Risk factors for MS onset, relapses and progression

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Vancouver CoastalHealth Research Institute
Healthier lives through discovery

MS National Multiple Sclerosis Society

Michael Smith Foundation for Health Research

Djavad Mowafaghian CENTRE FOR BRAIN HEALTH

MS Multiple Sclerosis Society of Canada | Société canadienne de la sclérose en plaques SP

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Disclosures

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MS Society of Canada; Scientific and Research Foundation

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American Academy of Neurology (2013-19)

Consortium of MS Centres (2013, 2018)

National MS Society, A/ECTRIMS (2013-19)

Speaker honoraria declined or requested to fund a trainee to attend a conference

Overview

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

Higher risk

Consistent &/or reasonable evidence

↑*serum* vitamin D levels

Direct sun

Being male (>12 years old)

HLA haplotypes

Epstein-Barr Virus

Cigarette Smoking

Obesity

Possible &/or emerging evidence

Diet

Coffee

Fish oil, vitamin D

?

Shift Work

Stress

SOLVENTS

Gut microbiota composition

Infectious agents

Timing and interaction between factors appears important

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

Tomas Olsson[1], Lisa F. Barcellos[2] and Lars Alfredsson[3]

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 can influence pathogenetic pathways, and some of them can be modified. Besides established MS-associated risk factors — high latitude, fe vitamin D levels caused by insufficient sun exposure and/or dietar (EBV) infection — strong evidence now supports obesity during ac increasing MS risk. Organic solvents and shift work have also been risk of the disease, whereas factors such as use of nicotine or alcol and a high coffee consumption are associated with a reduced risk. EBV infection and obesity — interact with HLA risk genes, pointin involving adaptive immunity. All of the described risk factors for M and/or innate immunity, which is thought to be the main pathway Unlike genetic risk factors, many environmental and lifestyle facto potential for prevention, particularly for people at the greatest risk with MS. Here, we review recent data on environmental and lifesty 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 the deteriorating c broadly on the imn adverse events. Tha an unmet medica

Organic solvents and MS susceptibility

Interaction with MS risk HLA genes

ARTICLE OPEN ACCESS

Anna Karin Hedström, MD, PhD, Ola Hössjer, PhD, Michail Katsoulis, PhD, Ingrid Kockum, PhD, Tomas Olsson, MD, PhD,* and Lars Alfredsson, PhD*

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Neurology® 2018;91:e455-e462. doi:10.1212/WNL.0000000000005906

RELATED ARTICLE

Editorial
Genes, smoking, and organic solvent exposure: An alarming cocktail for MS risk
Page 199

MORE ONLINE

Podcast
Dr. Stacey Clardy interviews Dr. Anna Hedström about MS risk and exposure to organic solvents.
NPub.org/3nj2m3

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Population attributable fractions and joint effects of key risk factors for multiple sclerosis

IA F van der Mei, RM Lucas, BV Taylor, PC Valery, T Dwyer, TJ Kilpatrick, MP Pender, D Williams, C Chapman, P Otahal and A-L Ponsonby

Multiple Sclerosis Journal
2016, Vol. 22(4) 461–469
DOI: 10.1177/1352458515594040

Abstract

MULTIPLE SCLEROSIS JOURNAL | MSJ

Meeting Review

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

Maria Pia Amato, Tobias Derfuss, Bernard Hemmer, Roland Liblau, Xavier Montalban, Per Soelberg Sørensen and David H Miller; For the 2016 ECTRIMS Focused Workshop Group*

Multiple Sclerosis Journal
2018, Vol. 24(5) 590–603
DOI: 10.1177/1352458516686847

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 aetiology 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 can lead to new and more effective approaches to patient counselling and, possibly, prevention and management of the disease. The 2016 focused workshop of the European Committee for Treatment and Research in Multiple

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MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Smoking and its interaction with genetics in MS etiology

