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ANNUKKA VERKKO

Epidemiology of Multiple Sclerosis in Western Finland in 1981-2010

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PunaMusta Oy – Yliopistopaino
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To my family.

ABSTRACT

The epidemiology of multiple sclerosis (MS), an autoimmune inflammatory disease of the central nervous system, is characterized by uneven global and regional distribution. The highest prevalence and incidence figures are reported from North America and Europe, where especially Scandinavia is considered an area of high MS risk. One area of globally high risk in Finland is the Seinäjoki region, South Ostrobothnia, in western parts of the country, which was already seen in the first epidemiological studies in the 1960s. Another area of high risk is located in Southwest Finland. Globally, the incidence and prevalence of MS have been rising, and studies from Western Finland show similar trends. Survival in MS is reported to be shortened by several years, and shorter if other illnesses, comorbidities, occur. MS is a progressive disease, eventually leading to disability accumulation and difficulties in everyday life, both of which are also increased by comorbidities. Risk of comorbid diseases is reported to be increased among the MS population, and especially vascular diseases worsen survival in MS. The risk of infections is high, and they are the main cause of death in this population.

The main aim of this thesis is to examine the trajectory of MS from an epidemiological point of view, divided in three more specific aims covered in four original studies. The first aim was to update incidence and prevalence trends and study disability distribution in high- and medium-risk areas in Western Finland (studies I and II). The second aim was to assess common comorbidities and their effects on survival for the first time in the Finnish MS population (study III). The third aim was to describe the end-of-life circumstances in the MS population, including disability distribution, causes, and places of death (study IV). The data were derived from hospital patient registers in Seinäjoki, Vaasa, Tampere, and Turku, and archives of Statistics Finland.

In study I, the incidence of MS increased significantly from 1981 to 2010, most remarkably among women and the relapsing-remitting course of the disease (RRMS). In Seinäjoki and Vaasa, the increasing trend stabilized in the last 10-year period of the study, 2000-2010. The age-adjusted incidence/10^5 was highest in Seinäjoki, 12.5, being twofold compared to 6.7 in Pirkanmaa, and significantly higher than 8.3 in

Vaasa. Following similar trends, the results of study II from 2000 to 2010 show that the prevalence of MS increased by 58% among women and 31% among men. Here as well, the increase was more remarkable in the RRMS group, 60%. The most remarkable increase was seen among women in Seinäjoki and Vaasa, where the standardized prevalence/10^5 in 2010 was 276 in Seinäjoki and 226 in Vaasa. In Pirkanmaa, the rate was 149. Disability in 2010 was mild in the majority of RRMS cases, whereas in the PPMS group, disability was more often severe (EDSS 6.0 or more). The analysis in study III assessing comorbidities and survival from 2004 to 2012 found significantly higher ORs in the MS population for cerebral stroke and hemorrhages, diabetes mellitus type 1, and infections. The mean lifetime survival in MS was 82.4 years, three years shorter than in the matched control population. With cardiovascular comorbidity, the survival time in MS was even worse, 79.5 years. Assessing the end-of-life circumstances of MS patients from 1981 to 2010 in study IV, the mean age at death was 57.4 years. In the majority of cases, disability before death was severe (EDSS 6.0 or more). The immediate cause of death (ICD) was an infection in 51% of cases, whereas MS was the main underlying cause of death (UCD) in 58% of cases. Cardiovascular causes were seen as ICD mainly in the ages 60 years and older and suicide in the youngest group, under 50 years old. Most often MS patients perished in hospital wards.

Our results corroborate earlier findings from the high-risk area in Western Finland and show increasing trends in the incidence and prevalence of RRMS, especially among women. In the future updating the epidemiological figures from this historically unique area of high MS risk remains important. Epidemiological studies provide important background information when plans for future health care are being made, as well as important data for future studies of the efficacy of disease modifying treatments, which are important reasons to continue research in this area. In future studies, we hopefully see the effects of new disease modifying medications on disability and survival. Cardiovascular comorbidities significantly affect survival in MS, which is why it is important to pay attention to the primary prevention of these diseases in the MS population. The inspection of disability results show that greater disability is more often seen in PPMS and is quite common at the end of life. Regarding the accumulation of disability toward the end of life, cut points to create plans for the care at the end of life should be adopted, to ensure proper utilization of palliative care in this patient group as well.

TIIVISTELMÄ

Multippeliskleroosin eli MS-taudin esiintyvyys on maailmanlaajuisesti ja alueellisesti epätasaista. Suurimmat esiintyvyydet on raportoitu Pohjois-Amerikasta ja Euroopasta, etenkin Skandinavian alueelta. Jo ensimmäisissä suomalaisissa tutkimuksissa 1960-luvulla todettiin, että Seinäjoen alue (Etelä-Pohjanmaa) Länsi-Suomessa edustaa korkean riskin aluetta, niin maamme sisällä kuin kansainvälisestikin. Vastaavanlainen korkea riski on todettu myös Lounais-Suomessa. Niin meillä kuin maailmallakin MS-taudin insidenssi ja prevalenssi ovat kasvaneet viimeisten vuosikymmenten aikana. MS-tauti on luonteeltaan etenevä, johtaen lisääntyvään toimintakyvyn heikkenemiseen. Oheissairastavuuden riski on MS-potilailla kohonnut, mikä on merkittävää siksi, että etenkin sydän- ja verisuonitaudit lyhentävät MS-potilaiden elinikää. Ilman oheissairauksiakin MS-potilaiden elinikä on lyhentynyt keskimäärin muutamilla vuosilla ikätovereihin nähden. Useimmiten MS-potilaan kuolinsyy on jokin infektio.

Tämä väitöskirja koostuu neljästä alkuperäisjulkaisusta. Tavoitteina oli päivittää tietoja insidenssista ja prevalenssista sekä toimintakyvyn alenemasta korkean ja keskisuuren riskin alueilta Länsi-Suomesta (tutkimukset I ja II). Lisäksi tavoitteena oli ensimmäistä kertaa selvittää oheissairauksien yleisyyttä ja niiden vaikutusta elinikään suomalaisessa MS-populaatiossa (tutkimus III). Kolmas tavoite oli kartoittaa elämän loppuvaihetta, eli toimintakykyä ennen kuolemaa, kuoleman paikkoja sekä kuolinsyitä (tutkimus IV). Aineistot tutkimuksiin kerättiin Seinäjoen ja Vaasan keskussairaaloiden sekä Tampereen ja Turun yliopistollisten sairaaloiden potilasrekistereistä sekä Tilastokeskuksen kuolintodistusarkistosta.

Tutkimuksessa I vuosien 1981 ja 2010 välillä ikävakioitu insidenssi/10^5 oli Seinäjoella 12.5, kaksinkertainen verrattuna Pirkanmaan lukemaan 6.7, ja korkeampi kuin 8.3 Vaasassa. Merkittävin nousu nähtiin naisten joukossa Seinäjoella ja Vaasassa 80- ja 90-lukujen välillä. Nousu tasoittui vuosituhanteen vaihteen jälkeen. Tutkimuksessa II todettiin prevalenssissa nousutrendi, kun vuodesta 2000 vuoteen 2010 nousua oli aaltomaisen tautimuodon ryhmässä 60%, ja koko aineistossa naisten joukossa 58%, miesten joukossa 31%. Merkittävin nousu todettiin Seinäjoen ja Vaasan alueilla naisten joukossa. Vuonna 2010 vakioitu prevalenssi/10^5 oli 276

Seinäjoella, 226 Vaasassa ja 149 Pirkanmaalla. Toimintakyvyn alenema vuonna 2010 näyttäytyi lievänä aaltomaisen tautimuodon ryhmässä, kun taas tasaisesti etenevässä ryhmässä useammin vaikeampana. Tutkimuksessa III vuosien 2004 ja 2012 välillä keskimääräinen elinaika oli 82.4 vuotta, joka oli 3 vuotta lyhyempi kuin ikä- ja sukupuolivakioidulla verrokkiväestöllä. Sydän- ja verenkiertoelimistön sairaus lyhensi MS-populaatiossa entisestään elinaikaa 79.5 vuoteen. MS potilailla oli kohonnut riski aivoinfarkteihin ja -verenvuotoihin, tyypin 1 diabetekseen sekä infektioihin. Tutkimuksessa IV vuosien 1981 ja 2010 välillä keskimääräinen MS-potilaiden kuolinikä oli 57.4 vuotta. Yleisin välitön kuolemansyy oli infektio 51 %:ssa tapauksista. MS-tauti puolestaan oli yleisin peruskuolemansyy, 58 %:ssa tapauksista. Sydän- ja verisuonitautien osuus korostui 60-vuotiaissa ja sitä vanhemmissa vainajissa, kun taas itsemurhat alle 50-vuotiaissa. Yleisin kuolinpaikka oli sairaalan tai terveyskeskuksen vuodeosasto. Useimmissa tapauksissa kuolemaa edeltänyt toimintakyvyn alenema oli vaikea-asteista.

Tämän väitöskirjan tulokset vahvistavat aiempaa käsitystä Länsi-Suomen korkean riskin alueista ja osoittavat tasoittuneen kasvutrendin insidensissa ja edelleen jatkuneen kasvutrendin prevalenssissa aaltomaisen tautimuodon ryhmässä, etenkin naisten joukossa. Tulevaisuudessa on edelleen tärkeää seurata tämän historiallisen pitkään seuratun korkean riskin alueen epidemiologisten lukujen kehitystä, etenkin kun uusien lääkehoitojen vaikutus sairauden kulkuun ja ennusteeseen alkaa toivon mukaan tulla esiin. Seuranta on merkityksellistä myös siksi, että epidemiologinen tutkimus tarjoaa taustatietoa tulevaisuuden terveyspalveluita suunniteltaessa. MS taudissa etenkin verisuoniperäinen oheissairastavuus vaikuttaa merkittävästi elinikään, minkä vuoksi näiden sairauksien ennaltaehkäisyyn tulisi panostaa tässäkin potilasjoukossa. Toimintakyvyn heikkeneminen on vaikeampaa tasaisesti etenevän tautimuodon ryhmässä ja etenkin elämän loppuvaiheessa, mitä voitaisiin tulevaisuudessa hyödyntää pohdittaessa elämän loppuvaiheen hoidon suunnittelun ajoittamista.

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ABBREVIATIONS

ACP	Advanced care plan
ADEM	Acute disseminated encephalomyelitis
APC	Antigen-presenting cell
BBB	Blood-brain barrier
BMI	Body mass index
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CI	Confidence interval
CIS	Clinically isolated syndrome
CLIPPERS	Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CNS	Central nervous system
COD	Cause of death
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DIS	Dissemination in space
DIT	Dissemination in time
DMT	Disease-modifying treatment
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
EDR	Excess death rate
EDSS	Expanded Disability Status Scale
ESP	European standard population
F/M-ratio	Female-to-male ratio
GA	Glatiramer acetate
ICOD	Immediate cause of death
HLA	Human leukocyte antigen
HR	Hazard ratio
ICD	International Classification of Diseases
IM	Infectious mononucleosis
INFβ	Interferon β
JCV	John Cunningham virus
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NA	Natalizumab
NAWM	Normal-appearing white matter
NEDA	No evidence of disease activity
NfL	Neurofilament light chain
NMOSD	Neuromyelitis optica spectrum disorders
OCB	Oligoclonal bands
OR	Odds ratio
PC	Palliative care
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SIR	Standardized incidence rate
SMR	Standardized mortality ratio
SNP	Single nucleotide polymorphism
SPMS	Secondary progressive MS
UCOD	Underlying cause of death
UV	Ultraviolet radiation
VEP	Visual evoked potential
WHO	World Health Organization

ORIGINAL PUBLICATIONS

This thesis is based on following publications. Later in the text they are referred with Roman numerals I-IV.[1]

Publication I Holmberg M, Murtonen A, Elovaara I, Sumelahti M-L. 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. Epub Nov 10. doi:10.1155/2013/182516

Publication II Murtonen A, Sumelahti M-L. Multiple sclerosis prevalence in 2000 and 2010 in Western Finland. Acta Neurol Scand 2020;141:311-318. Epub 2019 Dec 14. doi: 10.1111/ane.13203.

Publication III Murtonen A, Kurki S, Hänninen K, Soilu-Hänninen M, Sumelahti M-L. Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections. Mult Scler Relat Disord. 2018;19:109-114. Epub 2017 Nov 13. doi: 10.1016/j.msard.2017.10.019.

Publication IV Murtonen A, Lehto JT, Sumelahti M-L. End of life in multiple sclerosis: Disability, causes and place of death among cases diagnosed from 1981 to 2010 in Pirkanmaa hospital district in Western Finland. Mult Scler Relat Disord. 2021;54:103139. Epub Jul 07. doi: 10.1016/j.msard.2021.103139

[1] Since the publication of these studies, the surname of Annukka Verkko has changed. The previous surname is Murtonen.

AUTHOR'S CONTRIBUTION

Annukka Verkko is the first author in studies II–IV and the corresponding author in studies III and IV. In study I, Annukka Verkko was the second author.

In study I, Annukka Verkko participated in data collection from the patient archives of Tampere University Hospital and Seinäjoki Central Hospital, as well as to the statistical analyses, interpretation of results, creation of tables and figures, and writing of the manuscript with Markus Holmberg and Marja-Liisa Sumelahti.

In study II, Annukka Verkko participated in data collection from the patient archives of Tampere University Hospital and Seinäjoki Central Hospital, conducted statistical analyses and calculations, interpreted the results, created tables and figures, and wrote and edited the manuscript. All parts of the study were conducted with Marja-Liisa Sumelahti. Verkko prepared the manuscript for submission and submitted the manuscript. Revision of the manuscript and replies to the reviewers' comments were conducted together with Marja-Liisa Sumelahti.

In study III, Annukka Verkko participated in manual scrutinizing of MS cases with the diagnosis of cerebrovascular disorders collected from the patient archives of Turku University Hospital, interpreted the results, and created tables and figures with Marja-Liisa Sumelahti. Statistical analyses were made by Samu Kurki. With the rest of the study group, Marja-Liisa Sumelahti, Samu Kurki, Katariina Hänninen, and Merja Soilu-Hänninen, she participated in writing the manuscript. Verkko prepared the manuscript for submission and submitted the manuscript for the first submission. Revision of the manuscript and replies to the reviewers' comments were conducted together with Marja-Liisa Sumelahti.

In study IV, Annukka Verkko participated in data collection from the patient archives of Tampere University Hospital and death records from the archives of Statistics Finland, conducted statistical analyses, interpreted the results, created tables and figures, and wrote and edited the manuscript with Marja-Liisa Sumelahti and Juho Lehto. Verkko prepared the manuscript for submission and submitted the manuscript. Revision of the manuscript and replies to the reviewers' comments were conducted together with Marja-Liisa Sumelahti and Juho Lehto.

1 INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive autoimmune disease of the central nervous system (CNS). Pathological characteristics are inflammation in CNS, demyelination, and axonal injury. The onset of MS usually occurs between 20 and 40 years of age and women are twice as often affected as men (Filippi et al., 2018). Categorization into relapsing-remitting (RRMS) and primary progressive (PPMS) groups by disease course is widely used.

Uneven geographical distribution characterizes the epidemiology of MS. Scandinavia, North America, and Western Europe are areas of globally high incidence and prevalence (MS International Federation, 2021). Incidence of MS has been rising in many regions (Lane et al., 2022), mainly among RRMS and women (Hawkes et al., 2020; Koch-Henriksen & Sørensen, 2010), stabilizing within the latest two decades in some reports (Flemmen et al., 2020). Correspondingly, rising prevalence and a rising female-to-male (F/M) ratio have been reported (Kingwell et al., 2013). Other epidemiological characteristics of MS are regional differences within countries, such as high-risk areas in Sardinia (Urru et al., 2019), Scotland (Kearns et al., 2019), and Norway (Grytten et al., 2015), where the highest prevalences are more than $200/10^5$. In Finland, western parts of the country were already recognized as an area of high risk in the 1960s, when the first epidemiological surveys were made (Rinne et al., 1968). In subsequent studies on the incidence and prevalence of western Finland up to the 1990s, these findings have prevailed with increasing trends (Kinnunen et al., 1983; Sumelahti et al., 2001; Wikström & Palo, 1975).

According to the leading hypothesis, the onset of MS is a result of a multifactorial cascade of certain infectious and environmental events at certain time points in a person with genetic susceptibility (Goodin et al., 2021). At the beginning of the disease trajectory remyelination repairs the myelin damage, but as the disease progresses, reparative mechanisms become insufficient, and the accumulation of disability appears to increase (Kuhlmann et al., 2023). Disability and various symptoms cause suffering and have an impact on quality of life, affecting several aspects of daily living and working ability. MS is one of the major causes of early retirement among young adults in Finland (Heinonen et al., 2020b). Various means of rehabilitation are commonly needed through the disease trajectory. Toward the

end of life, the need for assistance and care often increases, and unplanned hospitalization is not a rare event. Most often, the cause of death of an MS patient is infection (Manouchehrinia et al., 2016; Sumelahti et al., 2010).

MS patients have been associated with an elevated risk for comorbidities (Chou et al., 2020) like infections, vascular disorders, and depression (Magyari & Sorensen, 2020), which in turn have a negative impact on overall functional ability, progression of MS, options for MS medication, and prognosis (Kowalec et al., 2017; McKay et al., 2018). Mortality in MS is almost threefold compared to the general population (Manouchehrinia et al., 2016; Sumelahti et al., 2010), and previously reported median survival time has ranged from six to twelve years less than in the population overall (Cutter et al., 2015; Kingwell et al., 2012). With vascular comorbidity, the gap is even wider, which is shown in study III. Other aspects of the end of life, like circumstances of death, disability, and care given before death, have been scarcely investigated.

Epidemiological studies provide important background information for the needs of future healthcare planning, which in the case of MS should be carefully made as the economic burden of MS is significant (Bebo et al., 2022; Purmonen et al., 2020). Information on survival and disability distribution from the era of the first disease-modifying treatments (DMT) provides an important historical cohort when future studies of the efficacy of medications are being conducted. In this thesis, an epidemiological trajectory of MS is being studied. In studies I and II, the aim was to update incidence and prevalence from an area of high and intermediate risk in Western Finland and investigate disability distribution. A survey on comorbidities of MS patients has not been conducted in Finland before, which is why we studied comorbidities and their effects on survival among the Finnish MS population in study III. In study IV of this thesis, we focused on the end of life, investigated causes of death among Finnish MS patients and, for the first time from Finnish data, studied places of death and stage of disability at the end of life.

