

Etiological research in pediatric multiple sclerosis: A tool to assess environmental exposures (PEDiatric Italian Genetic and enviRonment ExposurE Questionnaire)

Silvy Pilotto, Jessica Gencarelli, Stefania Bova, Leonardo Gerosa, Damiano Baroncini, Sara Olivotto, Enrico Alfei , Mauro Zaffaroni, Agnese Suppiej, Eleonora Cocco , Maria Trojano , Maria Pia Amato , Sandra D'Alfonso, Filippo Martinelli-Boneschi , Emmanuelle Waubant, Angelo Ghezzi , Roberto Bergamaschi and Maura Pugliatti 

Abstract

Background: The etiology of pediatric-onset multiple sclerosis is unknown although putative genetic and environmental factors appear to be involved. Among children multiple sclerosis onset occurs closer to the susceptibility window than in adults and the exposure to etiological environmental factors is more informative. An Italian multicentre case-control study (the PEDiatric Italian Genetic and enviRonment ExposurE, *PEDIGREE study*) was designed to investigate environmental exposures in pediatric-onset multiple sclerosis and their interaction with genetics.

Objectives: To collect evidence on exposures to environmental risk factors in pediatric-onset multiple sclerosis, a questionnaire was developed for the Italian population (PEDIGREE Questionnaire) and is presented.

Methods: PEDIGREE Questionnaire develops from an existing tool used in case-control studies on pediatric-onset multiple sclerosis in US Americans, and was translated, adapted and tested for the contents perceived relevance, acceptability, feasibility and reliability in a population of Italian pediatric subjects and their parents recruited from clinics and general population.

Results: PEDIGREE Questionnaire contents were overall deemed relevant by the study population, acceptable for 100% participants and feasible for at least 98%. PEDIGREE Questionnaire degree of reliability ranged 56% to 72%.

Conclusion: PEDIGREE Questionnaire proves to be an efficient tool to assess environmental exposures in the Italian pediatric population. We encourage the dissemination of population-specific questionnaires and shared methodology to optimize efforts in MS etiological research.

Keywords: multiple sclerosis, demyelinating diseases, pediatric onset, environmental exposure, risk factors, questionnaires

Date received: 18 June 2021; accepted 22 October 2021

Introduction

Multiple sclerosis (MS) in the population aged less than 18 years (ie., 'pediatric' population) is reported as 3–10% of total MS cases.^{1–3} The mean annual incidence of pediatric onset MS (POMS) worldwide

ranges from 0.05 to 2.85 per 100 000 children, while prevalence ranges from 0.69 to 26.92 per 100 000 children.^{1,4,5} The highest incidence rates are observed between 13 and 16 years of age.⁶ POMS etiology is unknown, although evidences support an

*Multiple Sclerosis Journal—
Experimental, Translational
and Clinical*

October–December 2021,
1–9

DOI: 10.1177/
20552173211059048

© The Author(s), 2021.
Article reuse guidelines:
sagepub.com/journals-
permissions



Azienda Ospedaliero-
Universitaria S. Anna, Via
Aldo Moro 8 – Settore 1C3,
44124 Ferrara, Italy.
maura.pugliatti@unife.it

Silvy Pilotto,

Department of Neuroscience
and Rehabilitation,
University of Ferrara,
Ferrara, Italy

Jessica Gencarelli,

Department of Medical
Sciences - Pediatric Section,
University of Ferrara,
Ferrara, Italy

Stefania Bova,

Pediatric Neurology Unit, V.
Buzzi Children's Hospital,
Milan, Italy

Leonardo Gerosa,

Department of Neuroscience
and Rehabilitation,
University of Ferrara,
Ferrara, Italy

Damiano Baroncini,

Multiple Sclerosis Centre,
ASST Valle Olona,
Gallarate, Italy

Sara Olivotto,

Enrico Alfei,
Pediatric Neurology Unit, V.
Buzzi Children's Hospital,
Milan, Italy