Anna K Hedström

Multiple Sclerosis Journal
1–7
DOI: 10.1177/1352458518801727

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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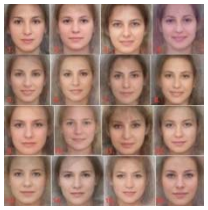
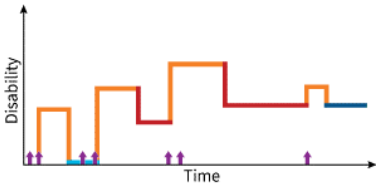
Some limitations to consider

Most evidence based on:



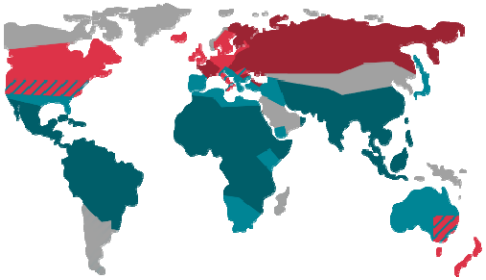


whites

women

relapsing-onset MS

people living in N. America, Europe, Australasia



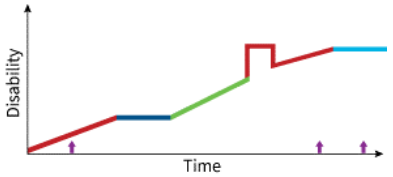
Findings may not generalize to:

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…

Oxford English Dictionary

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

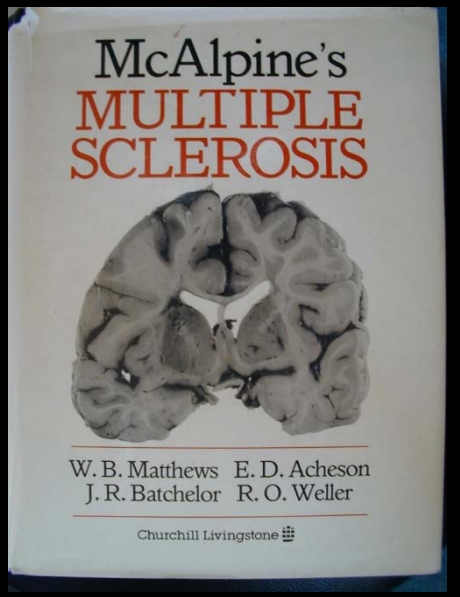
Is there an MS prodrome?