2 REVIEW OF THE LITERATURE

2.1 Clinical features of MS

2.1.1 Overview

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS), which most often manifests at 20–40 years and affects women twice as often as men (Filippi et al., 2018). There is also a subtype of pediatric onset MS, which is left outside the scope of this thesis. According to the clinical course, the disease is usually categorized into active relapsing-remitting (RRMS) and progressive disease courses (primary PPMS and secondary SPMS). The nature of the disease is progressive, and as time goes by, RRMS usually transforms into a secondary progressive phase (SPMS). Typical symptoms of MS are sensory, motor, visual, and bladder impairment, difficulties with gait, fatique, and optic neuritis (Thompson, Baranzini, et al., 2018).

Characteristics of MS include demyelinating inflammatory lesions in CNS, which may cause symptoms according to the site of the lesion. At the beginning, remyelination may take place after acute phases and symptoms recover, but as the disease progresses, the reparative mechanisms deteriorate, leading to accumulation of disability. Gradual progression becomes evident as the disease progresses (Kuhlmann et al., 2023; Thompson, Baranzini, et al., 2018).

Accumulation of disability leads to worsening of working ability and eventually affects activities of daily living. Through the disease trajectory, various rehabilitations are usually required, but, MS is still reported to be a major cause for early retirement (Heinonen et al., 2020a; Ruutiainen et al., 2016). In disabled persons, the risk of infections is high, and infections are most often the eventual cause of death among MS patients (Sumelahti et al., 2010). MS has been reported to shorten the average life of a patient by 6-12 years (Cutter et al., 2015; Kingwell et al., 2012).

The initiation of MS pathology remains a mystery, but according to current knowledge, certain environmental factors at certain timepoints in a person

genetically susceptible for MS are required to launch the cascade that eventually leads to the clinical appearance of MS.

2.1.2 Clinical course and disease progression

Descriptions of the clinical course of MS were originally presented in 1996 and revised in 2013 (Lublin et al., 1996, 2014). Approximately 85% of cases represent RRMS and the other 15% PPMS (Thompson et al., 2018). It has been estimated that within 15 years after onset, 40% of RRMS cases reach a secondary progressive phase (SPMS), when the steady worsening of disability begins (Scalfari et al., 2014). At the same time, worsening phases turn milder and eventually subside. The revised descriptions also mention clinically isolated syndrome (CIS) as a separate entity, the first clinical event of a disease suspected to be demyelinating one but not yet fulfilling diagnostic criteria of MS. The revision also presented an assessment of activity to be included in the descriptions of clinical phenotypes (Lublin et al., 2014).

RRMS is characterized by clinical exacerbations, where active inflammatory plaques can be seen in magnetic resonance imaging (MRI) and may cause symptoms according to the location of the active lesion. At the same time, there can be several active lesions reflected in the clinical appearance of the active phase. At the beginning of the disease trajectory, remyelination occurs up to some point, and the physical symptoms of worsening phases may recover completely. However, part of the demyelinated lesion remains, leading to the accumulation of lesion load as the disease progresses. Eventually, disability accumulates as well (Thompson, Baranzini, et al., 2018). According to the occurrence of worsening phases and MRI activity, RRMS can be categorized into active and highly active courses (Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Neurology, 2020).

The phenotype of PPMS is steadily progressive disability from the beginning. There are no clearly distinguishing worsening phases, but the accumulation of disability is the characterizing feature. PPMS usually begins 10–15 years later than RRMS but is connected to a worse prognosis than RRMS (Thompson, Baranzini, et al., 2018). Clinical courses and accumulation of disability are visualized in Figure 1.

Common initial symptoms of MS are different variations of motor and/or sensory deficits, optical neuritis, double vision, and gait difficulties (Sumelahti et al., 2003). Additional classical problems that tend to occur as the disease progresses are bladder dysfunctions, fatigue (which might be present even before diagnosis),

spasticity, ataxia and tremor, emotional problems, cognitive deficits, and neuropathic pain (Thompson, Baranzini, et al., 2018).

The most recent publications point out that the clinical course of MS should be considered as a continuum, where different pathological processes act concurrently, with variation between individuals and over time (Kuhlmann et al., 2023).

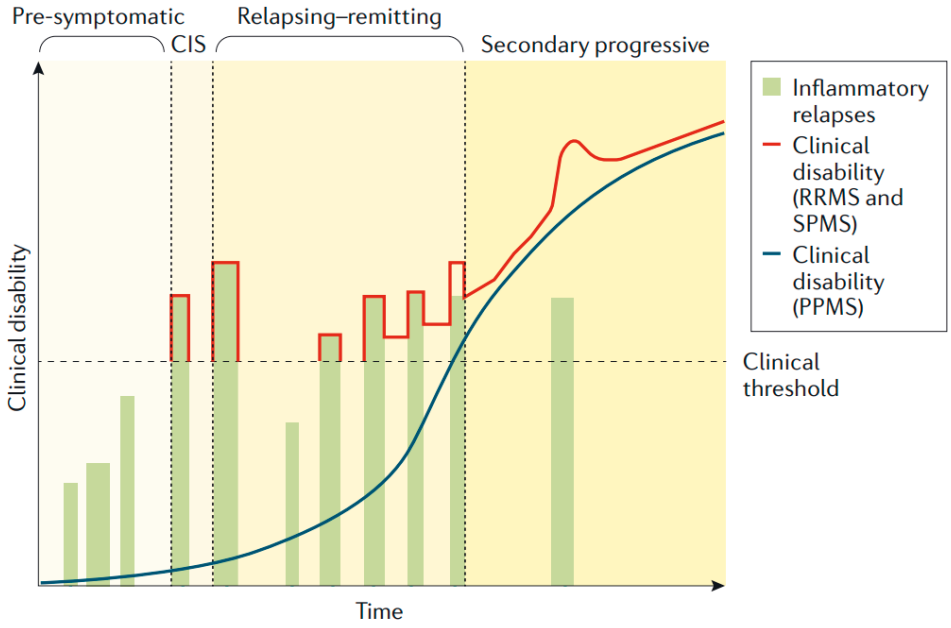

Figure 1. The clinical course of MS illustrated, showing the accumulation of disability and disease progression in active relapsing disease course, RRMS, eventually reaching the secondary progressive phase (the red line) and the steady progression of PPMS (the blue line). The light green columns represent inflammatory relapses, which are the hallmark of RRMS activity. All activity will not produce clinical exacerbations, which is indicated here with the dashed horizontal line of clinical threshold. The pathological events of MS initiate before clinical symptoms appear. Clinically isolated syndrome, CIS, is the first clinical event of a disease suspected to be demyelinating one but not yet fulfilling diagnostic criteria of MS. *Reprinted with the permission from Springer Nature.* (Filippi et al., 2018)

2.1.3 Diagnosis

Diagnostic criteria from 1970

Within the last decades, the diagnosis of MS has been defined by specific criteria. The core of all the recommendations and criteria has mainly remained the same over time. The main element is a diagnosis made by a neurologist, including neurological examination and paraclinical investigations, such as MRI, cerebrospinal fluid (CSF) analysis, and evoked potentials, especially in the time before MRI. It has always been essential to point out proof for the inflammatory and disseminated (in time and space) nature of the disease and exclude other options for disorders that could explain patients' symptoms and clinical findings. Currently, the revised McDonald criteria are the golden standard for diagnosis.

In 1965, a committee led by George A. Schumacher created and published diagnostic criteria, which became globally established. Based on clinical characteristics, a division into possible, probable, and clinically definite MS (CDMS) was made. Diagnosis required two or more attacks or progression of signs and symptoms, detectable abnormalities of CNS in the neurological examination, age between 10 and 50 years at onset, and exclusion of other explanations for the situation (Schumacher et al., 1965).

A group led by Charles M. Poser presented their criteria in 1983. The criteria consisted of two main categories, definite and probable, which both had two subgroups of clinical and laboratory-supported evidence. For the first time, laboratory-supported diagnosis was included, such as inflammatory findings of CSF (oligoclonal bands or pathological IgG-index) or pathological evoked potentials in neurophysiological studies. A CT scan of the brain, and later MRI, was also included as possible investigational methods. The diagnosis of clinically definite MS required at least two attacks in different anatomical sites, with a remission time of at least 30 days in between. The acceptable age at onset was also increased to 59 years (Poser et al., 1983).

The first version of McDonald international criteria was presented in 2001 by a panel led by William Ian McDonald (McDonald et al., 2001). MRI became more common and was also a more sensitive imaging method for pathological changes. Due to the development of imaging studies, more accurate criteria concerning the amount and location of lesions and gadolinium enhancement could be defined. Frederik Barkhof et al. created criteria for MRI findings in MS diagnosis (Barkhof et

al., 1997). After a first attack, certain findings in MRI, sometimes combined with CSF findings, could be sufficient to achieve the diagnosis of MS (demonstrating dissemination in time and space, DIT and DIS). Among patients with two attacks, dissemination in space could be pointed out with MRI. If there was objective proof of two lesions (i.e., findings in two different CNS regions in clinical neurological examination) in addition to the history of two attacks, there was no need for MRI. Cases that fulfilled the criteria only partly were called clinically isolated syndrome, CIS. Criteria for primary progressive MS were also introduced. They included positive CSF and MRI findings from the brain or spine and progression of at least one year or proof of DIT in MRI. The original panel revised the criteria in 2005, clarifying the determination of dissemination in time after onset (Polman et al., 2005). The position of spinal lesions was also clarified. Later revisions did not affect the materials of this thesis as data ascertainment was concluded on 31.12.2010. In the 2010 revision, the radiological criteria for demonstrating DIT and DIS were simplified, and they became possible to point out in a single imaging in some cases (Polman et al., 2011). The revisions of 2017 made setting the MS diagnosis more sensitive. Earlier diagnosis for a patient with CIS was made possible if DIS was demonstrated either clinically or radiologically and oligoclonal bands in the CSF were present. Radiological criteria were expanded to include a symptomatic lesion when demonstrating DIT and DIS (Thompson, Banwell, et al., 2018).

Disease course-specific diagnosis

The 2005 McDonald criteria for RRMS allowed for setting the diagnosis of MS based on two or more attacks without additional data, if objective clinical evidence of two or more lesions could be shown, which means objective findings in neurological examination in two different CNS areas. In the presence of two attacks but only one clinical evidence, DIS needed to be proved by MRI, or if MRI did not detect enough lesions, a positive CSF as well. A possibility was also to wait for a new attack to emerge from different a CNS cite. In case of one attack and objective evidence of two or more lesions, DIT needed to be proven by MRI or a second attack. If there are objective findings for only one lesion in the case of one attack, DIS needed to be shown by MRI or MRI + CSF if there are too few lesions, and DIT by MRI or a second attack. DIT was proven if a gadolinium enhancement was seen at least three months after initial onset in a site that did not relate to symptoms or if a new T2 lesion appeared after 30 days of a reference scan. To fulfill the criteria of DIS, three of the following four needed to be seen: at least one gadolinium-enhancing lesion or

nine T2 lesions if no enhancement; at least one infratentorial lesion; at least one juxtacortical lesion; and at least three periventricular lesions (Polman et al., 2005).

The criteria for PPMS as its own entity was presented in McDonald criteria in 2001. Criteria included positive CSF findings and imaging studies (DIS by MRI, in some cases with positive visual evoked potential [VEP], and DIT proved by MRI or progression of more than one year) (McDonald et al., 2001). In the revision of 2005, the criteria were simplified. Progression of at least one year was made the main thing. In addition, two of the following three were required: positive brain MRI (nine T2 lesions or four to eight with positive VEP), positive spinal MRI (two lesions), or positive CSF (Polman et al., 2005).

Differential diagnostics

An important aspect of all diagnostic criteria of MS is that other possible conditions that might explain a patient's symptoms and clinical signs must be ruled out. Conditions mimicking MS may be other inflammatory, demyelinating diseases of CNS or diseases without inflammatory background, such as neurodegenerative or hereditary diseases. When the overall situation of a patient seems not quite right for MS, it is especially essential to do blood tests and imaging studies with a larger scope than what the diagnostic criteria of MS expect (Miller et al., 2008).

Inflammatory diseases that might mimic MS include sarcoidosis and vasculitis, both of which can also have systemic manifestations, and NMOSD, ADEM, CLIPPERS, and Susac's syndrome in the CNS. Infectious causes are also possible, like brain abscess, Lyme disease, or tuberculosis as well as a rare cause. Noninflammatory causes include vascular disorders, such as multiple ischemic strokes (due to small vessel disorder or connective tissue disorders such as SLE or Sjögren's syndrome), MELAS, CADASIL, Fabry disease, Bechets's disease, and malignancies. Neurodegenerative disorders that may resemble PPMS include hereditary ataxias, spastic paraplegia, spinal stenosis, and amyotrophic lateral sclerosis.

2.1.4 Disability assessments

In MS, disability accumulates in association with relapses (poor recovery) and independently through the disease progression trajectory (Lublin et al., 2022; University of California Team et al., 2019). The level of disability and disease

progression have been shown to correlate to lesion volume, both cortical and deep grey matter atrophy (De Stefano et al., 2014; Moridi et al., 2022; University of California Team et al., 2019), and impairment of the glymphatic system (Carotenuto et al., 2022).

Systematic assessment of clinical findings, symptoms, and disability is an essential part of MS patient visits in health care, providing information on the current situation and eventual progression of the disease. It also gives important information when medication and rehabilitation are being considered. The most commonly used tool is the Expanded Disability Status Scale (EDSS) presented by John F. Kurtzke in 1983 (Kurtzke, 1983). It is a nonlinear scale with 20 steps, receiving values from 0 to 10 (0, 1.0, 1.5, 2.0… 10), which considers symptoms and signs from pyramidal, cerebellar, brainstem and sensory systems, and functions of the bladder, bowel, visual and cognitive abilities. According to the level of disability and disease burden, the scale receives higher values. EDSS points of 3.0 or less correspond to a mild disability. At EDSS point 6.0, a walking aid is required, at point 9.0 a patient is bedridden. Point 10.0 stands for death due to MS.

The EDSS has been criticized for several reasons (Weinstock-Guttman et al., 2022). One reason is inaccuracy, as it is based on clinical examination performed by clinicians, where differences in interpretation of certain findings may exist. The scale poorly acknowledges the spectrum of cognitive symptoms, fatigue, and quality of life, and functions of the upper extremity, as walking ability is the main physical function considered. Also, the EDSS has been shown to overestimate the accumulation of irreversible disability (Kalincik et al., 2015).

2.1.5 Disease–modifying treatments

The target of immunomodulatory MS treatment is to delay the progression of the disease and prevent new activity (Hauser & Cree, 2020). It has been shown that disease-modifying treatments (DMTs) indeed delay the reaching of EDSS milestones by years in RRMS (Lublin et al., 2022). From 1996 to 2012, DMTs have been available only for RRMS, which is why this section is mainly concentrated on these medications. After 2012, the field of MS medication has taken major developmental leaps as many new medications, such as sphingosine-1-phosphate receptor modulators and B-cell-depleting therapies, have been presented. Opportunities for treating active PPMS and SPMS have emerged as well. DMTs used in 2023 for MS in Finland are listed in Table 1. The treatment strategies have also changed. An

escalation approach, moving from milder to more efficient regimens when needed, was used when the data of this thesis were gathered. Later, early treatment with high-efficacy therapies in newly diagnosed RRMS patients has been presented and debate on the benefits and risks of both options is ongoing (Freeman et al., 2022).

First DMTs interferon β (INFβ) and glatiramer acetate (GA) were presented in the mid-1990s. They were soon found to be well-tolerated and became rapidly established. The mechanism of action of both is complex and not completely understood (Kieseier, 2011; Lalive et al., 2011). INFβ increases the effects of anti-inflammatory agents while reducing the expression of proinflammatory cytokines and diminishing the crossing of BBB by activated leukocytes (Kieseier, 2011). GA modulates the actions of antigen-presenting cells (APC) and antibody secretion of plasma cells, but enhancement of regulatory B-cell features may exist as well (Lalive et al., 2011).

For more aggressive forms of RRMS, help was presented in the mid-2000s when natalizumab (NA) was brought onto the market. NA is a humanized monoclonal antibody, which prevents the migration of lymphocytes into the CNS by inhibiting an adhesion molecule (α4β1 integrin) expressed in lymphocytes. NA is highly effective. Long-term exposure to NA includes a risk of progressive multifocal leukoencephalopathy (PML) in persons with JC-virus positivity, which is why careful follow-ups are needed (Pucci et al., 2011).

Acute relapses in RRMS are treated with glucocorticoids or plasmapheresis.

Table 1. Disease–modifying treatments (DMT) for MS in Finland in 2023.

Active RRMS	Highly active RRMS	Active PPMS	Active SPMS
Interferon β (INFβ)	Natalizumab (NA)	Ocrelizumab	Siponimod
Glatirameracetate (GA)	Fingolimod		
Dimethyl fumarate	Cladribine		
Teriflunomide	Ocrelizumab		
Ocrelizumab	Alemtuzumab		
Ofatumumab	Mitoxantron		
Diroximel fumarate	Ponesimod		

DMTs for MS in 2023. Until 2012 in Finland, medications were approved only to treat RRMS and only INFβ, GA and NA were in the market. Definitions for active and highly active RRMS, and for active PPMS and SPMS, are presented in the national Current Care Guideline of MS. (Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Neurology, 2020)

2.2 Etiology

2.2.1 Familial risk and genetics

Low familial risks of MS have been known for a long time. In Scandinavia, the highest lifetime risk of developing MS was found among siblings, 2.3–3.4% (Nielsen et al., 2005; Westerlind, Ramanujam, et al., 2014), especially among monozygotic twins, with a risk of 15.4% (Westerlind, Ramanujam, et al., 2014). The risk for a child of an MS patient was 1.2%, the risk of a sister was 3.1%, and a brother was 1.6% (Westerlind, Ramanujam, et al., 2014). A recent study found even greater differences: an age-adjusted risk for a sister of an MS patient was 5.4% and for a brother 0.5% (Sadovnick et al., 2021). A meta-analysis of 18 studies reported higher risks, but none of the included studies had a control population (O'Gorman et al., 2013).