Mauro Zaffaroni,

Multiple Sclerosis Centre,
ASST Valle Olona,
Gallarate, Italy

Agnes Suppiej,

Department of Medical
Sciences - Pediatric Section,
University of Ferrara,
Ferrara, Italy

Eleonora Cocco,

Department Medical Science
and Public Health, University
of Cagliari, Italy

Maria Trojano,

Department of Basic Medical
Sciences, Neuroscience and
Sense Organs, University of
Bari, Italy

Maria Pia Amato,

Department
NEUROFARBA, University
of Florence, Italy

Sandra D'Alfonso,

IRCCS Fondazione Don
Carlo Gnocchi, Florence,
Italy
Department of Health
Sciences, Interdisciplinary
Research Center of
Autoimmune Diseases,
University of Eastern
Piedmont Amedeo Avogadro
School of Medicine, Novara,
Italy

Filippo Martinelli-

Boneschi,
IRCCS Fondazione Ca'
Granda Ospedale Maggiore
Policlinico, Neurology Unit,

increased susceptibility related to both genetic and environmental factors.^{7,8} As for the latter, exposure to Epstein Barr virus (EBV) infection⁹ and cigarette smoking during childhood¹⁰ seems to play a major susceptibility role in POMS. In addition, decreased vitamin D serum levels, increased body mass index and obesity,^{11,12} pesticide-related exposures,¹³ as well as absence of infant breastfeeding¹⁴ have also been reported in association with increased risk of POMS. While low sunlight exposure in adolescence/teenage has been repeatedly found associated with an increased risk of adult-onset MS,^{15,16} the literature around this question in the pediatric population is scant. Lastly, the role of gut microbiota, maternal illness during pregnancy and caesarean section delivery in predisposing to POMS remains controversial.^{13,17}

MS onset among children is temporally much closer to the disease putative susceptibility period and the role of potential etiological environmental and/or genetic factors than it is among adults, such as HLA-DRB1*15 and exposure to EBV infection and cigarette smoking. Despite a much rarer disease, POMS therefore offers a unique opportunity for MS etiological research.

In this perspective, an Italian case control study (the PEDIatric Italian Genetic and enviRonment ExposurE, *PEDIGREE study*) was designed aimed to assess genetic risk factors and variants at genome-wide and mitochondrial DNA levels, familial aggregation, environmental factors and to explore gene-environment interactions as well as the role of gut microbial in association with POMS.

Within this framework, we developed the PEDIGREE Questionnaire (PEQ-IT) aimed to collect relevant information on past environmental exposures in the Italian pediatric population from pediatric participants of 14 to 17 years of age, from parents as informants on their children aged < 14 years and also for self-report information. We present the methodology adopted to develop PEQ-IT and results from a pilot study aimed to assess the questionnaire acceptability, feasibility, reliability and relevance for its contents in an Italian research setting.

Material and methods

Design and development

PEQ-IT builds on an existing tool used in case-control studies to investigate exposures to environmental risk factors potentially involved in the etiology of POMS

in the US population.^{13,18} The original English questionnaire consists of a single module to be administered to parents only, regardless of the age of pediatric cases and controls, and is structured into two main sections: 95 questions collecting information about the child's and 166 about parents' exposures.

A brief description of the original questionnaire contents follows.

Section 1 contains '*Questions about the child*'.

Section 1.1 – 'Child's delivery and development' - collects data on child's delivery (eg., place of birth, delivery duration, Apgar index, any complications occurred during the first weeks of life); detailed information about pre-school and kindergarten attended by the child, about siblings (number, sex, and date of birth), child's age-specific exposure to sunlight (i.e. skin phototype, frequency of outdoor activities in different seasons, of sun exposure during holidays, of sunscreens use and questions on degree of clothing in different seasons), child's place of residency, exposure to breastfeeding and any kind of milk assumed between birth and two years of age, any contact with pets.

Section 1.2 – 'Child's early medical history' - aims to investigate child's exposure to diseases or infections contracted between birth and 5 years of age (includes history of diarrhea, vomiting, fever, allergies and antibiotics intake), vitamins and minerals intake (i.e. vitamin A, D, E, K, iron and zinc).