Historically, the lead MS medical text book concluded…

a) Yes

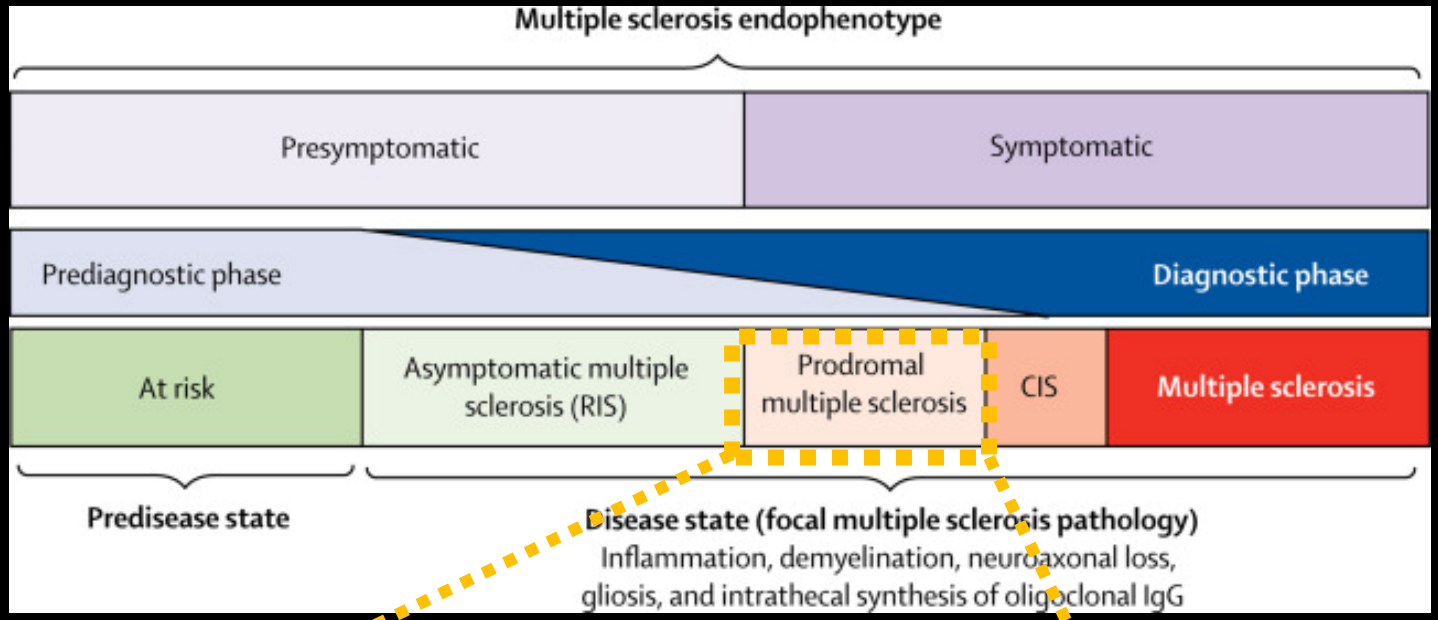
b) Maybe,
but more evidence needed

c) No



2nd Edition
(1985-2000)

The MS prodrome



Dr José Wijnands
Lancet Neurol 2017

Giovannoni, Editorial
Lancet Neurol 2017

Relatively little was known

'MS symptom onset' / CIS

MS diagnosis

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

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

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

Examined 5 years before:

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

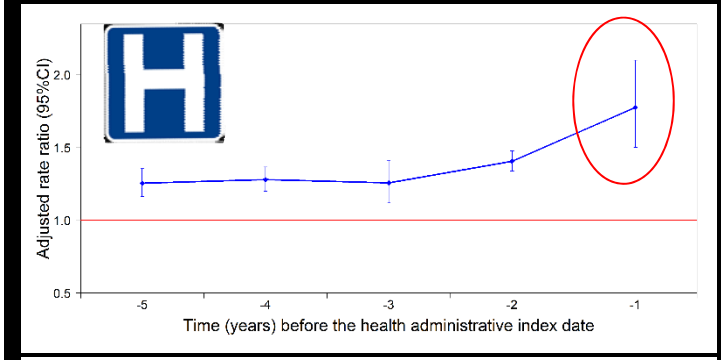
'MS symptom onset'
Retrospective
MS clinic data
(recorded by MS neurologist)

Lancet Neurol 2017

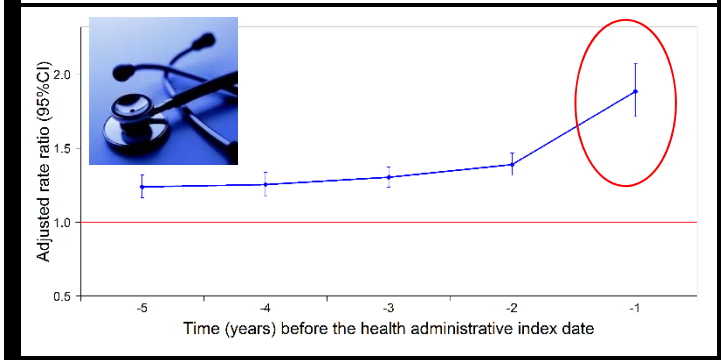
Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study

José M A Wijnands, Elaine Kingwell, Feng Zhu, Yinshan Zhao, Tanja Hogg, Karen Stadnyk, Okechukwu Ekuma, Xinyal Lu, Charity Evans, John D Fisk, Ruth Ann Marrie, Helen Tremlett

