Multiple adversity: Childhood abuse, adult abuse, and perinatal depression in women with multiple sclerosis

A register-based cohort study

Karine Eid

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

Multiple adversity: Childhood abuse, adult abuse, and perinatal depression in women with multiple sclerosis

A register-based cohort study

Karine Eid

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 23.02.2024

Year: 2024

Title: Multiple adversity: Childhood abuse, adult abuse, and perinatal depression in women with multiple sclerosis

Name: Karine Eid

Print: Skipnes Kommunikasjon / University of Bergen

Table of contents

Acknowledgements

I would like to thank my supervisors for the invaluable supervision and guidance throughout this ph.d. project. I am grateful for my main supervisor professor Marte-Helene Bjørk. Your counsel, clear vision and sharp mind has lifted the quality of this project. I am grateful for my co-supervisor professor Nils Erik Gilhus for the hours you have spent correcting drafts and discussing the scientific impact of our results. I am grateful for my co-supervisor professor Øivind Torkildsen for providing clear and decisive advice and for always checking up on me before deadlines. I am positive that I could not have had a better trio of supervisors than you.

I am very grateful for my team of co-authors who have provided valuable discussions and input; Kjell-Morten Myhr, Trond Riise, Trygve Holmøy, Jan Aarseth, Stig Wergeland, Elisabeth G. Celius, Marianna Cortese, Anne Kjersti Daltveit, Cecilie Torkildsen, Johannes Willumsen, Nina Øksendal, Mari Alstad, Alok Bhan, Heidi Flemmen, Åslaug Lorentzen, Cecilia Simonsen, Stephan Schüler and Akash Kapali. I am also thankful for the other neurologist and specialist nurses who helped us validate MS diagnoses from hospital journals at their respective departments.

I am fortunate to be part of the scientific community in Bergen Epilepsy Research Group. Our morning meetings continue to be one of the highlights of the week. I am also very grateful to be a part of the community in Neuro-SysMed and the MS Research Group.

To my colleagues and friends at the Department of Neurology at Haukeland University Hospital and in the Rotunden office, thank you for the great conversations and support throughout the years. A special thanks to Brit Ellen, Ingrid Anne, Håkon, Elisabeth, and Jenny for filling my office days with laughter and joy.

To my wonderful best friend and husband Marius, thank you for your thoughts, encouragement, and support. This ph.d. thesis would not have existed without you. To my wonderful boy Thor, thank you for giving life a new meaning. To my parents Karin and Kevin, and my younger siblings Lusie and Johannes, thank you for always being interested and especially for the good times around *bålpanna.*

Scientific environment

- Bergen Epilepsy Research Group (BERG), led by Professor Marte-Helene Bjørk
- Neuro-SysMed, led by Professor Kjell-Morten Myhr
- The Norwegian Multiple Sclerosis Competence Network
- Department of Clinical Medicine, University of Bergen, Bergen
- Department of Neurology, Haukeland University Hospital, Bergen

BERG is a research group located at the Department of Neurology, Haukeland University Hospital. BERG focuses on register-based neuroepidemiology within epilepsy, multiple sclerosis, and myasthenia gravis. Further, the group has active research projects on developing new electroencephalogram (EEG) technology and clinical epilepsy studies.

Neuro-SysMed is a national research center located at the University of Bergen and Haukeland University Hospital. Neuro-SysMed focuses on clinical treatment studies for the four neurological diseases: Multiple sclerosis, Parkinson's' disease, amyotrophic lateral sclerosis, and dementia. Neuro-SysMed was the first national Centre for Clinical Treatment Research funded by the Research Council of Norway.

The Norwegian Multiple Sclerosis Competence Network is located at Haukeland University Hospital. The Competence Network focuses on information, research and education of patients, families, and health personnel.

List of publications

Paper I

Eid K, Torkildsen Ø, Aarseth J, Aalstad M, Bhan A, Celius EG, Cortese M, Daltveit AK, Holmøy T, Myhr KM, Riise T, Schüler S, Torkildsen CF, Wergeland S, Gilhus NE, Bjørk MH.

Association of adverse childhood experiences with the development of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2022 Jun;93(6):645-650.

Paper II

Eid K, Torkildsen Ø, Aarseth J, Celius EG, Cortese M, Holmøy T, Kapali A, Myhr KM, Torkildsen CF, Wergeland S, Gilhus NE, Bjørk MH.

Abuse and revictimization in adulthood in multiple sclerosis: a cross-sectional study during pregnancy. J Neurol. 2022 Nov;269(11):5901-5909.

Paper III

Eid K, Torkildsen ØF, Aarseth J, Flemmen HØ, Holmøy T, Lorentzen ÅR, Myhr KM, Riise T, Simonsen C, Torkildsen CF, Wergeland S, Willumsen JS, Øksendal N, Gilhus NE, Bjørk MH.

Perinatal Depression and Anxiety in Women with Multiple Sclerosis: A Population-Based Cohort Study. Neurology. 2021 Jun 8;96(23):e2789-e2800.

Abbreviations

ACE(s)	Adverse childhood experience(s)
aOR	Adjusted odds ratio
BMI	Body Mass Index
CI	95% Confidence intervals
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
DMTs	Disease modifying therapies
EBV	Epstein-Barr Virus
e.g.	*exempli gratia* (latin: for example)
HLA	Human leukocyte antigen
HPA	Hypothalamic-pituitary-adrenal axis
HR	Hazard ratio
ICD-10	The International Classification of Diseases 10th Revision
i.e.	*id est* (latin: that is)
IM	Infectious mononucleosis
MBRN	The Medical Birth Registry of Norway
MoBa	The Norwegian Mother, Father, and Child Cohort Study
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MS Registry	The Norwegian Multiple Sclerosis Registry and Biobank
NfL	Neurofilament light
NPR	The Norwegian Patient Registry

PPMS	Primary-progressive multiple sclerosis
PTSD	Post-traumatic stress disorder
Q1	Questionnaire 1 (Pregnancy week 17–20)
Q3	Questionnaire 3 (Pregnancy week 30)
Q4	Questionnaire 4 (6 months after birth)
Q5	Questionnaire 5 (18 months after birth)
RIS	Radiologically Isolated Syndrome
RRMS	Relapsing-remitting multiple sclerosis
SCL-8	Symptom Checklist-8 (Short version of Hopkins Symptom Checklist)
SCL-4A	4-item score for anxiety from SCL-8
SCL-4D	4-item score for depression from SCL-8
SES	Socioeconomic status

Abstract

Background: Stress may play a role in multiple sclerosis (MS). Stress in childhood, such as abuse experiences, is associated with increased risk of chronic diseases in adulthood. It is unknown whether such stress increases the risk of MS. Exposure to childhood abuse can lead to a vicious cycle of adverse lifestyle behavior, repeated abuse experiences (revictimization) and mood disorders. Such multiple adversities may also lead to adverse pregnancy outcomes. Depression and anxiety are common in MS but have not been well studied in the pregnancy setting. The occurrence of abuse experiences and revictimization before and during MS was previously unknown.

Objective: The aims of this research project were to examine whether adverse childhood experiences increased the risk of MS as an adult, to examine the occurrence of abuse and revictimization as an adult and in relation to pregnancy in women with MS, and to examine the risk of perinatal depression and anxiety in women at different phases of the MS disease course.

Materials and methods: We used data from the Norwegian Mother, Father and Child Cohort Study (MoBa). Over 95,000 pregnant women were recruited 1999–2008, resulting in over 114,000 pregnancies in the cohort. The women answered detailed questionnaires during and after pregnancy, comprising information on a range of exposures and outcomes. MoBa was already linked to the Medical Birth Registry of Norway (MBRN). We further linked the dataset to the Norwegian Patient Registry (NPR) and the Norwegian Multiple Sclerosis Registry and Biobank (MS Registry), to identify and validate cases of MS. 125 unique women had an established MS diagnosis at the time of inclusion in MoBa (prevalent MS), and another 363 women developed MS after inclusion in MoBa and until December 31st, 2018, the time of data linkage (incident MS). We used cox regression analysis to measure the association between childhood abuse exposure and later risk of developing MS in incident MS cases (paper I). We used logistic regression to measure the risk of experiencing abuse in adulthood and pregnancy in women with prevalent MS compared to women without MS (paper II). We used logistic regression to measure the risk of perinatal depression and anxiety in women with prevalent and incident MS compared to women without MS (paper III).

All estimates were adjusted for potential confounders and calculated with 95% confidence intervals (CI).

Results: We found an increased risk of MS among the 14,477 women who had experienced adverse childhood events (paper I). The hazard ratio (HR) for MS was 1.65 (CI 1.13–2.39) after sexual abuse and 1.40 (CI 1.03–1.90) after emotional abuse in childhood. The estimates were stratified by birth year and adjusted for childhood social status, adverse socioeconomic status as an adult, history of smoking and being overweight. Having experienced physical abuse gave an HR of 1.31 (CI 0.83–2.06). The results suggested a dose-response relationship between a higher number of childhood abuse categories and increasing risk of MS; 1 category HR 1.11 (CI 0.79–1.56), 2 categories HR 1.66 (CI 1.04–2.67) and 3 categories HR 1.93 (CI 1.02–3.67). We found increased risk of abuse in adulthood in 106 women with prevalent MS compared to 77,278 women without MS (Paper II). The adjusted odds ratio (aOR) was 1.75 (CI 1.08–2.83) for systematic emotional abuse, 2.37 (CI 1.02–5.49) for rape, and 2.23 (CI 1.22–4.10) for revictimization, i.e., repeated abuse in adulthood after experiencing childhood abuse. The risk of abuse in relation to pregnancy was similar between the groups. We found increased risk of depression during pregnancy in 140 women with prevalent MS, aOR 2.0 (CI 1.2–3.1), and for postpartum depression in the 35 women diagnosed with MS in the postpartum period, aOR 3.1 (CI 1.3–7.2) (Paper III). Risk factors for perinatal depression were adverse socioeconomic factors, history of psychiatric disease, and abuse. In contrast to depression, the risk of perinatal anxiety was not increased. Among 308 women with incident MS, those who had MS symptom onset within 5 years after pregnancy had increased risk of perinatal depression, but those with more than 5 years until MS symptom onset did not: aOR 1.9 (CI 1.1–3.1 for ≤5 years and 1.2 (CI 0.7–2.0) for >5 years.

Conclusions: Adverse childhood experiences seem to increase the risk of developing MS as an adult. Women with MS have increased risk of adult emotional abuse, sexual rape, and repeated abuse in adulthood after childhood abuse. Women with MS have increased risk of perinatal depression, and a history of abuse, psychiatric disorder or adverse socioeconomic status further increase this risk.

Abstrakt [Norwegian]

Bakgrunn: Stress kan spille en rolle ved multippel sklerose (MS). Stress i barndommen forårsaket av vold og overgrep er assosiert med økt risiko for kroniske sykdommer i voksen alder. Det er ukjent om slikt stress kan øke risikoen for å utvikle MS. Å være utsatt for vold i barndommen kan føre til en ond sirkel med ugunstig livsstil, gjentatt eksponering for vold (reviktimisering) og stemningslidelser. Slike negative hendelser kan også føre til nedsatt helse for mor og barn ved svangerskap og fødsel. Depresjon og angst er vanlig ved MS, men har ikke blitt godt studert i perinatal perioden. Forekomsten av voldsopplevelser og reviktimisering før og under MS sykdommen har stort sett vært ukjent.

Mål: Forskningsprosjektet hadde som hovedmål å 1) undersøke om traumatiske hendelser i barndommen økte risikoen for å utvikle MS som voksen, 2) undersøke forekomsten av vold og reviktimisering i voksen alder, samt forekomsten av vold i perinatal perioden hos personer med MS, og 3) undersøke risikoen for perinatal depresjon og angst hos kvinner i ulike stadier av MS sykdommen.

Metode: Vi brukte data fra Den norske mor, far og barn undersøkelsen (MoBa). Over 95,000 gravide kvinner ble rekruttert i perioden 1999–2008, og data fra 114,000 svangerskap er inkludert i kohortstudien. Under og etter svangerskapet svarte kvinnene på detaljerte spørreskjema som inneholdt informasjon om en rekke eksponeringer og utfall. MoBa var allerede koblet med Medisinsk fødselsregister (MFR). Vi koblet filen videre med Norsk pasientregister (NPR) og Norsk Multippel Sklerose Register og Biobank (MS Registeret), for å identifisere og validere MS diagnoser i MoBa kohorten. 125 kvinner hadde etablert MS diagnose da de ble inkludert i MoBa (prevalent MS), og ytterligere 363 kvinner utviklet MS etter MoBa inklusjon frem til 31. desember 2018, dato for kobling av filene (insident MS). Vi brukte Cox regresjon for å beregne assosiasjonen mellom vold i barndommen og senere risiko for MS utvikling for insidente MS tilfeller (artikkel I). Vi brukte logistisk regresjon for å måle risikoen for å oppleve vold i voksen alder og i svangerskap hos kvinner med prevalent MS sammenliknet med kvinner uten MS (artikkel II), og til å måle risikoen for perinatal depresjon og angst hos kvinner med prevalent og insident MS sammenliknet

med kvinner uten MS (artikkel III). Alle risikoestimater ble justert for potensielle konfundere og beregnet med 95% konfidensintervall (KI)

Resultat: Vi fant økt risiko for MS blant 14,477 kvinner som hadde opplevd traumatiske hendelser i barndommen (artikkel I). Hazard ratioen (HR) for MS var 1.65 (KI 1.13–2.39) etter seksuell vold og 1.40 (KI 1.03–1.90) etter emosjonell vold i barndommen. Estimatene ble stratifisert for fødselsår og justert for sosial status i barndommen, lav sosioøkonomisk status som voksen, røyking, og overvekt. Fysisk vold medførte en HR på 1.31 (KI 0.83–2.06). Et økende antall voldskategorier gav økt risiko for MS i et dose-respons forhold; En kategori ga HR 1.11 (KI 0.79–1.56), to kategorier ga HR 1.66 (KI 1.04–2.67) og tre kategorier ga HR 1.93 (KI 1.02–3.67). Vi fant økt risiko for å bli utsatt for vold i voksen alder blant 106 kvinner med prevalent MS sammenliknet med 77,278 kvinner uten MS (artikkel II). Justert odds ratio (OR) var 1.75 (KI 1.08–2.83) for systematisk emosjonell vold, 2.37 (KI 1.02–5.49) for voldtekt, og 2.23 (KI 1.22–4.10) for reviktimisering; det vil si ny vold i voksen alder etter å ha opplevd vold i barndommen. Risikoen for vold i relasjon til svangerskap var lik mellom gruppene. Vi fant økt risiko for depresjon blant 140 kvinner med prevalent MS, OR 2.0 (KI 1.2–3.1), og for postpartum depresjon hos 35 kvinner nydiagnostisert med MS i postpartum perioden, OR 3.1 (KI 1.3–7.2) (artikkel III). Risikofaktorer for perinatal depresjon var lav sosioøkonomisk status, tidligere psykiatrisk sykdom og tidligere opplevd vold. Risikoen for perinatal angst var ikke økt. Blant 308 kvinner med insident MS var det økt risiko for perinatal depresjon hos dem med første MS symptom innen 5 år etter svangerskapet, men ikke økt risiko hos dem med mer enn 5 år til MS symptomdebut; OR 1.9 (KI 1.1–3.1 for ≤ 5 år og 1.2 (KI 0.7–2.0) for > 5 år.

Konklusjon: Traumatiske hendelser i barndommen er assosiert med økt risiko for å utvikle MS som voksen. Kvinner med MS har økt risiko for å bli utsatt for emosjonell vold og voldtekt som voksen, og også for nye voldsopplevelser som voksen etter vold i barndommen. Kvinner med MS har økt risiko for perinatal depresjon, og tidligere voldsopplevelser, psykiatrisk sykdom eller lav sosioøkonomisk status øker ytterligere denne risikoen.

1 Introduction

1.1 MS characteristics, epidemiology, and treatment

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that leads to demyelination and neurodegeneration. MS is usually diagnosed in young adults 20–40 years but can occur in all age groups.[1] Over 2.8 million people are living with MS worldwide,[2] with the highest prevalence in North America and Western Europe (Figure 1). Females are 2–3 times more likely to develop the disease than men.[2] The combination of a young age of onset with symptoms of fatigue and disability, results in MS being a leading cause of neurologic disability in young adults.

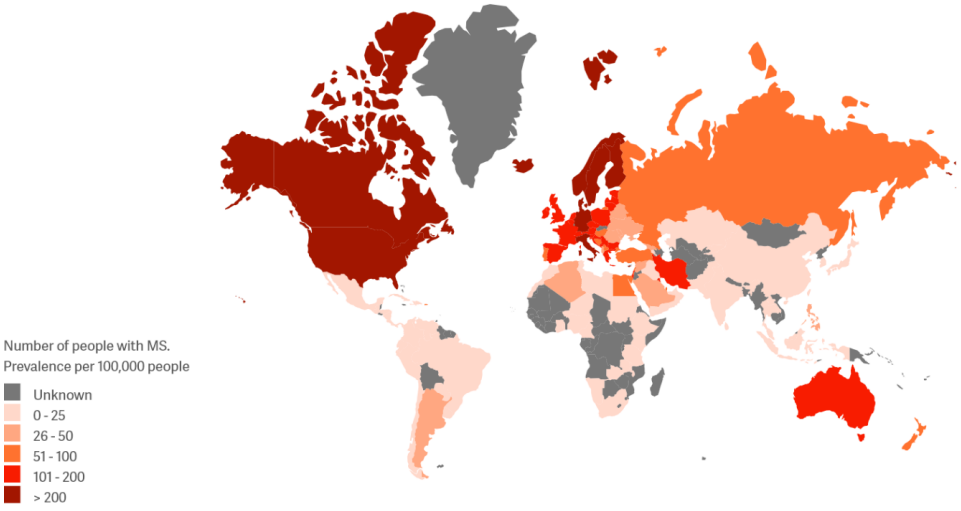


Figure 1: The prevalence of MS 2020-2022 by country
Open-source data from Multiple Sclerosis International Federation – Atlas of MS – 3rd Edition. Number of people with MS | Atlas of MS Accessed: July 12, 2023

In Norway, about 14,000 people are currently living with MS.[3] The MS occurrence is among the highest in the world, with a prevalence of 255 per 100,000 inhabitants and an annual incidence rate of 9 per 100,000.[3] The patterns of global variation in MS distribution have inspired theories of MS etiology – and engaged research in factors

such as sun exposure and vitamin D, diet, infectious agents and genetics.[4-7] Migration studies, largely inspired by the latitude gradient, have since the 1960s given rise to hypotheses on susceptibility periods for MS risk. These studies have shown adaptations in MS risk upon migration to a new country, where those migrating get a lower risk for MS when migrating from high- to low-risk areas, and higher risk for MS when migrating from low- to high-risk areas.[8,9] This change in risk is particularly seen if migration occurs in childhood and adolescence, although no clear age cut off was found in recent population-based studies.[10,11]

There is currently no established cure for MS. However, during the last few years highly efficient treatments have become available.[12-14] This has led to dramatic reduction in disease activity compared to earlier treatment options originating in the early 90s.[12] In Norway, almost 96% of newly diagnosed MS patients now start with high efficacy treatment such as rituximab.[3]

Despite a new era of disease modifying therapies (DMTs) reducing inflammation and neurological deficits, people with MS experience a range of physical and psychological symptoms and comorbidities that negatively affect their health and quality of life,[15] such as depression.

Some aspects that remain rather unexplored in people with MS is the history and burden of abuse experiences, depression in the perinatal setting, and the interplay and impact of these events on MS disease and comorbidities. In the process of optimizing prevention, care, and quality of life for people with MS, new insights in these areas are much warranted.

1.2 MS disease course

Classical MS symptoms that should lead to suspicion of the diagnosis include blurred vision and eye pain (optical neuritis), weakness or sensory changes in parts of the body, dizziness, and impaired balance.[16] An episode where a person's symptoms and objective findings represent a demyelinating event is often referred to as an MS attack or relapse. Other symptoms of MS include fatigue, cognitive impairment, and

dysfunction in the autonomic nervous system resulting in urinary, sexual, and gastrointestinal difficulties. The clinical presentations are unpredictable and vary between people according to location and size of MS lesions and injury in the CNS.

The first episode of MS symptoms is often detected retrospectively, after the diagnosis has been established and when the patient history is examined rigorously. The first episode is sometimes assessed prospectively as a clinically isolated syndrome (CIS). A person is defined as having CIS if an episode of acute neurological symptoms is highly suggestive of MS, yet insufficient to fulfill the diagnostic criteria for MS.[17]

MS is diagnosed after evidence of disease activity *over time* - several attacks or progression - and disease activity in *different locations* in the CNS.[17] Evidence of disease activity can be obtained through patient history and neurological examination, and from specific findings on CNS neuroimaging and in the cerebrospinal fluid.

About 90% of people with MS have relapsing onset disease defined by an evident first episode of neurological symptoms.[3,18] An MS relapse is usually followed by complete or partial recovery.[16] A minority of the people with MS experience a disease presentation with progressive onset, where the timing of symptom onset is indistinct and neurological deficits gradually increase over time. These two phenotypes have traditionally been considered to be distinctive types of MS with different biological mechanisms: namely relapsing-remitting MS (RRMS) and primary-progressive MS (PPMS).[19] Many people with relapsing onset MS will ultimately, with time, experience progressive worsening of the disease; defined as secondary progressive MS.[20] Increasing evidence now supports that these phenotypes represent parts of a continuum, with common underlying pathophysiological mechanisms[21] and risk factors.[22]

There is usually a time-lag between MS symptom onset and MS diagnosis. This diagnostic delay has decreased over the last two decades,[23,24] due to changes in diagnostic criteria, advances in magnetic resonance imaging (MRI) technology, better access to neurological services, and the need for early initiation of DMTs.[24,25]

1.2.1 The MS prodrome

A prodrome can be defined as subtle and non-specific symptoms or signs in an early phase of a disease that occurs before more typical manifestations. A prodromal phase exists for neurodegenerative diseases, such as Parkinson's,[26] and Alzheimer's,[27] and also for autoimmune disorders such as rheumatoid arthritis.[28]

Previously, it was believed that MS did not have an identifiable prodromal period.[29,30] During the last decade, emerging evidence have shed light on the possibility of a prodromal period before classical MS symptoms appears.[31] In 2017, an interesting study on the occurrence of an MS prodrome was published by Wijnands and colleagues in *The Lancet Neurology*.[32] Using population-based administrative data on >14,000 people with MS, the authors found increased health-care usage by people with MS during the last 5 years before MS symptom onset. Hospitalizations, physician visits, and dispensed drugs were higher among those who developed MS than controls, and especially high during the year before typical MS symptom onset. Several population-based studies have followed, and current evidence suggests that the prodrome consists of non-specific symptoms such as depression, headache, fatigue, pain, disruptions in sleep, bowel- and bladder dysfunction in the years before MS symptom onset.[31] Women with future MS was more likely to fill a prescription for hormonal contraceptives and less likely to get pregnant in the 5 years before MS symptom onset, compared to controls.[33] This might imply that a change in behavior occurs in the prodrome, possibly due to feeling unwell.

Biological support for an MS prodromal phase exists. Neurofilament light (NfL), a biomarker of neuroaxonal injury, is found to increase in blood at least a decade before the first classical symptom of MS in some individuals,[34,35] and especially closer to symptom onset. The evidence that neurodegeneration can occur many years prior to MS onset makes it less likely that the prodrome could be explained by reverse causality, e.g., that depression the year before MS onset is a causal factor for MS.

The duration of the prodrome is unknown. Current research suggests that the prodrome can be evident at least 5–10 years before MS symptom onset, and prodromal signs seem to increase as time approaches the first episode of classical MS symptoms.[32,33,36]

A Norwegian nested case-control study among > 20,000 men undergoing military conscription examination found lower cognitive performance among those who developed MS, compared to controls.[37] The cognitive performance was impaired up to 2 years before MS symptom onset, and up to 20 years before the first symptoms in those with progressive-onset MS. The length of the prodromal phase is likely to vary between individuals, and not all people who develop MS will necessarily have a noticeable prodrome. The disease course and prognosis of MS show wide heterogeneity between individuals, and the same heterogeneity most likely applies to prodromal features.

Radiologically isolated syndrome (RIS)

Over 90% of people with their first demyelinating event have multiple lesions on MRI,[38,39] indicating inflammation and demyelination occurring before the first classic MS symptoms.

Characteristic MS signs are sometimes found on MRI in individuals who undergoes imaging for other reasons than suspicion of MS, such as after head trauma or for research purposes. These incidental findings are defined as a radiologically isolated syndrome (RIS).[40] Individuals with RIS have over 50% 10-year risk of developing MS.[41] RIS is considered as occurring in asymptomatic individuals without any neurological dysfunction.[42] However, headache and mood disorders are among the most common reasons to conduct an MRI in people with RIS.[42] Of note, both headache and mood disorders could be symptoms of the MS prodrome.[31] Impaired cognitive function has been found in people with RIS.[43,44] The first randomized placebo-controlled trial investigating whether the use of DMTs could delay onset of MS among people with RIS, found an 82% reduced risk of experiencing MS symptoms for those who received dimethyl fumarate during almost 2 years of follow-up.[45] Thus, RIS has a potential role for early detection and, possibly, prevention of MS.

It is not known whether people with prodromal symptoms have MRI findings suggestive of RIS. Further research is warranted on whether RIS could be a potential

marker of the MS prodrome, and to clarify how RIS overlaps with the pre-diagnostic phases of MS.

An updated MS framework

In 2022, an updated framework for the natural history of MS was proposed, where the prodromal phase is included as the earliest symptomatic stage of MS (Figure 2).[46] After the biological onset of MS, an asymptomatic subclinical phase occurs. but with ongoing disease-associated pathological processes such as immune dysregulation. The subclinical phase is followed by the prodromal phase. The pathophysiological mechanisms of the prodrome are yet unknown, but hypothesized to consist of inflammation, demyelination, and neurodegeneration[31] Some people might progress directly to MS symptom onset from the subclinical phase.

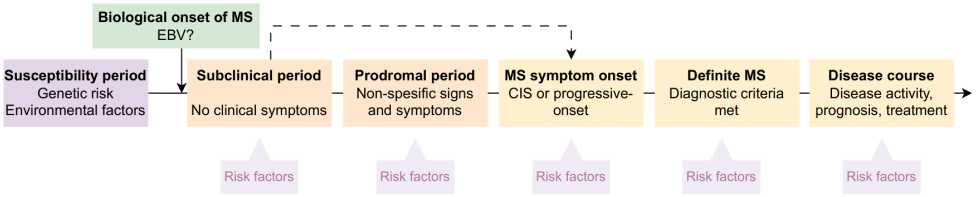


Figure 2. MS disease course and risk factor influence. Illustration of MS disease course inspired by Marrie et al.[46] MS is caused by environmental and genetic risk factors. A subclinical period starts when the biological onset of the disease occurs. The risk of MS is small without any previous Epstein-Barr Virus (EBV) infection. It is unknown if EBV is the one exposure in the causal chain leading to MS. The prodromal phase is characterized by a range of non-specific signs and symptoms. Some people might progress directly from the subclinical phase to classical MS symptom onset (dashed line) without a prodromal phase. Environmental risk factors and environment-gene interactions most probably affect all phases of the disease course, both influencing susceptibility and severity of MS.

As the signs and symptoms of the MS prodrome are non-specific and occur commonly in the general population, standardized criteria including appropriate biomarkers and MRI-findings need to be defined[46] to facilitate recognition and early intervention in those at risk for MS development.

1.2.2 Pediatric-onset MS

3–10% of people with MS have onset of classical symptoms before 18 years of age, with a peak incidence between 13 and 16 years.[47] Data on pediatric MS is limited worldwide, and there are several gaps in knowledge about occurrence, diagnosis, and treatment.[48] The same susceptibility genes and environmental factors found for adult-onset MS have also been found for pediatric-onset MS.[49] A prodromal phase has also been suggested for pediatric MS.[31] Pediatric-onset disease is distinct from adult-onset disease with more active inflammation and more frequent relapses, but also better relapse recovery.[50] Yet, given the early onset of disease, those who have pediatric-onset MS reach disability milestones at an earlier age than adult-onset MS.[50]

1.3 Genetic risk factors for MS

It is well established that the cascade of events leading to MS onset represents a complex construct, and that MS is caused by interaction between genetic susceptibility and environmental risk factors.

More than 200 genetic variants have been identified to increase MS risk, but none are exclusively found in people with MS.[51] Two human leukocyte antigen (HLA) variants are strongly associated with MS – where HLA-DRB1*15:01 increases risk and HLA-A*02 decreases risk.[52] The genetic risk variants contribute to MS risk in an additive manner, and a high burden of risk variants is linked to an earlier age at MS onset[52] and to higher risk of MS within families.[53]

In 2023, two genetic variants potentially influencing MS progression were described for the first time;[54] one significant and one suggestive variant – rs10191329 and rs149097173, respectively. Those with MS who had two copies of the significant progression-associated allele needed a walking aid 3.7 years earlier than those without the allele, and they had more cortical and brainstem lesions. Interestingly, the genes associated with MS risk and MS progression does not overlap.[51] The genes associated with MS susceptibility tend to be related to the immune system and the genes associated with MS progression tend to be related to the CNS.

1.4 Environmental risk factors and susceptibility periods

1.4.1 Epstein-Barr Virus

The hypothesis that MS is caused by an infectious disease was first proposed in the 19th century,[55] and numerous infectious diseases and microbes have been studied since.[56-58] Evidence throughout the last 40 years has linked the herpesvirus Epstein-Barr Virus (EBV) to MS development. Based on new evidence in 2022, the association is proposed to be causal,[59] meaning that MS development could be a rare complication of EBV infection. The study was the first to demonstrate a temporal relationship between EBV and MS. From a cohort of 10 million US military personnel, 800 of 801 people with MS were EBV seropositive. The authors were able to prospectively study a subgroup of 35 individuals who were EBV-negative at baseline, who later became EBV positive and ultimately developed MS. Estimated EBV seroconversion occurred up to 15 years before MS symptom onset, with a median of 7.5 years. The EBV infection was succeeded by an increase in NfL-levels in those who later developed MS, but not in those who did not develop MS.

EBV infection occurs in all age groups, but a primary infection is typically asymptomatic during childhood and symptomatic in adolescence and early adulthood, causing infectious mononucleosis.[60] Studies have found higher risk of MS after infectious mononucleosis in adolescence, than for mononucleosis in childhood or early adulthood. [61,62] This supports the hypothesis that adolescence is a critical period for MS susceptibility in adult-onset MS.[63]

1.4.2 Vitamin D, sun exposure, smoking, and body weight

Although an EBV infection is hypothesized to be an obligate step for MS development, over 90% of the world population are infected by EBV during the first decades of life[64] – where only a small fraction develops MS. EBV may also play a role in other autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus.[65,66] It is unknown if EBV infection is sufficient to cause MS by itself. Multiple environmental risk factors modify MS risk and development. The most consistent associations with increased MS risk have been found for vitamin D

deficiency, low sun exposure, history of smoking, and high body mass index (BMI).[56,67] Exposure at a young age, especially in adolescence, seems to be of importance also for these risk factors.[5,68-71]

Additional environmental factors have been studied in the search for insight in MS etiology.[56,72] Some factors of interest, but with limited evidence, include other infections in adolescence such as pneumonia,[73] CNS infections,[57] bacterial infections,[57] and infections with human herpesvirus 6A[74] and varicella zoster virus,[58]. A few studies have reported insufficient sleep during adolescence[75] and night shift work under the age of 20 years to be associated with increased MS risk,[76,77] in a dose-dependent manner.[75,77] Some studies have indicated that alcohol consumption[78,79] and physical activity[80,81] may reduce the risk of MS.

1.4.3 Interplay and interactions: Environmental and genetic risk factors

The details of how environmental risk factors are involved in MS pathogenesis are unknown, and the relationship between the environment, lifestyle, genetics, the immune system, and the brain in MS pathogenesis is complex. Interactions have been found between risk genes and environmental risk factors, in particular for the main risk allele HLA-DRB*15:01 with EBV infection, smoking, adolescent BMI, vitamin D and sun exposure[67,82,83] Interaction occurs when the combined exposure of two factors gives a risk estimate for MS that is higher than the sum of the risks calculated separately. The risk of MS is increased by 2.6 in those with high EBV antibody levels without the HLA risk allele, by 10 in those with high EBV antibody levels with one HLA risk allele, and by 20 in those with high EBV antibody levels with two HLA risk alleles (compared to those with low EBV antibody levels without the main HLA risk allele).[83] Environment-environment interactions also exist, where studies have found synergistic increase in MS risk for those with high antibody EBV levels and history of smoking,[82] and for those with high antibody EBV levels and low sun exposure.[84]

As the HLA genes encode for molecules that act in the immune system,[51] interactions with environmental risk factors suggest independent effects on immune related pathways. Smoking and high BMI both promote a proinflammatory environment.[85,86]

The main theory of how environmental factors interact with genetic risk variants is through epigenetic pathways.[87] DNA interacts with small molecules that can activate and deactivate genes. Environmental factors can alter how these molecules attach to the DNA, resulting in increased or decreased transcription of specific genes. This dynamic interaction can change characteristics of cells, thus leading to diseases, and determine prognosis of diseases. Epigenetic changes are seen both in brain and immune cells in people with MS.[88] High BMI is a trigger for epigenetic changes in MS.[89]

Over 200 genetic loci and a range of lifestyle and environmental risk factors have been identified for MS. None of them are sufficient to cause the disease alone.[90] Rather, a range of factors and stochastic mechanisms are probably involved – leading to a "perfect storm" with dysregulation of the immune system and inflammation in the CNS.[91]

1.4.4 Environmental factors throughout the disease course

It remains unknown how long prior to MS symptom onset one should investigate risk exposure to assess true causal factors. As discussed earlier, childhood and adolescence are repeatedly demonstrated to be of particular interest. With more sensitive MS diagnostic methods and the evidence that neurodegeneration may start before the first evident MS symptoms, it has been proposed that some previously studied risk factors should be reinvestigated to ensure temporality.[92]

Environmental factors may affect different aspects of the disease course and are thus relevant beyond disease risk (Figure 2). Exposure to risk factors in the subclinical or prodromal periods most likely mediates the clinical expression of the disease, e.g., that ongoing pathological processes reach or do not reach a clinical threshold. This hypothesis is supported by the observation that not all people with RIS or CIS will develop established MS.[41,93] The heterogeneity in clinical expression is further highlighted by autopsy findings, where some individuals had typical MS CNS pathology; but no symptoms of MS throughout life.[94] High BMI is associated with a higher risk of conversion from CIS to MS.[95] Environmental factors can also modulate the disease course in established MS. Smoking, high BMI and low levels of vitamin D

are shown to adversely modulate the disease course with higher disease activity.[95-97] People with MS who smoke or have high BMI have more brain atrophy compared to unexposed.[95,96,98] Moreover, smoking may reduce the efficacy of disease-modifying treatment.[99,100]

Environment-gene interactions may affect prognosis. Epigenetic changes are associated with disease severity in MS.[101] A 2023 study that used mendelian randomization analyses found that individuals with genetic variants that predicted high educational attainment and/or low risk of smoking had less disabling MS disease.[54]

Together, this evidence illustrates the dynamic interplay between genes and environment throughout the course of MS – and the potential for mitigation. The first clinical studies on vitamin D supplementation in established MS have found a modest reduction in both new MS lesions on MRI and relapse rates.[97] Smoking cessation in MS decreases disease activity and progression, in addition to other health benefits.[96]

1.5 Stress and MS

People with stress-disorders such as acute stress reaction and post-traumatic stress disorder (PTSD) have increased risk of autoimmune diseases in general.[102,103] Psychological stress has been considered to affect MS since the initial description of the disease in the 19th century.[104] However, research on stress exposures has been limited and results have been conflicting.[105] Studies that have reported an association between stress and MS have mostly been case-control studies, which are prone to recall bias. Previous studies have had heterogeneous study designs; some have combined disease activity and MS onset as one outcome, others have combined distant and recent stressors as one exposure.[105,106] The association between stress and MS disease activity has been studied more thoroughly than the association between stress and MS susceptibility.[105] The definitions and measurements of stress and MS disease activity have varied. Moreover, most studies have had no or insufficient adjustment for confounding factors.[106] Thus, it has been challenging to compare results across studies, and the impact of stress on MS remains a matter of debate.

1.5.1 Stress and MS disease activity

A systematic review summarizing the evidence 1900–2014 found that stress was associated with MS relapse in both prospective and case-control studies.[105] The risk of MS relapse was especially elevated in the 4–8 week period after a stressful event.[105] Stressful events comprised problems concerning personal relationships, work, finance, living conditions, illness, bereavement, and legal issues. Stressors of long duration and with moderate or severe intensity was more important for relapses, independent of exact stressor type. Moreover, accumulated stress was more associated with relapse than single events. However, a meta-analysis found that the effect size was modest.[107] Others have pointed to several weaknesses of these prior studies, and that the association between stress and MS relapse represents at most only a possibility.[108]

A study that followed 121 people with MS regularly for 48 weeks found that severe stressful life events increased the risk of new or enlarging MS lesions on MRI,[109] and interestingly, that positive life events had a protective effect for new lesions. Similarly, a randomized trial found that stress management prevented new brain lesions during the intervention period in people with MS.[110]

Several studies have found a bidirectional relationship between stress and MS disease activity; that worsening of MS disease increases the risk of self-reported stress.[105] Moreover, a longitudinal study in people with MS found that abnormal processing of stressful stimuli was associated with subsequent gray matter atrophy 2–3 years later.[111]

1.5.2 Stress and MS susceptibility

Whether stress has an influence on MS susceptibility has been debated.[105] Heterogeneity in study designs, temporal relationships between stress and MS, and varied definitions of stress can explain the inconsistent results. Most of the prior studies investigating stress and risk of MS onset have focused on stressful events close to MS symptom onset or diagnosis.[105,112,113] Sample sizes have mostly been small, which may result in too little power to detect true associations, or in inflated or untrue associations.

Adult stress

Only a few population-based studies have examined the association between adult stress and MS risk. A register-based cohort study from Denmark among 1.8 million individuals with a mean follow up of 16 years investigated the effect of adult life stressors such as divorce and death of a partner or a child and did not find an association between such adulthood stress and MS onset.[114] Despite similar study designs, they were in that study not able to reproduce earlier findings from Denmark that found increased risk of MS in bereaved parents that had experienced child loss.[115]

Marriage, divorce, child birth and child loss appear most often during established adulthood,[116] particularly in developed countries, and overlap with the typical age of MS symptom onset. Thus, exposure to such events may be after the critical time window for the start of the MS disease process. A large case-control study from Sweden that studied ten types of self-reported stressful events among 2930 people with MS, found that events such as divorce, interpersonal conflicts and accidents/sickness of core family members increased MS risk by 15–30%, with a dose-response relationship[117] Of note, this study found that most events occurred within 5 years preceding MS symptom onset. A similar, yet smaller study on stressful life events found that among 282 people with MS, a higher proportion reported serious illness during the last 12 months prior to diagnosis compared to controls.[112] These findings may illustrate how stressful events in the prodromal phase could boost ongoing pathological mechanisms to reach a clinical threshold.

Childhood stress

Adverse childhood experiences (ACEs) such as abuse, neglect and household dysfunction are known to have long-term negative consequences for lifestyle choices and health in adulthood.[118,119] Yet, few studies have investigated such childhood stressors and MS outcomes.

A Danish cohort study that assessed early life stressors such as parental divorce and death of parents or siblings found that exposure to a stressful event before the age of

18 years was associated with 11% increased risk for MS.[120] The association was mainly driven by exposure to parental divorce.

A cohort study that included 262 nurses with MS did not find that exposure to physical or sexual abuse in childhood or adolescence increased the risk of MS.[121] However, a German case-control study with 234 people with MS studied different categories of abuse and neglect and found an increased risk of having experienced sexual or emotional abuse, as well as emotional neglect in childhood, compared to controls.[122] A case-control study from Iran with 250 people with MS found a substantially increased risk of exposure to weekly physical abuse in childhood compared to controls.[123] Other smaller studies (< 100 MS cases) found both increased risk[124] and no increased risk[125] of self-reported abuse and neglect in childhood in people with MS.

Whether childhood stress increases the susceptibility to MS is unknown. As studies on other environmental factors highlight childhood and adolescence as a critical period for MS development,[63] this potential association needs further exploration.

1.5.3 Adverse childhood experiences (ACEs) and MS disease course

Stressors originating in childhood may have consequences for MS disease activity. Some studies have reported associations between exposure to several ACEs and earlier age of MS onset.[124,126] However, one study only had 67 participants, and the results from the other one were no longer significant after correction for multiple testing. The German case-control study did not find an association between ACEs and age of MS onset or disease severity, but found an increased relapse rate among those who reported severe childhood abuse.[122] The experience of childhood maltreatment in people with MS has also been associated with increased risk of exaggerated pain sensation,[127] fatigue,[128] and psychiatric comorbidity,[129] this compared to people with MS without such exposure. So far, only one study has investigated stressful events both in childhood and adulthood when considering MS disease activity.[130] The authors reported that the increased relapse rate in those with a history of childhood trauma might be explained by stressful events in adulthood.

