Risk factors for MS onset, relapses and progression

Helen Tremlett, PhD
Canada Research Chair in Neuroepidemiology and MS
Professor, Faculty of Medicine (Neurology)
University of British Columbia, Vancouver
helen.tremlett@ubc.ca
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Learning objective: Highlight opportunity for WCN attendees to advance understanding of risk factors for MS onset, relapses & progression

Big picture overview of (modifiable) risk factors for:
- MS onset
- MS relapses
- Progression of disability

Focus on 2 areas of emerging interest:
- MS prodrome: evidence and implications
- Are comorbidities associated with relapses or MS disability?
(Modifiable) factors associated with MS onset

Lower risk

- ↑serum vitamin D levels
- Direct sun
- Consistent &/or reasonable evidence
- Being male (>12 years old)
- HLA haplotypes

Higher risk

- Epstein-Barr Virus
- Cigarette Smoking
- Obesity
- Infectious agents
- Stress
- Shift Work
- Solvents
- Coffee
- Fish oil, vitamin D
- Gut microbiota composition
- Possible &/or emerging evidence
Timing and interaction between factors appears important

**Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis**

Tomas Olsson, Lisa F. Barcellos and Lars Alfredsson

Abstract | Genetic predisposition to multiple sclerosis (MS) only explains a fraction of the disease risk. Lifestyle and environmental factors are key contributors to the risk of MS. Importantly, these nongenetic factors influence pathogenic pathways, and some of them can be modified. Besides established MS-associated risk factors—high latitude, low vitamin D levels caused by insufficient sun exposure and/or diet (EBV) infection—strong evidence now supports obesity and increasing MS risk. Organic solvents and shift work have also been linked with increased MS risk. Whereas factors such as use of nicotine or alcohol and a high caffeine consumption are associated with a reduced risk. EBV infection and obesity interact with HLA risk genes, pointing toward adaptive immunity. All of the described risk factors for MS and/or innate immunity, which is thought to be the main pathway, are influenced by nongenetic risk factors, many lifestyle and environmental factors that are potential for prevention, particularly for people at the greatest risk with MS. Here, we review recent data on environmental and themation—gene-environment interactions.

Multiple sclerosis (MS) is a demyelinating disease that mainly affects young adults and is characterized by repeated waves of inflammatory cells that enter the CNS. This process is often subclinical, but can also be manifested clinically as slowly progressive disability. The pathogenesis of MS is multifactorial, involving both genetic and environmental factors. Helping to clarify the pathogenesis of MS is that the disease can manifest during the transition to adulthood, which is a period of significant sociodemographic stress and life changes. As the risk of MS increases with age, with the highest prevalence occurring between ages 22 and 40 years, these factors are particularly intriguing. Further, the risk of MS is higher in adults who are male (over 12 years old) or have more than one child. It is not known whether the risk of MS is due to the sex itself or to the number of children. The risk might be higher in other male sex, such as men who are not married or men who are married but have no children. The risk is also higher in men who are married and have children, but not in other men. In women, the risk is higher in those who are married and have children, but not in other women. The risk is also higher in women who are married and have children, but not in other women. The risk is also higher in women who are married and have children, but not in other women.

**Environmental modifiable risk factors for multiple sclerosis: Report from the 2016 ECTRIMS focused workshop**

Maria Pia Amato, Tobias Derflers, Bernard Hemmer, Roland Liblau, Xavier Montalban, Per Sadberg Srensen and David H Miller; For the ECTRIMS Focused Workshop Group

Abstract | Multiple sclerosis (MS) is an inflammatory and neurodegenerative demyelinating disease of the central nervous system (CNS), most likely autoimmune in origin, usually beginning in early adulthood. The etiology of the disease is not well understood; it is viewed currently as a multifactorial disease which results from complex interactions between genetic predisposition and environmental factors, of which a few are potentially modifiable. Improving our understanding of these factors could lead to new and more effective approaches to patient counseling and, possibly, prevention and management of the disease. The 2016 focused workshop of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) focused on the factors that may influence the risk of MS and the clinical course of the disease.

**Smoking and its interaction with genetics in MS etiology**

Anna K Hedström

Abstract | The etiology of multiple sclerosis (MS) involves multifaceted interactions between genetic loci and environmental factors. Smoking is an important risk factor for MS that overall increases the risk of the disease with approximately 50%. However, the precise effects of smoking on MS development vary considerably in different contexts and in different populations. This review focuses on the influence of smoking on MS risk and its interaction with genetics in MS etiology. The possible biological mechanisms are presented in this paper. Further research is needed to establish the mechanisms of causality and to explore preventive strategies.

**Keywords:** Multiple sclerosis, smoking, review, interaction

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Some limitations to consider

Most evidence based on:
- whites
- women
- relapsing-onset MS
- people living in N. America, Europe, Australasia

Findings may not generalize to:
- non-whites
- men
- primary-progressive MS
- people living in ‘other’ areas

Accurate capture of exposures is difficult

Accurate capture of exposures *prior* to MS onset is very difficult
Prodrome...

*An early symptom indicating the onset of a disease or illness...*

*...i.e., prior to our classical understanding of MS symptom onset*

*Oxford English Dictionary*
Is there an MS prodrome?

