TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN FINLAND

with the Emphasis on Hospitalization and Infection-related Admissions

Anna-Leena Pirttisalo

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1584 | MEDICA – ODONTOLOGICA | TURKU 2021

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN FINLAND

with the Emphasis on Hospitalization and Infection-related Admissions

Anna-Leena Pirttisalo

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1584 | MEDICA – ODONTOLOGICA | TURKU 2021

University of Turku

Faculty of Medicine
Clinical Neurosciences
Doctoral Programme in Clinical Research
Neurocenter
Turku University Hospital

Supervised by

Docent Merja Soilu-Hänninen
Clinical Neurosciences
University of Turku and
Neurocenter
Turku University Hospital
Turku, Finland

Docent Jussi Sipilä
Clinical Neurosciences
University of Turku and
Department of Neurology
Siun Sote North Karelia Central Hospital
Turku and Joensuu, Finland

Reviewed by

Professor Anne-Marie Landtblom
Department of Neuroscience
Uppsala University
Uppsala, Sweden

Docent Johanna Palmio
Neuromuscular Research Center
Tampere University Hospital and
Tampere University
Tampere, Finland

Opponent

Professor Jukka Peltola
Faculty of Medicine and Health
Technology
University of Tampere and
Department of Neurology
Tampere University Hospital
Tampere, Finland

ISBN 978-951-29-8623-1 (PRINT)
ISBN 978-951-29-8624-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2021

To Panu, Eino and Niilo

UNIVERSITY OF TURKU
Faculty of Medicine, Clinical Neurosciences
ANNA-LEENA PIRTTISALO: Epidemiology of Multiple Sclerosis in Finland with the Emphasis on Hospitalization and Infection-related Admissions
Doctoral Dissertation, 122 pp.
Doctoral Programme in Clinical Research, September 2021

ABSTRACT

Finland is a high-risk region for multiple sclerosis (MS) and there are marked regional differences in the epidemiology of MS in different parts of the country. Though the prevalence of MS is increasing worldwide, fortunately its treatment has developed considerably during recent decades. MS patients use health services more than the general population and carry an increased risk of suffering infections, which could potentially be further increased by new disease modifying therapies (DMTs).

The aim of this thesis was to evaluate regional differences in MS epidemiology in Finland by reviewing previous epidemiological studies of MS and introducing new epidemiological data from the western, southwestern and eastern regions of Finland. In order to assess the changing burden of MS on the health system and the effects of new DMTs, another aim was to investigate trends in hospital admission rates of MS patients and the role of infections in MS-related hospital admissions in Finland and to identify those factors predisposing to infection-related MS admissions. Data were derived from registers of hospitals and National Institute for Health and Welfare.

We estimated an age-standardized MS prevalence of 251/100,000 in Southwest Finland and 150/100,000 in eastern North Karelia in 2016. The highest MS prevalence of 288/100,000 was observed in South Ostrobothnia in 2007. The age-standardized MS incidence was 9.2/100,000 person-years in Southwest Finland and 6.5/100,000 person-years in North Karelia in 2012–2016. MS-related hospital admissions declined by 4.6% annually representing an annual aggregate reduction of cost of hospital admissions by 51% in Finland from 2004 to 2014. During the second study period 2009–2018, which focused on Southwest Finland, there were declines in both the annual number of MS-related hospital admissions and the number of infection-related admissions. Patients with infection-related admissions were older and more often male, had longer disease durations, more disability, more often a progressive disease and more comorbidities. DMTs were used less often by patients with infection admissions.

Our results confirmed clear regional differences of MS epidemiology in Finland with the highest epidemiological figures found in western and southwestern hospital districts. Stable increase in MS prevalence was observed over five decades while incidence has increased only since 1990s. Hospital admissions of MS patients declined during the study periods, a time period coinciding with an increase in the use of DMTs. Infection-related admissions lasted longer and had increased in-hospital mortality emphasizing the importance of the prevention of infections. The association of these admissions with advanced disease and the lesser use of DMTs underline the significance of preventing disability progression in infection prevention in MS.

KEYWORDS: Multiple sclerosis, Epidemiology, Hospitalization, Infections, Disease Modifying Therapies

TURUN YLIOPISTO
Lääketieteellinen tiedekunta, kliiniset neurotieteet
ANNA-LEENA PIRTTISALO: MS-taudin epidemiologia Suomessa – sairaalahoitoon ja infektioihin painottuvia tutkimuksia
Väitöskirja, 122 s.
Turun kliininen tohtoriohjelma, syyskuu 2021

TIIVISTELMÄ

Suomi kuuluu multippeliskleroosin (MS) korkean riskin alueeseen ja maassamme on todettu alueellisia eroja taudin epidemiologiassa. MS-taudin esiintyvyys kasvaa maailmanlaajuisesti, mutta myös taudin lääkehoito on kehittynyt nopeasti viimeisten vuosikymmenten aikana. MS-potilaat käyttävät runsaasti terveydenhuollon palveluita ja heillä on kohonnut infektioriski, jota uudet lääkkeet entisestään saattavat lisätä.

Tämän väitöskirjatyön tavoitteena oli tutkia aiempaa tarkemmin MS-taudin epidemiologian alueellisia eroja Suomessa tarkastelemalla aiempia epidemiologisia tutkimuksia ja selvittämällä uusia epidemiologisia lukuja Itä-, Länsi- ja Varsinais-Suomessa. Jotta MS-taudin aiheuttamasta terveydenhuollon kuormituksesta ja uusien lääkehoitojen vaikutuksista saataisiin uutta tietoa, toisena tavoitteena oli tutkia MS-potilaiden sairaalahoitojaksojen kehitystä Suomessa ja infektioiden osuutta näiden joukossa sekä tunnistaa sairaalahoitoa vaativille infektioille altistavia tekijöitä Varsinais-Suomessa. Tiedot haettiin sairaaloiden ja Terveyden ja hyvinvoinnin laitoksen rekistereistä.

MS-taudin ikävakioitu esiintyvyys oli vuonna 2016 Varsinais-Suomessa 251/100,000 ja Pohjois-Karjalassa 150/100,000. Korkein esiintyvyys oli 288/100,000 ja se todettiin Etelä-Pohjanmaalla vuonna 2007. Ikävakioitu ilmaantuvuus oli 9.2/100,000 henkilövuotta Varsinais-Suomessa ja 6.5/100,000 henkilövuotta Pohjois-Karjalassa ajanjaksolla 2012–2016. MS-potilaiden sairaalahoitojaksot vähenivät Suomessa ensimmäisen tutkimusjakson (2004–2014) aikana 4.6% vuodessa ja sairaalahoitojaksoihin liittyvät vuosittaiset kokonaiskustannukset vähenivät tutkimusjakson aikana 51%. Varsinais-Suomessa sekä kaikki MS-potilaiden sairaalahoitojaksot että infektioihin liittyvät hoitojaksot vähenivät ajanjaksolla 2009-2018. Infektion vuoksi sairaalaan joutuneet potilaat olivat vanhempia, pidempään MS-tautia sairastaneita ja useammin miehiä. Lisäksi heillä oli useammin etenevä MS-tauti sekä enemmän invaliditeettiä ja liitännäissairauksia verrattuna alueen muihin MS-potilaisiin. Verrokkipotilailla oli käytössä MS-taudin lääkehoito useammin kuin infektion vuoksi sairaalahoitoon joutuneilla potilailla.

Tutkimuksemme vahvisti, että Suomessa on merkittäviä alueellisia eroja MS-taudin epidemiologiassa ja taudin esiintyvyys on korkea Suomen länsi- ja lounaisosissa. MS-taudin esiintyvyys on noussut tasaisesti 50 vuoden aikana, mutta ilmaantuvuus on noussut vasta 1990-luvulta lähtien. MS-potilaiden sairaalahoitojaksot vähenivät tutkimusjaksojen aikana samanaikaisesti MS-taudin lääkehoidon yleistymisen kanssa. Infektioon liittyvät hoitojaksot olivat muita hoitojaksoja pidempiä ja sairaalakuolleisuus oli niihin liittyen korkeampi osoittaen infektioiden ehkäisyn tärkeyden. Infektioon liittyvien hoitojaksojen yhteys edenneeseen MS-tautiin ja vähäisempään MS-taudin lääkehoidon käyttöön korostaa taudin tehokkaan hoidon ja potilaiden hyvän toimintakyvyn merkitystä myös infektioiden ehkäisyssä.

AVAINSANAT: MS-tauti, Epidemiologia, Sairaalahoito, Infektiot, Lääkehoito

Table of contents

Abbreviations

APC	Antigen-presenting cell
BBB	Blood-brain barrier
BMI	Body mass index
CI	Confidence interval
CIS	Clinically isolated syndrome
CMV	Cytomegalovirus
CNS	Central nervous system
CRHC	Care register of health care
CSF	Cerebrospinal fluid
DIS	Dissemination in space
DIT	Dissemination in time
DMT	Disease modifying therapy
DZ	Dizygotic
EBV	Epstein-Barr virus
EDSS	Expanded disability status scale
ESP	European Standard Population
F/M	Female/male
Gd	Gadolinium
GWAS	Genome-wide association studies
HBV	Hepatitis B virus
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
ICD	International Classification of Diseases
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IQR	Interquartile range
KELA	Social Insurance Institution
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging

MS	Multiple sclerosis
MZ	Monozygotic
NEDA	No evidence of disease activity
OR	Odds ratio
OCB	Oligoclonal bands
PEG	Percutaneous endoscopic gastrostomy
POMS	Pediatric-onset multiple sclerosis
PPMS	Primary progressive multiple sclerosis
RR	Relative risk
RRMS	Relapsing remitting multiple sclerosis
SD	Standard deviation
SPMS	Secondary progressive multiple sclerosis
Th	T helper cell
THL	National Institute for Health and Welfare
Treg	T regulatory cell
UVB	Ultraviolet B
VZV	Varicella zoster virus
25OHD	25-hydroxyvitamin D

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I - IV:

I Pirttisalo AL, Soilu-Hänninen M, Sipilä JOT. Multiple sclerosis epidemiology in Finland: regional differences and high incidence. Acta Neurologica Scandinavica, 2019; 139(4): 353–359.

II Pirttisalo AL, Soilu-Hänninen M, Sumelahti ML, Krökki O, Murtonen A, Hänninen K, Sipilä JOT. Changes in multiple sclerosis epidemiology over five decades. Acta Neurologica Scandinavica, 2020; 142(3): 200–209.

III Pirttisalo AL, Sipilä JOT, Soilu-Hänninen M, Rautava P, Kytö V. Adult hospital admissions associated with multiple sclerosis in Finland in 2004–2014. Annals of Medicine, 2018; 50(4): 354–360.

IV Pirttisalo AL, Sipilä JOT, Viitala M, Soilu-Hänninen M. Trends and characteristics of infection-related hospital admissions in multiple sclerosis patients in Southwest Finland in 2009–2018. Multiple Sclerosis and Related Disorders, 2020; 44: 102328.

1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) typically causing a disability among young adults. The first clear scientific description of MS was made by the French neurologist Jean-Martin Charcot in 1868. His triad of nystagmus, scanning speech and intention tremor was the first attempt to separate "sclérose en plaques" from many other diseases affecting the nervous system. He was also the first scientist to publish a paper that recognized that the prevalence of MS was not uniform but regional differences appeared between France, Germany and England (Charcot 1877). Since then, MS has been the subject of extensive research and much knowledge has accumulated about the epidemiological features of MS.

Indeed, one of the marked epidemiological characteristics of MS is its uneven distribution across the world. The lowest prevalence is observed in sub-Saharan Africa and East Asia (<10/100,000) and the highest in North America and the northern parts of Europe (>100/100,000) (The Multiple Sclerosis International Federation 2020). Like the other Nordic countries, Finland belongs to the high-risk regions of MS. The first epidemiological studies of MS in Finland were published in the 1960s and several regional reports have been published since then. However, research has concentrated on western Finland while there are no epidemiological MS studies conducted in eastern Finland and only one in the southwestern high-risk area in the era of modern diagnostic methods.

MS is associated with a major economic burden and patients with MS use health services more than the general population (Paz-Zulueta et al. 2020; Pohar et al. 2007). The increased utilization of health services is observed already several years before any diagnosis of MS (Marrie et al. 2013). In addition, the risk of infections as well as infection-related mortality are increased in MS patients (Manouchehrinia et al. 2016). A higher susceptibility to infections has been observed already in the year before MS diagnosis (Castelo-Branco et al. 2020) and the infection risk may further increase along with the progression of the disability and its associated functional limitations. Treatment of MS has evolved significantly in the last 20 years and also new high-efficacy disease modifying therapies (DMTs) may increase the risk of

infections when compared to traditional injectable therapies (Winkelmann et al. 2016).

Epidemiological evaluations are required for allocating of health care resources and may provide important insights into the pathogenesis of MS. In this series of studies, we evaluated regional differences of MS epidemiology in Finland by reviewing previous studies of MS epidemiology and evaluating new epidemiological data on western, southwestern and eastern regions of Finland. In view of the advances in the treatment of MS and the increasing occurrence of MS, it is essential to gather information on health care use of MS patients in order to understand the changing burden of MS on the health care system and to assess risks and benefits of new DMTs. Therefore, we evaluated trends in hospital admissions of MS patients, the role of infections in MS-related hospitalizations and factors predisposing to infection-related hospital admissions.

2 Review of the literature

2.1 Etiology of multiple sclerosis

2.1.1 Pathogenesis

MS is considered to be an autoimmune disease, involving both humoral and cellular immune systems. The pathogenesis consists of a breakdown of the blood-brain barrier (BBB), multifocal inflammation, demyelination, loss of oligodendrocytes, reactive gliosis and axonal degeneration (Lassmann 2019). According to the current understanding, an infectious agent or some other environmental antigen may trigger a loss of self-tolerance towards CNS antigens in genetically susceptible individuals, probably by activating myelin-reactive T cells (Fujinami & Oldstone 1985). Release of autoantigens due to cellular damage caused by a viral agent may lead to an activation of autoreactive T cells due to molecular mimicry or bystander activation (Geginat et al. 2017). Once activated in the periphery, myelin-reactive T cells can migrate across the BBB. After migration into the CNS, autoreactive T cells can be reactivated by antigen-presenting cells (APCs; dendritic cells, macrophages, B cells) presenting the CNS autoantigens on major histocompatibility complex (MHC) molecules to the invading T cells. This may elicit an inflammatory cascade leading to release of cytokines and chemokines, recruitment of additional inflammatory cells including T cells, monocytes and B cells and persistent activation of microglia and macrophages resulting in myelin damage (Selter & Hemmer 2013).

T cells are categorised into two major subsets: CD4+ T helper (Th) cells and CD8+ cytotoxic T cells. CD4+ T cells release cytokines and immune mediators, which lead to attraction of macrophages and a further release of proinflammatory cytokines. An interaction with MHC II expressing cells, such as dendritic cells, macrophages or B cells, is required for the activation of CD4+ T cells. Th 1 cells releasing interferon-gamma and Th17 cells secreting interleukin (IL) 17, are believed to be the most important contributing factors in the inflammation within CNS. In contrast, Th2 cells secreting IL 4, 5 and 10, and regulatory T cells expressing Foxp3, are believed to have a counter-regulatory role attempting to limit Th1 and Th17

responses (Selter & Hemmer 2013, Hemmer et al. 2015). CD8+ T cells are believed to be involved in the pathogenesis of MS as well as they can induce axonal pathology by direct injury to MHC I/antigen-expressing cells, such as neurons and oligodendrocytes (Neumann et al. 2002). Immunopathogenesis of MS is illustrated in Figure 1.

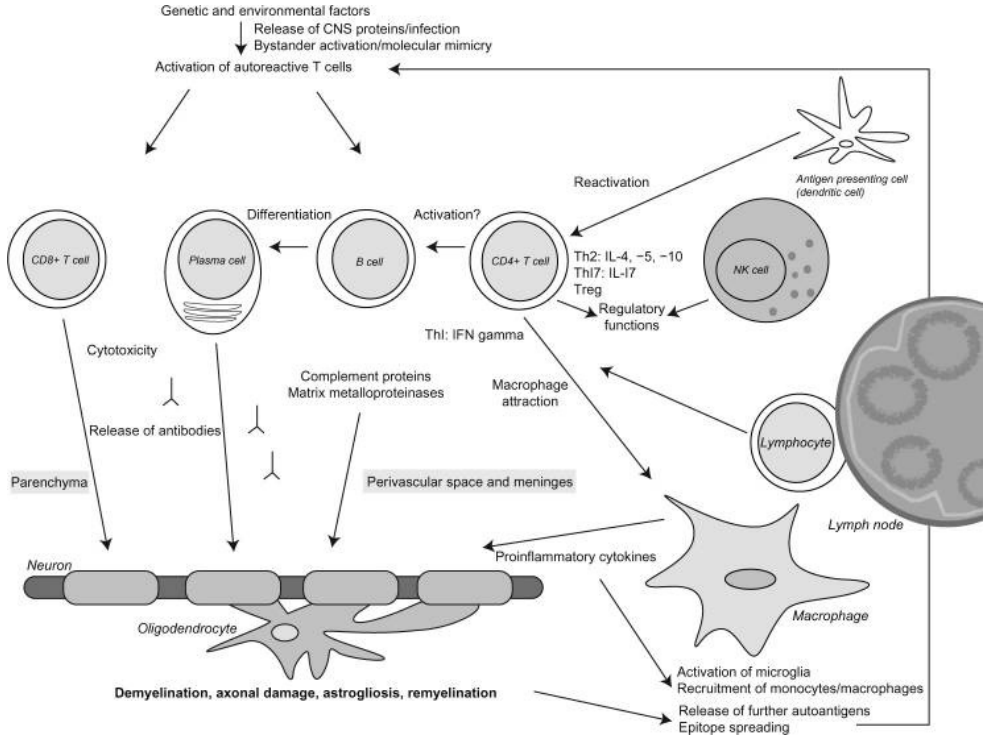

Figure 1. Immunopathogenesis of multiple sclerosis. CNS, central nervous system; IFN, interferon; IL, interleukin; NK cell, natural killer cell; Treg, regulatory T cell (Selter & Hemmer 2013, reprinted with permission from Dove Medical Press).

There is increasing evidence indicating that the B cells are involved in the pathogenesis of MS. B cells can differentiate into plasma cells and secrete autoantibodies that contribute to CNS inflammation. B cells are also important APCs in both the peripheral immune system and the CNS. They can recognize and internalize the CNS antigens and act as APCs to activate CNS-specific pathogenic T cells. Furthermore, different subsets of B cells in the CNS can modulate T cells and myeloid cell functions via the secretion of pro-inflammatory and anti-inflammatory cytokines (Hemmer et al. 2015).

Oligodendrocyte damage and demyelination occur as a result of the inflammation described above. Focal demyelinated lesions can be partly or completely repaired by remyelination. Axons are better preserved in the early stages of the disease but irreversible axonal damage develops as the disease progresses (Trapp et al. 1998). Inflammation is more pronounced in patients with relapsing remitting MS (RRMS) and neurodegenerative events are more severe in the progressive stage of the disease. During the progressive phase of MS, the contribution of the peripheral immune system decreases. CNS pathology changes from focal to diffuse white matter injury associated with microglia activation and diffuse lymphocytic and monocytic infiltrates and an increasing cortical involvement (Lassmann 2019).

2.1.2 Genetic risk factors

The interactions between susceptibility genes and the environment are believed to contribute to the development of MS. Evidence for a genetic background is found in the clustering of MS patients in families and the high disease concordance rate in monozygotic (MZ) twins. Twin studies have demonstrated an excess of MZ over dizygotic (DZ) concordance pointing to the importance of genetic factors in the etiology of MS. The MS risk of first-degree relatives of MS patients was shown to be 2–5% whereas in MZ twins of MS patients it was many times higher i.e. 25–30% (Sadovnick et al. 1993). In a Danish population study, first-degree relatives of MS patients had a sevenfold increased risk of MS compared with the background population (Nielsen et al. 2005). In the Finnish twin study conducted in 2008, the concordance for MZ twins was 30% and 14% in DZ twins. Concordance of MS in DZ twins had increased during the past two decades and the heritability estimate was low at 15.3%, suggesting that the reported increase in MS incidence in Finland had been predominantly caused by environmental factors (Kuusisto et al. 2008).

Genome-wide association studies (GWAS) have identified more than 200 genes linked to MS (Bashinskaya et al. 2015). In the human leukocyte antigen (HLA) region of chromosome 6, there is a group of genes associated with an increased MS risk. The strongest association has been observed with the HLA DRB1*15:01 allele with an average odds ratio (OR) of 3 (Hollenbach & Oksenberg 2015). This gene variant is not uncommon as it is carried by 25–30% of the population in northern Europe. Risk alleles of HLA have been associated with an earlier MS onset in women (Isobe et al. 2016). The strongest known protective MS gene variant is HLA A02 with an OR of 0.6 while the combined OR of presence of DRB1*15:01 and absence of HLA A02 is approximately 5 (Brynedal et al. 2007; Sawcer et al. 2011). In addition to these, GWAS have identified genetic variants with minor effects,

including 201 non-MHC and 32 MHC variants. In particular, an enrichment for MS genes has been seen in human microglia, suggesting that these may have a role in targeting an autoimmune process to CNS (International Multiple Sclerosis Genetics Consortium 2019). In addition, the genes involved in antigen presentation and lysosomal function have shown a substantial differential expression in MS patients´ samples compared to controls and thus provided support for the concept that these genes participate in the mechanisms behind MS (Li et al. 2021).