Several genetic factors, which promote dysregulation of immune responses and are triggered by environmental factors, are suggested to affect the susceptibility of MS. More than 200 risk alleles have been reported to relate to MS susceptibility (International Multiple Sclerosis Genetics Consortium, 2019). The most remarkable locus is the human leukocyte antigen (HLA) class II haplotype DRB1*15:01, which is carried by 28–33% of the Northern Caucasian MS population (Gourraud et al., 2012; Hollenbach & Oksenberg, 2015)Of healthy controls, 9–15% carry the gene. This haplotype has also been linked to younger age at disease onset and more aggressive progression of the disease (Gourraud et al., 2012). Other significant risk alleles from the same area are DRB1*04, *03:01 and *13:01, DQA1*01:02, and DQB1*06:02 plus 26 others (International Multiple Sclerosis Genetics Consortium, 2019). The HLA locus relates to risks for other autoimmune diseases as well, such as type I diabetes and rheumatoid arthritis (Gourraud et al., 2012). Several single nucleotide polymorphisms (SNP) also in non-HLA loci have been found, most in non-coding segments of the genomes (Canto & Oksenberg, 2018). Different genes, haplotypes, and combinations lead to different outcomes, and protective haplotypes have been identified as well (International Multiple Sclerosis Genetics Consortium, 2019). Besides known genetic risk loci, epigenetics has been found to have an important role as well, and MS-specific alterations have been recognized (van den Elsen et al., 2014).

2.2.2 Environmental risk factors

Besides genetic predisposition, several environmental events are most likely required to trigger the cascade that leads to the outburst of MS. It is suggested that the very first event precipitating MS might happen even during the intrauterine or post-natal period, such as maternal smoking or vitamin D deficiency (Goodin, 2009). Migration studies show that if a person moves from a high-risk area to a low-risk area before puberty, the risk of developing MS later in life adjusts to the level of the area they moved to. If moving happens later in life, the risk remains the same as what it was in the area they moved from (Munk Nielsen et al., 2019). This suggests that some major event takes place during the teenage years. Similarly, first-generation immigrants show prevalence that corresponds to the country they left from, whereas second-degree immigrants' risk gets closer to the level of the country they were born in (Munk Nielsen et al., 2019; Wändell et al., 2020).

The effect of certain events and their combinations is most likely individual and depends on genetic profile (Goodin, 2009). There is strong evidence that some environmental factors have a more notable significance than others, such as infectious mononucleosis, caused by Epstein-Barr virus (EBV), vitamin D3, obesity, and cigarette smoke (Correale & Gaitan, 2015).

EBV

It has been estimated that EBV infects 90% of people around the world by the age of 30 (Dunmire et al., 2015). On average, the primary infection is asymptomatic in early childhood. When contagion happens in adolescence or adulthood, the virus may cause infectious mononucleosis (IM). Especially in developed countries and among Caucasians, the disease is reported to occur more often in the teenage years, whereas in developing countries and among populations other than Caucasian, the virus is met much younger (Dunmire et al., 2018). The occurrence of IM is decreasing. One suggested explanation is changes in immune responses, not a decrease in viral contagions themselve (E. Visser et al., 2014). The virus persists in memory B-cells, creating a latent asymptomatic infection (Bar-Or et al., 2020). Besides MS, EBV has been connected to hematological and epithelial malignancies, such as gastric carcinoma and nasopharyngeal malignancies (Dunmire et al., 2018).

The connection between EBV and MS has been presented for a while, and the latest large seroepidemiological study confirmed earlier suggestions (Aloisi et al., 2023; Bjornevik et al., 2022). The interaction of genes and environment is thought

to explain why only a few of those with EBV infection eventually develop MS (Aloisi et al., 2023; Rubicz et al., 2013). History of infectious mononucleosis raises MS risk into two- to threefold higher than average (Ascherio & Munger, 2010; Xu et al., 2021). EBV seems to be a quite remarkable risk factor for MS, but only one in 500 infected with EBV will ever get MS (Ascherio & Munger, 2010).

It is suggested that in otherwise susceptible individuals, the virus induces abnormal regulation of the immune responses, which contributes to the pathogenesis of MS (Bar-Or et al., 2020; Correale & Gaitan, 2015). The effects are thought to mediate through cellular immunity, as CD8+ and CD4+ T-cell and B-cell responses are altered. Also, CD8+ EBV memory T -cells have been identified in MS plaques (Serafini et al., 2019). The surveillance of EBV is thought to be diminished in MS patients, which is why EBV gets to CNS (Veroni & Aloisi, 2021). It has been proposed that the entry of B -cells activated by EBV into CNS is causing infectious events in MS (Aloisi et al., 2023). Another hypothesis is that in susceptible individuals, the immune cells cross-react with myelin antigen after being activated by EBV. Molecular mimicry between the surface protein of EBV and myelin might exist (Wucherpfennig & Strominger, 1995), which is a base for the hypothesis(Aloisi et al., 2023).

Vitamin D

Like many other autoimmune diseases, the risk of MS has been connected to low serum levels of 25(OH)D (vitamin D), which has many immunoregulatory functions (Correale & Gaitan, 2015). Vitamin D inhibits CD4+ T-cell proliferation, promotes the secretion of anti-inflammatory cytokines and inhibits the secretion of proinflammatory cytokines, and induces regulatory T -cells. Higher vitamin D levels promote dendritic cell induction to a more stabilizing direction (Correale & Gaitan, 2015; Ostkamp et al., 2021). Vitamin D also induces the expression of the HLA-DRB*1501 gene (Ramagopalan et al., 2010), and it has been suggested to suppress antibody production by B -cells (Lucas et al., 2015). These immunomodulatory effects seem to be greater in women than in men (Orton et al., 2011).

High levels of vitamin D in serum relate to a lower risk of RRMS, especially before the age of 20 years (K. Munger et al., 2004). Low serum vitamin D levels during pregnancy affect the offspring's risk of developing MS later in life (Mirzaei et al., 2011; K. L. Munger et al., 2016). In active RRMS, higher serum levels correlate to fewer relapses and MRI lesions, whereas lower levels have been connected to more severe disease course (Ascherio, 2013). The severity and worsening of MS through

vitamin D serum levels have been found to correlate with higher latitude and lower ultraviolet (UV) radiation, with few exceptions such as Sardinia, where genetics is thought to explain the high occurrence (Ostkamp et al., 2021). The same is true in Finland, where the east-west gradient is suggested to relate to genetical differences (Pirttisalo et al., 2020).

Serum levels of vitamin D are lower in patients with RRMS compared to overall population levels. A cutoff value of <50 nmol/ml for high risk related to low vitamin D levels has been suggested (Ascherio, 2013). To accomplish the best immunomodulatory properties, a level of ≥100 nmol/ml is proposed (Fitzgerald et al., 2015). In general, supplemental vitamin D is needed to achieve these levels. Interestingly, in PPMS, it seems that these vitamin levels are similar to those in healthy controls (Correale & Gaitan, 2015).

Populational levels of vitamin D are lower than recommended. In Scandinavia, recommended vitamin D levels (serum level above 50 nmol/l) were found in 16–22% of children and 25–33% of adults (Holten-Andersen et al., 2020; Nälsén et al., 2020; Raulio et al., 2021); the lowest levels concern adolescents (Itkonen et al., 2020). In Finland, vitamin D levels were found to be insufficient in the 1990s (Lehtonen-Veromaa et al., 1999), and since then, slow actions have been made to correct the situation (Mäkitie, 2011). Low vitamin D levels have been reported from countries closer to the equator as well, where the amount of yearly UV radiation is higher than in northern latitudes (Karampoor et al., 2016). There, cultural dressing codes may affect the amount of UV radiation reaching the skin, thus diminishing the level of vitamin D generation.

Obesity

High BMI in childhood and adolescence has been shown to be a risk factor for MS (K. L. Munger et al., 2013). The prevalence of obesity and overweight among children and adolescents has increased significantly since the 1970s in Finland and globally (Di Cesare et al., 2019; Vuorela et al., 2011). Obesity (body mass index, BMI ≥30 kg/m2) raises the risk of MS by 41% compared to overweight (BMI ≥25 kg/m2). In a Mendelian randomization study, a 5 kg/m2 increment in BMI increased the risk of MS development by 30% (Vandebergh & Goris, 2020). Vitamin D, a fat-soluble molecule, has been proposed as one factor. In addition, obesity was found to be proinflammatory, altering T -cell responses and hormonal functions (Guerrero-García et al., 2016; Mokry et al., 2016). Higher BMI has been associated with worse outcome and disability in MS (Guerrero-García et al., 2016).

Smoking

Smoking habits have changed in the latter half of the 20th -century (Dai et al., 2022), concurrently with rising MS incidence and prevalence. In observational studies, the connection of MS to smoking has been established quite clearly (Rosso & Chitnis, 2020). MS risk for someone who has ever smoked is 50% higher than someone who has never smoked (Palacios et al., 2011), and smoking has also been correlated to worse disability and higher relapse rate (Arneth, 2020; Rosso & Chitnis, 2020). The exact mechanisms are not understood, as tobacco smoke contains a plethora of possible chemical compounds to study, some of which are known to be neurotoxic (Rosso & Chitnis, 2020). Inflammatory and immunomodulatory responses, such as proinflammatory cascade induced by epithelial irritation, have been suggested (Arneth, 2020).

In Finland, the occurrence of smoking has mainly declined in recent decades. In 1996, 23% of women and 28% of men aged 20–64 years smoked daily. By 2020, the figures were reduced to 12% and 14%. In 2020, 18% of current smokers were women and 20% were men (Official Statistics Finland, 2023). A questionnaire conducted in 2012–2013 among 20–34-year-old adults revealed that 19% of men and 15% of women smoked daily. Smoking was more prevalent in Northern and Eastern Finland. There were no major differences between genders in these two regions, whereas in the rest of country, smoking was more prevalent among men (Shemeikka et al., 2014). Despite these favorable changes in smoking habits, occurrence of MS in Finland has been rising and is, in fact, smallest in areas where smoking is most prevalent. This is probably partly due to a small effect size, which won't be reflected in MS incidence trends.

2.2.3 Gender-related factors

The overall risk of autoimmune diseases in women is higher than in men (Whitacre et al., 1999): in MS, rising incidence especially among women and with RRMS has been reported (Study I; Sumelahti et al., 2014). One possible factor presented to explain these trends are lifestyle changes of women through the latter half of the 20th -century: obesity has increased, the number of pregnancies has decreased, and smoking increased until the 1990s. Risks of obesity and especially cigarette smoke appear more relevant among women (Airas, 2015; Angeloni et al., 2021), as the proinflammatory effects of both are enhanced by estrogen-related circumstances. Fewer pregnancies and child births at older ages have been connected to increased

risk of MS (Airas, 2015; Magyari et al., 2013; Ponsonby et al., 2012). Another possible explanation is the development of MS diagnostics. It may be that a few decades ago, women with mild symptoms never saw a doctor and thus missed diagnosis.

In RRMS, onset in women tends to be a few years earlier, with a more frequent relapse rate (Airas, 2015; Confavreux & Vukusic, 2006; Kalincik et al., 2013). Men have a higher risk for worse long-term disability, faster progression, more severe phenotype, and more gray matter atrophy (Voskuhl et al., 2020). Conversion to SPMS may happen at a younger age in men (Voskuhl et al., 2020).

With late-onset MS, usually primarily progressive, these differences do not exist, suggesting that gender hormones play an essential role in regulating immune responses (Airas, 2015). Among women, the first time point is puberty: earlier menarche has been connected to an increased risk of MS (Nielsen et al., 2017). In men, puberty has not been seen to have a significant effect (Ysrraelit & Correale, 2019). During pregnancy, changes in hormone levels yield changes in immune responses, both cellular and humoral, to favor the survival of the fetus (Abu-Raya et al., 2020; Airas, 2015). As a result, the relapse rate diminishes up to 70% (Ysrraelit & Correale, 2019). After childbirth, the hormone levels drop markedly, and immune responses return to pre-pregnancy levels, leading to an increased risk of relapse (Ysrraelit & Correale, 2019). After menopause, it appears that disability worsens. The effect of aging per se, and what relates to hormonal changes, is unclear.

Sex chromosomes may also influence MS risk. The X chromosome contains many genes related to proinflammatory responses in the immune system, whereas genes located on the Y chromosome have more modulatory properties. On the other hand, the genes in the Y chromosome seem to cause more neuropathology and a worse clinical course (Voskuhl, 2020).

Immune cells also express sex hormone receptors, which is why it is thought that these hormones can affect the immune system (Ysrraelit & Correale, 2019). Estradiol for example, mainly promotes expression of anti-inflammatory agents, except for low concentrations, when it turns into favoring proinflammatory agents (Ysrraelit & Correale, 2019), and promotes the production of immunoglobulin G (Paavonen et al., 1981). Progesterone promotes anti-inflammatory responses in the immune system, and androgens are thought to have similar effects. Both hormones have neuroprotective effects, as well as prolactin, which also regulates immune responses (Ysrraelit & Correale, 2019).

2.2.4 Pathogenesis

Growing knowledge of MS pathogenesis has yielded a view of two types of inflammation that both initiate at the beginning of the disease. The first one dominates the acute and relapsing MS and is characterized by leakage of the blood-brain barrier (BBB) during relapses and an influx of immune cells to the CNS, leading to the formation of demyelinated plaques. The other is a slow gathering of the same immune cells to the connective tissue of CNS without BBB leakage, leading to the formation of aggregates. This type of slow inflammation may already exist at the beginning of MS and may gradually increase with the progression of the disease (Lassmann, 2019). The term "smoldering MS" has been adapted to describe this phenomenon. As part of this process, pre-existing plaques expand gradually and slowly. Outside plaques, a diffuse process of the normal-appearing white matter (NAWM) occurs, where abnormal activation of microglia and tissue resident lymphocytes occurs, leading to smoldering inflammation of the parenchyma. Destruction progresses steadily (Kamm et al., 2014; Lassmann, 2014), and is visible in MRI images as volume loss. In early RRMS, the aetiology of atrophy is inflammatory, whereas in the progressive phase, the atrophy becomes more neurodegenerative (De Stefano et al., 2010; Lublin et al., 2014). Cortical demyelination occurs especially in progressive forms of the disease, although it is present already in the early stages of RRMS as well, eventually leading to accelerating brain atrophy (Lassmann et al., 2007; Lucchinetti et al., 2011).

At the initiation of MS disease, autoreactive CD4+ T-lymphocytes, T-helper cells Th1 and Th17, and B -cells are activated in the peripheral lymphoid tissue and then cross the BBB (Balasa et al., 2020; Korn, 2008). The exact factor that activates these cells in the first place is not known. In the CNS, these cells are reactivated by local antigen-presenting cells (APC) with myelin antigen. Production of proinflammatory cytokines and chemokines begins, which stimulates the microglia and astrocytes, recruits other leukocytes, and induces structural changes in the BBB, allowing an influx of immune cells into the CNS and plasma cells to produce antibodies (Houen et al., 2020; Lassmann et al., 2007; Ortiz et al., 2014). CD8+ cytotoxic T -cells, granulocytes, and macrophages enter the parenchyma, targeting the myelin sheath. The result of this cascade is an inflammatory lesion in white matter, where demyelination and eventually axonal injury takes place (Kamm et al., 2014). BBB disruption is transient, and it is restored after an acute phase (Balasa et al., 2021). Likewise, remyelination repairs damaged tissue to some extent, but replacement by gliosis occurs as well (Lassmann, 2014).

The importance of B -cells in both relapses and disease progression has become clearer in recent years. Besides antibody production, B -cells are included in regulating T cell production and APC functions; produce proinflammatory cytokines, chemokines, and soluble toxic factors; form lymphoid aggregates in the meninges; and function as a reservoir for EBV (Kumar & Axtell, 2023). In MS, the regulatory properties of B cells are thought to deteriorate, leading to a disturbed balance between different lymphocyte populations. B cells also induce neurodegeneration and demyelination (Arneth, 2020).

In MS -lesions, microglia, macrophages, and oligodendrocytes contribute to the demyelinating process. In the acute phase of MS, the microglia secrete proinflammatory cytokines, and their homeostatic phenotypes are lost. Afterward, their activation changes into a more anti-inflammatory state, enabling remyelination. During the progressive phase, the microglia are acting again in a proinflammatory manner (Guerrero & Sicotte, 2020). In NAWM, the amount of activated microglia correlates to disease duration (Zrzavy et al., 2017).

Diagnostic biomarkers

MRI has been an important part of the diagnostic criteria of MS for more than 20 years (McDonald et al., 2001; Polman et al., 2011; Thompson, Banwell, et al., 2018). Besides diagnosis, MRI is used nowadays to assess treatment efficacy and safety (mainly due to the risk of PML, progressive multifocal leukoencephalopathy). Traditional parameters important in MS diagnosis are the number and distribution of T2 lesions and contrast-enhancing T1 lesions. The correlation of these with clinical outcomes is limited (Wattjes et al., 2015). Hypointense T1 lesions (black holes) have a better correlation with disability and reflect persisting damage. Brain atrophy is also measured through MRI, and its acceleration is related to disease progression (De Stefano et al., 2014). A clinical and radiological aim for treatment can be termed NEDA; no evidence of disease activity. The occurrence of new lesions during the first year of treatment correlates with the progression of disability (Río et al., 2009; Sormani & Bruzzi, 2013).

Several biomarkers indicating pathogenic processes of MS in cerebrospinal fluid (CSF) have been detected and included in the diagnostic criteria for nearly four decades (Poser et al., 1983). Detection of intrathecal immunoglobulins in the form of oligoclonal bands (OCB) from CSF with immunoelectrophoresis is one of the key procedures in assessing the possibility of MS diagnosis. OCB are present in 95% of MS patients. OCB indicate chronic production of immunoglobulins in the CNS,

meaning they can be present in other inflammatory situations as well (Deisenhammer et al., 2019; Freedman et al., 2005). Another marker for the same phenomenon is the IgG index, a quantitative measurement of intrathecally produced immunoglobulins. It is less sensitive for MS than OCB, as 60% of patients have elevated results of the index. Other cytokines related to inflammation can be detected from the CSF of MS patients as well, such as CXCL13 and certain interleukins, but they are not in clinical use currently. Other nonspecific changes that can be seen in the CSF of MS patients are slightly elevated leukocyte counts (where lymphocytes dominate) and protein concentrations (Deisenhammer et al., 2019).