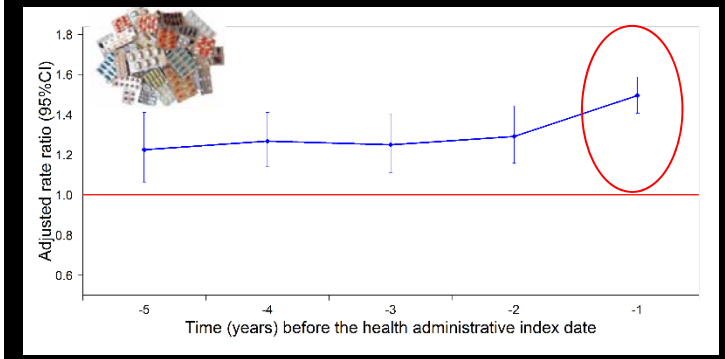
The MS prodrome: health care use was higher in the five years before a 1st demyelinating event or 'MS symptom onset'



78% higher rate of hospitalizations



88% higher rate of physician service use



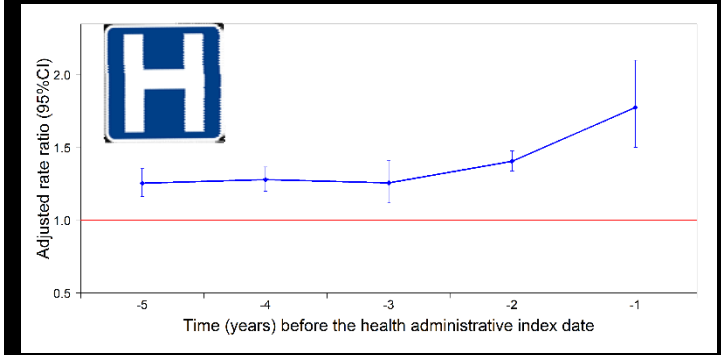
49% relative increase in Rx numbers (drug classes dispensed)

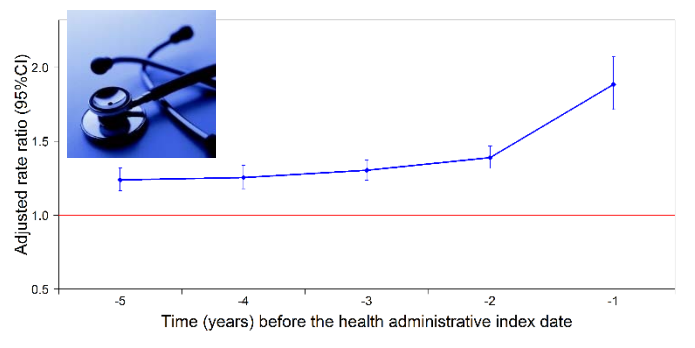
4 Canadian provinces
14,428 MS cases
72,059 matched controls

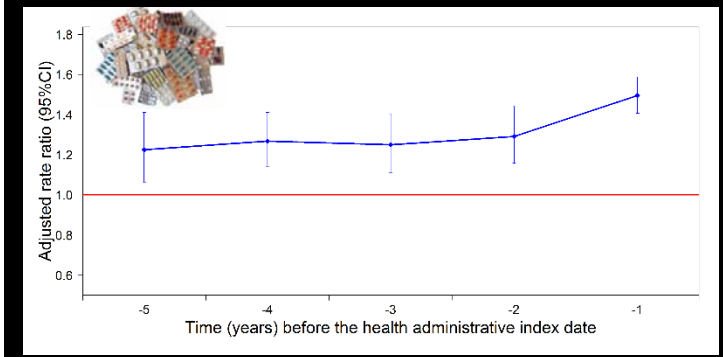
'....the definitive study on the MS prodrome'
Editorial. Lancet Neurol 2017

Wijnands Lancet Neurol 2017

Why were people who developed MS accessing health services in the 5 year 'prodromal period'?