Historically, the lead MS medical textbook concluded...

a) Yes

b) Maybe, 
   but more evidence needed

c) No
The MS prodrome

Relatively little was known

- 13 years Educational attainment
  Sinay, 2015
- 3.8 years ‘vague’ symptoms
  Gout, 2011
- 2 years Cognitive performance
  Cortesse, 2016
- 1/2 year Depression
  (n=29)
  Byatt, 2011

‘MS symptom onset’ / CIS  MS diagnosis

Giovannoni, Editorial Lancet Neurol 2017

Dr José Wijnands Lancet Neurol 2017
Is there a MS prodrome, measurable via healthcare use?

Linked health administrative and MS specific clinical data

‘Health administrative cohort’
4 Canadian provinces
14,428 MS cases
72,059 matched controls

Examined 5 years before:

1st demyelinating ICD code
Prospective
Administrative data
(physician or hospital visits)

‘MS clinical cohort’
2 provinces
3,202 MS cases
16,006 matched controls

‘MS symptom onset’
Retrospective
MS clinic data
(recorded by MS neurologist)

Lancet Neurol 2017

Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study
Joshua M A Wijersma, Eleftherios Georgiou, Feng Tan, Yinchen Zhao, Tangja Huijg, Karen Stoddart, Onne de Klerk, Xinyan Zhou, Chi Lo, Charlie Evans, John D’Silva, Barbara Maria, Stelios Tsoukatos
The MS prodrome: health care use was higher in the five years before a 1st demyelinating event or ‘MS symptom onset’

- 78% higher rate of hospitalizations
- 88% higher rate of physician service use
- 49% relative increase in Rx numbers (drug classes dispensed)

4 Canadian provinces
14,428 MS cases
72,059 matched controls

‘...the definitive study on the MS prodrome’
Editorial. Lancet Neurol 2017

Wijnands Lancet Neurol 2017
Why were people who developed MS accessing health services in the 5 year ‘prodromal period’?
‘Modifiable’ factors associated with MS relapses

Lower risk

- Consistent &/or reasonable evidence
  - ↑ serum vitamin D levels
  - Direct sun
  - 3rd trimester
  - Vitamin D suppl.
  - ‘Evidence of benefit lacking’ Cochrane Review 2018

Higher risk

- Higher risk
  - Cigarette Smoking
  - Post-partum
  - Stress
  - Gut microbiota composition
  - Infectious agents

Possible &/or emerging evidence
‘Modifiable’ factors associated with MS progression

Lower risk

Consistent &/or reasonable evidence

Vitamin D suppl.
‘Evidence of benefit lacking’
*Cochrane Review 2018*

Possible &/or emerging evidence

↑*serum vitamin D Levels?*

Higher risk

Cigarette Smoking

↑BMI / obesity

*Depression Comorbidity*

*Obesity/vascular disorders*
Are **comorbidities** associated with relapses or EDSS disability?

1. Yes for some comorbidities and *relapse rates*

2. Yes for some comorbidities and *disability outcomes*

3. Yes to 1 & 2

4. No
Are comorbidities associated with relapses or EDSS disability?

MS clinic cohort
EDSS, relapses

Drug exposure

MS, physical and mental comorbidity

Death data

Residency
Sex, age
Socioeconomic status

n=855 prevalent R-MS
4 provinces
prospectively enrolled
2 year follow-up
confirmed relapses (outcome)

incident onset MS
2 provinces; EDSS outcome

n=3166
8.4 year follow-up (mean)

n=2312
10.5 year follow-up (mean)

Comorbidity increases the risk of relapse in multiple sclerosis
A prospective study

Kowalec Neurology 2017

Physical comorbidity
HEART DISEASE
DIABETES
EPILEPSY

Zhang Neurology 2018

McKay Neurology 2018
Comorbidity associated with higher: relapse rate & disability (EDSS) risk

**General effect:**
total number of comorbidities ➞ increased relapses & EDSS

**Specific effects:**
↑relapse rates
↑EDSS, mean

67% higher relapse rate
adj. RR: 1.7 (95%CI 1.1-2.6)

higher EDSS:
adj.β:0.28 (95%CI 0.12-0.44)

38% higher relapse rate
adj.RR 1.38 (95%CI 1.01-1.89)

higher EDSS:
adj.β:0.68 (95%CI 0.11-1.26)

Adjustments: age, sex, disease duration or course, SES, MS drug exposure
Summary

Huge opportunity and need for WCN attendees from all disciplines to advance understanding of risk factors for MS

Big picture overview of the risk factors for:

- **MS onset**
- **MS relapses**
- **Disability progression**
Summary

Areas of emerging interest:

The **MS prodrome**...

...is measurable as higher healthcare use 5 years **before** clinical recognition of MS

Suggests earlier window of opportunity to identify and manage MS?

*Needs to be very carefully considered when searching for risk factors for MS onset*

Are **comorbidities** associated with relapses or EDSS disability?

Hyperlipidemia, migraine ➔ ↑relapse rates
Mental health, heart disease, epilepsy ➔ ↑EDSS disability

*Could a focus on comorbidity management alter MS outcomes?*
References

Reviews/ books: risk factors for MS onset, relapses and progression


Original studies: the MS prodrome


Original studies: comorbidities and outcomes in MS