The latest finding in the field of biomarkers is neurofilament light chain (NfL), which can be detected from CSF and serum. NfL is a protein expressed in neurons, and they are released in any kind of injury (Varhaug et al., 2019). This means that as a biomarker, it is not sensitive to MS. Higher levels of NfL both in serum and CSF correlate to the number of active T2 lesions and gadolinium enhancement in MRI, relapses, atrophy, and worsened disability, suggesting that they could also be used as a biomarker of overall disease activity (Kuhle et al., 2019; Novakova et al., 2017). NfL levels are individual and vary due to many reasons, for example due to obesity (Benkert et al., 2022). Unambiguous reference values are therefore difficult to determine. Consequently, NfL is currently utilized mainly in research. One target in clinical practice in the future might be determining, whether a patient has an ongoing active worsening phase, if the NfL baseline of the patient is known.

2.3 Epidemiological features

2.3.1 Incidence

Incidence is the proportion of certain events in a specific population in a certain period. In the context of this thesis, the event is fulfilling the diagnostic criteria of MS. In the literature of MS epidemiology, the incidence is typically reported per 100 000 (10^5) people and calculated with the following formula (Centers for Disease Control and Prevention, accessed 14.3.2023):

$$\text{Incidence} = \frac{\text{number of new cases during a certain period of time}}{\text{number of population at the same period of time}} \times 100\,000$$

Incidence is suggested to be a suitable tool in assessing MS risk, as it does not depend on survival time, and possible ascertainment problems before the period in question will not affect it (Koch-Henriksen & Sørensen, 2010).

The MS International Federation estimated, that in 2020, a new MS diagnosis was made every 5 minutes, corresponding to a global incidence of $2.1/10^5$ (Walton et al., 2020). Globally, rising incidence especially among women and RRMS has been reported (Hawkes et al., 2020; Koch-Henriksen & Sørensen, 2010), with a stabilizing trend during recent decades in some studies (Flemmen et al., 2020). Table 2 summarizes recent incidences and temporal trends from countries with traditionally high MS risk (Canada, UK, Scandinavia) and from those with lower risks (Iran and Kuwait). In all these studies, the incidence of MS in women was greater than in men.

Table 2. MS incidence/10^5 in medium- and high-risk areas reported from 1996–2008 to 2013–2018.

Citation	Country	Time	Incidence /10^5	Trend
Kingwell et al., 2015	British Columbia, Canada	1996–2008	7.8*	Stable
Ribbons et al., 2016	Newcastle, Australia	2001–2011	6.7	Increasing
Kearns et al., 2019	Scotland, UK	2010–2017	8.6*	Not reported
Hosseinzadeh et al., 2021	Iran, nationwide	2006	2.2	Increasing
		2016	6.7	
Alroughani et al., 2019	Kuwait, nationwide	2013–2018	5.4	Stable
Koch-Henriksen et al., 2018	Denmark, nationwide	2000–2009	9.4*	Increasing
Ahlgren et al., 2014	Sweden, nationwide	2001–2008	10.2	Stable
Flemmen et al., 2020	Telemark, Norway	2013–2018	14.4*	Increasing
Elíasdóttir et al., 2011	Iceland, nationwide	2002–2007	7.6	Not reported

Figures with * are standardized, the rest of the figures are crude.

There are several suggested reasons attributed to the rising incidence. Established diagnostics via magnetic resonance imaging (MRI), enhanced diagnostic criteria, and an increased number of neurologists are evident. However, the increasing trend started before the generalizing of MRI and the era of new diagnostic criteria, which is why changes in environmental factors such as smoking and later and fewer pregnancies have been suggested to impact changing epidemiology (Koch-Henriksen et al., 2018). It has also been presented that changes in the social status of women in the 20th -century have had an impact on female incidence (Koch-Henriksen & Magyari, 2021).

Incidence studies in Finland

Several incidence studies have been conducted in Uusimaa and Western Finland. The very first study is from 1964 to 1978, where the incidence/10^5 was 3.3 in Western Finland and 2.2 in the south (Kinnunen, 1984). Since then, a rising trend has been shown in subsequent studies, up to the high incidence/10^5 of 14.7 in Seinäjoki and 11.7 in Vaasa in 2000–2010. Temporal changes of regional MS incidence/10^5 in Finland from studies between 1980–2016 are shown in Figure 2.

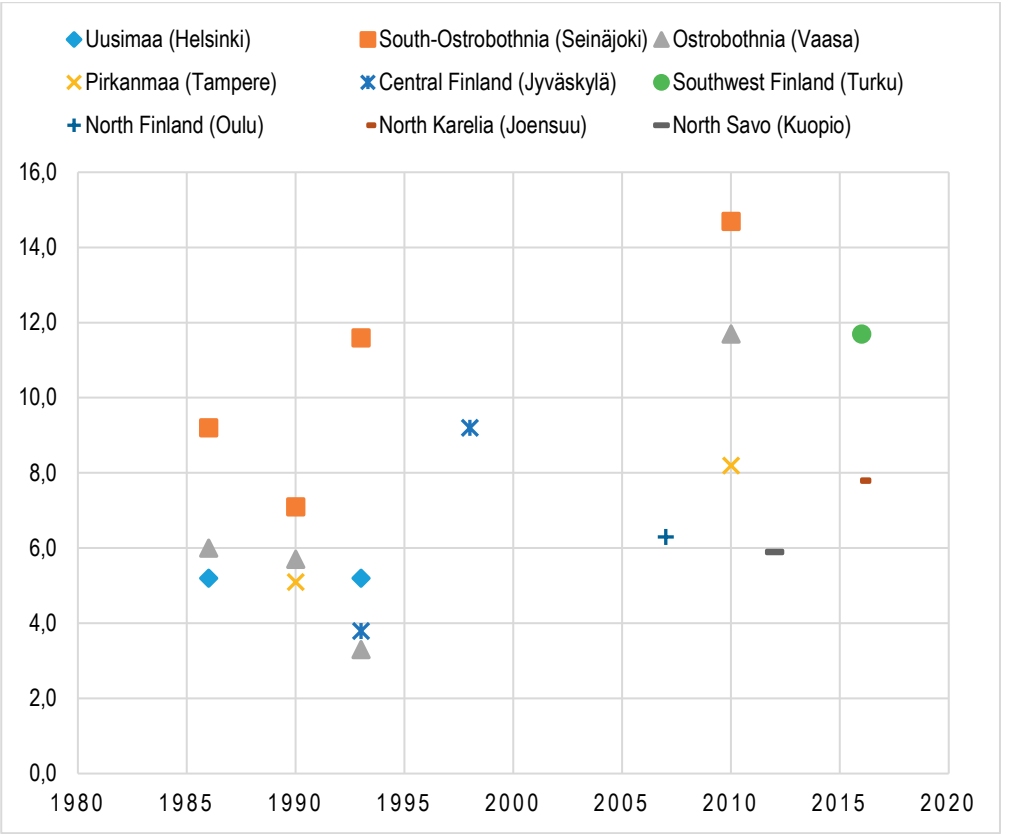

Figure 2. Temporal changes of regional crude MS incidence/10^5 in Finnish studies from 1980 to 2016. Region's largest city in brackets (Holmberg et al., 2013; Krökki et al., 2011; Metsäniitty & Remes, 2016; Pirttisalo et al., 2019; Sarasoja et al., 2004; Sumelahti et al., 2003).

During the first survey from 1964 to 1978, the incidence of MS in women had already started to rise compared to men (Kinnunen, 1984). In the survey from 1979 to 1993, the main denominator for the increasing trend was the incidence in women (Sumelahti et al., 2000). The same phenomenon was seen in Central Finland in 1979–1993 and persisted in 1981–2010 in Seinäjoki, Vaasa, and Pirkanmaa, while male incidence decreased in Vaasa and Seinäjoki. Significantly higher female incidence was also reported in Southwest Finland, whereas in the intermediate-risk area of North Karelia, there was no significant difference between genders (Pirttisalo et al., 2019).

Age-specific incidence

The peak age groups in different incidence cohorts vary. In Finnish surveys from 1979–1993 (Sumelahti et al., 2000) and 1981–2010 (study I) in Vaasa, Uusimaa, and Central Finland (Sarasoja et al., 2004) (intermediate risk areas), the peak was found in ages 30–39 years. In the high-risk area of Seinäjoki, the incidence peak took place in the age group of 40–49 years. Female incidence showed a clear peak in this age group, whereas male incidence showed a more stable, plateau-like curve (Sumelahti et al., 2000). Similar findings among females and males were reported in a national study from the UK during 1991–2000, where female peak incidence was at 40–44 years (Alonso et al., 2007). In 2001–2008 in Sweden, female incidence peaked at 30–35 years (Ahlgren et al., 2014). Such a clear peak was not visible for men.

2.3.2 Prevalence

Prevalence is the proportion of certain cases among a certain population. In the epidemiological literature on MS, prevalence is most often reported as the number of cases per 100 000 (10^5) people at a certain time point (point prevalence) and calculated with the following formula (NIMH Information Resource Center, accessed 14.3.2023) :

$$\text{Prevalence} = \frac{\text{number of cases at a certain time point}}{\text{number of population at the same time point}} \times 100\,000$$

The estimated global MS prevalence was $35.9/10^5$ in 2020, meaning that 2.8 million people worldwide were estimated to be affected by MS (MS International Federation, 2021). In Europe, the estimated prevalence was $133/10^5$ in 2020 (Collaborators, 2019; Walton et al., 2020). The global distribution of the prevalence of MS is uneven. Prevalence higher than $100/10^5$ has been reported in several European countries, North America, and Australia, nations with Caucasian ancestry. Scandinavia has represented an area of high prevalence since the early epidemiological studies of MS. In 2020, in addition to Finland, countries with a high prevalence of more than $200/10^5$, were Sweden, Denmark, Iceland, Germany, Italy, the USA, and Canada

(Walton et al., 2020). Data from Norway were missing from this survey, but a high prevalence up to 203/10^5 has been reported in Norwegian studies (Flemmen et al., 2020; Grytten et al., 2015). Data from Africa and other low-income countries were also scarce in the Atlas report.

Rising prevalence has been reported globally. From 2013 to 2020, the absolute increase has ranged from 32% in Europe to 87% in North America, with an annual increase of 4.7–6.3% (Kingwell et al., 2015; Wallin et al., 2019). A Norwegian review from 1961 to 2014 included 29 studies and found that prevalence/10^5 increased from 20 to 203 (Grytten et al., 2015). Increasing prevalence has also been reported from several countries previously considered to have low risk of MS, such as Saudi Arabia and Argentina. A meta-analysis of data from countries around the Persian Gulf yielded an overall prevalence of 39.3/10^5 (Etemadifar et al., 2020), although the pooled results were from quite a large timespan. MS prevalences from medium- and high-risk areas are listed in Table 3. Significantly smaller prevalence has been reported for native people in New Zealand, the USA, and Canada (Marrie et al., 2018; Taylor et al., 2010), pointing to genetic susceptibility in persons with Caucasian ancestry.

Table 3. MS prevalence/10^5 in medium- and high-risk areas reported from 2005 to 2019.

Citation	Location	Year	Prevalence /10^5	Trend
Kingwell et al., 2015	British Columbia, Canada	2008	195	Increasing
Rotstein et al., 2018	Ontario, Canada	2013	265*	Increasing
Wallin et al., 2019	USA, nationwide	2010	265	Increasing
Bezzini et al., 2020	Tuscany, Italy	2017	209	Increasing
Visser et al., 2012	Scotland, UK	2009	238	Increasing
Campbell et al., 2019	Australia, nationwide	2017	104	Increasing
Luetic & Menichini, 2020	Santa Fe Province, Argentina	2019	30	Not reported
Almasi-Hashiani et al., 2020	Tehran, Iran	2018	151	Increasing
Alroughani et al., 2019	Kuwait, nationwide	2018	105	Increasing
Flemmen et al., 2020	Telemark, Norway	2019	260	Increasing
Ahlgren et al., 2011	Sweden, nationwide	2008	189	Not reported
Svenningsson et al., 2015	Västerbotten, Sweden	2010	215	Increasing
Bentzen et al., 2010	Denmark, nationwide	2005	173	Increasing
Elíasdóttir et al., 2018	Iceland, nationwide	2007	167	Not reported

Crude prevalences, except for Rotstein et al., marked with *, which is standardized.

Prevalence studies in Finland

The prevalence of MS has been studied in Finland since the 1960s. The first reported crude prevalence/10^5 in Finland was 20 in 1964 by Rinne et. al. In the Uusimaa region, the prevalence was 18, in Vaasa 30, and Seinäjoki 39 (Rinne et al., 1968). Regional differences were already seen at that time. The writers estimated that the true rates were higher due to case ascertainment and lack of proper diagnostic criteria. In the following studies, still increasing trends and persisting regional differences were reported, with an area of high risk in Seinäjoki (Wikström & Palo, 1975). Through the decades, the highest prevalences have been in Seinäjoki and Southwest Finland; the lowest have been in eastern parts of the country. Figure 3 illustrates the temporal changes of MS prevalence in Finland. In 2020, it was estimated that 12 080 Finnish people were living with MS, corresponding to a national prevalence of 218/10^5 (MS International Federation, 2021).

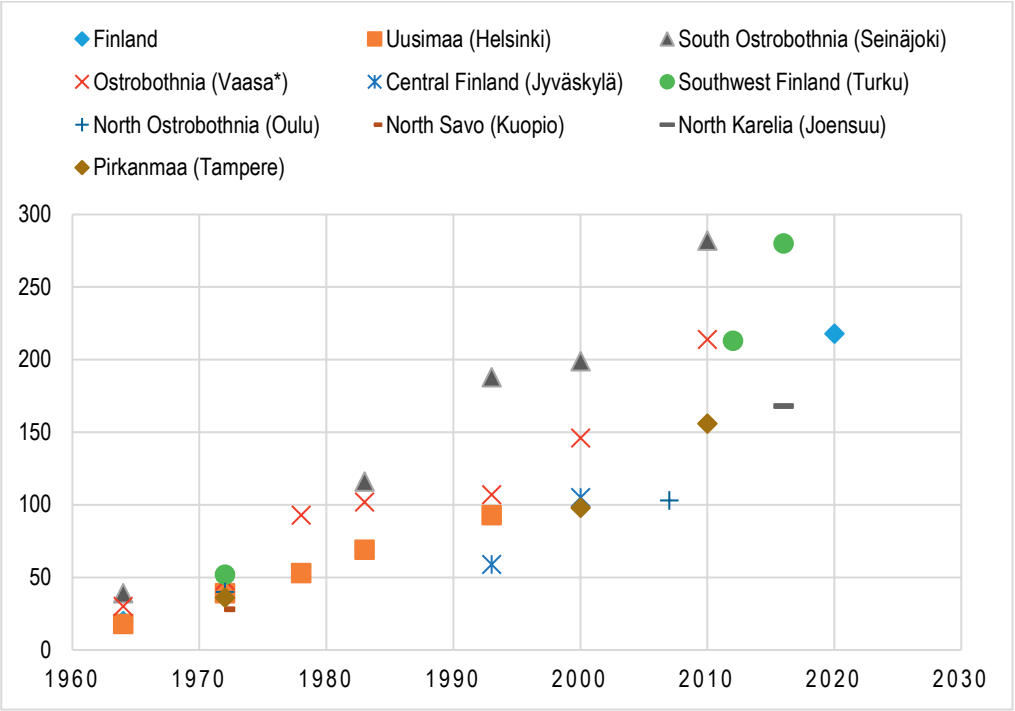

Figure 3. Temporal changes of regional crude MS prevalence/10^5 in Finnish studies from 1960 to 2020. Region's largest city in brackets. * In 1972 and 1978, the Vaasa region included the neighboring areas of Kokkola and Seinäjoki. Figures from Seinäjoki, Vaasa, and Pirkanmaa in 2000 and 2010 and from Southwest Finland and North Karelia in 2016 are ESP-standardized, other figures are crude. (Åivo et al., 2017; Kinnunen et al., 1983; Krökki et al., 2011; Pirttisalo et al., 2019; Rinne et al., 1968; Sarasoja et al., 2004; Sumelahti et al., 2001; Wikström & Palo, 1975)

Age-specific prevalence

Differences in the peak age groups have been reported globally. Concurrently with rising prevalence, a shift of peak prevalence age range has been seen in Canada from 45–49 to 55–59 years, and the same was reported in the USA (Kingwell et al., 2015; Wallin et al., 2019). In the latest Finnish study, the peak age group was 40–49 years (Pirttisalo et al., 2019). Interestingly, the peak age in developing countries seems younger than in countries already known for high risk (AlJumah et al., 2020; Almasi-Hashiani et al., 2020; Alroughani et al., 2019; Etemadifar et al., 2020).

2.3.3 Latitudinal gradient and high-risk areas

A division into three risk zones by prevalence was presented by John F. Kurtzke in the 1970s: high $\geq 30/10^5$, medium 5–$30/10^5$, and low $\leq 5/10^5$ (J. F. Kurtzke, 1975). Traditional areas of high risk are Scandinavia, Western Europe, and North America. (Collaborators, 2019) It has traditionally been suggested that the global MS risk increases by latitude, getting higher as the distance from the equator increases. However, these suggestions were based on studies from Western countries and have exceptions, like Sardinia. Meta-analyses utilizing standardized figures have shown that the suggested latitudinal component has nearly vanished in the northern hemisphere, especially in Europe, but remains in the southern hemisphere (Koch-Henriksen & Sørensen, 2010). Especially, the incidence gradient seemed nonexistent, whereas the gradient of prevalence was mild (Koch-Henriksen & Sorensen, 2011). On the other hand, another meta-analysis found a latitudinal effect in incidence, although after the 1980s the effect attenuated (Alonso & Hernán, 2008). A more recent meta-analysis showed a global latitudinal gradient of prevalence, with the exceptions of Scandinavia and Italy, where the gradient was inverse (Simpson et al., 2019).

Whether there has ever been a true latitudinal gradient in the northern hemisphere has also been questioned. If this were the case, the gradient seen in prevalence would then reflect immigration, survival differences, and incomplete case ascertainment in older cohorts (Koch-Henriksen & Sørensen, 2010; Koch-Henriksen & Sørensen, 2011).

2.3.4 Regional differences

Besides suggested latitudinal differences, national regional differences exist in many countries, such as Sardinia (Urru et al., 2019) and Scotland (Kearns et al., 2019), where temporally persistent high prevalence has been reported. In both regions, genetic causes are suggested to explain high susceptibility for MS (Rosati, 2001). Regional differences have been reported in Norway as well, with higher incidence in inland areas and lower in southern rural parts of the country (Grytten et al., 2015). Studies from Sweden have also demonstrated counties with higher risk than others, with an increasing gradient from south to north (Ahlgren et al., 2011).