Section 1.3 – 'Child's medical history' - collects lifetime data about child's diseases, use of drugs and interventions (i.e. X-ray exposure, hereditary or congenital defects; thyroid disorders, overweight and underweight conditions; exposure to anticonvulsants, chemotherapy, steroids, amphetamines, anti-inflammatory drugs, poisoning, possible vaccinations and history of travelling abroad).

Section 2 contains '*Questions about the parents*'.

Section 2.1 – 'Child's family history' - collects data on parents' civil status, cause of death if applicable, biometric features (for mothers before and during pregnancy), skin phototype and skin reaction to first sun exposure, places of residence, current and previous occupation, annual income before and after childbirth, educational level, and information on any other maternal and paternal figures who may have taken care of the child.

Section 2.2 – ‘Environmental factors’ - explores parents' cigarette smoking habits and child smoking exposure; frequency of sun exposure, of sunscreen use, clothing, dietary habits, any contact with pets and stressful events in the biological mother during pregnancy. In addition, there are questions on past exposures and duration to environmental agents such as antibacterial soap, insects, rats, mice control products and repellents, weed/plants control products, paint, stains, or lacquers, adhesives or petroleum products, indoor sprays, dusts, powders, or skin applications for fleas or ticks, or flea or tick collars.

Section 2.3 – ‘Biological mother’s medical history (before and during pregnancy with the child)’ - collects data on number and outcomes of pregnancies, mother’s disorders before or during pregnancy (i.e. depression, anxiety, diabetes, high blood pressure, fever, infections, nausea, vomiting, anemia, swelling of hands or feet), use of contraceptives, drugs, antibiotics, vitamins, herbal substances and history of vaccinations within 3 months prior to pregnancy.

Section 2.4 – ‘Biological mother’s medical history (while breastfeeding the child)’ - is addressed only to women who have breastfed and explores features of breastfeeding such as duration, dietary habits, and intake of vitamins, minerals, drugs, antibiotics and herbal substances.

Translation and adaptation

The original questionnaire^{13,18} was translated into Italian by means of back-to-back translation.¹⁹ A native Italian-speaking professional translator faithfully translated the original English version into Italian. This version was then translated by a native English professional translator back into English and the two English versions were then compared with one another by the research team members to ensure semantic and conceptual equivalence.¹⁹ Discrepancies of terms in the two English versions were reconciled by ad hoc revising the Italian version and until a final consensus on correct wording was reached.

Adaptation consisted of two main stages: (i) removal of questions and/or terms specifically referred to US contexts, and (ii) revision of final Italian wording and assessment of perceived relevance of questions in the Italian version (see further on PEQ-IT pilot test).

In order to minimize the possibility for missing information, consensus was reached by the PEDIGREE

research team as to rearrange the questionnaire main structure as follows: (i) a module to assess parents' past exposures to environmental factors (for mothers: before, during and after pregnancy period) to be filled out by parents; (ii) a module to assess exposures for pediatric subjects from birth up to study time to be filled out by parents if children under study are aged 0–13 years; (iii) a module to assess exposures for pediatric subjects of 14 to 17 years which they will themselves fill out to avoid potential bias on sensitive and informative issues, should parents response on their behalf (eg., on cigarette smoking habit). These teen-agers will still have the possibility to receive help from parents to provide complete data.

Pilot test phase

In this phase we specifically aimed at creating a culturally adapted version of the questionnaire to the Italian research context by assessing acceptability, feasibility, reliability and perceived relevance of contents. To this purpose, ad hoc evaluating questions were developed according to reference methodology.^{20,21} A first draft of the Italian translated and adapted version of the questionnaire was tested through a pilot study conducted in a population of pediatric subjects and their parents recruited from (a) pediatric clinics and (b) general population by convenience in five Italian participating sites: Ferrara, Pavia, Milan, Gallarate and Novara. Subjects with any diagnosis of demyelinating inflammatory disease of the central nervous system were excluded from the test phase while samples from other pediatric populations (ie., families of and children with diseases other than demyelinating disorders of the central nervous system) were selected as proxy to ‘diseased’ children and relative families.