2.1.3 Environmental risk factors

Several environmental factors have been shown to contribute to the development of MS as well as progression of the disease. Migration studies support the role of environmental exposure and suggest that these factors exert their effect early in life (Kurtzke 2013). In a recent nationwide study in Denmark, the MS risk among first-generation immigrants migrated to Denmark before puberty was lower compared to ethnic Danes but higher compared to their country of birth while the MS risk among those individuals who migrated at a later age remained closer to their country of origin (Nielsen et al. 2019). Similar results have been observed in Sweden and Norway (Ahlgren et al. 2012; Berg-Hansen et al. 2015). In a Canadian study, the MS risk among immigrants increased with longer residence in new high-risk region and decreased with age at arrival. However, a considerable risk persisted even with migration in adulthood, suggesting that envinronmental exposures may influence the MS risk also beyond childhood and adolescence. The risk of developing MS varied also widely by region of origin, pointing out the importance of genetic susceptibility (Rotstein et al. 2019).

The association between increasing latitude and MS risk has been observed for decades. Correlating with latitude, exposure to sunlight has been connected with MS susceptibility and a low sunlight exposure in childhood and adolescence has been observed to increase the MS risk (Bjørnevik et al. 2014). Month of birth and thus sunlight exposure during pregnancy also appear to influence the MS risk; it has been found to be significantly greater for people born in May than in November (Willer et al. 2005). Vitamin D is likely the major link between sunlight exposure and MS risk but ultraviolet B rays (UVB) may also have a beneficial role in immunity through a specific immunomodulatory effect independent of vitamin D synthesis (Lucas et al. 2015).

The main mechanism of action of vitamin D in MS appears to be immunomodulatory and involves various categories of T and B lymphocytes in the general immune system. Vitamin D insufficiency is a clear risk factor for MS and increasing serum levels of 25-hydroxyvitamin D (25OHD) have been shown to

decrease the risk of MS (Munger et al. 2006). The risk of developing MS was reduced by 41% in women taking 400 IU or more vitamin D per day compared with women not taking vitamin supplement (Munger et al. 2004). The risk associated with vitamin D insufficiency may start early i.e. a large case-control study in the Finnish Maternity Cohort observed that children of women with vitamin D deficiency early in their pregnancy had a nearly doubled risk for developing MS as an adult (Munger et al. 2017). In addition to MS susceptibility, vitamin D levels also affect the course of MS. Higher 25OHD levels have been demonstrated to predict reduced MS relapse activity and as a lower rate of progression over the 5 years of follow-up (Ascherio et al. 2014).

Many viral infections have been suspected to have an association with MS but only Epstein-Barr virus (EBV) has been shown to be a consistent and strong risk factor. When compared with the population without EBV infection, about a 10-fold greater MS risk has been observed in individuals with an undiagnosed EBV infection in childhood and at least a 20-fold greater MS risk in population with clinical mononucleosis (Ascherio & Munger 2007). High EBV seropositivity rates have been consistently observed among patients with MS or clinically isolated syndrome (CIS). In a recent large cohort study, 100% of 901 patients with RRMS or CIS were EBV-seropositive. In comparison, the population EBV seropositivity increased with age and was ≥98% in a population aged 45–79 but did not reach 100% in any age group (Abrahamyan et al. 2020). The EBV seropositivity is clearly less common in children and pediatric MS patients have shown to be significantly more likely than healthy controls to have serological evidence of a prior EBV infection (83% vs. 42%) (Alotaibi et al. 2004).

Cigarette smoking is another known risk factor for MS. The risk of MS increases with duration and intensity of smoking and is stronger in men than in women (Poorolajal et al. 2017). Recent systematic review and meta-analysis showed that smoking increases the MS risk by 50% and SPMS risk by 80% (Degelman & Herman 2017). Smoking is also associated with a greater MRI lesion load and brain atrophy, even in the earliest disease phase (Zivadinov et al. 2009). In contrast, a Swedish case-control study reported that use of oral snuff was not associated with an elevated risk for MS; in fact, a greater use of snuff rather decreased the risk of developing MS (Hedström et al. 2009). In addition, some evidence supports an association between organic solvent exposure and MS (Landtblom et al. 2019).

Considering the growing worldwide obesity epidemic and the increasing prevalence of MS, the relationship between obesity and MS has also been a subject of research. A prospective study of over 200,000 US women found an association between obesity in late adolescence (age 18) and more than a doubled risk of MS (Munger et al. 2009). In a Danish study, a higher BMI during childhood and early

adolescence was also associated with an increased MS risk but mainly only among girls (Munger et al. 2013). Similar findings have been reported from Norway (Wesnes et al. 2015). In the UK Biobank study, the effect of childhood obesity on MS risk was greater among individuals with a high genome-wide genetic risk (Jacobs et al. 2021).

All things considered, it is likely that many environmental risk factors are at play and that the development of MS results from a complex interplay between susceptibility genes and different environmental factors. Genes may alter the susceptibility to environmental factors and the environment may also influence gene expression. Studies of these interactions have focused on known risk genes. In the presence of a risk gene variant HLA DRB1*15:01 and the absence of the protective HLA A02, interactions have been demonstrated with EBV infection, smoking and adolescent obesity. The consequence of these gene-environment interactions is a higher than expected combined OR on the basis of the sum of the effects associated with each factor individually (Waubant et al. 2019). However, causality remains challenging to establish for many environmental factors and further studies are warranted to explore the etiology of MS (Magalhaes et al. 2015).

2.2 Epidemiology of multiple sclerosis

2.2.1 Global epidemiology

Already in the 1970s, the incidence and prevalence of MS were observed to increase with latitude north or south of the equator (Kurtzke 1975). However, the latitude gradient of MS incidence has been observed to attenuate over time and even the presence of this gradient has been questioned recently in the northern hemisphere (Alonso & Hernan 2008; Koch-Henriksen & Sørensen 2010). In Australia and New Zealand, the gradient is still apparent (Koch-Henriksen & Sørensen 2010). The prevalence of MS has been mainly shown to follow this gradient even in latest meta-analyzes but also an inverse gradient above 60° north latitude has been reported (Simpson et al. 2011, 2019). In Europe, MS prevalence and incidence are higher in the Nordic countries and northern regions of the British Isles, supporting the role of latitude (Kingwell et al. 2013). Within the Nordic countries, a latitudinal prevalence gradient has been observed in Sweden but not in Norway (Ahlgren et al. 2011; Berg-Hansen et al. 2014). The prevalence estimates of MS worldwide are illustrated in Figure 2.

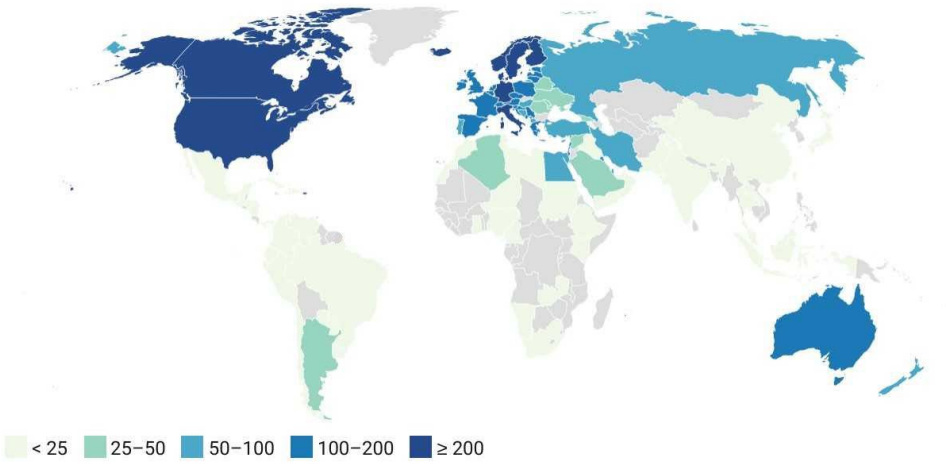

Figure 2. The prevalence estimates of MS per 100,000 worldwide. Modified from The Multiple Sclerosis International Federation 2020.

The increase in epidemiological estimates of MS in Nordic countries has been concurrently reported. In Norway, the prevalence has increased by 10-fold during the past five decades and the nationwide MS prevalence was high at 208/100,000 in 2013. The incidence has also increased during the last half century but regional differences in this rate can be observed (Grytten, et al. 2015, 2016; Willumsen et al. 2020; Benjaminsen et al. 2014). In Sweden, the nationwide MS prevalence of 189/100,000 was reported in 2008 and the incidence of 10.2/100,000 person-years in 2001–2008 (Ahlgren et al. 2011; Ahlgren et al. 2014). A steady increase in MS prevalence and incidence in Iceland has also been observed (Sveinbjornsdottir et al. 2014). Extensive epidemiological data is derived from prospective Danish MS Registry showing that MS incidence has increased steadily from the 1950s to the 2000s simultaneously with the increasing prevalence (Bentzen et al. 2010; Koch-Henriksen et al. 2018).

In addition to Northern Europe, North America is a region with a high MS occurrence. A high nationwide prevalence estimate of 309/100,000 in US population aged over 10 years was reported in 2010 with an increasing prevalence gradient from south to north (Wallin et al. 2019). Canadian studies have reported increasing MS prevalence concurrently with a stable incidence suggesting that declining mortality and longer survival may well explain the rising prevalence rates (Kingwell et al. 2015; Rotstein et al. 2018). In Australia, a nationwide MS prevalence of 104/100,000 was observed with a persisting latitude gradient while the prevalence in southern Tasmania was almost double compared to northern Queensland (Ahmad et al. 2018). In contrast, low prevalence rates have been reported in Eastern Asian and Latin

American populations (Cristiano & Rojas 2017; Eskandarieh et al. 2016). Epidemiological figures are also low in Africa but the studies are scarce or nonexistent in most countries (Heine et al. 2020).

The mortality and survival of MS patients have an important impact on epidemiological figures. MS patients have an increased risk of premature death compared to the general population, and a reduced life expectancy has been reported to range from 7 to 14 years from data from several large cohort registries (Scalfari et al. 2013). DMTs have been demonstrated to prolong survival (Goodin et al. 2012) but in a Danish nationwide register study, the decrease in excess mortality of MS patients was observed to start already decades before the introduction of DMTs (Koch-Henriksen et al. 2017). However, a recent meta-analysis of mortality studies in MS suggested that the excess mortality has not changed over the past 50 years when compared to the general population but the increase in the survival of MS patients rather parallels the increased life expectancy in the general population. Death due to cardiovascular disease, suicide and infection was higher in MS patients in comparison to the general population and there was increased mortality in women with MS than in their male counterparts (Manouchehrinia et al. 2016). However, unchanged excess mortality can be questioned as studies included in meta-analysis were compared only by midyear of their follow-up while longitudinal studies conducted in the same population have observed a reduction in this excess mortality rate (Brønnum-Hansen et al. 2004; Koch-Henriksen et al. 2017).

2.2.2 Prevalence in Finland

Even the first epidemiological studies of MS in 1964 showed that the geographical distribution of patients was not even but concentrated in the western and southwestern parts of Finland (Figure 3). Data consisted of all MS cases diagnosed in hospitals in the period 1955–1965 or in individuals drawing a national pension for MS. The prevalence was highest in the districts of South Ostrobothnia, Vaasa, Turku and Åland and lowest in eastern districts of Finland (North Karelia, Kainuu and all three regions of Savonia). No correlation was observed between the distribution of MS patients and medical facilities. Rinne et al. explained the low nationwide prevalence (20.1/100,000) by the stringency of the patient ascertainment in the absence of diagnostic criteria and the actual prevalence was estimated to be 30–40/100,000 (Rinne et al. 1966; Rinne et al. 1968).

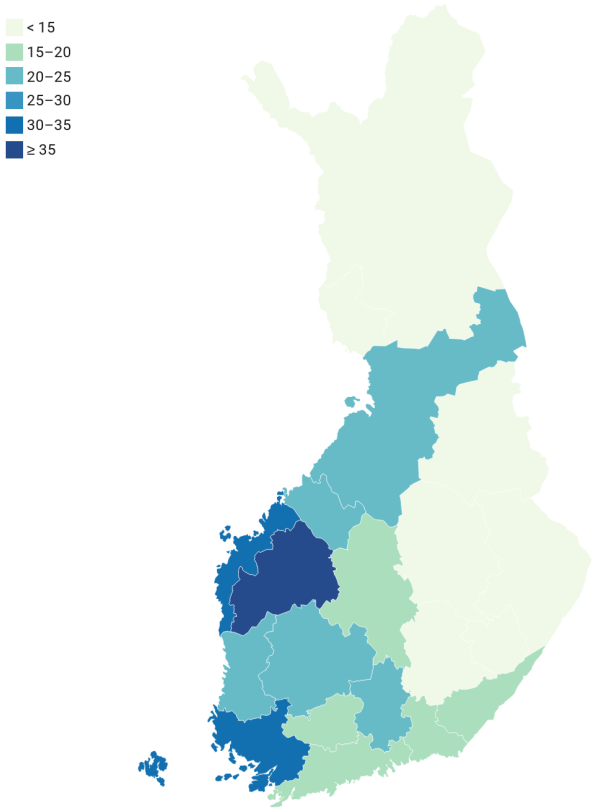

Figure 3. The prevalence of MS per 100,000 in the first nationwide study conducted by Rinne et al. in 1964.

In another nationwide study in the beginning of 1972, MS prevalence matched the earlier extrapolated estimate being 39.6/100,000. The highest prevalence rates were again from the western and southwestern counties with the lowest rates from eastern and southeastern counties. A narrow zone with a lower MS prevalence was revealed in the country's western coast of the mostly Swedish-speaking residents (Wikström & Palo 1975).

MS prevalence was re-evaluated in western Vaasa and South Ostrobothnia and southern Uusimaa in the beginning of 1979. A three-fold increase in prevalence since 1964 was observed. While incidence figures were stable, improved registration of patients was considered as most likely to explain the change in prevalence (Kinnunen et al. 1983). Sumelahti et al. reassessed MS prevalence in the same areas from 1983 to 1993. The prevalence increased in every region during the study period with the highest rates (200–300/100,000) being reported in the southern and western parts of South Ostrobothnia. In South Ostrobothnia, a 1.7-fold increase in prevalence during

the study period was observed in both genders whereas in Uusimaa the increase was largely due to the elevated prevalence rates in women. The simultaneous increase in MS incidence and prevalence was only reported in the male population of South Ostrobothnia while the incidence was stable or decreased among other populations (Sumelahti et al. 2001).

In Vaasa, South Ostrobothnia and Pirkanmaa, the MS prevalence increased further by 45% from 2000 to 2010 and age-standardized prevalence (European Standard Population (ESP) 2013) was 192/100,000 in the whole western area in the end of 2010 (Murtonen & Sumelahti 2019). The first epidemiological MS study since 1970s in northern Finland, estimated the prevalence as 103/100,000 in North Ostrobothnia at the end of 2007 (Krökki et al. 2011). At the end of 2012, a high MS prevalence of 213/100,000 was reported in the hospital district of Southwest Finland (Åivo et al. 2017). MS prevalence rates in the regional MS studies conducted in different hospital districts are summarized in Table 1.

Table 1. Prevalence of MS per 100,000 in regional studies of different hospital districts of Finland.

	1979	1983	1993	2000	2007	2010	2012
Southwest Finland							213[f]
Vaasa		102[b]	107[b]			214[e]	
South Ostrobothnia		116[b]	188[b]			282[e]	
Pirkanmaa						149[e]	
Uusimaa	52[a]	69[b]	93[b]				
Central Finland		39[c]	59[c]	105[c]			
North Ostrobothnia					103[d]		

[a] Kinnunen et al. 1983, [b] Sumelahti et al. 2001, [c] Sarasoja et al. 2004, [d] Krökki et al. 2011, [e] Murtonen & Sumelahti 2019, [f] Åivo et al. 2017.

2.2.3 Incidence in Finland

The first study concerning MS incidence in Finland, was conducted in the western high-risk province of Vaasa and South Ostrobothnia and the southern medium-risk province of Uusimaa 1964–1978. The total incidence remained stable during the study period, but was higher in Vaasa and South Ostrobothnia (3.3/100,000) than in Uusimaa (2.2/100,000) (Kinnunen 1984). The incidence of MS was reassessed in the same area during 1979–1993. The regional difference between the areas remained as the incidence was 11.6/100,000 in South Ostrobothnia and 5.1–5.2/100 000 in Vaasa

and Uusimaa. An increasing incidence trend was observed in South Ostrobothnia, especially in men, while the incidence remained stable in Uusimaa and decreased in Vaasa (Sumelahti et al. 2000). In Central Finland, the MS incidence was stable from 1979 to 1993 (3.8/100,000) but increased up to 9.2/100,000 in 1994–1998. The rapid increase in the incidence was considered to be due to the improved diagnostics as MRI became available in the area in 1994. However, no change was observed in a diagnostic delay (Sarasoja et al. 2004).

In 1981–2010, the incidence of MS was studied in the western Pirkanmaa, South Ostrobothnia and Vaasa. From 1980s to 1990s, incidence doubled in Vaasa and South Ostrobothnia whereas a mild increase was observed in Pirkanmaa during the entire study period. The highest incidence of 15.3/100,000 was reported in South Ostrobothnia in 1991–2000. The MS risk in South Ostrobothnia was nearly doubled that of Vaasa and Pirkanmaa (Holmberg et al. 2013). The MS incidence increased also in North Ostrobothnia in 1992–2007 due to a pronounced rise in the female incidence (Krökki et al. 2011). In North Savo in 2004–2012, MS incidence was stable at 5.9/100,000 (Metsäniitty & Remes 2016). The incidence rates in different hospital districts are summarized in Table 2.

Table 2. Incidence of MS per 100,000 person-years in different hospital districts.

	1964–1968	1969–1973	1974–1978	1979–1986	1979–1993	1981–1990	1987–1993	1991–2000	1992–2007	1994–1998	2001–2010	2004–2012
Vaasa				6.0[b]		5.7[d]	3.3[b]	11.7[d]			11.7[d]	
South Ostrobothnia				9.4[b]		7.1[d]	11.6[b]	15.3[d]			14.7[d]	
Vaasa + South Ostrobothnia	3.1[a]	3.6[a]	3.1[a]									
Pirkanmaa						5.1[d]		6.5[d]			8.2[d]	
Uusimaa	2.0[a]	2.7[a]	1.9[a]	5.1[b]			5.2[b]					
Central Finland					3.8[c]					9.2[c]		
North Ostrobothnia									6.3[e]			
North Savo												5.9[f]

[a] Kinnunen 1984, [b] Sumelahti et al. 2000, [c] Sarasoja et al. 2004, [d] Holmberg et al. 2013, [e] Krökki et al. 2011, [f] Metsäniitty & Remes 2016.

2.2.4 Regional differences

The only nationwide epidemiological MS studies in Finland were conducted in the 1960s and 1970s. However, several regional studies conducted during the past decades have demonstrated that MS occurrence is still unevenly distributed in Finland. The MS epidemiology in western regions of Vaasa, South Ostrobothnia and Pirkanmaa has been a subject of particular research while no epidemiological studies have been conducted in eastern Finland since 1970s.

MS prevalence and incidence have consistently been highest in the western region of South Ostrobothnia and especially in its southern area of Jalasjärvi. The western area can be divided into three distinct regions based on their historical settlement: coastal region of Vaasa with MS prevalence of 107/100,000 in the end of 1993 was settled by Swedes during the 13th century, northern South Ostrobothnia with MS prevalence of 136/100,000 was inhabited later in the 16th century with a population moving from eastern Finland and southern South Ostrobothnia with highest MS prevalence of 219/100,000 was populated from the 13th century onwards from individuals living in southwestern Finland. The distinctive settlement history, historical link with southwestern high-risk foci and molecular genetic evidence have been thought to suggest that a founder effect may be behind the high MS risk in western Finland (Tienari et al. 2004).

Wikström et al. studied further the high-risk western county for MS in the level of single communes, villages and even houses in 1972. A clustering of the birthplaces of MS patients was found in the small high-risk area of Jalasjärvi and along its nearby rivers. This accounted for every fourth of the MS patients born in the whole area and thus it was higher than expected (16%). The MS prevalence was 60.7/100,000 in the western county and 11% of MS patients born in the high-risk area of Jalasjärvi had a positive familial history of MS. In Helsinki, the prevalence was 44.2/100,000 but only 2% of MS patients born in Helsinki had a positive familial history of MS. The findings could not be explained by chance and the author suggested that pronounced the clustering of the birthplaces in the small high-risk area seemed to highlight the importance of environmental influences in early childhood rather than genetic factors (Wikström 1975).

Several investigators have suggested that possible environmental exposures exert their effect early in life. After the Second World War, the majority of the southeastern province of Viipuri was ceded to the Soviet Union and its population of 406,000 was evacuated to other parts of Finland. In 1971, MS prevalence among the war evacuees was observed to be only half of that found among the nonevacuated population and no accumulation of MS was found among the evacuees living in the high-risk areas (Jokelainen et al. 1979). Contemporary immigrant studies also seem

to point to the importance of environmental exposures in childhood or adolescence in the etiology of MS (Nielsen et al. 2019; Ahlgren et al. 2012; Berg-Hansen et al. 2015).