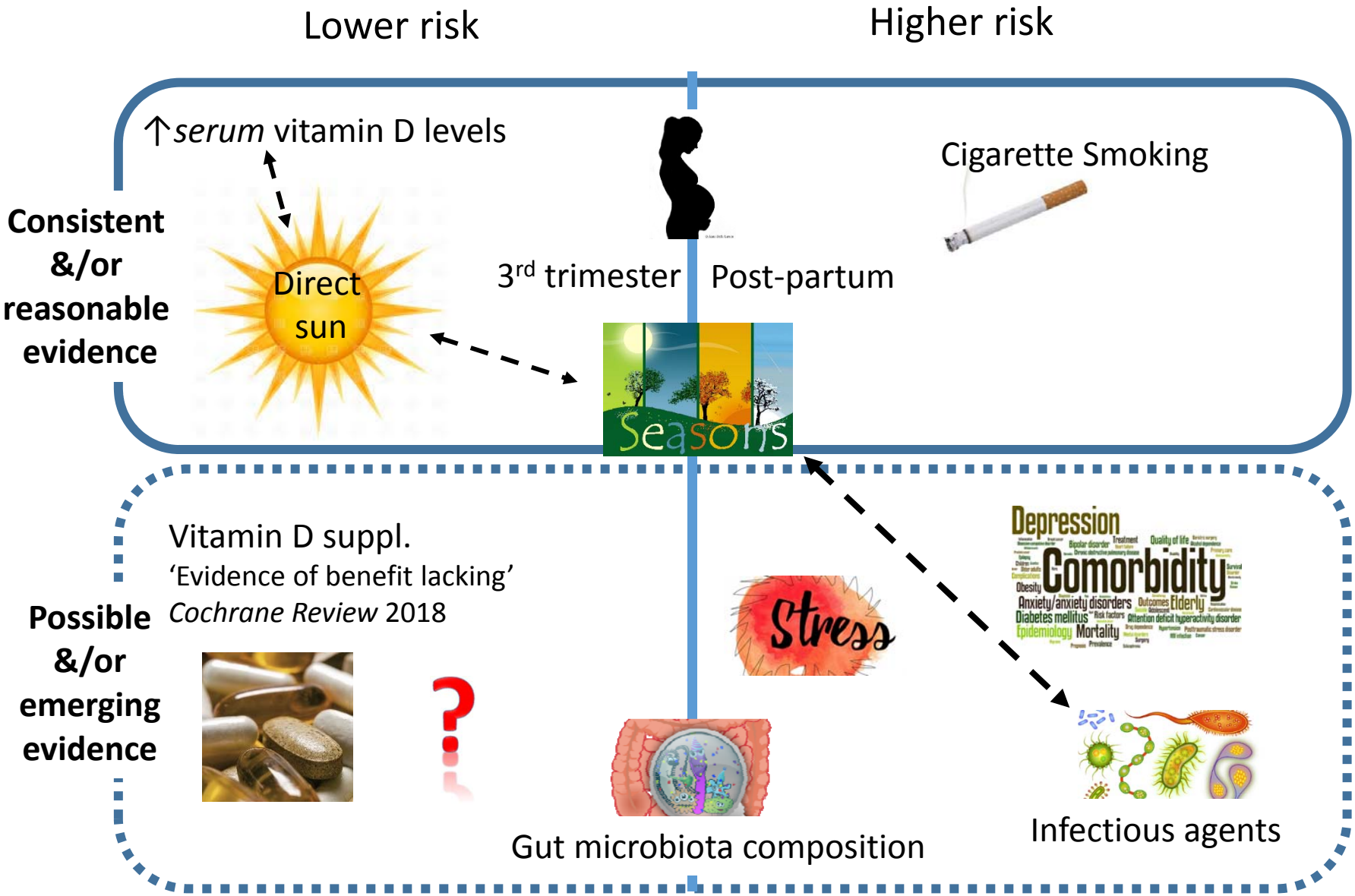




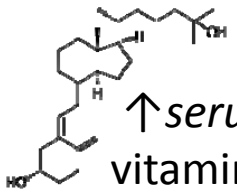


?