As for *acceptability* we assessed how acceptable the questionnaire was for respondents to complete in terms of potential distress during response.²⁰ For each question, participants had to address additional statements which were purposely created for the pilot phase: ‘*I have no problem to answer this question*’ or ‘*I will not answer this question as this is too sensitive for me*’.

Feasibility refers to how easy the instrument is for participants to respond,²⁰ both in terms of understanding the language (grammar and/or syntax) and of the possibility to provide an appropriate answer. For this purpose, participants had to choose between the following statements: ‘*I find this question easy to understand*’ or ‘*I find this question difficult to understand*,

Milan, Italy
Dino Ferrari Center,
Department of
Pathophysiology and
Transplantation, University
of Milan, Milan, Italy

Emmanuelle Waubant,
Department of Neurology,
UC San Francisco, San
Francisco, California, USA

Angelo Ghezzi,
Multiple Sclerosis Centre,
ASST Valle Olona,
Gallarate, Italy;
Department of Health
Sciences, Interdisciplinary
Research Center of
Autoimmune Diseases,
University of Eastern
Piedmont Amedeo Avogadro
School of Medicine, Novara,
Italy

Roberto Bergamaschi,
Multiple Sclerosis Center,
IRCCS Mondino
Foundation, Pavia, Italy

Maura Pugliatti,
Department of Neuroscience
and Rehabilitation,
Interdepartmental Research
Center for the Study of
Multiple Sclerosis and
Inflammatory and
Degenerative Diseases of the
Nervous System, University
of Ferrara, Ferrara, Italy

the question is ambiguous, not clear. In order to capture feedbacks from participants who found the question easy to understand but who just did not have the answer, the option *'I do not respond because I do not know the answer'* could be chosen in addition to one of the previous statements. Feasibility was also measured as the proportion of valid responses given for each item, as well as the time needed to complete the questionnaire.

Relevance represents the respondents' perception of the tool's accuracy in achieving the study aims. An ad-hoc question was generated for each questionnaire section and participants were asked to evaluate relevance using a four-point scale (*'not relevant'* to *'very relevant'*).²²

As for *reliability* we assessed the degree of reproducibility and internal consistency of the questionnaire.²⁰ For this purpose, participants who had filled out the questionnaire once (test) were invited to fill out the same version again two weeks after (retest).^{20,23}

During the test phase and in line with a methodology previously adopted,^{20,21,24} participants were also given the possibility to provide free text comments and suggestions to improve the questionnaire in terms of relevance, grammar, preferred wording, etc.

The final version of the translated, adapted and tested questionnaire – 'PEQ-IT' – was obtained after revision based on the results from the pilot phase.

Statistical analysis

Descriptive statistics (means, medians, standard deviations and percentages) were used to present acceptability and feasibility. Kappa values for dichotomous variables and weighted kappa for ordinal variables were used to assess test–retest reliability.²⁵ The level of acceptability, feasibility, relevance and reliability was judged using conventional guidelines.²⁶ values lower than 0.40 indicated fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial and over 0.80 an almost perfect agreement. The strength of agreement between responses to continuous variables was examined using Spearman correlation coefficients with 95% confidence intervals. Significance was set at 0.05. All analyses were performed with Statistical Package for the Social Sciences (SPSS) versions 20 and 27.

Ethical issues

This study is part of the project PEDIGREE Study and received ethical clearance from institutional review

boards (IRBs) of all participating centres. Written informed consent was obtained from parents for participants of all ages and anonymity was ensured all throughout the pilot phase through the use of alphanumeric codes in the dataset entry.

Results

The testing phase was conducted across the participating MS Centres between August 7th, 2020 and September 13th, 2020. Baseline characteristics of the study population participating to PEQ-IT development are reported in Table 1.

Data were collected from 67 pediatric subjects and 66 corresponding parents. As for the pediatric cohort, 28 subjects were recruited from pediatric clinics to which they were referred for various conditions such as minor traumas, minor surgery, epileptic seizures, and 39 were pediatric subjects recruited from the general population by means of convenience approach.