1.5.4 Impact of childhood stress on MS: Potential pathways

ACEs is associated with a type of stress often called toxic stress, which comprises prolonged and excessive activation of biological stress response systems. Exposure to ACEs increases the risk a wide range of physical diseases both in childhood and in adult life, including cardiovascular disease, cancer, autoimmune and metabolic diseases, and psychological diseases such as depression and anxiety.[119] Figure 3 illustrates how ACEs may affect adult outcomes through dysregulation of pathways important for brain development, immune response systems and epigenetic modifications.

Similarly, toxic stress may affect MS susceptibility through several direct and indirect pathways.

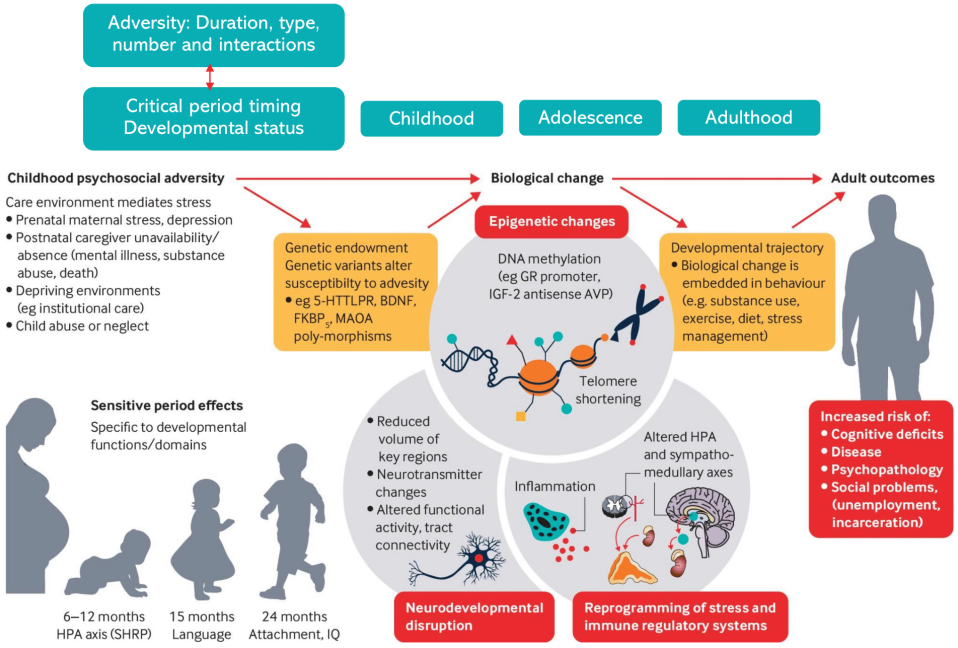


Figure 3. An illustration of potential pathways where adverse childhood experiences can interact with an individuals' genetic susceptibility and behavioral trajectories. Toxic stress responses cause disruptions in neuro-endocrine-immune-metabolic pathways and alter genetic function and expression, thus increasing the risk of adverse health and disease throughout the lifespan. Reproduced in line with Creative Commons CC-BY-NC 4.0 license. ©2020 by British Medical Journal Publishing Group[131]

Neurodevelopment. The nervous system is particularly vulnerable during some periods in childhood and early adulthood.[132] Different brain regions and neuronal pathways are probably sensitive to childhood abuse at different ages,[133] and a range of associated molecular mechanisms may alter brain structure.[132] Ultimately, such alterations may increase the risk of neurological and neuropsychiatric disorders.

Dysregulation of stress responses and the immune system. Abuse and trauma are associated with chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and inflammation,[134] and such inflammation is hypothesized to be a key mechanism that links ACEs to adverse adult health. Several studies have found that ACEs are associated with elevated pro-inflammatory markers that persists into adulthood.[135,136] Inflammation is a central part of MS pathobiology,[21] and a dysregulated HPA-axis is seen in MS.[137]

EBV. Emotional stress can reactivate herpes viruses such as EBV.[138] EBV is normally in a latent resting state in immuno-competent individuals. Studies have found that early-life maltreatment is associated with high EBV antibody titers as an adult.[139-141] Infection with EBV increases MS risk 32-fold,[59] but is also associated with an increased risk of other autoimmune conditions[142] and also different types of cancer.[143]

Genetics and Epigenetics. An individual's risk of developing stress-related disorders after ACEs probably depends on genetic susceptibility. Epigenetic modifications have been seen in those exposed to childhood abuse; with altered expression of stress-related genes and increased risk of PTSD in adulthood.[144] Stress disorders such as PTSD is associated with an increased risk of MS.[102,103] Studies are yet to investigate the occurrence of epigenetic changes in people with MS who have been exposed to ACEs.

Behavioral consequences. ACEs are associated with a range of behavioral and lifestyle factors that are also associated with increased MS risk, e.g., smoking, high BMI, adverse socioeconomic status, and physical inactivity.[56,67,80,81,119,145] This highlights the importance of taking such factors into account when examining the impact of stress on MS.

1.5.5 Stress: Moderating factors

Social support is thought to be the strongest moderating factor on the impact of stress.[146] Some studies have found that people with MS seek less social support in stressful situations,[125,147] and use less favorable stress coping styles, such as avoidant coping,[125,148] compared to people without MS. Moreover, a study reported that people with MS have higher trait anxiety than controls,[125] which is associated with exaggerated perception of stressful events.[149]

Childhood maltreatment and abuse increase the risk of unfavorable coping to stress[150] and increase stress reactivity.[151] Thus, ACEs do not only cause traumatic and long-lasting stress by itself, but it also negatively affect the response to a wide variety of stressors in adult life. People with MS and a history of ACEs may therefore be exposed to a vicious chain of stressful events and unfavorable coping. Stress and adverse coping are associated with increased MS disease activity and reduced function.[105,125] Worsening of MS symptoms is then again associated with an elevated perception of stress.

1.6 Burden of adult abuse experiences in MS

Childhood abuse is associated with increased risk of experiencing abuse as an adult. Such repeated abuse experiences are known as revictimization.[152] Research on adult abuse in MS have gained even less attention than research on childhood abuse. Yet, people with physical disabilities, depression, and cognitive impairment have increased risk of experiencing abuse and maltreatment.[153] All these risk factors are frequent in people with MS. Moreover, women with disabilities have higher risk of domestic abuse compared to men with disabilities,[153] and the risk is also high during and after pregnancy.[154]

A US cross-sectional study of adults with advanced MS found that over 50% of participants reported abuse by their caregivers,[155] where emotional abuse was the most common type followed by economical abuse.

Abuse experiences could also increase the risk of adverse outcomes in the perinatal setting, such as depression, anxiety, prolonged labor, preterm birth and low birth weight.[156-158] The perinatal period is a high-risk period for experiencing intimate partner violence,[159] thus increasing the risk even further for negative outcomes for the mother and child.[160]

Whether people with MS are at increased risk of experiencing abuse as adults, and whether this risk is heightened in the perinatal setting needs to be investigated further.

1.7 MS in the perinatal setting

MS is typically diagnosed in the period when people are starting a family and planning to have children. Historically, women with MS were discouraged to get pregnant due to the belief that pregnancy would negatively affect the course of MS.[161,162] This gradually changed during the late 1980s and 1990s following new research that demonstrated no overall adverse effects of pregnancy on MS.[163] Recent surveys on family planning among people with MS have found that up to 30% changed their plans for having children after MS diagnosis, due to aspects of the MS disease such as risk of MS worsening, symptoms not compatible with parenthood activities, risk of harm to the baby due to drug exposure, or fear of the baby inheriting MS.[164,165]

Women with MS have lower pregnancy and birth rates compared to the general population.[166,167] Presumably, MS does not directly affect biological fertility.[168] Factors that may explain the birth rates include psychological aspects such as voluntary childlessness,[164,169] and a range of physical aspects such as fatigue, comorbid endocrinological conditions, and sexual dysfunction. Lower pregnancy rates and increased prescription of hormonal contraceptives are seen in the MS prodrome, which might suggest altered behavior (consciously or unconsciously) to avoid pregnancy due to health complaints.[33]

However, as pregnancy rates have gone down in the general population in the recent years, the trend seems to go the other way for women with MS.[170] This could be due to increased knowledge and positive attitudes on family planning among neurologists and

MS patients. Some of this increase might also be explained by changes in diagnostic criteria for MS which enable women with less active disease to get diagnosed earlier.[171] Moreover, improved treatment options for MS resulting better MS prognosis might result in more women with MS wanting to have children.

1.7.1 Disease course and treatment in the perinatal period

The perinatal period consists of the antenatal period (from conception to childbirth) and the postpartum period, which can be defined as the first year after giving birth.[172]

A hallmark study on MS disease activity in the perinatal period was published by Confavreux et al. in 1998.[173] The authors followed 241 untreated pregnant women with MS and demonstrated that annual relapse rates decreased during pregnancy and then increased in the first three months postpartum, before returning to the pre-pregnancy baseline. This phenomenon has been replicated in several studies during the last decades,[174] and is attributed to immunological changes of pregnancy and postpartum. The risk of relapses both before, during, and after pregnancy, has decreased in modern cohorts from 2010 and onwards.[174,175]

During the recent years, new knowledge has clarified how to combine medications with pregnancy, which increase the possibility of disease stability in the perinatal period.[176] It is generally recommended to discontinue DMTs before conception due to potential harm to the child, and to re-initiate treatment shortly after giving birth. Safety data on breastfeeding while using DMTs has increased during the last years.[176,177] This allows some women to breastfeed while receiving MS treatment, despite not all DMT options being formally approved as safe. It is hypothesized that the combination of breastfeeding and DMTs may reduce the risk of postpartum disease activity more than treatment alone, but more research is needed.[174,176]

1.7.2 Perinatal mental health in MS

The physical outcomes of pregnancy and childbirth in MS have been well studied. There is a slightly higher risk of urinary tract infections, induced labor, elective

caesarean sections and having a child small for gestational age in pregnancies of women with MS compared to the general population.[178-180] A recent study also reported increased risk of antepartum bleeding and placental abruption.[180]

Perinatal mental health in MS have received less attention, despite depression and anxiety being frequent in MS.[181] A Canadian cohort study found 27% increased risk of perinatal depression among 360 mothers and fathers with MS compared to matched controls.[182] The risk was particularly increased for fathers with MS. The authors also studied subsequent psychiatric disorders in the children and found higher risk of mood disorders in children of parents with MS, and in children of parents who experienced perinatal depression, regardless of MS status.

Depression in people with MS negatively affect quality of life to the same extent as neurological disability.[15] Depression in MS can have various causes, including inflammation,[183,184] structural brain changes due to MS lesions or atrophy,[185,186] dysregulation of the HPA-axis,[187] psychosocial aspects of having a chronic disease,[188] and common environmental risk factors such as obesity.[189] Recent mendelian randomization studies have not found common genetic susceptibility for MS and depression.[189,190] The etiology of depression in the perinatal setting in MS is unknown.

The potential consequences of maternal perinatal depression and anxiety for the child's development are widespread, long-lasting, and affects all domains of development from infancy through adolescence.[191] Perinatal depression also increases the risk of obstetric complications and mortality.[192,193] Preventing and intervening on adverse perinatal mental health is of critical importance. To be able to do this, knowledge about how MS affects perinatal mental health and associated risk factors is needed.

2 Aims of this thesis

Exposure to abuse can lead to a vicious cycle of adverse lifestyle choices, mood disorders and repeated abuse experiences. Prospective and population-based cohort studies in pregnancy give a unique opportunity to study a range of such exposures and outcomes, in both prevalent and incident cases of diseases. We used the Norwegian Mother, Father, and Child Cohort Study together with national registries to examine the history of childhood and adult abuse and the risk of perinatal depression in women with both established and future MS. Our specific aims were:

1. To investigate whether adverse childhood experiences, including sexual, emotional, and physical abuse before the age of 18 years, were associated with an increased MS risk as an adult (paper I).

2. To investigate the occurrence of abuse in women with MS during adulthood and in relation to pregnancy, as well as to investigate their risk of revictimization: i.e., repeated abuse in adulthood after childhood abuse (paper II).

3. To investigate the occurrence of perinatal depression and anxiety in women with MS at different stages of the disease. Further, to determine risk factors for depression in pregnancy in women with MS (paper III).

3 Material and Methods

3.1 The Norwegian Mother, Father, and Child Cohort Study (MoBa)

The main data source for this thesis was pregnant women enrolled in MoBa. MoBa is a nationwide, prospective cohort study carried out by the Norwegian Institute of Public Health and linked to the Medical Birth Registry of Norway (MBRN), a compulsory registry containing information on all births in Norway.[194]

The overall aim of MoBa is to study causes of diseases.[195] Through a large number of recorded exposures, researchers can study associations to pregnancy outcomes and subsequent health problems through MoBa follow-up and linkage to other national health registers.

MoBa started recruitment of pregnant women in 1999.[194,196] Initially, recruitment took place in Hordaland County and was then gradually extended to the whole country. Fathers were invited to the study from the year 2000. By 2004, the recruitment was nationwide, and 50 out of 52 maternity units participated. Recruitment was completed in 2008, and the final participation rate was 41%.[195,196] The long recruitment period resulted in many women participating more than once.

The MoBa cohort includes more than 95,000 mothers, 75,000 fathers and 114,000 children.[195] The follow-up of the cohort is ongoing, and the goal of MoBa is to follow the participating children into adulthood.

A postal invitation to the study was sent out to all pregnant women together with their appointment letter to routine ultrasound examination at the local hospital.[195,196] 98% of all pregnant women in Norway attend ultrasound screening in pregnancy weeks 17-20.[196] The midwife could also recruit to MoBa if the woman had not decided prior to the appointment or not received a postal invitation. There were no exclusion criteria, but the questionnaires were only in Norwegian, thus restricting participation to Norwegian-speaking women.

3.1.1 Data collection (questionnaires)

Mothers in MoBa received three questionnaires during pregnancy, while the fathers received one.[194] The women responded to the first questionnaire (Q1) in pregnancy weeks 17–20 during enrollment to the study. They responded to the second questionnaire in pregnancy week 22 (Q2), and to the third questionnaire in pregnancy week 30 (Q3).[194] We used data from Q1 and Q3 in our study, which contained detailed questions on sociodemographic background, medical history, as well as detailed questions on current health issues and a variety of exposures. These included symptoms of anxiety and depression and the history of abuse experiences.

After childbirth, questionnaires were sent out at 6 months postpartum (Q4) and 18 months postpartum (Q5).[194] We used data from Q4 and Q5 in paper I, which contained information on health of the mother and child, including symptoms of depression and anxiety.

Several subsequent questionnaires and biological samples have been collected from the participants in MoBa,[197] but these data have not been used in this thesis.

3.2 Other data sources

In Norway, all inhabitants receive a unique personal identification number which are used in all registries and hospital records and makes data-linkage across registers and the MoBa cohort possible.

The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) is an administrative registry with contains diagnostic codes, dates for admissions, discharges, and out-patient visits for the specialist health care, including public hospitals and private practice specialists with public reimbursement.[198] Registration in the NPR after visits to the specialist health care system is mandatory. After every patient visit, a diagnostic code is registered according to the 10th revision of the International Classification of Diseases (ICD-10). The registry was established in 1997 but made available at an individual level in 2008 when registration with personal identification numbers became mandatory by law

amendment. Thus, information from 2008 and onwards are available for linkage with other health registries.

The Norwegian Multiple Sclerosis Registry and Biobank

The Norwegian Multiple Sclerosis Registry and Biobank (MS Registry) was established in 2001, and aims to optimize research, treatment, and quality of health care services for people with MS.[199] The registry is based on voluntary consent. The MS Registry contains demographic and clinical data and has a national coverage of 87% at present.[3] The national coverage is calculated by comparing included cases in the MS Registry to those included in NPR. Registration became web-based in 2015. A new law from 2019 stated that it is mandatory for health care units to report information to quality registries such as the MS Registry. The inclusion of prevalent and new MS cases has increased steadily during the recent years. The registry is located at Haukeland University Hospital, Bergen.

Hospital records

Due to incomplete national coverage of the MS Registry at the date of data linkage (described in next section), we used hospital records for validation and assessment of MS variables in some cases.

3.3 Data linkage and validation of MS diagnoses

We cross-linked the female study participants in MoBa with NPR and with the MS Registry on December 31st, 2018, through their personal identification numbers. 545 participants in MoBa had the ICD-10 code G.35 Multiple sclerosis registered in the NPR.

We considered the MS diagnosis as validated if the woman was registered both in the MS Registry and in NPR with the code G.35. The national coverage for MS diagnoses was estimated to be 97% in NPR and 69% in the MS Registry at the time of our data-linkage.[200] All individuals with MS identified through data linkage with the MS Registry were also registered in NPR. Of the 545 women with a G.35 code in NPR, 148 were not included in the MS Registry. We sent a letter of invitation to collaborate

with our study to all MS Registry contacts at the local neurology departments throughout Norway. Thus, through a national collaboration with neurologists and specialist nurses we were able to decide whether the MS diagnoses only registered in NPR was correct or not. Our expert contacts examined the hospital records to ensure that the patient had MS according to the 2017 diagnostic criteria.[17] We did an additional round of validations after the first published paper to provide more MS cases in the subsequent papers (Table 1). These individuals were subsequently invited to be enrolled in the MS Registry.

We identified 478 unique women with MS in the MoBa cohort after the final validation. This comprised both prevalent and incident MS cases. Prevalent cases were defined as women living with MS at the time of MoBa inclusion, whereas incident cases were defined as women who got an MS diagnosis after MoBa inclusion and up until the date of our data linkage.

Table 1. Validation of 545 MS diagnoses in NPR with information from the MS Registry and hospital records

MS validation status	**Paper III[a]**	**Paper I and II**
Confirmed MS[b]	452	478
Refuted MS[c]	40	47
Uncertain MS	1	1
Not available for validation[d]	52	19
Total NPR-cases	**545**	**545**

[a]Paper III (MS and perinatal depression) was the first paper we published

[b]Confirmed diagnosis through linkage with the MS Registry or by using hospital records

[c]Refuted diagnoses did not fulfill diagnostic criteria for MS or had an erroneous coding of G.35.

[d]We did not get a response from all the invited neurology departments. After we published the paper on MS and perinatal depression (Paper III), we repeatedly contacted local MS Registry contacts who had not responded to the first round of validation. For the remaining 19 MS diagnoses from NPR, we did not have access to the hospital records due to no response from local MS Registry contacts. These remaining cases were mainly from small, local neurology departments.

Prevalent MS cases

We defined prevalent MS cases as women who were diagnosed with MS before pregnancy or up to pregnancy weeks 17–20 (time for inclusion in MoBa). This was based on either a) self-report of an MS diagnosis at the questionnaire in week 17–20 *or* b) year of diagnosis from the MS Registry earlier than year of giving birth registered in MoBa/MBRN, or c) both.

This group with prevalent MS was referred to as *MS before baseline/inclusion/enrolment* in paper I and II, and *MS before pregnancy* in paper III.

In total, this group comprised 125 unique women.

Incident MS cases

We defined incident MS cases as women who were diagnosed with MS after inclusion in MoBa, up until the time of our data linkage on December 31st, 2018. This group was referred to as and *MS after baseline/inclusion/enrolment* in paper I and II, and *MS after pregnancy* in paper III.

In total, this group comprised 363 unique women.

An overview of data sources, MoBa questionnaires and MS individuals included in this thesis is shown in Figure 4.

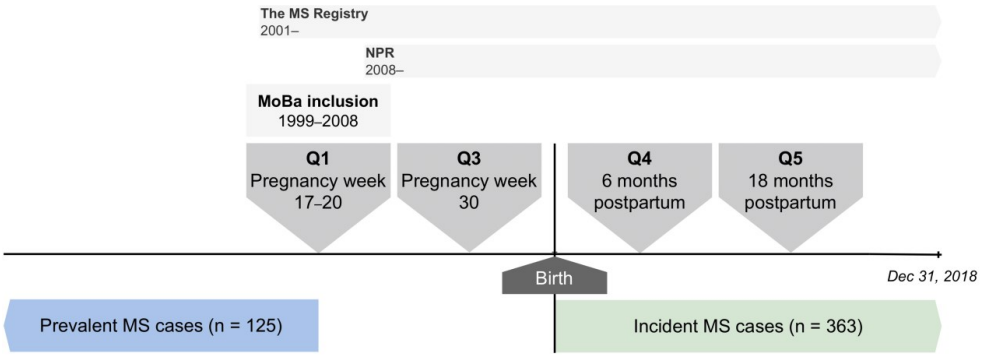


Figure 4. Overview of included data sources, MoBa questionnaires and MS cases in this thesis

3.4 Study population and study design

The study population was based on MoBa version 12, available from January 2019.

Paper I was a prospective cohort study. The study population was unique women in MoBa who answered the questionnaire in pregnancy week 30, including the childhood abuse items. We studied the risk of developing MS after MoBa inclusion (incident MS).

Paper II was a cross-sectional study. The study population was unique women in MoBa who answered the abuse items in the questionnaires both in pregnancy week 17–20 and in week 30. The main study group was women with established MS at enrolment (prevalent MS).

Paper III was a prospective cohort study. The study population consisted of all pregnancies in MoBa, with three main study groups: 1) Women diagnosed with MS before pregnancy, 2) Women diagnosed with MS after pregnancy with MS symptom onset before pregnancy, and 3) Women diagnosed with MS after pregnancy with MS symptom onset after pregnancy. We also studied a subgroup of women (from group 2 and 3) who were diagnosed with MS in the postpartum period, defined as 0–18 months after giving birth.

3.5 Variables

3.5.1 Adverse childhood experiences: Childhood abuse (Paper I)

A history of childhood abuse was assessed through the questionnaire in pregnancy week 30 by four items covering different abuse categories: Emotional abuse (humiliation and threat), physical abuse, and sexual abuse (Paper I, Methods). Exposure to either of these categories was defined as ticking "yes, as a child < 18 years". The abuse items in Q3 were adapted from the validated NorVold Abuse Questionnaire.[201]

3.5.2 Abuse in adulthood, during pregnancy, and revictimization (Paper II)

A history of adult abuse was assessed through the same questionnaire as childhood abuse in Q3, for this assessment responding "yes, as an adult > 18 years". Q3 also included questions about the responsible person (stranger, family/relative, or another known person). Questions on severity and type of sexual abuse was included in Q1. Thus, we were able to define a subcategory of sexual rape in the analyses (Paper II, Methods and Supplemental material). We defined revictimization as an experience of abuse both in childhood and in adulthood.

Information on abuse during pregnancy or in the 6-month period before pregnancy was collected from Q1 and Q3. Q1 included two questions covering sexual and physical abuse in the perinatal period adapted from the Abuse Assessment Screen.[202]. In Q3, the women could report whether the abuse had happened during the last year. (Paper II, Methods and Supplemental material).

3.5.3 Perinatal depression and anxiety (Paper III)

Symptoms of depression and anxiety were based on a short version of the validated screening tool Hopkins Symptom Checklist-25.[203-205] The subscale Symptom Checklist-8 (SCL-8) was used in the questionnaires in pregnancy week 30, and 6 and 18 months postpartum (Q3–Q5). SCL-8 contains four items measuring symptoms of depression and four items measuring symptoms of anxiety (Paper III, Supplemental data), covering symptoms during the two weeks prior to assessment. SCL-8 was thus separated into SCL-4D (depression) and SCL-4A (anxiety). Each item was scored on a Likert-type scale ranging from 1 ("not at all bothered") to 4 ("very much bothered"). We separately calculated mean scores for depression and anxiety and used a validated cut-off of >1.75 to define presence of symptoms.[206]

Perinatal depression or anxiety was defined as symptoms in pregnancy week 30 or 6 months postpartum and reported as point prevalence for each assessment. The assessment at 18 months postpartum was used as a prognostic measure for women

diagnosed with MS before pregnancy and as a point prevalence for women diagnosed with MS postpartum.

We validated the depression score at 6 months postpartum with a short version of the Edinburgh Postnatal Depression Scale, present in Q4 (Paper III, Methods).

3.5.4 MS characteristics and demographic, socioeconomic and lifestyle factors

We collected MS variables from the MS Registry and hospital records: Year and age of MS symptom onset (first clinical symptom), time and age at MS diagnosis, and MS-subtype at disease onset (relapsing-remitting, primary progressive, or unspecified). These variables were registered by neurologists or specialist nurses. MS symptom onset was based on either patient history or medical records suggestive of a prior MS event.

Other relevant variables were collected through the MoBa questionnaires or through linkage to MBRN: Age at MoBa inclusion, year of childbirth, participant birth year, history of smoking (ever/never), overweight (pre-pregnancy BMI ≥ 25 kg/m^2), low household income (<60% of cohort median in the given inclusion year), short education (≤9 years of elementary school), non-cohabiting mother, alcohol use during the first trimester (≥1 unit per month (Paper II and III)), illicit drug use (ecstasy, cocaine, cannabis, amphetamine, heroin) last month before or during pregnancy (Paper II), low educational level of partner (≤9 years (Paper II)). Additional covariables associated with perinatal depression were included (Paper III): Parity (pregnancies ≥24 gestation weeks), unplanned pregnancy, smoking during pregnancy (≥1 occasion per month), social security disability or work assessment allowance, adverse pregnancy events (prior history of stillbirth or miscarriage >12 weeks, first trimester vaginal bleeding, current or prior preeclampsia), comorbidities (asthma, pre-pregnancy hypertension, renal disease, rheumatoid arthritis, type 1 diabetes, epilepsy), adverse life events last 12 months reported as “difficult or painful” (work/study conflict, financial issues, divorce/separation/breakup, conflict with family/friends, severe injury or illness, severe traffic accident, death of close relative/friend, fire or robbery), lifetime history of sexual and physical abuse (Q1), pre-pregnancy history of major

depression (Lifetime major depression score)[207], self-reported history of anxiety, self-reported use of antidepressants during pregnancy, and a combined score of anxiety and depression in Q1 (5-item Hopkins Symptom Checklist). Early drop-out from school (≤9 years of elementary school) was used as a proxy for childhood social status in paper I.

3.6 Statistical analysis

We used IBM SPSS Statistics software version 26 (Paper I–III), Stata version 16 and version 17 (Paper I–III) to perform the statistical analyses.

3.6.1 Paper I

We performed Cox proportional hazards regression to calculate the hazard ratio for MS development comparing women in MoBa who were exposed to adverse childhood experiences to those without any such exposure. In the time-to-event analysis, we calculated time in years from MoBa enrolment (start of observation period) until time of MS diagnosis or censoring (end of study, December 31st, 2018). We analyzed incidence rates per 100,000 person-years and hazard ratios for the different abuse categories and for severity of abuse (number of categories), accounting for possible confounders (the women's birth year and childhood social status) and possible mediators (smoking, overweight, adult socioeconomic status).

We performed a sensitivity analysis excluding women that might have been in the prodromal period of MS when experiencing abuse to limit the influence of reverse causality, and a sensitivity analysis including both prevalent and incident MS cases to examine if the exclusion of women with prevalent MS affected our results.

3.6.2 Paper II

We compared women with established MS with all female participants in MoBa without MS. We examined odds ratios for experiencing abuse in adulthood, being revictimized, and experiencing abuse in pregnancy with logistic regression adjusted for possible confounders (age, smoking, overweight, and socioeconomic status). We

considered low education of the partner to be a potential mediator and adjusted for this in a secondary analysis. We included the interaction terms *low socioeconomic status x MS* and *childhood abuse x MS* in a secondary analysis of abuse risk as an adult, to examine whether the combination of MS and these factors increased the risk more than each factor alone (synergistic effects).

We performed a sensitivity analysis comparing abuse risk as an adult in women with established MS to women who developed MS > 5 years after MoBa inclusion, as these women did not yet have the "vulnerability" of having a chronic condition.

3.6.3 Paper III

We compared different MS groups with all the female participants in MoBa without MS. We examined odds ratios for depression and anxiety in the perinatal period with logistic regression adjusted for possible confounders (age, parity, overweight, and socioeconomic status). Potential clustering for women with more than one participation in MoBa was accounted for with robust standard error estimations.

We also examined risk factors associated with depression in pregnancy week 30 among women with established MS with a backward stepwise elimination method. In this secondary analysis, we included relevant interaction terms in the multiple regression model.

We performed sensitivity analysis with higher cutoff for depression on the SCL-4D score, and a sensitivity analysis to check whether depression occurred independent of fatigue. Fatigue is common in MS, and symptoms of fatigue could be similar to symptoms of depression.

3.6.4 Missing data

We included flowcharts of included and excluded participants in paper I–III, and specified numbers of missing respondents for table 1-variables in paper I and II. In paper III, we imputed missing answers to the depression and anxiety score variables with the expectation-maximization algorithm in SPSS, given certain requirements

(Paper III, Methods). We also compared dropout rates from Q3 to Q5 for women with depression in the various study groups (Paper III, Supplemental material). In paper I, we compared baseline characteristics of participants with missing data (non-responders to Q3, and non-responders to the abuse-items in Q3) with the total study population (Paper I, Supplemental material).

3.7 Ethics

This research project was approved by The Regional Committee for Medical and Health Research Ethics with reference number 2016/906. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committees for Medical and Health Research Ethics. The MoBa cohort is regulated by the Norwegian Health Registry Act. Participation in MoBa and registration in the MS Registry is voluntary. Written informed consent for use of information in research and for data linkage was acquired during enrolment in both MoBa and the MS Registry.

The subject in this thesis is abuse and perinatal depression, which are sensitive topics that may be associated with stigma. Answering questions on abuse may provoke an emotional response among participants. When conducting research on abuse and mental health, researchers should provide an option for referral to appropriate services for victims of abuse or current depression. As far as we know, this was not provided in MoBa.

Throughout the project, we have had user involvement for discussion of optimal presentation of the results, both scientifically and in the media. Having experienced abuse is often associated with guilt or the feeling of being responsible for the abuse. The findings from this thesis should not be misconstrued by people with multiple sclerosis and prior abuse so that they feel responsible for having MS or feel responsible for experiencing current abuse or depression. Rather, we hope that the findings from this thesis will lead the way for new opportunities in both MS research and managing MS in the clinical setting.

4 Summary of results

MoBa version 12 contains 95,129 women with 114,629 pregnancy registrations. At the time of MoBa inclusion, 125 women had an MS diagnosis (prevalent MS). There were 363 new diagnoses of MS after MoBa inclusion (incident MS), with a median time to diagnosis of 7 years (range 0–17). Women with prevalent MS had a mean age of 26 years (range 14–39) when receiving an MS diagnosis, whereas women with incident MS had a mean age of 36 years (range 21–52) at diagnosis. An overview of the different MS groups used in the papers of this thesis is shown in Table 2.

Table 2. Overview of women with MS included in the main analyses

	Prevalent MS women 125	**Incident MS women 363**
Paper I	*Sensitivity analysis*[a]	**300** women with MS after baseline
Paper II	**106** women with established MS	*Sensitivity analysis*[b]
Paper III	**140** pregnancies[c] in women with MS before pregnancy	**406** pregnancies[c] in women with MS after pregnancy • 98 with symptom onset before pregnancy • 308 with symptom onset after pregnancy ▪ ≤ 5 years (n = 136) ▪ > 5 years (n = 172)

The number of women varies between papers because of different construction of MS groups and due to different response rates to questions/questionnaires used to define exposures and outcomes.

[a]A sensitivity analysis including all women with MS in MoBa was included in paper I.

[b]A sensitivity analysis including women with first symptom of MS > 5 years after study inclusion was included in paper II.

[c] Paper III comprised data from women in MoBa participating more than once, and we used pregnancies for cases. In paper I and II we used unique women. 26 additional MS cases were validated and included in paper I and II after paper III (which was the first project in this thesis).

4.1 Adverse childhood experiences and the risk of adult-onset MS

We found an association between exposure to abuse in childhood and the risk of developing MS as an adult, after accounting for birth year, early school dropout, adverse socioeconomic factors, overweight and smoking (Paper I). We found that the hazard rate for developing MS was 31% higher for those who had experienced any type of sexual, emotional, or physical abuse before the age of 18 years. The risk of MS was highest after sexual abuse, followed by emotional abuse, when examining the categories separately. The estimates were similar or became stronger when we excluded women that could have been in the MS prodromal phase before the age of 18 years.

We found that the risk of MS increased by the number of abuse categories the women had experienced, suggestive of a dose-response relationship. The hazard rate was 93% higher for those who had experienced all three categories of abuse, compared to those who had experienced no abuse.

We found no effect of childhood abuse on age of MS symptom onset or MS diagnosis.

4.2 Revictimization, abuse in adulthood and the perinatal period

We found that women with MS had higher risk of experiencing revictimization, i.e., further abuse in adulthood after childhood abuse (Paper II). The odds was 61% higher for experiencing emotional abuse as an adult for women with MS, compared to women without MS. Women with MS had almost 2.4 times higher odds of experiencing rape as an adult after adjusting for age and adverse socioeconomic status. We found synergistic effects between adverse socioeconomic status and MS, and between history of childhood abuse and MS, on the risk of adult abuse. The risk of emotional abuse was attenuated when adjusting for low partner education in a mediation analysis.

The risk of abuse in the perinatal period was similar for women with MS and without MS. For both groups, 1 in 3 women who had a history of abuse in adulthood also had experienced abuse close to, or during, pregnancy.

4.3 Perinatal depression and anxiety

We found that women with established MS had 2.0 times higher odds of depression during the third trimester of pregnancy, compared to women without MS (Paper III). The risk of postpartum depression was not increased per se, but more women with MS and third trimester depression had continuous depression measured at 6 months postpartum, compared to women without MS who had third trimester depression. The prognosis at 18 months postpartum was similar for women with MS and women without MS. The risk of perinatal anxiety was not increased.

We studied 17 risk factors for third trimester depression among women with established MS and found that previous sexual and/or physical abuse, adverse socioeconomic status, and previous depression and/or anxiety were predictors for depression.

We found increased risk of postpartum depression among 35 women who were diagnosed with MS in the postpartum period. They had 3.0 times higher odds of depression 6 months postpartum and 5.0 times higher odds of depression 18 months postpartum, compared to women without MS.

We divided women with incident MS into two main groups, defined by when they experienced their first MS symptoms in relation to MoBa inclusion and pregnancy:

- 98 women already had experienced MS symptoms prior to MoBa inclusion/pregnancy but were diagnosed after pregnancy. They did not have increased risk of neither depression nor anxiety in the perinatal period.
- 308 women experienced MS symptom onset after MoBa inclusion/pregnancy. We found that those who had symptom onset ≤5 years after pregnancy had increased risk of both depression and anxiety in the perinatal period, but those who had > 5 years until MS symptom onset did not.

5 Discussion

5.1 Methodological considerations

5.1.1 Validation of MS diagnoses

We identified 478 unique women with MS in the MoBa cohort through linkage with NPR, the MS Registry and evaluation of hospital records (Table 3).

Among the 125 women with MS diagnosis at the time of MoBa inclusion (prevalent cases), 4 women did not report an MS-diagnosis in the MoBa-questionnaire. Moreover, 10 women who reported an MS-diagnosis was not registered with MS in the NPR or MS Registry. The MS Registry was established in 2001 but did not have a functional electronical form until 2015 and had incomplete coverage at the time of our data linkage in 2018. NPR information is available from 2008,[198] and MoBa inclusion occurred 1999–2008. We decided to include these 10 women in our analyses, most probably they had not been registered in NPR after 2008 because of a "benign" disease. Some of these women might had follow up by their general practitioner, by private neurologists or no follow up. A 2019 validation study of MS diagnoses in NPR from Nordland County in Norway found that 3% of those with MS were not registered in the NPR because they had been diagnosed before data in NPR were available for identification (before 2008), and had no MS-registered contact in public specialist health care up to the time of validation.[208] The percentage of MS cases not registered in NPR is similar to what we found in our study, when we included the 10 unvalidated cases with self-reported MS: $\frac{10}{478+10} = 2\%$

Hence, 98% of the MS cases used in our study were validated. It is in our opinion a high probability that also the remaining 2% had MS. The validation of the G.35 NPR codes from women in MoBa is illustrated in table 3.

Table 3. 2x2 Cross-table of MS cases included in our study

		MS disease[a]	
		Yes	No
NPR[b]	Yes	478 *True positive*	47 *False positive*
	No	10 *False negative*	94,574[c] *True negative*

[a] Confirmed or refuted MS-diagnosis according to the MS Registry and hospital records. 10 women reported an MS diagnosis in the MoBa questionnaire but were not registered in NPR and thus not available for validation. We defined these 10 as true diagnoses.

[b] Registered with an MS diagnosis in NPR. Of the 545 G.35 codes from NPR, 20 cases were not available for validation (Table 1) and are not included here.

[c] The remaining women in MoBa who did not self-report an MS diagnosis in the MoBa questionnaires and were not registered with an MS diagnosis in NPR or in the MS Registry as of Dec 31st 2018.

The validation process gave an overall positive predictive value of $\frac{478}{478+47} = 0.91$ for an MS diagnosis in NPR.

When we assume that the 10 self-reported MS diagnoses are correct, this yields a sensitivity of $\frac{478}{478+10} = 0.98$ for MS diagnosis in NPR.

This is similar to the previous validation study of MS cases in NPR, which found a positive predictive value of 0.92 and a sensitivity of 0.97.[208]

A positive predictive value of 0.91–0.92 means that 8–9% of the MS-diagnoses registered in NPR is erroneous, i.e., false positives. An incorrect diagnosis in NPR could be due to reevaluation and refutation of an initial suspected MS diagnosis, or erroneous coding of another diagnosis.[3] An incorrect NPR-diagnostic code will never be deleted. Some of the 47 "false positives" might have had suspected MS but was yet to fulfill diagnostic criteria at the time of validation. As the national coverage in the MS Registry was only 69% at the time of our data-linkage, it was necessary to use the NPR to detect additional MS cases. Ultimately, using the MS Registry and hospital records for validation of the NPR-diagnoses ensured a high percentage of confirmed MS cases in this thesis.

Some women in MoBa without MS might have developed or were diagnosed with MS after data linkage in 2018. However, as this group comprised more than 90,000 women, we do not believe this would have affected our results by much.

Twenty cases of MS from the NPR were not available for identification from hospital records, because we did not get a response form the corresponding neurology department. They were not registered in the MS registry. The incomplete registration of MS cases in the MS registry at the time of data linkage was due to limited resources or disregard of the registration process at different neurology departments.[3] The missing registrations was unrelated to aspects of the disease, or to the exposures or outcomes in this study. It is in our opinion unlikely that exclusion of these cases should have affected our results by much.

5.1.2 Sources of errors and bias in MoBa

The results of this thesis are obtained from the information and data-collection of the population-based MoBa cohort study. Cohort studies are usually preferred over other observational study designs, such as case-control studies, as they are less prone to bias.[209]

However, when studying rare diseases such as MS, it may be challenging to gain enough power to examine exposure-outcome associations if the exposure and outcomes if interest are rare. Moreover, a cohort study with a large range of collected information may lack necessary details of exposures and outcomes to make nuanced assessments of exposure-outcomes associations. On the other hand, the comprehensive collection of exposures and outcomes is a strength to the MoBa cohort and gives endless possibilities to study exposure-outcome associations. The prospective collection of data gives a unique possibility to study incident cases and clarify temporal relationships between exposures and outcomes.

Observational studies are well suited when the exposure of interest is unfeasible or unethical to allocate in an interventional study, e.g., for studying consequences of childhood abuse. All observational studies are invariably subject to errors, which may

be random or systematic. Systematic errors lead to bias, i.e., the results or interpretation of the results are skewed or deviates from the truth. Bias in epidemiological studies can mainly be put into three categories: selection bias, information bias, and confounding.[209] It is important to critically assess these biases to consider the validity of a study. Internal validity relates to how well a study can correctly measure the exposure, the outcome, and the relationship between them. Bias is a threat to internal validity. Internal validity is necessary for external validity, which relates to how well you can generalize your findings to the population you intended to find knowledge for (target population), or to populations in other contexts.

In the previous section, I discussed the validity of the MS diagnoses uses in this thesis. Next, I will discuss the potential sources of errors in MoBa.

Random errors

Random errors are errors that happen by chance, and can occur during study inclusion, filling or reading of questionnaire data, and in the analyses. Random errors occur equally in both directions from the true value and reduce statistical precision. A large sample size will minimize the effect of random errors. MoBa has a large study population, but for some analyses, especially in subgroups of exposures, there is a possibility that random errors have influenced our results. One example is in the analyses of those who had experienced three categories of childhood abuse and later developed MS (n=10). The statistical imprecision is mirrored in the wide confidence interval: 1.02–3.67.

Selection bias

Selection bias occurs when the population in the study differs from the target population that the participants were selected from, and when this results in finding associations between exposures and outcomes, which, in reality, are not there.[210] Non-participation, non-response to questionnaire data, and loss-to-follow up may distort the study population and skew the effect of the exposure on the outcome. However, there is a distinction between selection bias and the process of selecting subjects that may

not be generalizable to the target population. This affects the external validity of the study, but not necessarily the internal validity. Thus, any error in selection needs to affect both the exposure and the outcome to cause selection bias.