2.2.5 Gender differences

In the beginning of the 20th century, MS was considered as a male predominant disease (Brain 1930). However, men were probably more likely to receive a diagnosis as they needed to remain capable of functioning and providing for their family. Furthermore, a misdiagnosis of hysteria in women was not uncommon at the same time (Stone et al. 2005). Since then, the MS incidence has increased especially in women and the female/male (F/M) ratio has reversed to 2–3 (Koch-Henriksen & Sørensen 2010). A comparison of F/M ratio in MS populations from different geographical regions revealed an increased F/M ratio over time in RRMS and also demonstrated that there was a latitude gradient in this increase (Trojano et al. 2012). No such similar increasing of the F/M ratio was seen in PPMS (Sumelahti et al. 2014; Westerlind et al. 2016). A recent nationwide population-based study from Denmark reported that the MS incidence had more than doubled in women from 1950 to 2009, while it increased only modestly in men. The increase in the incidence was most pronounced in women older than 50 years (Koch-Henriksen et al. 2018).

In Finland, the F/M ratio in MS prevalence was only barely over 1.0 in the first epidemiological study conducted in 1964. However, regional differences in the ratio were observed, since there were more female patients in the largest hospital districts of Helsinki, Tampere and Turku (F/M ratio 1.5–1.8) (Rinne et al. 1968). A change in this ratio was observed already in the first Finnish MS incidence study performed in 1964–1978 as the F/M ratio in incidence increased from 1.2 to 2.0 in Uusimaa and from 1.0 to 2.2 in Vaasa and South Ostrobothnia during the study period. The total incidence remained stable; evidence of an increased incidence in women and a decreased incidence in men (Kinnunen 1984), thus suggesting that women´s facilitated access to medical services could not explain the changing ratio. Since then, the F/M ratio in new MS diagnoses has remained mainly over two in Finnish studies but some regional differences can be seen. In Vaasa and South Ostrobothnia, the F/M ratio showed a slight increase still in the 2000s (Holmberg et al. 2013). The F/M ratios in different hospital districts are summarized in Table 3.

Table 3. Female to male ratio in MS incidence in different hospital districts in Finland.

	1964–1968	1974–1978	1979–1993	1979–1998	1981–1990	1991–2000	1992–2007	2001–2010	2004–2012
Vaasa			2.2[b]		1.8[d]	2.1[d]		2.8[d]	
South Ostrobothnia			1.6[b]		1.8[d]	1.9[d]		2.3[d]	
Vaasa + South Ostrobothnia	1.0[a]	2.2[a]							
Pirkanmaa					2.5[d]	2.1[d]		2.2[d]	
Uusimaa	1.2[a]	2.0[a]	2.4[b]						
Central Finland				2.2[c]					
North Ostrobothnia							2.2[e]		
North Savo									2.4[f]

[a] Kinnunen 1984, [b] Sumelahti et al. 2000, [c] Sarasoja et al. 2004, [d] Holmberg et al. 2013, [e] Krökki et al. 2011, [f] Metsäniitty & Remes 2016.

The reasons for the increasing F/M ratio are unknown but a multifactorial explanation is likely and such rapid change point to environmental rather than genetic factors. Especially Western women´s lifestyles have changed over the past 50 years, including changes in smoking, obesity, nutrition, hormonal therapies and later and fewer childbirths. However, it is noteworthey that studies from Iran and Kuwait have reported similarly an increasing F/M ratio in MS patients despite probably less evident changes in women´s lifestyle (Alshubaili et al. 2005; Maghzi et al. 2010).

It is known that in particular women´s smoking has increased since the middle of the last century and may partly explain the increasing F/M ratio in MS incidence. Indeed, a correlation between changing smoking patterns in men and women and the increasing F/M ratio in MS incidence has been observed (Palacios et al. 2011). Fewer childbirths may also contribute as MS patients have been observed to have fewer pregnancies and childbirths within five years before the clinical MS onset when compared to controls (Magyari et al. 2013). Concurrently with reducing childbirths, women´s age at first childbirth has increased but this has not been observed to influence the MS risk (Magyari et al. 2013; Westerlind et al. 2014). In addition, the use of oral contraceptives has not been shown to have exerted any major impact on the MS risk (Alonso & Clark 2009).

In addition to these hormonal factors concerning only women, women are more susceptible to some environmental factors than men. For example, vitamin D3 has stronger immunomodulatory effects in female MS patients compared to male MS

patients and healthy controls (Correale et al. 2010), and obesity in childhood has been found to be a stronger risk factor for MS in girls than in boys (Munger et al. 2013). Changes in these environmental and lifestyle factors over the last half century may have contributed to the increased F/M ratio in MS incidence.

2.3 Clinical multiple sclerosis

2.3.1 Clinical course

Clinically isolated syndrome (CIS) is the initial presentation in 85% of MS cases and it encompasses an acute clinical episode affecting one or more CNS areas. The clinical features depend on the areas of the brain or spinal cord involved, typically optic nerves, brainstem or spinal cord. Around two-thirds of patients with CIS assessed with MRI exhibit multiple white matter brain lesions suggestive of demyelination. It seems that the long-term risk for clinically definite MS to be 60–80% when lesions are present and 20% when the MRI scan is normal apart from the symptomatic lesion (Miller et al. 2012). Furthermore, the number of these lesions, the presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) and a lower age at CIS onset are all associated with increased risk of conversion from CIS to clinically definite MS. In CIS patients with both OCBs and a high number of brain lesions (>9), an 86% risk of conversion to MS has been reported within five years (Kuhle et al. 2015).

In 85% of MS patients, the clinical course at onset is relapsing remitting. Relapses are episodes of neurological dysfunction lasting at least 24 h in the absence of infection or metabolic disturbances. Relapses result in residual deficits in almost half of attacks, which lead to a stepwise accrual of impairment (Lublin et al. 2003). In some 80% of RRMS patients, the relapsing course is followed by a secondary progressive disease course within 20 years (Kremenchutzky et al. 2006). SPMS consists of periods of progression with possible superimposed relapse activity. There are no available paraclinical markers of progression and diagnosis of SPMS is based on clinical grounds. In a recent study of 15,717 global MS patients, older age, a longer disease duration, a higher EDSS score, a more rapid disability trajectory and a greater number of relapses in the previous year were associated with an increased risk of conversion to SPMS, while improving disability and DMT exposure were associated with a lower risk (Fambiatos et al. 2020). A typical clinical course and MRI activity of RRMS is shown in Figure 4.

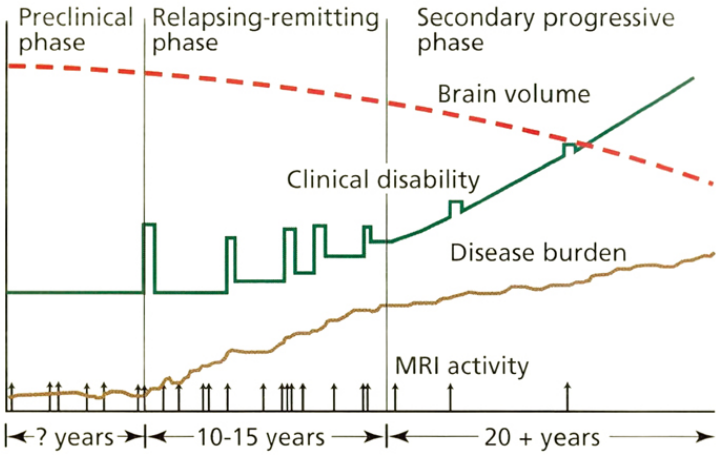

Figure 4. Typical clinical and MRI activity of RRMS. MRI activity indicates an inflammatory process visible with brain MRI as Gadolinium-enhancement or a new T2 lesion. Loss of brain volume and an increase in the disease burden (total volume of lesions) are indicative of permanent tissue damage (Fox and Cohen 2001, reprinted with permission from Cleveland Clinic Journal of Medicine).

Primary progressive multiple sclerosis (PPMS) is diagnosed in 10–15% of MS patients. PPMS is characterized by a slow progression of disability over time, typically without clear relapses or remissions, though phases of stability or fluctuations in disability may still occur. It is considered part of the spectrum of progressive MS phenotypes and the progression of disability proceeds typically at a similar rate in PPMS and SPMS. Compared to relapse-onset multiple sclerosis, PPMS patients are older at onset and a higher proportion are men (Miller & Leary 2007).

The disability progression in MS is measured using the established assessment scale of Kurtzke Expanded Disability Status scale (EDSS), which has a scoring range from 0 to 10. Early accumulation of disability is mostly driven by incomplete recovery from relapses, while neurodegeneration has a more important role in later phases of the disease. Regardless of the onset type of MS, the disability seems to progress at the same rate among all patients after a certain threshold is reached. Several patient registries show that progression after EDSS 4 occur at a predictable rate similar across MS phenotypes (Hurwitz 2011). However, a change to a milder direction in the disease course of MS has been observed during the past decade as patients appear to reach disability milestones at an older age. The improved prognosis has been suggested to result from changes in the diagnostic criteria and epidemiology of MS, impact of wider and earlier use of DMTs and an improvement of the patients' general state of health (Sorensen et al. 2020).

The term “benign MS” is used to describe patients with a mild disease course over first 10–20 years of the disease. The most common definition has traditionally been a disease duration of 15 years and an EDSS value of 3 or lower (Reynders et al. 2017). However, these criteria are based on EDSS alone and neglect neuropsychological symptoms, for example, a relatively high unemployment rate has been observed in these patients with benign MS. Therefore, stricter criteria consisting of ability to work, absence of disability and EDSS ≤1 have been suggested. With these stricter criteria, only 5% of a large German MS cohort were classified as having a benign disease course while with the earlier criteria, it appeared to be present in as many as 42% of these patients. A relapsing disease course, younger age at disease onset and female gender have been associated with a more favorable disease course (Ellenberger et al. 2020).

Pediatric-onset MS (POMS) is generally defined as MS with an onset before the age of 16 years. It has distinctive features and the disease course is typically different compared to adult-onset MS. Relapses appear to be more frequent in POMS patients and progression may be slower due to neuroplasticity but nonetheless, disability is reached at a younger age. POMS is more difficult to diagnose than adult-onset MS and it is considered underdiagnosed and undertreated (Alroughani & Boyko 2018).

2.3.2 Diagnostics

The first and purely clinical diagnostic criteria for MS were developed by Schumacher et al. in 1965. A clinically definite diagnosis required objective evidence for the disease affecting at least two white matter areas of the CNS and occurring in at least two episodes lasting more than 24 hours and separated by one month or more. Alternatively, gradual progression over six months was required. According to these criteria, age of MS onset was restricted to 10–50 years (Schumacher et al. 1965). Clinical criteria were supplemented by paraclinical evidence using neuroimaging, cerebrospinal fluid (CSF) and evoked potentials in the Poser criteria issued in 1983. Patients were subclassified to have probable or definite MS, which could be laboratory-supported in the presence of OCBs in CSF or increased CNS synthesis of immunoglobulin G (IgG) (Poser et al. 1983). The diagnostic criteria of definite MS proposed by Poser are summarized in Table 4.

Table 4. Diagnostic criteria for definite MS by Poser. Modified from Poser et al. 1983.

	Number of relapses	Clinical evidence	Paraclinical evidence	CSF OCBs/IgG
Clinically definite	2 2	2 1 and	 1	
Laboratory-supported definite	2 1 1	1 or 2 1 and	1 1	+ + +

CSF, cerebrospinal fluid; IgG, immunoglobulin G; OCB, oligoclonal band.

With the advance of neuroradiological techniques and the increased availability of MRI, the McDonald criteria were developed by the International Panel on Diagnosis of Multiple Sclerosis in 2001 giving more weight to MRI in the diagnosis of MS (McDonald et al. 2001). Since then, the McDonald criteria have been revised in 2005, 2010 and most recently in 2017 (Polman et al. 2011, 2005; Thompson et al. 2018). The diagnosis of MS is based on both clinical features including the history and neurological examination findings and paraclinical measures including MRI and CSF examination. A demonstration of dissemination of lesion in space (DIS) and time (DIT) and exclusion of other neurological conditions is required. Revisions to the McDonald MRI criteria are summarized in Table 5 and current 2017 McDonald diagnostic criteria for RRMS and PPMS in Table 6. Earlier diagnosis has become more important with the availability of DMTs for MS and each revision of the diagnostic criteria has allowed an earlier and more accurate diagnosis of MS. The revised criteria have been shown to facilitate an earlier MS diagnosis especially in patients with CIS (Brownlee et al. 2015; Schwenkenbecher et al. 2019).

Table 5. Evolution of MRI criteria for dissemination in space and time, McDonald criteria. Modified from McNicholas et al. 2018.

	McDonald 2001	**McDonald 2005**	**McDonald 2010**	**McDonald 2017**
DIS	≥3 of the following: 9 T2 lesions or 1 Gd-enhancing lesion ≥3 PV lesions ≥1 JC lesions ≥1 IT lesions A cord lesion can replace one brain lesion	≥3 of the following: 9 T2 lesions or 1 Gd-enhancing lesion ≥3 PV lesions ≥1 JC lesions ≥1 IT lesions A cord lesion can replace an infratentorial lesion Any number of cord lesions can be included in the total lesion count	≥1 lesions in each of ≥2 characteristic locations: PV JC IT Cord All lesions in symptomatic regions excluded in BS and cord syndromes	≥1 lesions in each of ≥2 characteristic locations: PV JC/Cortical IT Cord All lesions in symptomatic regions included
DIT	A Gd-enhancing lesion at least 3 months after CIS onset A new T2 lesion relative to a prior scan, at least 3 months after CIS onset	A Gd-enhancing lesion at least 3 months after CIS onset A new T2 lesion relative to a baseline scan, obtained at least 30 days after CIS onset	A new T2 lesion on follow-up MRI regardless of timing or baseline scan Concomitant enhancing and non-enhancing asymptomatic lesions	A new T2 lesion on follow-up MRI regardless of timing of baseline scan Concomitant enhancing and non-enhancing lesions – symptomatic or asymptomatic (optic nerve lesions are an exception)

BS, brainstem; CIS, clinically isolated syndrome; DIS, dissemination in space; DIT, dissemination in time; Gd, Gadolinium; IT, infratentorial; JC, juxtacortical; PV, periventricular.

Table 6. 2017 McDonald diagnostic criteria for RRMS and PPMS. Modified from Thompson et al. 2018.

Number of attacks	Number of lesions with objective clinical evidence	Additional criteria for diagnosis of MS
≥2	≥2	None
≥2	1	DIS: further attack or MRI
1	≥2	DIT: further attack or MRI or OCB
1	1	DIS and DIT
0		One year of disease progression and 2/3: - ≥1 cranial lesions: periventricular, cortical/juxtacortical or infratentorial - ≥2 cord lesions - Positive CSF

CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; MRI, magnetic resonance imaging; OCB, oligoclonal bands.

2.3.3 Comorbidities

Compared to the general population, MS patients are more likely to develop comorbid disorders. A systematic review of 249 studies showed that comorbidities are very common in MS patients with the most prevalent conditions being depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%) and chronic lung disease (10.0%). The most prevalent autoimmune diseases were thyroid disease and psoriasis. The review suggested that several comorbidities occur more often in MS patients compared to people without MS, including anxiety, depression, bipolar disorder, meningiomas, epilepsy, inflammatory bowel disease, irritable bowel syndrome and restless legs syndrome (Marrie et al. 2015). Moreover, multiple comorbidities, including hypertension, diabetes, ischemic heart disease, depression, anxiety, fibromyalgia, chronic lung disease and epilepsy, were noted to be more common in MS population already at least five years before MS diagnosis (Marrie et al. 2016). The risk of cancer has been reported to be lower in MS than in the general population with the exception of an increased incidence of brain and urinary system cancer, which could be due to a surveillance bias from increased MRI use and urology examinations (Marrie et al. 2015). In a nested case-control study assessing the cancer risk among Finnish MS patients, it appeared that MS patients had a similar overall cancer risk compared to the general population although they did seem to have a higher age at breast cancer diagnosis (Hongell et al. 2019).

In a Finnish study of 491 MS patients, 17% of patients had at least one neurological comorbidity. Only epilepsy was more frequently present (4.7%) in MS patients compared to the epidemiological data of the general population (Krökki et al. 2017). Another Finnish study of 1074 MS patients observed that the mean survival time was lower for MS patients with any circulatory disease. MS patients had a specifically high risk for stroke (OR 1.5–2.5) and type 1 diabetes (OR 2.1) compared to the control population (Murtonen et al. 2018). In addition, the risk for osteoporotic fractures has been observed to be increased among the MS population (Åivo et al. 2017).

Comorbidities result in a decreased quality of life and higher mortality rates (Warren et al. 2009; Berrigan et al. 2016; Marrie et al. 2015). A psychiatric comorbidity has also been associated with impaired cognitive function. Altogether 40–70% of MS patients develop a cognitive impairment, with prominent decrements in information processing speed and episodic memory (Rocca et al. 2015). Studies have shown that anxiety and depression are related to impaired cognitive function in MS patients, in particular in their information processing speed (Goretti et al. 2014; Niino et al. 2014).

An increased risk of relapses has also been associated with comorbidities in patients with MS. A Canadian prospective study reported that MS patients with migraine, hyperlipidemia or a high comorbidity burden (3 or more conditions) had an increased relapse rate over two years (Kowalec et al. 2017). In addition to relapses, physical and psychiatric comorbidities have been associated with a greater disability progression in MS. Vascular comorbidity was observed to increase the risk of ambulatory disability in MS patients (Marrie et al. 2010). In a Canadian cohort study, the presence of a mood or anxiety disorder was associated with a higher EDSS score (McKay et al. 2018). A Swedish prospective study reported that MS patients with a musculoskeletal or mental comorbidity had a higher risk for receiving a disability pension compared to MS patients without such comorbidities (Tinghög et al. 2014). In addition, an increased number of comorbidities has been associated with a lower likelihood of initiating treatment with a DMT for MS (Zhang et al. 2016).

2.3.4 Treatment

Treatment of MS has evolved significantly since the first injectable therapies became available in the 1990s. The first of interferons (IFN), IFN-beta 1b was approved for treatment of MS in Finland in 1995 but reimbursement was not granted until in 1998. Several new DMTs have become available since then: glatiramer acetate in 2004, natalizumab in 2006, fingolimod in 2011, alemtuzumab and teriflunomide in 2013, dimethyl fumarate and pegylated IFN-beta in 2014, cladribine and ocrelizumab in

2018 and siponimod in 2020. In addition to these DMTs still available, daclizumab was introduced in 2016 but was withdrawn from the market already in 2018 after reports of serious inflammatory brain disorders associated with the drug (Bianchi & Ciccarelli 2019).

The aim of MS treatment is to achieve an inactive phase in the disease without MS relapses or disability progression or new MRI T2 lesions or atrophy, a condition summarized as "no evidence of disease activity" (NEDA). There are two therapeutic approaches used in the clinical setting. The escalation approach consists of starting with a DMT with a potentially lower risk of adverse effects and lower efficacy and escalating to a DMT with a potentially higher risk of adverse effects and higher efficacy, if breakthrough disease is observed. However, the inflammatory process is typically most active during the first years of the disease and the early highly effective therapy approach is thus increasing. The induction approach consists of using a higher-efficacy DMT as first-line therapy, already early in the disease course. Early use of these higher-efficacy DMTs has been associated with potential long-term benefits in the disease course. A cohort study of 1555 RRMS patients reported that initial treatment with fingolimod, natalizumab or alemtuzumab was associated with a lower risk of conversion to SPMS compared with interferon beta or glatiramer acetate (Brown et al. 2019). Because of the concerns about safety issues and monitoring requirements concerning newer DMTs and extensive safety experience with platform therapies, the escalation approach is still more widely used.

In the Finnish Current Care Guidelines for MS therapy, the choice of DMT depends on the disease activity. RRMS is classified as active or highly active based on the relapse rate and MRI findings and the choice of DMT is recommended accordingly (Table 7). In addition, ocrelizumab has an indication for active PPMS and siponimod for active SPMS.

Table 7. Disease modifying therapies for active and highly active RRMS and active PPMS and SPMS in Finland. Modified from Current Care Guidelines of MS.

MS Type	DMT
Active RRMS	Dimethyl fumarate
	Glatiramer acetate
	IFN beta
	Ocrelizumab
	Teriflunomide
Highly Active RRMS	Alemtuzumab
	Cladribine
	Fingolimod
	Mitoxantrone
	Natalizumab
	Ocrelizumab
Active PPMS	Ocrelizumab
Active SPMS	Siponimod

DMT, disease modifying therapy; IFN, interferon; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Self-injectable therapies include IFN-beta, pegylated IFN and glatiramer acetate. IFN beta and glatiramer acetate have well-established and comparable long-term safety profiles and efficacy, reducing the frequency of relapses by 30% (Duquette et al. 1995; Mikol et al. 2008). Newer pegylated IFNs have shown similar efficacy and safety compared to their earlier non-pegylated counterparts (Calabresi et al. 2014). Orally administered platform therapies include teriflunomide and dimethyl fumarate while another oral DMT, fingolimod, is used for highly active RRMS. Teriflunomide has been shown to have an efficacy comparable to injectable therapies (Vermersch et al. 2014). In register studies, dimethyl fumarate and fingolimod have shown similar or slightly superior efficacy on the inflammatory disease activity compared to teriflunomide (Buron et al. 2019; Ontaneda et al. 2019; Prosperini et al. 2018). The newest oral DMT, cladribine, is a pulsed therapy that is used for the treatment of highly active RRMS in two treatment cycles separated by one year. This approach has been reported to reduce the relapse rate, the risk of disability progression and MRI measures of disease activity significantly and higher efficacy compared to injectable DMTs has been suggested (Giovannoni et al. 2010; Kalincik et al. 2018).