Measures of PEQ-IT relevance, acceptability, feasibility and reliability are summarized in Table 2. PEQ-IT was deemed 'relevant', acceptable in 100%

Table 1. Baseline characteristics of the study population (N = 133).

	Section 1: Questions about the child	Section 2: Questions about the parents
Responders: N (%)	67 (50.4)	66 (49.6)
Female sex: N (%)	35 (52.2)	54 (81.8)
Population source: N (%)		
General population	40 (59.7)	39 (50.1)
Hospital population	27 (40.3)	27 (40.9)
Age range: N (%)		
0–13 years	33 (49.3)	31 (47.0)
14–17 years	34 (50.7)	29 (43.9)
Mean (SD) age of target sample: years	10.3 (6.1)	44.2 (6.3)

Table 2. Degree of relevance, acceptability, feasibility, and reliability of PEQ-IT expressed by median of answers.

	Relevance ^a	Acceptability (%)		Feasibility (%)		Reliability ^b
		'No problem to answer'	Response rate	'Easy to understand'	'I don't know the answer'	
Section 1: Questions about the child						
Section 1.1: Child birth and development	2	100.0	91.0	98.5	3.0	0.61
Section 1.2: Child's early health history/ Section 1.3: Child's medical history	2	100.0	94.0	100.0	1.5	0.56
Section 2: Questions about the parents						
Section 2.1: Child's family history	2	100.0	86.4	98.4	0.0	0.72
Section 2.2: Environmental factors	2	100.0	89.4	100.0	0.0	0.64
Section 2.3: Biological mother's health history (before and during pregnancy with the child) / Section 2.4: Biological mother's health history (while breastfeeding the child)	2	100.0	87.9	100.0	3.1	0.58

^a1 = very relevant; 2 = relevant; 3 = hardly relevant; 4 = not relevant.
^bK value²⁵: <0.40 = fair agreement, 0.41 to 0.60 = moderate agreement, 0.61 to 0.80 = substantial agreement, > 0.80 an almost perfect agreement.

of participants, feasible for at least 98.4% of participants and showed an overall 56% to 72% degree of reliability (Table 2).

The mean (SD) time needed to fill out PEQ-IT was 41 (21.0) and 49 (23.8) minutes, for Section 1 and Section 2, respectively, with a heterogeneous range (Table 3).

By virtue of adaptation to the Italian research context, 29 (11.1%) of the US questionnaire 261 items could not be literally translated and included in PEQ-IT; however, 14 additional informative questions were added in PEQ-IT to preserve the cross-cultural data collection. The detailed degree of reciprocal overlap,

and further results can be found on online supplementary data [link].

Discussion

Little is known about the environmental risk determinants in POMS and literature reports on study methodology including suitable tools to collect such data in observational studies are scant.

To the best of our knowledge, PEQ-IT represents the only tested and published questionnaire specifically developed to assess exposure to environmental risk factors in POMS. The pilot testing process performed in an Italian population attempts to ensure solid

Table 3. PEQ-IT. Mean (SD) time and range of time (minutes) spent for filling out the questionnaire by the study population.

	Mean (SD) time (minutes)	Range of time (minimum–maximum) (minutes)
Section 1: Question about the child		
Pediatric population (overall)	41 (21.0)	15–90
Pediatric population aged 0–13 years	39 (22.0)	15–79
Pediatric population aged 14–17 years	41 (20.8)	15–90
Sex		
Males	42 (20.8)	15–90
Females	39 (21.9)	15–90
Status		
General population	39 (20.5)	15–90
Hospital population	43 (22.0)	20–90
Section 2: Question about the parents		
Parents (overall)	49 (23.8)	15–120
Parents of children aged 0–13 years	45 (20.4)	26–90
Parents of children aged 14–17 years	53 (27.3)	15–120
Sex		
Males	29 (4.7)	23–34
Females	52 (24.1)	15–120
Status		
General population	45 (25.2)	15–120
Hospital population	54 (22.2)	30–90

scientific bases for the conduct of the study at large including bias mitigation and control of possible confounding factors and cross-cultural validity.