‘Modifiable’ factors associated with MS relapses



‘Modifiable’ factors associated with MS progression

	Lower risk	Higher risk
Consistent &/or reasonable evidence		Cigarette Smoking 
Possible &/or emerging evidence	Vitamin D suppl.  ‘Evidence of benefit lacking’ *Cochrane Review* 2018  ↑*serum* vitamin D Levels? $$$ 	↑BMI / obesity  

?

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

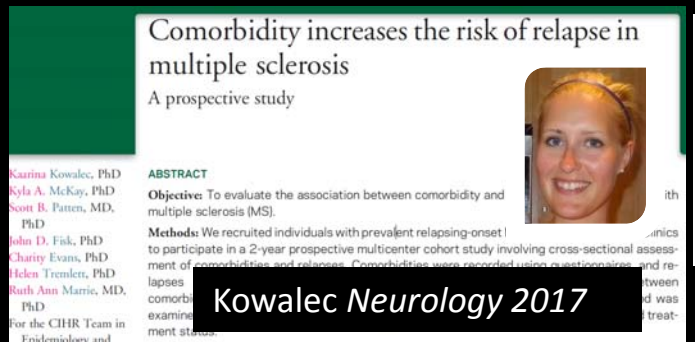
Residency Sex, age Socioeconomic status

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

Karina Kowalec, PhD
Kyla A. McKay, PhD
Scott B. Patten, MD, PhD
John D. Fisk, PhD
Charity Evans, PhD
Helen Tremlett, PhD
Ruth Ann Marrie, MD, PhD
For the CIHR Team in Epidemiology and

ABSTRACT

Objective: To evaluate the association between comorbidity and multiple sclerosis (MS).

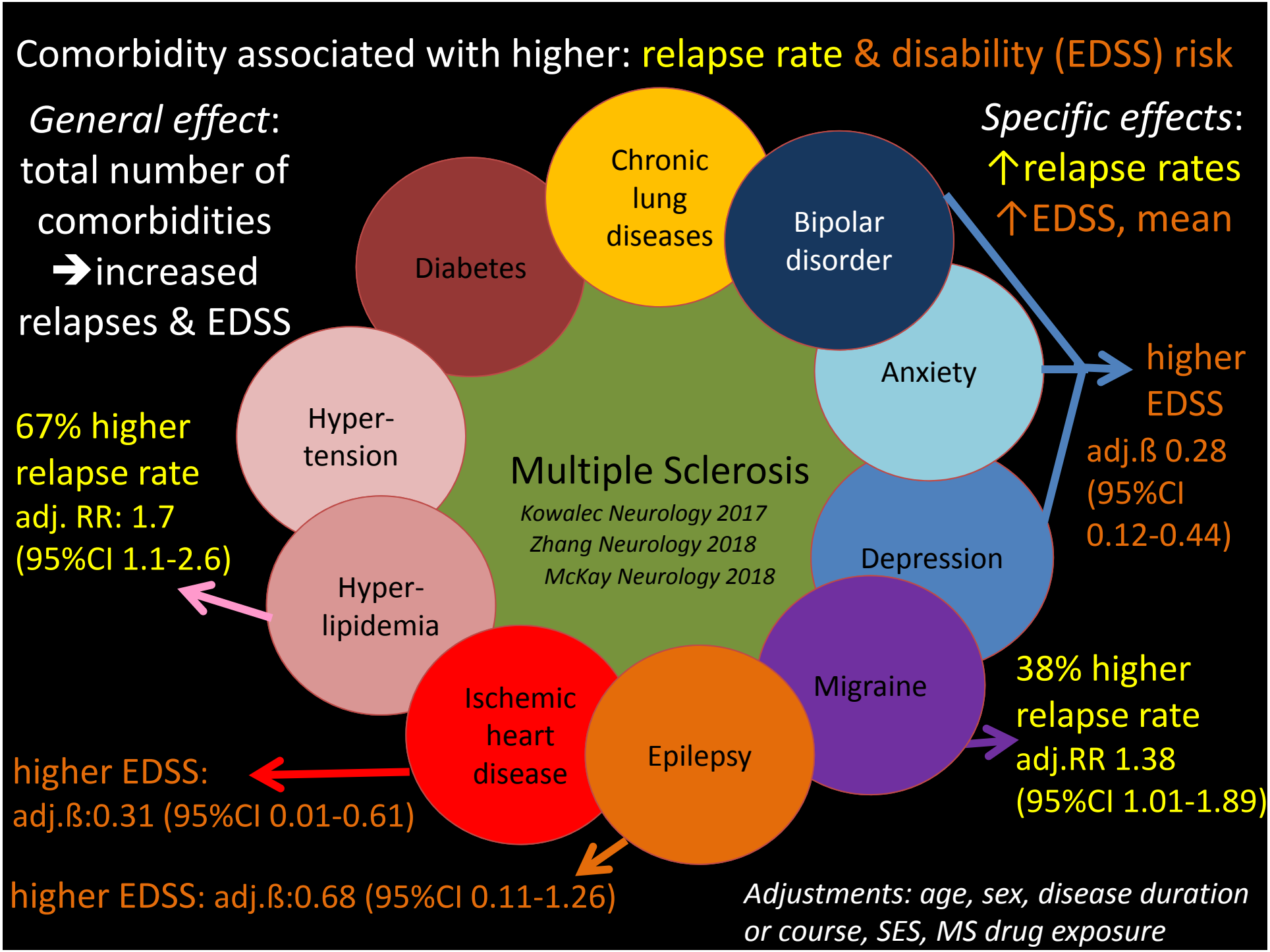
Methods: We recruited individuals with prevalent relapsing-onset MS to participate in a 2-year prospective multicenter cohort study involving cross-sectional assessment of comorbidities and relapses. Comorbidities were recorded using questionnaires and re-examined