Some DMTs have a relatively high risk of serious adverse effects. A selective adhesion-molecule inhibitor, natalizumab, was shown to be effective in RRMS but was associated with a significant risk of evoking progressive multifocal leukoencephalopathy (PML) in patients seropositive for John Cunningham virus (JCV) (Polman et al. 2006; Williamson & Berger 2017). In addition, an anti-CD52 monoclonal antibody, alemtuzumab, reduced the clinical and MRI disease activity significantly, but over 20% of patients developed secondary autoimmune disorders (Cohen et al. 2012; Cossburn et al. 2011). The chemotherapeutic agent, mitoxantrone, is only rarely used due to the increased risk of malignancies (Neuhaus et al. 2006).

The increased understanding of the disease process and the role of B cells in MS pathophysiology has resulted in the development of B cell-targeting antibodies as DMTs. Long-term experience of safety of anti-CD20 therapy is provided by rituximab, which was developed and approved for treating rheumatoid arthritis and hematologic malignancies. It has been shown to reduce inflammatory activity also in RRMS (Hauser et al. 2008). An observational study has demonstrated rituximab to be safe and effective in the treatment of MS but due to the absence of phase 3 randomized placebo-controlled trials, rituximab is only used off-label in MS patients (Salzer et al. 2016). Humanized anti-CD20 monoclonal, ocrelizumab, is however officially indicated for MS treatment and has been observed to reduce effectively relapses and MRI lesions and also a slowing of the worsening of disability progression in RRMS patients (Hauser et al. 2017).

The first treatment options for the progressive forms of MS became available only recently. In addition to RRMS, ocrelizumab has been shown to reduce disability progression and MRI activity also in PPMS and it is the only DMT indicated for the treatment of PPMS (Montalban 2017). The latest of the current DMTs, orally administered siponimod, is the first DMT to demonstrate a reduction in the risk of disability progression in patients with SPMS (Kappos et al. 2018).

Acute relapses of moderate functional severity or worse, are treated with 3–5 days cure of high-dose methylprednisolone administered orally or intravenously. While they have no long-term effect on disease course, corticosteroids tend to shorten the duration of the relapse (Le Page et al. 2015). In rapidly progressive or severe relapses, plasma exchange is occasionally used alone or as an adjunctive therapy.

2.4 Infections in multiple sclerosis patients

2.4.1 Infection risk in general

MS patients have an increased risk of infections and this risk has been observed already in the year before MS diagnosis (Castelo-Branco et al. 2020). Higher susceptibility to infections is thus suggested even before treatment with DMTs and the progression of disability while functional limitations increase this risk further. Bladder and bowel dysfunction are common in the MS population and may predispose these individuals to urinary tract and gastrointestinal infections (Hennessey et al. 1999). The respiratory infection risk may be elevated by dysphagia and an inability to cough and clear the lungs (Aiello et al. 2008). Immobilization due to disability may predispose MS patients to decubitus. Infections increase the risk for relapses and relapses associated to infections have been observed to lead to more sustained neurological damage than other relapses (Buljevac et al. 2002). Moreover, mortality due to infections was reported to be higher in MS patients compared to the general population (Manouchehrinia et al. 2016).

Infection-related health care utilization was observed to be increased in MS patients across all age groups, with a higher burden for men (Wijnands et al. 2017). A large cohort study of over 15,000 MS patients in US and UK confirmed that MS patients have an increased risk of infections, and a two-fold risk of requiring hospitalizations for infections compared with the general population. The greatest risk was evident for renal and urinary tract infections (Persson et al. 2020). In a Swedish population, MS patients were over four times more likely to be hospitalized due to infection compared to the general population. When compared with patients with other immune-mediated diseases, the elevated risk remained but was lower. In comparison with these other immune-mediated diseases, MS patients had a greater risk of hospitalization for urinary tract infection (relative risk (RR) 3.18), influenza (RR 2.57), respiratory infections (RR 2.13), bacterial pneumonia (RR 2.01) and septicaemia (RR 1.60)). In addition, the mortality rate after hospitalization was higher in MS patients as compared to general population (Montgomery et al. 2013).

2.4.2 Infection risk related to disease modifying therapies

DMTs of MS modulate or suppress the immune system, limiting inflammation in the CNS. They may cause lymphocytopenia, neutropenia or hypogammaglobulinemia predisposing to infections and thus MS patients with immunosuppression carry a risk of a reactivation of latent pathogens, worsening of asymptomatic chronic infections

or developing new infections. DMTs have diverse mechanisms of action: natalizumab, fingolimod and siponimod alterate lymphocyte trafficking, alemtuzumab, ocrelizumab and cladribine cause lymphocyte depletion and mitoxantrone and teriflunomide disrupt lymphocyte replication. The mechanism of action of dimethyl fumarate is unknown, but it clearly causes lymphocytopenia (Schweitzer et al. 2020). Changes of the peripheral lymphocyte counts are treatment specific and require different monitoring and management.

First-generation, injectable DMTs interferon beta and glatiramer acetate do not appear to carry an increased risk of infections. However, all other MS treatments impair immune surveillance to various degrees and may predispose patients to general and opportunistic infections (Soelberg Sorensen 2017; Winkelmann et al. 2016). A cohort study in British Columbia showed that first-generation DMTs (IFN-beta, glatiramer acetate) were not associated with an increased risk of infection-related health care use in MS patients but exposure to second-generation DMTs (natalizumab, fingolimod, dimethyl fumarate) was associated with an increased risk of infections. None of the DMTs were associated with a risk of infection-related hospital admissions (Wijnands et al. 2018). Among second-generation drugs, the infection risk differs also by treatment. In a US study, treatment with monoclonal antibodies did not explain increased the general infection risk observed in MS patients. However, serious infections requiring hospital care were more common in patients treated with these DMTs (Persson et al. 2020). It was also noted in the Swedish cohort study, that the risk of serious infections was higher in MS patients treated with off-label rituximab as compared to patients using natalizumab and fingolimod (Luna et al. 2019).

Alemtuzumab has been associated with serious infections, such as listeriosis by a Gram-positive bacterium Listeria monocytogenes. This is a foodborne infection, which can be acquired by introducing contaminated deli and dried meat or unpasteurized milk products. In immunocompetent hosts, listeriosis may be mild with self-limiting fever, diarrhoea and abdominal cramps. In contrast, in immunocompromised patients, bloodstream and CNS infections may complicate the clinical course. In MS patients treated with alemtuzumab, the prevalence of listeriosis was estimated to be 0.26%. In order to reduce the risk of listeriosis, patients treated with alemtuzumab are recommended to adhere to a Listeria-free diet for one month after treatment (Buonomo et al. 2018).

Immunosuppressive therapy increases the risk of reactivation of latent herpesvirus infection, including herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV) and cytomegalovirus (CMV). Alemtuzumab is associated with a high rate of HSV infections when compared with interferon treatment (Cohen et al. 2012). Thus, prophylaxis acyclovir treatment is recommended in connection with

alemtuzumab therapy. Two fatal VZV cases have been reported during fingolimod treatment but patients involved received concomitantly also corticosteroids. However, a higher risk of VZV infections in MS patients using fingolimod was reported when compared to placebo and vaccination before immunosuppression is recommended (Arvin et al. 2015). Serious HSV and VZV infections have also been reported in MS patients treated with natalizumab (Fine et al. 2013), while the risk of mild to moderate herpes virus infections was increased during ocrelizumab treatment (Riederer 2017).

Treatment of MS with dimethyl fumarate, fingolimod, ocrelizumab, rituximab and especially natalizumab is associated with an increased risk of PML (Williamson & Berger 2017). PML is an opportunistic infection of CNS, which is caused by activation of JCV in an immunodeficient patient. In natalizumab-treated MS patients, the PML risk has been observed to be increased in the presence of anti-JC virus-antibodies in serum, treatment duration over two years and prior treatment with immunosuppressant (Bloomgren et al. 2012). Anti-JCV antibody levels in serum/plasma can help to assess the PML risk in JCV antibody-positive MS patients receiving natalizumab (Plavina et al. 2014). In Finland, PML has been mainly observed in patients with malignancies, HIV or systemic connective tissue disorder. Only three PML cases in MS patients were identified in 2004–2014 (Sipilä et al. 2019).

B cell depleting drugs such as ocrelizumab, rituximab, alemtuzumab and cladribine, carry a high risk of hepatitis B virus (HBV) -related hepatitis reactivation (Pei et al. 2010). Thus, screening for the presence of HBV infection with HBsAg and anti-HBc is necessary before starting immunosuppressive therapy. If an HBV infection is detected, antiviral prophylaxis can be used (Reddy et al. 2015).

2.5 Health care use of multiple sclerosis patients

MS is associated with a high economic burden, which typically increases with disease progression. According to recent systematic review, the estimated total annual cost per MS patient in Europe was on average 40,300 euros. The higher the severity of MS, the higher were the associated costs. The costs of drugs represented the main cost determinants for less severe MS cases and informal care and production loss for the most severe MS cases (Paz-Zulueta et al. 2020). In 2015, annual cost of MS in Finland was estimated to be around 330 million euros and an early retirement contributed most to the total cost burden (37%) (Ruutiainen et al. 2016). Although inpatient care accounted for only 3.4% of the total costs, hospital admissions consume a significant amount of health care resources.

Patients with MS use health resources more than the general population (Pohar et al. 2007) and higher health care use already several years before the first demyelinating event has been reported (Marrie et al. 2013; Wijnands et al. 2017). As life expectancy of MS patients has increased, the strain on the health care system is potentially also growing. Hospital admissions may cause a prolonged burden to patients as well as hospitalization due to an acute illness has been associated with a worsening of MS-related disability equivalent to 2.5 years of time-related disease progression (Garland et al. 2017).

Among other health care use, the hospital admission rate in MS patients is higher than in the general population. However, the hospitalization in MS patients has become more infrequent in the past decades. In British Columbia, hospital admissions in the MS population decreased 1.4% annually from 1986 to 2008. Age, primary progressive MS and longer disease duration were associated with higher admission rates (Evans et al. 2012). Marrie et al. studied changes in the hospital admission rates in 5797 MS patients from 1984 to 2011 compared with a matched large general population cohort. They observed a decrease of 75% in 27 years in MS admissions, while in the general population, the admission rates decreased in the same time period by 41%. Despite the clear decline in the hospitalization rate, admissions remained higher in MS patients than in the general population (Marrie et al. 2014). In Portugal, the rate of MS-related hospitalizations decreased by 44% between 2008 and 2013 (Pereira et al. 2016). In recent decades, a reduction in hospitalizations has been observed to be associated with increased DMT use (Al-Sakran et al. 2019). However, the decline in these rates started already before the introduction of DMTs and may reflect changes in health care delivery, including treatment of MS patients as outpatients rather than in an inpatient setting, increased use of home care services and improved symptom management (Evans et al. 2012; Marrie et al. 2014).

The need of health services in MS patients is associated with the comorbidity burden (Marrie et al. 2015). Fatigue, depression, anxiety, disruptive pain and perceived cognitive difficulties as well as lower health-related quality of life have been shown to display an association to higher rates of health service use (Ytterberg et al. 2013; Johansson et al. 2009; McKay et al. 2018). The presence of a comorbidity was shown to increase the risk of all-cause hospitalization but has had little impact on MS-related admissions (Marrie et al. 2015). The higher comorbidity burden is associated with a higher hospitalization rate. In the Canadian study, increased hospitalization rates were observed especially during the earlier stages of MS, when the disease is typically more active. A decrease in MS-specific admissions with age and longer disease duration was observed while all-cause hospitalization of MS patients increased with age (Al-Sakran et al. 2020). This is reasonable, since many

MS-specific admissions are related to relapses and rate of relapses typically declines as the disease progresses (Tremlett et al. 2008).

Studies of health care utilization of MS patients have been conducted primarily in Canada, while there are few European studies on this subject. However, western lifestyle and health care system are similar in Canada and Nordic countries. The current era of evolving MS treatment may appear to have changed the health care use of MS patients and revealing those patterns can help to understand changing burden of MS on the health system as well as to assess the effects of emerging therapies.

3 Aims of the study

Finland is a high-risk country for MS with regional differences in epidemiology. Epidemiological research has concentrated on western Finland while no epidemiological MS studies have been conducted in eastern Finland and only one in the southwestern high-risk region since the 1970s. MS is associated with a high economic burden and MS patients use health services more than the general population. Considering the increasing MS prevalence worldwide and significantly evolved treatment of MS during the past decades, changes in health care use of MS patients are of interest. MS patients are at an increased risk for infections, which may be further increased by new and more potent DMTs. This may be reflected in the rate of serious infections requiring hospitalization. The specific aims of this study were:

1. To update the epidemiology of MS in Southwest Finland and compare it with the easternmost hospital district of Finland, North Karelia.

2. To review previous studies of Finnish MS epidemiology and to introduce new data on MS prevalence in western parts of Finland as well as analyzing further previous data of MS incidence in North Ostrobothnia.

3. To evaluate trends in MS hospital admission rates and the role of infections in MS-related hospital admissions in Finnish hospitals.

4. To further study MS hospital admissions in Southwest Finland in order to identify the factors predisposing to infection-related MS admissions.

4 Materials and methods

4.1 Setting

Finland is located between the latitudes 60° and 70° in Northern Europe. It is divided into 21 hospital districts. In 2016, the total population of Finland was 5.5 million of whom 4.9 million were aged 10 years or older. The population is aging rapidly and in 2016 the median age of the Finnish population was 43 years while in 1960 it was only 28 years. The population density in Finland is unevenly distributed from 2 to 178 inhabitants per square kilometer (km^2), with the population now concentrated in the southern and western parts of the country. The mean population density is low at 18 inhabitants per km^2. While in the 1950s, most people in Finland lived in rural areas, in 2016 already 85% of population lived in urban regions which cover only about 5% of the country´s total area. The degree of urbanization was highest in southern Uusimaa and lowest in Åland and eastern Finland.

Study periods and regions of each study are shown in Table 8. Southwest Finland is third largest hospital district in Finland caring for a population of 478,546 at the end of 2016. Treatment and diagnosis of MS patients in the region is centralized to Turku University Hospital. Another hospital district involved in the epidemiological study, North Karelia, is the easternmost hospital district in Finland. At the end of 2016, North Karelia Central Hospital provided health services to the population of 167,599. Southwest Finland is more densely populated than North Karelia (45 vs. 25 inhabitants per km^2). In Finland, MS is exclusively diagnosed and mostly treated by neurologists working in public health care. MS patients with more advanced disease and without DMT may be followed up in municipal health centers.

Table 8. Characteristics of the studies I–IV.

	Study I	Study II	Study III	Study IV
Study topic	MS prevalence and incidence	MS prevalence	Hospital admissions	Hospital admissions
Study region	Southwest Finland North Karelia	Pirkanmaa South Ostrobothnia Vaasa	Finland	Southwest Finland
Study period	Prevalence Dec 31 2016 Incidence 2012–2016	1980 1990 2000 2007	2004–2014	2009–2018

4.2 Data collection

The StellarQ MS register is a MS treatment register and decision-making tool (www.neurorekisteri.fi). Most hospital districts in Finland have joined the service and most of them have integrated it into their electronic patient documentation system (Laakso et al. 2019). The register was introduced in the hospital district of Southwest Finland in 2014 and prior disease history data for each MS patient was filled in manually. The register data of MS patients is updated regularly during control visits in the MS outpatient clinic. The Care Register for Health Care (CRHC) is a mandatory database maintained by National Institute for Health and Welfare (THL) for all public health care hospital discharges in Finland. The Social Insurance Institution (KELA) pays reimbursements for prescribed medicines for all permanent residents of Finland and maintains a statistical database on these reimbursements. These numerous registers of public health care provide extensive data on Finnish MS patients.

4.2.1 Study I

All patient records with MS ICD-10 code (G35) were identified by searching the hospital administrative data in Southwest Finland from 2004 to 2016. In North Karelia, all public health care (both primary and specialized) visits and admissions with the diagnostic code of MS were searched from the discharge register of the hospital district during 2012–2016. The incidence and prevalence calculations were based on the cases with a definitive diagnosis and case ascertainment was performed by review of the medical records. The diagnosis of MS in each case in the incidence cohort had been established by a neurologist according to the McDonald 2010 criteria. Population data was obtained from Statistics Finland.

4.2.2 Study II

Relevant articles in the PubMed Medline database were searched (last search: 2 January 2020) using the following keywords: ”multiple sclerosis prevalence in Finland” or ”multiple sclerosis incidence in Finland”. Of 147 hits, 32 were excluded and 15 considered relevant for the presentation of development of Finnish MS epidemiology. References of articles were scrutinized to identify additional relevant publications. Altogether 17 articles on MS epidemiology in Finland were included in the review.

In addition to reviewing previous studies, MS prevalence in the hospital districts of Pirkanmaa, South Ostrobothnia and Vaasa was calculated from 1980 to 2007 by using previously unpublished data obtained from a retrospective search of hospital administrative registries. Cases were ascertained by neurologists to meet the diagnostic criteria proposed by Poser and only definite diagnoses of MS were included. Age-standardized prevalence rates were calculated also in Southwest Finland, North Karelia and North Ostrobothnia using data obtained for previous studies (Åivo et al. 2017; Krökki et al. 2011).

4.2.3 Study III

CRHC was searched for all discharges from neurological, medical, surgical, neurosurgical and intensive care units with MS as a primary diagnosis (ICD-10 code G35) or an auxiliary diagnosis for primary infection diagnosis during the study period 2004–2014. The search included all five university hospitals and 39 other hospitals in Finland. Only patients ≥ 16 years of age were included. The annual number of recorded procedures (intrathecal baclofen delivery device implantation, percutaneous endoscopic gastrostomy (PEG) implantation, plasmaferesis) during the admissions was examined. The Diagnosis Related Group (NordDRG categorization) daily cost of MS hospital care was obtained from THL statistical reports for 2006 (343.35 euros/day) and 2011 (473.91 euros/day) and the mean of these figures (408.63 euros/day) was used in the economic calculations. Drug reimbursement data was obtained from the statistics of KELA.

4.2.4 Study IV

Hospital admissions with MS as a primary or an auxiliary diagnosis in all wards of Turku University Hospital between years 2009–2018 were searched from the hospital administrative data. Admissions were divided into those that were associated with an infection (infection diagnosis as a primary or the first auxiliary

diagnosis for a primary MS diagnosis) and those that were not. Patients from other hospital districts without regular contact to Turku University Hospital were excluded (47 patients and 74 hospital admissions).

To study the risk factors for infection–related hospitalizations, baseline demographics of the MS patients with infection admissions (infection cohort) were compared with other MS patients in Southwest Finland (reference cohort) at the end of 2008. Only patients diagnosed with MS before this baseline date were included into this analysis. The validity of the MS diagnoses of the study population was scrutinized by neurologists. The demographics of all MS patients in the area were obtained from the Finnish MS register. Patients' age, gender, BMI, smoking status, time since MS diagnosis, disease course (RRMS, SPMS, PPMS), ongoing DMT, latest EDSS (within two years from the baseline date), the number of relapses in past year and number of diagnosed comorbidities at the study baseline were searched. Comorbidities of interest (hypertension, diabetes, asthma, chronic obstructive pulmonary disease, ischemic heart attack, stroke and transient ischemic attack, Crohn´s disease, ulcerative colitis, rheumatoid arthritis, cancer, depression and bipolar disorder) were chosen based on previous studies regarding the impact of comorbidities. MS patients with more than two infection admissions during the study period were analyzed separately.

4.3 Statistical analysis

4.3.1 Study I

Total prevalence, gender-specific and 10-year age-specific prevalences were calculated per population of 100,000 (aged ≥ 10 years) at the end of 2016. Total incidence, gender-specific and 10-year age-specific incidence of MS were calculated per 100,000 person-years in the age group 10–69 years. Mann-Whitney's U-test was used to compare the duration of the diagnostic delay between the genders.

Standardization of epidemiological values makes possible more reliable comparisons between different studies and populations with different age structures. Study populations are adjusted to have the same age structure as the chosen standard population. In our study, incidence and prevalence rates were standardized for age by a direct method using European standard population (ESP2013) and the World Health Organization (WHO) standard population. In Original article I, age-standardized prevalence and incidence rates were calculated using the same at-risk population as a reference similar to the calculation of crude rates. Prevalence

calculations were based on the population aged ≥10 years and incidence calculations on the population aged 10–69 years.

4.3.2 Study II

Age-standardized prevalence rates of MS were calculated from the new data from western hospital districts of Pirkanmaa, South Ostrobothnia and Vaasa in 1980, 1990, 2000 and 2007 and old data obtained for previous studies from North Ostrobothnia in 2007, Southwest Finland in 2012 and 2016 and North Karelia in 2016**.** Direct method and European standard population (ESP2013) were used as a reference. Here, the whole population was used as a reference instead of the at-risk population used in Study I. This is a more common practice in many international studies and may allow wider comparisons between different studies. Additionally, age-standardized incidence rates of Study I were recalculated for this thesis using the same reference population. The MS incidence in North Ostrobothnia 1992–2007 was analyzed using Poisson regression, adjusted because of overdispersion.