Finland shows a marked east-west gradient, as Western Finland represents an area of high risk and Eastern Finland intermediate risk (Pirttisalo et al., 2020). The difference is not unique for MS, as there are many other features sharing the same

differences. The genetic differences between eastern and western inhabitants of Finland is exceptional and can be dated even back to the Iron Age (Salmela, 2023). Differences in the colonization of these areas exist as well, as it is estimated that population growth in Eastern Finland began 400 years later, with different origins than in Western Finland (Salmela, 2012). Diseases other than MS share the same division, although the risk of cardiovascular diseases is significantly higher in Eastern Finland (Vartiainen, 2018). The overall burden of illness is highest in Eastern and Northern Finland (Finnish Institute for Health and Welfare, 2023). Lifestyle habits, such as food consumption, are also quite different. Smoking was more generally in Eastern Finland especially among men, declining from 70% in the 1960's to 15% in 2016 (Vartiainen, 2018).

2.3.5 Female predominance

MS affects women twice as often as men. The global estimate in 2020 of a female-to-male ratio (F/M) was 2.2 (Walton et al., 2020). The ratio has been reported to increase over time and to correlate with birth year (Koch-Henriksen et al., 2018; Walton et al., 2020). In the earliest birth cohorts of the 1930s, the ratio ranged between 1.33–2.35 and increased markedly, peaking in the latest birth year cohorts of the 1970s and 1980s, where the range was 2.73–4.55 (Alonso & Hernán, 2008; Kampman et al., 2013; Koch-Henriksen et al., 2018; Orton et al., 2006; Rojas et al., 2017; Westerlind, Boström, et al., 2014). The increasing trend mainly concerned RRMS (Kampman et al., 2013; Trojano et al., 2012).

An international study covering a 60-year follow-up revealed the most remarkable increase in the northern hemisphere, from 1.93 to 4.55, being emphasized in the northern parts, while a stable trend was seen in the southern hemisphere (Trojano et al., 2012). More recently, F/M ratios ranging from 1.9 to 3.5 were reported, with the highest ratios from areas of higher occurrence (Bergamaschi et al., 2020; Bezzini et al., 2020; Campbell et al., 2019; Kingwell et al., 2013; Koch-Henriksen et al., 2018; Svenningsson et al., 2015; Wallin et al., 2019). An interesting decreasing trend was observed in a new area of rising risk in Iran, from 3.7 in 2010 to 2.14 in 2018 (Almasi-Hashiani et al., 2020).

A similar increasing trend has been seen in Finland as well, from 1.3 in 1972 (Wikström & Palo, 1975) to 2.2 in Central Finland (1979–1998) (Sarasoja et al., 2004) and 2.2 later in Western Finland (1981–2010) in study I, and up to 2.6 in Southwest Finland in 2016, while the ratio was 1.0 in Eastern Finland (Pirttisalo et al., 2019). In

2020 the Atlas of MS estimated that the general F/M ratio was 2.4 in Finland (MS International Federation, 2021).

2.3.6 Comorbidity

General aspects

Comorbidity is a condition, that appears in a patient with a certain disease and is not a complication of the disease. (Feinstein, 1970) MS patients have a higher risk for developing multiple comorbidities than the general population (Chou et al., 2020). Risk is especially elevated for cerebro- and cardiovascular diseases; other autoimmune diseases such as type I diabetes, thyroid disease, inflammatory bowel diseases; psychiatric disorders such as depression and anxiety; and migraine (Magyari & Sorensen, 2020; Marrie et al., 2023). Major differences between RRMS and PPMS have not been reported in the literature.

Comorbidities may affect the clinical picture of MS, starting and choosing a treatment and adherence to it (T. Zhang et al., 2016), disability progression, and prognosis (Kowalec et al., 2017; Marrie et al., 2023; McKay et al., 2018). Diabetes, ischemic heart disease, and psychiatric disorders increase the hazard of death in MS cohorts (Chou et al., 2020; Marrie, Cohen, et al., 2015). Also, comorbidities may affect working ability, amount of healthcare utilization, and quality of life (Thormann, Sørensen, Koch-Henriksen, Thygesen, et al., 2017). If present at the onset of MS, comorbid disorders may hamper diagnostics and increase the diagnostic delay (Thormann, Sørensen, Koch-Henriksen, Laursen, et al., 2017). Comorbidities overall are shown to associate with increased mortality (Thormann, Sørensen, Koch-Henriksen, Laursen, et al., 2017).

The most prevalent comorbidities among MS patients are depression in 20–24% of MS patients, anxiety in 11–22%, hypertension in 15–19%, hypercholesterolemia in 7–11%, chronic lung disease in 10–12%, ischemic heart disease in 7%, and diabetes in 6% (Marrie, Cohen, et al., 2015; Marrie, Patten, et al., 2016; Marrie, Reingold, et al., 2015). However, it must be noted, that besides being a possible comorbidity, depression and anxiety may relate to MS itself (Brasanac et al., 2022).

Autoimmune diseases, especially type I diabetes mellitus, have been found to have high co-occurrence with MS in Denmark, Sardinia, and Finland (Study III; Marrosu et al., 2004; Nielsen et al., 2006), and suggestions of common genetic pathogenic factors in non-HLA regions have been made (Booth et al., 2009; Pitzalis

et al., 2008; Tettey et al., 2015). Thyroid disorders have also been reported, but it has to be noted, that thyroid dysfunction may be an adverse effect of DMT. The risk of inflammatory bowel disease is increased by 50% in MS patients compared to the general population and vice versa; patients with inflammatory bowel disease have a higher risk of MS (Kosmidou et al., 2017).

The risks for cancer and asthma in the MS population is under debate, as results of higher and normal risks have been published (Magyari & Sorensen, 2020). The overall risk of cancer appears, however, to be lower than in the general population (Marrie et al., 2014), but differences between cancer types exist. The incidence of bladder cancer is increased among the MS population, whereas that of breast and colorectal cancers is not (Marrie, Maxwell, Mahar, Ekuma, McClintock, Seitz, Webber, et al., 2021). However, women with MS and breast cancer have lower all-cause survival than women without MS (Marrie, Maxwell, Mahar, Ekuma, McClintock, Seitz, & Groome, 2021).

Vascular comorbidity

Vascular comorbidity increases the risk of disability progression (Marrie et al., 2010) and as a sole risk factor increases mortality in MS (Palladino et al., 2020). Higher occurrence of hypertension, hyperlipidemia, and cerebro- and cardiovascular diseases in the MS population has been found in several studies and reviews from Denmark, Canada, and England (Magyari & Sorensen, 2020; Marrie, Reider, et al., 2015; Palladino et al., 2020; Thormann et al., 2016; Wens et al., 2013). The risk is reported to be higher among women (Christiansen et al., 2010; Jadidi et al., 2013; Palladino et al., 2020). Lipid-lowering medication significantly reduced the risk, although it was still higher compared to the control population (Palladino et al., 2020). Increased risk of deep vein thrombosis (DVT) has also been reported, being threefold higher in the PPMS group and twofold higher in RRMS and SPMS (Roshanisefat et al., 2014). Besides the risk of DVT, reported differences between RRMS and PPMS regarding comorbidity risks are scarce. A meta-analysis found a higher risk of any type of vascular brain attack (ischemic or hemorrhagic stroke and transient ischemic attack, TIA) among MS patients. Especially among patients younger than 40 years of age, the risk of ischemic stroke was high (Hong et al., 2019). Higher risk of comorbidities existed already at the time of diagnosis (Chou et al., 2020).

In Finland neurological comorbidities have been previously estimated in one study, where stroke was associated with decreased survival in MS. However, due to the small sample size no statistical significance was seen (Krökki et al., 2014).

Cardiovascular risk factors were shown to be more common among MS patients than healthy controls in the US. These patients also showed increased lesion burden and more advanced brain atrophy (Kappus et al., 2016). In addition, smoking is more common among the MS population, which increases CVD risk (Polick et al., 2023). However, elevated cardiovascular risks may not be explained purely by traditional vascular risk factors (Marrie et al., 2019). Accumulation of immobility as MS progresses may also increase the risk. Another potential factor is possible adverse effects of DMTs; for example, teriflunomide may elevate blood pressure. Other autoimmune diseases have also been connected to an increased risk of cardiovascular diseases (Roifman et al., 2011); in fact, autoimmunity seems to have an essential role in atherogenesis (Matsuura et al., 2014). Inflammatory disease activity might induce endothelial dysfunction leading to an increased risk of vascular problems (D'haeseleer et al., 2011).

However, the data considering single CVD risk factors, like obesity, hypertension, type II diabetes, and hyperlipidemia, have been inconsistent (Marrie, Reider, et al., 2015; Wens et al., 2013), and suffering from methodological problems (Marrie, Cohen, et al., 2015), making it difficult to make comparisons.

2.3.7 Mortality, survival, and causes of death

Mortality

The mortality of MS patients is usually reported as a standardized mortality ratio, SMR, which is a relation of the observed number of deaths to the expected in a certain population (Nicholls, 2020). To determine the expected number, a control population matched by age and sex is usually used. In some reports, the excess death rate (EDR) is also given to describe the number of lost lives per 1000 person-years of observation (Koch-Henriksen et al., 2017).

Mortality of MS is nearly threefold compared to the general population (SMR 2.5–2.9) (Brønnum-Hansen et al., 2004; Burkill et al., 2017; Hirst et al., 2008; Koch-Henriksen et al., 2017; Lunde et al., 2017; Manouchehrinia et al., 2016; Smestad et al., 2009; Sumelahti et al., 2010). Excess mortality begins to appear in the second decade after diagnosis (Leray et al., 2015; Smestad et al., 2009; Sumelahti et al., 2010)

and is greater among women and those who were younger at disease onset (Hirst et al., 2008; Kingwell et al., 2012; Manouchehrinia et al., 2016; Sumelahti et al., 2010). Mortality related to PPMS, SMR 3.9 is higher than to RRMS, SMR 2.4 (Kingwell et al., 2012; Lunde et al., 2017). Reports of declining mortality have been published from Scandinavia (Brønnum-Hansen et al., 2004; Burkill et al., 2017; Koch-Henriksen et al., 2017; Lunde et al., 2017), but contradicting results with temporally stable mortality have been reported as well (Kingwell et al., 2012; Manouchehrinia et al., 2016).

In the literature, several factors have been suggested to explain possibly declining mortality. Established diagnostics have had an important role, as more benign cases have been diagnosed when diagnostic criteria with MRI techniques have evolved. It has also been suggested that the progress of rehabilitation methods, as well as treatments for MS and comorbid diseases, may have had an impact on mortality too.

Survival

In the study field of MS epidemiology, survival describes the time to death from different time points, usually from birth or the diagnosis. The lifespan of MS patients has been considered shorter than the general populations. In reports from Denmark, Norway, UK, USA, and Canada, median survival times from birth were 6–12 years less than expected when compared to the matched population (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Hirst et al., 2008; Kingwell et al., 2012; Koch-Henriksen et al., 2017; Lunde et al., 2017). Patients with RRMS had a few years' better overall survival than patients with PPMS in one dataset from Norway (Lunde et al., 2017), whereas in another Norwegian study, survival from MS diagnosis was better in RRMS, but no difference in age at death was seen (Smestad et al., 2009). Similar findings were reported in a Canadian study as well (Kingwell et al., 2012).

A survival advantage has been linked to female gender (Kingwell et al., 2012; Lunde et al., 2017) when assessed from disease onset but was disadvantageous when assessed from birth; a median survival time was 11 years shorter than in the general population. For men, the same gap was 7 years (Koch-Henriksen et al., 2017; Smestad et al., 2009). Also, worse survival was reported among patients who were younger at onset, dying of MS-related causes (Hirst et al., 2008), and had increased disability (Cutter et al., 2015).

Improvement of survival has been seen in longitudinal studies (Koch-Henriksen et al., 2017; Lunde et al., 2017), but opposing results have been reported as well (Kingwell et al., 2012; Manouchehrinia et al., 2016). While life expectancy has

increased in general, the survival of MS patients has been suggested to improve on its own as well (Burkill et al., 2017; Koch-Henriksen et al., 2017). Until now, modest but promising results about the effects of DMT on survival have been found (Kingwell et al., 2019). In the majority of studies cited here, the data included only a few patients who had been using DMT. Hence, at the moment, the effects of DMT use cannot be assessed reliably (Koch-Henriksen et al., 2017).

Causes of death

The data for studies of causes of death (COD) among MS patients are usually driven from death certificates. There is heterogeneity in the categorization and recording of CODs. The most commonly used are all causes, immediate cause of death (ICOD), underlying cause of death (UCOD), and any mention in the death certificate. Variation also occurs in how different diseases or disorders are categorized and reported as CODs. Cause-specific SMRs, odds ratios (OR), or hazard ratios (HR) are reported quite often, and sometimes the distribution of causes is given. Comparison between studies is also hampered by differences in case ascertainment, as there are no uniform practices among clinicians for recording CODs, even though recommendations have been made by the World Health Organization (WHO).

The main causes of death and their risks are listed in Table 4. A leading cause of death among MS patients, besides MS itself, is infections. Cardiovascular causes seem more common among MS deaths compared to the general population, increasing in older age groups.(Harding et al., 2020; Kingwell et al., 2020; Lalmohamed et al., 2012; Lunde et al., 2017; Manouchehrinia et al., 2016). However, the results of similarity between MS and the general population have been reported as well (Hirst et al., 2008; Smestad et al., 2009). Both higher (Lalmohamed et al., 2012; Lunde et al., 2017) and similar (Brønnum-Hansen et al., 2004; Hirst et al., 2008; Kingwell et al., 2020; Manouchehrinia et al., 2016; Smestad et al., 2009) SMRs and risks concerning cancer as a COD have been reported. The reported risks of suicides also varied from elevated (Brønnum-Hansen et al., 2004; Kingwell et al., 2020; Lunde et al., 2017; Manouchehrinia et al., 2016; Smestad et al., 2009; Sumelahti et al., 2010) to similar (Hirst et al., 2008; Lalmohamed et al., 2012) to the general population. Differences between RRMS and PPMS are scarcely reported.

Table 4. Main causes of death in MS populations, grouped by used statistical measures HR, OR, and SMR.

		Infections	UTI	Respiratory	Cardiovascular	Suicide	Accidents	PU
HR	Burkill et al., 2017	4.07		5.07	2.06	1.85	2.24	
	Lalmohamed et al., 2012	7.69[a]		6.35	2.42		1.14	
OR	Harding et al., 2020	1.34	10.2	3.03[b]				5.06
SMR	Hirst et al., 2008	29.6		11.7	1.06			
	Kingwell et al., 2020	1.83	2.71	2.69	1.57	2.40	2.71	
	Manouchehrinia et al., 2016	2.91[a]			1.29	2.13		
	Lunde et al., 2017	4.5[a]			3.3[c]		9.6[d]	

UTI=urinary tract infections
PU=pressure ulcers and other skin conditions
[a] includes respiratory infections
[b] OR for aspiration pneumonia 7.15
[c] includes cerebrovascular causes
[d] includes suicides

MS was mentioned in 70–82% of death certificates (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Hirst et al., 2008; Kingwell et al., 2020; Smestad et al., 2009). As the immediate cause of death, MS was recorded in 50–56% of cases (Lunde et al., 2017; Smestad et al., 2009), except for only 9% recorded in Wales (Hirst et al., 2008). Other immediate causes were cardio- and cerebrovascular diseases in 14–15%, cancer in 10–14.1%, respiratory and infectious diseases in 4–9%, and accidents and suicides in 4–5% of cases (Lunde et al., 2017; Smestad et al., 2009).

Recording of MS as an UCOD varied from 41–64% (Brønnum-Hansen et al., 2004; Burkill et al., 2017; Cutter et al., 2015; Harding et al., 2020; Kingwell et al., 2020; Smestad et al., 2009), and it was more common in younger age groups (Cutter et al., 2015; Harding et al., 2020; Smestad et al., 2009). Other UCODs after MS were cardiovascular disease in 15–17%, cancer in 10–11.4%, pneumonia in 4.2%, septicemia in 2.3%, and suicides and accidents in 1.6–4.5% (Brønnum-Hansen et al., 2004; Cutter et al., 2015). Cancer and cardiovascular causes became more frequent and suicides rarer with increasing age at death (Cutter et al., 2015). A different distribution of UCODs have been reported from Wales: respiratory disease, including infections 48%, cardiovascular disease 16%, other infections 9.5%, cancer 9.5%, and no suicides (Hirst et al., 2008).

Among Finnish patients diagnosed from 1964 to 1993, SMR for all causes of death was 2.8, 3.4 among women, and 2.2 among men (Sumelahti et al., 2010), similar to those in other contemporary studies (Brønnum-Hansen et al., 2004; Burkill et al., 2017; Hirst et al., 2008; Koch-Henriksen et al., 2017; Lunde et al., 2017; Manouchehrinia et al., 2016; Smestad et al., 2009). From 1964 to 1993 a 25-year survival from the clinical onset was 78% and a 40-year survival 53%, being higher than in the Danish cohort (Brønnum-Hansen et al., 2004; Sumelahti et al., 2010). When assessed from the onset, the survival advantage was associated with RRMS, younger age at onset, and optic neuritis or sensory symptoms at disease onset (Sumelahti et al., 2002). On the other hand, MS diagnosis after the age of 35 was related to a better overall prognosis.

In a cohort study from 1971 to 2006 (Sumelahti et al., 2010), SMR for respiratory diseases was 3.3, quite similar than reported from Canada (Kingwell et al., 2020), and 1.7 for suicide, which was a bit less than in other studies (Kingwell et al., 2020; Manouchehrinia et al., 2016). In a cohort from 1964 to 1993, the proportion of cardiovascular causes of death was lower than expected (26%), and violent deaths (19%) and neoplasms (35%) were higher compared to the general population. The percentage of suicides was only slightly higher than in the population overall (5% and 3%). Among deaths, 70% of deaths were due to MS or MS related (Sumelahti et al., 2002). Compared to other studies assessing causes of death (Brønnum-Hansen et al., 2004; Burkill et al., 2017; Cutter et al., 2015; Kingwell et al., 2020; Lunde et al., 2017; Smestad et al., 2009), the proportion of cardiovascular causes, violent deaths and neoplasms were higher in this Finnish cohort.