Non-participation in MoBa is an example of such a selection. Of all the invited women, 41% agreed to participate. There is an overrepresentation of participants with Norwegian ethnicity and high socioeconomic status compared to the general population, and an underrepresentation of women who smoke, are single, multiparous, and under 25 years.[211] A study of self-selection bias in MoBa concluded that for eight examined associations, there was no biased exposure-outcome risk estimates, but biased prevalence of exposures, such as smoking.[211] Similar results have been found for other population-based cohorts with lower participation rates than MoBa.[212,213]

Healthy people are more likely to participate in research.[214] Women with MS may have fatigue or other complaints in pregnancy that resulted in lower participation rates than the general population. On the other hand, women with MS may also be more willing to participate, as MoBa aimed to study risk factors of disease in the next generation. High risk genes for MS are potentially heritable, and this could result in a personal wish to participate in such a study.

125 of 95,129 women in MoBa had established MS at inclusion during 1999–2008. This yields a prevalence of 0,13% or ≈130 per 100,000 pregnancies. It is unknown if this is similar to the prevalence of women with MS giving birth in the total population. Few studies have calculated prevalence of pregnant women with MS at comparable time periods. A population-based study in California found an MS prevalence of 27 per 100,000 pregnancies between 2001–2009.[178] This is much lower than the prevalence in MoBa. However, California has a completely different healthcare system than Norway. Having a chronic disease and giving birth is possibly costly and dependent on having insurance, which may yield a selected group of women with MS giving birth. Due to the lack of comparable prevalence studies, it is hard to determine if women with MS were more or less likely to participate in MoBa than the general population.

For women with pre-diagnostic MS (incident cases) the invitation to participate in MoBa was presented before they were diagnosed with MS, and the participation of this group should not be affected by selection bias. However, some women with early signs of MS might have declined participation due to unspecific symptoms or health complaints.

Women with psychological distress or a history of abuse may have been less willing to participate in MoBa. This should apply to both women with and without MS and thus not cause bias in exposure-outcome associations but could have attenuated prevalence estimates. Women with MS have increased risk of depression and abuse. If women with (prevalent) MS are overrepresented in MoBa this could cause exaggerated risk estimates. Vice versa, if women with MS are underrepresented in MoBa this would cause bias towards the null.

Loss-to-follow up is another type of selection bias that may affect internal validity. Women who did not respond to the questionnaire in the third trimester had similar demographic and socioeconomic characteristics as those who did respond (Paper I, supplement table 3) We found similar dropout rates for the subsequent questionnaires among women with and without MS who were depressed in the third trimester (Paper III, supplement table e-2). Thus, loss-to-follow up were not likely to affect the outcomes reported in this thesis.

Incomplete response to questionnaire data may potentially lead to selection bias. Missing data for individual variables is a common challenge for questionnaire-based studies. Imputation is a way of handling missing data. In paper III, we used a single imputation method to missing answers on the screening tools for depression or anxiety if the number of missing values were under 20–38% (depending on the scale). During the recent years, there has been increasing focus on missing values in research and ways to handle these, including more sophisticated imputation methods such as multiple imputation.[215] In paper III, we did not provide details on missing data for background variables, but we did so in the other (subsequent) papers. Such missing data gives loss of power and statistical precision, and in some cases, bias. Incomplete responses could be “missing completely at random” (e.g., overlooking a question) or

"missing at random" (e.g., not answering income-questions due to depression), or "missing not at random" (e.g., not answering depression-score due to depression).[215] The latter two could lead to bias. In paper I and II, missingness for covariables such as confounders was generally low (mostly <5%) and similar for exposed and unexposed. We thus believe that this did not make any notable impact on our analyses. In paper I we found that those who did not respond to the childhood abuse items (but did respond to the Q3 questionnaire) had a lower socioeconomic status than those with complete response (Paper I, supplemental table 3). They also had higher rates of missingness for smoking, BMI, and the depression items. This could be due to "missing at random", i.e., women with low socioeconomic status tended to generally have incomplete responses, or due to "missing not at random", i.e., that women who were exposed to abuse were more likely to skip the abuse items. Both may lead to a distorted selection of participants eligible for analysis, but most likely affected women with (undiagnosed) MS and the reference group in similar ways. Moreover, these missing responses comprised only 0,8% of respondents to Q3.

Taken together, the analyses comprising women with prevalent MS may be vulnerable to selection bias through participation, but the analyses comprising women with incident MS should not be. Definite evidence on whether women with prevalent MS is under- or overrepresented in MoBa could be provided through a population-based study on the occurrence of MS among pregnancies in Norway 1999–2008.

Information bias

Information bias is distorted exposure-outcome associations originating from measurement errors of key study variables during data collection, or from systematic differences in acquired information from exposed and unexposed cases.[209] Incorrectly defining an exposed case as unexposed, a case as a control, or vice versa, leads to misclassification bias.

Recall bias is a type of misclassification bias, where cases of a disease tend to remember (and report) more details from a distant event than controls, and thus may exaggerate their exposure status. If this applies to cases more than controls, this bias is

termed as differential.[210] In this thesis, we studied women who reported childhood abuse vs. women who did not, and the association to a future MS diagnosis. Questions on childhood abuse were collected years after exposure for all participants, but also years before the outcome (MS). Thus, potential errors in recall for childhood abuse affected all participants equally.

Mood-congruent memory bias occurs when recall depends on current mood.[216] For example, if depressed individuals tend to remember more negative childhood events than positive. However, longitudinal studies with repeated abuse-assessments have found that mental health have negligible effects on reporting or not reporting child abuse.[217] We did not adjust for depression in paper I and II because depression would be a collider variable on the association-pathway between MS and abuse.[218]

Limitations in sensitivity and specificity of screening tools may cause misclassification. Depression, anxiety, and abuse are measured in MoBa with only a few questionnaire items or short-form versions of larger screening tools. Although the short-form questionnaires for depression and anxiety have been validated previously, these are tools meant for screening and not diagnosis. The abuse questionnaires were adapted from other validated screening tools, but the overall scales used in MoBa were not validated per se. Thus, there is a potential for misclassification. However, such misclassification errors would affect exposed and unexposed women equally and be nondifferential. Nondifferential misclassification results in bias towards the null.[210]

Confounding and effect mediation

When investigating associations between exposures and outcomes, it is important to be aware of any potential third variable that could be a common cause of both the exposure and the outcome – a confounder. (Figure 5). A confounder can partially or fully generate an association between an exposure and an outcome, when (in reality) there is no causal relationship.

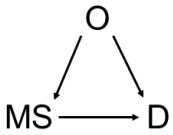


Figure 5. Illustration of a confounder. Overweight (O) is a common cause (increases the risk) of both MS and depression (D). Overweight was one of the potential confounders in Paper III.

Confounders can be considered in the analyses by stratifying or adjusting the regression model. All observational studies, including this thesis, will have residual confounding or unmeasured confounding, meaning that confounders are measured imperfectly or not measured at all. Yet, it is unlikely that this potential bias fully explains our results. The comprehensive questionnaires of MoBa yield detailed information on potential confounders and mediators, which we accounted for in all papers. A mediator is an intermediate variable between an exposure and an outcome and contributes to the total effect (Figure 6). An approach to measure the direct effect of an exposure on the outcome is to condition on mediators in regression analyses.

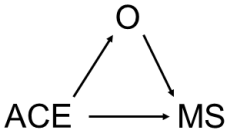


Figure 6. Illustration of a mediator. Overweight (O) is a potential effect of Adverse Childhood Experiences (ACE) and a risk factor for MS. A mediator explains indirect mechanisms of how the exposure is related to the outcome. Overweight was regarded as a potential mediator in Paper I.

In paper III, we adjusted for confounders such as age, parity, overweight, and socioeconomic status; all associated with increased risk for both MS and depression. In retrospect, we could also have adjusted for childhood abuse and smoking. However, we regarded our study to have too few depression events in the MS group to adjust for all possible relevant confounders, which can result in an overfitted and unstable regression model.[219]

We did not have information on vitamin D status. Low vitamin D is associated with increased MS risk and with perinatal depression.[56,220] Whether low vitamin D is a risk factor, or a consequence of depression is unknown. Moreover, low vitamin D interacts with childhood abuse experiences on the risk of adult depression; and gives even

higher risk of depression if exposure to both.[221] Vitamin D might in theory be a mediator on the pathway between childhood abuse and MS risk (Paper I), since childhood abuse may alter an unfavorable diet in young adulthood.[222]

We adjusted for low socioeconomic status (SES) as a potential confounder in paper II and III, and as a potential mediator in paper I, on the basis that low SES might be a risk factor for MS.[145] The latter is, however, debated.[223] Low SES might as well be a consequence of MS. Cognitive difficulties are common in MS and may appear years before MS symptom onset.[37] Cognitive and physical impairment may limit work and financial achievements.[224] Thus, low SES may be a common effect of childhood abuse and MS and thus be a collider variable in the analyses in Paper I (Figure 7). Conditioning on colliders might cause bias.[218]

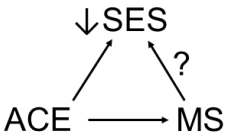


Figure 7. Illustration of a collider. A collider is a common effect of the exposure and outcome. Adverse socioeconomic status (SES) as an adult could be an effect of adverse childhood experiences (ACE) and potentially an effect of MS.

SES is a complex construct and could be a proxy for other unmeasured factors that increase risk of adverse lifestyle and health. Thus, SES will often be a potential confounder or a proxy of a confounder when studying risk of diseases. We used "high school dropout" as a proxy for low childhood SES in paper I and defined it as a confounder. We combined low household income, short education, and non-cohabiting woman as indicators of low SES in all papers to avoid collinearity and overfitting.[219] However, we acknowledge that no single variable or combination of variables can fully capture the full picture of SES.

5.1.3 External validity

As discussed in chapter 5.1.2, we did not identify any major sources of bias that could have limited the internal validity of our results. Overall, we also believe that our findings are generalizable to pregnant women with MS. However, there may be limitations in external validity if considering relevance for men or non-pregnant women with MS, and for people with MS of other ethnicities.

MoBa is a population-based study, meaning that all pregnant women in Norway were eligible to be included. Population-based studies have high external validity as they have the potential to include the whole population of a geographical area. However, MoBa started recruiting in the city of Bergen in 1999 and gradually became nationwide by 2004.[196] Consequently, 40% of pregnant women 1999–2008 were invited to the study, and of these, 41% accepted participation.[211] The questionnaires were only available in Norwegian. It could therefore be debated whether MoBa really is, by a strict definition, population based. Nevertheless, a strength of MoBa is the large number of participating women from all parts of Norway.

Women of high SES are overrepresented in the MoBa cohort, but pregnant women with and without MS had similar occurrence of adverse SES. Women with prevalent MS in MoBa may be different from pregnant women with MS who did not participate, or different from non-pregnant women with MS. Women with MS who are able or willing to get pregnant may be a subgroup of women with MS. Most pregnant women with MS have minimal disability.[174,180] We did not have information about MS severity available for our cohort. The recruitment period was 1999–2008, which was a time when diagnostic criteria, treatment options and approaches to family planning was different from today.[13,171,176] Thus, pregnant women with MS in MoBa might differ from pregnant women with MS today.

Women with depression or abuse experiences might have been less motivated to participate in MoBa or answer questions about these subjects. However, we found similar overall occurrence of perinatal depression in MoBa as in other Norwegian population-based studies with over 90% participation rate.[225] For occurrence of abuse, it has been difficult to find comparable studies due to discrepancies in study design

and abuse assessment. The 2023 prevalence study from the Norwegian Competence Centre for Violence and Traumatic Stress found higher prevalence of both childhood and adult abuse than reported by the participants in MoBa.[226] For example, 28% of women reported any childhood abuse compared to 19% in MoBa, and 18% reported both childhood and adult abuse, compared to 9% in MoBa. This telephone survey included 4000 people and had lower response rates than MoBa (10% vs 41%) and it included digital sexual violence. Prevalence estimates of abuse might not be generalizable to other populations, but the association between exposure and outcomes should still be.

5.1.4 Study design and temporality

Paper I and III had a prospective design, which is a strength when assessing temporality between exposure and outcomes. Paper I assessed the association between childhood abuse and MS risk. Despite a prospective design, the questions regarding childhood abuse were retrospective. Adult recall of childhood abuse is the most common type of assessment for such exposures.[119] Studies have found good test-retest reliability of maternal self-reported childhood abuse in perinatal settings.[227] Prospective assessment of childhood abuse may select only the severe types of abuse,[228] e.g., when using registered contacts in health care or law systems. Thus, we believe retrospective reports of abuse are well suited to assess the full range of abuse experiences on a population-level.

We used age at MS diagnosis instead of age at MS symptom onset as the endpoint in paper I to minimize the risk of recall bias and misclassification of "MS onset" as recorded in the MS Registry. Date of MS symptom onset is to a larger extent based on patient recall than date of MS diagnosis. For those patients not registered in the MS registry, information on symptom onset and date of diagnosis was obtained from hospital records which did not always contain details on symptom onset.

Paper II had a cross-sectional design and explored the association between prevalent MS and exposure to abuse in adulthood. We did not have information on the exact

timing of adult abuse, which limited the possibility to address temporality between MS and adult abuse.

5.2 Discussion of results

5.2.1 Adverse childhood experiences and risk of adult-onset MS

The findings from this thesis suggest that childhood stress, especially resulting from emotional and sexual abuse, increases the risk of adult-onset MS, and in a dose-response relationship. Moreover, our results support that childhood and adolescence represent a susceptibility period for exposure to environmental factors that increase the risk for MS. The design and size of our study allowed us to examine the temporal relationship between childhood stress and MS with an approach which, to our knowledge, has not been done before. The large Nurses' Health Study was able to prospectively study a subgroup of only 49 people with MS when investigating the relationship between childhood stressors and MS.[121] We were able to adjust for relevant associated factors that could have confounded or mediated the relationship between childhood stress and MS risk. None of the previous studies accounted for BMI, and only three accounted for smoking history.[121,129,229]

The association between early-life stress and MS was supported by an animal study that triggered early-life emotional and physical trauma in mice and found increased susceptibility and severity of experimental autoimmune encephalomyelitis,[230] which is a standard animal model for MS.

Several studies on ACEs and MS risk were published the same year as our study, but all were retrospective. A Canadian case-control study among people with immune mediated inflammatory diseases, including 232 with MS, found an increased risk of childhood maltreatment among those with disease compared to healthy controls.[129] The association was strongest for emotional abuse. A larger case-control study from California including 1422 MS cases did not find any increased risk of reporting ACEs.[126] The ACEs included parental divorce, death or illness of core family,

disruption in living situation, and abuse (physical and verbal combined). A cross-sectional study from the Icelandic Stress-And-Gene-Analysis cohort with 28,000 women and including 214 women with MS, investigated 13 ACEs. The authors did not find any significant associations with MS.[229] They found elevated risk estimates for bullying, physical neglect, parental separation, and severe sexual abuse; but the confidence intervals were wide and contained the null after adjustment for confounders.

Among the available studies on childhood stress and MS risk, six found an association with MS risk[120,122-124,129], including our study,[231] whereas four did not.[121,125,126,229] Among the studies that did not find an association, two studies found slightly elevated risk estimates, especially for severe or repeated sexual abuse,[121,229] but the associations were not significant. Although all studies included ACEs, the definition and number of ACEs differed substantially. The most studied ACE was abuse, but types and assessment of abuse varied. The cohort study from Nurses' Health Study investigated physical and sexual abuse, but did not include emotional abuse.[121] The largest case-control study combined physical and verbal abuse into one abuse exposure, but did not study sexual abuse.[126] All studies used self-reported measurements of abuse via different questionnaire screening tools, except for one that used computer-assisted telephone interview.[126] Among the studies that used validated abuse questionnaires such as the Childhood Trauma Questionnaire,[122,129] or Adverse Childhood Experiences Questionnaire[124,229], all except one study found increased MS risk.[229]

High number of ACEs have been associated with earlier age of MS onset in one study,[124] but results are conflicting.[122,126] We found no association between the number of ACEs and age of MS onset. However, we did not include this in paper I. We doubted that we could draw valid conclusions from this finding as we studied women in a pregnancy cohort where particularly women in younger age groups (below 30 years) were underrepresented.

The heterogeneity in studies investigating the effects of stress on MS highlights the difficulty to measure stress consistently and objectively across studies. We examined

three types of childhood abuse but did not have information on other types of ACEs such as neglect, parental illness, or bullying.

The types of stress and combinations of stressors give a wide range of possible exposures. Stressors can differ in severity, chronicity, and they can co-occur and accumulate. Further, the reaction to similar stressors varies between individuals due to behavioral and emotional coping mechanisms. The reaction to stressors may also vary within individuals across the lifespan. Due to the overlap, heterogeneity, and individual response differences of ACEs, it has been proposed that researchers should measure perceived stress instead of defined events in future studies on childhood adversity.[232] However, as most studies on childhood stressors are based on recall of distant events, one could argue that it could be hard for participants to evaluate and distinguish perceived stress in childhood from current stress related to past events. Further, we believe it is important to assess all three main types of abuse when examining exposure to abuse, and not omit one type of abuse, such as emotional abuse.

5.2.2 Adult abuse, revictimization, and abuse in the perinatal period

The findings from this thesis show that women with MS have an increased risk of experiencing abuse also as adults. We examined a cohort of relatively young and healthy women. Our findings extend previous knowledge on the occurrence of abuse in people with advanced MS at an older age.[155] Moreover, we found that women with MS had higher risk of adult abuse if they had experienced abuse during childhood, this compared to those who had experienced childhood abuse in the reference group. To the best of our knowledge, no other study has investigated the occurrence of abuse in both childhood and adulthood in people with MS and thus the risk of revictimization.

We found that 26% of women with MS had experienced abuse as adults, compared to 20% of women without MS. Two other studies were published the same year as our study. An Iranian cross-sectional study found high occurrence of domestic abuse among 275 married women with MS, ranging from 20% to 63% for different categories of abuse.[233] A US study among two cohorts of women with MS (200 and

121 cases, respectively), found that 35–38% reported lifetime abuse, and 15–17% of women with abuse experiences also had experienced abuse during the last 12 months.[234] The lifetime prevalence is comparable to women with prevalent MS in our MoBa cohort, where 38% (40 out of 106) either had experienced childhood or adult abuse.

Taken together, available evidence shows that women with MS are at increased risk of experiencing abuse as adults across different ages, disability severity, and geographical areas. However, the existing studies, including ours, are limited by relatively small sample sizes. The other studies on abuse as adults lacked comparison groups.

Emotional abuse was one of the most common types of abuse in all studies, including ours.[155,233,234] We found that the risk of emotional abuse attenuated when adjusting for low partner education as a possible mediating factor. This suggests that some of the association between women with MS and emotional abuse was mediated through the partner. Caregivers and partners are the main perpetrators of abuse in women with disabilities.[235] However, women with disabilities are also at increased risk of boundary violations and maltreatment by health care providers, friends, and colleagues. The US Study found that the intimate partner of the woman with MS was the most common perpetrator for emotional and physical abuse.[234] The other studies exclusively investigated abuse by partners or caregivers.[155,233] These findings highlight the need for targeted psychoeducation for caregivers of MS.[236]

We found synergistic effects between adverse socioeconomic status and the risk of abuse in women with MS, illustrating that women with adverse socioeconomic status are at increased risk of abuse. The Iranian study also found that low income, short education, and unemployment in both the woman with MS and her husband were independent risk factors for domestic abuse.[233] The other studies on adult abuse in MS found that physical disability, fatigue and cognitive impairment were risk factors for abuse.[155,234] Particularly, neurological disability was demonstrated as a risk factor for emotional abuse, but not for sexual or physical abuse.[234] A possible explanation is that increased disability results in increased dependency on others in daily life activities,

which may result in increased vulnerability to humiliation, discrimination, and degradation from family, partners, and other people in the community.

We did not find any increased risk of abuse in the pre-pregnancy period or during pregnancy for women with MS compared to women without MS. However, 8% of women with MS did report exposure to abuse in that period. That comprised 30% of those who had experienced abuse as adults. As far as we know, no other study has investigated the risk of abuse among people with MS in a perinatal setting. We did not have information on abuse postpartum, which is also a high-risk period for abuse.[237]

5.2.3 Depression and anxiety in the perinatal period

The findings from this thesis show that women with MS have increased risk of perinatal depression, and that women who are diagnosed with MS shortly after giving birth have particularly increased risk of postpartum depression. The use of prospective and repeated measurements of depression and anxiety extends previous knowledge on occurrence of perinatal mood disorders in parents with MS,[182] where particularly fathers with MS had an increased risk. Moreover, we were able to adjust for important potential confounders such as age, parity, overweight, and socioeconomic factors.

A US retrospective cohort study with 143 pregnancies in women with MS was published after our study and found a 13% period prevalence of perinatal depression.[238] The study lacked a non-MS comparison group and was thus not able to provide any risk estimates for depression. The authors measured depression that was mentioned in the health records but were not able to include any validated assessment of depression such as screening-tools or diagnostic codes. Thus, depression prevalence was probably underestimated.

We identified adverse socioeconomic status, previous physical or sexual abuse, and previous depression or anxiety as predictors for depression in women with MS. These are all well known risk factors for perinatal depression in the general population.[239,240] Of note, we found synergistic effects between adverse socioeconomic status and MS and between prior abuse and MS on the depression risk. This means that women with

MS and these risk factors had higher risk of depression compared to women without MS who also had these risk factors. We were not able to study the association between emotional abuse and depression, because emotional abuse was not included in the Q1 baseline questionnaire, and we wanted to study risk factors prospectively from Q1 to the subsequent depression assessments in Q3–Q5. However, all types of abuse are associated with perinatal depression in the general population.[241] Further, childhood abuse, adult abuse, and intimate partner violence are all independently associated with perinatal depression.[239,242]

We did not have information on MS disease activity, but a recent MS diagnosis and receiving disability benefits were not predictors for depression. We did not have information on protective factors for depression, such as social support. Our dataset did not include information on breastfeeding. Breastfeeding is associated with reduced risk of depression and could have mediated the relationship between MS and postpartum depression.[243] The US cohort study found that increased maternal age, primiparity, and prior depression were risk factors for perinatal depression among women with MS.[238] They did not find that high disability status, gadolinium-enhancing lesions on MRI, or perinatal relapses were predictors for depression. However, as the study might have been underpowered to find such associations, further research on specific MS risk factors and protective factors for perinatal depression is warranted.

We found increased risk of both depression and anxiety in women with incident MS and less than 5 years until onset of MS symptoms, but not for those with more than 5 years until MS onset. This supports previous findings that depression and anxiety is a part of the MS prodrome.[33,36] A Canadian population-based cohort study found increased occurrence of psychiatric disorders during the last 5 years before diagnosis for a group of immune-mediated diseases; MS, inflammatory bowel disease and rheumatoid arthritis.[244] A longitudinal Norwegian study measured microstructural brain changes on MRI in 45 newly diagnosed MS patients, and assessed depression and anxiety two years later.[186] The authors found that increased free-water, a proxy for inflammation, predicted future depression. Together, this supports that depression in

MS can be caused by increased inflammatory activity in the brain.[183,184] Studies have found that people with depression and a history of childhood abuse has higher levels of inflammatory markers in blood compared to people with depression without prior abuse,[245] and that a dysregulated HPA-axis might be the link between childhood abuse and depression.[246]

The Canadian cohort study on MS and other immune-mediated diseases found that the incidence of depression and anxiety peaks in the year of diagnosis and remains elevated during the years after diagnosis.[244] We found that women who were newly diagnosed with MS or other chronic diseases postpartum had particularly increased risk of postpartum depression. The burden of having a chronic disease may cause emotional distress and depressive symptoms.[188]

The potential mechanisms for perinatal depression in MS remain unknown. It is debated whether depression in the perinatal period is a unique entity with different mechanisms from non-perinatal depression.[247,248] In addition to shared risk factors with non-perinatal depression, perinatal depression has some unique genetic, hormonal, and inflammatory characteristics.[247,249] There might be different phenotypes of depression in the perinatal period.[250] Moreover, genetic and epigenetic factors that are associated with perinatal depression are modified by stressful events and childhood adversity.[251]

5.2.4 Implications for the clinical setting

The available research on abuse experiences and perinatal depression in MS was scarce prior to this research project. Several papers were published shortly after or in parallel with our papers. Our results on ACEs and future MS risk have been reported by several media sources,[252-254] and the results considering perinatal depression were highlighted in an editorial in Neurology.[255] Together, this mirrors a growing awareness about the impact and the importance of addressing these topics in the MS setting.

Having experienced prior or current abuse increases the risk of morbidity, mortality, and adverse perinatal health, including perinatal depression.[156-158] Further, perinatal depression increases the risk of adverse maternal and neonatal outcomes.[191-193] As

women with MS have increased risk of both, extra attention to signs of prior or current traumatic experiences in people with MS is warranted. Warning signs include chronic pain, unexplained somatic symptoms, and mood disorders.[256] The vicious chain of childhood trauma on adverse health and repeated abuse experiences can be broken if properly addressed through trauma-informed care.[257] Clinicians should be aware of the association between abuse and depression and ask for symptoms of depression when encountering a person with MS in the perinatal setting.

The world health organization recommended screening for perinatal depression in their 2022 guidelines.[258] In Norway, there is currently no formal screening for abuse or depression with validated instruments in the perinatal period.[259] Yet, most women are routinely asked for depression and abuse experiences during the assessments from the nurses at the local health centers, referred to as case finding. Although being addressed in primary health care, neurologists and neurologic nurses should address these adversities in the presence of warning signs. When needed, people with MS should be referred to appropriate management of depressive symptoms, traumatic experiences, or both. Interpersonal and cognitive behavior therapy is effective for both prevention and treatment of perinatal depression,[260,261] and medical therapies such as selective serotonin reuptake inhibitors can be considered.[176]

The results from this thesis highlight the need for prevention of childhood adversities. Optimally, no child should be exposed to adverse events such as abuse. However, eliminating childhood adversities may be unfeasible. Possible prevention include free educational courses and home visiting services to strengthen parenting skills.[262] Prevention at a society level could include strengthening of young families' financial security and ensuring affordable childcare and after-school services.[262] When children are exposed, intervention and treatment at an early age is crucial to avoid accumulation of ACEs and try to overcome its harmful effects. Routine screening of pediatric patients has been proposed,[263] but the benefit of screening children is debated.[264,265] Increased awareness and action by family members, teachers, health personnel, and other caregivers in the child's community is the key for early intervention.

6 Conclusions

We have found that exposure to adverse childhood experiences is associated with increased risk of MS as an adult. The risk for MS was elevated after emotional and sexual abuse. We also found a dose-response relationship between the number of childhood abuse categories and elevated MS risk. Women with MS had increased risk of experiencing emotional abuse and sexual rape as adults, compared to women without MS. Moreover, women with MS who had experienced abuse during childhood had higher risk of revictimization, i.e., also experiencing abuse as an adult. The risk of abuse in the perinatal setting was not increased compared to women without MS, but as many as 8% of women with MS had experienced abuse close to, or during pregnancy. Women with established MS had increased risk of perinatal depression, but not perinatal anxiety. We found that women with MS and adverse socioeconomic status or childhood abuse experiences were particularly vulnerable to both perinatal depression and repeated abuse experiences. Taken together, the results from this thesis show that women with MS are at increased risk of experiencing a vicious cycle of multiple adversities after childhood abuse. Women with less than five years to MS symptom onset had increased risk of both perinatal depression and anxiety, whereas women with more than five years to MS symptoms had no such increased risk. Women who were diagnosed with MS during the first 18 months after giving birth had increased risk of postpartum depression.

The consequences of childhood abuse, adult abuse and perinatal depression are potentially severe and have long-term impact for mental and physical health across generations. The findings from this thesis stress the need for increased attention, intervention, and treatment of these multiple adversities in people with MS, as well as in the society in general.

7 Future perspectives

This thesis contributes to novel knowledge concerning the association between childhood abuse and MS, and on the risk of adult abuse and perinatal depression in women with MS. These associations should be further examined in larger studies with more people with MS, including men, non-white individuals, and people in different age groups. Prospective population-based studies are preferred to avoid recall and selection bias. One ideal prospective study could be a Nordic Collaboration Pregnancy cohort, where the same exposures were measured in all five countries in both women and their partners. Since the Nordic countries have similar health registries, it would be possible to do the same data-linkage as in our study. However, pregnancy cohort studies require considerable resources and take decades to plan and conduct. Large case-control studies would provide important data on this subject.

The first step in increasing the knowledge and replicate findings on childhood adversity in people with MS would be to use consistent measures of ACEs across studies, such as the ACE International Questionnaire developed by the World Health Organization.[266] That questionnaire includes childhood stressors such as bullying and war trauma, which almost no studies have assessed in people with MS. Further, studies that examine interactions between genetic risk alleles and ACEs would provide important knowledge on gene-environment interactions. Interaction studies on other environmental risk factors and ACEs, such as markers of EBV infection, would provide insight in potential mechanisms for the increased susceptibility to MS. We have planned a postdoctoral project within the MoBa cohort, where we in one of the subprojects will examine whether adverse childhood experiences and EBV infection have synergistic effects on MS risk.

Further studies on the occurrence, risk, and perpetrator of abuse in adulthood in people with MS would provide insight to better identify those with MS who are at risk and to help those in need.

There is a need for studies on optimal prevention and treatment of perinatal depression in MS. That could include interventional studies that compared different types of drug

and non-drug psychotherapies. More studies to confirm the safety on breastfeeding while receiving DMTs would help support women with MS to breastfeed, and breastfeeding might reduce the risk of postpartum depression and postpartum disease activity.

8 Errata

Paper I, Figure 2: 10,484 women are reported as excluded from the study population in the flowchart. This number includes those “pregnant 18 months postpartum”. However, this subgroup was only excluded from the analyses examining depression and anxiety 18 months after birth, and not from the main analysis. The correct number of excluded women from the study population should be 2456 individuals.

9 References

1. Qian Z, Li Y, Guan Z, et al. Global, regional, and national burden of multiple sclerosis from 1990 to 2019: Findings of global burden of disease study 2019. *Front Public Health*. 2023;11:1073278. doi:10.3389/fpubh.2023.1073278
2. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler*. Dec 2020;26(14):1816-1821. doi:10.1177/1352458520970841
3. Norsk Multippel Sklerose Register og Biobank. *Årsrapport 2022*. 2023. 15th June. https://www.kvalitetsregistre.no/sites/default/files/2023-06/%C3%85rsrapport%202022%20Norsk%20MS-register%20og%20biobank.pdf
4. Simpson S, Jr., Wang W, Otahal P, Blizzard L, van der Mei IAF, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. *J Neurol Neurosurg Psychiatry*. Nov 2019;90(11):1193-1200. doi:10.1136/jnnp-2018-320189
5. Magalhaes S, Pugliatti M, Riise T, et al. Shedding light on the link between early life sun exposure and risk of multiple sclerosis: results from the EnvIMS Study. *Int J Epidemiol*. Aug 1 2019;48(4):1073-1082. doi:10.1093/ije/dyy269
6. Bjornevik K, Munz C, Cohen JI, Ascherio A. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. *Nat Rev Neurol*. Mar 2023;19(3):160-171. doi:10.1038/s41582-023-00775-5
7. Handel AE, Handunnetthi L, Giovannoni G, Ebers GC, Ramagopalan SV. Genetic and environmental factors and the distribution of multiple sclerosis in Europe. *Eur J Neurol*. Sep 2010;17(9):1210-1214. doi:10.1111/j.1468-1331.2010.03003.x
8. Gale CR, Martyn CN. Migrant studies in multiple sclerosis. *Prog Neurobiol*. Nov-Dec 1995;47(4-5):425-48.
9. Berg-Hansen P, Celius EG. Socio-economic factors and immigrant population studies of multiple sclerosis. *Acta Neurol Scand*. 2015;132(199):37-41. doi:10.1111/ane.12429
10. Munk Nielsen N, Corn G, Frisch M, et al. Multiple sclerosis among first- and second-generation immigrants in Denmark: a population-based cohort study. *Brain*. Jun 1 2019;142(6):1587-1597. doi:10.1093/brain/awz088
11. Rotstein DL, Marrie RA, Maxwell C, et al. MS risk in immigrants in the McDonald era: A population-based study in Ontario, Canada. *Neurology*. Dec 10 2019;93(24):e2203-e2215. doi:10.1212/WNL.0000000000008611
12. Margoni M, Preziosa P, Filippi M, Rocca MA. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. *J Neurol*. Mar 2022;269(3):1316-1334. doi:10.1007/s00415-021-10744-x
13. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis - success from bench to bedside. *Nat Rev Neurol*. Jan 2019;15(1):53-58. doi:10.1038/s41582-018-0082-z
14. Spelman T, Magyari M, Piehl F, et al. Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients With Relapsing-Remitting Multiple Sclerosis: Data From 2 Different National Strategies. *JAMA Neurol*. Oct 1 2021;78(10):1197-1204. doi:10.1001/jamaneurol.2021.2738
15. Marrie RA, Fisk JD, Fitzgerald K, et al. Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Front Immunol*. 2023;14:1197195. doi:10.3389/fimmu.2023.1197195
16. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA*. Feb 23 2021;325(8):765-779. doi:10.1001/jama.2020.26858

17. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. Feb 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2
18. Multiple Sclerosis International Federation. Atlas of MS – 3rd Edition - Type of MS at initial diagnosis. Accessed 28 Jun 2023, https://www.atlasofms.org/chart/united-kingdom/epidemiology/disease-course-at-onset
19. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. Jul 15 2014;83(3):278-86. doi:10.1212/WNL.0000000000000560
20. Cree BAC, Arnold DL, Chataway J, et al. Secondary Progressive Multiple Sclerosis: New Insights. *Neurology*. Aug 24 2021;97(8):378-388. doi:10.1212/WNL.0000000000012323
21. Kuhlmann T, Moccia M, Coetzee T, et al. Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol*. Jan 2023;22(1):78-88. doi:10.1016/S1474-4422(22)00289-7
22. Hedstrom AK, Hillert J, Olsson T, Alfredsson L. Factors affecting the risk of relapsing-onset and progressive-onset multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Oct 2021;92(10):1096-1102. doi:10.1136/jnnp-2020-325688
23. Swedish MS registry (SMSREG). Web-based platform for live visualization and interactive statistical analysis: Average time between onset and diagnosis divided by year of diagnosis. Accessed 23 June 2023, https://vap.carmona.se/open/msvap/graf/medeltid_deb_dia/
24. Blaschke SJ, Ellenberger D, Flachenecker P, et al. Time to diagnosis in multiple sclerosis: Epidemiological data from the German Multiple Sclerosis Registry. *Mult Scler*. May 2022;28(6):865-871. doi:10.1177/13524585211039753
25. Schwenkenbecher P, Wurster U, Konen FF, et al. Impact of the McDonald Criteria 2017 on Early Diagnosis of Relapsing-Remitting Multiple Sclerosis. *Front Neurol*. 2019;10:188. doi:10.3389/fneur.2019.00188
26. Heinzel S, Berg D, Gasser T, et al. Update of the MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. Oct 2019;34(10):1464-1470. doi:10.1002/mds.27802
27. Rafii MS, Aisen PS. Detection and treatment of Alzheimer's disease in its preclinical stage. *Nat Aging*. May 2023;3(5):520-531. doi:10.1038/s43587-023-00410-4
28. Frazzei G, van Vollenhoven RF, de Jong BA, Siegelaar SE, van Schaardenburg D. Preclinical Autoimmune Disease: a Comparison of Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis and Type 1 Diabetes. *Front Immunol*. 2022;13:899372. doi:10.3389/fimmu.2022.899372
29. Tremlett H, Marrie RA. The multiple sclerosis prodrome: Emerging evidence, challenges, and opportunities. *Mult Scler*. Jan 2021;27(1):6-12. doi:10.1177/1352458520914844
30. Matthews WB, Acheson ED, Batchelor JR, Weller RO. *McAlpine's Multiple sclerosis*. 2nd ed ed. Churchill Livingstone; 1985.
31. Makhani N, Tremlett H. The multiple sclerosis prodrome. *Nat Rev Neurol*. Aug 2021;17(8):515-521. doi:10.1038/s41582-021-00519-3
32. Wijnands JMA, Kingwell E, Zhu F, et al. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. *Lancet Neurol*. Jun 2017;16(6):445-451. doi:10.1016/S1474-4422(17)30076-5
33. Wijnands JM, Zhu F, Kingwell E, et al. Five years before multiple sclerosis onset: Phenotyping the prodrome. *Mult Scler*. Jul 2019;25(8):1092-1101. doi:10.1177/1352458518783662
34. Jons D, Zetterberg H, Bistrom M, et al. Axonal injury in asymptomatic individuals preceding onset of multiple sclerosis. *Ann Clin Transl Neurol*. Jun 2022;9(6):882-887. doi:10.1002/acn3.51568
35. Bjornevik K, Munger KL, Cortese M, et al. Serum Neurofilament Light Chain Levels in Patients With Presymptomatic Multiple Sclerosis. *JAMA Neurol*. Jan 1 2020;77(1):58-64. doi:10.1001/jamaneurol.2019.3238
36. Disanto G, Zecca C, MacLachlan S, et al. Prodromal symptoms of multiple sclerosis in primary care. *Ann Neurol*. Jun 2018;83(6):1162-1173. doi:10.1002/ana.25247

37. Cortese M, Riise T, Bjornevik K, et al. Preclinical disease activity in multiple sclerosis: A prospective study of cognitive performance prior to first symptom. *Ann Neurol*. Oct 2016;80(4):616-24. doi:10.1002/ana.24769
38. Filippi M, Preziosa P, Meani A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. *Lancet Neurol*. Feb 2018;17(2):133-142. doi:10.1016/S1474-4422(17)30469-6
39. Filippi M, Preziosa P, Meani A, et al. Performance of the 2017 and 2010 Revised McDonald Criteria in Predicting MS Diagnosis After a Clinically Isolated Syndrome: A MAGNIMS Study. *Neurology*. Jan 4 2022;98(1):e1-e14. doi:10.1212/WNL.0000000000013016
40. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology*. Mar 3 2009;72(9):800-5. doi:10.1212/01.wnl.0000335764.14513.1a
41. Lebrun-Frenay C, Kantarci O, Siva A, et al. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. *Ann Neurol*. Aug 2020;88(2):407-417. doi:10.1002/ana.25799
42. Lebrun-Frenay C, Okuda DT, Siva A, et al. The radiologically isolated syndrome: revised diagnostic criteria. *Brain*. Mar 2 2023;doi:10.1093/brain/awad073
43. Menascu S, Stern M, Aloni R, Kalron A, Magalshvili D, Achiron A. Assessing cognitive performance in radiologically isolated syndrome. *Mult Scler Relat Disord*. Jul 2019;32:70-73. doi:10.1016/j.msard.2019.04.030
44. Oh J, Suthiphosuwan S, Sati P, et al. Cognitive impairment, the central vein sign, and paramagnetic rim lesions in RIS. *Mult Scler*. Dec 2021;27(14):2199-2208. doi:10.1177/13524585211002097
45. Okuda DT, Kantarci O, Lebrun-Frenay C, et al. Dimethyl Fumarate Delays Multiple Sclerosis in Radiologically Isolated Syndrome. *Ann Neurol*. Mar 2023;93(3):604-614. doi:10.1002/ana.26555
46. Marrie RA, Allegretta M, Barcellos LF, et al. From the prodromal stage of multiple sclerosis to disease prevention. *Nat Rev Neurol*. Sep 2022;18(9):559-572. doi:10.1038/s41582-022-00686-x
47. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. *BMC Neurol*. Mar 9 2018;18(1):27. doi:10.1186/s12883-018-1026-3
48. Multiple Sclerosis International Federation. *Atlas of MS, 3rd Edition. Part 1: Mapping multiple sclerosis around the world*. 2020. Accessed July 13 2023. https://www.msif.org/wp-content/uploads/2020/10/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf
49. Teleanu RI, Niculescu AG, Vladacenco OA, Roza E, Perjoc RS, Teleanu DM. The State of the Art of Pediatric Multiple Sclerosis. *Int J Mol Sci*. May 4 2023;24(9)doi:10.3390/ijms24098251
50. Jakimovski D, Awan S, Eckert SP, Farooq O, Weinstock-Guttman B. Multiple Sclerosis in Children: Differential Diagnosis, Prognosis, and Disease-Modifying Treatment. *CNS Drugs*. Jan 2022;36(1):45-59. doi:10.1007/s40263-021-00887-w
51. International Multiple Sclerosis Genetics C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. Sep 27 2019;365(6460)doi:10.1126/science.aav7188
52. International Multiple Sclerosis Genetics C, Wellcome Trust Case Control C, Sawcer S, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. Aug 10 2011;476(7359):214-9. doi:10.1038/nature10251
53. Goris A, Vandebergh M, McCauley JL, Saarela J, Cotsapas C. Genetics of multiple sclerosis: lessons from polygenicity. *Lancet Neurol*. Sep 2022;21(9):830-842. doi:10.1016/S1474-4422(22)00255-1
54. International Multiple Sclerosis Genetics C, Multiple MSC. Locus for severity implicates CNS resilience in progression of multiple sclerosis. *Nature*. Jun 28 2023;doi:10.1038/s41586-023-06250-x