From a broader perspective, our ultimate aim was to provide Italian researchers with a tool capable to ensure harmonization of evidence both from existing studies and from newly collected data on the role played by the environment in determining POMS.²⁷ Based on reference methodology,²⁰ PEQ-IT was developed through translation and adaptation of a questionnaire used in POMS US studies^{13,18} and aims to collect detailed data on the putatively most relevant domains of environmental exposures in MS, such as perinatal events, lifestyle exposures, childhood infections. PEQ-IT features and overall good to very good degree of contents perceived relevance, acceptability, feasibility and reliability among parents of children and from general and hospital populations, and from adolescents in different Italian study sites.

Few studies have attempted to solve the enigmatic etiology of POMS providing new evidence in this field.

*The Pediatric MS Tool Kit*²⁸ was designed to enhance exposure measurement when designing studies in

POMS as well as to ensure comparability of results across studies, thus circumventing issues of small sample sizes, given the rare condition. Magalhaes et al. suggested principles for harmonizing data in the longer term as the milestone for epidemiological research in pediatric MS.²⁸ Benefitting from rigorous methodology, the Pediatric MS Tool-Kit, represents a measurement framework guideline but only for some core variables only (cigarette smoking habit, vitamin D and sunlight exposure).

Similar experience is reported but for the adult MS population.

Validated and structured questionnaires measuring recent summer and winter sun exposure were used in the *Australian Multicentre Study of Environment and Immune Function* (or *Ausimmune Study*),²⁹ a multicentre, case-control study specifically aimed to investigate latitude-related exposures in cases with a first demyelinating event in the Australian resident population aged between 18 and 59 years.

The *Environmental Risk Factors in MS Study* (or *EnvIMS study*)³⁰ was designed for etiological research in adult-onset MS. Its overall study methodology as

well as the ad hoc developed questionnaire (EnvIMS-Q) has been published^{20,30} to enable investigators to treasure other researchers' experiences when designing their own studies. EnvIMS, a multinational case-control study, enrolled 2800 cases with MS and over 5000 population-based controls in Canada, Italy, Norway, Serbia and Sweden. Because of the large population size, the study was designed to investigate the most commonly implicated risk factors for MS etiology and through a self-report postal questionnaire.

PEQ-IT and EnvIMS-Q share much of the methodological approach in their development and test phases, but because POMS is a much rarer condition than adult MS, PEQ-IT is purposely intended to collect exposures more comprehensively and from different populations sources (i.e. children and parents). Furthermore, with the aim to increase data accuracy and limit the potential bias while measuring these exposures from parents, a module dedicated to lifestyles and habits of subjects aged 10 to 17 years has been included in PEQ-IT (PEQ-IT, Section 3, see Supplementary files).

The main limitation of this study is represented by the overall *moderate* reliability in the test-retest phase which is primarily related to the high level of details in the original tool^{13,18} which interfered with consistent recall in the retest phase. Based on the scores reported in this test phase and on the comments provided by the participants, 88 questions scoring *low* for reliability were substantially revised to fit culturally and 29 questions were removed because redundant or unclear. The following are some examples of revisions: the question on vaccinations was modified based on Italian vaccination guidelines; the options for parents' previous occupation were modified based on Italian national health statistics classification; options for parents' education were adapted according to the Italian school system classification; questions on the other mother figure's race or ethnic group and income were removed because they were never answered; too detailed questions on breastfeeding duration as well as repeated questions on child sun and cigarette smoking exposure were removed because they were judged too difficult to answer. In addition, PEQ-IT includes 14 additional questions based on suggestions made by participants. As examples, a multicolor picture of different skin shades that the participant can match his/her skin with was added; questions on lifestyle and clothing have been split for each different season; three questions on maternal smoking habit and cigarette smoking habit and drug use for teen-agers were added.