4.3.3 Study III

Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess the distribution of continuous variables and Mann–Whitney U-test or independent samples of the Kruskall–Wallis test when appropriate to analyze patient characteristics. Poisson regression was used in the analysis of count data, Cox regression in the analysis of in-hospital mortality and linear regression in the analysis of length of stay (log transformed due to skewness) and admission costs. Trend analyses were age- and sex-adjusted except for the admission cost analysis (sex- and age-specific data was not available). Results of univariate analyses were comparable to multivariate models. When differences in length of stay were analyzed, generalized estimating equations to accompany repeated admissions from individual subjects were used.

4.3.4 Study IV

Pearson´s chi-squared test was used to calculate P-values for categorical variables except that Fisher´s exact test was used for the number of relapses in the past year and comorbidities. P-values for continuous variables were calculated using independent samples t-test or Wilcoxon rank sum test as appropriate. P-values of Pearson's chi-squared test and Wilcoxon rank sum test were adjusted using the Benjamini & Hochberg method (1995) where the false discovery rate is controlled

by penalising smaller p-values more than higher p-values. Annual admission numbers were analyzed using Poisson regression, adjusted for overdispersion.

To examine the predictors of infection-related admissions, multivariable logistic regression was used. The proposed adjusted variables included age, gender, disease course (RRMS vs. SPMS/PPMS), categorized diagnosis year (<1995 vs. ≥1995, latest EDSS and ongoing DMT. The data was modelled with the study population with a known disease course and the latest EDSS (357 patients). The best model was selected using manual forward selection where a simple model was the starting point and terms were added based on deviance analysis until model did not significantly improve.

4.4 Ethics

According to Finnish law, ethical committee approval was not required for these studies since all of them were based on administrative register data and included no contact with patients. Study I was approved by Turku University Hospital Clinical Research Center (Turku CRC) and North Karelia Central Hospital Clinical Research Administration. Study II was approved by THL of Finland and Ethics Committees of Tampere University Hospital and Northern Ostrobothnia. Study III was approved by Turku CRC and THL of Finland. Study IV was approved by Turku CRC. The data processing practices followed the EU Data Protection Directive rules.

5 Results

5.1 Epidemiology (Studies I and II)

5.1.1 Prevalence

At the end of 2016 (I), altogether 1184 MS patients (70.4% women) were identified in Southwest Finland and 253 MS patients (67.2% women) in North Karelia. The prevalence was 275/100,000 (95% Cl 260–291) in Southwest Finland and 167/100,000 (95% Cl 146–187) in North Karelia in the population aged ≥10 years. The prevalence among men was 168/100,000 (95% Cl 150–186) in Southwest Finland and 110/100,000 (95% Cl 86–134) North Karelia and among women 377/100,000 (95% Cl 351–402) in Southwest Finland and 233/100,000 (95% Cl 191–259) in North Karelia.

5.1.2 Incidence

During the study period 2012–2016 (I), 211 new MS diagnoses were made in Southwest Finland (RRMS 88%, PPMS 11%, SPMS 0.5%) and 49 in North Karelia (RRMS 86%, PPMS 10%, SPMS 4%). The overall MS incidence in Southwest Finland was 11.7/100,000 person-years (95% CI 10.2–13.3) and in North Karelia 7.8/100,000 person-years (95% CI 5.6–9.9) in the age group 10–69 years. The incidence of MS among men was 6.6/100,000 person-years (95% CI 5.0–8.5) in Southwest Finland and 7.7/100,000 person-years (95% Cl 5.0–11.3) in North Karelia and among women 16.9/100,000 person-years (95% Cl 14.3–19.8) in Southwest Finland and 7.8/100,000 person-years (95% Cl 5.0–11.7) in North Karelia. Age- and sex-specific incidence rates are shown in Table 9. The F/M ratio was 2.58 in Southwest Finland, while there was no gender difference in North Karelia (F/M ratio 0.96). The mean age at diagnosis in Southwest Finland was 38.3 years in men and 36.5 years in women and in North Karelia 35.5 years in men and 41.2 years in women.

Table 9. Age- and gender-specific incidence rates of MS in Southwest Finland and North Karelia in 2012–2016. 95% confidence intervals in parenthesis.

	Southwest Finland			**North Karelia**		
Age group	All	Men	Women	All	Men	Women
10–19	1.6 (0.4–4.0)	0 (0–2.8)	3.2 (0.9–8.3)	1.1 (0–6.3)	0 (0–8.1)	2.3 (0.1–12.8)
20–29	18.6 (14.0–24.1)	9.9 (5.5–16.3)	27.4 (19.6–37.1)	13.9 (7.6–23.3)	16.9 (7.7–32.2)	10.4 (3.4–24.4)
30–39	26.2 (20.7–32.7)	14.6 (9.2–22.2)	38.1 (28.8–49.5)	13.6 (7.0–23.8)	17.2 (7.4–34.1)	9.6 (2.6–24.5)
40–49	13.5 (9.6–18.4)	7.3 (3.7–13.1)	19.8 (13.2–28.4)	13.2 (6.8–23.1)	8.7 (2.4–22.3)	17.9 (7.7–35.2)
50–59	7.6 (4.9–11.3)	5.1 (2.2–10.1)	10.1 (5.8–16.3)	6.2 (2.7–12.2)	6.1 (1.7–15.6)	6.3 (1.7–16.0)
60–69	2.7 (1.2–5.1)	1.9 (0.4–5.5)	3.5 (1.3–7.6)	1.5 (0.2–5.4)	0 (0–5.4)	3.1 (0.4–11.2)

The mean diagnostic delay from the onset of symptoms was 2.8 years (SD 4.4) in Southwest Finland and 4.3 years (SD 4.7) in North Karelia. The duration of the diagnostic delay was similar for both genders in Southwest Finland (p=0.246) and in North Karelia (p=0.437).

Incidence data from North Ostrobothnia in 1992–2007 was analyzed further in study II. The MS incidence increased by 4.2% annually (95% CI 1.6–6.8%, p=0.002) over the study period. The mean incidence was 5.3/100,000 person-years in 1992–1999 and 7.3/100,000 person-years in 2000–2007.

5.1.3 Age-standardized rates

At the end of 2016, the age-standardized prevalence (ESP2013) was 251/100,000 (95% CI 236–265) in Southwest Finland and 150/100,000 (95% CI 132–170) in North Karelia in the whole population. The age-standardized incidence in 2012–2016 was 9.2/100,000 (95% CI 8.0–10.5) in Southwest Finland and 6.5/100 000 (95% CI 4.9–8.4) in North Karelia. Age-standardized prevalence rates calculated from 1980 to 2007 in Vaasa, South Ostrobothnia and Pirkanmaa, in 2007 in North Ostrobothnia and 2012 in Southwest Finland are shown in Table 10 together with the earlier reported age-standardized prevalence rates in 2010 in the western hospital districts (Murtonen & Sumelahti 2019).

Table 10. Age-standardized prevalence (European standard population 2013) of MS per 100,000 in different hospital districts of Finland. 95% CI in parentheses.

	Southwest Finland	Vaasa	South Ostrobothnia	Pirkanmaa	North Ostrobothnia	North Karelia
1980		66 (54–80)	36 (28–46)	34 (29–40)		
1990		103 (88–120)	90 (77–104)	61 (54–69)		
2000		154 (135–174)	206 (187–227)	94 (86–104)		
2007		214 (192–237)	288 (265–313)	123 (113–133)	106 (96–117)	
2010		226 (202–250)	276 (268–284)	149 (121–178)		
2012	215 (202–228)					
2016	251 (236–265)					150 (132–170)

5.2 Hospital admissions in Finnish multiple sclerosis patients (Study III)

A total of 12 276 hospital admissions for 4296 patients were identified during the study period 2004–2014. Characteristics of hospital admissions are described in Table 11. The number of admissions declined by 4.6% annually ($p=0.0024$) and the trend was similar in both genders (interaction $p=0.93$ between genders). Most of the admissions occurred in neurology wards (79.9%) with internal medicine (13.4%) and surgical wards (6.8%) coming next. The mean length of stay was 4.2 days (SD 5.2) with a declining trend during the study period ($\beta=-0.05$, $p<0.001$). The length of stay was longer in men than women (mean 4.5, SD 5.7 vs. mean 4.1, SD 4.9; age and study-year adjusted $p<0.001$). The in-hospital mortality rate was 0.59% (0.29–0.94% or 4–11 deaths per year) and there was no difference between genders ($p=0.318$) or any evidence of a trend ($p=0.212$).

Table 11. Characteristics of hospital admissions associated with MS in study III and IV.

	2004–2014	2009–2018
Admissions, n	12276	1380
Men (%)	3788 (30.9)	521 (37.8)
Women (%)	8488 (69.1)	859 (62.2)
Infections (%)	11.7	24.3
Mean LOS (days, SD)	4.2 (5.2)	6.1 (13.0)

LOS, length of stays; SD, standard deviation

An infection was the primary diagnosis in 11.7% of hospital admissions and the proportion increased (β=0.87, p=0.001) during the study period with no change in their frequency (p=0.68, Figure 5). The most common infections were pyelonephritis (29.1%) and unspecified/bacterial pneumonia (24.4%). Infection-related admissions lasted longer than non-infectious admissions (mean 6.6, SD 6.2 vs. mean 3.8, SD 4.9 days, p<0.001). Admissions primarily for infectious cause were associated with an increased in-hospital mortality (HR 9.39; CI 5.25–16.77; p<0.001, adjusted for age, gender and study-year) compared to non-infectious admissions. The annual numbers of procedures of interest were low during the study period and thus the analysis was performed only on intrathecal baclofen implantations with no evidence of a trend (p=0.059). The annual aggregate NordDRG-based cost of hospital admissions declined by 51% during the study period: from 2,515,118 e in 2004 to 1,234,471 e in 2014 (β=-0.95, p<0.001).

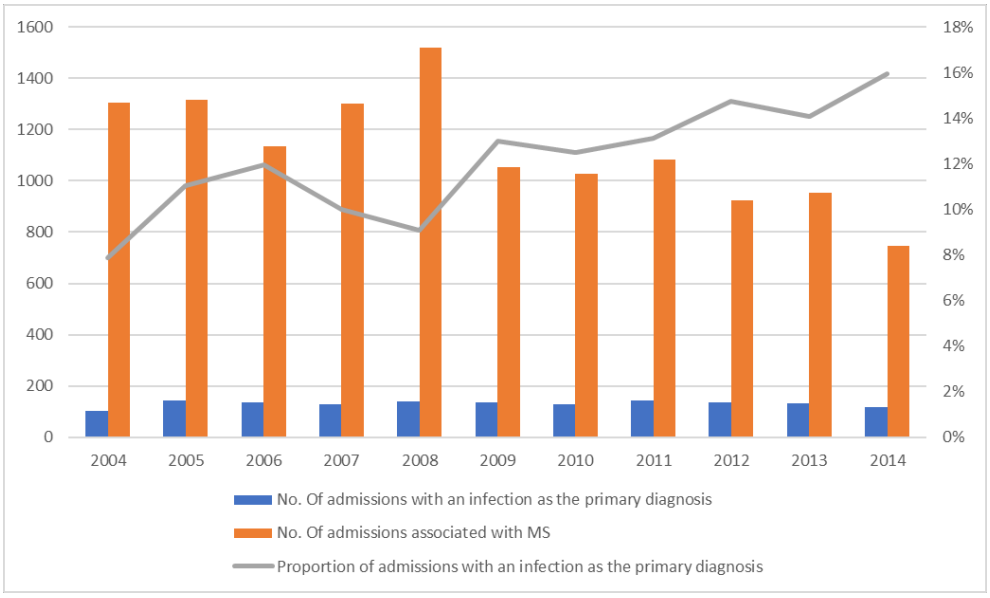

Figure 5. All hospital admissions and proportion of infection-related admissions of MS patients in Finland in 2004–2014. From original publication III, reproduced with permission of Taylor & Francis.

5.3 Infection-related hospital admissions in multiple sclerosis patients in Southwest Finland (Study IV)

Altogether 1380 hospital admissions for 532 patients were identified in Southwest Finland during the study period 2009–2018 (characteristics shown in Table 11). An infection was associated with 24.3% (336) of the admissions and the most common infections were unspecified pneumonia (27.3%) and pyelonephritis (14.9%). The number of all admissions decreased by 8.9% (95% CI 13.0–4.6; $p<0.001$) annually over the study period with no difference between genders in the rate of decline ($p=0.736$). The proportion of infection-related admissions declined from 26.5% (SD 3.1) in 2009–2013 to 19.5% (SD 5.6) in 2014–2018 ($p=0.049$, Figure 6). Infection-related admissions lasted longer than non-infectious admissions (mean 7.3, SD 14.8 vs. mean 3.8, SD 13.4; $p<0.001$) and were associated with an increased in-hospital mortality (3.57% vs. 0.29%; $p<0.001$).

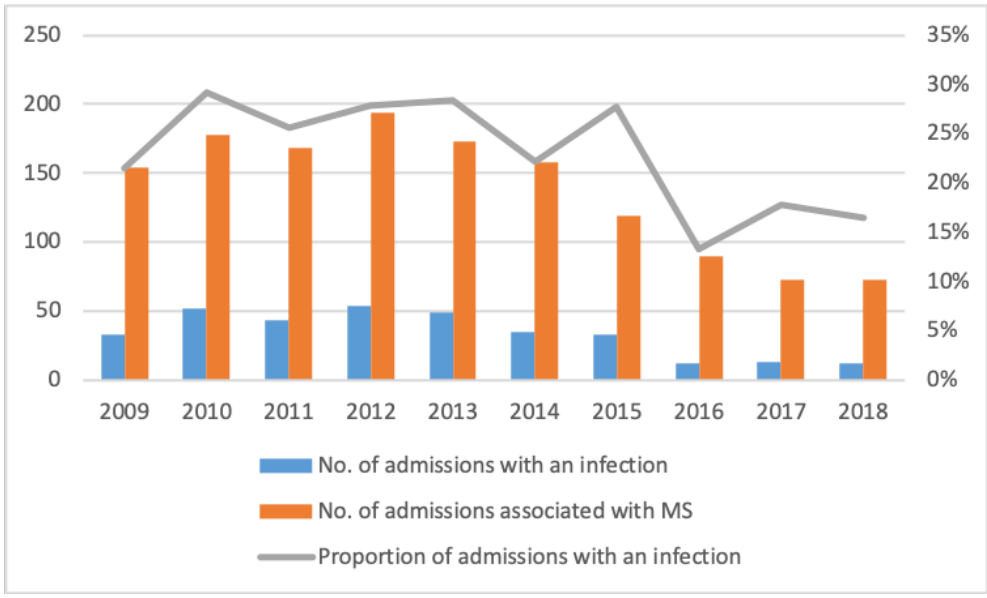

Figure 6. All hospital admissions and proportion of infection-related admissions of MS patients in Southwest Finland in 2009–2018. From original publication IV, reproduced with permission of Elsevier.

Over the study period, 336 infection-related admissions were found for 181 MS patients with 137 of them diagnosed before the beginning of the study period and with the available disease history documentation in the MS register. A comparison of baseline characteristics of these patients and other MS patients in hospital district without infection-related admissions during the study period (reference population, N=761) is shown in Table 12. MS patients with infection-related admissions were older ($p<0.001$), more disabled ($p<0.001$) and more often male ($p<0.001$) as compared to reference population. They had longer disease duration ($p<0.001$) and more often progressive disease ($p<0.001$) than patients without infection-related admissions. They were more likely to have comorbidities ($p=0.006$). The proportion of patients diagnosed before any DMTs were available for MS in Finland (year 1995) was higher in the infection admission cohort ($p<0.001$). Patients without infection-related admissions had a DMT at the beginning of the study period more often than patients in the infection cohort ($p<0.001$). The number of recent relapses was not associated with infection-related admissions nor were BMI or smoking, but data was available for only a minority of patients. Nearly every fifth (19.7%) of patients in the infection cohort died during the study period with the mean age at death being 67.9 years (SD 12.3).

Table 12. Demographic baseline characteristics of MS patients hospitalized for infection during 2009–2018 compared to other MS patients in Southwest Finland.

	Infection (N=137)	Other (N=761)	Adjusted p-value
Sex – N (%)			<0.001
Women	76 (55.5)	566 (74.4)	
Age (years) – N;Mean (SD)	137; 54.3 (11.02)	761; 46.1 (12.67)	<0.001
Disease Course – N (%)			<0.001
RRMS	40 (29.2)	540 (71.0)	
SPMS	67 (48.9)	135 (17.7)	
PPMS	23 (16.8)	54 (7.1)	
UNS	7 (5.1)	32 (4.2)	
Time Since MS Diagnosis (years) – N; Mean (SD)	137; 15.4 (9.63)	761; 10.1 (9.18)	<0.001
Diagnosis Year – N (%)			<0.001
<1995	69 (50.4)	189 (24.8)	
Latest EDSS score – N; Median (min, max)	33; 5.0 (0.0, 7.5)	324; 2.0 (0.0, 8.0)	<0.001
Ongoing DMT – N (%)			<0.001
Yes	29 (21.2)	387 (50.9)	
Number of relapses in past year – N (%) *			0.057
0	90 (65.7)	530 (69.6)	
1	17 (12.4)	103 (13.5)	
2	0	31 (4.1)	
≥3	0	11 (1.4)	
Comorbidities			0.006
0	104 (75.9)	661 (86.9)	
1	28 (20.4)	83 (10.9)	
2	4 (2.9)	16 (2.1)	
≥3	1 (0.7)	1 (0.1)	
Mean (SD)	0.3 (0.56)	0.2 (0.44)	

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; UNS, course of the disease unspecified. *, only patients with RRMS and SPMS included.

Altogether 35 patients (57.1% male) had recurrent (>2) admissions due to an infection during the study period. The median number of admissions was 3 (IQR 3–5). At the time of the first admission, these patients were severely disabled (median EDSS 8, IQR 7–8) with a mean age of 57.5 years (SD 10.0). Most of them had never used a DMT (71.4%) and only 14.3% of them had been treated with a DMT during the study period. At the time of admission due to the first infection, three of these patients were being prescribed natalizumab and one patient used azathioprine while the rest did not have an ongoing DMT.

In the multivariable logistic regression analysis, gender, age and latest EDSS score were predictors of infection-related admissions while disease course, diagnosis year and ongoing DMT were not predictive. The probability for women to fall into infection group was 45% lower than for men (OR 0.55; 95% CI 0.31–0.99; p=0.042). Keeping gender and latest EDSS score at a fixed value, every year of increase in age increased odds to fall into the infection group by 6% (OR 1.06; 95% CI 1.02–1.10; p=0.003). Every unit increase in latest EDSS score increased the odds to fall into infection group by 48%, when gender and age were kept at a fixed value (OR 1.48; 95% CI 1.20–1.84; p<0.001).

6 Discussion

6.1 Interpretation of study results

6.1.1 Epidemiology of multiple sclerosis (Studies I and II)

Earlier studies have shown Finland to be a high-risk country for MS with prominent interregional differences in the occurrence (Sumelahti et al. 2001; Sarasoja et al. 2004; Åivo et al. 2017). Our epidemiological study was the first to cover any part of eastern Finland during the era of modern diagnostic methods and confirmed that there is an east-west gradient in the MS epidemiology in Finland. The incidence and prevalence rates were a third higher in southwest compared to the easternmost region, but incidence rates differed only in the age group of 20–39 years. Gender distributions between the studied regions are different as the population of North Karelia is declining and young women tend to migrate to southern Finland more often than men. Indeed, the male population with the age of 20–39 years is more than 10% larger than female population in North Karelia while in Southwest Finland, the gender difference is a mere 2%. Considering the high MS incidence in young women, demographic factors may partly explain the difference in MS epidemiology in our study.

Similarly to our results, already the first Finnish epidemiological studies on MS in 1960s reported regional differences in MS prevalence with the highest occurrence in western and southwestern area and lowest in eastern area (Rinne et al. 1968). The reasons for these interregional differences are unknown, but it is probable that gene–environment interactions play a part. There are marked genetic differences between eastern and western Finns (Kerminen et al. 2017) but no significant regional variation has been reported in Finland concerning gene variants HLA DRB1*15:01 and HLA A02 which are believed to have the strongest association with the MS risk. The HLA B35 haplotype is more common in eastern than western Finland (Sirén et al. 1996) but findings on the effect of this allele on the MS risk are conflicting. Previous studies have reported a protective effect in MS but a recent Bahraini study observed HLA B35 to be more common in MS patients compared to controls (Al-

Nashmi et al. 2018; Madigand et al. 1982; Saleem et al. 2007; Salier et al. 1986). Genetic background differs also in the known high-risk MS region of South Ostrobothnia while the southern part with highest MS occurrence was inhabited from the southwestern and northern part from eastern Finland (Tienari et al. 2004). During the last century, the South Ostrobothnian population has however remained genetically relatively stable compared to other Finnish regions (Kerminen et al. 2021). In addition to genetics, environmental and lifestyle factors may have a role in uneven MS occurrence. The properties of soil and drinking water were speculated as possible explanations in early epidemiological studies in Finland (Wikström 1975). Indeed, MS clustering in western regions of Finland has been observed to coincide well with mires and severe acid sulphate soils in terms of metal leaching (Fältmarsch 2010; Häsänen et al. 1986). Unfortunately, there is no data available on the association of the uneven geographic distribution of MS in Finland and known environmental risk factors for MS, such as vitamin D levels, EBV-infections and smoking.