55. Murray J. Infection as a cause of multiple sclerosis. *BMJ*. Nov 16 2002;325(7373):1128. doi:10.1136/bmj.325.7373.1128
56. Belbasis L, Bellou V, Evangelou E, Tzoulaki I. Environmental factors and risk of multiple sclerosis: Findings from meta-analyses and Mendelian randomization studies. *Mult Scler*. Apr 2020;26(4):397-404. doi:10.1177/1352458519872664
57. Xu Y, Smith KA, Hiyoshi A, Piehl F, Olsson T, Montgomery S. Hospital-diagnosed infections before age 20 and risk of a subsequent multiple sclerosis diagnosis. *Brain*. Sep 4 2021;144(8):2390-2400. doi:10.1093/brain/awab100
58. Khalesi Z, Tamrchi V, Razizadeh MH, et al. Association between human herpesviruses and multiple sclerosis: A systematic review and meta-analysis. *Microb Pathog*. Apr 2023;177:106031. doi:10.1016/j.micpath.2023.106031
59. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*. Jan 21 2022;375(6578):296-301. doi:10.1126/science.abj8222
60. Rostgaard K, Balfour HH, Jr., Jarrett R, et al. Primary Epstein-Barr virus infection with and without infectious mononucleosis. *PLoS One*. 2019;14(12):e0226436. doi:10.1371/journal.pone.0226436
61. Xu Y, Hiyoshi A, Smith KA, et al. Association of Infectious Mononucleosis in Childhood and Adolescence With Risk for a Subsequent Multiple Sclerosis Diagnosis Among Siblings. *JAMA Netw Open*. Oct 1 2021;4(10):e2124932. doi:10.1001/jamanetworkopen.2021.24932
62. Loosen SH, Doege C, Meuth SG, Luedde T, Kostev K, Roderburg C. Infectious mononucleosis is associated with an increased incidence of multiple sclerosis: Results from a cohort study of 32,116 outpatients in Germany. *Front Immunol*. 2022;13:937583. doi:10.3389/fimmu.2022.937583
63. Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV. Environmental factors and their timing in adult-onset multiple sclerosis. *Nat Rev Neurol*. Mar 2010;6(3):156-66. doi:10.1038/nrneurol.2010.1
64. Dunmire SK, Verghese PS, Balfour HH, Jr. Primary Epstein-Barr virus infection. *J Clin Virol*. May 2018;102:84-92. doi:10.1016/j.jcv.2018.03.001
65. Ball RJ, Avenell A, Aucott L, Hanlon P, Vickers MA. Systematic review and meta-analysis of the sero-epidemiological association between Epstein-Barr virus and rheumatoid arthritis. *Arthritis Res Ther*. Sep 29 2015;17:274. doi:10.1186/s13075-015-0755-6
66. Li ZX, Zeng S, Wu HX, Zhou Y. The risk of systemic lupus erythematosus associated with Epstein-Barr virus infection: a systematic review and meta-analysis. *Clin Exp Med*. Feb 2019;19(1):23-36. doi:10.1007/s10238-018-0535-0
67. Hedstrom AK, Olsson T, Kockum I, Hillert J, Alfredsson L. Low sun exposure increases multiple sclerosis risk both directly and indirectly. *J Neurol*. Apr 2020;267(4):1045-1052. doi:10.1007/s00415-019-09677-3
68. Hoglund RAA, Meyer HE, Stigum H, et al. Association of Body Mass Index in Adolescence and Young Adulthood and Long-term Risk of Multiple Sclerosis: A Population-Based Study. *Neurology*. Dec 7 2021;97(23):e2253-e2261. doi:10.1212/WNL.0000000000012957
69. Cortese M, Riise T, Bjornevik K, et al. Timing of use of cod liver oil, a vitamin D source, and multiple sclerosis risk: The EnvIMS study. *Mult Scler*. Dec 2015;21(14):1856-64. doi:10.1177/1352458515578770
70. Oturai DB, Bach Sondergaard H, Koch-Henriksen N, et al. Exposure to passive smoking during adolescence is associated with an increased risk of developing multiple sclerosis. *Mult Scler*. Feb 2021;27(2):188-197. doi:10.1177/1352458520912500
71. Xu Y, Hiyoshi A, Brand JS, et al. Higher body mass index at ages 16 to 20 years is associated with increased risk of a multiple sclerosis diagnosis in subsequent adulthood among men. *Mult Scler*. Jan 2021;27(1):147-150. doi:10.1177/1352458520928061
72. Yuan S, Xiong Y, Larsson SC. An atlas on risk factors for multiple sclerosis: a Mendelian randomization study. *J Neurol*. Jan 2021;268(1):114-124. doi:10.1007/s00415-020-10119-8

73. Smith KA, Hiyoshi A, Burkill S, et al. Hospital diagnosed pneumonia before age 20 years and multiple sclerosis risk. *BMJ Neurol Open*. 2020;2(1):e000044. doi:10.1136/bmjno-2020-000044
74. Wu J, Engdahl E, Gustafsson R, et al. High antibody levels against human herpesvirus-6A interact with lifestyle factors in multiple sclerosis development. *Mult Scler*. Mar 2022;28(3):383-392. doi:10.1177/13524585211022011
75. Akerstedt T, Olsson T, Alfredsson L, Hedstrom AK. Insufficient sleep during adolescence and risk of multiple sclerosis: results from a Swedish case-control study. *J Neurol Neurosurg Psychiatry*. May 2023;94(5):331-336. doi:10.1136/jnnp-2022-330123
76. Hedstrom AK, Akerstedt T, Hillert J, Olsson T, Alfredsson L. Shift work at young age is associated with increased risk for multiple sclerosis. *Ann Neurol*. Nov 2011;70(5):733-41. doi:10.1002/ana.22597
77. Gustavsen S, Sondergaard HB, Oturai DB, et al. Shift work at young age is associated with increased risk of multiple sclerosis in a Danish population. *Mult Scler Relat Disord*. Sep 2016;9:104-9. doi:10.1016/j.msard.2016.06.010
78. Hedstrom AK, Hillert J, Olsson T, Alfredsson L. Alcohol as a modifiable lifestyle factor affecting multiple sclerosis risk. *JAMA Neurol*. Mar 2014;71(3):300-5. doi:10.1001/jamaneurol.2013.5858
79. Andersen C, Sondergaard HB, Bang Oturai D, et al. Alcohol consumption in adolescence is associated with a lower risk of multiple sclerosis in a Danish cohort. *Mult Scler*. Oct 2019;25(12):1572-1579. doi:10.1177/1352458518795418
80. Wesnes K, Myhr KM, Riise T, et al. Physical activity is associated with a decreased multiple sclerosis risk: The EnvIMS study. *Mult Scler*. Feb 2018;24(2):150-157. doi:10.1177/1352458517694088
81. Li C, Lin J, Yang T, Xiao Y, Jiang Q, Shang H. Physical activity and risk of multiple sclerosis: A Mendelian randomization study. *Front Immunol*. 2022;13:872126. doi:10.3389/fimmu.2022.872126
82. Jacobs BM, Giovannoni G, Cuzick J, Dobson R. Systematic review and meta-analysis of the association between Epstein-Barr virus, multiple sclerosis and other risk factors. *Mult Scler*. Oct 2020;26(11):1281-1297. doi:10.1177/1352458520907901
83. Hedstrom AK, Hillert J, Brenner N, et al. DRB1-environment interactions in multiple sclerosis etiology: results from two Swedish case-control studies. *J Neurol Neurosurg Psychiatry*. Jul 2021;92(7):717-722. doi:10.1136/jnnp-2020-325676
84. Hedstrom AK, Huang J, Brenner N, et al. Low sun exposure acts synergistically with high Epstein-Barr nuclear antigen 1 (EBNA-1) antibody levels in multiple sclerosis etiology. *Eur J Neurol*. Dec 2021;28(12):4146-4152. doi:10.1111/ene.15082
85. Alrouji M, Manouchehrinia A, Gran B, Constantinescu CS. Effects of cigarette smoke on immunity, neuroinflammation and multiple sclerosis. *J Neuroimmunol*. Apr 15 2019;329:24-34. doi:10.1016/j.jneuroim.2018.10.004
86. Correale J, Marrodan M. Multiple sclerosis and obesity: The role of adipokines. *Front Immunol*. 2022;13:1038393. doi:10.3389/fimmu.2022.1038393
87. Huynh JL, Casaccia P. Epigenetic mechanisms in multiple sclerosis: implications for pathogenesis and treatment. *Lancet Neurol*. Feb 2013;12(2):195-206. doi:10.1016/S1474-4422(12)70309-5
88. Castro K, Casaccia P. Epigenetic modifications in brain and immune cells of multiple sclerosis patients. *Mult Scler*. Jan 2018;24(1):69-74. doi:10.1177/1352458517737389
89. Castro K, Ntranos A, Amatruda M, et al. Body Mass Index in Multiple Sclerosis modulates ceramide-induced DNA methylation and disease course. *EBioMedicine*. May 2019;43:392-410. doi:10.1016/j.ebiom.2019.03.087
90. Goodin DS, Khankhanian P, Gourraud PA, Vince N. Multiple sclerosis: Exploring the limits and implications of genetic and environmental susceptibility. *PLoS One*. 2023;18(6):e0285599. doi:10.1371/journal.pone.0285599

91. Bar-Or A, Pender MP, Khanna R, et al. Epstein-Barr Virus in Multiple Sclerosis: Theory and Emerging Immunotherapies. *Trends Mol Med*. Mar 2020;26(3):296-310. doi:10.1016/j.molmed.2019.11.003
92. Tremlett H, Munger KL, Makhani N. The Multiple Sclerosis Prodrome: Evidence to Action. *Front Neurol*. 2021;12:761408. doi:10.3389/fneur.2021.761408
93. Chung KK, Altmann D, Barkhof F, et al. A 30-Year Clinical and Magnetic Resonance Imaging Observational Study of Multiple Sclerosis and Clinically Isolated Syndromes. *Ann Neurol*. Jan 2020;87(1):63-74. doi:10.1002/ana.25637
94. Phadke JG, Best PV. Atypical and clinically silent multiple sclerosis: a report of 12 cases discovered unexpectedly at necropsy. *J Neurol Neurosurg Psychiatry*. May 1983;46(5):414-20. doi:10.1136/jnnp.46.5.414
95. Manuel Escobar J, Cortese M, Edan G, et al. Body mass index as a predictor of MS activity and progression among participants in BENEFIT. *Mult Scler*. Jul 2022;28(8):1277-1285. doi:10.1177/13524585211061861
96. Rosso M, Chitnis T. Association Between Cigarette Smoking and Multiple Sclerosis: A Review. *JAMA Neurol*. Feb 1 2020;77(2):245-253. doi:10.1001/jamaneurol.2019.4271
97. Smolders J, Torkildsen O, Camu W, Holmoy T. An Update on Vitamin D and Disease Activity in Multiple Sclerosis. *CNS Drugs*. Dec 2019;33(12):1187-1199. doi:10.1007/s40263-019-00674-8
98. Mowry EM, Azevedo CJ, McCulloch CE, et al. Body mass index, but not vitamin D status, is associated with brain volume change in MS. *Neurology*. Dec 11 2018;91(24):e2256-e2264. doi:10.1212/WNL.0000000000006644
99. Hedstrom AK, Alfredsson L, Lundkvist Ryner M, Fogdell-Hahn A, Hillert J, Olsson T. Smokers run increased risk of developing anti-natalizumab antibodies. *Mult Scler*. Jul 2014;20(8):1081-5. doi:10.1177/1352458513515086
100. Petersen ER, Oturai AB, Koch-Henriksen N, et al. Smoking affects the interferon beta treatment response in multiple sclerosis. *Neurology*. Feb 13 2018;90(7):e593-e600. doi:10.1212/WNL.0000000000004949
101. Campagna MP, Xavier A, Lea RA, et al. Whole-blood methylation signatures are associated with and accurately classify multiple sclerosis disease severity. *Clin Epigenetics*. Dec 30 2022;14(1):194. doi:10.1186/s13148-022-01397-2
102. Song H, Fang F, Tomasson G, et al. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. *JAMA*. Jun 19 2018;319(23):2388-2400. doi:10.1001/jama.2018.7028
103. Bookwalter DB, Roenfeldt KA, LeardMann CA, Kong SY, Riddle MS, Rull RP. Posttraumatic stress disorder and risk of selected autoimmune diseases among US military personnel. *BMC Psychiatry*. Jan 15 2020;20(1):23. doi:10.1186/s12888-020-2432-9
104. Charcot JM. *Lectures on the diseases of the nervous system*. vol v.1-2, c.2. The New Sydenham Society; 1877.
105. Briones-Buixassa L, Mila R, J MfA, Bufill E, Olaya B, Arrufat FX. Stress and multiple sclerosis: A systematic review considering potential moderating and mediating factors and methods of assessing stress. *Health Psychol Open*. Jul 2015;2(2):2055102915612271. doi:10.1177/2055102915612271
106. Jiang J, Abduljabbar S, Zhang C, Osier N. The relationship between stress and disease onset and relapse in multiple sclerosis: A systematic review. *Mult Scler Relat Disord*. Nov 2022;67:104142. doi:10.1016/j.msard.2022.104142
107. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *BMJ*. Mar 27 2004;328(7442):731. doi:10.1136/bmj.38041.724421.55
108. Goodin DS. The epidemiology of multiple sclerosis: insights to a causal cascade. *Handb Clin Neurol*. 2016;138:173-206. doi:10.1016/B978-0-12-802973-2.00011-2
109. Burns MN, Nawacki E, Kwasny MJ, Pelletier D, Mohr DC. Do positive or negative stressful events predict the development of new brain lesions in people with multiple sclerosis? *Psychol Med*. Jan 2014;44(2):349-59. doi:10.1017/S0033291713000755

110. Mohr DC, Lovera J, Brown T, et al. A randomized trial of stress management for the prevention of new brain lesions in MS. *Neurology*. Jul 31 2012;79(5):412-9. doi:10.1212/WNL.0b013e3182616ff9
111. Meyer-Arndt L, Hetzer S, Asseyer S, et al. Blunted neural and psychological stress processing predicts future grey matter atrophy in multiple sclerosis. *Neurobiol Stress*. Nov 2020;13:100244. doi:10.1016/j.ynstr.2020.100244
112. Saul A, Ponsonby AL, Lucas RM, et al. Stressful life events and the risk of initial central nervous system demyelination. *Mult Scler*. Jun 2017;23(7):1000-1007. doi:10.1177/1352458516667566
113. Abdollahpour I, Nedjat S, Mansournia MA, Eckert S, Weinstock-Guttman B. Stress-full life events and multiple sclerosis: A population-based incident case-control study. *Mult Scler Relat Disord*. Nov 2018;26:168-172. doi:10.1016/j.msard.2018.09.026
114. Nielsen NM, Bager P, Simonsen J, et al. Major stressful life events in adulthood and risk of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Oct 2014;85(10):1103-8. doi:10.1136/jnnp-2013-307181
115. Li J, Johansen C, Bronnum-Hansen H, Stenager E, Koch-Henriksen N, Olsen J. The risk of multiple sclerosis in bereaved parents - A nationwide cohort study in Denmark. *Neurology*. Mar 9 2004;62(5):726-729. doi:Doi 10.1212/01.Wnl.0000113766.21896.B1
116. Mehta CM, Arnett JJ, Palmer CG, Nelson LJ. Established adulthood: A new conception of ages 30 to 45. *Am Psychol*. May-Jun 2020;75(4):431-444. doi:10.1037/amp0000600
117. Jiang X, Olsson T, Hillert J, Kockum I, Alfredsson L. Stressful life events are associated with the risk of multiple sclerosis. *Eur J Neurol*. Dec 2020;27(12):2539-2548. doi:10.1111/ene.14458
118. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. May 1998;14(4):245-58. doi:10.1016/s0749-3797(98)00017-8
119. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. Aug 2017;2(8):e356-e366. doi:10.1016/S2468-2667(17)30118-4
120. Nielsen NM, Pedersen BV, Stenager E, Koch-Henriksen N, Frisch M. Stressful life-events in childhood and risk of multiple sclerosis: a Danish nationwide cohort study. *Mult Scler*. Oct 2014;20(12):1609-15. doi:10.1177/1352458514528761
121. Riise T, Mohr DC, Munger KL, Rich-Edwards JW, Kawachi I, Ascherio A. Stress and the risk of multiple sclerosis. *Neurology*. May 31 2011;76(22):1866-71. doi:10.1212/WNL.0b013e31821d74c5
122. Spitzer C, Bouchain M, Winkler LY, et al. Childhood trauma in multiple sclerosis: a case-control study. *Psychosom Med*. Apr 2012;74(3):312-8. doi:10.1097/PSY.0b013e31824c2013
123. Eftekharian MM, Ghannad MS, Taheri M, et al. Frequency of viral infections and environmental factors in multiple sclerosis. *Hum Antibodies*. Jun 8 2016;24(1-2):17-23. doi:10.3233/HAB-150289
124. Shaw MT, Pawlak NO, Frontario A, Sherman K, Krupp LB, Charvet LE. Adverse Childhood Experiences Are Linked to Age of Onset and Reading Recognition in Multiple Sclerosis. *Front Neurol*. 2017;8:242. doi:10.3389/fneur.2017.00242
125. Briones-Buixassa L, Mila R, Arrufat FX, et al. A case-control study of psychosocial factors and their relationship to impairment and functionality in multiple sclerosis. *J Health Psychol*. Jul 2019;24(8):1023-1032. doi:10.1177/1359105317692142
126. Horton MK, McCurdy S, Shao X, et al. Case-control study of adverse childhood experiences and multiple sclerosis risk and clinical outcomes. *PLoS One*. 2022;17(1):e0262093. doi:10.1371/journal.pone.0262093
127. MacDonald TM, Fisk JD, Bernstein CN, et al. The association between childhood maltreatment and pain catastrophizing in individuals with immune-mediated inflammatory diseases. *J Psychosom Res*. Jun 2021;145:110479. doi:10.1016/j.jpsychores.2021.110479

128. Pust GEA, Dettmers C, Randerath J, et al. Fatigue in Multiple Sclerosis Is Associated With Childhood Adversities. *Front Psychiatry*. 2020;11:811. doi:10.3389/fpsyt.2020.00811
129. Wan A, Bernstein CN, Graff LA, et al. Childhood Maltreatment and Psychiatric Comorbidity in Immune-Mediated Inflammatory Disorders. *Psychosom Med*. Jan 1 2022;84(1):10-19. doi:10.1097/PSY.0000000000001025
130. Polick CS, Ploutz-Snyder R, Braley TJ, Connell CM, Stoddard SA. Associations among stressors across the lifespan, disability, and relapses in adults with multiple sclerosis. *Brain Behav*. Jul 2023;13(7):e3073. doi:10.1002/brb3.3073
131. Nelson CA, Scott RD, Bhutta ZA, Harris NB, Danese A, Samara M. Adversity in childhood is linked to mental and physical health throughout life. *BMJ*. Oct 28 2020;371:m3048. doi:10.1136/bmj.m3048
132. Ibrahim P, Almeida D, Nagy C, Turecki G. Molecular impacts of childhood abuse on the human brain. *Neurobiol Stress*. Nov 2021;15:100343. doi:10.1016/j.ynstr.2021.100343
133. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci*. Sep 19 2016;17(10):652-66. doi:10.1038/nrn.2016.111
134. Danese A, Baldwin JR. Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annu Rev Psychol*. Jan 3 2017;68:517-544. doi:10.1146/annurev-psych-010416-044208
135. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry*. May 2016;21(5):642-9. doi:10.1038/mp.2015.67
136. Renna ME, Peng J, Shrout MR, et al. Childhood abuse histories predict steeper inflammatory trajectories across time. *Brain Behav Immun*. Jan 2021;91:541-545. doi:10.1016/j.bbi.2020.11.012
137. Anagnostouli M, Markoglou N, Chrousos G. Psycho-neuro-endocrino-immunologic issues in multiple sclerosis: a critical review of clinical and therapeutic implications. *Hormones (Athens)*. Dec 2020;19(4):485-496. doi:10.1007/s42000-020-00197-8
138. Sausen DG, Bhutta MS, Gallo ES, Dahari H, Borenstein R. Stress-Induced Epstein-Barr Virus Reactivation. *Biomolecules*. Sep 18 2021;11(9)doi:10.3390/biom11091380
139. Slopen N, McLaughlin KA, Dunn EC, Koenen KC. Childhood adversity and cell-mediated immunity in young adulthood: does type and timing matter? *Brain Behav Immun*. Feb 2013;28:63-71. doi:10.1016/j.bbi.2012.10.018
140. Slopen N, McLaughlin KA, Dunn EC, Koenen KC. Reply to letter Re: Childhood adversity and cell-mediated immunity in young adulthood. *Brain Behav Immun*. Nov 2013;34:177-9. doi:10.1016/j.bbi.2013.08.002
141. Fagundes CP, Glaser R, Malarkey WB, Kiecolt-Glaser JK. Childhood adversity and herpesvirus latency in breast cancer survivors. *Health Psychol*. Mar 2013;32(3):337-44. doi:10.1037/a0028595
142. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. *Front Immunol*. 2020;11:587380. doi:10.3389/fimmu.2020.587380
143. Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. *Infect Agent Cancer*. 2014;9(1):38. doi:10.1186/1750-9378-9-38
144. Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci*. Jan 2013;16(1):33-41. doi:10.1038/nn.3275
145. Bjornevik K, Riise T, Cortese M, et al. Level of education and multiple sclerosis risk after adjustment for known risk factors: The EnvIMS study. *Mult Scler*. Jan 2016;22(1):104-11. doi:10.1177/1352458515579444

146. Wang Y, Chung MC, Wang N, Yu X, Kenardy J. Social support and posttraumatic stress disorder: A meta-analysis of longitudinal studies. *Clin Psychol Rev*. Apr 2021;85:101998. doi:10.1016/j.cpr.2021.101998
147. McCabe MP, McKern S, McDonald E. Coping and psychological adjustment among people with multiple sclerosis. *J Psychosom Res*. Mar 2004;56(3):355-61. doi:10.1016/S0022-3999(03)00132-6
148. Hajhashemi A, Vaziripour HD, Baratian H, Kajbaf MB, Etemadifar M. Recognition of the kind of stress coping in patients of multiple sclerosis. *Indian J Psychol Med*. Jul 2010;32(2):108-11. doi:10.4103/0253-7176.78507
149. Elwood LS, Wolitzky-Taylor K, Olatunji BO. Measurement of anxious traits: a contemporary review and synthesis. *Anxiety Stress Coping*. Nov 2012;25(6):647-66. doi:10.1080/10615806.2011.582949
150. Gruhn MA, Compas BE. Effects of maltreatment on coping and emotion regulation in childhood and adolescence: A meta-analytic review. *Child Abuse Negl*. May 2020;103:104446. doi:10.1016/j.chiabu.2020.104446
151. Albott CS, Forbes MK, Anker JJ. Association of Childhood Adversity With Differential Susceptibility of Transdiagnostic Psychopathology to Environmental Stress in Adulthood. *JAMA Netw Open*. Nov 2 2018;1(7):e185354. doi:10.1001/jamanetworkopen.2018.5354
152. Butler N, Quigg Z, Bellis MA. Cycles of violence in England and Wales: the contribution of childhood abuse to risk of violence revictimisation in adulthood. *BMC Med*. Nov 16 2020;18(1):325. doi:10.1186/s12916-020-01788-3
153. Public Health England. *Disability and domestic abuse. Risk, impacts and response*. 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/480942/Disability_and_domestic_abuse_topic_overview_FINAL.pdf
154. Brown HK, Saunders N, Chen S, et al. Disability and Interpersonal Violence in the Perinatal Period. *Obstet Gynecol*. Nov 1 2022;140(5):797-805. doi:10.1097/AOG.0000000000004950
155. Morrison EH, Sorkin D, Mosqueda L, Ayutyanont N. Abuse and neglect of people with multiple sclerosis: A survey with the North American Research Committee on Multiple Sclerosis (NARCOMS). *Mult Scler Relat Disord*. Nov 2020;46:102530. doi:10.1016/j.msard.2020.102530
156. Alhusen JL, Ray E, Sharps P, Bullock L. Intimate partner violence during pregnancy: maternal and neonatal outcomes. *J Womens Health (Larchmt)*. Jan 2015;24(1):100-6. doi:10.1089/jwh.2014.4872
157. Nesari M, Olson JK, Vandermeer B, Slater L, Olson DM. Does a maternal history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-analysis. *BMC Pregnancy Childbirth*. Oct 16 2018;18(1):404. doi:10.1186/s12884-018-2030-8
158. Gisladottir A, Luque-Fernandez MA, Harlow BL, et al. Obstetric Outcomes of Mothers Previously Exposed to Sexual Violence. *PLoS One*. 2016;11(3):e0150726. doi:10.1371/journal.pone.0150726
159. Stewart DE, MacMillan H, Kimber M. Recognizing and Responding to Intimate Partner Violence: An Update. *Can J Psychiatry*. Jan 2021;66(1):71-106. doi:10.1177/0706743720939676
160. Pastor-Moreno G, Ruiz-Perez I, Henares-Montiel J, Escriba-Aguir V, Higueras-Callejon C, Ricci-Cabello I. Intimate partner violence and perinatal health: a systematic review. *BJOG*. Apr 2020;127(5):537-547. doi:10.1111/1471-0528.16084
161. Birk K, Smeltzer SC, Rudick R. Pregnancy and multiple sclerosis. *Semin Neurol*. Sep 1988;8(3):205-13. doi:10.1055/s-2008-1041379
162. Frith JA, McLeod JG. Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Apr 1988;51(4):495-8. doi:10.1136/jnnp.51.4.495
163. Finkelsztejn A, Brooks JB, Paschoal FM, Jr., Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. *BJOG*. Jun 2011;118(7):790-7. doi:10.1111/j.1471-0528.2011.02931.x

164. Bonavita S, Lavorgna L, Worton H, Russell S, Jack D. Family Planning Decision Making in People With Multiple Sclerosis. *Front Neurol*. 2021;12:620772. doi:10.3389/fneur.2021.620772
165. Lavorgna L, Esposito S, Lanzillo R, et al. Factors interfering with parenthood decision-making in an Italian sample of people with multiple sclerosis: an exploratory online survey. *J Neurol*. Mar 2019;266(3):707-716. doi:10.1007/s00415-019-09193-4
166. Houtchens MK, Edwards NC, Hayward B, Mahony MC, Phillips AL. Live birth rates, infertility diagnosis, and infertility treatment in women with and without multiple sclerosis: Data from an administrative claims database. *Mult Scler Relat Disord*. Nov 2020;46:102541. doi:10.1016/j.msard.2020.102541
167. Moccia M, Affinito G, Fumo MG, et al. Fertility, pregnancy and childbirth in women with multiple sclerosis: a population-based study from 2018 to 2020. *J Neurol Neurosurg Psychiatry*. Sep 2023;94(9):689-697. doi:10.1136/jnnp-2022-330883
168. Kopp TI, Pinborg A, Glazer CH, Magyari M. Women with female infertility seeking medically assisted reproduction are not at increased risk of developing multiple sclerosis. *Hum Reprod*. May 30 2022;37(6):1324-1333. doi:10.1093/humrep/deac041
169. Ferraro D, Simone AM, Adani G, et al. Definitive childlessness in women with multiple sclerosis: a multicenter study. *Neurol Sci*. Aug 2017;38(8):1453-1459. doi:10.1007/s10072-017-2999-1
170. Houtchens MK, Edwards NC, Schneider G, Stern K, Phillips AL. Pregnancy rates and outcomes in women with and without MS in the United States. *Neurology*. Oct 23 2018;91(17):e1559-e1569. doi:10.1212/WNL.0000000000006384
171. Tintore M, Cobo-Calvo A, Carbonell P, et al. Effect of Changes in MS Diagnostic Criteria Over 25 Years on Time to Treatment and Prognosis in Patients With Clinically Isolated Syndrome. *Neurology*. Oct 26 2021;97(17):e1641-e1652. doi:10.1212/WNL.0000000000012726
172. National Institute for Health and Care Excellence. Antenatal and postnatal mental health. Guideline 192. Updated 11 February 2020. Accessed 07.01.2021, https://www.nice.org.uk/guidance/cg192/chapter/1-recommendations
173. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med*. Jul 30 1998;339(5):285-91. doi:10.1056/NEJM199807303390501
174. Dobson R, Jokubaitis VG, Giovannoni G. Change in pregnancy-associated multiple sclerosis relapse rates over time: a meta-analysis. *Mult Scler Relat Disord*. Sep 2020;44:102241. doi:10.1016/j.msard.2020.102241
175. Yeh WZ, Widyastuti PA, Van der Walt A, et al. Natalizumab, Fingolimod and Dimethyl Fumarate Use and Pregnancy-Related Relapse and Disability in Women With Multiple Sclerosis. *Neurology*. Apr 20 2021;96(24):e2989-3002. doi:10.1212/WNL.0000000000012084
176. Krysko KM, Dobson R, Alroughani R, et al. Family planning considerations in people with multiple sclerosis. *Lancet Neurol*. Apr 2023;22(4):350-366. doi:10.1016/S1474-4422(22)00426-4
177. Anderson A, Rowles W, Poole S, et al. Anti-CD20 monoclonal antibody therapy in postpartum women with neurological conditions. *Ann Clin Transl Neurol*. Sep 7 2023;doi:10.1002/acn3.51893
178. Fong A, Chau CT, Quant C, Duffy J, Pan D, Ogunyemi DA. Multiple sclerosis in pregnancy: prevalence, sociodemographic features, and obstetrical outcomes. *J Matern Fetal Neonatal Med*. Feb 2018;31(3):382-387. doi:10.1080/14767058.2017.1286314
179. Andersen JB, Kopp TI, Sellebjerg F, Magyari M. Pregnancy-Related and Perinatal Outcomes in Women With Multiple Sclerosis: A Nationwide Danish Cross-sectional Study. *Neurol Clin Pract*. Aug 2021;11(4):280-290. doi:10.1212/CPJ.0000000000001035
180. Fink K, Gorczyca A, Alping P, et al. Multiple sclerosis, disease-modifying drugs and risk for adverse perinatal and pregnancy outcomes: Results from a population-based cohort study. *Mult Scler*. May 2023;29(6):731-740. doi:10.1177/13524585231161492

181. Boeschoten RE, Braamse AMJ, Beekman ATF, et al. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. *J Neurol Sci*. Jan 15 2017;372(Jan 2017):331-341. doi:10.1016/j.jns.2016.11.067
182. Razaz N, Tremlett H, Marrie RA, Joseph KS. Peripartum depression in parents with multiple sclerosis and psychiatric disorders in children. *Mult Scler*. Dec 2016;22(14):1830-1840. doi:10.1177/1352458516631037
183. Rossi S, Studer V, Motta C, et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology*. Sep 26 2017;89(13):1338-1347. doi:10.1212/WNL.0000000000004411
184. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med*. Sep 2019;49(12):1958-1970. doi:10.1017/S0033291719001454
185. Masuccio FG, Gamberini G, Calabrese M, Solaro C. Imaging and depression in multiple sclerosis: a historical perspective. *Neurol Sci*. Mar 2021;42(3):835-845. doi:10.1007/s10072-020-04951-z
186. Riemer F, Skorve E, Pasternak O, et al. Microstructural changes precede depression in patients with relapsing-remitting Multiple Sclerosis. *Commun Med (Lond)*. Jun 22 2023;3(1):90. doi:10.1038/s43856-023-00319-4
187. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. *Nat Rev Neurol*. Sep 2014;10(9):507-17. doi:10.1038/nrneurol.2014.139
188. Akyirem S, Forbes A, Wad JL, Due-Christensen M. Psychosocial interventions for adults with newly diagnosed chronic disease: A systematic review. *J Health Psychol*. Jun 2022;27(7):1753-1782. doi:10.1177/1359105321995916
189. Harroud A, Marrie RA, Fitzgerald KC, et al. Mendelian randomization provides no evidence for a causal role in the bidirectional relationship between depression and multiple sclerosis. *Mult Scler*. Nov 2021;27(13):2077-2084. doi:10.1177/1352458521993075
190. Binzer S, Jiang X, Hillert J, Manouchehrinia A. Depression and multiple sclerosis: A bidirectional Mendelian randomisation study. *Mult Scler*. Oct 2021;27(11):1799-1802. doi:10.1177/1352458521996601
191. Rogers A, Obst S, Teague SJ, et al. Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. *JAMA Pediatr*. Nov 1 2020;174(11):1082-1092. doi:10.1001/jamapediatrics.2020.2910
192. Ghimire U, Papabathini SS, Kawuki J, Obore N, Musa TH. Depression during pregnancy and the risk of low birth weight, preterm birth and intrauterine growth restriction- an updated meta-analysis. *Early Hum Dev*. Jan 2021;152:105243. doi:10.1016/j.earlhumdev.2020.105243
193. Johannsen BM, Larsen JT, Laursen TM, Bergink V, Meltzer-Brody S, Munk-Olsen T. All-Cause Mortality in Women With Severe Postpartum Psychiatric Disorders. *Am J Psychiatry*. Jun 1 2016;173(6):635-42. doi:10.1176/appi.ajp.2015.14121510
194. Magnus P, Irgens LM, Haug K, et al. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. Oct 2006;35(5):1146-50. doi:10.1093/ije/dyl170
195. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. Apr 2016;45(2):382-8. doi:10.1093/ije/dyw029
196. Schreuder P, Alsaker E. The Norwegian Mother and Child Cohort Study (MoBa) – MoBa recruitment and logistics. *Norsk Epidemiologi [Norwegian Epidemiology]*. 2014;24doi:https://doi.org/10.5324/nje.v24i1-2.1754
197. Ronningen KS, Paltiel L, Meltzer HM, et al. The biobank of the Norwegian Mother and Child Cohort Study: a resource for the next 100 years. *Eur J Epidemiol*. 2006;21(8):619-25. doi:10.1007/s10654-006-9041-x
198. Bakken IJ, Ariansen AMS, Knudsen GP, Johansen KI, Vollset SE. The Norwegian Patient Registry and the Norwegian Registry for Primary Health Care: Research potential of two nationwide health-care registries. *Scand J Public Health*. Feb 2020;48(1):49-55. doi:10.1177/1403494819859737

199. Myhr KM, Grytten N, Torkildsen O, Wergeland S, Bo L, Aarseth JH. The Norwegian Multiple Sclerosis Registry and Biobank. *Acta Neurol Scand*. 2015;132(199):24-8. doi:10.1111/ane.12427
200. The Norwegian Directorate of Health [Helsedirektoratet]. Analysis of National Coverage: The Norwegian MS Registry and Biobank 2008-2016 [Dekningsgradsanalyse: Norsk MS-register og biobank 2008-2016]. 2022,. https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr/innhold-og-kvalitet-i-npr/16-13323-12%20Dekningsgrad_rapport_MS_4.pdf/_/attachment/inline/851b6ae3-76d3-48e0-a297-1838565bf0e0:0c2af0b445da062adbc8c038a6d9df79c470853a/16-13323-12%20Dekningsgrad_rapport_MS_4.pdf
201. Swahnberg IM, Wijma B. The NorVold Abuse Questionnaire (NorAQ): validation of new measures of emotional, physical, and sexual abuse, and abuse in the health care system among women. *Eur J Public Health*. Dec 2003;13(4):361-6. doi:10.1093/eurpub/13.4.361
202. McFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy. Severity and frequency of injuries and associated entry into prenatal care. *JAMA*. Jun 17 1992;267(23):3176-8. doi:10.1001/jama.267.23.3176
203. Lundin A, Hallgren M, Forsell Y. The validity of the symptom checklist depression and anxiety subscales: A general population study in Sweden. *J Affect Disord*. Sep 1 2015;183(Sep 2015):247-52. doi:10.1016/j.jad.2015.05.024
204. Tambs K, Moum T. How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatr Scand*. May 1993;87(5):364-7.
205. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic journal of psychiatry*. 2003;57(2):113-8. doi:10.1080/08039480310000932
206. Nettelbladt P, Hansson L, Stefansson CG, Borgquist L, Nordstrom G. Test characteristics of the Hopkins Symptom Check List-25 (HSCL-25) in Sweden, using the Present State Examination (PSE-9) as a caseness criterion. *Soc Psychiatry Psychiatr Epidemiol*. Jul 1993;28(3):130-3.
207. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Arch Gen Psychiatry*. Nov 1993;50(11):863-70. doi:10.1001/archpsyc.1993.01820230054003
208. Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB. Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry. *Brain Behav*. Nov 2019;9(11):e01422. doi:10.1002/brb3.1422
209. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet*. Jan 19 2002;359(9302):248-52. doi:10.1016/S0140-6736(02)07451-2
210. Celentano DD, Moyses Szjko,. *Gordis Epidemiology*. 6th ed. 2018:289-299.
211. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. Nov 2009;23(6):597-608. doi:10.1111/j.1365-3016.2009.01062.x
212. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. Jul 2006;17(4):413-8. doi:10.1097/01.ede.0000220549.14177.60
213. Batty GD, Gale CR, Kivimaki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ*. Feb 12 2020;368:m131. doi:10.1136/bmj.m131
214. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*. Nov 1 2017;186(9):1026-1034. doi:10.1093/aje/kwx246
215. Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol*. Aug 1 2019;48(4):1294-1304. doi:10.1093/ije/dyz032

216. Faul L, LaBar KS. Mood-congruent memory revisited. *Psychol Rev*. Oct 6 2022;doi:10.1037/rev0000394
217. Fergusson DM, Horwood LJ, Boden JM. Structural equation modeling of repeated retrospective reports of childhood maltreatment. *International Journal of Methods in Psychiatric Research*. 2011;20(2):93-104. doi:10.1002/mpr.337
218. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. May 2003;14(3):300-6.
219. Stoltzfus JC. Logistic regression: a brief primer. *Acad Emerg Med*. Oct 2011;18(10):1099-104. doi:10.1111/j.1553-2712.2011.01185.x
220. Trujillo J, Vieira MC, Lepsch J, et al. A systematic review of the associations between maternal nutritional biomarkers and depression and/or anxiety during pregnancy and postpartum. *J Affect Disord*. May 2018;232:185-203. doi:10.1016/j.jad.2018.02.004
221. Bonk S, Hertel J, Zacharias HU, et al. Vitamin D moderates the interaction between 5-HTTLPR and childhood abuse in depressive disorders. *Sci Rep*. Dec 28 2020;10(1):22394. doi:10.1038/s41598-020-79388-7
222. Cammack AL, Gazmararian JA, Suglia SF. History of child maltreatment and excessive dietary and screen time behaviors in young adults: Results from a nationally representative study. *Prev Med*. Oct 2020;139:106176. doi:10.1016/j.ypmed.2020.106176
223. Alfredsson L, Hillert J, Olsson T, Hedstrom AK. Observed associations between indicators of socioeconomic status and risk of multiple sclerosis in Sweden are explained by a few lifestyle-related factors. *Eur J Neurol*. Apr 2023;30(4):1001-1013. doi:10.1111/ene.15705
224. Kavaliunas A, Danylaite Karrenbauer V, Binzer S, Hillert J. Systematic Review of the Socioeconomic Consequences in Patients With Multiple Sclerosis With Different Levels of Disability and Cognitive Function. *Front Neurol*. 2021;12:737211. doi:10.3389/fneur.2021.737211
225. Eid K, Torkildsen OF, Aarseth J, et al. Perinatal Depression and Anxiety in Women With Multiple Sclerosis: A Population-Based Cohort Study. *Neurology*. Jun 8 2021;96(23):e2789-e2800. doi:10.1212/WNL.0000000000012062
226. Nasjonalt kunnskapssenter om vold og traumatisk stress. *Omfang av vold og overgrep i den norske befolkningen 2023 [Occurence of violence and abuse in the norwegian population 2023]*. 2023. Accessed 27th September 2023. https://www.nkvts.no/content/uploads/2023/03/NKVTS_Rapport_1_23_Omfang_vold_overgrep.pdf
227. Cammack AL, Hogue CJ, Drews-Botsch CD, et al. Test-retest reliability of retrospective self-reported maternal exposure to childhood abuse and neglect. *Arch Womens Ment Health*. Apr 2016;19(2):415-21. doi:10.1007/s00737-015-0536-x
228. Baldwin JR, Reuben A, Newbury JB, Danese A. Agreement Between Prospective and Retrospective Measures of Childhood Maltreatment: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. Jun 1 2019;76(6):584-593. doi:10.1001/jamapsychiatry.2019.0097
229. Gatto NM, Thordardottir EB, Tomasson G, et al. Association between Adverse Childhood Experiences and Multiple Sclerosis in Icelandic Women-A Population-Based Cohort Study. *Brain Sci*. Nov 16 2022;12(11)doi:10.3390/brainsci12111559
230. Khaw YM, Majid D, Oh S, Kang E, Inoue M. Early-life-trauma triggers interferon-beta resistance and neurodegeneration in a multiple sclerosis model via downregulated beta1-adrenergic signaling. *Nat Commun*. Jan 4 2021;12(1):105. doi:10.1038/s41467-020-20302-0
231. Eid K, Torkildsen O, Aarseth J, et al. Association of adverse childhood experiences with the development of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Apr 4 2022;doi:10.1136/jnnp-2021-328700
232. Smith KE, Pollak SD. Rethinking Concepts and Categories for Understanding the Neurodevelopmental Effects of Childhood Adversity. *Perspect Psychol Sci*. Jan 2021;16(1):67-93. doi:10.1177/1745691620920725