3 AIMS OF THE STUDY

In general, the main aim of this thesis was to describe the epidemiological characteristics of MS in Western Finland from 1981 to 2010.

Detailed aims were as follows:

1. Evaluate regional and gender-specific incidence trends.
2. Study the prevalence and its changes by age, gender, disease course, and disability.
3. Assess common comorbidities related to survival.
4. Investigate factors related to the end of life, including disability, places, and causes of death.

4 MATERIALS AND METHODS

4.1 Geography and population

Finland lies in Scandinavia at 60°–70° latitude. A map of Finland (Figure 4) shows the locations of the study areas. In 2010, Finland's population was 5 375 276: 485 911 in Pirkanmaa, 198 469 in South Ostrobothnia, and 166 250 in Ostrobothnia. The biggest city in South Ostrobothnia is Seinäjoki, where the central hospital is also located; Vaasa is the biggest city in Ostrobothnia and Tampere in Pirkanmaa. From here on, following prior epidemiological MS publications from these areas, Seinäjoki refers to the whole of South Ostrobothnia and Vaasa to Ostrobothnia. In study III, the data were collected from Turku University Hospital in Southwest Finland, where the population in 2012 was 472 139.

The median age in Finland was 37.5 years in 1990 and 41.4 years in 2010, with no major differences between the study areas. The population structure has gotten older for the past 20 years (Statistics Finland, 2023), and at the same time, urbanization has increased. Tampere and Turku are more urbanized, being bigger cities than Seinäjoki and Vaasa. In the Vaasa region, there are more Swedish-speaking inhabitants than in the other two counties. Genetically and socioeconomically, there are no major differences between these western areas.

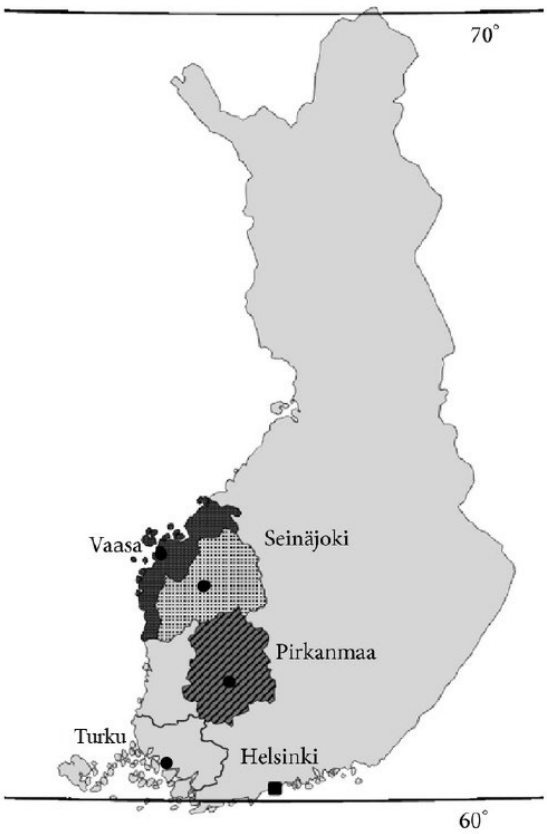

Figure 4. Map of Finland with the study areas illustrated. Data in studies I and II were derived from areas of Vaasa, Seinäjoki and Pirkanmaa, in study III from Turku, and in study IV from Pirkanmaa. *Modified from the original publication, reproduced and modified under the terms of the Creative Commons Attribution 3.0 Unported License* (Creative Commons, Holmberg et al., 2013).

4.2 Ethics

The Ethics Committee of the National Institute for Health and Welfare approved studies I, II, and IV, the regional Ethics Committee of Tampere University Hospital area studies I–IV and Turku Clinical Research Center study III. Guidelines for the Responsible Conduct of Research were followed. The personal data of patients were handled according to General Data Protection Regulation by the European Union.

4.3 Data collection

For studies I, II, and IV, a retrospective search from hospital administrative registries were made for diagnoses of multiple sclerosis, morbus demyelinans, and optic- and retrobulbar neuritis from 1950 up to 31.12.2010. The classification by the WHO (World Health Organization), International Statistical Classification of Diseases and Related Health Problems, ICD, versions 8–10 were used within the study period. The catchment area covered three central hospital districts in Western Finland: Tampere in Pirkanmaa, Seinäjoki in South Ostrobothnia, and Vaasa in Ostrobothnia, all of which are part of the Tampere University Hospital district. Patient records revealed by the search were scrutinized, and information was obtained regarding the following: the time point of initial symptoms and diagnosis, initial symptoms, diagnostic procedures (e.g., CSF examination, MRI, evoked potentials) and their results, disability status and its progression, disease-modifying treatment usage, marital status, and number of children. From records of deceased patients in Pirkanmaa, information on the latest disability prior to the situation that led to death was also recorded. Cases were reassessed to fulfill the criteria of definite MS (clinical and laboratory-supported) by Poser (Poser et al., 1983). Similarly, reassessment was conducted for the disease course according to the criteria of Lublin and Reingold (Lublin et al., 1996). The category of RRMS by course at onset included cases that later progressed to SPMS.

Cases diagnosed between January 1st, 1981, and December 31st, 2010, were included in study I. Inclusion criteria for study II were residency in the study area and a definite MS diagnosis per Poser criteria at prevalence dates 31.12.2000 and 31.12.2010. In study III, resident and confirmed MS cases between January 1st, 2004 and December 31st, 2012, were included. Study IV included incident cases fulfilling the diagnostic criteria for definite MS from January 1st, 1981, to December 31st, 2010, with a death certificate at the hospital district of Pirkanmaa.

In studies II and IV, disability assessment was based on descriptions in the patient records at yearly follow-up visits according to EDSS. In some cases, the EDSS value was already given in the patient records, and in others, the value was determined based on the description of symptoms and findings in the neurological examination. Values were categorized into three classes: The first included cases with mild disability, EDSS less than 3.0, in which case there was no mention of handicap or any symptom needing treatment or rehabilitation, or several symptoms and signs in clinical assessment. The second class of moderate disability, EDSS 3.0 to 5.5, included cases with reported handicaps in several functions of CNS. The third class,

EDSS 6.0 or more, was severe disability with a significant handicap, shortened walking distance, and regular use of a walking aid.

The death certificates in study IV were obtained from the archives of Statistics Finland, which keeps records of causes of death. Personal identity code, which all residents of Finland have had since 1967, was used as a key to find out correct certificates. Certificates were scrutinized to collect detailed information concerning the death, care given prior to death, and possible DNR (do not resuscitate) statements.

The data in study III were derived from the administrative Clinical Data Repository of the University Hospital of Turku, which contains electronic health records from the Hospital District of Southwest Finland. Resident cases with MS diagnosis from January 1st, 2004, to December 31st, 2012, were included. The ICD-10 classification was used. Cases were scrutinized for definite MS base on McDonald criteria (McDonald et al., 2001). Patient records of confirmed cases of cardiac or cerebral infarction or other vascular diseases of the brain were further scrutinized. The ICD codes for causes of death were collected from records of patients who died during the study period. Comorbid diagnoses mentioned in the patient records before and after MS diagnosis were recorded. Information on CVDs, cardiac arrhythmias, cancers, infections, diabetes mellitus types I and II, hyperlipidemia, obesity, and migraine were gathered. A randomly chosen tenfold gender- and age-matched control population were drawn from the same population, as well as a similar tenfold control population that was used to verify the stability of the results.

4.4 Statistical analysis

The statistical analysis in studies I, II, and IV were conducted with SPSS. Analyses in study III were made with R Statistics with standard packages. In all studies, P-values less than 0.05 were considered statistically significant.

In study I, incidence per 10^5 was calculated from January 1980 to December 2010 in 10-year periods, based on age and gender with 95% confidence intervals (CI) by districts. To assess differences in regional risks, indirect standardization was used due to the small number of cases in age-specific data. Pirkanmaa was used as the standard population, the basis for which expected numbers of new cases per each 10-year period were calculated for Seinäjoki and Vaasa. Expected numbers were then compared with observed numbers, resulting in a standardized incidence rate, SIR, a ratio of observed and expected cases. SIRs were calculated in a total and gender-specific manner with 95% CIs. Distributions of age at onset and diagnosis, onset symptoms, diagnostic delay, and F/M ratio were observed in the whole study population and in three study districts. The significance of differences between districts was investigated with the Chi-square test.

In study II, the prevalence was calculated using a direct standardization method with the European standard population in 2013 (ESP 2013) in age-standardized and sex-specific rates per 10^5 with 95% confidence intervals (CI). The ESP 2013 is based on the Eurostat report. To calculate the crude total and sex- and disease course-specific prevalence, population statistics from Statistics Finland were used. Disability was assessed using the EDSS score. The significance of differences in EDSS distribution between disease courses and sexes was investigated with a Chi-square test. Mean ages, F/M ratios, disease durations, and diagnostic delays in prevalence years 2000 and 2010 were determined. To assess the significance of comparisons of variables with normal distribution such as age, independent samples T-tests were used. Distributions of disease durations and diagnostic delays were skewed, so in order to determine the significance of their differences between prevalence cohorts, one-way ANOVA was utilized. Differences between the two initial disease course groups were assessed as well, and significance was investigated with independent samples T-test or one-way ANOVA, depending on the distributions of variables.

In study III, mean survival times were assessed with Kaplan-Meier (KM) analysis. To investigate the effect of cardio- and cerebrovascular comorbidity, a separate KM analysis was conducted. Log-rank test was used to assess the significance. Odds ratios (OR) for different comorbidities were calculated with 95% Cis, and significance was estimated with Pearson's $\chi 2$ test.

In study IV, a retrospective observational study, causes of death were investigated in three age groups <50 years, 50–59 years, and 60 years and older, by following groups according to diagnosis: MS, infections, cardiovascular, cerebrovascular, pulmonary embolism, cancer, gastrointestinal, other neurological causes, suicides, and traumas. Infections were further investigated in groups of respiratory, gastrointestinal and urinary infections, sepsis, and infection of unknown focus. The significance of differences in diagnoses in age groups was investigated with the Chi-square test.

Disability before death was assessed in similar EDSS groups than in study II. The significance of differences in disability between age groups and initial disease course was investigated with the Chi-square test. Distributions with a mean age of death in total, sex-specific, and different disease courses were observed. The significance of differences was investigated with an independent samples T-test.

5 RESULTS

5.1 Study I – Regional and gender-specific incidence trends in 1981–2010

From January 1981 to December 2010, a total of 1617 patients diagnosed with MS were identified in the catchment area. The median age at onset was 32 years and at diagnosis 37 years in the whole cohort. From 1981–1990 to 2000–2010, the median diagnostic delay decreased significantly from 4.0 years to 2.0 years.

Within the study period, the age-adjusted incidence/10^5 was 6.7 (95% CI 6.2–7.2) in Pirkanmaa, 12.5 (95% CI 11.5–13.5) in Seinäjoki, and 8.3 (95% CI 7.4–9.2) in Vaasa. Standardized incidence ratios (SIR) are shown in Table 5.

Table 5. The standardized incidence ratios (SIR) of MS in Seinäjoki, Vaasa, and Pirkanmaa (comparator) in 2010.

	All		Men		Women	
	SIR	95% CI	SIR	95% CI	SIR	95% CI
Pirkanmaa	1.0		1.0		1.0	
Seinäjoki	1.9	1.7–2.1	2.0	1.7–2.3	1.8	1.7–2.0
Vaasa	1.2	1.1–1.4	1.4	1.2–1.7	1.5	1.3–1.7

The SIRs show that the risk of MS is nearly twofold in Seinäjoki compared to Pirkanmaa and significantly higher than in Vaasa as well. *Previously unpublished table containing data from study I.*

Incidence in 10-year periods in the study areas are illustrated in Figure 5. A slight but steady increase was seen in Pirkanmaa, and a twofold increase in Seinäjoki and Vaasa. Among women, the incidence was higher in all districts and age groups and had an increasing trend. F/M ratio increased in Seinäjoki and Vaasa, reflecting the increased incidence among women, but it decreased in Tampere. Regional F/M ratios in 10-year periods are presented in Figure 6.

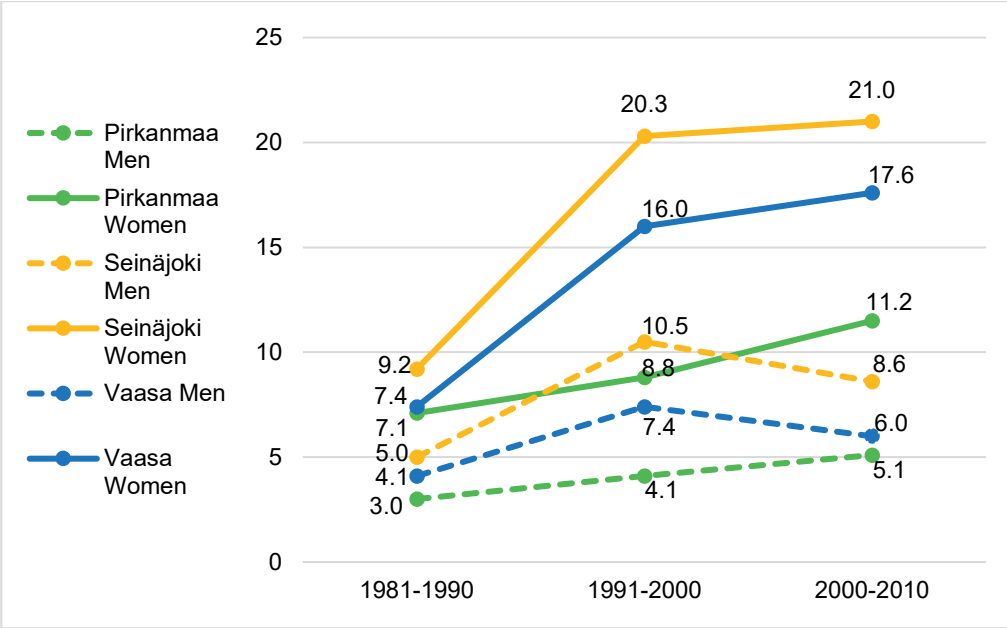

Figure 5. Temporal changes of regional incidence/10^5 in 10-year intervals from 1981 to 2010 in Pirkanmaa, Seinäjoki, and Vaasa. *Previously unpublished figure containing data from study I.*

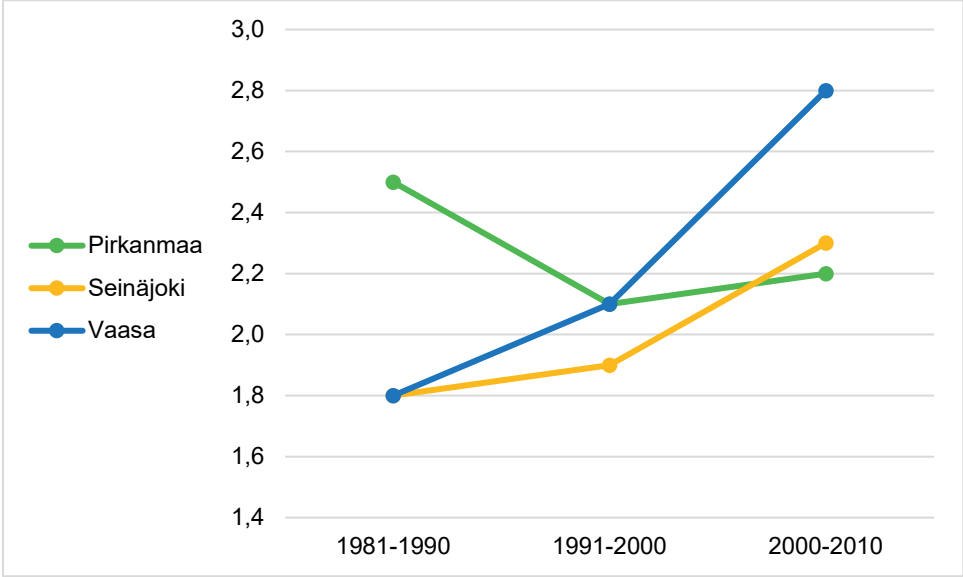

Figure 6. Temporal changes of regional F/M ratios in 10-year intervals from 1981 to 2010. *Previously unpublished figure containing data from study I.*

The F/M ratio in the whole cohort was 2.2, with a slightly increasing trend from 2.1 and 2.0 in the first two decades to 2.4 in the last decade. In 10–year age groups, the highest F/M ratios were found in 10–19-year-olds in Vaasa and Pirkanmaa (there were no men in this age group in Seinäjoki) and 30–49-year-olds in Seinäjoki.

During 1981–2010 in Seinäjoki, the age-specific incidence peaked among 30–49-year-olds and in Vaasa among 30–39-year-olds. The trend was seen in total and among women, whereas there was no such clear peak among men, with quite stable incidence between 20–59 years in both areas. In Pirkanmaa, there was no such clear peak age group as the highest incidences overall were in age groups 20–49 years.

Differences between disease courses in Seinäjoki, Vaasa, and Pirkanmaa were assessed in another study conducted with the same data and by the same working group (Sumelahti et al., 2014). The rising overall MS incidence reflected the rising incidence/10^5 of RRMS, from 4.2 in 1982–1990 to 9.7 in 2000–2010, while the incidence of PPMS declined from 1.2 to 0.7. The same is reflected in differences in F/M ratios: in the RRMS group, the ratio increased from 1.9 to 2.3, whereas in PPMS, it decreased from 1.6 to 1.2. Mean age at diagnosis in RRMS was 36 years and in PPMS 45 years.

5.2 Study II – Prevalence and disability

In December 2000, 1080 MS cases were living in the study area with an F/M ratio of 2.0. In 2010, the corresponding number was 1666 with an F/M ratio of 2.2. The mean age was 50 years in both time points. PPMS patients were significantly older than RRMS patients, and their mean age increased form 57 years in 2000 to 62 years in 2010, while the mean age of RRMS patients remained at 48 years.

A significant increase in prevalence was seen especially among women and RRMS, while prevalence of PPMS decreased. Table 6. shows the ESP2013 standardized and crude prevalences with CIs in 2000 and 2010.

Table 6. ESP-standardized and crude MS prevalences/10^5 and 95% confidence intervals (CI) in 2000 and 2010 in the study district in Western Finland.