Overall, PEQ-IT represents a tool to assess past exposures around POMS with a rather high level of detail and granularity. While this may limit its use in some clinical settings (eg., during routine out-patients visits), PEQ-IT can be administered in research settings through interview, under researchers' supervision or splitting the timing, thus ensuring good quality of data. It is worth to highlight that the *PEDIGREE* study represents a unique valuable opportunity to investigate the etiological role of environment and the gene-environment interaction in POMS.

An additional potential limit of this study is represented by the noninvolvement of the target population (POMS) in the development of the tool. This was purposely done so as not to 'waste' an opportunity for participation to the study at large from our rare POMS population which – in case of a needed extended revision of the tool – should have either been ruled out from re-administration, or, if included instead, could have reported biased response after participation to the first trial. As proxy of 'diseased' children and relative families, samples from other pediatric clinics were used apart from a control population. While this may be perceived as a limitation, there are evidences showing that similar tools (eg., EnvIMS-Q²⁰) are acceptable, feasible and reliable cross-culturally to the same degree in patients with MS as in healthy subjects, and in the case-control study at large, the response rate of the MS population to EnvIMS-Q turned out to be much higher than that of controls.³⁰

By means of translating and adapting existing population-specific questionnaires, we encourage the development, pilot testing and dissemination of such research tools so as to share methodology, optimize efforts, save costs, and – ultimately – ensure comparability of evidence across different settings which is of vital importance in epidemiological and etiological research.^{30,31}

Acknowledgements

We are particularly grateful to children and parents who took part in PEQ-IT testing phase, and for their precious contribution in ameliorating its layout.

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) disclosed receipt of the following financial support for the research, authorship, and/or publication of

this article: This work was supported by the Fondazione Italiana Sclerosi Multipla (grant N. 12/18/F14, P.I. Angelo Ghezzi, and grant N. 2019/PR-Single/024, P.I. Maura Pugliatti).

ORCID iDs

Enrico Alfei  <https://orcid.org/0000-0001-6737-5163>
 Eleonora Cocco  <https://orcid.org/0000-0002-3878-8820>
 Maria Trojano  <https://orcid.org/0000-0002-6329-8946>
 Maria Pia Amato  <https://orcid.org/0000-0003-3325-3760>
 Filippo Martinelli-Boneschi  <https://orcid.org/0000-0002-9955-1368>
 Angelo Ghezzi  <https://orcid.org/0000-0001-9794-6481>
 Maura Pugliatti  <https://orcid.org/0000-0001-9396-8683>

Supplemental material

Supplemental material for this article is available online.