233. Manouchehri E, Ghavami V, Larki M, Saeidi M, Latifnejad Roudsari R. Domestic violence experienced by women with multiple sclerosis: a study from the North-East of Iran. *BMC Women's Health*. 2022;22(1)doi:10.1186/s12905-022-01905-9
234. Pol-Patil J, Glanz B, Safar L, et al. MeTooMS: Sexual, physical, and emotional abuse experience among women with multiple sclerosis. *Mult Scler*. Feb 2023;29(2):287-294. doi:10.1177/13524585221122169
235. Plummer SB, Findley PA. Women with disabilities' experience with physical and sexual abuse: review of the literature and implications for the field. *Trauma Violence Abuse*. Jan 2012;13(1):15-29. doi:10.1177/1524838011426014
236. Douglas SL, Plow M, Packer T, Lipson AR, Lehman MJ. Psychoeducational Interventions for Caregivers of Persons With Multiple Sclerosis: Protocol for a Randomized Trial. *JMIR Res Protoc*. Aug 26 2021;10(8):e30617. doi:10.2196/30617
237. Bowen E, Heron J, Waylen A, Wolke D, Team AS. Domestic violence risk during and after pregnancy: findings from a British longitudinal study. *BJOG*. Aug 2005;112(8):1083-9. doi:10.1111/j.1471-0528.2005.00653.x
238. Krysko KM, Anderson A, Singh J, et al. Risk factors for peripartum depression in women with multiple sclerosis. *Mult Scler*. May 2022;28(6):970-979. doi:10.1177/13524585211041108
239. Kim JH, Kim JY, Lee S, et al. Environmental risk factors, protective factors, and biomarkers for postpartum depressive symptoms: an umbrella review. *Neurosci Biobehav Rev*. Sep 2022;140:104761. doi:10.1016/j.neubiorev.2022.104761
240. Yin X, Sun N, Jiang N, et al. Prevalence and associated factors of antenatal depression: Systematic reviews and meta-analyses. *Clin Psychol Rev*. Feb 2021;83:101932. doi:10.1016/j.cpr.2020.101932
241. Zhang S, Wang L, Yang T, et al. Maternal violence experiences and risk of postpartum depression: A meta-analysis of cohort studies. *Eur Psychiatry*. Jan 2019;55:90-101. doi:10.1016/j.eurpsy.2018.10.005
242. Sorbo MF, Grimstad H, Bjorngaard JH, Lukasse M, Schei B. Adult physical, sexual, and emotional abuse and postpartum depression, a population based, prospective study of 53,065 women in the Norwegian Mother and Child Cohort Study. *BMC Pregnancy Childbirth*. Sep 8 2014;14:316. doi:10.1186/1471-2393-14-316
243. Dias CC, Figueiredo B. Breastfeeding and depression: a systematic review of the literature. *J Affect Disord*. Jan 15 2015;171(Jan 2015):142-54. doi:10.1016/j.jad.2014.09.022
244. Marrie RA, Walld R, Bolton JM, et al. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. *Epidemiol Psychiatr Sci*. Jun 2019;28(3):333-342. doi:10.1017/S2045796017000579
245. Chen MA, LeRoy AS, Majd M, et al. Immune and Epigenetic Pathways Linking Childhood Adversity and Health Across the Lifespan. *Front Psychol*. 2021;12:788351. doi:10.3389/fpsyg.2021.788351
246. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. Jul 2008;33(6):693-710. doi:10.1016/j.psyneuen.2008.03.008
247. Kiewa J, Meltzer-Brody S, Milgrom J, et al. Perinatal depression is associated with a higher polygenic risk for major depressive disorder than non-perinatal depression. *Depress Anxiety*. Mar 2022;39(3):182-191. doi:10.1002/da.23232
248. Batt MM, Duffy KA, Novick AM, Metcalf CA, Epperson CN. Is Postpartum Depression Different From Depression Occurring Outside of the Perinatal Period? A Review of the Evidence. *Focus (Am Psychiatr Publ)*. Apr 2020;18(2):106-119. doi:10.1176/appi.focus.20190045
249. Osborne LM, Monk C. Perinatal depression--the fourth inflammatory morbidity of pregnancy?: Theory and literature review. *Psychoneuroendocrinology*. Oct 2013;38(10):1929-52. doi:10.1016/j.psyneuen.2013.03.019

250. Putnam KT, Wilcox M, Robertson-Blackmore E, et al. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. *Lancet Psychiatry*. Jun 2017;4(6):477-485. doi:10.1016/S2215-0366(17)30136-0
251. Elwood J, Murray E, Bell A, Sinclair M, Kernohan WG, Stockdale J. A systematic review investigating if genetic or epigenetic markers are associated with postnatal depression. *J Affect Disord*. Jun 15 2019;253:51-62. doi:10.1016/j.jad.2019.04.059
252. Svendsen M. Ny forskning: Traumer i barndommen øker risiko for MS. *NRK*. 17th April, 2022. https://www.nrk.no/trondelag/ny-forskning_-traumatiske-opplevelser-i-barndom-oker-risiko-for-ms-1.15933699
253. Pihlstrøm L. Multippel urettferdighet. Dystre, men viktige funn fra norsk epidemiologi-studie. *Morgenbladet*. 5th May, 2022. https://www.morgenbladet.no/aktuelt/forskning/2022/05/06/multippel-urettferdighet-overgrep-oker-risikoen-for-ms/
254. Skrøder K. Studie: Dette kan utløse MS. *Dagbladet*. 27th April, 2022. https://www.dagbladet.no/tema/studie-dette-kan-utlose-ms/75888626
255. Leavitt VM, Dobson R, Svennigsson A. Perinatal Depression and Anxiety in Multiple Sclerosis: Treatable Distress. *Neurology*. Jun 8 2021;96(23):1067-1068. doi:10.1212/WNL.0000000000012101
256. Stewart DE, Macmillan H, Kimber M. Recognizing and Responding to Intimate Partner Violence: An Update. *The Canadian Journal of Psychiatry*. 2021;66(1):71-106. doi:10.1177/0706743720939676
257. Raja S, Hasnain M, Hoersch M, Gove-Yin S, Rajagopalan C. Trauma informed care in medicine: current knowledge and future research directions. *Fam Community Health*. Jul-Sep 2015;38(3):216-26. doi:10.1097/FCH.0000000000000071
258. World Health Organization. WHO recommendations on maternal and newborn care for a positive postnatal experience. Updated March 30. Accessed 9th October, 2023. https://www.who.int/publications/i/item/9789240045989
259. [Helsedirektoratet] TNDoH. National guidelines for perinatal health care [Svangerskapsomsorgen: Nasjonal faglig retningslinje]. Updated June 6th 2023. Accessed October 9th, 2023. https://www.helsedirektoratet.no/retningslinjer/svangerskapsomsorgen
260. Curry SJ, Krist AH, Owens DK, et al. Interventions to Prevent Perinatal Depression. *JAMA*. 2019;321(6):580. doi:10.1001/jama.2019.0007
261. Nillni YI, Mehralizade A, Mayer L, Milanovic S. Treatment of depression, anxiety, and trauma-related disorders during the perinatal period: A systematic review. *Clin Psychol Rev*. Dec 2018;66:136-148. doi:10.1016/j.cpr.2018.06.004
262. Division of Violence Prevention CDC. *Adverse Childhood Experiences (ACEs) Prevention*. 2019. https://www.cdc.gov/violenceprevention/pdf/ACEs-Prevention-Resource_508.pdf
263. Barnes AJ, Anthony BJ, Karatekin C, Lingras KA, Mercado R, Thompson LA. Identifying adverse childhood experiences in pediatrics to prevent chronic health conditions. *Pediatric Research*. 2020;87(2):362-370. doi:10.1038/s41390-019-0613-3
264. Loveday S, Hall T, Constable L, et al. Screening for Adverse Childhood Experiences in Children: A Systematic Review. *Pediatrics*. Feb 1 2022;149(2)doi:10.1542/peds.2021-051884
265. Baldwin JR, Caspi A, Meehan AJ, et al. Population vs Individual Prediction of Poor Health From Results of Adverse Childhood Experiences Screening. *JAMA Pediatrics*. 2021;175(4):385. doi:10.1001/jamapediatrics.2020.5602
266. World Health Organization. Adverse Childhood Experiences International Questionnaire (ACE-IQ). https://www.who.int/publications/m/item/adverse-childhood-experiences-international-questionnaire-(ace-iq)

10 Papers I–III

I

OPEN ACCESS

Original research

Association of adverse childhood experiences with the development of multiple sclerosis

Karine Eid ,[1,1] Øivind Torkildsen,[2,3] Jan Aarseth,[2,4] Mari Aalstad,[5] Alok Bhan,[3,6] Elisabeth G Celius ,[7,8] Marianna Cortese ,[3,9] Anne Kjersti Daltveit,[10,11] Trygve Holmøy,[12,13] Kjell-Morten Myhr,[2,3] Trond Riise,[2,11] Stephan Schüler,[14] Cecilie F Torkildsen,[3,15] Stig Wergeland,[2,4] Nils Erik Gilhus,[1,3] Marte-Helene Bjørk[1,3]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328700).

For numbered affiliations see end of article.

Correspondence to
Dr Karine Eid, Department of Neurology, Haukeland University Hospital, Bergen 5053, Norway; karine.eid@uib.no

Received 20 December 2021
Accepted 22 February 2022
Published Online First 4 April 2022

ABSTRACT

Objective To study whether exposure to childhood emotional, sexual or physical abuse is associated with subsequent multiple sclerosis (MS) development.

Methods A nationwide, prospective cohort study based on participants in the Norwegian Mother, Father and Child cohort study. Enrolment took place 1999–2008, with follow-up until 31 December 2018. Childhood abuse before age 18 years was obtained from self-completed questionnaires. We identified MS diagnoses through data-linkage with national health registries and hospital records. The Cox model was used to estimate HRs for MS with 95% CIs, adjusting for confounders and mediators.

Results In this prospective cohort study, 14 477 women were exposed to childhood abuse and 63 520 were unexposed. 300 women developed MS during the follow-up period. 71 of these (24%) reported a history of childhood abuse, compared with 14 406 of 77 697 (19%) women that did not develop MS. Sexual abuse (HR 1.65, 95% CI 1.13 to 2.39) and emotional abuse (HR 1.40, 95% CI 1.03 to 1.90) in childhood were both associated with an increased risk of developing MS. The HR of MS after exposure to physical abuse was 1.31 (95% CI 0.83 to 2.06). The risk of MS was further increased if exposed to two (HR 1.66, 95% CI 1.04 to 2.67) or all three abuse categories (HR 1.93, 95% CI 1.02 to 3.67).

Interpretation Childhood sexual and emotional abuse were associated with an increased risk of developing MS. The risk was higher when exposed to several abuse categories, indicating a dose–response relationship. Further studies are needed to identify underlying mechanisms.

Key messages

What is already known on this topic

⇒ Trauma in childhood and adolescence can alter the immune system and may increase the risk of autoimmune disorders. Whether stress and adverse events in childhood can have an impact on multiple sclerosis (MS) susceptibility is not known.

What this study adds

⇒ Women with exposure to adverse childhood experiences had increased risk of developing MS. This association was most pronounced for sexual abuse and for the combination of several categories of abuse.

How this study might affect research, practice or policy

⇒ These results open doors for prevention and insight to disease mechanisms.

INTRODUCTION

Trauma and stressful life events have been associated with an increased risk of autoimmune disorders.[1] Any impact of stress on multiple sclerosis (MS) is debated,[2] but a recent population-based study from Sweden with 2930 MS cases indicated a link between major stressors in adult life, such as loss of a loved one, divorce or personal conflict and subsequent MS disease.[3] Adverse childhood experiences such as abuse, neglect and household dysfunction are extreme types of stress, and increase the risk of psychiatric and physical disorders in adulthood,[4] including cardiovascular disease, cancer and autoimmune disease.[5]

Whether adverse events in childhood can have an impact on MS susceptibility is not known. A Danish population-based study found a 13% increased risk of developing MS if exposed to parental divorce,[6] but they were unable to adjust for associated lifestyle changes such as smoking and obesity. Few have studied the association between childhood abuse and MS, and these studies were not prospective and arrived at different conclusions.[7 8]

Some of the most consistent environmental risk factors for MS, including low vitamin D levels, low sun exposure, Epstein-Barr virus infection and obesity seem to have critical periods of susceptibility for MS in childhood and particularly, adolescence.[9–11] Exposure to tobacco smoke at a young age may also have an impact.[12 13] Better understanding of risk factors and timing of risk exposures, may open doors for prevention and give further insight to disease mechanisms.

Our aim was to investigate whether adverse childhood experiences may contribute to the risk of MS. In this prospective and population-based study, we assessed the association between exposure to childhood emotional, sexual and physical abuse and the risk of developing MS, examining nationwide

Check for updates

To cite: Eid K, Torkildsen Ø, Aarseth J, *et al*. *J Neurol Neurosurg Psychiatry* 2022;**93**:645–650.

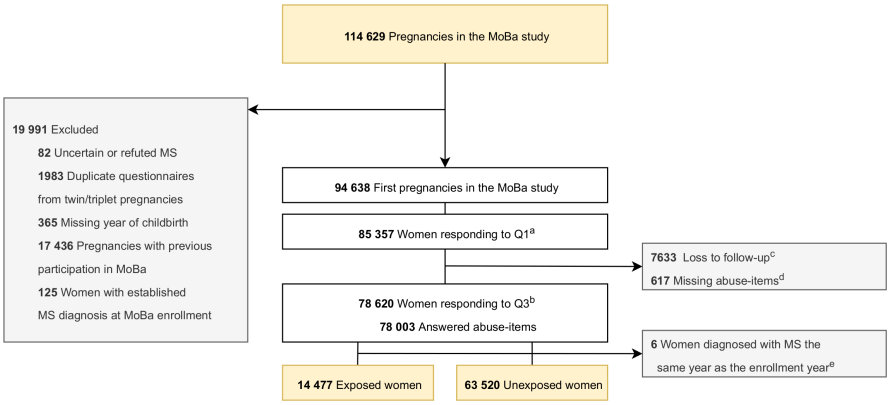


Figure 1 Flow chart of included and excluded study participants. [a]The first questionnaire (Q1) in the MoBA study was sent out to participants in pregnancy week 18. [b]The third questionnaire (Q3) in the MobA study was sent out to participants in pregnancy week 30. [c]Lost to follow-up from pregnancy week 18 to pregnancy week 30. A total of 896 women responded to Q3 without responding to Q1, hence the difference of 6737 from Q1 to Q3. [d]A total of 617 of the women who responded to Q3 did not answer the abuse items. [e]These women were not eligible for the time-to-event analysis since they had 0 observation years. MoBa, The Norwegian mother, father and Child cohort study; MS, multiple sclerosis; Q, Questionnaire.

data from a prospective cohort study in combination with health registries and hospital records.

METHODS

Study design and population

We conducted a national, prospective cohort study using the Norwegian Mother, Father and Child cohort (MoBa). The MoBa study included pregnant Norwegian-speaking women from all over Norway in 1999–2008,[14] and 41% of the invited women consented to participation. There were no exclusion criteria, and the follow-up is ongoing. The MoBa cohort is linked to The Medical Birth Registry (MBRN), which is a national health registry containing information about all births in Norway. Information in the MBRN is registered by health personnel and registration is mandatory.

We acquired information on childhood adverse experiences and potential confounding and mediating factors at study baseline, which we defined as the year the women were enrolled in the MoBa study. The women completed self-administered questionnaires which included information on demographic and socioeconomic factors (pregnancy weeks 17–20) and history of any previous abuse (pregnancy week 30).

This study is based on version 12 of the MoBa data files, covering 114 629 pregnancies. We excluded duplicate questionnaires due to multiple gestations (n=1983) and recurrent participations in MoBa (n=17 436) to include only one observation per woman (figure 1). We also excluded women with refuted or unvalidated MS diagnosis (n=82), women who did not respond to the questionnaire in pregnancy week 30 including the abuse items, as well as women with missing year of childbirth. Women with an established MS diagnosis at study baseline were excluded to avoid a potential recall bias (n=125). Women who received the MS diagnosis the same year as they were enrolled in the study (observation time=0 years) were not eligible to be included in the time-to-event analysis and thus excluded (n=6).

Outcome measure

Our primary outcome was development of MS. On 31 December 2018, we cross-linked the MoBa cohort with the Norwegian Multiple Sclerosis Registry and Biobank (MSR) and the Norwegian Patient Registry (NPR) to identify all women in MoBa who developed MS after baseline and to ensure validated diagnoses. The MSR had 60% national coverage of MS cases at the time of data-linkage, and we further linked the data to NPR to identify the remaining MS cases. After every consultation in specialist care, registration of diagnoses in NPR is mandatory for health practitioners. The MS diagnosis in NPR have a sensitivity of 97% and a positive predictive value 0.92.[15] If the woman was registered in NPR with an MS diagnosis, but not in the MSR, we used hospital records to further validate the diagnosis using the 2017 diagnostic criteria for MS.[16] We were able to refute incorrect MS diagnoses from the NPR based on the information from the hospital records. NPR-identified MS cases for whom we did not have access to the hospital records for validation, were excluded.

Exposure

A history of adverse childhood experiences before age 18 years was defined by four abuse items in the pregnancy week 30 questionnaire; humiliation ('Has anyone over a long period of time systematically tried to subdue, degrade or humiliate you?'), threat ('Has anyone threatened to hurt you or someone close to you?'), physical abuse ('Have you been subjected to physical abuse?') and sexual abuse ('Have you been forced to do sexual actions?'). We merged the items on humiliation and threat into one category of emotional abuse. Exposure to either emotional, sexual, or physical abuse was defined as responding 'yes, as a child <18 years' to the respective category. We considered women who answered 'no, never' to the abuse items as non-exposed. The abuse questions in MoBa are adapted from the NorVold Abuse Questionnaire and modified into four screening items. The NorVold Abuse Questionnaire has previously been shown to have good reliability and validity.[17]

Covariables

MS-specific covariables were assessed from the Norwegian MS Registry and hospital records: Age at MS onset (defined as first clinical symptom), age at MS diagnosis and subtype of MS

(relapsing-remitting, primary progressive or unspecified). Other covariables were acquired through the self-completed MoBa questionnaires or through linkage to the MBRN: Age at baseline, birth year, smoking (ever/never), body mass index (BMI) prior to pregnancy (<25/≥25 kg/m^2), drop-out before or during high school (completed ≤9 years of elementary school). Adverse socioeconomic status in adulthood was defined as either having low household income (<60% of the study population median income in year of study baseline), being a non-cohabiting mother or short education (≤9 years of school). Depression at study baseline (during pregnancy) was measured by a validated short version of the Hopkins Symptom Checklist 25[18] in pregnancy week 30.

Statistical analysis

For the time-to-event analysis, the observation period began at enrolment in MoBa (online supplemental figure 1). Time was measured in years from start of the observation period until year of MS diagnosis or end of study period (31 December 2018).

We used Cox proportional-hazards models to measure the risk of MS after exposure to childhood abuse, estimating HRs and 95% CIs. Confidence intervals not including 1 were considered statistically significant. In addition to examining any childhood abuse, we separately examined the HRs for subtypes of abuse (emotional, sexual, physical) and severity of abuse (exposure to one, two or three subtypes). The models were stratified by the women's birth year in groups and adjusted in a two-step approach for (1) possible confounders and (2) possible confounders and mediators.

We considered birth year and childhood social status[19] as possible confounders and used early drop-out from school as a proxy for the latter. Birth year was taken into account as the incidence of child maltreatment probably has decreased during the last decades prior to inclusion in MoBa.[20] Possible mediators were smoking, high BMI, and adverse socioeconomic status as an adult—factors associated with both childhood abuse[4 21] and MS.[11 22–24]

The statistical models were checked for the proportional hazard assumption both by visual inspection and statistical test of the Schoenfeld residuals. We included birth year as a stratification factor in the Cox model, but no other variables violated the proportional hazard assumption.

Statistical analyses were performed using IBM SPSS Statistics V.26 and Stata V.16 (StataCorp).

Sensitivity analysis

Adolescents with preclinical MS disease activity may theoretically be affected in ways that increase the susceptibility of being exposed to abuse. To limit the possibility of reverse causality, we performed a sensitivity analysis excluding women that might have been in the prodromal phase of MS when exposed to abuse, that is, women with their first clinical symptom of MS before and including age 22 years (within 5 years after the end of the exposure window) (n=15) (online supplemental figure 2A).

To ensure that the exclusion of women that already had MS at the time of enrolment did not affect our results, we performed a sensitivity analysis comprising all women with MS in MoBa, both prevalent and incident cases (online supplemental figure 2B). In this sensitivity analysis, the observation period was calculated from age 18 years.

Table 1 Background characteristics of the study population exposed and unexposed to childhood abuse

	Exposed n=14 477	Unexposed n=63 520
Age at study baseline;* mean (SD)	29 (5)	30 (5)
Missing; n (%)	0 (0)	1 (<1)
Observation years;† median (IQR)	13 (4)	13 (4)
Adverse socioeconomic status‡; n (%)	2349 (16)	5787 (9)
Missing; n (%)	187 (1)	686 (1)
Low household income; n (%)	1578 (11)	3942 (6)
Maternal short education; n (%)	514 (4)	1036 (2)
Non-cohabiting mother; n (%)	582 (4)	1192 (2)
Ever smoker; n (%)	8785 (61)	30 745 (48)
Missing; n (%)	207 (1)	933 (2)
BMI ≥25; n (%)	4963 (34)	18 717 (30)
Missing; n (%)	561 (4)	2140 (3)
Depression at study baseline (pregnancy); n (%)	2573 (18)	4732 (8)
Missing; n (%)	105 (<1)	447 (<1)
Age at end of study§; mean (SD)	42 (6)	43 (5)
Missing; n (%)	0 (0)	1 (<1)
Age at MS diagnosis; mean (SD)	36 (6)	36 (5)
Missing; n (%)	0 (0)	0 (0)
Age at MS onset; mean (SD)	33 (7)	33 (6)
Missing; n (%)	0 (0)	0 (0)
Type of MS; n (%)		
RRMS	71 (100)	219 (95)
PPMS	0 (0)	4 (2)
Uncertain	0 (0)	6 (3)

*Study baseline is the year the women were enrolled in the MoBa study, and when the information on exposure were acquired.
†Observation years in the time-to-event analysis are calculated from enrollment in MoBa.
‡Adverse socioeconomic status is one of the following: non-cohabiting mother, short education <9 years or low household income (<60% of study population median in the given enrolment year).
§Age in 2018 among participants who did not experience the event (censored).
BMI, body mass index; MoBa, The Norwegian mother, father and Child cohort study; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing remitting MS.

RESULTS

We included 77 997 women from the MoBa cohort in our study and they contributed with a total of 1 010 926 person-years at risk (mean follow-up 13 years, IQR 11–15). A total of 14 477 women (19%) were exposed to adverse childhood experiences and 63 520 (81%) were unexposed (table 1). The women exposed to childhood abuse more often had a history of smoking, were overweight and had more depression at study baseline. During follow-up, 300 women developed MS of whom 71 (24%) reported a history of childhood abuse, compared with 14 406 (19%) among the 77 697 women who did not develop MS.

The MS incidence rates were 41, 49 and 40 per 100 000 person-years for women exposed to emotional, sexual, and physical abuse, respectively, and 28 per 100 000 person-years in women unexposed to childhood abuse (table 2).

We found an association between exposure to emotional or sexual abuse and subsequent MS development after adjustment for potential confounders and when accounting for possible mediators, HR 1.40 (95% CI 1.03 to 1.90) and HR 1.65 (95% CI 1.13 to 2.39), respectively (table 2). In the fully adjusted analyses, the HR for MS after exposure to physical abuse was 1.31

Table 2 Incidence rates and HRs for Multiple Sclerosis among women exposed to childhood abuse

Exposure	N (%) total cohort	N (%) women with MS	Person Time 100 000 Years	IR* (95% CI)	Unadjusted HR (95% CI)	HR† (95% CI)	HR‡ (95% CI)
No childhood abuse	63 520 (81)	229 (76)	8.2	28 (25 to 32)	Ref	Ref	Ref
Any childhood abuse	14 477 (19)	71 (24)	1.9	38 (30 to 48)	1.36 (1.04 to 1.78)	1.34 (1.03 to 1.76)	1.31 (0.99 to 1.72)
Emotional abuse	10 702 (14)	56 (20)	1.4	41 (31 to 53)	1.46 (1.09 to 1.95)	1.43 (1.06 to 1.93)	1.40 (1.03 to 1.90)
Emotional abuse: Humiliation	9414 (13)	48 (17)	1.2	40 (30 to 53)	1.42 (1.04 to 1.94)	1.39 (1.01 to 1.90)	1.37 (0.99 to 1.89)
Emotional abuse: Threat	3406 (5)	20 (8)	0.4	46 (30 to 71)	1.64 (1.04 to 2.58)	1.59 (1.00 to 2.52)	1.42 (0.86 to 2.29)
Sexual abuse	5416 (8)	34 (13)	0.7	49 (35 to 68)	1.74 (1.21 to 2.49)	1.75 (1.21 to 2.51)	1.65 (1.13 to 2.39)
Physical abuse	4287 (6)	22 (9)	0.6	40 (26 to 61)	1.42 (0.92 to 2.20)	1.41 (0.91 to 2.19)	1.31 (0.83 to 2.06)
No of abuse categories (Ref: 0)							
1	9947 (13)	40 (13)	1.3	31 (23 to 43)	1.12 (0.80 to 1.56)	1.09 (0.78 to 1.54)	1.11 (0.79 to 1.56)
2	3132 (4)	21 (7)	0.4	52 (34 to 80)	1.85 (1.19 to 2.90)	1.87 (1.19 to 2.92)	1.66 (1.04 to 2.67)
3	1398 (2)	10 (3)	0.2	56 (30 to 104)	1.99 (1.06 to 3.75)	2.00 (1.05 to 3.77)	1.93 (1.02 to 3.67)

*Incidence rates per 100 000 person-years. The incidence rate is lower for 'any childhood abuse' than for the separate subcategories of abuse because of longer person-time (more individuals under observation in the total abuse group). IR = 'Number of new cases'/'Total person-time at risk'.
†HRs adjusted for school drop-out (≤9 years elementary school). Birth year was included as a stratification factor in the Cox model.
‡HRs adjusted for adverse socioeconomic factors (≤9 years elementary school, non-cohabiting mother or low household income), smoking (ever vs never) and BMI ≥25 before study baseline). Birth year was included as a stratification factor in the Cox model, but no other covariable violated the proportional hazard assumption.
BMI, body mass index; IR, incidence rate; MS, multiple sclerosis.

(95% CI 0.83 to 2.06) and the HR for MS after exposure to any type of childhood abuse was 1.31 (95% CI 0.99 to 1.72).

The risk of MS was further increased in women exposed to two (HR 1.66, 95% CI 1.04 to 2.67), or all three categories of childhood abuse (HR 1.93, 95% CI 1.02 to 3.67).

Sensitivity analyses

We found similar or stronger associations between childhood abuse and MS in the sensitivity analysis after excluding women that could have been in a prodromal phase of MS when experiencing abuse (online supplemental table 1). The HR was 1.77 (95% CI 1.22 to 2.57) for sexual abuse and 1.40 (95% CI 1.01 to 1.95) for emotional abuse.

The association between childhood emotional and sexual abuse and MS persisted when including women that already had an MS diagnosis at baseline (online supplemental table 2).

Missing data

A total of 7633 of 85 357 (9%) women who answered the questionnaire in pregnancy week 18 did not answer the questionnaire in week 30 that included the abuse items. Their baseline characteristics were similar to our included participants (online supplemental table 3). A total of 617 of 78 620 (0.8%) women who answered the questionnaire in week 30 did not complete the abuse items. These women had more often an adverse socioeconomic status (online supplemental table 3).

DISCUSSION

In this nationwide, prospective cohort study, women who were exposed to childhood sexual or emotional abuse had an increased risk of developing MS. There was a similar tendency for exposure to physical abuse. The risk estimates were higher when exposed to several abuse categories, indicating a dose–response relationship.

Our results are supported by previously published retrospective studies.[7 25] The increased risk of MS after exposure to childhood sexual and emotional abuse may have a biological explanation. Childhood abuse can cause dysregulation of the hypothalamic–pituitary–adrenal axis,[26] lead to oxidative stress[27] and induce a proinflammatory state decades into adulthood.[28] Psychological stress has been shown to disrupt the blood–brain barrier[29] and cause epigenetic changes that may increase the risk of neurodegenerative disorders, including MS.[30] Neonatal emotional and physical stress increased the susceptibility and severity of MS-like disease in mice, due to downregulation of adrenergic receptors in innate immune cells.[31]

We found a higher risk of MS in women exposed to more than one type of abuse. A similar dose–response association has been observed between the risk of adult autoimmune disease hospitalisations and the number of childhood adverse events.[5]

This is the first fully prospective study that has assessed the association between childhood adverse events and subsequent MS. Previous studies on adverse events have mainly focused on adulthood and have found that most events happened during the last 1–5 years before MS onset.[3 32 33]

The nationwide cohort design, long follow-up and the inclusion of thoroughly validated MS cases through data-linkage with national health registries contribute to a high validity of our study. Sensitivity analyses minimised the possibility that our findings can be explained by reverse causality. We were able to adjust for important confounders and mediators, including childhood social status, adult socioeconomic factors, smoking and obesity. These environmental factors are associated with both exposure to childhood abuse[4 21] and the risk of developing MS.[11 22–24] The risk estimates for MS after exposure to emotional and sexual abuse slightly decreased after adjusting for these factors, but the associations remained significant. This suggests that childhood abuse may have an independent effect on MS susceptibility.

The sensitivity analysis showed consistent results also when including prevalent cases of MS, although the HR estimates were slightly reduced. The group of women with established MS did not report higher occurrence of childhood abuse than women with future MS as one might have expected from a recall bias perspective.

Women exposed to childhood abuse had higher depression rates when included during pregnancy. Retrospective reports of childhood trauma may be biased by current mood.[34] However, some suggest such bias is minor.[35] A more plausible explanation may be that exposure to childhood abuse gives increased risk of depression, in particular depression during pregnancy.[36]

Limitations

External validity represents a potential limitation of our study as we studied pregnant women and only 41% of the invited women consented to participation. Women with low socioeconomic status are underrepresented in the MoBa-cohort,[37] and women who skipped the abuse items in the questionnaire had lower socioeconomic status than the included population. Further, these findings may not be generalisable to men or non-white individuals.

As in all observational studies, residual confounding may be another limitation. We had detailed information on behavioural risk factors in adulthood such as smoking and obesity, but childhood abuse may be associated with other environmental factors such as diet, nutrition, physical exercise, and parental smoking, which could be independent risk factors for MS.

We used a screening questionnaire to assess the three main categories of abuse. Childhood abuse tends to be under-reported rather than over-reported in adulthood.[35] This could influence our prevalence rates but not affect exposure–outcome associations.

We did not have information on death or emigration which may bias observation time. Among Norwegian women in the age group 20–49 years,[38] 0.003% emigrate[39] and 0.0005% die[40] each year. Thus, these events should have minimal effects on our results.

We lacked information on chronicity of abuse. Exposure to abuse as a one-time incident could have different impact compared with repetitive abuse. Nevertheless, our finding of a dose–response relationship probably represents higher level of abuse severity. We do not know the age at abuse, and there may exist vulnerable periods during childhood and adolescence for MS development. We had no information on potential protective mechanisms such as social network, caregivers, family/friends or therapeutic interventions. Future studies may be strengthened through more nuanced exposure assessment.

In conclusion, children exposed to adverse experiences had an increased risk of developing MS later in life, independent of known environmental risk factors for MS. The risk increased with number of abuse categories in a dose–response manner. The underlying mechanisms behind this association should be investigated further.

Author affiliations
[1]Department of Neurology, Haukeland University Hospital, Bergen, Norway
[2]Neuro-SysMed, Department of Neurology, Haukeland University Hospital, Bergen, Norway
[3]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[4]The Norwegian Multiple Sclerosis and Biobank, Haukeland University Hospital, Bergen, Norway
[5]Department of Neurology, Innlandet Hospital Trust, Lillehammer, Norway
[6]Department of Neurology, Stavanger University Hospital, Stavanger, Norway
[7]Department of Neurology, Oslo University Hospital, Oslo, Norway
[8]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[9]Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA
[10]Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway
[11]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[12]Department of Neurology, Akershus University Hospital, Lorenskog, Norway
[13]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[14]Department of Neurology, Nord-Trøndelag Hospital Trust, Namsos, Norway
[15]Department of Obstetrics and Gynecology, Stavanger University Hospital, Stavanger, Norway

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

Twitter Elisabeth G Celius @CeliusElisabeth

Acknowledgements The Norwegian Mother, Father and Child Cohort study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We acknowledge Heidi Ø. Flemmen MD (Department of Neurology, Telemark Hospital Trust, Skien, Norway); Åslaug R. Lorentzen MD PhD (Department of Neurology, Sørlandet Hospital, Kristiansand, Norway); Cecilia S. Simonsen MD (Department of Neurology, Vestre Viken Hospital Trust, Drammen, Norway); Johannes Sverre Willumsen MD (Department of Neurology, Molde Hospital, Molde, Norway); Nina Øksendal MD (Department of Neurology, Nordland Hospital Trust, Bodø, Norway); Barbara Ratajczak-Tretel MD (Department of Neurology, Østfold Hospital, Østfold, Norway); Britt Bruland CNS (Department of Neurology, Førde Hospital, Førde, Norway) for contributing with data extraction and validation of MS diagnoses. We are grateful to all the participating families in Norway who take part in this ongoing cohort study. The results from this study were presented as an oral presentation at the ECTRIMS 2021 Conference.

Contributors KE: conception and design of the study, acquisition and analysis of data, drafting the manuscript. KE acts as the guarantor of the study and takes full responsibility for the work. K-MM, CFT, TR, NEG and M-HB: conception and design of the study, acquisition and analysis of data. ØT, JA, MA, AB, EGC, MC, AKD, TH, SS and SW: acquisition and analysis of data. All authors revised the manuscript and approved the final draft.

Funding KE has governmental funding (doctoral scholarship) from the Western Norway Regional Health Authority (Grant F-12503). Neuro-SysMed is funded by the Norwegian Research Council grant 288164.

Competing interests KE has received unrestricted research grant from Novartis. ØT has received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis. AB has received unrestricted research from Novartis. EGC has received honoraria for lecturing and advice from Biogen, Bristol Meyers Squibb, Janssen, Novartis, Merck, Roche and Sanofi, and her department has received grants from Novartis and Sanofi. AKD has received project funding from Pfizer. TH has received speaker honoraria from Biogen, Merck, Novartis, Roche, Bristol Myers Squibb, and Sanofi, and has participated in clinical trials organised by Biogen, Merck, and Roche. K-MM has received unrestricted research grants to his institution; scientific advisory board and speaker honoraria from Biogen, Merck, Novartis, Roche and Sanofi, and has participated in clinical trials organised by Biogen, Merck, Novartis, Roche and Sanofi. CFT has served on scientific advisory board for Astra Zeneca. SW has received honoraria from Biogen, Novartis and Sanofi. NEG has received honoraria from UCB, Ra, Argenx, Roche, Merck, Immunovant, Alexion. M-HB has received personal honoraria for lecturing from Teva, Lilly, Eisai and Novartis, and consultancy honoraria and unrestricted research support from Novartis. Institutional contract research fees from Sanofi.

Patient consent for publication Not applicable.

Ethics approval The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committees for Medical and Health Research Ethics (REK). The MoBa cohort is regulated by the Norwegian Health Registry Act.Ethics approval for the current study was obtained from REK (reference 2016/906). Written informed consent for use of information in research and for data linkage was acquired during enrolment in MoBa and MSR.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Enquiries regarding access to data from MoBa and the MBRN can be directed to the Norwegian Institute of Public Health. Data from the MSR are accessible for researchers by application (http://norskmsregister.no).

ORCID iDs
Karine Eid http://orcid.org/0000-0002-5158-7636
Elisabeth G Celius http://orcid.org/0000-0002-9127-6488

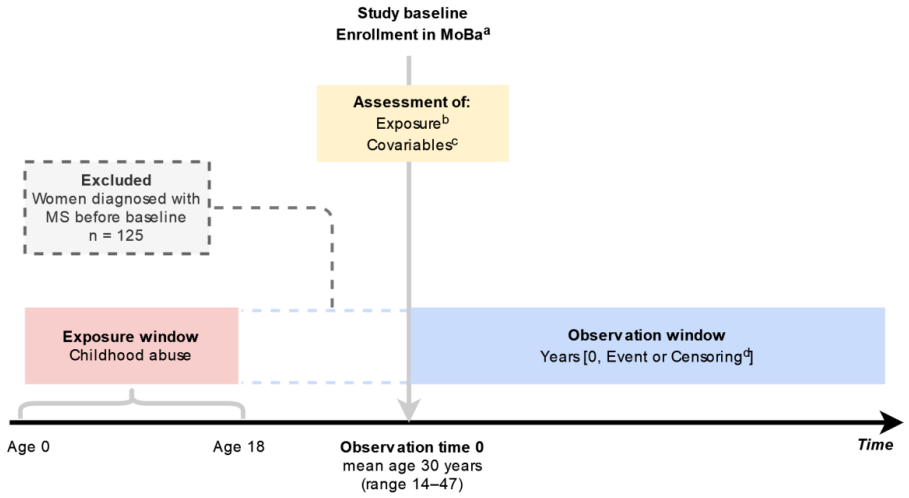
Marianna Cortese http://orcid.org/0000-0002-3665-2006

REFERENCES

1 Song H, Fang F, Tomasson G, *et al*. Association of stress-related disorders with subsequent autoimmune disease. *JAMA* 2018;319:2388–400.
2 Briones-Buixassa L, Milà R, Mª Aragonès J, *et al*. Stress and multiple sclerosis: a systematic review considering potential Moderating and mediating factors and methods of assessing stress. *Health Psychol Open* 2015;2:205510291561227.
3 Jiang X, Olsson T, Hillert J, *et al*. Stressful life events are associated with the risk of multiple sclerosis. *Eur J Neurol* 2020;27:2539–48.
4 Felitti VJ, Anda RF, Nordenberg D, *et al*. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *Am J Prev Med* 1998;14:245–58.
5 Dube SR, Fairweather D, Pearson WS, *et al*. Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med* 2009;71:243–50.
6 Nielsen NM, Pedersen BV, Stenager E, *et al*. Stressful life-events in childhood and risk of multiple sclerosis: a Danish nationwide cohort study. *Mult Scler* 2014;20:1609–15.
7 Spitzer C, Bouchain M, Winkler LY, *et al*. Childhood trauma in multiple sclerosis: a case-control study. *Psychosom Med* 2012;74:312–8.
8 Riise T, Mohr DC, Munger KL, *et al*. Stress and the risk of multiple sclerosis. *Neurology* 2011;76:1866–71.
9 Handel AE, Giovannoni G, Ebers GC, *et al*. Environmental factors and their timing in adult-onset multiple sclerosis. *Nat Rev Neurol* 2010;6:156–66.
10 Cortese M, Riise T, Bjørnevik K, *et al*. Timing of use of cod liver oil, a vitamin D source, and multiple sclerosis risk: the EnvIMS study. *Mult Scler* 2015;21:1856–64.
11 Høglund RAA, Meyer HE, Stigum H, *et al*. Association of body mass index in adolescence and young adulthood and long-term risk of multiple sclerosis: a population-based study. *Neurology* 2021;97:e2253–61.
12 Mikaeloff Y, Caridade G, Tardieu M, *et al*. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. *Brain* 2007;130:2589–95.
13 Salzer J, Hallmans G, Nyström M, *et al*. Smoking as a risk factor for multiple sclerosis. *Mult Scler* 2013;19:1022–7.
14 Magnus P, Birke C, Vejrup K, *et al*. Cohort profile update: the Norwegian mother and child cohort study (MobA). *Int J Epidemiol* 2016;45:382–8.
15 Benjaminsen E, Myhr K-M, Grytten N, *et al*. Validation of the multiple sclerosis diagnosis in the Norwegian patient registry. *Brain Behav* 2019;9:e01422.
16 Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162–73.
17 Swahnberg IMK, Wijma B. The NorVold abuse questionnaire (NorAQ): validation of new measures of emotional, physical, and sexual abuse, and abuse in the health care system among women. *Eur J Public Health* 2003;13:361–6.
18 Tambs K, Moum T. How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatr Scand* 1993;87:364–7.
19 Briggs FBS, Acuña BS, Shen L, *et al*. Adverse socioeconomic position during the life course is associated with multiple sclerosis. *J Epidemiol Community Health* 2014;68:622–9.
20 Gilbert R, Fluke J, O'Donnell M, *et al*. Child maltreatment: variation in trends and policies in six developed countries. *Lancet* 2012;379:758–72.
21 Houtepen LC, Heron J, Suderman MJ, *et al*. Associations of adverse childhood experiences with educational attainment and adolescent health and the role of family and socioeconomic factors: a prospective cohort study in the UK. *PLoS Med* 2020;17:e1003031.
22 Degelman ML, Herman KM. Smoking and multiple sclerosis: a systematic review and meta-analysis using the Bradford Hill criteria for causation. *Mult Scler Relat Disord* 2017;17:207–16.
23 Bjørnevik K, Riise T, Cortese M, *et al*. Level of education and multiple sclerosis risk after adjustment for known risk factors: the EnvIMS study. *Mult Scler* 2016;22:104–11.
24 Hedström AK, Hillert J, Olsson T, *et al*. Factors affecting the risk of relapsing-onset and progressive-onset multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2021;92:1096–102.
25 Shaw MT, Pawlak NO, Frontario A, *et al*. Adverse childhood experiences are linked to age of onset and reading recognition in multiple sclerosis. *Front Neurol* 2017;8:242.
26 Heim C, Newport DJ, Mletzko T, *et al*. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 2008;33:693–710.
27 Karanikas E, Daskalakis NP, Agorastos A. Oxidative dysregulation in early life stress and posttraumatic stress disorder: a comprehensive review. *Brain Sci* 2021;11. doi:10.3390/brainsci11060723. [Epub ahead of print: 29 05 2021].
28 Baumeister D, Akhtar R, Ciufolini S, *et al*. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry* 2016;21:642–9.
29 Esposito P, Gheorghe D, Kandere K, *et al*. Acute stress increases permeability of the blood-brain-barrier through activation of brain mast cells. *Brain Res* 2001;888:117–27.
30 Babenko O, Kovalchuk I, Metz GA. Epigenetic programming of neurodegenerative diseases by an adverse environment. *Brain Res* 2012;1444:96–111.
31 Khaw YM, Majid D, Oh S, *et al*. Early-life-trauma triggers interferon-β resistance and neurodegeneration in a multiple sclerosis model via downregulated β1-adrenergic signaling. *Nat Commun* 2021;12:105.
32 Warren S, Greenhill S, Warren KG. Emotional stress and the development of multiple sclerosis: case-control evidence of a relationship. *J Chronic Dis* 1982;35:821–31.
33 Saul A, Ponsonby A-L, Lucas RM, *et al*. Stressful life events and the risk of initial central nervous system demyelination. *Mult Scler* 2017;23:1000–7.
34 Gaddy MA, Ingram RE. A meta-analytic review of mood-congruent implicit memory in depressed mood. *Clin Psychol Rev* 2014;34:402–16.
35 Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry* 2004;45:260–73.
36 Eid K, Torkildsen Øivind Fredvik, Aarseth J, *et al*. Perinatal depression and anxiety in women with multiple sclerosis: a population-based cohort study. *Neurology* 2021;96:e2789–800.
37 Nilsen RM, Vollset SE, Gjessing HK, *et al*. Self-Selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;23:597–608.
38 Norway S. 05196: population, by sex, age and citizenship 1977-2021: statistics Norway, 2021. Available: https://www.ssb.no/en/statbank/table/05196/ [Accessed 18 Aug 2021].
39 Norway S. 09203: immigration, emigration and net migration, by sex and age 2001-2020: statistics Norway, 2021. Available: https://www.ssb.no/en/statbank/table/09203 [Accessed 18 Aug 2021].
40 Norway S. 08462: deaths, by sex and 10-year age groups (C) 1974-2020: statistics Norway, 2021. Available: https://www.ssb.no/en/statbank/table/08426/ [Accessed 18 Aug 2021].