	2000		2010		
	Prevalence	CI	Prevalence	CI	Change, %
ESP2013 standardized					
Total	133	126.7–139.7	192	184.3–200.2	+ 45
Women	176	170.6–185.6	277	270.4–283.6	+ 58
Men	91	87.4–94.8	119	114.6–123.5	+ 31
RRMS	111	105.4–117.1	179	171.0–186.0	+ 60
PPMS	21	18.8–24.0	18.0	15.4–20.6	- 16
Crude					
Total	129	121.4–136.8	195.5	186.5–202.05	+ 51
Women	156	131.5–180.7	260	244.6–274.6	+ 66
Men	79	61.0–97.4	119	108.9–129.5	+ 51
RRMS	107	99.7–113.7	170	161.5–178.8	+ 59
PPMS	21	17.7–23.9	20	17.1–23.1	- 3.4

Previously unpublished table containing data from study II.

In 2010, the age-standardized (ESP2013) prevalence/10^5 was 149.3 (95% CI 120.9–177.8) in Pirkanmaa, 275.6 (95% CI 267.6–283.5) in Seinäjoki, and 226.1 (95% CI 202.1–250.2) in Vaasa. The regional crude prevalences by sex in both time points of the study are shown in Figure 7.

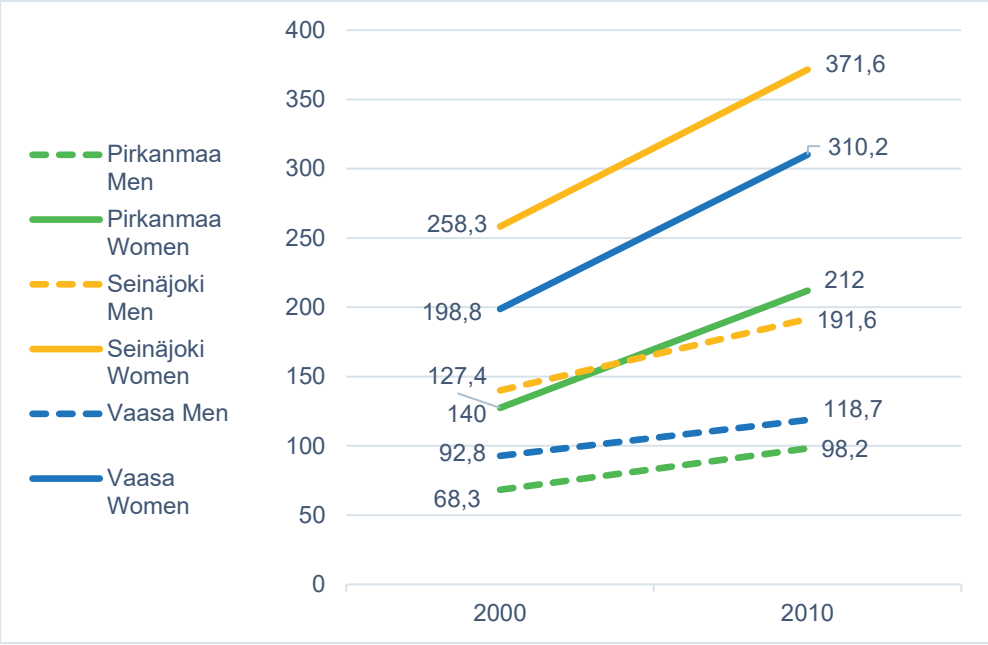

Figure 7. The trends of crude prevalence/10^5 by gender in 2000 and 2010 in Seinäjoki, Vaasa, and Pirkanmaa. *Previously unpublished figure containing data from study II.*

Regional crude prevalences by municipalities in 2010 were calculated in Seinäjoki and Vaasa (South Ostrobothnia and Ostrobothnia), representing the historical high-risk area of MS in Western Finland. Distribution of prevalence/10^5 in three groups (<200, 200–300, >300) are illustrated in a map (Figure 8). Areas with highest rates are located in Seinäjoki district (South Ostrobothnia).

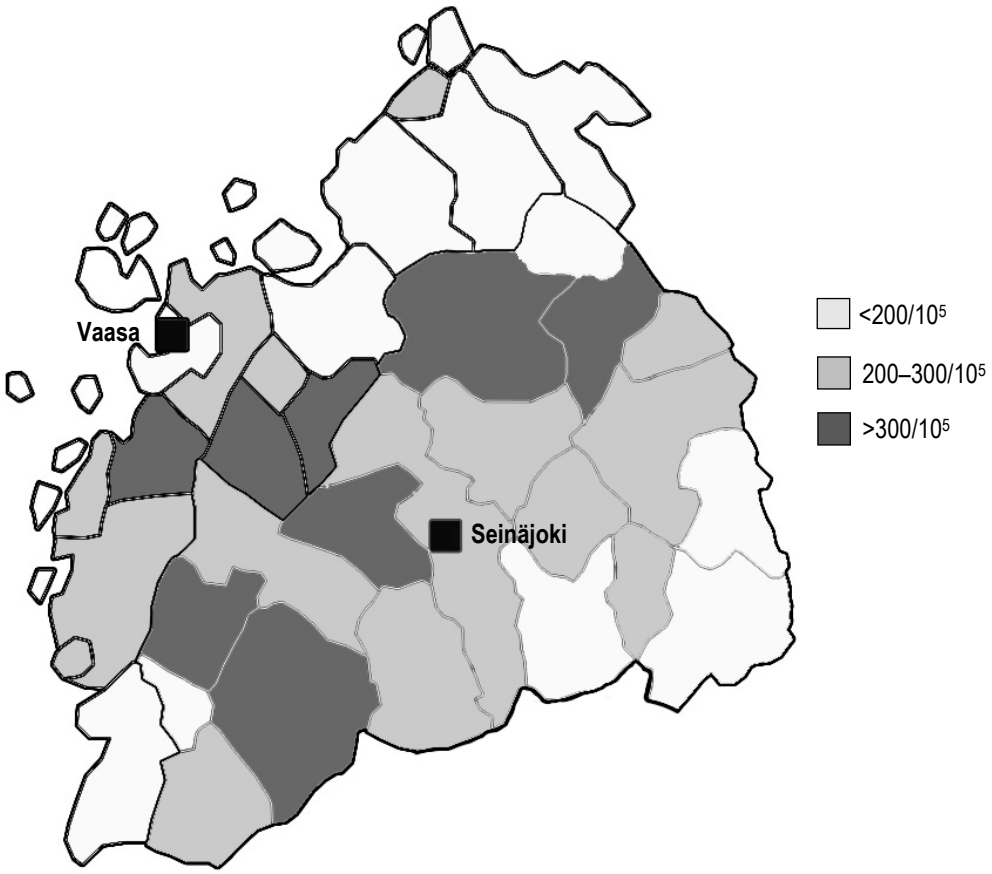

Figure 8. MS prevalence/10^5 by local municipalities in Vaasa (14) and Seinäjoki (20) in 2010. *Previously unpublished figure containing data from study II.*

Total age-standardized prevalence in the 10-year age groups peaked at 50–59 years in 2000 and at 40–49 years ten years later. Among women, the peak was in the 40–49 group at both time points. Among men, the peaks were at 50–59 years in 2000 and 40–49 years in 2010.

Mild disability, EDSS 0–2.5, was seen in 46% of cases in 2010. Moderate disability, EDSS 3.0–5.5, was reported in 16%; severe disability, EDSS 6.0 or more, occurred in 23% of cases. Mild disability was seen more in the RRMS group, where 52% of cases were classified in the mild category. On the contrary, 44% of PPMS cases were categorized into the severe group. Figure 9 illustrates the distribution of disability in disease groups in 2010.

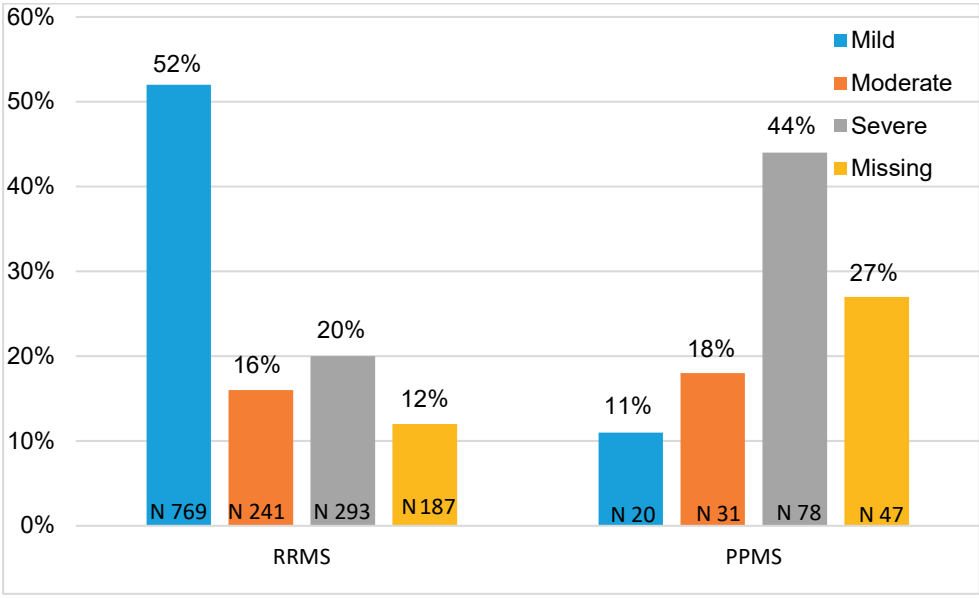

Figure 9. MS disability status distribution and number of cases in RRMS (1490) and PPMS (176) groups in 2010 in Western Finland prevalence cohort. Mild = EDSS 0–2.5, moderate = EDSS 3.0–5.5, severe = EDSS 6.0 or more. *Previously unpublished figure containing data from study II.*

In 14% of cases, the disability information in hospital records was missing. These cases represented older age groups and longer disease duration. Mean age was 60.7 years in the RRMS group and 66.6 years in the PPMS, and the mean disease duration was 20.7 years in the RRMS group and 21.8 in the PPMS.

In 2010, 56% of RRMS patients (835/1490) were using DMT. Among these patients, disability was mild in 50%, and a majority of these were in the youngest age group, <31 years. EDSS value was given in patient records of 94.6% of cases.

5.3 Study III – Comorbidities related to survival

From 2004 to 2012, a total of 1074 MS cases were identified in the Hospital District of Southwest Finland, of whom 315 were men and 759 were women. During the study period, 70 (6%) died; the main cause of death was infections in 38 cases (54%). In one case, the cause of death was acute myocardial infarction, ischemic stroke in four cases, and subarachnoid hemorrhage in one. Other causes were respiratory

insufficiency (six cases), cancer (three cases), and intoxication (two cases). Other individual causes were recorded in 16 cases. The mean lifetime survival was 82.4 years in MS, whereas it was 85.6 years in the control population. The difference was statistically significant. Cardiovascular diseases, CVD (ICD diagnoses I06-I71), significantly affected the survival of MS patients. The mean lifetime survival of these patients was 79.5 years, while the corresponding time of those MS patients without CVDs was 85.4 years. Figure 10 illustrates the survival of MS patients with and without CVD and controls.

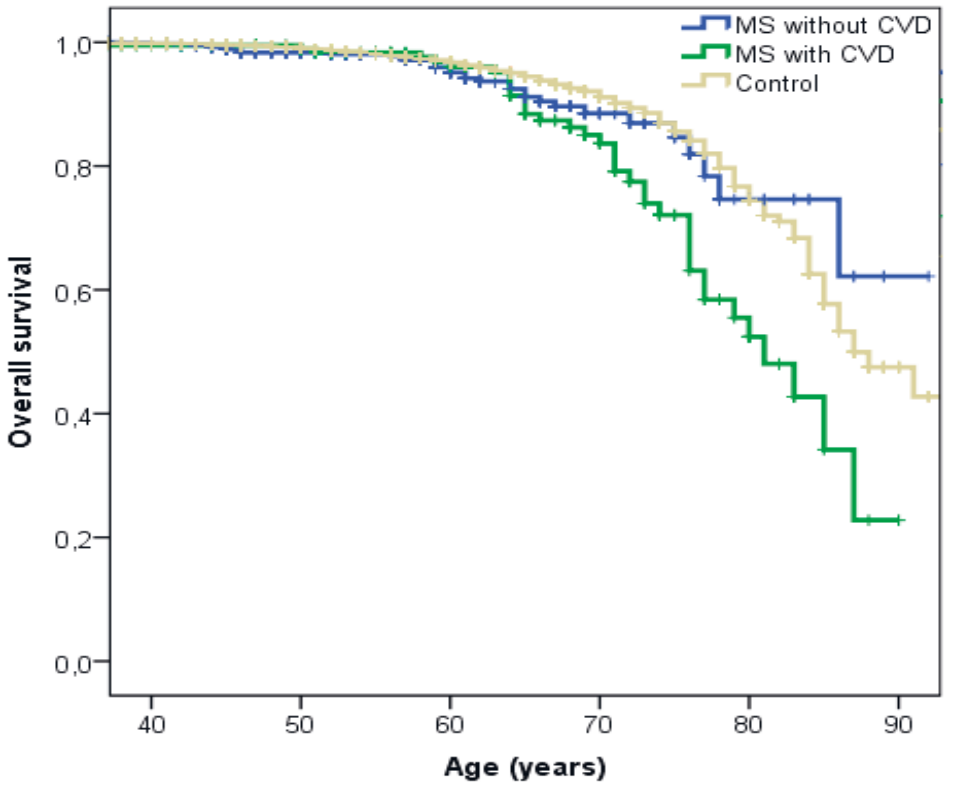

Figure 10. Kaplan-Meier curve showing survival of MS patients in Southwest Finland without CVD, with CVD, and age- and gender-matched controls from birth to death or end of follow-up. From 2004 to 2012 in a cohort of 1074 patients, 70 deaths (6%) occurred. *From the original publication, reprinted with permission from Elsevier.* (Murtonen et al., 2018)

MS patients had over 1.5-fold higher risk for cerebral infarct than the control population and over twofold risk for other vascular diseases of the brain, such as subarachnoid and cerebral haemorrhages. In 21 cases, ischemic stroke was a comorbid diagnosis, and in 4 cases an immediate cause of death. Ischemic strokes were more common among men. There were no significant differences between men and women in the mean age at cerebral infarct, which was 69.5 years. When common CVD risk factors such as hypertension, hyperlipidemia, obesity, and cardiac arrhythmia were investigated, nonsignificant risks were seen. Smoking was not included in this analysis. The risk for acute myocardial infarction did not show any statistically significant difference. Risk of diabetes mellitus type I was increased as well. ORs for CVD and their risk factors are shown in Table 7.

Table 7. Odds Ratios (OR) with 95% confidence intervals (CI) for CVD and their risk factors in the MS cohort from Southwest Finland in 2010.

Disease	MS		Controls			
	N	%	N	%	OR	95% CI
Acute myocardial infarct	18	1.68	121	1.13	1.49	0.91–2.43
Cerebral infarct	25	2.33	161	1.5	1.55	1.03–2.35
Other vascular disease of the brain*	9	0.84	36	0.34	2.5	1.24–5.06
TIA	12	1.12	136	1.27	0.88	0.49–1.59
Atrial fibrillation or flutter	18	1.68	350	3.26	0.51	0.33–0.81
Other cardiac arrythmia	18	1.68	189	1.76	0.95	0.59–1.54
Essential hypertension	93	8.66	1034	9.63	0.90	0.74–1.10
Atherosclerosis	12	1.12	102	0.95	1.18	0.65–2.13
Type I diabetes mellitus	20	1.86	95	0.89	2.11	1.32–3.36
Type II diabetes mellitus	39	3.63	391	3.64	1.00	0.72–1.38
Hyperlipidemia	17	1.16	336	3.13	0.51	0.32–0.81
Obesity	21	1.96	328	3.05	0.64	0.42–0.99

Number of cases, percentages, and odds ratios with confidence intervals for CVDs and their risk factors for MS cases compared to age- and gender- matched controls.

* Other vascular disease of the brain includes subarachnoid and cerebral hemorrhages.

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Risks for hospital-treated infections were high in MS patients, especially for urinary (acute pyelonephritis OR 7.59, 95% CI 6.01–9.57, and cystitis OR 6.98, 95% CI 5.48–8.89), respiratory (unspecified acute lower respiratory infection, OR 7.0, 95% CI 3.06–16.03, chronic bronchitis OR 5.71, 95% CI 5.48–8.89, pneumonia OR 3.37, 95% CI 2.73–4.15, acute bronchitis OR 2.45, 95% CI 1.61–3.73) and periodontal infections (dental caries OR 2.78, 95% CI 1.82–4.24, gingivitis and periodontal diseases OR 2.28, 95% CI 1.47–3.53, other disorders of teeth and supporting structures OR 2.09, 95% CI 1.28–3.43).

5.4 Study IV – End of life

From 1981 to 2010, 113 deaths occurred among 684 confirmed MS cases in Pirkanmaa. Among the deceased, the mean age at onset was 36.2 years, and the mean age at death was 57.4 years. There were no significant differences in the age of death between men and women. Of all cases, 80% were RRMS and 20% were PPMS. Characteristics of decedent MS patients are described in Table 8. Compared to the data from Turku, it appears that these patients perished significantly younger, which is probably due to the different study periods. In 1981–1990, the mean age at death was 46.8 years (N 10), 54.3 years (N 37) in 1991–2000, and 60.8 years (N 66) in 2001–2010.

MS was mentioned in 92% of death certificates and as an immediate cause of death (ICD) in 12% (N 13). Infections were the most common ICD in 51% (N 58) of deaths, including respiratory (46%), gastrointestinal, and urinary (1.8%) infections and sepsis with unknown focus (3.5%). Cardiovascular causes as ICD were mainly seen in the oldest age group, 60 years and older, whereas suicides were recorded in the youngest age group. Differences in ICD between the three age groups were statistically significant.

MS was more common as an underlying cause of death (UCD), where it was mentioned in 58% of records (N 65). As UCD, infections (N 5), cancer (13), vascular causes (19), gastrointestinal causes, other neurological disorders, trauma, and suicide (altogether 14 cases) were mentioned. CODs among the three age groups are listed in Table 8.

MS was not recorded in 9 (8%) certificates. Among these, the mean age at death was 47 years and causes of death were accident or suicide in three cases, acute myocardial infarction in three, pulmonary embolism in one, and cancer in one case.

Place of death was central or university or community hospital in most cases. Nursing home, home, and hospice care were in the minority. There were no significant differences between age groups in places of death. Distribution of places of death in the three age groups is described in Table 8.

