development. *Acta Paediatr* 2015; 104(1): 12–18.
3. Nielsen NM, Frisch M, Gøtz S, et al. Smoking during pregnancy and risk of multiple sclerosis in offspring and mother: A Danish nationwide register-based cohort study. *Mult Scler*. Epub ahead of print 19 November 2023. DOI: 10.1177/13524585231208310.
4. Jasper EA, Nidey NL, Schweizer ML, et al. Gestational vitamin D and offspring risk of multiple sclerosis: A systematic review and meta-analysis. *Ann Epidemiol* 2020; 43: 11–17.
5. Sabel CE, Pearson JF, Mason DF, et al. The latitude gradient for multiple sclerosis prevalence is established in the early life course. *Brain* 2021; 144(7): 2038–2046.
6. Wild CP. Complementing the genome with an “exposome”: The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 2005; 14(8): 1847–1850.
7. Inglese M and Amato MP. Presymptomatic MS or radiologically isolated syndrome should be actively monitored and treated: Commentary. *Mult Scler* 2023; 29(7): 797–798.