References

- Dell'Avvento S, Sotgiu MA, Manca S, et al. Epidemiology of multiple sclerosis in the pediatric population of Sardinia, Italy. *Eur J Pediatr* 2016; 175: 19–29.
- Ghezzi A, Baroncini D, Zaffaroni M, et al. Pediatric versus adult MS: similar or different? *Mult Scler Demyelinat Dis* 2017; 2: 5.
- Marric RA, O'Mahony J, Maxwell C, et al. Canadian Pediatric demyelinating disease network. Incidence and prevalence of MS in children: a population-based study in Ontario, Canada. *Neurology* 2018; 91: e1579–e1590.
- Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology* 2009; 72: 232–239.
- Jeong A, Oleske DM and Holman J. Epidemiology of pediatric-onset multiple sclerosis: a systematic review of the literature. *J Child Neurol* 2019; 34: 705–712.
- Alroughani R and Boyko A. Pediatric multiple sclerosis: a review. *BMC Neurol* 2018; 18: 27.
- Disanto G, Magalhaes S, Handel AE, et al. HLA-DRB1 confers increased risk of pediatric-onset MS in children with acquired demyelination. *Neurology* 2011; 76: 781–786.
- Gontika M, Skarlis C, Artemiadis A, et al. HLA-DRB1 allele impact on pediatric multiple sclerosis in a hellenic cohort. *Mult Scler J Exp Transl Clin* 2020; 6: 2055217320908046
- Waubant E, Mowry EM, Krupp L, et al. Common viruses associated with lower pediatric multiple sclerosis risk. *Neurology* 2011; 76: 1989–1995.
- Mikaeloff Y, Caridade G, Tardieu M, et al. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. *Brain* 2007; 130: 2589–2595.
- Langer-Gould A, Brara SM, Beaber BE, et al. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. *Neurology* 2013; 80: 548–552.
- Gianfrancesco MA, Stridh P, Rhead B, et al. Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset MS. *Neurology* 2017; 88: 1623–1629.
- Graves JS, Chitnis T, Weinstock-Guttman B, et al. **Network of pediatric multiple sclerosis centers.** Maternal and perinatal exposures Are associated With risk for pediatric-onset multiple sclerosis. *Pediatrics* 2017; 139: e20162838.
- Brenton JN, Engel CE, Sohn MW, et al. Breastfeeding during infancy Is associated With a lower future risk of pediatric multiple sclerosis. *Pediatr Neurol* 2017; 77: 67–72.
- Bjørnevik K, Riise T, Casetta I, et al. Sun exposure and multiple sclerosis risk in Norway and Italy: the EnvIMS study. *Mult Scler* 2014; 20: 1042–1049.
- Islam T, Gauderman WJ, Cozen W, et al. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. *Neurology* 2007; 69: 381–388.
- Tremlett H and Waubant E. The Gut Microbiota and pediatric multiple sclerosis: recent findings. *Neurotherapeutics* 2018; 15: 102–108.
- Mar S, Liang S, Waltz M, et al. Several household chemical exposures are associated with pediatric-onset multiple sclerosis. *Ann Clin Transl Neurol* 2018; 5: 1513–1521.
- Beaton D, Bombardier C, Guillemin F, et al. Recommendations for the cross-cultural adaptation of the DASH & QuickDASH outcome measures. Institute for Work & Health 2002, 2007.
- Pugliatti M, Casetta I, Drulovic J, et al. A questionnaire for multinational case-control studies of environmental risk factors in multiple sclerosis (EnvIMS-Q). *Acta Neurol Scand Suppl* 2012; 195: 43–50.
- Fitzpatrick R, Davey C, Buxton MJ, et al. Evaluating patient based outcome measures for use in clinical trials. *Health Technol Assess* 1998; 2: i-iv.
- Bradette-Laplante M, Carbonneau É, Provencher V, et al. Development and validation of a nutrition knowledge questionnaire for a Canadian population. *Public Health Nutr* 2017; 20: 1184–1192.
- Streiner DL and Norman GR. *Health measurement scales: a practical guide to their development and use.* Oxford: Oxford University Press, 1995.
- Manns S, Cramp F, Lewis R, et al. A qualitative evaluation of the appropriateness, validity, acceptability, feasibility and interpretability of the Bristol impact of hypermobility (BioH) questionnaire. *Musculoskelet Sci Pract* 2018; 38: 69–76.
- Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Measur* 1960; 20: 37–46.
- Landis JR and Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–173.
- Magalhaes S and Wolfson C. Harmonization: a methodology for advancing research in multiple sclerosis. *Acta Neurol Scand* 2012; 126: 31–35.
- Magalhaes S, Banwell B, Bar-Or A, et al. A framework for measurement and harmonization of pediatric

- multiple sclerosis etiologic research studies: the pediatric MS tool-kit. *Mult Scler* 2019; 25: 1170–1177.
29. Lucas R, Ponsonby AL, McMichael A, et al. Observational analytic studies in multiple sclerosis: controlling bias through study design and conduct. The Australian multicentre study of environment and immune function. *Mult Scler* 2007; 13: 827–839.
30. Magalhaes S, Pugliatti M, Casetta I, et al. The EnvIMS study: design and methodology of an international case-control study of environmental risk factors in multiple sclerosis. *Neuroepidemiology* 2015; 44: 173–181.
31. Schilling LM, Kozak K, Lundhal K, et al. Inaccessible novel questionnaires in published medical research: hidden methods, hidden costs. *Am J Epidemiol* 2006; 164: 1141–1144.