In most MS studies conducted in Finland, internationally comparable standardized rates were not available. This makes comparison of different studies difficult as standardization of epidemiological figures enables more reliable spatial and temporal comparisons between studies conducted in different populations and time periods. Reporting of only crude rates is unfortunately common as a review on epidemiological studies from Europe reported that only 37% of included studies had provided standardized rates (Kingwell et al. 2013). To enhance comparability of the epidemiological figures in Study II, we calculated age-standardized prevalence rates in several hospital districts using both unpublished and old data. We recalculated these rates also for Southwest Finland and North Karelia using the whole population as a reference instead of the at-risk population used in Study I. The highest age-standardized prevalence was observed in known high-risk areas of MS, South Ostrobothnia (288/100,000) and Southwest Finland (251/100,000). Accordingly, a high MS incidence of 14.7–15.3/100,000 has been reported earlier from South Ostrobothnia (Holmberg et al. 2013) and our results from Southwest Finland were quite similar when the same at-risk reference population was used. Age-standardized MS incidence in the whole population of Southwest Finland was naturally lower, 9.2/100,000 person-years. Indeed, inter-study comparisons are further hampered by the use of different reference populations.

Similarly to earlier reports worldwide, a clear trend of increasing MS prevalence throughout the decades was observed in our study. Taking into account the rather stable incidence figures during most of this time, the most important factor behind the increasing prevalence is probably the improved survival of MS patients. This is supported by the shift towards an older age distribution in the age-specific

prevalence curve during the last decades. In addition, earlier and more accurate diagnostics and increasing F/M ratio combined with the longer life expectancy of women may contribute to the increasing prevalence figures. Our review of previous epidemiological studies also detected some increase in the MS incidence in Finland as well, but when comparing only studies with the same background population and methods, a marked increase occurred in several regions only in the 1990s concurrently with improved availability of MRI. The use of MRI in MS diagnostics increased from 36% of cases in 1980s to 98% in 2000s in western hospital districts and from 10% in 1979–1983 to 97% in 1994–1998 in Central Finland (Holmberg et al. 2013; Sarasoja et al. 2004), allowing a better case ascertainment. The introduction of new diagnostic criteria for MS in 1983, 2001, 2005, 2010 and 2017 have each enabled earlier MS diagnosis and thus may have increased the number of new diagnoses, but an increase in incidence figures can be also seen between revisions. In addition to improved diagnostics, the first injectable DMTs entered the market in Finland in 1995 and made earlier diagnosis more relevant compared to era with no treatment options available for MS. However, longitudinal studies in neighboring countries show increasing MS incidence already decades before the widespread use of MRI, the new diagnostic criteria and the introduction of DMTs (Grytten et al. 2016; Koch-Henriksen et al. 2018). Overall, it is likely that changes in the diagnostics of MS partly explain increase in incidence, but regional differences in these changing rates suggest also the influence of environmental factors.

The high MS rates and increasing epidemiological figures in Finland are similar to other Nordic countries. The most reliable longitudinal data on MS incidence is from Denmark and Norway, where the incidence has increased during the last half century but regional differences are prominent, similar to Finland (Benjaminsen et al. 2014; Grytten et al. 2016; Koch-Henriksen et al. 2018; Willumsen et al. 2020). In Sweden, a high nationwide prevalence of 189/100,000 was reported in 2008 and in Norway an even higher prevalence of 208/100,000 was estimated in 2013 (Ahlgren et al. 2011; Grytten et al. 2015). No nationwide study has been conducted in Finland during the last decades but our results together with previous reports suggest rather similar nationwide figures. The traditional latitude gradient of MS epidemiology has been questioned recently in the northern hemisphere (Koch-Henriksen & Sørensen 2010) and Finnish results do not truly support this gradient. The high MS rates in Nordic countries do, however, suggest that their geographical position may be associated with the risk of MS. The possibility of shared environmental factors is supported by the fact that Finland is a genetic isolate with its own disease heritage (Cavalli-Sforza & Piazza 1993; Norio 2003a, 2003b, 2003c) while Swedes are genetically closer to Germans and Britons than to Finns (Salmela et al. 2008).

A female preponderance and the increasing F/M ratio in MS incidence have been reported globally (Koch-Henriksen & Sørensen 2010). We reported a ratio of 2.6 in Southwest Finland, which is in line with these observations but there was surprisingly no gender difference in North Karelia in new MS diagnoses. For some unknown reason, the age-specific incidence for women aged 20–39 was quite low in North Karelia and the F/M ratio in this age group was only 0.5. The cause of the globally reported growing female preponderance is not clear, but the rapidly changing F/M ratio suggests environmental factors and could be derived from women´s changing lifestyles over the past decades. Urbanization has been postulated as one possible factor accounting for the increased female incidence of MS. Among Cretans, the F/M ratio increased markedly over three decades in tandem with a transition from rural to urban living while the ratio remained more stable in rural areas (Kotzamani et al. 2012). Taking into account migration from eastern Finland, urbanization could have a role in our results as well. As another possible explanation for increasing F/M ratio, it is known that particularly women´s smoking has increased during the second half of the 20th century. Interestingly, smoking decreased markedly among men while increasing slightly among women in Finland concurrently with the increasing F/M ratio in the MS incidence in 1964–1978 (Leppo & Puska 2003).

Our results strengthen earlier reports that there is an uneven distribution of MS in Finland and bring new and comparable data on MS epidemiology in eastern, western and southwestern regions of Finland. The reasons for these interregional differences remain unknown but a multifactorial explanation is probable including interactions between susceptibility genes and environmental factors.

6.1.2 Hospital admissions in multiple sclerosis patients (Studies III and IV)

MS patients use health care services more than the general population (Pohar et al. 2007). In view of the increasing MS prevalence observed in our study as well as worldwide, it is to be expected that the burden on the health care system will grow. Despite this, previous studies from Canada have reported decreased hospitalization rates for MS patients over the last decades (Evans et al. 2012; Marrie et al. 2014). Our results were consistent with those Canadian findings as hospital admissions of MS patients were shown to decrease over the study period 2004–2014 in Finland and 2009–2018 in Southwest Finland.

The reduction in the hospitalization rate observed in our study may be related to a more fundamental change in the management of MS. Generally in severe and

disabling diseases with unknown etiological mechanisms, direct health care costs consist largely of hospital admissions while overall costs also take into account production losses. When underlying mechanisms of diseases become more clear and effective treatments are introduced, costs typically shift from inpatient care and rehabilitation to outpatient care (Kobelt et al. 2017). Similar changes can be detected in MS. Before the mid-1990s, hospital admissions were reported to account for the majority of direct health care costs in MS patients but in parallel with improved diagnostics and treatment protocols, costs have shifted towards outpatient care (Asche et al. 1997; Henriksson 1998; Kobelt et al. 2006). In a recent Finnish study, DMTs were responsible for over 50% of direct health care costs while inpatient care accounted for 38%. These direct costs represented 25% of the total costs i.e. productivity losses contributed most to the total cost burden (Ruutiainen et al. 2016).

In a recent population-based cohort study, increased DMT use over two decades was associated with a reduction in all-cause and MS-specific hospitalizations among Canadian population (Al-Sakran et al. 2019). Even though the association with DMT use was not examined in our study, the study periods were selected to coincide with the apparent change in the treatment of MS in Finland. Treatment evolved significantly from 2004 to 2018 while several new and more potent DMTs became available in Finland. Statistics of reimbursements from KELA show that the number of patients eligible for reimbursed DMTs almost doubled during the first study period 2004–2014. The use of natalizumab increased also from 2006 to 2012 steadily before decreasing to 300 patients in 2014. Earlier initiation and wider use of MS therapies and use of more effective DMTs has been shown to reduce the rate of relapses as well as delaying the progression of MS to the severe disability stage (Rae-Grant et al. 2018; Claflin et al. 2019; Kavaliunas et al. 2017). As relapses are a frequent cause of hospitalizations in MS, the development of DMTs may have reduced the need of inpatient care of relapses in our study patients. The number of procedures used for advanced MS, such as intrathecal baclofen delivery device implantation, PEG implantation and plasmapheresis, remained rather low throughout our study period 2004–2014 and no apparent change in the numbers of these procedures was observed but the study period may have been too short to detect such a change.

In Canadian studies, the decline in hospitalization rates started already before introduction of DMTs and was suggested to relate to changes in health care delivery (Evans et al. 2012; Marrie et al. 2014). In our study, decreased hospital admissions may reflect some changes in the delivery of health care services, including the treatment and management of MS patients in an outpatient rather than an inpatient setting. In addition, a general transition from inpatient to outpatient care has occurred in Finland during our study period while the number of hospitals and hospital beds

in Finland has declined significantly (Statistics of OECD). However, the annual reports of somatic health care by THL showed only a slight decrease in nationwide hospital admissions to specialized health care and rather increasing admission rates to neurology wards during the study periods (THL statistics of specialized somatic health care). The decline in hospitalizations is not explained by any change in MS prevalence since the number of MS patients has increased in Southwest Finland and occurrence is increasing in other Finnish regions as well.

6.1.3 Infection-related admissions (Studies III and IV)

Previous studies have shown that MS patients are more likely to be hospitalized for infections than the general population (Wijnands et al. 2017; Al-Sakran et al. 2020). Higher susceptibility to infections has been observed already before MS diagnosis and functional limitations may increase the infection risk further (Castelo-Branco et al. 2020). The rate of these infection-related hospital admissions has not been studied before to our knowledge. In our nationwide admission study of MS patients, the annual number of infection-related hospital admissions remained stable, but their proportion of all admissions increased as the overall admissions had decreased over the study period 2004–2014. However, the subsequent study of Southwest Finland showed that both frequency and proportion of admissions related to infections decreased from 2009 to 2018. In view of the increasing use of more potent DMTs and infection risk related to them, this was unexpected. After all, a decrease of infection-related admissions may be related to the adoption of the new therapeutic options for MS during the past decade, because DMTs may delay disease progression and thus decrease the risk of serious infections (Claflin et al. 2019).

Our results showed that patients with infection-related admissions were older and they had a longer disease duration, more often progressive disease and more disability compared to other MS patients in the hospital district. In line with F/M ratio in epidemiological figures, only one quarter of MS patients in the reference cohort were male and the majority of all patients admitted to hospital were female. However, the proportion of males was clearly higher among the patients with infection-related admissions and more than half of the patients with recurrent infection admissions were male. A similar gender distribution in infection-related health care use has been reported in Canada and Sweden (Wijnands et al. 2017; Montgomery et al. 2013). A more rapid disease progression is often observed in men. In a large register-based study, male relapse-onset patients were observed to accumulate disability faster than female patients. No similar gender difference in the progression rate was reported in PPMS patients (Ribbons et al. 2015). However, PPMS is more common in men with F/M ratio of 1 and patients with PPMS often

accumulate disability faster compared to relapse-onset MS (Miller & Leary 2007; Menon et al. 2013;). Indeed, functional limitations related to more advanced disease may increase the infection risk of male patients and explain the gender distribution in the infection cohort. Patients with infection-related admissions had also more comorbidities compared to other MS patients, which has been shown to be associated with an increased risk of hospitalizations in MS population (Marrie et al. 2015).

Although MS treatment may predispose patients to general and opportunistic infections, MS patients with infection-related admissions had received less DMTs than the reference group and most MS patients with recurrent infection admissions had never had a DMT for MS. They had more advanced disease and use of DMTs is indeed more common in younger patients with a relapsing form of MS and a lower level of disability. Similar results have been reported concerning the current coronavirus infection (COVID-19) pandemic as the severity of COVID-19 has been observed to be associated with neurological disability in MS patients rather than the use of DMTs (Louapre et al. 2020). Increased susceptibility to COVID-19 has been reported in MS patients similar to other infections, but the use of DMTs has not been associated with the risk or outcome of COVID-19 apart from increased risk of severe infection suggested for anti-CD20 therapy (Sormani et al. 2021; Sepúlveda et al. 2021).

A recent Swedish study observed that the use of second-generation DMTs and especially off-label use of rituximab were associated with a higher risk of serious infections (Luna et al. 2019). In our study, the use of these DMTs was limited as the proportion of traditional injectable therapies among all of the used DMTs was 76% in the infection cohort and even 90% in the reference cohort. Natalizumab was slightly more common in the infection cohort and there were three patients with recurrent infection admissions using natalizumab at the time of the first infection. In one of these patients, PML was the infection causing the first hospital admission and related clearly to natalizumab therapy. Treatment practices may differ between countries and particularly off-label use of rituximab is much less common in Finland than in Sweden. In 2019, 12% of the MS patients receiving DMTs in Turku University Hospital and 2% of the MS patients on DMTs in Finland were using rituximab (www.neurorekisteri.fi). In Sweden, the use of rituximab is markedly higher and the rate of rituximab prescriptions in relation to other annually started DMTs reported to be as high as 53% (Berntsson et al. 2018). In addition, the baseline date i.e. the end of 2008 restricted the proportion of patients with the newest DMTs in our data as several high-efficacy DMTs have only been introduced during the last decade. Therefore, firm conclusions on their risk of infections cannot be drawn in this setting.

MS patients have been observed to have an increased risk for infection-related mortality (Montgomery et al. 2013; Manouchehrinia et al. 2016). Similarly to these earlier reports, our study showed that infection-related admissions were longer and associated with an increased in-hospital mortality when compared to other hospital admissions of MS patients. The most common infection diagnoses were acute pyelonephritis (N10) and bacterial or unspecified pneumonia (J15.9/J18.9), which is in line with earlier findings (Wijnands et al. 2017; Persson et al. 2020). Functional limitations associated with MS, such as bladder dysfunction and dysphagia, may predispose to these infections. Indeed, common infections in MS patients leading to hospitalization are the usual types and although some DMTs may increase the incidence of PML or hepatitis B, these diseases remain rare in the whole MS population. As disability increases the risk of serious infections, effective MS therapy is highly important in preventing infections in MS patients. However, it is necessary to undertake an in-depth assessment of infectious risks associated with DMTs in order to ensure safe and successful MS treatment.

6.2 Strengths and limitations

Study I was the first epidemiological report covering any part of eastern Finland utilizing current diagnostic methods. The hospital districts of Southwest Finland and North Karelia comprise over 11% of the population of Finland and the results confirmed an east-west gradient in MS epidemiology in Finland. In Finland, MS is exclusively diagnosed and mostly treated by neurologists working in public health care, which is why the prevalence and incidence cohorts in the regions of interest are highly representative. In Study II, methodological differences hampered direct comparisons of different studies. In order to enable comparisons of studies from different regions and study periods, we calculated age-standardized prevalence rates in several hospital districts from 1980 to 2016.

Our Studies III and IV were the first to examine health care use of MS patients in Finland. Limitations of these studies include their retrospective design and reliance on administrative data. However, Finnish CRHC has been observed to be reliable for data collection (Sund 2012) and coverage and validity of Finnish MS register is high. Since the MS register was launched in the beginning of 2014 and only patients alive at the time were included, we do not have the descriptive data of MS patients dying before the initiation of the register. In addition, the MS register does not extend to primary health care and thus may lack some data on patients without DMT followed-up in the later stages of the disease in municipal health centers. Some patients with advanced disease and no neurological follow-up may

have been taken into primary care wards with infections. However, including these cases would only have strengthened our conclusions as these patients do not have ongoing DMTs. The proportion of patients with the most potent new DMTs was modest in our data, which prevents us from making firm conclusions on their risk of infections.

6.3 Clinical implications and suggestions for future research

Our results confirmed that Finland is a high-risk MS region with marked regional differences in MS epidemiology. The reasons behind an uneven geographic distribution of MS are not known but gene-environment interactions are suggested. More detailed and comprehensive studies on MS epidemiology are still needed to yield important information concerning the etiology of the disease. Investigating birth cohort exposures in different Nordic regions with distinct MS incidence trends could provide new insights on the subject (Sipilä 2021). Reliable nationwide research on MS epidemiology would also be warranted in Finland similarly to its neighboring countries, i.e. the last Finnish countrywide MS studies date back to 1970s before the introduction of modern diagnostic methods. An increasing use of prospective MS registries may be of great value for future epidemiological evaluations. Moreover, similar internationally comparable standardization of epidemiological figures would make it possible to obtain better geographical and temporal comparisons. These epidemiological evaluations could have important scientific implications for the pathogenesis, clinical work and health care planning of MS.

Hospital admissions of Finnish MS patients have not been studied before. Our study showed that hospital admission rates and costs related to hospital admissions in MS patients declined markedly from 2004 to 2014 in Finland. During the second study period (2009–2018), admissions decreased further in the hospital district of Southwest Finland. Considering the increasing prevalence of MS, information on the health care use of MS patients is essential if one wishes to understand the changing burden of MS on the health system, assess costs and benefits of new DMTs, and plan for future needs. Intermittent follow-up of these hospitalization rates is an important part of a comprehensive cost-effectiveness and safety evaluation of developing MS therapies. Infection-related hospitalizations were longer and displayed an increased in-hospital mortality, highlighting the health impact of infections and the importance of infection prevention among MS population. The association of infection-related hospital admissions with advanced disease and the lesser use of DMTs underline the

importance of preventing disability progression in infection prevention in MS. More studies are needed to clarify the role of DMTs in preventing the long-term disability progression in MS.

7 Conclusions

In this thesis, we evaluated regional differences of MS epidemiology in Finland by reviewing previous studies on the subject and introducing new epidemiological data on western, southwestern and eastern regions of Finland. Another aim was to examine trends in hospital admissions of MS patients, role of infections and factors predisposing to infection-related admissions. On the basis of the results of this thesis, the following conclusions can be drawn.

1. We observed age-standardized MS prevalence of 251/100,000 in Southwest Finland and 150/100,000 in North Karelia in the end of 2016, highlighting regional differences in MS epidemiology in Finland. The age-standardized MS incidence in 2012–2016 was 9.2/100,000 person-years in Southwest Finland and 6.5/100,000 person-years in North Karelia. In addition to possible gene-environment interactions, demographic circumstances may partly explain these regional differences.
2. A clear and stable increase in MS prevalence was observed over five decades while the incidence has increased only since the 1990s. The uneven geographic distribution of MS in Finland was confirmed with the concentration of the disease in the western and southwestern parts of the country. We detected the highest regional age-standardized MS prevalence of 288/100,000 in South Ostrobothnia in 2007. Age-standardization of epidemiological figures enables a comparison of different epidemiological studies worldwide.
3. Annual MS-related hospital admissions and costs related to them declined in Finland from 2004 to 2014 while the proportion associated with infections increased. Infection-related admissions lasted longer and were associated with increased in-hospital mortality emphasizing the importance of infection prevention.
4. Hospital admissions, with or without infections, decreased further in MS patients of Southwest Finland from 2009 to 2018. Infection-related admissions were associated with male gender, older age and disability

while DMT use was more common in the control population. This underlines the importance of preventing disability progression in infection prevention in MS.

Our study confirmed clear regional differences and high epidemiological figures in western and southwestern hospital districts of Finland. In addition, our results revealed the decreasing rate of hospital admissions in MS patients during the study periods which coincided with an increase in the use of DMTs. Importantly, patients with infection-related hospital admissions had used less DMTs than the reference population.

Acknowledgements

This study was carried out in the Department of Clinical Neurosciences in the University of Turku and Turku University Hospital during the years 2017–2021. I wish to express my sincere gratitude to:

My supervisors, Docent Merja Soilu-Hänninen and Docent Jussi Sipilä, for your expertise, guidance, and patience. Without you, this study would not have been possible. Merja, I am grateful that you encouraged me to start this study project and introduced me the basics of research. Your knowledge and experience in both clinical and academic field of neuroimmunology are inspiring. Jussi, thank you for accepting the invitation to be my other supervisor and for the great efforts you made for this study. I admire your enthusiastic attitude towards science and genuinely wonder how you find time for all your work.

Professor Anne-Marie Landtblom and Docent Johanna Palmio, the reviewers of this thesis, thank you for all your time and constructive comments, which improved the outcome. Professor Juhani Ruutiainen and Docent Eero Rissanen, for your work in my steering group. Ewen MacDonald, for precise English revision of this thesis.

My co-authors Katariina Hänninen, MD, Olga Krökki, MD, PhD, Docent Ville Kytö, Annukka Murtonen, MD, Professor Päivi Rautava, Docent Marja-Liisa Sumelahti and Matias Viitala, MSc, for helping me during this thesis project.

The former and current Heads of the Department of Clinical Neurosciences in the University of Turku, Professor Risto O. Roine and Professor Jaakko Rinne, for providing facilities for this study and the possibility to combine research with clinical work. My colleagues and co-workers at Neurocenter in Turku University Hospital and previously in Satasairaala, for creating a warm, joyful and supportive atmosphere. Executive secretary Leila Laakso-Kantonen, thank you for always helping out when needed.

I am fortunate to have many great friends in my life. My childhood friends Heidi, Heini, Kaisa and Mirve, I value your friendship and hope we will soon get to spend time together again after such a long time. My another childhood friend Kaisa, thank you for sharing many significant turning points in your life with me and for always supporting me. My friends from medical school Ella, Hanna, Henrika, Linda, Mari

and Tiia, I am grateful for all the good times we have spent together and the peer support during these doctoral studies. Essi, Marika and Nea as well as the rest of our group of Mares, thank you for all the joyful and relaxing gatherings over the years.

My parents Jaana and Juha, for always believing in me and supporting me in many ways throughout my life. Without your help during these busy years, this thesis could not have been finished. My siblings, Marjukka, Paavo and Katariina, for all the good times together including our traditional Days of Amusement. My grandmother Aila and my late grandfather Erkki, for the inspiration and encouraging me to embark on research. My mother-in-law Elina, for support and help whenever needed.