Kowalec *Neurology 2017*

Physical comorbidity
HEART DISEASE
DIABETES
EPILEPSY

Zhang *Neurology 2018*

McKay *Neurology 2018*

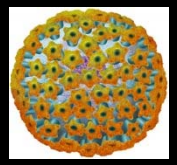

Comorbidity associated with higher: relapse rate & disability (EDSS) risk
General effect: total number of comorbidities ➔increased relapses & EDSS
Specific effects: ↑relapse rates ↑EDSS, mean
Chronic lung diseases
Diabetes
Bipolar disorder
Anxiety
Hyper-tension
Depression
Hyper-lipidemia
Migraine
Ischemic heart disease
Epilepsy
Multiple Sclerosis
Kowalec Neurology 2017
Zhang Neurology 2018
McKay Neurology 2018
higher EDSS
adj.ß 0.28 (95%CI 0.12-0.44)
67% higher relapse rate
adj. RR: 1.7 (95%CI 1.1-2.6)
38% higher relapse rate
adj.RR 1.38 (95%CI 1.01-1.89)
higher EDSS: adj.ß:0.31 (95%CI 0.01-0.61)
higher EDSS: adj.ß:0.68 (95%CI 0.11-1.26)
Adjustments: age, sex, disease duration or course, SES, MS drug exposure

Summary

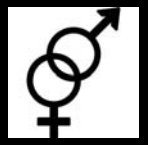
Huge opportunity and need for WCN attendees from all disciplines to advance understanding of risk factors for MS

Big picture overview of the risk factors for:

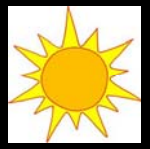
MS onset







MS relapses




Disability progression

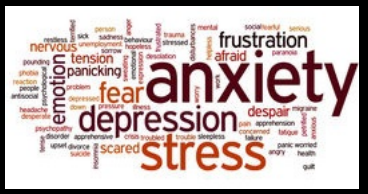


Summary

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?

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Original studies: the MS prodrome

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Original studies: comorbidities and outcomes in MS

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