Supplemental material for "Association of adverse childhood experiences with the development of multiple sclerosis"

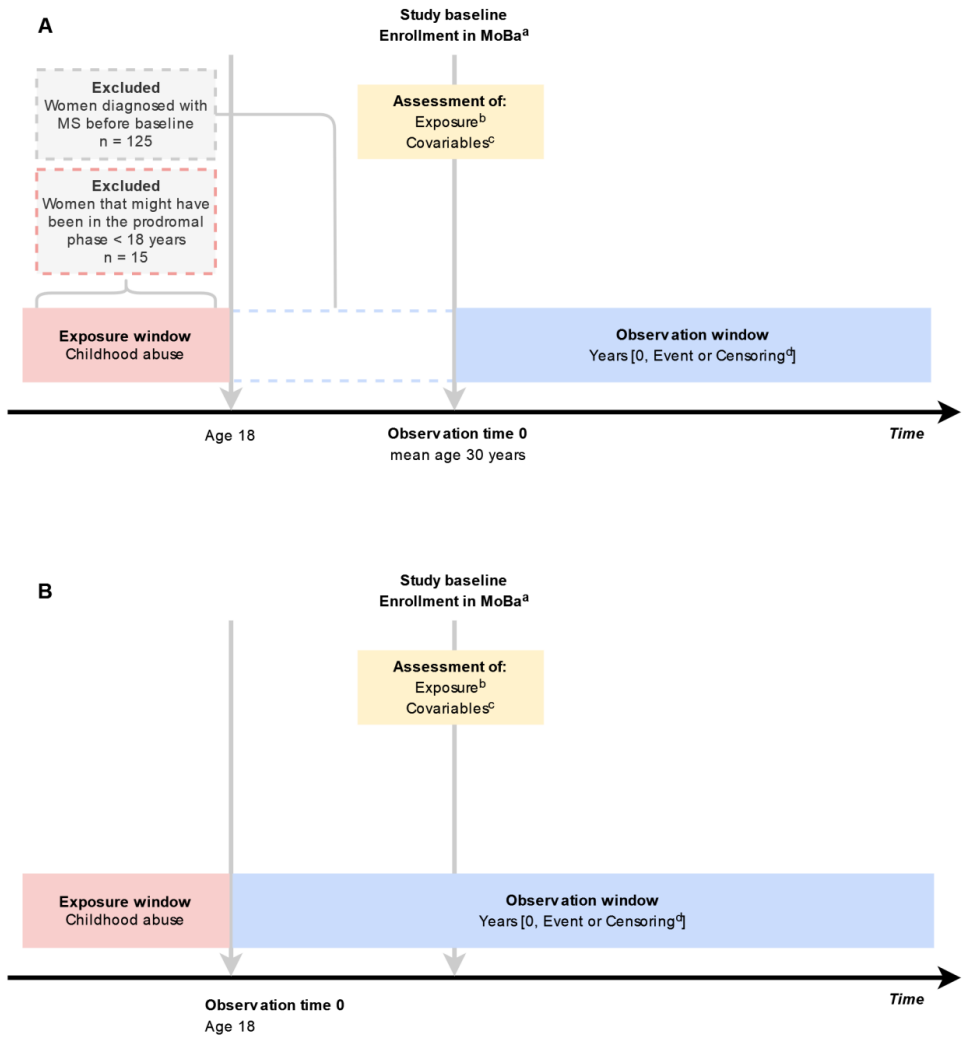
Supplementary figure 1. Study Design of the Main Analysis



Abbreviations: MoBa = The Norwegian Mother, Father and Child cohort study; MS = Multiple sclerosis

[a] Enrollment in MoBa took place in pregnancy weeks 15–18
[b] Exposure (childhood abuse) was assessed through self-completed questionnaires in pregnancy week 30
[c] Covariables were assessed through self-completed questionnaires in pregnancy week 18 and through data-linkage with the Norwegian Medical Birth Registry
[d] End of follow-up was December 31, 2018

Supplementary figure 2: Study Design of the Sensitivity Analyses



Abbreviations: MoBa = The Norwegian Mother, Father and Child cohort study; MS = Multiple sclerosis

A: Sensitivity analysis with exclusion of women that might have been in the prodromal phase of MS when exposed to abuse (< 18 years).

B: Sensitivity analysis with all women in MoBa with MS, both prevalent and incident diagnoses.

[a] Enrollment in MoBa took place in pregnancy weeks 15–18
[b] Exposure (childhood abuse) was assessed through self-completed questionnaires in pregnancy week 30
[c] Covariables were assessed through self-completed questionnaires in pregnancy week 18 and through data-linkage with the Norwegian Medical Birth Registry
[d] End of follow-up was December 31st, 2018

Supplementary table 1. Hazard Ratios of Multiple Sclerosis by Type of Childhood Abuse: Excluding Women with First Clinical Symptom of MS Before Age 23 Years

Exposure	N (%) Total cohort	N (%) Women with MS	HR[a]	HR[b]
No childhood abuse: ref	63 508 (81)	217 (76)	Ref	Ref
Any childhood abuse	14 474 (19)	68 (24)	1.39 (1.05–1.82)	1.35 (1.02–1.79)
Emotional abuse	10 699 (14)	53 (20)	1.47 (1.08–1.98)	1.40 (1.01–1.95)
Emotional abuse: Humiliation	9412 (13)	46 (17)	1.44 (1.05–1.99)	1.42 (1.02–1.97)
Emotional abuse: Threat	3405 (5)	19 (8)	1.62 (1.01–2.60)	1.52 (0.93–2.47)
Sexual abuse	5415 (8)	33 (13)	1.80 (1.25–2.61)	1.77 (1.22–2.57)
Physical abuse	4287 (6)	22 (9)	1.50 (0.97–2.34)	1.41 (0.90–2.23)

Abbreviations: MS= Multiple sclerosis; HR = Hazard ratio

Of the 300 women who developed MS during the follow-up period, 15 women had their first clinical symptom of MS up to the age of 22 years and were excluded in this sensitivity analysis.

[a] Hazard ratios adjusted for school dropout (≤ 9 years elementary school). Birth year was included as a stratification factor in the Cox model.

[b] Hazard ratios adjusted for adverse socioeconomic factors (≤ 9 years elementary school, single mother or low household income), smoking (ever vs. never) and BMI≥ 25 before study baseline). Birth year was included as a stratification factor in the Cox model. No other covariable violated the proportional hazard assumption.

Supplementary table 2. Hazard Ratios of Multiple Sclerosis by Type of Childhood Abuse: Including All Women with MS in the MoBa Study

Exposure	N (%) Total cohort	N (%) Women with MS	HR[a]	HR[b]
No childhood abuse: ref	63 596 (81)	306 (77)	Ref	Ref
Any childhood abuse	14 497 (19)	91 (23)	1.33 (1.05–1.68)	1.29 (1.02–1.65)
Emotional abuse	10 717 (14)	71 (19)	1.40 (1.08–1.82)	1.37 (1.05–1.79)
Emotional abuse: Humiliation	9426 (13)	60 (16)	1.34 (1.01–1.77)	1.32 (0.99–1.75)
Emotional abuse: Threat	3412 (5)	26 (8)	1.64 (1.10–2.46)	1.49 (0.98–2.27)
Sexual abuse	5421 (8)	39 (11)	1.55 (1.11–2.17)	1.46 (1.04–2.06)
Physical abuse	4293 (6)	28 (8)	1.40 (0.95–2.06)	1.32 (0.88–1.96)

Abbreviations: MS= Multiple sclerosis; MoBa = The Norwegian Mother, Father and Child cohort study; HR = Hazard ratio
Sensitivity analysis with all the women with MS in the MoBa-study. Observation time calculated from age 18 years to event. Of the 125 women with current MS diagnosis at the time of enrollment in MoBa, 91 were eligible to be included in the cox regression analyses.

[a] Hazard ratios adjusted for school dropout (≤ 9 years elementary school) and stratified by birthyear

[b] Hazard ratios adjusted for adverse socioeconomic factors (≤ 9 years elementary school, single mother or low household income), smoking (ever vs. never) and BMI≥ 25 before study baseline) and stratified by birthyear

Supplementary table 3. Characteristics of Participants with Missing Data Compared to the Study Population

	Non-responders Q3[a] n = 7633	Missing abuse items[b] n = 617	Study population n = 77 997
Age at study baseline[c]; mean (SD)	30 (5)	30 (5)	30 (5)
Missing; n (%)	-	-	1 (< 1)
Adverse socioeconomic status[d]; n (%)	1368 (11)	147 (24)	8137 (10)
Missing; n (%)	11 (< 1)	43 (7)	873 (1)
Low household income; n (%)	847 (11)	88 (14)	5520 (7)
Maternal short education; n (%)	369 (5)	60 (10)	1551 (2)
Single mother; n (%)	367 (5)	32 (5)	1774 (2)
Ever smoker; n (%)	4241 (56)	294 (48)	39 533 (51)
Missing; n (%)	83 (1)	44 (7)	1140 (2)
BMI ≥ 25; n (%)	2290 (30)	145 (24)	23 681 (30)
Missing; n (%)	326 (4)	78 (13)	2701 (4)
Depression at study baseline (pregnancy)[e]; n (%)	n/a	49 (8)	7305 (9)
Missing; n (%)	n/a	31 (54)	552 (< 1)

Abbreviations: SD = Standard deviation; BMI = Body Mass Index; Q = Questionnaire

[a] 7633 women who responded to the first questionnaire in pregnancy week 18 did not respond to the questionnaire in pregnancy week 30 (Q3)

[b] 617 women responded to Q3, but did not complete the abuse-items

[c] Study baseline is the year of enrollment in the MoBa-study

[d] Low household income (< 60% of median income in the given year of study baseline), being a single mother, or completed ≤ 9 years of school.

[e] Depression was measured by a validated short version of the Hopkins Symptom Checklist in pregnancy week 30. Not available for those who did not respond to Q3.

II

Journal of Neurology (2022) 269:5901–5909
https://doi.org/10.1007/s00415-022-11249-x

ORIGINAL COMMUNICATION

Abuse and revictimization in adulthood in multiple sclerosis: a cross-sectional study during pregnancy

Karine Eid[1,2] · Øivind Torkildsen[2,3] · Jan Aarseth[3,4] · Elisabeth G. Celius[5,6] · Marianna Cortese[2] · Trygve Holmøy[6,7] · Akash Kapali[8] · Kjell-Morten Myhr[2,3] · Cecilie F. Torkildsen[2,9] · Stig Wergeland[3,4] · Nils Erik Gilhus[1,2] · Marte-Helene Bjørk[1,2]

Received: 28 April 2022 / Revised: 17 June 2022 / Accepted: 20 June 2022 / Published online: 3 July 2022

Abstract

Background Knowledge concerning exposure to abuse in adulthood and in pregnancy in people with multiple sclerosis (MS) is sparse.

Objective To determine the occurrence of adult abuse and abuse in relation to pregnancy in women with MS and their risk of revictimization (repeated abuse as adults after childhood abuse).

Methods This cross-sectional study comprised pregnant women from the Norwegian Mother, Father and Child Cohort study. Information on abuse was acquired through self-completed questionnaires. We used logistic regression to estimate adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

Results We identified 106 women with MS at enrollment through linkage with national health registries. The reference group consisted of 77,278 women without MS. Twenty-seven women (26%) with MS reported any adult abuse compared to 15,491 women (20%) without MS, aOR 1.33 (0.85–2.09). Twenty-two (21%) women with MS reported systematic emotional abuse compared to 13% without MS, aOR 1.75 (1.08–2.83). Ten women (10%) with MS reported sexual abuse, compared to 6% without MS, aOR 1.72 (0.89–3.33). More women with MS reported rape as an adult, aOR 2.37 (1.02–5.49). Women with MS had higher risk of revictimization as adults, after childhood abuse, aOR 2.23 (1.22–4.10). The risk of abuse during pregnancy or 6 months preceding pregnancy was similar between the groups.

Conclusions Women with MS had increased occurrence of systematic emotional abuse, rape, and revictimization as adults, compared to women without MS.

Keywords Violence · Revictimization · The Norwegian Mother, Father, and Child Cohort study · MoBa · The Medical Birth Registry of Norway

✉ Karine Eid
karine.eid@uib.no

[1] Department of Neurology, Haukeland University Hospital, Jonas Lies vei 71, 5053 Bergen, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Neurology, Neuro-SysMed, Haukeland University Hospital, Bergen, Norway

[4] The Norwegian Multiple Sclerosis Registry and Biobank, Haukeland University Hospital, Bergen, Norway

[5] Department of Neurology, Oslo University Hospital, Oslo, Norway

[6] Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[7] Department of Neurology, Akershus University Hospital, Lørenskog, Norway

[8] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[9] Department of Obstetrics and Gynecology, Stavanger University Hospital, Stavanger, Norway

Introduction

People with multiple sclerosis (MS) are more often exposed to abuse and neglect in childhood than the general population [1–4]. Mistreatment in childhood is a strong predictor of abuse later in life, known as revictimization [5]. It is not known whether abuse occurs more frequently in adulthood or during pregnancy for people with MS. However, people with physical impairment or activity limitations are at increased risk of experiencing any forms of sexual, physical, or emotional mistreatment [6, 7], including partner violence [8].

A US study found that 55% of people with advanced MS reported maltreatment by unpaid caregivers [9], most frequently emotional abuse. A focus group study found that people with advanced MS were reluctant to report being abused even though the caregiver admitted mistreatment [10]. No previous study has examined the occurrence of abuse in adulthood or the relationship to the abuser in general MS populations. Moreover, no study has examined the risk of experiencing abuse during pregnancy in women with MS.

Experiencing abuse has long-term consequences for mental and physical health [11]. Women who have previously experienced abuse may be more vulnerable for abuse during pregnancy [12]. Abuse during pregnancy is of particular concern due to the increased risk of adverse maternal and neonatal outcomes [13]. We have previously found that a history of physical or sexual abuse was a risk factor for perinatal depression in women with MS [14]. There is a need for increased attention to this issue to protect people with MS at risk and to support and provide trauma-informed care [15] for those in need.

Our aim was to investigate the occurrence of abuse in adulthood in pregnant women with MS and their risk of experiencing revictimization after childhood abuse. Further, we aimed to study their relationship to the abuser.

Materials and methods

Study design and data collection

We conducted a cross-sectional analysis based on questionnaire data from all women participating in the Norwegian Mother, Father, and Child Cohort Study (MoBa). MoBa is a nationwide, prospective cohort study, which included Norwegian-speaking pregnant women from all over Norway between 1999 and 2008 [16]. There were no exclusion criteria, and 41% of the invited women consented to participation. The MoBa cohort is linked to The Medical Birth Registry of Norway (MBRN), a nationwide medical registry containing information about all births in Norway. Registration of information in the MBRN is mandatory and performed by health personnel.

We acquired information on demographic and socioeconomic factors, medical history, and any experience of abuse from questionnaires self-administered during pregnancy weeks 17–20 and 30.

Our study is based on version 12 of the MoBa data files, covering 114,629 pregnancies. We included women who completed both the questionnaire in pregnancy week 18 and week 30, including the abuse items. To include only one observation per woman, we excluded duplicate questionnaires due to twin and triplet pregnancies and additional questionnaires from women with recurrent participations in MoBa (Fig. 1). We also excluded women who were under age 18 years at inclusion.

MS diagnosis

To validate the self-reported MS diagnosis from the questionnaires, we cross-linked the MoBa cohort with the Norwegian Patient Registry (NPR) and the Norwegian Multiple Sclerosis Registry and Biobank (The MS Registry). We also included information from hospital records. After every consultation in specialist care, registration of all relevant diagnoses in NPR is mandatory for health practitioners. The MS diagnosis in NPR has a sensitivity of 97% and a positive predictive value of 0.92 [17]. We considered the MS diagnosis as validated if registered both in the NPR and in the MS registry. The MS registry had 69% national coverage at the time of data linkage [18]. If an MS diagnosis was registered only in NPR but not in the MS registry, we reviewed hospital records to validate the diagnosis using the 2017 diagnostic criteria for MS [19]. The linkage made it possible to identify women with MS who failed to report a history of MS at inclusion in MoBa ($n=4$). We were also able to refute incorrect MS diagnoses from the NPR based on the information from the hospital records. NPR-identified MS cases not included in the MS registry and without access to the hospital records for validation were excluded (Fig. 1). This data linkage also identified women who developed MS after inclusion in MoBa up until December 31, 2018 (date of data linkage). These women were excluded from the main analyses but included in a sensitivity analysis.

Abuse experience

Abuse categories

In pregnancy week 30, the women answered four questions concerning experiences of abuse (Questionnaire S1); emotional abuse—humiliation ("Has anyone over a long

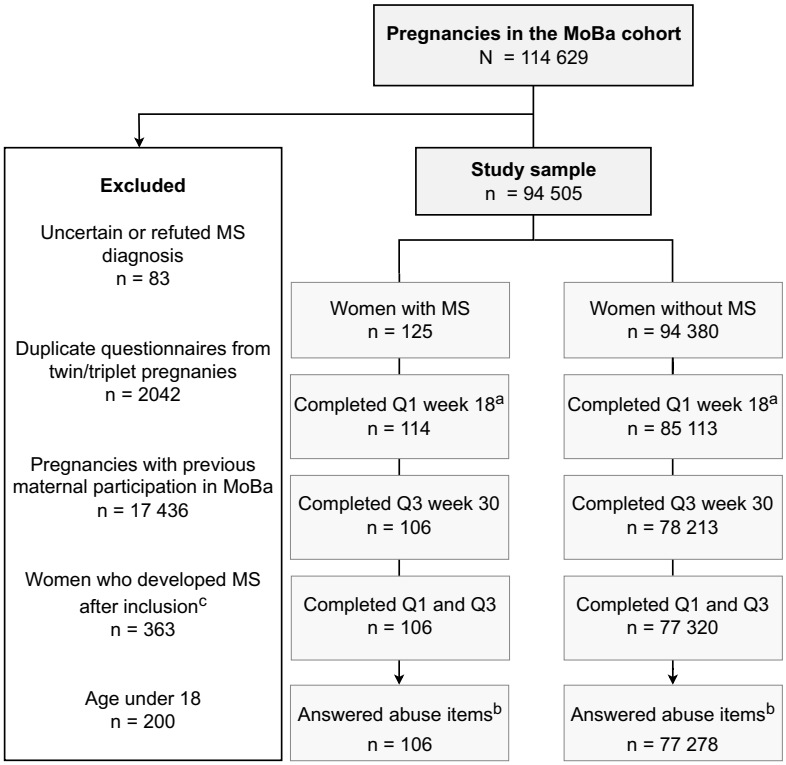


Fig. 1 Flowchart of included and excluded study participants. *MoBa* The Norwegian Mother, Father and Child cohort study, *MS* multiple sclerosis, *Q* Questionnaire. [a]Pregnancy week 17–20 (Q1). [b]Women who completed the abuse questions in either week 17–20 (Q1) or week 30 (Q3) were included in our study. [c]Women who developed MS after inclusion in MoBa until December 31, 2018 (date of data linkage) were excluded from the reference group

period of time systematically tried to subdue, degrade or humiliate you?"), emotional abuse—threat ("Has anyone threatened to hurt you or someone close to you?"), physical abuse ("Have you been subjected to physical abuse?"), and sexual abuse ("Have you been forced to do sexual actions?"). The question regarding humiliation was considered as systematic emotional abuse. The abuse questions in MoBa have been adapted from the NorVold Abuse Questionnaire showing good validity and reliability [20].

An experience of either emotional, sexual, or physical abuse as an adult was defined as responding "yes, as an adult > 18 years" to the respective categories.

Type and severity of sexual abuse in were assessed in the questionnaire in weeks 17–20; "Have you ever been pressured or forced to have sexual intercourse during this pregnancy, the last 6 months before pregnancy, or earlier?" The response options were "yes, pressured", "yes, forced with violence" and "yes, raped." We merged "forced with violence" and "rape" into one category of rape. This question did not distinguish between childhood and adulthood. We considered an experience of rape > 18 years of age if the woman also had reported sexual abuse as an adult in the questionnaire in week 30. Women who answered "no, never" were categorized as not having experienced rape.

Childhood abuse and revictimization

An experience of childhood abuse was defined as responding "yes, as a child < 18 years" to any of the abuse categories in the questionnaire in week 30. Women were defined as revictimized if they reported either emotional, sexual, or physical abuse both as a child (< 18 years) and as an adult (> 18 years).

Perpetrator

The questionnaire in week 30 included a question regarding the person responsible of abuse; "Who was responsible for this?". The options were: "A stranger", "Family or relative", or "Another known person".

Abuse during pregnancy or in the 6 months preceding pregnancy

The questionnaire in weeks 17–20 included two questions regarding whether the woman had experienced physical or sexual abuse during the current pregnancy or the last 6 months before pregnancy. These questions have been modified from the Abuse Assessment Screen, developed to detect abuse among pregnant women [21]. The women could also state in the week 30 questionnaire if the abuse had happened during the last 12 months. As the women were 7 months pregnant at this assessment, this comprised abuse during pregnancy and up to 5 months before pregnancy. Women who answered "yes" to either of these questions were defined as having experienced abuse during the current pregnancy or in the last 6 months before pregnancy.

Covariables

MS-specific covariables were obtained from the MS registry and hospital records: Age at MS onset (defined as first clinical symptom), age at MS diagnosis, and subtype of MS (relapsing–remitting, primary progressive, or unspecified). Other covariables were acquired through the self-completed MoBa questionnaires or through linkage to the MBRN: age, smoking (ever/never), body mass index (BMI) prior to pregnancy ($<25/\geq 25$ kg/m^2), alcohol use ≥ 1 occasion per month during the first trimester or substance use (cannabis, amphetamine, ecstasy, cocaine, heroin) the last month before or during pregnancy. Adverse socioeconomic status in adulthood was defined as either having low household income (< 60% of the study population median income in the year of participation), being a non-cohabiting mother, or having low level of education (≤ 9 years of school). Low education level of the partner was defined as ≤ 9 years of school. Depression during pregnancy was measured by a validated short version of the Hopkins Symptom Checklist 25 [22], included in the same questionnaire as the abuse questions.

Statistical analysis

The MS group was compared to a reference group of all women in MoBa without MS. We analyzed the risk for experiencing abuse by logistic regression with estimated odds ratios (ORs) and 95% confidence intervals (CIs). We considered age, history of smoking, overweight, and socioeconomic status (≥ 1 of the following: non-cohabiting mother, low level of education, low household income) as possible confounders and adjusted all models for these covariables. Low education of the woman's partner was adjusted for in a secondary analysis when considering the person responsible of abuse, as this variable could potentially be a mediator for the association between MS and abuse. Depression was regarded as a collider and therefore not adjusted for [23]. Estimates with CIs not including 1 were considered statistically significant. Categorical variables were compared with the Pearson Chi-square test or Fisher exact test if any table cell count was expected to be < 5. Continuous variables were compared with t tests. We performed interaction analyses with logistic regression models by including interaction terms between the exposure (MS) and (1) low socioeconomic status and (2) childhood abuse on the outcome (adult abuse), adjusted for potential confounders. This was done to investigate whether women with MS were more susceptible to abuse as adults if they had low socioeconomic status or had experienced abuse in childhood. Statistical analyses were performed using IBM SPSS Statistics version 26 and Stata version 17 (StataCorp LLC).

Sensitivity analysis

As the questionnaires did not specify the exact period for the abuse experience, we lacked data on the timing of adult abuse with respect to the date of MS diagnosis. We therefore performed a sensitivity analysis comparing abuse risk in women with established MS to women who developed MS after inclusion in MoBa. The aim was to explore the direction of the associations. As women with future MS did not have the vulnerability of having a chronic condition [6, 8], higher rates of abuse in this group could signify that adult abuse predating the diagnosis could be risk or trigger factor for MS [24, 25], or associated with unknown confounders, rather than being a consequence of MS. In this analysis, we excluded women who had their first symptom of MS within 5 years after MoBa inclusion and could have been in a prodromal phase of MS [26].

Results

We identified 106 eligible women with MS and 77,278 women without MS in the cohort at baseline. Women with MS tended to be more depressed, overweight, and with a history of smoking at study baseline, and they more often had a partner with low level of education (Table 1).

Twenty-seven women (26%) with MS reported any category of adult abuse compared to 15,491 women (20%) without MS, adjusted OR (aOR) 1.33 (0.85–2.09) (Table 2). The interaction term between MS and adverse socioeconomic status on the risk of any adult abuse yielded a p value of 0.041.

Twenty-two women (21%) with MS reported systematic emotional abuse in the form of humiliation compared to 9778 women (13%) without MS, aOR 1.75 (1.08–2.83). Ten women (10%) with MS reported sexual abuse, compared to 4280 women (6%) without MS, aOR 1.72 (0.89–3.33).

Table 1 Background characteristics of women with and without MS in MoBa

	Women with MS $n=106$	Women without MS $n=77,278$	p value
Age; mean (SD) [range]	31 (4) [21–42]	30 (5) [18–47]	0.02
Missing; *n* (%)	0 (0)	0 (0)	
Adverse socioeconomic status[a]; *n* (%)	9 (9)	8123 (11)	0.42
Missing; *n* (%)	1 (1)	15 (< 1)	
Low household income; *n* (%)	4 (4)	5492 (7)	
Low level of education; *n* (%)	< 3	1563 (2)	
Non-cohabiting mother; *n* (%)	4 (4)	1754 (2)	
Low level of education partner[b]; *n* (%)	10 (10)	3171 (4)	0.01
Missing; *n* (%)	8 (8)	7033 (9)	
Depression at study baseline[c]; *n* (%)	14 (13)	7162 (9)	0.15
Missing; *n* (%)	2 (2)	795 (1)	
Ever smoker; *n* (%)	57 (54)	39,357 (51)	0.61
Missing; *n* (%)	0 (0)	459 (1)	
BMI ≥ 25 kg/m^2; *n* (%)	37 (35)	23,676 (31)	0.40
Missing; *n* (%)	1 (1)	1911 (3)	
Alcohol or substance use during pregnancy[d]; *n* (%)	4 (4)	2559 (3)	0.78
Missing; *n* (%)	0 (0)	0 (0)	
Age at MS diagnosis; mean (SD) [range]	26 (4) [14–36]	n/a	n/a
Missing; *n* (%)	7 (7)		
Age at MS onset[e]; mean (SD) [range]	24 (4) [14–36]	n/a	n/a
Missing; *n* (%)	7 (7)		
Type of MS		n/a	n/a
RRMS	94 (89)		
PPMS	< 3		
Uncertain	11 (10)		

P values are calculated from Pearson χ^2 test or Fisher exact test for categorical variables, and *t* test of continuous variables

MoBa The Norwegian Mother, Father and Child cohort study, *MS* multiple sclerosis, *SD* standard deviation, *BMI* body mass index, *RRMS* relapsing remitting multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *n/a* not applicable

[a]Adverse socioeconomic status is one of the following: non-cohabiting mother, low level of education ≤ 9 years of school, low household income (< 60% of the study population median in the enrollment year)

[b] ≤ 9 years of school

[c]Depression was measured through validated short versions of the Hopkins Symptom Checklist-25 during pregnancy week 30

[d]Alcohol use ≥ 1 occasion per month during the first trimester or substance use (cannabis, amphetamine, ecstasy, cocaine, heroin) the last month before or during pregnancy

[e]MS onset defined as the first clinical symptom of MS

Women with MS more often reported to have been raped as an adult (6% vs. 3%), aOR 2.37 (1.02–5.49). The risk of physical or emotional abuse in the form of threats was not increased. Nine women (8%) with MS reported that the abuse had happened during pregnancy or in the 6-month period before pregnancy, compared to 5006 (6%) women without MS, aOR 1.44 (0.72–2.86).

Twenty-two women (21%) with MS had experienced childhood abuse, compared to 14,164 women (19%) without MS, aOR 1.24 (0.77–2.0). Women with MS had a higher risk of experiencing revictimization as adults (abuse both in childhood and adulthood), aOR 2.23 (1.22–4.10) (Table 2). Interaction analysis indicated a synergistic effect between MS and a history of childhood abuse on the risk of experiencing adult abuse ($p=0.054$).

For all categories of abuse, the most common abuser was "another known person" for both women with and without MS (Table S1). For emotional abuse, 7 women with MS (27%) reported a family member or relative as responsible compared to 2474 women (19%) without MS. Very few women ($n<3$) with MS reported a stranger as the abuser. The risk of emotional abuse attenuated when adjusting for

Table 2 Abuse as adults in women with and without MS

	Women with MS $n=106$ Yes/no[a]; *n* (%)	Women without MS $n=77,278$ Yes/no[a]; *n* (%)	OR (95% CI)	aOR[b] (95% CI)
Any adult abuse	27 (26)/78 (74)	15,491 (20)/61,255 (80)	1.37 (0.88–2.12)	1.33 (0.85–2.09)
Emotional abuse	26 (25)/79 (75)	12,764 (17)/63,982 (83)	1.65 (1.06–2.57)	1.61 (1.03–2.53)
Systematic humiliation	22 (21)/83 (79)	9778 (13)/66,968 (87)	1.81 (1.13–2.91)	1.75 (1.08–2.83)
Threat	8 (8)/97 (92)	6065 (8)/70,681 (92)	0.96 (0.47–1.98)	0.93 (0.45–1.93)
Sexual abuse	10 (10)/95 (90)	4280 (6)/72,466 (94)	1.78 (0.93–3.42)	1.72 (0.89–3.33)
Rape[c]	6 (6)/86 (94)	1890 (3)/62,526 (97)	2.31 (1.01–5.29)	2.37 (1.02–5.49)
Physical abuse	3 (3)/102 (97)	4395 (6)/72,351 (94)	0.48 (0.15–1.52)	0.45 (0.14–1.42)
Abused during pregnancy or last 6 months before pregnancy[d]	9 (8)/97 (92)	5006 (6)/72,271 (94)	1.34 (0.68–2.65)	1.44 (0.72–2.86)
Revictimization: adult and childhood abuse	13 (16)/69 (84)	4964 (9)/52,055 (91)	1.98 (1.09–3.58)	2.23 (1.22–4.10)

Total N may differ for some of the abuse categories because of different response rates to the different abuse items and different definitions of «no abuse». Of the 106 women with MS, 1 woman answered the abuse questions in Q1 but not in Q3. Of the 77,278 women without MS, 532 women answered the Q1 abuse questions but not the Q3 abuse questions

MS multiple sclerosis, *OR* odds ratio, *CI* confidence interval

[a]«No» means "no adult abuse" for the respective type of adult abuse category (emotional, sexual, physical). For "rape", «no» means no experience of sexual abuse. For "abused during pregnancy or last 6 months before pregnancy" «no» means either previous or no experience of abuse. For "Revictimization", «no» means no exposure to neither childhood nor adult abuse

[b]Odds ratios are adjusted for age and adverse socioeconomic status

[c]Based on one question from the questionnaire in pregnancy weeks 17–20 (Q1) and combined with a report of sexual abuse as an adult in week 30 (Q3)

[d]Based on questions from the questionnaire in weeks 17–20 (Q1) ("during this pregnancy" or "last 6 months before pregnancy") and the question in week 30 (Q3) ("have this occurred during the last 12 months")

partner education in addition to the potential confounders, aOR 1.39 (0.86–2.26). The risk of sexual abuse was slightly increased, aOR 1.84 (0.95–3.58), after this additional adjustment. The risk of physical abuse remained unchanged.

Sensitivity analysis

We found an increased risk of emotional abuse for women with MS when comparing them to women who developed MS in the future (≥ 5 years after study inclusion), aOR 2.79 (1.24–6.25) (Table S2). The aOR was 2.37 (0.76–7.46) for sexual abuse and 0.72 (0.15–3.55) for physical abuse.

Discussion

Our study found an increased risk of emotional abuse as well as rape in adulthood in women with MS. For emotional abuse, the risk was highest for systematic humiliation. Furthermore, women with MS had a higher occurrence of revictimization compared to women without MS.

Our population-based study extends previous knowledge on abuse in women with MS. A previous cross-sectional study examined abuse by caregivers and found that this occurred in 55% of 206 people with MS who needed assistance or care from family or friends; this compared to 26% in our population. The previous study selected MS patients with advanced disease and had a response rate of only 17%. Thus, their prevalence estimates are not directly comparable.

We found an increased risk of revictimization in women with MS. The interaction analysis indicated that having experienced abuse in childhood may increase the risk of abuse in adulthood to a larger extent in women with MS than in women without MS. Childhood abuse is a known risk factor for abuse as adults in the general population [5]. Factors associated with an increased risk of revictimization are exposure to multiple forms of childhood abuse [5, 27] and feeling shame [28].

Women with MS most often reported "another known person" as responsible for all the types of adult abuse. When adjusting the estimates for low partner education, the risk of emotional abuse decreased. In contrast, the risk of sexual abuse increased. This may indicate an association between emotional abuse and a low education in the current partner, but not so for sexual abuse. Emotional abuse was the most common abuse category in our study, similar to the previous study on caregiver abuse [9]. Sexual abuse was the least reported type of abuse by the caregivers [9]. Caregivers of people with MS often experience high levels of stress [29]. Low level of education increased the risk for fatigue and mental health problems in caregivers of MS patients [30]. Caregiver mental health problems increased

the risk for caregiver abuse in people with advanced MS [9]. Increased focus on information, support, and the healthcare needs of caregivers could therefore potentially reduce the abuse risk of women with MS.

We found an interactive effect between MS and an adverse socioeconomic status the risk of abuse, meaning that women with MS and adverse socioeconomic status were more susceptible to abuse compared to women without MS who had the same socioeconomic status. Other risk factors for abuse among adults with disabilities are depression, anxiety, and impaired cognition [7, 31–33]. Neurologists should be aware of these associations, as these symptoms occur with increased frequency in MS [34–36].

The risk of abuse in the months preceding or during pregnancy was not increased in women with MS compared to women without MS. However, as many as 8% of women with MS had experienced abuse in close relation to pregnancy. Abuse during pregnancy is of particular concern because of the increased risk of physical and mental pregnancy complications [13], including perinatal depression [14].

Strengths of our study include the use of a population-based dataset with a thorough validation of the MS diagnoses. We have detailed information regarding different categories of abuse, and we adjusted for relevant confounders. Our study has some limitations. We do not know the timing of the abuse in relation to the timing of the MS diagnosis. However, we found that women with established MS had higher risk of emotional abuse compared to women who got MS more than 5 years after our assessment. This suggests that women with MS may have experienced emotional abuse because of increased vulnerability due to a manifest disease [6–8]. Our study has a limited sample size, which resulted in few cases in some of the abuse subcategories. Women with MS in our study were young and had short disease duration, which may limit the generalizability to what people with MS experiences during the life and disease course. We had no information on MS severity. However, we studied pregnant women with MS, who constitute a physically healthy and less disabled part of the MS population with low Expanded Disability Status Scale scores [37–40]. Therefore, physical disability should not represent a major determinant for our findings. The MoBa cohort has a participation rate of 41%, which may result in lower generalizability. However, similar response rates are considered acceptable for large prospective studies [41]. Women with Norwegian ethnicity and high socioeconomic status are overrepresented in the MoBa cohort [42], which may influence the generalizability to the whole maternal population. Nonparticipation and the underrepresentation of women with adverse socioeconomic status may underestimate the abuse prevalence but should not affect the exposure-outcome associations [41–44].

In conclusion, we found increased risk of systematic emotional abuse, rape, and revictimization in adulthood in women with MS compared to women without MS. Women with adverse socioeconomic status had a particularly increased risk. Clinicians should be aware of these associations when treating women with MS, as abuse experiences have severe and long-term impact on physical and mental health.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11249-x.

Acknowledgements The Norwegian Mother, Father and Child Cohort study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We acknowledge Alok Bhan MD (Department of Neurology, Stavanger University Hospital, Stavanger, Norway); Heidi Ø. Flemmen MD (Department of Neurology, Telemark Hospital Trust, Skien, Norway); Åslaug R. Lorentzen MD PhD (Department of Neurology, Sørlandet Hospital, Kristiansand, Norway); Kathrine K. Lian MD (Department of Neurology, St. Olavs Hospital, Trondheim, Norway), Stephan Schüler MD PhD (Department of Neurology, Namsos Hospital, Namsos, Norway); Cecilia S. Simonsen MD (Department of Neurology, Vestre Viken Hospital Trust, Drammen, Norway); Johannes Sverre Willumsen MD (Department of Neurology, Molde Hospital, Molde, Norway); Nina Øksendal MD (Department of Neurology, Nordland Hospital Trust, Bodø, Norway); Barbara Ratajczak-Tretel MD (Department of Neurology, Østfold Hospital, Østfold, Norway); Britt Bruland CNS (Department of Neurology, Førde Hospital, Førde, Norway) for contributing with data extraction and validation of MS diagnoses. We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

Author contributions KE, ØFT, JA, K-MM, CFT, SW, N-EG, M-HB performed conceptualization; KE and M-HB did methodology; KE done formal analysis and investigation, writing—original draft preparation; all authors contributed to writing—review and editing; KE, M-HB were involved in funding acquisition; ØFT, NEG, M-HB supervised the study.