Finally, my deepest gratitude belongs to my dear spouse Panu for all your support and love. Your help and encouragement have been irreplaceable during this project. Our lovely children, Eino and Niilo, for the most delightful and sometimes also the most demanding times during these past years. You remind me what is truly important in life – you mean everything to me.

This work was financially supported by the Finnish MS Foundation, the Paulo Foundation, Turku University Foundation and VTR funding from Turku University Hospital.

Turku, August 2021
Anna-Leena Pirttisalo

References

Abrahamyan S, Abrahamyan S, Eberspächer B, Hoshi MM, Aly L, Luessi F et al. (2020) Complete Epstein-Barr virus seropositivity in a large cohort of patients with early multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 91(7): 681–686.

Ahlgren C, Odén A, Lycke J. (2011) High nationwide prevalence of multiple sclerosis in Sweden. *Mult Scler.* 17(8): 901–908.

Ahlgren C, Odén A, Lycke J. (2012) A nationwide survey of the prevalence of multiple sclerosis in immigrant populations of Sweden. *Mult Scler.* 18(8): 1099–1107.

Ahlgren C, Odén A, Lycke J. (2014) High nationwide incidence of multiple sclerosis in Sweden. PLoS One. 9(9): e108599.

Ahmad H, Palmer A, Campbell J, Van der Mei I, Taylor B. (2018) Health Economic Impact of Multiple Sclerosis in Australia in 2017.

Aiello M, Rampello A, Granella F, Maestrelli M, Tzani P, Immovilli P et al. (2008) Cough efficacy is related to the disability status in patients with multiple sclerosis. *Respiration.* 76(3): 311–316.

Åivo J, Kurki S, Sumelahti ML, Hänninen K, Ruutiainen J, Soilu-Hänninen M. (2017) Risk of osteoporotic fractures in multiple sclerosis patients in southwest Finland. *Acta Neurol Scand.* 135(5): 516–521.

Al-Nashmi M, Taha S, Salem AH, Alsharoqi I, Bakhiet M. (2018) Distinct HLA class I and II genotypes and haplotypes are associated with multiple sclerosis in Bahrain. *Biomed Rep.* 9(6): 531–539.

Al-Sakran L, Marrie RA, Blackburn DF, Knox KB, Evans CD. (2020) Predictors of hospitalization in a Canadian MS population: A matched cohort study. *Mult Scler Relat Disord.* 41: 102028.

Al-Sakran L, Marrie RA, Blackburn D, Knox K, Evans C. (2019) Association between disease-modifying therapies for multiple sclerosis and healthcare utilisation on a population level: A retrospective cohort study. *BMJ Open.* 9(11): e033599.

Al-Sakran L, Marrie RA, Blackburn D, Knox K, Evans C. (2020) Impact of comorbidity on hospitalizations in individuals newly diagnosed with multiple sclerosis: A longitudinal population-based study. *Mult Scler Relat Disord.* 40: 101955.

Alonso A, Hernan MA. (2008) Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology.* 71(2): 129–135.

Alonso A, Clark CJ. (2009) Oral contraceptives and the risk of multiple sclerosis: A review of the epidemiologic evidence. *J Neurol Sci*. 286(1–2): 73–75.

Alotaibi S, Kennedy J, Tellier R, Stephens D, Banwell B. (2004) Epstein-Barr Virus in Pediatric Multiple Sclerosis. *JAMA.* 291(15): 1875–1879.

Alroughani R, Boyko A. (2018) Pediatric multiple sclerosis: A review. *BMC Neurol.* 18(1): 27.

Alshubaili AF, Alramzy K, Ayyad YM, Gerish Y. (2005) Epidemiology of multiple sclerosis in Kuwait: New trends in incidence and prevalence. *Eur Neurol.* 53(3): 125–131.

Arvin AM, Wolinsky JS, Kappos L, Morris MI, Reder AT, Tornatore C et al. (2015) Varicella-zoster virus infections in patients treated with fingolimod: Risk assessment and consensus recommendations for management. *JAMA Neurol.* 72(1): 31–39.

Asche CV, Ho E, Chan B, Coyte PC. (1997) Economic consequences of multiple sclerosis for Canadians. *Acta Neurol Scand.* 95(5): 268–274.

Ascherio A, Munger KL. (2007) Environmental risk factors for multiple sclerosis. Part I: The role of infection. *Ann Neurol.* 61(4): 288–299.

Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH et al. (2014) Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol.* 71(3): 306–314.

Bashinskaya VV, Kulakova OG, Boyko AN, Favorov AV, Favorova OO. (2015) A review of genome-wide association studies for multiple sclerosis: classical and hypothesis-driven approaches. *Hum Genet.* 134(11–12): 1143–1162.

Benjaminsen E, Olavsen J, Karlberg M, Alstadhaug KB. (2014) Multiple sclerosis in the far north – incidence and prevalence in Nordland County, Norway, 1970–2010. *BMC Neurol.* 14: 226.

Bentzen J, Meulengracht Flachs E, Stenager E, Brønnum-Hansen H, Koch-Henriksen N. (2010) Prevalence of multiple sclerosis in Denmark 1950–2005. *Mult Scler.* 16(5): 520–525.

Berg-Hansen P, Moen SM, Harbo HF, Celius EG. (2014) High prevalence and no latitude gradient of multiple sclerosis in Norway. *Mult Scler.* 20(13): 1780–1782.

Berg-Hansen P, Moen SM, Sandvik L, Harbo HF, Bakken IJ, Stoltenberg C et al. (2015) Prevalence of multiple sclerosis among immigrants in Norway. *Mult Scler.* 21(6): 695–702.

Berntsson SG, Kristoffersson A, Boström I, Feresiadou A, Burman J, Landtblom AM. (2018) Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden — Outlier or predecessor? *Acta Neurol Scand.* 138(4): 327–331.

Berrigan LI, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S et al. (2016) Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. *Neurology.* 86(15): 1417–1424.

Bianchi A, Ciccarelli O. (2019) Daclizumab-induced encephalitis in multiple sclerosis. *Mult Scler.* 25(12): 1557–1559.

Bjørnevik K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T et al. (2014) Sun exposure and multiple sclerosis risk in Norway and Italy: The EnvIMS study. *Mult Scler.* 20(8): 1042–1049.

Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A et al. (2012) Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. *N Engl J Med.* 366(20): 1870–1880.

Brain W. (1930) Critical review: disseminated sclerosis. *Q J Med.* 23: 343–391.

Brønnum-Hansen H, Koch-Henriksen N, Stenager E. (2004) Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain*. 127: 844–850.

Brown JWL, Coles A, Horakova D, Havrdova E, Izquierdo G, Prat A et al. (2019) Association of Initial Disease-Modifying Therapy with Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA.* 321(2): 175–187.

Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. (2015) Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. *J Neurol Neurosurg Psychiatry*. 86(5): 584–585.

Brynedal B, Duvefelt K, Jonasdottir G, Roos IM, Åkesson E, Palmgren J et al. (2007) HLA-A confers an HLA-DRB1 independent influence on the risk of multiple sclerosis. *PLoS One*. 2(7): e664.

Buljevac D, Flach HZ, Hop WCJ, Hijdra D, Laman JD, Savelkoul HFJ et al. (2002) Prospective study on the relationship between infections and multiple sclerosis exacerbations. *Brain.* 125: 952–960.

Buonomo AR, Zappulo E, Viceconte G, Scotto R, Borgia G, Gentile I. (2018) Risk of opportunistic infections in patients treated with alemtuzumab for multiple sclerosis. *Expert Opin Drug Saf.* 17(7): 709–717.

Buron MD, Chalmer TA, Sellebjerg F, Frederiksen J, Góra MK, Illes Z et al. (2019) Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. *Neurology*. 92(16): e1811–e1820.

Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J et al. (2014) Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol.* 13(7): 657–665.

Castelo-Branco A, Chiesa F, Conte S, Bengtsson C, Lee S, Minton N et al. (2020) Infections in patients with multiple sclerosis: A national cohort study in Sweden. *Mult Scler Relat Disord.* 45: 102420.

Cavalli-Sforza LL, Piazza A. (1993) Human genomic diversity in Europe: a summary of recent research and prospects for the future. *Eur J Hum Genet.* 1(1): 3–18.

Charcot J. (1877) Lectures on the Diseases of the Nervous System. Volumes 1–2. (Translated by Sigerson G). London: *The New Sydenham Society.*

Claflin SB, Tan B, Taylor BV. (2019) The long-term effects of disease modifying therapies on disability in people living with multiple sclerosis: A systematic review and meta-analysis. *Mult Scler Relat Disord.* 36: 101374.

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP et al. (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet.* 380(9856): 1819–1828.

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP et al. (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet.* 380(9856): 1819–1828.

Correale J, Ysrraelit MC, Gaitán MI. (2010) Gender Differences in 1,25 Dihydroxyvitamin D 3 Immunomodulatory Effects in Multiple Sclerosis Patients and Healthy Subjects. *J Immunol.* 185(8): 4948–4958.

Cossburn M, Pace AA, Jones J, Ali R, Ingram G, Baker K et al. (2011) Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. *Neurology.* 77(6): 573–579.

Cristiano E, Rojas JI. (2017) Multiple sclerosis epidemiology in Latin America: An updated survey. *Mult Scler J Exp Transl Clin*. 3(2): 2055217317715050.

Degelman ML, Herman KM. (2017) Smoking and multiple sclerosis: A systematic review and meta-analysis using the Bradford Hill criteria for causation. *Mult Scler Relat Disord.* 17: 207–216.

Duquette P, Despault L, Knobler L, Lublin FD, Kelley L, Francis GS et al. (1995) Interferon beta-lb in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. *Neurology.* 57(12): 3–9.

Ellenberger D, Flachenecker P, Haas J, Hellwig K, Paul F, Stahmann A et al. (2020) Is benign MS really benign? What a meaningful classification beyond the EDSS must take into consideration. *Mult Scler Relat Disord.* 46: 102485.

Eskandarieh S, Heydarpour P, Minagar A, Pourmand S, Sahraian MA. (2016) Multiple Sclerosis Epidemiology in East Asia, South East Asia and South Asia: A Systematic Review. *Neuroepidemiology.* 46: 209–221.

Evans C, Kingwell E, Zhu F, Oger J, Zhao Y, Tremlett H. (2012) Hospital admissions and MS: Temporal trends and patient characteristics. *Am J Manag Care.*18(11): 735–742.

Fältmarsch R. (2010) Biochemistry in acid sulphate soil landscapes and small urban centres in Western Finland [dissertation, Åbo Akademi University].

Fambiatos A, Jokubaitis V, Horakova D, Kubala Havrdova E, Trojano M, Prat A et al. (2020) Risk of secondary progressive multiple sclerosis: A longitudinal study. *Mult Scler*. 26(1): 79–90.

Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. (2013) Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. *Clin Infect Dis.* 57(6): 849–852.

Fox RJ, Cohen JA. (2001) Multiple sclerosis: The importance of early recognition and treatment. *Cleve Clin J Med.* 68(2): 157–171.

Fujinami RS, Oldstone MBA. (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: Mechanism for autoimmunity. *Science.* 230(4729): 1043–1045.

Garland A, Metz LM, Bernstein CN, Peschken CA, Hitchon CA, Marrie RA. (2017) Hospitalization is associated with subsequent disability in multiple sclerosis. *Mult Scler Relat Disord.* 14: 23–28.

Geginat J, Paroni M, Pagani M, Galimberti D, De Francesco R, Scarpini E et al. (2017) The enigmatic role of viruses in multiple sclerosis: Molecular mimicry or disturbed immune surveillance? *Trends Immunol.* 38(7): 498–512.

Giovannoni G. (2017) Personalized medicine in multiple sclerosis. *Neurodegener Dis Manag.* 7: 13–17.

Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sørensen PS et al. (2010) A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. *N Engl J Med.* 362(5): 416–426.

Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J et al. (2012) Survival in MS A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. *Neurology.* 78(17): 1315–1322.

Goretti B, Viterbo RG, Portaccio E, Niccolai C, Hakiki B, Piscolla E et al. (2014) Anxiety state affects information processing speed in patients with multiple sclerosis. *Neurol Sci.* 35(4): 559–563.

Grytten N, Aarseth JH, Lunde HMB, Myhr KM. (2016) A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. *J Neurol Neurosurg Psychiatry.* 87(1): 100–105.

Grytten N, Torkildsen Ø, Myhr KM. (2015) Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. *Acta Neurol Scand.* 132: 29–36.

Häsänen E, Kinnunen E, Alhonen P. (1986) Relationships between the prevalence of multiple sclerosis and some physical and chemical properties of soil. *Sci Total Environ.* 58(3): 263–272.

Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B et al. (2017) Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med.* 376(3): 221–234.

Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ et al. (2008) B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis. *N Engl J Med.* 358(7): 676–688.

Hedström AK, Bäärnhielm M, Olsson T, Alfredsson L. (2009) Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. *Neurology.* 73(9): 696–701.

Heine M, Maartens D, Hanekom S, Derman W. (2020) Multiple Sclerosis in sub-Saharan Africa – a scoping review. *Mult Scler Relat Disord.* 42: 102133.

Hemmer B, Kerschensteiner M, Korn T. (2015) Role of the innate and adaptive immune responses in the course of multiple sclerosis. *Lancet Neurol*. 14: 406–419.

Hennessey A, Robertson NP, Swingler R, Compston DAS. (1999) Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. *J Neurol.* 246(11): 1027–1032.

Henriksson F. (1998) The economic cost of multiple sclerosis in Sweden in 1994. *Pharmacoeconomics.* 13: 597–606.

Hollenbach, JA, Oksenberg JR. (2015) The immunogenetics of multiple sclerosis: A comprehensive review. *J Autoimmun.* 64: 13–25.

Holmberg M, Murtonen A, Elovaara I, Sumelahti ML. (2013) Increased Female MS Incidence and Differences in Gender-Specific Risk in Medium- and High-Risk Regions in Finland from 1981–2010. *Mult Scler Int.* 2013: 182516.

Hongell K, Kurki S, Sumelahti ML, Soilu-Hänninen M. (2019) Risk of cancer among Finnish multiple sclerosis patients. *Mult Scler Relat Disord*. 35: 221–227.

Hurwitz BJ. (2011) Analysis of current multiple sclerosis registries. *Neurology*. 76(1): 7–13.

International Multiple Sclerosis Genetics Consortium (IMSGC). (2019) Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science.* 365: eaav7188.

Isobe N, Keshavan A, Gourraud PA, Zhu AH, Datta E, Schlaeger R et al. (2016) Association of HLA genetic risk burden with disease phenotypes in multiple sclerosis. *JAMA Neurol.* 73(7): 795–802.

Jacobs BM, Noyce AJ, Bestwick J, Belete D, Giovannoni G, Dobson R. (2021) Gene-Environment Interactions in Multiple Sclerosis – A UK Biobank Study. *Neurol Neuroimmunol Neuroinflamm.* 8(4): e1007.

Johansson S, Ytterberg C, Gottberg K, Widén Holmqvist L, von Koch L. (2009) Use of health services in people with multiple sclerosis with and without fatigue. *Mult Scler.* 15(1): 88–95.

Jokelainen M, Wikström J, Palo J. (1979) Effect of birthplace on the development of amyotrophic lateral sclerosis and multiple sclerosis. A study among finnish war evacuees. *Acta Neurol Scand.* 60(5): 283–288.

Kalincik T, Jokubaitis V, Spelman T, Horakova D, Havrdova E, Trojano M et al. (2018) Cladribine versus fingolimod, natalizumab and interferon β for multiple sclerosis. *Mult Scler.* 24(12): 1617–1626.

Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R et al. (2018) Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 391(10127): 1263–1273.

Kavaliunas A, Manouchehrinia A, Stawiarz L, Ramanujam R, Agholme J, Hedström AK et al. (2017) Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler.* 23(9): 1233–1240.

Kerminen S, Cerioli N, Pacauskas D, Havulinna AS, Perola M, Jousilahti P et al. (2021) Changes in the fine-scale genetic structure of Finland through the 20th century. *PLoS Genet.* 17(3): e1009347.

Kerminen S, Havulinna AS, Hellenthal G, Martin AR, Sarin AP, Perola M et al. (2017) Fine-scale genetic structure in Finland. *G3.* 7(10): 3459–3468.

Kingwell E, Marriott JJ, Jetté N, Pringsheim T, Makhani N, Morrow SA et al. (2013) Incidence and prevalence of multiple sclerosis in Europe: A systematic review. *BMC Neurol.* 13: 128.

Kingwell E, Zhu F, Marrie RA, Fisk JD, Wolfson C, Warren S et al. (2015) High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991–2010). *J Neurol.* 262(10): 2352–2363.

Kinnunen E. (1984) Multiple sclerosis in Finland: evidence of increasing frequency and uneven geographic distribution. *Neurology.* 34(4): 457–461.

Kinnunen E, Wikström J, Porras J, Palo J. (1983) The epidemiology of multiple sclerosis in Finland: increase of prevalence and stability of foci in high-risk areas. *Acta Neurol Scand.* 67(5): 255–262.

Kobelt G, Berg J, Lindgren P, Fredrikson S, Jönsson B. (2006) Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 77(8): 918–926.

Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. (2017) New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler.* 23(8): 1123–1136.

Koch-Henriksen N, Laursen B, Stenager E, Magyari M. (2017) Excess mortality among patients with multiple sclerosis in Denmark has dropped significantly over the past six decades: A population based study. *J Neurol Neurosurg Psychiatry.* 88(8): 626–631.

Koch-Henriksen N, Sørensen PS. (2010) The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 9(5): 520–532.

Koch-Henriksen N, Thygesen LC, Stenager E, Laursen B, Magyari M. (2018) Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. *Neurology*. 90(22): e1954–e1963.

Kotzamani D, Panou T, Mastorodemos V, Tzagournissakis M, Nikolakaki H, Spanaki C et al. (2012) Rising incidence of multiple sclerosis in females associated with urbanization. *Neurology.* 78(22): 1728–1735.

Kowalec K, McKay KA, Patten SB, Fisk JD, Evans C, Tremlett H et al. (2017) Comorbidity increases the risk of relapse in multiple sclerosis. *Neurology.* 89(24): 2455–2461.

Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. (2006) The natural history of multiple sclerosis: A geographically based study 9: Observations on the progressive phase of the disease. *Brain*. 129: 584–594.

Krökki O, Bloigu R, Reunanen M, Remes AM. (2011) Increasing incidence of multiple sclerosis in women in Northern Finland. *Mult Scler.* 17(2): 133–138.

Krökki O, Bloigu R, Ansakorpi H, Reunanen M, Remes AM. (2017) Neurological comorbidity and survival in multiple sclerosis. *Mult Scler Relat Disord*. 3(1): 72–77.

Kuhle J, Disanto G, Dobson R, Adiutori R, Bianchi L, Topping J et al. (2015) Conversion from clinically isolated syndrome to multiple sclerosis: A large multicantre study. *Mult Scler.* 21(8): 1013–1024.

Kurtzke JF. (1975) A reassessment of the distribution of multiple sclerosis: part one. *Acta Neurol Scand.* 51(2): 110–136.

Kurtzke JF. (2013) Epidemiology in multiple sclerosis: a pilgrim's progress. *Brain.* 136: 2904–2917.
Kuusisto H, Kaprio J, Kinnunen E, Luukkaala T, Koskenvuo M, Elovaara I. (2008) Concordance and heritability of multiple sclerosis in Finland: Study on a nationwide series of twins. *Eur J Neurol.* 15(10): 1106–1110.
Laakso SM, Viitala M, Kuusisto H, Sarasoja T, Hartikainen P, Atula S et al. (2019) Multiple sclerosis in Finland 2018—Data from the national register. *Acta Neurol Scand.* 140(5): 303–311.
Landtblom AM, Kristoffersson A, Boström I. (2019) Organic solvent exposure as a risk factor for multiple sclerosis: An updated review. *Rev Neurol.* 175(10): 625–630.
Lassmann H. (2019) Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. *Front Immunol.* 9: 3116.
Le Page E, Veillard D, Laplaud DA, Hamonic S, Wardi R, Lebrun C et al. (2015) Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): A randomised, controlled, double-blind, non-inferiority trial. *Lancet.* 386(9997): 974–981.
Leppo K, Puska P. (2003) Tobacco control in Finland. *Suomen Lääkärilehti.* 58: 2953–2957.
Li H, Hou X, Liang Y, Xu F, Zhang X, Cui P et al. (2021) Gene-Based Tests of a Genome-Wide Association Study Dataset Highlight Novel Multiple Sclerosis Risk Genes. *Front Neurosci.* 15: 614528.
Louapre C, Collongues N, Stankoff B, Giannesini C, Papeix C, Bensa C et al. (2020) Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. *JAMA Neurol.* 77(9): 1079–1088.
Lublin FD, Baier M, Cutter G. (2003) Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology.* 61(11): 1528–1532.
Lucas RM, Byrne SN, Correale J, Ilschner S, Hart PH. (2015) Ultraviolet radiation, vitamin D and multiple sclerosis. *Neurodegener Dis Manag.* 5(5): 413–424.
Luna G, Alping P, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M et al. (2019) Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. *JAMA Neurol.* 77(2): 184–191.
Madigand M, Oger JJF, Fauchet R, Sabouraud O, Genetet B. (1982) HLA profiles in multiple sclerosis suggest two forms of disease and the existence of protective haplotypes. *J Neurol Sci*. 53(3): 519–529.
Magalhaes S, Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmøy T et al. (2015) The EnvIMS study: Design and methodology of an international case-control study of environmental risk factors in multiple sclerosis. *Neuroepidemiology*. 44(3): 173–181.
Maghzi AH, Ghazavi H, Ahsan M, Etemadifar M, Mousavi SA, Khorvash F et al. (2010) Increasing female preponderance of multiple sclerosis in Isfahan, Iran: A population-based study. *Mult Scler*. 16(3): 359–361.
Magyari M, Koch-Henriksen N, Pfleger CC, Sørensen PS. (2013) Reproduction and the risk of multiple sclerosis. *Mult Scler.* 19(12): 1604–1609.
Magyari M, Sorensen PS. (2019) The changing course of multiple sclerosis: rising incidence, change in geographic distribution, disease course, and prognosis. *Curr Opin Neurol.* 32(3): 320–326.
Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. (2016) Mortality in multiple sclerosis: Meta-analysis of standardised mortality ratios. *J Neurol Neurosurg Psychiatry.* 87(3): 324–331.
Marrie RA, Rudick R, Horwitz R, Cutter G, Tyry T, Campagnolo D et al. (2010) Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology.* 74(13): 1041–1047.
Marrie RA, Cohen J, Stuve O, Trojano M, Sørensen PS, Reingold S et al. (2015) A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. *Mult Scler*. 21(3): 263–281.
Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S et al. (2015) Effect of comorbidity on mortality in multiple sclerosis. *Neurology.* 85(3): 240–247.

Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Tennakoon A et al. (2014) Dramatically changing rates and reasons for hospitalization in multiple sclerosis. *Neurology.* 83(10): 929–937.

Marrie RA, Elliott L, Marriott J, Cossoy M, Tennakoon A, Yu N. (2015) Comorbidity increases the risk of hospitalizations in multiple sclerosis. *Neurology.* 84(4): 350–358.

Marrie RA, Patten SB, Tremlett H, Wolfson C, Warren S, Svenson LW et al. (2016) Sex differences in comorbidity at diagnosis of multiple sclerosis. *Neurology*. 86(14): 1279–1286.

Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Sorensen PS et al. (2015) A systematic review of the incidence and prevalence of cancer in multiple sclerosis. *Mult Scler.* 21(3): 294–304.

Marrie RA, Yu N, Wei Y, Elliott L, Blanchard J. (2013) High rates of physician services utilization at least five years before multiple sclerosis diagnosis. *Mult Scler.* 19(8): 1113–1119.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. (2001) Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol.* 50(1): 121–127.

McKay KA, Marrie RA, Fisk JD, Patten SB, Tremlett H. (2018) Comorbidities Are Associated with Altered Health Services Use in Multiple Sclerosis: A Prospective Cohort Study. *Neuroepidemiology.* 51(1–2): 1–10.

McKay KA, Tremlett H, Fisk JD, Zhang T, Patten SB, Kastrukoff L et al. (2018) Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology.* 90(15): e1316–e1323.

McNicholas N, Hutchinson M, McGuigan C, Chataway J. (2018) 2017 McDonald diagnostic criteria: A review of the evidence. *Mult Scler Relat Disord.* 24: 48–54.

Menon S, Shirani A, Zhao Y, Oger J, Traboulsee A, Freedman MS et al. (2013) Characterising aggressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 84(11): 1192–1198.

Metsäniitty H, Remes A. (2016) Epidemiology of multiple sclerosis in Northern Savonia region and the role of benign multiple sclerosis [thesis, University of Eastern Finland].

Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR et al. (2008). Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol.* 7(10): 903–914.

Miller DH, Chard DT, Ciccarelli O. (2012) Clinically isolated syndromes. *Lancet Neurol*. 11(2): 157–169.

Miller DH, Leary SM. (2007) Primary-progressive multiple sclerosis. *Lancet Neurol.* 6(10): 903–912.

Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G et al. (2017) Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med.* 376(3): 209–220.

Montgomery S, Hillert J, Bahmanyar S. (2013) Hospital admission due to infections in multiple sclerosis patients. *Eur J Neurol.* 20(8): 1153–1160.

Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC et al. (2004) Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 62(1): 60–65.

Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, Sørensen TI et al. (2013) Childhood body mass index and multiple sclerosis risk: A long-term cohort study. *Mult Scler.* 19(10): 1323–1329.

Munger KL, Chitnis T, Ascherio A. (2009) Body size and risk of MS in two cohorts of US women. *Neurology.* 73(19): 1543–1550.

Munger KL, Hongell K, Åivo J, Soilu-Hänninen M, Surcel HM, Ascherio, A. (2017) 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort. *Neurology.* 89(15): 1578–1583.

Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 296(23): 2832–2838.

Murtonen A, Kurki S, Hänninen K, Soilu-Hänninen M, Sumelahti ML. (2018) Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections. *Mult Scler Relat Disord.* 19: 109–114.

Murtonen A, Sumelahti ML. (2019) Multiple sclerosis prevalence in 2000 and 2010 in Western Finland. *Acta Neurol Scand.* 141(4): 311–318.

Neuhaus O, Kieseier BC, Hartung HP. (2006) Therapeutic role of mitoxantrone in multiple sclerosis. *Pharmacol Ther.* 109(1–2): 198–209.

Neumann H, Medana IM, Bauer J, Lassmann H. (2002) Cytotoxic T lymphocytes in autoimmune and degenerative CNS diseases. *Trends Neurosci.* 25(6): 313–319.

Nielsen NM, Corn G, Frisch M, Stenager E, Koch-Henriksen N, Wohlfahrt J et al. (2019). Multiple sclerosis among first-and second-generation immigrants in Denmark: A population-based cohort study. *Brain.* 142(6): 1587–1597.

Nielsen NM, Westergaard T, Rostgaard K, Frisch M, Hjalgrim H, Wohlfahrt J et al. (2005) Familial risk of multiple sclerosis: A nationwide cohort study. *Am J Epidemiol.* 162(8): 774–778.

Niino M, Mifune N, Kohriyama T, Mori M, Ohashi T, Kawachi I et al. (2014) Apathy/depression, but not subjective fatigue, is related with cognitive dysfunction in patients with multiple sclerosis. *BMC Neurol*. 14: 3.

Norio R. (2003a) Finnish Disease Heritage I: Characteristics, causes, background. *Hum Genet*. 112(5–6): 441–456.

Norio R. (2003b) Finnish Disease Heritage II: Population prehistory and genetic roots of Finns. *Hum Genet.* 112(5–6): 457–469.

Norio R. (2003c) The Finnish disease heritage III: The individual diseases. *Hum Genet*. 112(5–6): 470–526.

Ontaneda D, Nicholas J, Carraro M, Zhou J, Hou Q, Babb J et al. (2019) Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US. *Mult Scler Relat Disord.* 27: 101–111.

Organisation for Economic Co-operation and Development Statistics. Available online: https://stats.oecd.org/index.aspx?queryid=30183#.

Palacios N, Alonso A, BrØnnum-Hansen H, Ascherio A. (2011) Smoking and Increased Risk of Multiple Sclerosis: Parallel Trends in the Sex Ratio Reinforce the Evidence. *Ann Epidemiol.* 21(7): 536–542.

Paz-Zulueta M, Parás-Bravo P, Cantarero-Prieto D, Blázquez-Fernández C, Oterino-Durán, A. (2020) A literature review of cost-of-illness studies on the economic burden of multiple sclerosis. *Mult Scler Relat Disord.* 43:102162.

Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH et al. (2010) Reactivation of hepatitis B virus following rituximab-based regimens: A serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol.* 89(3): 255–262.

Pereira M, Lambrelli D, Ramagopalan SV. (2016) Decrease in rate of multiple sclerosis-related hospitalizations in Portugal. *F1000Res*. 5: 1353.

Persson R, Lee S, Ulcickas Yood M, Wagner Usn Mc CM, Minton N, Niemcryk S et al. (2020) Infections in patients diagnosed with multiple sclerosis: A multi-database study. *Mult Scler Relat Disord.* 41: 101982.

Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S et al. (2014) Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol.* 76(6): 802–812.

Pohar SL, Jones CA, Warren S, Turpin KVL, Warren K. (2007) Health status and health care utilization of multiple sclerosis in Canada. *Can J Neurol Sci.* 34(2): 167–174.

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH et al. (2006) A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med.* 354(9): 899–910.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol.* 69(2): 292–302.

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L et al. (2005) Diagnostic criteria for multiple sclerosis: 2005 Revisions to the "McDonald Criteria." *Ann Neurol*. 58(6): 840–846.

Poorolajal J, Bahrami M, Karami M, Hooshmand E. (2017) Effect of smoking on multiple sclerosis: A meta-analysis. *J Public Health.* 39(2): 312–320.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC et al. (1983) New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Ann Neurol.* 13(3): 227–231.

Prosperini L, Lucchini M, Haggiag S, Bellantonio P, Bianco A, Buscarinu MC et al. (2018) Fingolimod vs dimethyl fumarate in multiple sclerosis a real-world propensity score-matched study. *Neurology.* 91(2): e153–e161.

Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS et al. (2018) Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis. *Neurology*. 93(17): 769.

Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. (2015) American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology.* 148(2): 455.

Reynders T, D'haeseleer M, De Keyser J, Nagels G, D'hooghe MB. (2017) Definition, prevalence and predictive factors of benign multiple sclerosis. *ENeurologicalSci*. 7: 37–43.

Ribbons KA, McElduff P, Boz C, Trojano M, Izquierdo G, Duquette P et al. (2015) Male sex is independently associated with faster disability accumulation in relapse-onset MS but not in primary progressive MS. *PloS One.* 10(6): e0122686.

Rinne UK, Panelius M, Kivalo E, Hokkanen E, Meurman T. (1968) Multiple Sclerosis in Finland. Further studies on its distribution and prevalence. *Acta Neurol Scand.* 44: 631–642.

Rinne UK, Panelius M, Kivalo E, Hokkanen E, Palo J. (1966) Distribution of Multiple Sclerosis in Finland with special reference to some geological factors. *Acta Neurol Scand.* 42: 385–399.

Rocca MA, Amato MP, De Stefano N, Enzinger C, Geurts JJ, Penner IK et al. (2015) Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol.* 14(3): 302–317.

Rotstein DL, Chen H, Wilton AS, Kwong JC, Marrie RA, Gozdyra P et al. (2018) Temporal trends in multiple sclerosis prevalence and incidence in a large population. *Neurology.* 90(16): e1435–e1441.

Rotstein DL, Marrie RA, Maxwell C, Gandhi S, Schultz SE, Fung K et al. (2019) MS risk in immigrants in the McDonald era. *Neurology.* 93(24): e2203–e2215.

Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. (2016) Burden of illness in multiple sclerosis (DEFENSE) study: The costs and quality-of-life of Finnish patients with multiple sclerosis. *J Med Econ.* 19(1): 21–33.

Sadovnick AD, Armstrong H, Rice GPA, Bulman D, Hashimoto L, Party DW et al. (1993) A population-based study of multiple sclerosis in twins: Update. *Ann Neurol.* 33(3): 281–285.

Saleem MA, Mukhelif HF, Moussawi KM, Al-Khafaji JT. (2007) Human leukocyte antigen typing in Iraqi multiple sclerosis patients. *Neurosciences.* 12(2): 127–132.

Salier JP, Sesboue R, Martin-Mondiere C, Daveau M, Cesaro P, Cavelier B et al. (1986) Combined influences of Gm and HLA phenotypes upon multiple sclerosis susceptibility and severity. *J Clin Invest.* 78(2): 533–538.

Salmela E, Lappalainen T, Fransson I, Andersen PM, Dahlman-Wright K, Fiebig A et al. (2008) Genome-wide analysis of single nucleotide polymorphisms uncovers population structure in Northern Europe. *PLoS One*. 3(10): e3519.

Salzer J, Svenningsson R, Alping P, Novakova L, Björck A, Fink K et al. (2016) Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. *Neurology.* 87(20): 2074–2081.

Sarasoja T, Wikstrom J, Paltamaa J, Hakama M, Sumelahti ML. (2004) Occurrence of multiple sclerosis in central Finland: a regional and temporal comparison during 30 years. *Acta Neurol Scand.* 110(5): 331–336.

Sawcer S, Hellenthal G, Pirinen M, Spencer CCA, Patsopoulos NA, Moutsianas L et al. (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 476(7359): 214–219.

Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. (2013) Mortality in patients with multiple sclerosis. *Neurology*. 81(2): 184–192.

Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, McDowell F et al. (1965) Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci.* 122: 552–568.

Schweitzer F, Laurent S, Fink GR, Barnett MH, Hartung HP, Warnke C. (2020) Effects of disease-modifying therapy on peripheral leukocytes in patients with multiple sclerosis. *J Neurol.* https://doi.org/10.1007/s00415-019-09690-6

Schwenkenbecher P, Wurster U, Konen FF, Gingele S, Sühs KW, Wattjes MP, et al. (2019) Impact of the McDonald Criteria 2017 on Early Diagnosis of Relapsing-Remitting Multiple Sclerosis. *Front Neurol.* 10: 188.

Selter RC, Hemmer B. (2013) Update on immunopathogenesis and immunotherapy in multiple sclerosis. *Immunotargets Ther.* 2: 21–30.

Sepúlveda M, Llufriu S, Martínez-Hernández E, Catalá M, Artola M, Hernando A et al. (2021) Incidence and Impact of COVID-19 in MS. A Survey From a Barcelona MS Unit. *Neurol Neuroimmunol Neuroinflamm.* 8(2): e954.

Simpson S, Blizzard L, Otahal P, Van Der Mei I, Taylor B. (2011) Latitude is significantly associated with the prevalence of multiple sclerosis: A meta-analysis. *J Neurol Neurosurg Psychiatry.* 82(10): 1132–1141.

Simpson S, Wang W, Otahal P, Blizzard L, Van Der Mei IAF, Taylor BV. (2019) Latitude continues to be significantly associated with the prevalence of multiple sclerosis: An updated meta-analysis. *J Neurol Neurosurg Psychiatry.* 90(11): 1193–1200.

Sipilä JOT. (2021) Nordic clues for uncovering the aetiology of Multiple Sclerosis. *Mult Scler Relat Disord*. 50: 102804.

Sipilä JOT, Soilu-Hänninen M, Rautava P, Kytö V. (2019) Progressive multifocal leukoencephalopathy in Finland: a cross-sectional registry study. *J Neurol.* 266(2): 515–521.

Sirén MK, Sareneva H, Lokki ML, Koskimies S. (1996) Unique HLA antigen frequencies in the Finnish population. *Tissue Antigens.* 48(6): 703–707.

Soelberg Sorensen P. (2017) Safety concerns and risk management of multiple sclerosis therapies. *Acta Neurol Scand.* 136(3): 168–186.

Sorensen PS, Sellebjerg F, Hartung HP, Montalban X, Comi G, Tintoré M. (2020) The apparently milder course of multiple sclerosis: Changes in the diagnostic criteria, therapy and natural history. *Brain.* 143(9): 2637–2652.

Sormani MP, De Rossi N, Schiavetti I, Carmisciano L, Cordioli C, Moiola L et al. (2021) Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. *Ann Neurol.* 89: 780–789.

Stone J, Smyth R, Carson A, Lewis S, Prescott R, Warlow C et al. (2005) Systematic review of misdiagnosis of conversion symptoms and "hysteria." *BMJ.* 331(7523): 989.

Sumelahti ML, Holmberg MHA, Murtonen A, Huhtala H, Elovaara I. (2014) Increasing Incidence in Relapsing-Remitting MS and High Rates among Young Women in Finland: A Thirty-Year Follow-Up. *Mult Scler Int.* 2014: 1–8.

Sumelahti ML, Tienari PJ, Wikstrom J, Palo J, Hakama M. (2001) Increasing prevalence of multiple sclerosis in Finland. *Acta Neurol Scand*. 103(3): 153–158.

Sumelahti ML, Tienari PJ, Wikström J, Palo J, Hakama M. (2000) Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979–1993. *Neuroepidemiology.* 19(2): 67–75.

Sumelahti ML, Tienari PJ, Wikström J, Palo J, Hakama M. (2001) Increasing prevalence of multiple sclerosis in Finland. *Acta Neurol Scand*. 103(3): 153–158.

Sund R. (2012) Quality of the Finnish Hospital Discharge Register: A systematic review. *Scand J Public Health*. 40(6): 505–515.

Sveinbjornsdottir S, Magnusson H, Benedikz JEG. (2014) Multiple sclerosis in Iceland from 1900 to 2000: A total population study. *Mult Scler Relat Disord.* 3(3): 375–383.

The Multiple Sclerosis International Federation, Atlas of MS 2013: Mapping Multiple Sclerosis Around the World (2013).

The Multiple Sclerosis International Federation, Atlas of MS 2020, 3rd edition (2020).

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 17(2): 162–173.

Tienari PJ, Sumelahti ML, Rantamäki T, Wikström J. (2004) Multiple sclerosis in western Finland: Evidence for a founder effect. *Clin Neurol Neurosurg*. 106(3): 175–179.

Tinghög P, Björkenstam C, Carstensen J, Jansson C, Glaser A, Hillert J et al. (2014) Co-morbidities increase the risk of disability pension among MS patients: A population-based nationwide cohort study. *BMC Neurol*. 14: 117.

Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. (1998) Axonal Transection in the Lesions of Multiple Sclerosis. *N Eng J Med*. 338(5): 278–285.

Tremlett H, Zhao Y, Joseph J, Devonshire V. (2008) Relapses in multiple sclerosis are age- and time-dependent. *J Neurol Neurosurg Psychiatry.* 79(12): 1368–1374.

Trojano M, Lucchese G, Graziano G, Taylor BV, Simpson S, Lepore V et al. (2012) Geographical Variations in Sex Ratio Trends over Time in Multiple Sclerosis. *PLoS One*. 7(10): e48078.

Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L et al. (2014) Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: A randomised, controlled phase 3 trial. *Mult Scler*. 20(6): 705–716.

Wade BJ. (2014) Spatial Analysis of Global Prevalence of Multiple Sclerosis Suggests Need for an Updated Prevalence Scale. *Mult Scler Int*. 2014: 124578.

Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA et al. (2019) The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology.* 95(15): 688.

Warren SA, Turpin KVL, Pohar SL, Jones CA, Warren KG. (2009) Comorbidity and Health-Related Quality of Life in People with Multiple Sclerosis. *IJMSC*. 11: 6–16.

Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L et al. (2019) Environmental and genetic risk factors for MS: an integrated review. *Ann Clin Transl Neurol.* 6(9): 1905–1922.

Wesnes K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T et al. (2015) Body size and the risk of multiple sclerosis in Norway and Italy: The EnvIMS study. *Mult Scler*. 21(4): 388–395.

Westerlind H, Boström I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. (2014) New data identify an increasing sex ratio of multiple sclerosis in Sweden. *Mult Scler.* 20(12): 1578–1583.

Westerlind H, Stawiarz L, Fink K, Hillert J, Manouchehrinia A. (2016) A significant decrease in diagnosis of primary progressive multiple sclerosis: A cohort study. *Mult Scler.* 22(8): 1071–1079.

Wijnands JMA, Kingwell E, Zhu F, Zhao Y, Fisk JD, Evans C et al. (2017) Infection-related health care utilization among people with and without multiple sclerosis. *Mult Scler.* 23(11): 1506–1516.

Wijnands JMA, Kingwell E, Zhu F, Zhao Y, Högg T, Stadnyk K et al. (2017) Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. *Lancet Neurol.* 16(6): 445–451.

Wijnands JMA, Zhu F, Kingwell E, Fisk JD, Evans C, Marrie RA et al. (2018) Disease-modifying drugs for multiple sclerosis and infection risk: A cohort study. *J Neurol Neurosurg Psychiatry*. 89(10): 1050–1056.

Wikström J. (1975) Studies on the clustering of multiple sclerosis in Finland II: microepidemiology in one high-risk county with special reference to familial cases. *Acta Neurol Scand.* 51(3): 173–183.

Wikström J, Palo J. (1975) Studies on the clustering of multiple sclerosis in Finland I: Comparison between the domiciles and places of birth in selected subpopulations. *Acta Neurol Scand.* 51(2): 85–98.

Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC. (2005) Timing of birth and risk of multiple sclerosis: Population based study. *BMJ*. 330(7483): 120.

Williamson EML, Berger JR. (2017) Diagnosis and Treatment of Progressive Multifocal Leukoencephalopathy Associated with Multiple Sclerosis Therapies. *Neurotherapeutics.* 14(4): 961–973.

Willumsen JS, Aarseth JH, Myhr KM, Midgard R. (2020) High incidence and prevalence of MS in Møre and Romsdal County, Norway, 1950–2018. *Neurol Neuroimmunol & Neuroinflamm.* 7(3): e713.

Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK. (2016) Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol.* 12(4): 217–233.

Ytterberg C, Lundqvist S, Johansson S. (2013) Use of health services in people with multiple sclerosis with and without depressive symptoms: A two-year prospective study. *BMC Health Serv Res*. 13: 365.

Zhang T, Tremlett H, Leung S, Zhu F, Kingwell E, Fisk JD et al.. (2016) Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis. *Neurology*. 86(14): 1287–1295.

Zivadinov R, Weinstock-Guttman B, Hashmi K, Abdelrahman N, Stosic M, Dwyer M et al. (2009) Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis. *Neurology*. 73(7): 504–510.

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2021

ISBN 978-951-29-8623-1 (PRINT)
ISBN 978-951-29-8624-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)