Funding Open access funding provided by University of Bergen (incl Haukeland University Hospital). K. Eid has governmental funding (doctoral scholarship) from the Western Norway Regional Health Authority [Grant number F-12503]. Neuro-SysMed is funded by the Norwegian Research Council [Grant number 288164].

Data availability Enquiries regarding access to data from MoBa and the MBRN can be directed to the Norwegian Institute of Public Health. Data from the MS Registry are accessible for researchers by application [45].

Declarations

Conflicts of interest K. Eid has received unrestricted research grant and speaker honoraria from Novartis. Ø. Torkildsen has received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis. J. Aarseth has no competing interests to declare that are relevant to the content of this article. E. G. Celius has received honoraria for lecturing and advice from Biogen, Bristol Meyers Squibb, Janssen, Novartis, Merck, Roche and Sanofi, and her department has received grants from Novartis and Sanofi. M. Cortese has no competing interests to declare that are relevant to the content of this article. T. Holmøy has received speaker honoraria

from Biogen, Merck, Novartis, Roche, Bristol Myers Squibb, and Sanofi and has participated in clinical trials organized by Biogen, Merck, and Roche. A. Kapali has no competing interests to declare that are relevant to the content of this article. K.M. Myhr has received unrestricted research grants to his institution; scientific advisory board and speaker honoraria from Biogen, Merck, Novartis, Roche, and Sanofi and has participated in clinical trials organized by Biogen, Merck, Novartis, Roche, and Sanofi. C.F. Torkildsen has served on scientific advisory board for Astra Zeneca. S. Wergeland has received honoraria from Biogen, Novartis, Janssen, and Sanofi. N.E. Gilhus has received honoraria from UCB, Ra, Argenx, Roche, Merck, Immunovant, Alexion. M.H. Bjørk has received personal honoraria for lecturing from Teva, Lilly, Eisai, and Novartis, consultancy honoraria from Jazz pharmaceuticals, Lundbeck and Novartis, unrestricted research support from Novartis and institutional contract research fees from Sanofi.

Ethics approval The establishment of MoBa was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committees for Medical and Health Research Ethics (REK). The MoBa cohort is regulated by the Norwegian Health Registry Act. Ethics approval for the current study was obtained from REK (reference 2016/906).

Informed consent Written informed consent for use of information in research and for data linkage was acquired during enrollment in MoBa and the MS Registry.

References

1. Spitzer C, Bouchain M, Winkler LY, Wingenfeld K, Gold SM, Grabe HJ, Barnow S, Otte C, Heesen C (2012) Childhood trauma in multiple sclerosis: a case-control study. Psychosom Med 74:312–318. https://doi.org/10.1097/PSY.0b013e31824c2013
2. Shaw MT, Pawlak NO, Frontario A, Sherman K, Krupp LB, Charvet LE (2017) Adverse childhood experiences are linked to age of onset and reading recognition in multiple sclerosis. Front Neurol 8:242. https://doi.org/10.3389/fneur.2017.00242
3. Wan A, Bernstein CN, Graff LA, Patten SB, Sareen J, Fisk JD, Bolton JM, Hitchon C, Marriott JJ, Marrie RA, Burden CTiDt, Managing the Effects of Immune-mediated Inflammatory D (2022) Childhood maltreatment and psychiatric comorbidity in immune-mediated inflammatory disorders. Psychosom Med 84:10–19. https://doi.org/10.1097/PSY.0000000000001025
4. Eid K, Torkildsen O, Aarseth J, Aalstad M, Bhan A, Celius EG, Cortese M, Daltveit AK, Holmoy T, Myhr KM, Riise T, Schuler S, Torkildsen CF, Wergeland S, Gilhus NE, Bjork MH (2022) Association of adverse childhood experiences with the development of multiple sclerosis. J Neurol Neurosurg Psychiatry. https://doi.org/10.1136/jnnp-2021-328700
5. Butler N, Quigg Z, Bellis MA (2020) Cycles of violence in England and Wales: the contribution of childhood abuse to risk of violence revictimisation in adulthood. BMC Med 18:325. https://doi.org/10.1186/s12916-020-01788-3
6. Plummer SB, Findley PA (2012) Women with disabilities' experience with physical and sexual abuse: review of the literature and implications for the field. Trauma Violence Abuse 13:15–29. https://doi.org/10.1177/1524838011426014
7. Dammeyer J, Chapman M (2018) A national survey on violence and discrimination among people with disabilities. BMC Public Health 18:355. https://doi.org/10.1186/s12889-018-5277-0
8. Cohen MM, Forte T, Du Mont J, Hyman I, Romans S (2005) Intimate partner violence among Canadian women with activity limitations. J Epidemiol Community Health 59:834–839. https://doi.org/10.1136/jech.2004.022467
9. Morrison EH, Sorkin D, Mosqueda L, Ayutyanont N (2020) Abuse and neglect of people with multiple sclerosis: a survey with the North American Research Committee on Multiple Sclerosis (NARCOMS). Mult Scler Relat Disord 46:102530. https://doi.org/10.1016/j.msard.2020.102530
10. Shapiro J, Wiglesworth A, Morrison EH (2013) Views on disclosing mistreatment: a focus group study of differences between people with MS and their caregivers. Mult Scler Relat Disord 2:96–102. https://doi.org/10.1016/j.msard.2012.09.006
11. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS (1998) Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14:245–258. https://doi.org/10.1016/s0749-3797(98)00017-8
12. Taillieu TL, Brownridge DA (2010) Violence against pregnant women: prevalence, patterns, risk factors, theories, and directions for future research. Aggress Violent Beh 15:14–35. https://doi.org/10.1016/j.avb.2009.07.013
13. Alhusen JL, Ray E, Sharps P, Bullock L (2015) Intimate partner violence during pregnancy: maternal and neonatal outcomes. J Womens Health (Larchmt) 24:100–106. https://doi.org/10.1089/jwh.2014.4872
14. Eid K, Torkildsen OF, Aarseth J, Flemmen HO, Holmoy T, Lorentzen AR, Myhr KM, Riise T, Simonsen C, Torkildsen CF, Wergeland S, Willumsen JS, Oksendal N, Gilhus NE, Bjork MH (2021) Perinatal depression and anxiety in women with multiple sclerosis: a population-based cohort study. Neurology 96:e2789–e2800. https://doi.org/10.1212/WNL.0000000000012062
15. Raja S, Hasnain M, Hoersch M, Gove-Yin S, Rajagopalan C (2015) Trauma informed care in medicine: current knowledge and future research directions. Fam Community Health 38:216–226. https://doi.org/10.1097/FCH.0000000000000071
16. Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, Handal M, Haugen M, Hoiseth G, Knudsen GP, Paltiel L, Schreuder P, Tambs K, Vold L, Stoltenberg C (2016) Cohort profile update: the Norwegian mother and child cohort study (MoBa). Int J Epidemiol 45:382–388. https://doi.org/10.1093/ije/dyw029
17. Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB (2019) Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry. Brain Behav 9:e01422. https://doi.org/10.1002/brb3.1422
18. The Norwegian Directorate of Health [Helsedirektoratet]. Analysis of National Coverage: The Norwegian MS Registry and Biobank 2008–2016 [Dekningsgradsanalyse: Norsk MS-register og biobank 2008–2016] https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr/innhold-og-kvalitet-i-npr/16-13323-12%20Dekningsgrad_rapport_MS_4.pdf/_/attachment/inline/851b6ae3-76d3-48e0-a297-1838565bf0e0:0c2af0b445da062adbc8

c038a6d9df79c470853a/16-13323-12%20Dekningsgrad_rapport_MS_4.pdf2022
19. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintore M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162–173. https://doi.org/10.1016/S1474-4422(17)30470-2
20. Swahnberg IM, Wijma B (2003) The NorVold Abuse Questionnaire (NorAQ): validation of new measures of emotional, physical, and sexual abuse, and abuse in the health care system among women. Eur J Public Health 13:361–366. https://doi.org/10.1093/eurpub/13.4.361
21. McFarlane J, Parker B, Soeken K, Bullock L (1992) Assessing for abuse during pregnancy. Severity and frequency of injuries and associated entry into prenatal care. JAMA 267:3176–3178. https://doi.org/10.1001/jama.267.23.3176
22. Tambs K, Moum T (1993) How well can a few questionnaire items indicate anxiety and depression? Acta Psychiatr Scand 87:364–367
23. Lu H, Cole SR, Platt RW, Schisterman EF (2021) Revisiting overadjustment bias. Epidemiology 32:e22–e23. https://doi.org/10.1097/EDE.0000000000001377
24. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernandez de la Cruz L, Almqvist C, Fall K, Valdimarsdottir UA (2018) Association of stress-related disorders with subsequent autoimmune disease. JAMA 319:2388–2400. https://doi.org/10.1001/jama.2018.7028
25. Jiang X, Olsson T, Hillert J, Kockum I, Alfredsson L (2020) Stressful life events are associated with the risk of multiple sclerosis. Eur J Neurol 27:2539–2548. https://doi.org/10.1111/ene.14458
26. Wijnands JM, Zhu F, Kingwell E, Zhao Y, Ekuma O, Lu X, Evans C, Fisk JD, Marrie RA, Tremlett H (2019) Five years before multiple sclerosis onset: phenotyping the prodrome. Mult Scler 25:1092–1101. https://doi.org/10.1177/1352458518783662
27. Coid J, Petruckevitch A, Feder G, Chung W, Richardson J, Moorey S (2001) Relation between childhood sexual and physical abuse and risk of revictimisation in women: a cross-sectional survey. Lancet 358:450–454. https://doi.org/10.1016/s0140-6736(01)05622-7
28. Aakvaag HF, Thoresen S, Wentzel-Larsen T, Dyb G (2017) Adult victimization in female survivors of childhood violence and abuse: the contribution of multiple types of violence. Violence Against Women 23:1601–1619. https://doi.org/10.1177/1077801216664427
29. Maguire R, Maguire P (2020) Caregiver burden in multiple sclerosis: recent trends and future directions. Curr Neurol Neurosci Rep 20:18. https://doi.org/10.1007/s11910-020-01043-5
30. Petrikis P, Baldouma A, Katsanos AH, Konitsiotis S, Giannopoulos S (2019) Quality of life and emotional strain in caregivers of patients with multiple sclerosis. J Clin Neurol 15:77–83. https://doi.org/10.3988/jcn.2019.15.1.77
31. Majeed-Ariss R, Rodriguez PM, White C (2020) The disproportionately high prevalence of learning disabilities amongst adults attending Saint Marys Sexual Assault Referral Centre. J Appl Res Intellect Disabil 33:595–603. https://doi.org/10.1111/jar.12703
32. Dong X, Simon M, Beck T, Evans D (2014) Decline in cognitive function and elder mistreatment: findings from the Chicago Health and Aging Project. Am J Geriatr Psychiatry 22:598–605. https://doi.org/10.1016/j.jagp.2012.11.004
33. Nosek MA, Hughes RB, Taylor HB, Taylor P (2006) Disability, psychosocial, and demographic characteristics of abused women with physical disabilities. Violence Against Women 12:838–850. https://doi.org/10.1177/1077801206292671
34. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, Uitdehaag BMJ (2017) Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. J Neurol Sci 372:331–341. https://doi.org/10.1016/j.jns.2016.11.067
35. Benedict RHB, Amato MP, DeLuca J, Geurts JJG (2020) Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol 19:860–871. https://doi.org/10.1016/S1474-4422(20)30277-5
36. Sparaco M, Lavorgna L, Bonavita S (2021) Psychiatric disorders in multiple sclerosis. J Neurol 268:45–60. https://doi.org/10.1007/s00415-019-09426-6
37. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T (1998) Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med 339:285–291. https://doi.org/10.1056/NEJM199807303390501
38. Bsteh G, Algrang L, Hegen H, Auer M, Wurth S, Di Pauli F, Deisenhammer F, Berger T (2020) Pregnancy and multiple sclerosis in the DMT era: a cohort study in Western Austria. Mult Scler 26:69–78. https://doi.org/10.1177/1352458518816614
39. Alroughani R, Alowayesh MS, Ahmed SF, Behbehani R, Al-Hashel J (2018) Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. Neurology 90:e840–e846. https://doi.org/10.1212/WNL.0000000000005065
40. Langer-Gould A, Gupta R, Huang S, Hagan A, Atkuri K, Leimpeter AD, Albers KB, Greenwood E, Van Den Eeden SK, Steinman L, Nelson LM (2010) Interferon-gamma-producing T cells, pregnancy, and postpartum relapses of multiple sclerosis. Arch Neurol 67:51–57. https://doi.org/10.1001/archneurol.2009.304
41. Nohr EA, Frydenberg M, Henriksen TB, Olsen J (2006) Does low participation in cohort studies induce bias? Epidemiology 17:413–418. https://doi.org/10.1097/01.ede.0000220549.14177.60
42. Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, Alsaker ER, Haug K, Daltveit AK, Magnus P (2009) Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol 23:597–608. https://doi.org/10.1111/j.1365-3016.2009.01062.x
43. Batty GD, Gale CR, Kivimaki M, Deary IJ, Bell S (2020) Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ 368:m131. https://doi.org/10.1136/bmj.m131
44. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE (2017) Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 186:1026–1034. https://doi.org/10.1093/aje/kwx246
45. Norwegian MS Registry and Biobank. Søke tilgang til data [applying for data access] [cited 2022 April 2022]. https://helse-bergen.no/norsk-ms-register-og-biobank/soke-tilgang-til-data#retningslinjer. Accessed Jan 2022

Supplemental material for "Abuse and Revictimization in Adulthood in Multiple Sclerosis: A Cross-sectional Study During Pregnancy". J Neurol

Karine Eid, Øivind Torkildsen, Jan Aarseth, Elisabeth G. Celius, Marianna Cortese, Trygve Holmøy, Akash Kapali, Kjell-Morten Myhr, Cecilie F. Torkildsen, Stig Wergeland, Nils Erik Gilhus, Marte-Helene Bjørk

Corresponding author:

Karine Eid, MD

karine.eid@uib.no

Department of Neurology, Haukeland University Hospital, Bergen, Norway

Department of Clinical Medicine, University of Bergen, Bergen, Norway

Contents:

Questionnaire S1: Abuse experiences from self-completed questionnaires

Q1: Pregnancy weeks 17─20

Have you ever in your adult life been slapped, hit, kicked, or bothered in any way physically?	During this pregnancy	Last 6 months before pregnancy	Earlier
Yes			
No			
Don't remember			
Have you ever been pressured or forced to have sexual intercourse?	During this pregnancy	Last 6 months before pregnancy	Earlier
No, never			
Yes, pressured			
Yes, forced with violence			
Yes, raped			

Q3: Pregnancy week 30

Have you ever experienced any of the following?	No, never	Yes, as a child (under 18)	Yes, as an adult (over 18)	Who was responsible for this? (A stranger/Family or relative/Another known person)	Has this occurred during the last 12 months? (No/Yes)
Has anyone over a long period of time systematically tried to subdue, degrade, or humiliate you?					
Has anyone threatened to hurt you or someone close to you?					
Have you been subjected to physical abuse?					
Have you been forced to do sexual actions?					

Table S1. Perpetrator of abuse in adulthood in women with and without MS

Abuser	Women with MS n (%)	Women without MS n (%)	P-value[a]
Emotional abuse	**26 (100)**	**12,764 (100)**	0.52
Stranger	< 3	906 (7)	
Family/relative	7 (27)	2474 (19)	
Another known person	16 (62)	9210 (72)	
Missing	*< 3*	*174 (1)*	
Sexual abuse	**10 (100)**	**4280 (100)**	1.00
Stranger	< 3	708 (17)	
Family/relative	< 3	384 (9)	
Another known person	8 (80)	3078 (72)	
Missing	*< 3*	*110 (3)*	
Physical abuse	**3 (100)**	**4395 (100)**	1.00
Stranger	0 (0)	689 (16)	
Family/relative	0 (0)	771 (18)	
Another known person	3 (100)	2816 (64)	
Missing	*0 (0)*	*119 (3)*	

Based on the questionnaire in week 30. Cells with values less than 3 are censored
[a]P-values based on 2-sided Fisher exact test

Table S2. Abuse in adulthood in women with MS and women who developed MS more than 5 years after assessment (future MS)

	Women with established MS n = 106	Women with future MS[a] n = 119		
	Yes/no abuse[b]; n (%)	**Yes/no abuse[b]; n (%)**	**OR (95% CI)**	**aOR[c] (95% CI)**
Any adult abuse	27 (26) / 78 (74)	22 (19) / 96 (81)	1.51 (0.80–2.86)	1.67 (0.82–3.40)
Emotional abuse	26 (25) / 79 (75)	15 (13) / 103 (87)	2.26 (1.12–4.55)	2.79 (1.24–6.25)
Systematic humiliation	22 (21) / 83 (79)	11 (9) / 107 (91)	2.58 (1.18–5.62)	3.08 (1.23–7.68)
Threat	8 (8) / 97 (92)	7 (6) / 111 (94)	1.31 (0.48–3.74)	2.26 (0.63–8.14)
Sexual abuse	10 (10) / 95 (90)	6 (5) / 112 (95)	1.97 (0.69–5.61)	2.37 (0.76–7.46)
Rape[d]	6 (6) / 86 (94)	5 (5) / 93 (95)	1.30 (0.38–4.41)	1.44 (0.39–5.33)
Physical abuse	3 (3) / 102 (97)	6 (5) / 112 (95)	0.55 (0.13–2.25)	0.72 (0.15–3.55)
Abused during pregnancy or last 6 months before pregnancy[e]	9 (8) / 97 (91)	8 (7) / 111 (93)	1.29 (0.48–3.47)	2.10 (0.65–6.81)
Revictimization: Adult and childhood abuse	13 (16) / 69 (84)	8 (10) / 76 (90)	1.79 (0.70–4.58)	2.60 (0.86–7.86)

Abbreviations: MS = Multiple sclerosis; OR = Odds Ratio; CI = Confidence Interval

Total N may differ for some of the abuse categories because of different response rates to the different abuse items and different definitions of «no abuse».

[a]185 women in MoBa got their first symptom of MS > 5 years after study inclusion. 119 of them answered both the abuse items in pregnancy week 17–20 and week 30.

[b] «No» means "no adult abuse" for the respective type of adult abuse category (emotional, sexual, physical). For "rape", «no» means no experience of sexual abuse. For "abused during pregnancy or last 6 months before pregnancy" «no» means either previous or no experience of abuse. For "Revictimization", «no» means no exposure to neither childhood nor adult abuse.

[c] Odds ratios are adjusted for age and adverse socioeconomic status

[d] Based on one question from the questionnaire in pregnancy weeks 17–20 and combined with a report of sexual abuse as an adult in week 30.

[e] Based on questions from the questionnaire in weeks 17-20 ("during this pregnancy" or "last 6 months before pregnancy") and the question in week 30 ("have this occurred during the last 12 months").

III

ARTICLE OPEN ACCESS

Perinatal Depression and Anxiety in Women With Multiple Sclerosis

A Population-Based Cohort Study

Karine Eid, MD, Øivind Fredvik Torkildsen, MD, PhD, Jan Aarseth, PhD, Heidi Øyen Flemmen, MD, Trygve Holmøy, MD, PhD, Åslaug Rudjord Lorentzen, MD, PhD, Kjell-Morten Myhr, MD, PhD, Trond Riise, PhD, Cecilia Simonsen, MD, Cecilie Fredvik Torkildsen, MD, Stig Wergeland, MD, PhD, Johannes Sverre Willumsen, MD, Nina Øksendal, MD, Nils Erik Gilhus, MD, PhD, and Marte-Helene Bjørk, MD, PhD

Correspondence
Dr. Eid
karine.eid@uib.no

Neurology® 2021;96:e2789-e2800. doi:10.1212/WNL.0000000000012062

Abstract

Objective

To assess the occurrence of perinatal depression and anxiety in women before and after diagnosis of multiple sclerosis (MS).

Methods

A total of 114,629 pregnant women were included in the Norwegian Mother, Father and Child Cohort study (1999–2008). We assessed depression and anxiety by questionnaires during and after pregnancy. Women with MS were identified from national health registries and hospital records and grouped into (1) MS diagnosed before pregnancy (n = 140) or MS diagnosed after pregnancy with (2) symptom onset before pregnancy (n = 98) or (3) symptom onset after pregnancy (n = 308). Thirty-five women were diagnosed with MS in the postpartum period. The reference group (n = 111,627) consisted of women without MS.

Results

Women with MS diagnosed before pregnancy had an adjusted odds ratio of 2.0 (95% confidence interval, 1.2–3.1) for depression in the third trimester. Risk factors were adverse socioeconomic factors and history of psychiatric disease and physical/sexual abuse. The risk of anxiety was not increased. Women diagnosed with MS in the postpartum period had especially high risk of postpartum depression. Women with MS symptom onset within 5 years after pregnancy had increased risk of both depression and anxiety during pregnancy, whereas women with more than 5 years until symptom onset did not.

Conclusion

Women diagnosed with MS have increased risk of perinatal depression. Women with MS symptom onset within 5 years after pregnancy have increased risk of both depression and anxiety during pregnancy.

RELATED ARTICLE

Editorial
Perinatal Depression and Anxiety in Multiple Sclerosis: Treatable Distress
Page 1067

MORE ONLINE

Infographic
http://links.lww.com/WNL/B412

CME Course
NPub.org/cmelist

From the Departments of Clinical Medicine (K.E., Ø.F.T., K.-M.M., C.F.T., N.E.G., M.-H.B.) and Global Public Health and Primary Care (T.R.), University of Bergen; Neuro-SysMed (Ø.F.T., J.A., K.-M.M., T.R., S.W.), The Norwegian Multiple Sclerosis Registry and Biobank (J.A., S.W.), and The Norwegian Multiple Sclerosis Competence Centre (J.A., T.R.), Department of Neurology (K.E., S.W., N.E.G., M.-H.B.), Haukeland University Hospital, Bergen; Department of Neurology (H.Ø.F.), Telemark Hospital Trust, Skien; Department of Neurology (T.H.), Akershus University Hospital, Lørenskog; Institute of Clinical Medicine (T.H., C.S.), University of Oslo; Department of Neurology and The Norwegian National Advisory Unit on Tick-borne Diseases (Å.R.L.), Sørlandet Hospital, Kristiansand; Department of Neurology (J.S.W.), Møre og Romsdal Hospital Trust, Molde; Department of Neurology (N.Ø.), Nordland Hospital Trust, Bodø; Department of Neurology (C.S.), Vestre Viken Hospital Trust, Drammen; Department of Obstetrics and Gynecology (C.F.T.), Stavanger University Hospital; and Department of Neuromedicine and Movement Science (J.S.W.), Norwegian University of Science and Technology, Trondheim, Norway.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

aOR = adjusted odds ratio; **CI** = confidence interval; **EPDS** = Edinburgh Postnatal Depression Scale; **HPA** = hypothalamic-pituitary-adrenal axis; **HSCL-25** = Hopkins Symptom Checklist 25; **LTMD** = lifetime history of major depression; **MBRN** = Medical Birth Registry of Norway; **MoBa** = Norwegian Mother, Father and Child Cohort Study; **MS** = multiple sclerosis; **MSR** = Norwegian Multiple Sclerosis Registry and Biobank; **NPR** = Norwegian Patient Registry; **OR** = odds ratio; **REK** = Regional Committee for Medical and Health Research Ethics; **SCL-4A** = Symptom Checklist 4-item anxiety subscale; **SCL-4D** = Symptom Checklist 4-item depression subscale.

People with multiple sclerosis (MS) have an increased prevalence of depression and anxiety compared to the general population.[1] Several factors contribute, including pathobiological mechanisms of MS itself.[2,3] Perinatal depression is the most common complication of pregnancy and is often underrecognized. It is defined as depression during pregnancy and up to 1 year after birth.[4-6]

There is limited knowledge of the occurrence of depression and anxiety in the perinatal setting among women with MS. One study found that 26% of mothers and fathers with MS had depression or anxiety in relation to pregnancy,[7] compared to 19% of parents without MS. Psychiatric comorbidity in mothers influence mental health and developmental vulnerability in children.[8-10] Because mothers with MS are at increased risk of depression and anxiety, it is important to identify risk factors associated with these symptoms in the perinatal setting to provide optimal prevention, treatment, and follow-up for women at risk.

Our primary aim was to investigate the occurrence of depression and anxiety during pregnancy and 6 months postpartum. We studied (1) women with an established MS diagnosis, (2) women who had experienced MS symptoms but not yet received a diagnosis, and (3) women with clinical MS symptom onset in the subsequent months or years after giving birth. The last 2 groups were included as they might have had subclinical or prodromal manifestations of MS during the perinatal period.[11-13] Our secondary aim was to investigate to what degree MS-related factors and psychosocial aspects influenced the occurrence of these symptoms.

Methods

Study Design and Population

This is a prospective, population-based cohort study that includes women participating in the Norwegian Mother, Father and Child Cohort study (MoBa). The MoBa study is conducted by the Norwegian Institute of Public Health and is linked to the Medical Birth Registry of Norway (MBRN), to which registration is mandatory for Norwegian health care providers.[14] Participants were recruited from all over Norway from 1999 through 2008. All Norwegian-speaking women were invited to the study after the routine ultrasound examination in pregnancy week 15–17. There were no exclusion criteria. In total, 50 of 52 maternity units with over 100 births per year participated, and 41% of the invited women consented to participation. Follow-up of the cohort is ongoing. Our current study is based on version 12 of the quality-assured data files released for research on September 5, 2019.

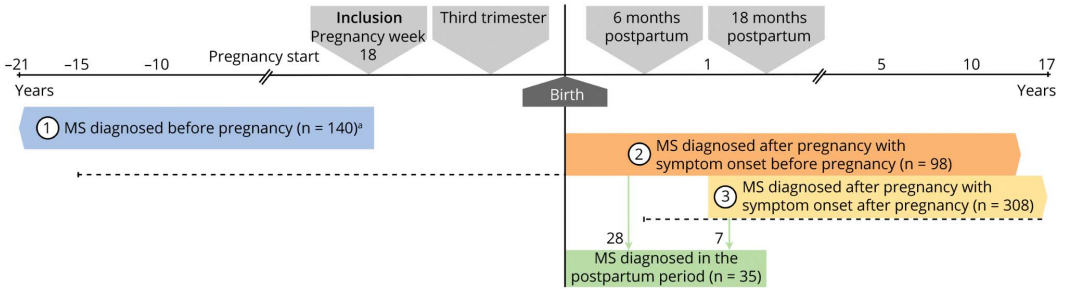
We obtained information on demography, socioeconomic factors, medical history, and symptoms of anxiety and depression by self-completed questionnaires. We used the questionnaires answered during pregnancy weeks 17–20 and 30, and 6 and 18 months postpartum.

The MS diagnoses reported in the questionnaires were validated through data linkage with the Norwegian Multiple Sclerosis Registry and Biobank (MSR), which also provided information on MS subtype and date of symptom onset and diagnosis.[15] The MSR had 60% coverage of MS cases in Norway at the time of linkage. To validate cases not registered in MSR, the cohort was linked to the Norwegian Patient Registry (NPR). The registration of patients in NPR is mandatory for health practitioners, and all consultations with an MS diagnosis in Norwegian specialist care have been registered since March 2007 (data available from Dryad, figure e-1, doi.org/10.5061/dryad.g4f4qrfpkv). The MS diagnosis in NPR has previously been validated, with a sensitivity of 97% and positive predictive value 0.92.[16] MS diagnoses registered in NPR, but not in the MSR, were validated with information from hospital records using the 2017 diagnostic criteria for MS.[17]

The linkage between health registries made it possible to identify women with MS who failed to report a history of MS at inclusion in MoBa, as well as women diagnosed with MS after pregnancy. We followed these women until December 31, 2018. To differentiate between women with early symptomatic yet undiagnosed MS and women with inactive (preclinical) disease during pregnancy, we divided those diagnosed with MS after pregnancy according to the timing of their first MS symptoms. Hence, we defined 3 main groups: (1) MS diagnosed before pregnancy, (2) MS diagnosed after pregnancy with symptom onset before pregnancy, (3) MS diagnosed after pregnancy with symptom onset after pregnancy (figure 1). The reference group consisted of all women in MoBa without MS.

We also defined a subgroup of women who were diagnosed with MS during the first 18 months after pregnancy. In

Figure 1 Multiple Sclerosis (MS) Diagnosis and Symptom Onset in Relation to Pregnancy and Childbirth



We identified 546 women with MS from the Norwegian Mother, Father and Child Cohort (MoBa). Women were divided into 3 groups defined by their MS status on inclusion. The periods of established MS diagnosis are illustrated by colored arrows. Periods of symptom onset are shown with dotted lines for the groups with MS diagnosed after pregnancy. We also studied a subgroup of women who were diagnosed with MS in the postpartum period (0–18 months). [a]MS diagnosed up to pregnancy weeks 18–20.

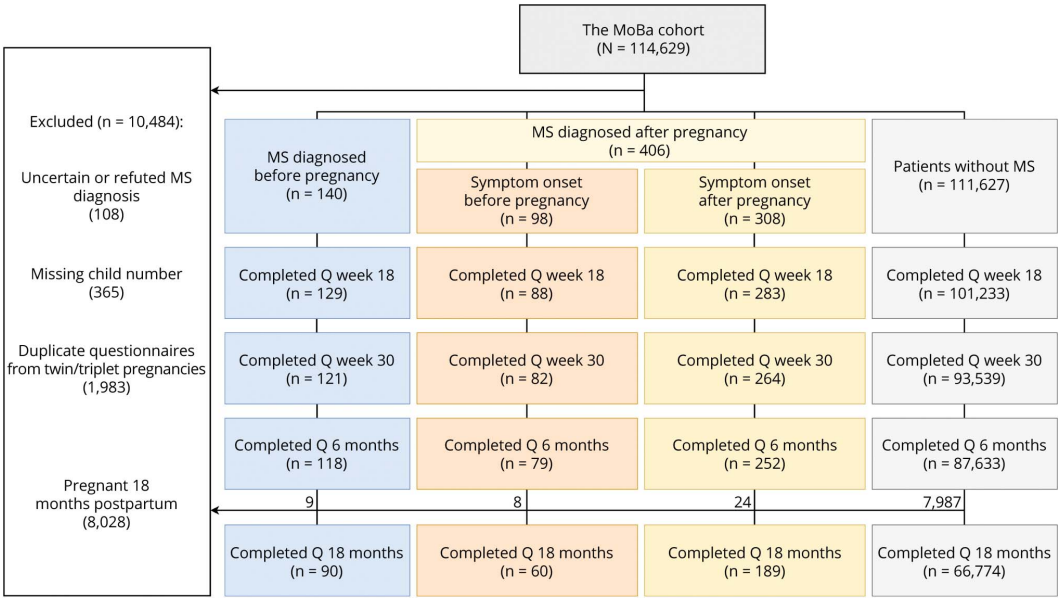
addition to being compared with the reference group, these women were also compared with a subgroup of the reference group that reported, at the 18-month assessment, that they had been diagnosed with a chronic disease other than MS during the last 12 months.

We excluded women with uncertain or refuted MS diagnosis, pregnancies with missing child number, and duplicate questionnaires from multiple gestations to include only one observation per pregnancy (figure 2). Women who were pregnant 18 months postpartum were excluded from the analysis at 18 months after birth.

Primary Outcome Measure

Depression and anxiety were measured separately by validated short versions of the Hopkins Symptom Checklist 25 (HSCL-25).[18-20] These are widely used screening tools designed to detect depression and anxiety. The subscale SCL-

Figure 2 Flowchart of Excluded and Included Cases



Pregnancies included in the Norwegian Mother, Father and Child Cohort (MoBa) study version 12. MS = multiple sclerosis; Q = questionnaire.

8 includes 4 items capturing symptoms of depression (SCL-4D) and 4 capturing symptoms of anxiety (SCL-4A), screening for symptoms during the last 2 weeks before assessment (data available from Dryad, e-Questionnaire, doi.org/10.5061/dryad.g4f4qrfpkv). Items were scored on a Likert scale ranging from 1 ("not at all bothered") to 4 ("very much bothered"). We used a validated mean score of >1.75 as cutoff for presence of depression or anxiety, respectively.[18,21] SCL-8 was used in pregnancy week 30 and 6 and 18 months postpartum. We defined perinatal depression or anxiety as symptoms occurring during pregnancy or in the postpartum period up to 6 months after birth. The proportion of women with symptoms was interpreted as the point prevalence of either depression or anxiety. Scores from the 18-month assessment were used as a prognostic measure for women with MS before pregnancy (group 1) and as point prevalence for those diagnosed with MS 0–18 months after birth.

Postpartum depression based on SCL-4D scores 6 months after birth was validated with a 6-item version of the Edinburgh Postnatal Depression Scale (EPDS-6)[22] with a threshold score of ≥7/18 defining postpartum depression.[23] The kappa agreement between SCL-4D and EPDS-6 was 88% within the MS groups in this study, with a coefficient of 0.52. A prior validation of the entire MoBa cohort showed 91% overall agreement of SCL-4D and EPDS-6 at 6 months postpartum.[24]

Covariates

MS-specific covariates were assessed from the MSR and hospital records: time of MS onset, defined as first clinical symptom; time of MS diagnosis; and subtype of MS (relapsing-remitting MS, primary progressive MS, or unspecified) at disease onset. Relevant covariates that have been identified as possible risk factors for perinatal depression[25,26] were selected from the MoBa questionnaires and the MBRN: maternal age at inclusion, parity (pregnancies >24 gestational weeks), low household income (<60% of median income in the given year), short education (≤9 years), single mother, unplanned pregnancy, overweight (prepregnancy body mass index >25), smoking and alcohol use during pregnancy (≥1 consumption per month for each), and disability benefits such as social security disability or work assessment allowance. Comorbidities included asthma, prepregnancy hypertension, renal disease, rheumatoid arthritis, type 1 diabetes, and epilepsy, which are the available diagnoses in the MBRN and registered by health personnel. Adverse pregnancy events were defined as a prior history of stillbirth or miscarriage past 12 weeks, prior or current preeclampsia, and first trimester vaginal bleeding. Adverse life events were defined as having experienced one of the following and defining it as "painful or difficult" during the last 12 months: conflict at work or study, financial problems, divorce/separation/partnership breakup, conflict with family or friends, severe injury or illness in the woman herself or a loved one, severe traffic accident, fire or robbery, or death of a close relative or friend. Lifetime physical and sexual abuse was evaluated by questions adapted from the Abuse Assessment Screen.[27] A history of major depression was assessed by the lifetime major depression score (LTMD).[28] Previous history of anxiety was self-reported in the questionnaire in pregnancy week 18. Use of antidepressants during pregnancy was self-reported in pregnancy weeks 18 and 30. A combined score of anxiety and depression (SCL-5) was used in pregnancy week 18 to evaluate early pregnancy psychiatric symptoms.

Statistical Analysis

IBM SPSS Statistics software version 26 was used to make variables and imputations. Stata version 16 was used in the remaining analyses.

The different MS groups were compared to a reference group of all women without MS in MoBa. Matching was not performed. Continuous variables were analyzed with Student *t* test when normally distributed and skewed data with the Mann-Whitney *U* test. Categorical variables were compared with the Pearson χ^2 test or with Fisher exact test if any crosstable cell had an expected count <5. We analyzed the risk of depression and anxiety by logistic regression with estimated odds ratios (ORs) and 95% confidence intervals (CIs). OR estimates were adjusted for the possible confounders age, parity, overweight, and adverse socioeconomic factors (≥1 of the following: single mother, low household income, or short education). We accounted for clustering among women with more than 1 pregnancy (n = 14,379) with robust standard error estimations. Estimates with CIs not including 1 were considered statistically significant.

Secondary Outcome

For women with diagnosed MS before pregnancy and women in the reference group, we manually performed a backward stepwise logistic regression analysis with third trimester depression as the dependent variable and a list of 17 independent variables as potential predictors (data available from Dryad, table e-1, doi.org/10.5061/dryad.g4f4qrfpkv). The alpha to enter the multivariate model was ≤0.1 and alpha for variable removal was ≥0.05. To evaluate whether the predictors differed between women with MS and the reference group we included relevant interaction terms in the model.

Imputation of Missing Values

The missing values analysis procedure in SPSS with the expectation-maximization algorithm was used to impute missing values when some of the SCL or LTMD items were not completed. Our requirements for imputation were that maximum 1 in 5 items (20%) was missing in SCL-5 and maximum 3 of the 8 (38%) in SCL-8. In LTMD, the first and sixth item had to be completed, and maximum 2 of 6 items (33%) missing to allow for imputation. If these requirements were exceeded, the cases were set as missing.

Sensitivity Analyses

Various cutoff points for the subscales of HSCL-25 have been suggested.[19] We therefore did a sensitivity analysis of severe

depression with a high cutoff for depression in the third trimester, defined as SCL-4D score greater than the population mean +2 SD.

One of the items in SCL-4D, "Have you been bothered by … feeling everything is an effort?" can be interpreted as a proxy of fatigue, which is a common symptom in MS.[29] As MS-related fatigue could influence this part of the depression score, the distribution of the answers to this question was analyzed with the χ^2 and Fisher exact test, comparing the MS groups with the reference group. The answers to this question did not differ between women with MS diagnosis before pregnancy and women without MS.

Standard Protocol Approvals, Registrations, and Patient Consents

The establishment and initial data collection in MoBa were based on a license from the Norwegian Data Protection Agency and approval from the Regional Committees for Medical and Health Research Ethics (REK). The MoBa cohort is regulated by the Norwegian Health Registry act.

The current study was approved by REK (reference 2016/906). Written informed consent for use of the information in research and for data linkage was obtained during enrollment from all participants in MoBa and MSR.

Data Availability

Enquiries regarding access to data from MoBa and the MBRN can be directed to the Norwegian Institute of Public Health. Data from the MSR are accessible for researchers by application (norskmsregister.no).

Results

Cohort

The cohort consisted of 114,629 pregnant women (figure 2). Of these women, 546 were diagnosed with MS and divided into 3 groups:

1. One hundred forty women were diagnosed with MS before pregnancy
2. Ninety eight women were diagnosed with MS after pregnancy and had symptom onset before pregnancy
3. Three hundred eight women were diagnosed with MS after pregnancy and had symptom onset after pregnancy

Women who did not develop MS during the follow-up period (n = 111,627) served as the reference group and had a median follow-up time of 13 years (range 9–19).

Women in group 2 had experienced their first MS symptom years or months before pregnancy (figure 1). However, they were undiagnosed at inclusion and had a median time of 4 years to MS diagnosis after pregnancy (table 1). Women in group 3 experienced their first MS symptom up to 17 years after pregnancy, with a median of 6 years until symptom onset. Median follow up-time for women with MS diagnosed after pregnancy was 7 years (range 0–17).

The characteristics of women diagnosed with MS before pregnancy and the reference group were similar for socioeconomic and lifestyle factors and previous anxiety and depression (table 1). However, women diagnosed with MS before pregnancy were older and more likely to receive disability benefits. Compared to the reference group, women who had experienced MS symptoms but were not yet diagnosed with MS (group 2) more often had planned pregnancies and were more likely to smoke during pregnancy. Women who had their first MS symptom after pregnancy (group 3) were younger, more often overweight, more frequently smoked during pregnancy, and had experienced more physical or sexual abuse compared to the reference group.

Dropout rates in MoBa at 6 and 18 months postpartum among the women who screened positive for depression in the third trimester were similar for all examined groups (data available from Dryad, table e-2, doi.org/10.5061/dryad.g4f4qrfpkv).

Women Diagnosed With MS Before Pregnancy

A total of 15% of women diagnosed with MS before pregnancy had depression in the third trimester compared to 9% in the reference group without MS (table 2). The crude OR was 1.8 (95% CI, 1.1–2.9). The OR was 2.0 (95% CI, 1.2–3.1) after adjusting for age, parity, overweight, and socioeconomic factors.

The increased risk was confirmed in the sensitivity analysis when we used a higher cutoff for depression: 8% of women with diagnosed MS had severe depression compared to 4% in the reference group, with adjusted OR (aOR) 2.2 (95% CI, 1.2–4.2).

There was no difference in depression point prevalence 6 months after birth between women diagnosed with MS and the reference group. However, among the women with MS who were depressed in the third trimester, 77% of those responding to both questionnaires (n = 13) were still depressed 6 months postpartum compared to 38% in the reference group (aOR, 5.2; 95% CI, 1.4–18.8). Nevertheless, the proportion of women who had recovered from perinatal depression 18 months postpartum was similar; 52% recovery for women with MS diagnosis before pregnancy and 61% for women in the reference group (aOR, 1.3; 95% CI, 0.5–2.9).

Among the women with perinatal depression, this represented their first-ever episode of depression in 50% with diagnosed MS and in 51% of the reference group (aOR, 1.3; 95% CI, 0.6–3.2).

Self-reported use of antidepressants during pregnancy did not differ between the groups. Among the women diagnosed with

Table 1 Characteristics of Participants at Inclusion in the Mother, Father, and Child Cohort Study

Demographic characteristics	Group 1: MS diagnosed before pregnancy, n = 140	MS diagnosed after pregnancy		Reference group, n = 111,627
		Group 2: Symptom onset before pregnancy, n = 98	Group 3: Symptom onset after pregnancy, n = 308	
Age at inclusion, y	31 (4)[n]	30 (4)	28 (5)[n]	30 (5)
Parity[a]	1 (0–4)	1 (0–4)	1 (0–3)	1 (0–4)
Low household income[b]	5 (4)	5 (6)	22 (9)	7,402 (8)
Maternal short education[c]	3 (2)	2 (2)	8 (3)	2,751 (3)
Single mother	5 (4)	3 (4)	5 (2)	2,371 (2)
Unplanned pregnancy	17 (13)	8 (9)[m]	57 (20)	19,486 (20)
Comorbidity[d]	5 (4)	9 (10)	21 (7)	7,452 (7)
Social security disability[e]	22 (17)[n]	0 (0)	8 (3)	1,653 (2)
Adverse life events[f]	49 (41)	30 (37)	87 (33)	30,462 (33)
Adverse pregnancy events[g]	40 (31)	28 (31)	77 (26)	28,702 (28)
Previous anxiety/depression[h]	37 (26)	20 (20)	69 (22)	24,912 (22)
Physical/sexual abuse[i]	20 (17)	17 (21)	58 (22)[m]	15,484 (17)
Smoking in pregnancy	13 (11)	14 (18)[m]	38 (15)[m]	8,405 (9)
Alcohol in pregnancy[j]	5 (4)	2 (2)	5 (2)	2,643 (3)
Prepregnancy BMI >25	43 (34)	30 (35)	101 (37)[m]	30,803 (31)
Depression/anxiety week 18[k]	20 (16)	6 (7)	38 (14)	10,682 (11)
MS characteristic				
Age at diagnosis, y	26 (5)	34 (6)	37 (6)	NA
Years with/until MS diagnosis	5 (0 to 21)	−4 (−13 to 0)	−8 (−17 to −1)	NA
Years since/until onset[l] of MS	7 (1 to 21)	2 (0 to 15)	−6 (−17 to −1)	NA
Years from onset[l] to diagnosis	1 (0 to 16)	8 (0 to 22)	1 (0 to 11)	NA
Type of MS				NA
RRMS	115 (82)	91 (93)	298 (97)	
PPMS	1 (<1)	4 (4)	4 (1)	
Unspecified	24 (17)	3 (3)	6 (2)	

Abbreviations: BMI = body mass index; MS = multiple sclerosis; NA = not applicable; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.
Women were divided into 3 groups defined by their MS status in pregnancy. The reference group consisted of all women without MS diagnosis during the follow-up period. The number may vary within the columns due to missing data. Categorical variables were compared with Pearson χ^2 test or Fisher exact test. Continuous variables were analyzed with Student *t* test when normally distributed and skewed data with the Mann-Whitney *U* test. Values are mean (SD), median (range), or n (%).
[a] Number of all prior pregnancies >24 gestational weeks. Maximum value is 4, representing 4 or more.
[b] Total household income <60% of the cohort median income in the given measurement year.
[c] Maternal short education ≤9 years.
[d] Prepregnancy chronic diseases registered by health personnel in the Medical Birth Registry of Norway: asthma, prepregnancy hypertension, renal disease, rheumatoid arthritis, type 1 diabetes, or epilepsy.
[e] Permanent social security disability or work assessment allowance funded by the government.
[f] ≥1 of the following: problems at work/study, financial problems, divorce/separation/breakup, conflict with family or friends, severe injury or illness to the woman or a loved one, involvement in a severe traffic accident, fire or robbery, or death of a close relative or friend during the last 12 months and defining it as "painful or difficult."
[g] Prior history of stillbirth or miscarriages >12 weeks, prior or current preeclampsia, or first trimester vaginal bleeding.
[h] Self-reported history of anxiety or positive screening on the lifetime history of major depression score.
[i] Physical or sexual abuse during childhood or adulthood. Questions adapted from the Abuse Assessment Screen.
[j] Alcohol consumption ≥1 occasion per month during pregnancy.
[k] A combined score of depression and anxiety (Symptom Checklist 5) was used in pregnancy weeks 17–20.
[l] First MS symptom.
[m] Level of significance compared to the reference group $p < 0.05$.
[n] Level of significance compared to the reference group $p < 0.001$.

Table 2 Depression and Anxiety in Women With Multiple Sclerosis (MS) Diagnosed Before Pregnancy and During the Postpartum Period

	MS diagnosed before pregnancy, n = 140			MS diagnosed postpartum, n = 35			
	N (%)	OR (95% CI)	*p* Value	N (%)	OR (95% CI)	*p* Value	Reference group, n = 111,627, n (%)
Depression							
Third trimester[a]	18 (15)[b]	2.0 (1.2–3.1)[b]	0.006[b]	0 (0)[b]	—	0.043[b]	8,410 (9)
6 months postpartum	16 (14)	1.5 (0.8–2.5)	0.182	7 (23)[b]	3.1 (1.3–7.2)[b]	0.010[b]	8,246 (10)
18 months postpartum	15 (17)	1.4 (0.8–2.5)	0.279	10 (42)[b]	5.0 (2.1–11.9)[b]	<0.001[b]	8,333 (13)
Anxiety							
Third trimester[a]	5 (4)	0.8 (0.4–2.0)	0.705	1 (3)	0.5 (0.1–4.1)	0.552	5,089 (6)
6 months postpartum	4 (4)	0.8 (0.3–2.2)	0.692	3 (10)	2.4 (0.7–7.7)	0.149	4,058 (5)
18 months postpartum	6 (7)	1.4 (0.6–3.2)	0.419	0 (0)	—	0.640	3,591 (6)

Point prevalence of depression and anxiety from pregnancy until 18 months postpartum is shown. Adjusted *p* values and odds ratios (ORs) with 95% confidence intervals (CIs) for depression and anxiety in women diagnosed with MS before pregnancy and in the postpartum period compared to women without MS are shown. The number (n) may vary within the columns because of missing data. Depression and anxiety are defined as Hopkins Symptom Checklist (SCL-4D and SCL-4A, respectively) mean >1.75. Estimates are adjusted for age, parity, overweight (body mass index >25), and adverse socioeconomic factors (single mother, low household income <60% of median, and short education ≤9 years).
[a] Pregnancy week 30.
[b] Statistically significant.

MS and depression in the third trimester, 17% had used antidepressants up to this time in pregnancy, compared to 12% of the depressed women in the reference group (aOR, 1.2; 95% CI, 0.4–4.5).

There were no differences in point prevalence of anxiety between women with diagnosed MS and the reference group during and after pregnancy.

Secondary Outcome

The backward stepwise logistic regression analysis identified several predictors for depression in the third trimester in women diagnosed with MS before pregnancy (table 3). Interaction analyses indicated a synergistic effect between MS and adverse socioeconomic factors and MS and history of sexual or physical abuse on the risk of depression. Previous depression or anxiety did not modify the effect of MS on depression. Recent MS diagnosis, MS type, and receiving disability benefits were not predictors for depression (data available from Dryad, table e-1, doi.org/10.5061/dryad.g4f4qrfpkv).

Women Diagnosed With MS After Pregnancy

Women diagnosed with MS after pregnancy with symptom onset before pregnancy (group 2) did not have increased frequency of depression or anxiety in the perinatal period (table 4).

Table 3 Predictors for Third Trimester Depression in Women With Multiple Sclerosis (MS) Diagnosed Before Pregnancy and Women Without MS

	MS (n = 140)		Reference group (n = 111,627)		Interaction term MS × predictor, *p* value
Predictor	***p* Value**	**OR (95% CI) (multivariable)**	***p* Value**	**OR (95% CI) (multivariable)**	
Adverse socioeconomic factors[a]	0.006	6.0 (1.7–28.0)	<0.001	1.9 (1.7–2.0)	0.061
Sexual/physical abuse[b]	0.003	5.5 (1.8–17.5)	<0.001	1.8 (1.7–1.9)	0.068
Previous depression/anxiety[c]	0.009	4.6 (1.5–14.6)	<0.001	3.6 (3.4–3.8)	0.692

Odds ratios (ORs) with 95% confidence intervals (CIs) for predictors of depression in the third trimester in women with MS diagnosis before pregnancy and women in the reference group are shown. We manually performed a backward stepwise logistic regression analysis within the group of women with MS diagnosed before pregnancy, with third trimester depression as the dependent variable and 17 independent variables as potential predictors (data available from Dryad, table e-1, doi.org/10.5061/dryad.g4f4qrfpkv). The alpha to enter the multivariate model was ≤0.1 and ≥0.05 for variable removal. Predictors remaining in the model are shown here. The final model was subsequently run on the reference group to compare estimates of ORs. We performed separate backward stepwise logistic regression analyses on the reference group (data available from Dryad, figure e-1). The remaining predictors for the MS population were included as interaction terms in logistic regression analyses on the entire population with third trimester depression as the dependent variable with adjustment for age, parity, socioeconomic factors, and prepregnancy body mass index >25.
[a] Single mother, low household income <60% of median, or short education ≤9 years.
[b] Physical or sexual abuse during childhood or adulthood. Questions adapted from the Abuse Assessment Screen.
[c] Self-reported history of anxiety or positive screening on the lifetime history of major depression score.

Table 4 Perinatal Depression and Anxiety in Women Diagnosed With Multiple Sclerosis (MS) After Pregnancy

	Symptom onset before pregnancy, n = 98		Symptom onset after pregnancy, n = 308				
			≤5 years after pregnancy, n = 136		>5 years after pregnancy,[a] n = 172		Reference group, n = 111,627, n (%)
	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	
Depression							
Third trimester[b]	5 (6)	0.5 (0.2–1.4)	17 (14)[c]	1.9 (1.1–3.1)[c]	16 (11)	1.2 (0.7–2.0)	8,410 (9)
6 months postpartum	9 (11)	1.3 (0.6–2.6)	16 (14)	1.8 (0.99–3.1)	17 (12)	1.2 (0.7–2.0)	8,246 (10)
Anxiety							
Third trimester[b]	3 (4)	0.7 (0.2–2.2)	11 (9)[c]	2.0 (1.1–3.7)[c]	8 (6)	0.7 (0.3–1.6)	5,089 (6)
6 months postpartum	4 (5)	1.1 (0.4–3.1)	7 (6)	1.3 (0.6–3.0)	11 (8)	1.8 (0.9–3.2)	4,058 (5)

The number (n) may vary within the columns due to missing data.
Point prevalence of depression and anxiety from pregnancy until 6 months postpartum is shown. Adjusted *p* values and odds ratios (ORs) with 95% confidence intervals (CIs) for depression and anxiety in women diagnosed with MS after pregnancy compared to a reference group of women without MS are shown. Depression and anxiety are defined as Hopkins Symptom Checklist (SCL-4D and SCL-4A, respectively) mean >1.75. Estimates are adjusted for age, parity, overweight (body mass index >25), and adverse socioeconomic factors (single mother, low income <60% of median, and short education ≤9 years).
[a] 6–17 years after pregnancy.
[b] Pregnancy week 30.
[c] Statistically significant.

Among women with symptom onset after pregnancy (group 3), those with their first MS symptom within 5 years after pregnancy (n = 136) had higher frequency of depression and anxiety in the third trimester compared to the reference group (depression: 14% vs 9%, anxiety: 9% vs 6%) (table 4). In contrast, women with more than 5 years to onset of symptoms (n = 172) did not have higher frequency of depression or anxiety at any assessment in the perinatal period.

Women Diagnosed With MS Postpartum

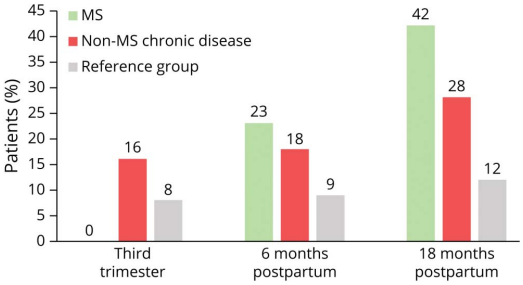
Thirty-five women were diagnosed with MS during the 18-month postpartum period (figure 1). Although none of these was depressed at the assessment in the third trimester, they had a higher frequency of depression compared to the reference group both at 6 months (23% vs 10%) and at 18 months postpartum (42% vs 13%) (table 2). There were no differences in point prevalences of anxiety between women with postpartum MS diagnosis and the reference group. Median time from symptom onset to diagnosis was 2 years (range 0–12) in women with postpartum depression in this group, compared to 1 year (range 0–12) for this MS group as a whole.

Women in the reference group who were diagnosed with other chronic diseases in the postpartum period (n = 2,640) more often had postpartum depression compared to the remaining "healthy" proportion of the reference group, but numerically lower than for women with postpartum MS diagnosis (figure 3). The aORs of postpartum depression in women diagnosed with MS postpartum compared to women diagnosed with other chronic diseases in the same period was 1.5 (95% CI, 0.6–3.4) at 6 months and 1.9 (95% CI, 0.8–4.2) 18 months postpartum.

Discussion

Our study found increased risk of depression during pregnancy in women with an established MS diagnosis. Furthermore, women with MS and depression in pregnancy had more prolonged depressive symptoms, lasting into the postpartum period. However, the prognosis for recovery was similar 18 months postpartum. Women who were diagnosed with MS in the postpartum period had a high risk of postpartum depression.

Figure 3 Perinatal Depression in Women Diagnosed With Multiple Sclerosis (MS) or Other Chronic Disease in the Postpartum Period



Point prevalence of depression from pregnancy week 30 until 18 months postpartum in women who were diagnosed with MS (n = 35) or another chronic disease (n = 2,640) in the 18-month postpartum period. Women without MS or another postpartum chronic diagnosis (n = 108,987) represents the reference group. Depression is defined as Hopkins Symptom Checklist 4D mean >1.75. N values are given for the first assessment and are later lower due to missing data. Women who were pregnant 18 months postpartum were excluded (figure 2).

The use of validated questionnaires and a population-based design in the current study extends previous knowledge on perinatal depression in MS. We have identified one other study on prevalence and risk estimations of perinatal depression in people with MS. This other population-based study found a 26% prevalence of perinatal depression or anxiety in 255 women with MS, compared to 21% in 904 women without MS (OR, 1.28; 95% CI, 0.99–1.65).[7] Our point prevalence figures were lower (15% vs 9%), whereas the risk estimate for depression in the third trimester for women with MS was higher in our study. The estimates are not strictly comparable due to different methodology. We evaluated depressive and anxiety symptoms separately and used several assessments of point prevalence instead of period prevalence. The previous study used diagnostic codes in addition to antidepressant and anxiolytic prescriptions as proxies for depression and anxiety.

The increased occurrence of depression during pregnancy in women with an established MS diagnosis could be explained by several factors. Perinatal depression is linked to dysregulation of the maternal hypothalamic-pituitary-adrenal (HPA) axis.[30,31] The HPA axis is also involved in the mechanisms of MS.[32] The knowledge of having a severe and potentially progressive disease may cause psychological distress. Uncertainty and lack of hope are shown to be independent predictors for depression in MS, regardless of disability status.[33] In addition, depression might be caused by inflammation[3] or manifest lesions in the brain.[34] All these mechanisms can interact or have reciprocal effects.

In contrast to women with an established MS diagnosis before pregnancy, women who were diagnosed with MS postpartum had a substantially increased risk of postpartum depression. Depressive symptoms in these women could be triggered by disease awareness in a vulnerable period when caring for a newborn baby. Women who were diagnosed with other chronic diseases in the postpartum period also had higher occurrence of depression, but not as marked as for women diagnosed with MS. Many of these women with a recent MS diagnosis probably had ongoing disease activity and inflammation, which may have contributed to the depressive symptoms.[3,35]

We found low risk estimates for perinatal anxiety for women with established MS. Previous studies have shown that depression and anxiety probably have diverse attributable factors and mechanisms in MS, which may explain why the risk estimates differed. One study found correlation between inflammation and social and state anxiety, while trait anxiety was associated with disease duration.[3] Depression, but not anxiety, has been associated with subsequent disability progression.[36] Another study found an association between depression and brain atrophy, but no association between anxiety and atrophy.[34]

Key predictors for pregnancy-related depression in women with established MS in our study were adverse socioeconomic factors, a history of sexual or physical abuse, and depression or anxiety prior to pregnancy. The same predictors for perinatal depression have previously been found in women with epilepsy,[24] and are also known predictors for perinatal depression in the general maternal population.[25,26] However, the interaction analyses indicated a synergistic effect between MS and adverse socioeconomic status and between MS and a history of sexual or physical abuse. This means that having experienced abuse or having adverse socioeconomic status seemed to increase the risk of depression substantially more in women with MS than in women without MS. Accordingly, women with these risk factors need special attention and follow-up.

Perinatal depression in women with MS requires intervention, as it reduces quality of life, often leads to paternal depression,[37] and reduces adherence to MS treatment.[38] It may also influence the mother–infant bond negatively,[39] and is associated with higher risk of psychiatric disorders in children.[7,8]

We found that women with MS symptom onset within 5 years after pregnancy had increased risk of both depression and anxiety during pregnancy. Conversely, women with more than 5 years until onset of MS symptoms did not have any increased risk. Depression and anxiety are recognized as parts of MS prodromal syndrome.[11,12] Previous studies in nonpregnant MS populations have shown increased occurrence of depression and anxiety 2 years before MS diagnosis[40] and up to 5–10 years before the first demyelinating event.[12,13] The risk gradually increased closer to the year of the first event.

Women who were yet to be diagnosed with MS who had already experienced their first MS-associated symptom did not show any increased frequencies of depression or anxiety in pregnancy. Of note, they had the lowest rate of unplanned pregnancies, which may protect against perinatal depression.[41] Their median time from MS onset to diagnosis was 8 years compared to only 1 year in the other 2 MS groups. This suggests that this group had a different disease course with milder onset symptoms, and thus later diagnostic attention.

Strengths of our study include a large and detailed population-based dataset. Our database linkage resulted in a unique study design that gave the opportunity to compare pregnant women with MS in different stages of the disease both with the general population and with women who contracted other chronic diseases postpartum. The MS diagnosis was thoroughly validated in a nationwide collaboration with local neurology departments. The data were prospectively collected with longitudinal measurements of depression and anxiety with validated screening tools.[42] Sensitivity analyses confirmed that depression in women with established MS was independent of fatigue, and our findings were valid with higher cutoff for depression. The dropout rates among the depressed women in the different MS groups and the reference group were similar, which limits the possibility of attrition bias.

There are some limitations to our study. Depression and anxiety were not diagnosed by a physician. However, anonymous questionnaires using the SCL screening tools have previously been shown to more accurately capture psychiatric symptoms than interviews.[43] Screening positive on SCL subscales has been predictive of subsequent hospitalization with depression and dispensation of antidepressants.[44] Women with psychological distress may have been less motivated to participate in the MoBa study. This potential bias could underestimate the depression prevalence, but should not influence the risk differences between women with and without MS. Hence, the exposure–outcome associations found in our study are generalizable to the maternal population. A moderate participation rate of 41% can result in a slightly selected sample, but is as expected from population-based cohorts.[45] A study on selection bias in the MoBa cohort found an underrepresentation of adverse socioeconomic exposure variables in the participating women, which may give biased estimates of exposure and outcome prevalence.[46] Previous population-based studies in Norway with 90% participation rates have found 9%–11% prevalence of perinatal depression, scored with EPDS, from the second trimester in pregnancy into the postpartum period.[47-49] We found the same prevalence in our reference group. Thus, a potential selection bias seems to have minimal effect on the outcomes in our study. Due to personal data protection regulations, we received date of MS onset/diagnosis as well as birth year, but we did not know date of birth. Hence, we could not estimate the exact relation between MS onset and diagnosis to childbirth for a subgroup of patients. A few women may have been misclassified into the group "MS diagnosed after pregnancy with symptom onset before pregnancy." A total of 3–6 women in this group could have been diagnosed with MS in late pregnancy and a maximum of 25 women could have had their symptom onset during pregnancy. We had no information on MS severity such as the Expanded Disability Status Scale. Furthermore, our material lacks MRI data and clinical information on MS disease activity to assess effect on depression and its influence by inflammation. Breastfeeding may influence postpartum depression,[50] but information on breastfeeding was not available in our dataset. We had limited information on medication, both antidepressants and MS-specific disease-modifying drugs. Further research that includes potential effects of these variables is necessary for the understanding of pathobiologic mechanisms in perinatal depression in MS.

The increased risk and prolonged duration of perinatal depression in women with MS shown in this study should lead to special attention with timely prevention and treatment. Clinicians should be especially aware of signs of depression in women diagnosed with MS in the postpartum period.

Acknowledgment

The Norwegian Mother, Father and Child Cohort study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. The authors thank Alok Bhan, MD (Department of Neurology, Stavanger University Hospital, Norway); Britt Bruland, CNS (Department of Neurology, Førde Hospital, Norway); Kathrine K. Lian, MD (Department of Neurology, St. Olavs Hospital, Trondheim, Norway); and Stephan Schüler, MD, PhD (Department of Neurology, Namsos Hospital, Norway) for contributing to data extraction and validation of MS diagnoses; and the participating families in Norway who take part in this ongoing cohort study.

Study Funding

The authors received research support from Novartis Norway, the Western Norway Regional Health Authority, and the University of Bergen. Neuro-SysMed is funded by the Norwegian Research Council grant 288164.

Disclosure

K. Eid has received an unrestricted research grant from Novartis. Ø. Torkildsen has received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck, and Novartis. J. Aarseth reports no disclosures. H. Flemmen has received research grants and speaker honoraria from Biogen Idec and Novartis and has received speaker honoraria from Sanofi and Merck. T. Holmøy has received lecture fees and research grants from Biogen, Roche, Novartis, Merck, and Sanofi and is on the Medical Committee of the Norwegian MS Association. Å.R. Lorentzen reports no disclosures. K.M. Myhr has received unrestricted research grants to his institution; scientific advisory board and speaker honoraria from Almirall, Biogen, Genzyme, Merck, Novartis, Roche, and Teva; and has participated in clinical trials organized by Biogen, Merck, Novartis, and Roche. T. Riise reports no disclosures relevant to the manuscript. C.S. Simonsen has received an unrestricted research grant from Novartis and has received speaker honoraria from and served on scientific advisory boards for Sanofi, Merck, and Biogen Idec. C. Torkildsen has served on a scientific advisory board for Astra Zeneca. S. Wergeland has received speaker honoraria from and served on scientific advisory boards for Biogen, Alexion, Sanofi-Aventis, and Novartis. J.S. Willumsen has received an unrestricted research grant from Novartis. N. Øksendal has received speaker and consultant honoraria from Biogen and has served on a scientific advisory board for Novartis. N.E. Gilhus has received speaker and consultant honoraria from UCB, RaPharma, Argenx, Octapharma, Alexion, Roche, and Merck. M.H. Bjørk has received research support, consultant honoraria, and speakers honoraria from Novartis and speakers honoraria from Teva, Lilly, and Allergan. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 10, 2020. Accepted in final form March 11, 2021.

Appendix Authors

Name	Location	Contribution
Karine Eid, MD	University of Bergen and Haukeland University Hospital, Norway	Analyzed and interpreted the data, drafted and revised the manuscript for intellectual content, had full access to all the data, provided funding
Øivind Fredvik Torkildsen, MD, PhD	University of Bergen and Haukeland University Hospital, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Jan Aarseth, PhD	Haukeland University Hospital, Bergen, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Heidi Øyen Flemmen, MD	Telemark Hospital Trust, Skien, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Trygve Holmøy, MD, PhD	Department of Neurology, Akershus University Hospital and University of Oslo, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Åslaug Rudjord Lorentzen, MD, PhD	Department of Neurology and The Norwegian National Advisory Unit on Tick-borne diseases, Sørlandet Hospital, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Kjell-Morten Myhr, MD, PhD	University of Bergen and Haukeland University Hospital, Norway	Designed and conceptualized study, interpretation of the data, revised the manuscript for intellectual content, final approval of manuscript
Trond Riise, PhD	University of Bergen and Haukeland University Hospital, Norway	Designed and conceptualized study, interpretation of the data, revised the manuscript for intellectual content, final approval of manuscript
Cecilia Simonsen, MD	Department of Neurology, Vestre Viken Hospital Trust, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Cecilie Fredvik Torkildsen, MD	University of Bergen and Stavanger University Hospital, Norway	Designed and conceptualized study, revised the manuscript for intellectual content, final approval of manuscript
Stig Wergeland, MD, PhD	Haukeland University Hospital, Bergen, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Johannes Sverre Willumsen, MD	Møre og Romsdal Hospital Trust, Molde, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Nina Øksendal, MD	Nordland Hospital Trust, Bodø, Norway	Data collection, revised the manuscript for intellectual content, final approval of manuscript
Nils Erik Gilhus, MD PhD	University of Bergen and Haukeland University Hospital, Norway	Design and conceptualized study, interpreted the data, revised the manuscript for intellectual content, provided funding
Marte-Helene Bjørk, MD PhD	University of Bergen and Haukeland University Hospital, Norway	Design and conceptualized study, interpreted the data, revised the manuscript for intellectual content, had full access to all the data, provided funding

References

1. Boeschoten RE, Braamse AMJ, Beekman ATF, et al. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci.* 2017; 372:331-341.
2. Patten SB, Marrie RA, Carta MG. Depression in multiple sclerosis. *Int Rev Psychiatry.* 2017;29(5):463-472.
3. Rossi S, Studer V, Motta C, et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology.* 2017;89(13):1338-1347.
4. World Health Organization. *International Statistical Classification of Diseases, 10th Revision.* World Health Organization: 2004.
5. National Institute for Health and Care Excellence. *Antenatal and Postnatal Mental Health, Guideline 192.* 2014. Accessed January 7, 2021. nice.org.uk/guidance/cg192/chapter/1-recommendations.
6. O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. *Best Pract Res Clin Obstet Gynaecol.* 2014;28(1):3-12.
7. Razaz N, Tremlett H, Marrie RA, Joseph KS. Peripartum depression in parents with multiple sclerosis and psychiatric disorders in children. *Mult Scler.* 2016;22(14): 1830-1840.
8. Razaz N, Tremlett H, Boyce T, Guhn M, Marrie RA, Joseph KS. Incidence of mood or anxiety disorders in children of parents with multiple sclerosis. *Paediatr Perinat Epidemiol.* 2016;30(4):356-366.
9. Madigan S, Oatley H, Racine N, et al. A meta-analysis of maternal prenatal depression and anxiety on child socioemotional development. *J Am Acad Child Adolesc Psychiatry.* 2018;57(9):645-657.
10. Razaz N, Joseph KS, Boyce WT, et al. Children of chronically ill parents: relationship between parental multiple sclerosis and childhood developmental health. *Mult Scler.* 2016;22(11):1452-1462.
11. Wijnands JMA, Kingwell E, Zhu F, et al. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. *Lancet Neurol.* 2017;16(6):445-451.
12. Disanto G, Zecca C, MacLachlan S, et al. Prodromal symptoms of multiple sclerosis in primary care. *Ann Neurol.* 2018;83(6):1162-1173.
13. Wijnands JM, Zhu F, Kingwell E, et al. Five years before multiple sclerosis onset: phenotyping the prodrome. *Mult Scler.* 2019;25(8):1092-1101.
14. Magnus P, Birke C, Vejrup K, et al. Cohort profile update: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol.* 2016;45(2):382-388.
15. Myhr KM, Grytten N, Torkildsen O, Wergeland S, Bo L, Aarseth JH. The Norwegian Multiple Sclerosis Registry and Biobank. *Acta Neurol Scand.* 2015; 132(199):24-28.
16. Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB. Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry. *Brain Behav.* 2019;9(11): e01422.
17. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173.
18. Nettelbladt P, Hansson L, Stefansson CG, Borgquist L, Nordstrom G. Test characteristics of the Hopkins symptom check list-25 (HSCL-25) in Sweden, using the present state examination (PSE-9) as a caseness criterion. *Soc Psychiatry Psychiatr Epidemiol.* 1993;28(3):130-133.
19. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic J Psychiatry.* 2003;57(2):113-118.
20. Tambs K, Moum T. How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatr Scand.* 1993;87(5):364-367.
21. Winokur A, Winokur DF, Rickels K, Cox DS. Symptoms of emotional distress in a family planning service: stability over a four-week period. *Br J Psychiatry.* 1984;144: 395-399.
22. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150:782-786.
23. Solberg O, Dale MT, Holmstrom H, Eskedal LT, Landolt MA, Vollrath ME. Emotional reactivity in infants with congenital heart defects and maternal symptoms of postnatal depression. *Arch Womens Ment Health.* 2011;14(6):487-492.

24. Bjork MH, Veiby G, Reiter SC, et al. Depression and anxiety in women with epilepsy during pregnancy and after delivery: a prospective population-based cohort study on frequency, risk factors, medication, and prognosis. *Epilepsia*. 2015;56(1):28-39.
25. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. *Lancet*. 2014;384(9956):1775-1788.
26. Norhayati MN, Hazlina NH, Asrenee AR, Emilin WM. Magnitude and risk factors for postpartum symptoms: a literature review. *J Affect Disord*. 2015;175:34-52.
27. McFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy: severity and frequency of injuries and associated entry into prenatal care. *JAMA*. 1992;267:3176-3178.
28. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women: reliability of diagnosis and heritability. *Arch Gen Psychiatry*. 1993;50(11):863-870.
29. Rooney S, Wood L, Moffat F, Paul L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of multiple sclerosis. *Mult Scler Relat Disord*. 2019;28:276-282.
30. Glynn LM, Davis EP, Sandman CA. New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. *Neuropeptides*. 2013;47(6):363-370.
31. Rich-Edwards JW, Mohllajee AP, Kleinman K, et al. Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. *J Clin Endocrinol Metab*. 2008;93(5):1946-1951.
32. Anagnostouli M, Markoglou N, Chrousos G. Psycho-neuro-endocrino-immunologic issues in multiple sclerosis: a critical review of clinical and therapeutic implications. *Hormones*. 2020;19(4):485-496.
33. Lynch SG, Kroencke DC, Denney DR. The relationship between disability and depression in multiple sclerosis: the role of uncertainty, coping, and hope. *Mult Scler*. 2001;7(6):411-416.
34. Zorzon M, de Masi R, Nasuelli D, et al. Depression and anxiety in multiple sclerosis: a clinical and MRI study in 95 subjects. *J Neurol*. 2001;248(5):416-421.
35. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.
36. McKay KA, Tremlett H, Fisk JD, et al. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology*. 2018;90(15):e1316-e1323.
37. Letourneau NL, Dennis CL, Benzies K, et al. Postpartum depression is a family affair: addressing the impact on mothers, fathers, and children. *Issues Ment Health Nurs*. 2012;33(7):445-457.
38. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997;54(5):531-533.
39. Rossen L, Mattick RP, Wilson J, et al. Mother-infant bonding and emotional availability at 12-months of age: the role of early postnatal bonding, maternal substance use and mental health. *Matern Child Health J*. 2019;23(12):1686-1698.
40. Hoang H, Laursen B, Stenager EN, Stenager E. Psychiatric co-morbidity in multiple sclerosis: the risk of depression and anxiety before and after MS diagnosis. *Mult Scler*. 2016;22(30):347-353.
41. Faisal-Cury A, Menezes PR, Quayle J, Matijasevich A. Unplanned pregnancy and risk of maternal depression: secondary data analysis from a prospective pregnancy cohort. *Psychol Health Med*. 2017;22(1):65-74.
42. Lundin A, Hallgren M, Forsell Y. The validity of the Symptom Checklist depression and anxiety subscales: a general population study in Sweden. *J Affect Disord*. 2015;183:247-252.
43. Moum T. Mode of administration and interviewer effects in self-reported symptoms of anxiety and depression. *Soc Indic Res*. 1998;45(1-3):279-318.
44. Magnusson Hanson LL, Westerlund H, Leineweber C, et al. The Symptom Checklist–core depression (SCL-CD6) scale: psychometric properties of a brief six item scale for the assessment of depression. *Scand J Public Health*. 2014;42(1):82-88.
45. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. 2006;17(4):413-418.
46. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23(6):597-608.
47. Eberhard-Gran M, Eskild A, Tambs K, Samuelsen SO, Opjordsmoen S. Depression in postpartum and non-postpartum women: prevalence and risk factors. *Acta Psychiatr Scand*. 2002;106(6):426-433.
48. Eberhard-Gran M, Tambs K, Opjordsmoen S, Skrondal A, Eskild A. Depression during pregnancy and after delivery: a repeated measurement study. *J Psychosom Obstet Gynaecol*. 2004;25(1):15-21.
49. Glavin K, Smith L, Sorum R. Prevalence of postpartum depression in two municipalities in Norway. *Scand J Caring Sci*. 2009;23(4):705-710.
50. Dias CC, Figueiredo B. Breastfeeding and depression: a systematic review of the literature. *J Affect Disord*. 2015;171:142-154.

Perinatal Depression and Anxiety in Women With Multiple Sclerosis: A Population-Based Cohort Study

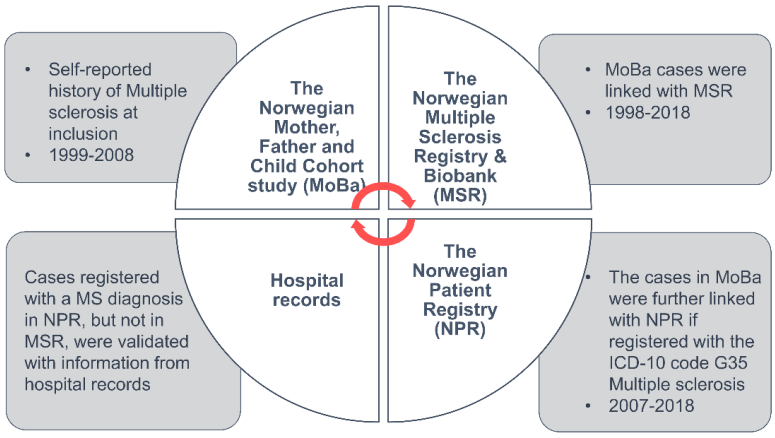
Karine Eid, Øivind Fredvik Torkildsen, Jan Aarseth, et al.

Neurology 2021;96;e2789-e2800 Published Online before print April 21, 2021
DOI 10.1212/WNL.0000000000012062

Supplemental data

Perinatal Depression and Anxiety in Women with Multiple Sclerosis

Figure e-1



Data linkage procedure

Cases were linked via personal identification codes, a lifelong unique number available in all the included health databases. The NPR has national coverage of all ICD-10 codes, hospital visits and outpatient visits in specialist health services.

e-Questionnaire: SCL-8 used in pregnancy week 30, 6 months and 18 months postpartum

"Have you been bothered by any of the following during the last two weeks?"

SCL-4D "Depression"

- Feeling hopeless about the future
- Feeling blue
- Worrying to much about things
- Feeling everything is an effort

SCL-4A "Anxiety"

- Feeling fearful
- Nervousness or shakiness inside
- Feeling tense or keyed up
- Suddenly scared for no reason

Table e-1: Backward stepwise logistic regression: Predictors for third trimester depression

	Women with MS diagnosed before pregnancy (n = 140)				Reference group (n = 111,627)			
	Univariable analyses		Final model (multivariable)		Univariable analyses		Final model (multivariable)	
Predictor	**Crude p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**Crude p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Adverse socioeconomic status[a]	**0.004**	**7.4 (1.9–29.0)**	**0.006**	**6.0 (1.7–21.8)**	**<0.001**	**2.3 (2.2–2.4)**	**<0.001**	**1.2 (1.2–1.3)**
Disability benefits[b]	0.582	1.4 (0.4–4.8)	-	-	**<0.001**	**3.4 (3.0–3.9)**	**0.012**	**1.2 (1.1–1.4)**
Comorbidity[c]	**0.016**	**9.9 (1.5–64.2)**	-	-	**<0.001**	**1.3 (1.2–1.4)**	-	-
Sexual/physical abuse[d]	**<0.001**	**8.2 (2.7–25)**	**0.003**	**5.5 (1.8–17.5)**	**<0.001**	**2.7 (2.5–2.8)**	**<0.001**	**1.3 (1.3–1.4)**
Adverse pregnancy events[e]	0.936	0.95 (0.3–2.9)	-	-	**<0.001**	**1.1 (1.1–1.2)**	-	-
Adverse life events[f]	**0.006**	**4.7 (1.5–14.2)**	-	-	**<0.001**	**3.1 (3.0–3.2)**	**<0.001**	**2.0 (1.9–2.1)**
Smoking in pregnancy	**0.055**	**3.7 (0.97–14.3)**	-	-	**<0.001**	**2.3 (2.2–2.5)**	**<0.001**	**1.3 (1.2–1.5)**
Alcohol in pregnancy	-	-	-	-	**0.019**	**1.2 (1.0–1.3)**	-	-
Early pregnancy anxiety/depression[g]	**<0.001**	**6.4 (2.1–19.7)**	-	-	**<0.001**	**11.6 (11.0–12.2)**	**<0.001**	**6.8 (6.4–7.3)**
Previous anxiety/depression[h]	**<0.001**	**5.6 (2.0–16.3)**	**0.009**	**4.6 (1.5–14.6)**	**<0.001**	**4.2 (4.0–4.4)**	**<0.001**	**2.2 (2.1–2.4)**
Unplanned pregnancy	0.311	1.9 (0.5–6.7)	-	-	**<0.001**	**2.1 (2.0–2.2)**	**<0.001**	**1.4 (1.3–1.5)**
Recent MS diagnosis[i]	0.460	0.6 (0.2–2.2)	-	-	-	-	-	-
Relapsing-remitting MS	0.931	0.9 (0.1–8.2)	-	-	-	-	-	-
Unspecified MS type	0.931	1.1 (0.1–9.9)	-	-	-	-	-	-
Pre-pregnancy BMI > 25	0.154	2.1 (0.8–5.8)	-	-	**<0.001**	**1.2 (1.1–1.2)**	**0.012**	**1.1 (1.0–1.1)**
≥ 4 previous childbirths	0.185	2.2 (0.7–7.1)	-	-	**<0.001**	**1.1 (1.1–1.2)**	**0.012**	**1.1 (1.0–1.2)**
Maternal age > 38 years	0.581	1.9 (0.2–19.5)	-	-	0.466	1.1 (0.9–1.2)	-	-

Abbreviations: MS = Multiple sclerosis; RRMS = Relapsing Remitting MS; BMI = Body Mass Index.

Odds ratios (ORs) with 95% confidence intervals (CIs) for predictors of depression in the third trimester in women with MS diagnosed before pregnancy (n = 140) and the reference group (n = 111,627). Backward stepwise logistic regression analysis was manually performed with third trimester depression as the dependent variable and 17 independent variables as potential predictors. The alpha to enter the multivariable model was ≤ 0.1 and alpha ≥ 0.05 for variable removal. Estimates that reached significance for entering and remaining in the model for each group are highlighted in bold.

[a] Single mother, low household income < 60% of median and/or short education ≤ 9 years.

[b] Permanent social security disability or work assessment allowance funded by the government.

[c] Pre-pregnancy chronic diseases registered by health personnel in the MBRN: Asthma, pre-pregnancy hypertension, renal disease, rheumatoid arthritis, type 1 diabetes and/or epilepsy.

[d] Physical or sexual abuse during childhood or adulthood. Questions adapted from the Abuse Assessment Screen.

[e] Prior history of stillbirth or miscarriages > 12 weeks, prior or current preeclampsia and/or first trimester vaginal bleeding.

[f] ≥ 1 of the following: Conflict at work/study, financial problems, divorce/separation/partnership breakup, conflict with family or friends, severe injury or illness to the woman or a loved one, involvement in a severe traffic accident, fire or robbery, or death of a close relative or friend - during the last 12 months and defining it as "painful or difficult".

[g] Maternal depression/anxiety in pregnancy week 17–20 (mean > 1.75 on Hopkins symptom checklist-5).

[h] Self-reported history of anxiety or positive screening on the LTMD score.

[i] Last 2 years. Correlation analysis and linear regression analysis with depression score as the dependent variable and disease duration as the independent variable showed no association or linear relationship between the two variables (not included in the paper). We chose this cutoff because higher depression scores were seemingly accumulated among the women diagnosed in the years closest to pregnancy in the scatter plot.

Table e-2. Dropout rates among the depressed women in the third trimester

		MS diagnosed after pregnancy		
Questionnaire	**MS diagnosed before pregnancy**	**Symptom onset before pregnancy**	**Symptom onset after pregnancy**	**Reference group**
Pregnancy week 30; n (%)	18 (100)	5 (100)	33 (100)	8410 (100)
6 months postpartum; n (%)	16 (89)	5 (100)	31 (94)	7226 (86)
18 months postpartum; n (%)	14 (78)	5 (100)	25 (76)	5975 (71)

Dropout rates were compared with X^2 test and Fisher exact test. P-values not shown.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230868003 (print)
9788230856772 (PDF)