Do not resuscitate was stated in five certificates.

Table 8. Characteristics of the deceased MS cases in Pirkanmaa from 1981 to 2010.

	Age groups, n (%)				
	0–49 years	50–59 years	60 and over	Total	%
N (%)	34 (30.1)	33 (29.2)	46 (40.7)	113	
Mean age at death (SD) years	41.3 (6.1)	55.1 (2.3)	71.0 (7.6)	57.4	
Mean duration of MS (SD) years	10.9 (5.2)	15.7 (7.2)	21.1 (8.7)	16.5 (8.5)	
Disability (N, %)					
EDSS < 3.0	7 (28)	7 (28)	11 (44)	25 (100)	22.1%
EDSS 3.0–5.5	8 (38.1)	5 (23.8)	8 (38.1)	21 (100)	18.6%
EDSS 6.0 or greater	19 (31.1)	18 (29.5)	24 (39.3)	61 (100)	54.0%
Immediate cause of death (N)					
Infection	16	22	20	58	51.3%
MS	4	5	4	13	11.5%
Cardiovascular	2	0	10	12	10.6%
Cancer	3	2	5	10	8.8%
Accident	3	0	2	5	4.4%
Pulmonary embolism	3	2	0	5	4.4%
Cerebrovascular	0	0	4	4	3.5%
Gastrointestinal	0	3	0	3	2.7%
Suicide	3	0	0	3	2.7%
Place of death (N)					
Central or university hospital ward	17	15	16	48	42.5%
Community hospital ward	6	14	12	32	28.3%
Nursing home	1	0	14	15	13.3%
Home	6	3	2	11	9.7%
Hospice	2	1	1	4	3.5%
Other	2	0	1	3	2.7%

Characteristics of the deceased MS cases, disability distributions prior to death, immediate causes of death, and places of death in three age-groups. *From the original publication, reprinted under the terms of the Creative Commons Attribution 4.0 International License. (Creative Commons, Murtonen et al., 2021)*

Disability before death was severe (EDSS 6.0 or more) in most cases. In five cases, 4.4% of the deceased, there was no adequate information on disability. No statistically significant differences existed between age groups, disease courses, or men and women. Distribution of disability before death by disease course groups is illustrated in Figure 10.

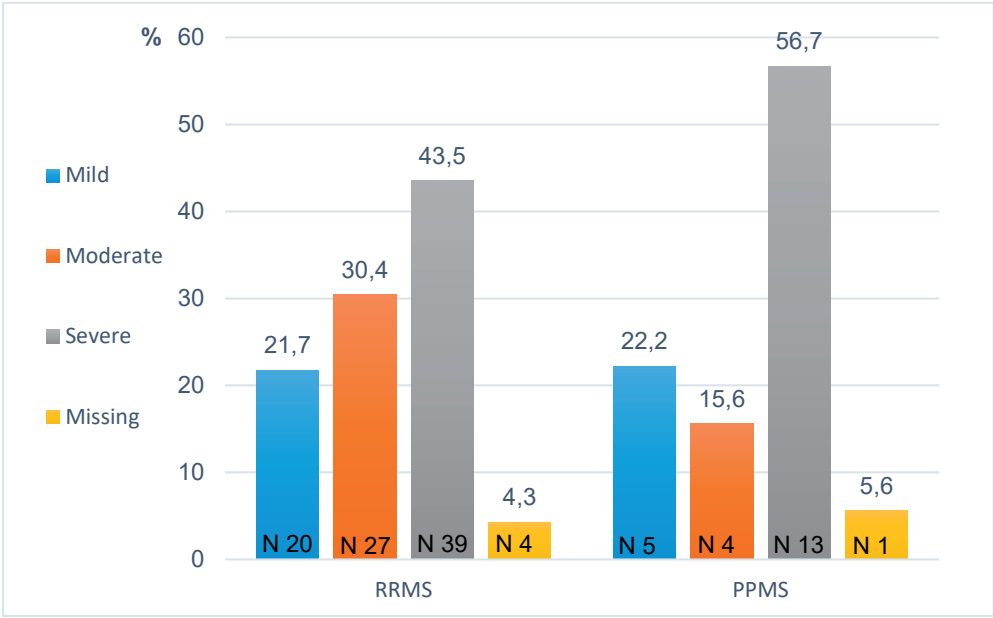

Figure 11. MS disability distribution (percentages within a group) by disease course before the period prior to death. The number of cases is given in each column. Mild = EDSS 0–2.5, Moderate = EDSS 3.0–5.5, Severe = EDSS 6.0 or more. *Previously unpublished figure containing data from study IV.*

6 DISCUSSION

6.1 Interpretation of results

6.1.1 Increasing prevalence and incidence

MS prevalence data were obtained by a cross-sectional study in the years 2000 and 2010. The estimation of incidence was based on follow-up of new cases in 1981–1990, 1991–2000, and 2001–2010. Observations in this thesis show that the study locations belong to the globally high-risk areas of MS, and the results corroborate global and temporal trends in MS occurrence. The overall age-standardized (ESP 2013) prevalence/10^5 of all three districts increased by 45%, being 192 in 2010, a high rate in Finland and globally. Crude prevalence/10^5 increased from 2000 to 2010 by 49%, being 196 in 2010. Results share similarities with Scandinavian and other high-prevalence countries. The nationwide prevalence/10^5 in Sweden was 189 in 2008 (Ahlgren et al., 2011), in Norway 208 in 2013 (Grytten et al., 2015), in Denmark 155 in 2005 (Bentzen et al., 2010), and 167 in Iceland in 2007 (Elíasdóttir et al., 2018). In Ontario, Canada, a prevalence of 265 was reported in 2013 (Rotstein et al., 2018), 202 in Scotland in 2009 (E. M. Visser et al., 2012), and 209 in Tuscany, Italy in 2019 (Bezzini et al., 2020).

The trends in global incidence have shown variation in studies over the past 30 years. In this study, incidence/10^5 increased 1.6-fold in Pirkanmaa (up to 8.2 in 2010), and twofold in Seinäjoki and Vaasa (up to 14.7 and 11.7 in 2010) over the 30-year follow-up. A major increasing trend in incidence was seen especially between 1981–1990 and 1991–2000. In 2001–2010, the trend remained high but stabilized. Similar rates and trends were reported in other high-risk areas. In 2019 in Norway, the incidence/10^5 was 14.4 (Flemmen et al., 2020), and in 2009, it was 12.3 among women in Denmark (Koch-Henriksen et al., 2018). A nationwide study from Sweden reported the incidence of 10.2 in 2001–2008 (Ahlgren et al., 2014). In Canada from 1996 to 2008, the rate was 7.8 with a stable trend (Kingwell et al., 2015), 8.8 in Scotland between 2010–2017 (Kearns et al., 2019), and 6.7 in Newcastle, Australia,

from 2001 to 2011, with a linear increasing trend for 50 years (Ribbons et al., 2016). The increasing trend stabilized in Denmark from 2000 to 2010 and in Sweden from 2001 to 2008 (Ahlgren et al., 2014; Koch-Henriksen et al., 2018). In many studies, the trend has stabilized after 2000.

We also observed stabilization, like in other contemporary studies. It could be speculated that the stabilization of diagnostic methodology is among the causes of our observation, in addition to improved awareness and better access to health care. It is also true that the newer McDonald diagnostic criteria enable the diagnosing of milder cases earlier than older criteria. However, this was not reflected in the shortening of diagnostic delay in our data (Sumelahti et al., 2014).

Once diagnostic methods become established, it can be expected that temporal changes eventually reflect more actual changes in incidence. Perhaps even the last decade of this study period, 2001–2010, might be the first decade to reflect less on the impact of establishing diagnostics. Future studies will show if this is the case.

In the literature the temporal increase of MS prevalence, and simultaneously observed increase of several autoimmune diseases, (Lerner et al., 2015) are suggested to point at factors affecting immunity. Several lifestyle changes may have taken place during the study period: smoking has diminished, vitamin D intake has increased, pregnancies have diminished, and obesity has increased. The general awareness of MS has increased, along with improved availability of MRI from the early 1990s and evolving diagnostic criteria, including increased use of paraclinical studies such as CSF examination have made differential diagnostics more accurate. At the same time, the number of neurologists has increased. All these factors have impacted the number of new diagnoses and have decreased diagnostic delay.

In our results, the increasing trends in both incidence and prevalence concerned mainly RRMS disease course, while the prevalence of PPMS decreased. One possible explanation is that due to enhanced and established diagnostics, it is probable that milder cases are being diagnosed. According to a recently presented view, the trajectory of MS should be seen more as a continuum from active relapsing form to the progressive, not dichotomized, like the traditional view has been (Kuhlmann et al., 2023). The view of two pathological processes occurring from the very beginning supports this suggestion. At the beginning of MS, the inflammatory process is more prominent, leading to the relapsing-remitting phenotype, and as the disease progresses, the role of degenerative process increases. Eventually, due to physiological changes in immunity, the inflammatory process extinguishes and the degenerative process continues, leading to progressive phenotype. If this were the case, then our results here could relate to the fact that MS is being diagnosed earlier,

with milder symptoms than before, and that some PPMS patients in our data represent SPMS course, according to the traditional categorization. The revised MacDonald criteria have increased the sensitivity of diagnostics and enabled setting the MS diagnosis earlier, which may reflect into these findings as well. It may also be, that some PPMS cases in our data have had a silent or very mild inflammatory phase before a more active degenerative phase due to individual variation. Emerging DMTs from the 1990s may have encouraged more precise diagnostics between RRMS and PPMS, as until 2018, DMTs were only reimbursed for the treatment of RRMS, which may also be one explaining factor for decreasing PPMS prevalence.

Prevalence trends generally relate to changes in incidence and survival. Effects of rising incidence also show in age distribution and can be seen in a shift of prevalence peak age groups toward younger groups in our data. In some reports, increased survival has also been suggested to affect increased prevalence. However, at the moment, the relationship between incidence, prevalence, and survival is not straightforward based on observations in recent global studies showing conflicting results. A stable trend, a suggested true improvement of survival (Brønnum-Hansen et al., 2004), and a trend purely reflecting the overall improved survival of the population and increased lifespan (Kingwell et al., 2012; Manouchehrinia et al., 2016) have all been reported. Overall, no strong conclusions can currently be drawn on the impact of survival in the increased prevalence.

Uneven geographical distribution is also a traditional long-term observation in MS epidemiology in Finland. Similar findings have been reported in Italy (Sicily and Sardinia) (Puthenparampil et al., 2022), Norway (several counties) (Grytten et al., 2015), and Sweden (several counties around the two major lakes and two coastal regions) (Landtblom et al., 2005). Such a high prevalence cluster has been located in Western Finland, and prevalence in the districts in our study corroborates the findings in previous studies from the 1960s of the east-west MS gradient in Finland. The high-risk area in the country's western region is higher compared to the eastern region, shown also by results in 2016 in the west, with a prevalence of $275/10^5$, and in the east with a prevalence of $167/10^5$ (Pirttisalo et al., 2019). One consequence of the findings of Finnish epidemiology studies is that the north-south gradient has not been found in Finland.

The causes for such a gradient point to differences in MS risk factors. In Finland, genetic differences are evident as the genetic background of Finnish people is original and heterogeneous. Evidence of a strong genetic dividing line between Western and Eastern Finland can be dated back to the Iron Age, and since then, migration from central Europe and Scandinavia to Western Finland and from Russia

to Eastern Finland has even amplified these differences. Historical events may also have a role in amplification as well, as this genetic division follows a medieval border between Sweden and Russia. The small Finnish population and various bottlenecks have led to a genetic random distribution (Salmela, 2012). The cluster and large MS pedigrees in Seinäjoki and Vaasa may reflect genetic differences where the enrichment of several predisposing genes is highly possible. (Kuokkanen et al., 1997) Indeed, genetic studies from the MS population diagnosed in 1979–1993 in Seinäjoki point to a possible founder effect, being one possible contributor of the high MS risk in this area (Tienari et al., 2004). However, in 1993, the highest MS prevalences were found in southern parts of South Ostrobothnia (Sumelahti et al., 2001), whereas in 2010, the areas with highest prevalences were more dispersed and found also in northern parts of the county.

Besides genetic differences, several other factors distinguish Western and Eastern Finland according to the same genetic division. Unemployment is more common in Eastern and Northern Finland, and the burden of overall illnesses is also higher in these areas. Especially cardio- and cerebrovascular diseases, problems related to alcohol, psychiatric disorders, and pulmonary diseases are more common in Eastern and Northern Finland (Finnish Institute for Health and Welfare, 2023). Health behaviors differ as well, as smoking and dietary habits predisposing to vascular problems are more common in these areas (Vartiainen, 2018). Since the gradient of MS risk is the opposite when compared to aforementioned factors, it is reasonable to suggest that genetic predisposition and certain immunological events are more important in the development of MS than dietary habits or smoking.

Genetic changes in stable populations are slow, thus the differences in temporal changes are likely explained by environmental factors. However, environmental factors affect the risk of both genders, while the increasing trends have mainly been seen among women. Gender-specific changes behind the increasing risk from the 1990s among women may relate to hormonally mediated factors. It may also be quite possible that the same environmental risk factors affect different genders in different ways, which is also suggested in recent modeling from Canadian data (Goodin et al., 2023). However, the exact environmental risk factor that would act differently in men and women is unclear. These are among the large body of observations that needs further investigation. A recent interesting meta-analysis reported transcriptomic and functional genetic differences between women and men, which may relate to differences between genders in responses to environmental factors (Català-Senent et al., 2023).

The F/M ratio is a robust marker in MS epidemiology, which describes the relation of the number of females to males and reflects concurrent changes in incidence. This ratio is used to compare gender occurrences at different time points of the same population as well as to compare data in different studies. Increasing trends of F/M ratio have been reported globally, for example in Norway from 1.7 to 2.6 between birth cohorts of 1930 and 1979 (Kampman et al., 2013) and in Denmark from 1.3 to 2.0 between 1950 and 2009 (Koch-Henriksen et al., 2018). Trends concerned mainly relapsing onset MS (Orton et al., 2006; Trojano et al., 2012). In our incidence cohort, the F/M ratio increased from 2.1 in 1981–1990 to 2.4 in 2001–2010 in Western Finland. In the prevalence cohort, F/M ratios were 2.0 in 2000 and 2.2 in 2010. In the literature, several causes have been presented to explain the rising ratio. Lifestyle changes are one, and another is hormonal effects, like fewer number of pregnancies. It has also been suggested that part of the globally rising incidence especially among women relates to changes in women's social position and access to health care in the 20th -century. One aspect is also that women seek health care services more often than men in many cultures. This may be reflected in the milder cases observed among women. On the other hand, since women tend to have milder courses of the disease they may have been more easily neglected before the era of McDonald's diagnostic criteria.

6.1.2 Disability in the MS population

In a clinically heterogenous disease such as MS, individual needs for care and treatment vary and often increase over the disease trajectory. One aim of the study was to assess the severity of the disability, which can be useful in making plans for health care, rehabilitation, and other needs, such as assistance. Previous reports on disability distribution in the MS population in the literature are scarce. In New Zealand, the mean disability in a large cohort was 4.4, measured on the EDSS scale. Higher disability was related to older age, longer disease duration, and PPMS (Alla et al., 2016). In a Swedish study, the median EDSS score was 5.0 in 2009, in a small cohort with only 48% of RRMS cases (Chruzander et al., 2013).

Disability here was assessed through the widely used EDSS scale. Although the scale is nonlinear in terms of the time spent at various ranges of the scale, it gives a rough estimate of the current burden of the disease. The scale is established as a marker for disability in MS. It has recently been suggested that when referring to increases in disability in patients with RRMS, the term "worsening" should be used

in place of "progression", and "progression" should be reserved for patients in the progressive phase of MS (Kappos et al., 2017; Lorscheider et al., 2016; Lublin et al., 2014).

To reach a thorough description of disability, we studied the EDSS distribution in the RRMS, PPMS, and different age groups. In our study, EDSS represents the reached stable disability status, as it was assessed in routine clinical control visits. The risk of biased rating may be lower in higher disability states where assessment is heavily based on ambulatory status. Interrater bias is also possible in our data, meaning that EDSS is a measurement drawn by the clinician based on their neurological examination and interpretation, which creates a possible source of bias. Also, there are a few aspects of MS symptoms that the scale does not consider, such as factors affecting the quality of life for MS patients, like pain, which have no impact on the scale.

The prognosis of MS is unpredictable and variable. In an international review, the median time of RRMS progression into SPMS was reported to be 20 years after disease onset, but the variation is broad (Cree et al., 2021). Accordingly, disability accumulates eventually, and the median time to reach EDSS 6 has been reported to be 15–20 years (Leray et al., 2010). In several studies, the PPMS cases reach EDSS 6.0 faster than in RRMS. We have not studied the disability evolution here, but in our prevalence data in 2010, EDSS 6.0 or more was recorded in 20% of initial RRMS cases and 44% of PPMS. The mean age at diagnosis was 36 years and the disease duration 13 years in the RRMS group (including cases that later transitioned to secondary progression), and in PPMS, the mean age at diagnosis was 43 years and the disease duration 19 years. Mild disability (corresponding to EDSS 2.5 or less) was observed mostly in the youngest RRMS group. Our data represent a long follow-up in this cohort and show the progressive nature of the disease based on increasing disability in older age groups.

Today, there is scarce but increasing evidence of DMTs' effect on disability accumulation (Cobo-Calvo et al., 2023; Tedeholm et al., 2012). In 2010, 56% (N=835) of RRMS cases in our data were using DMT, which is less than 79% in Switzerland in 2020 (Bossart et al., 2022), but quite the same as the US in 2018, at 48–55% (variation due to different registries) (Y. Zhang et al., 2021). In our study, the disability was mild in this group. However, the disease trajectory is long, and it may be that 15 years is too short a period to assess DMT effects in the MS population. Also, it is notable that DMTs are commonly started in early phases of MS, and their effects are limited to the inflammatory phase.

6.1.3 Comorbidity related to survival

Survival and comorbidities were assessed between 2004 and 2012 in Southwest Finland. Comorbid diseases shorten the lifespan overall and concern MS patients as well. Most remarkably, vascular comorbidity has been shown to significantly impact survival in MS. During the long trajectory of MS, several other comorbid diseases concern the MS population as well. Comorbidity with vascular diseases has been shown to cause survival disadvantage globally (Brønnum-Hansen et al., 2004; Christiansen et al., 2010; Krökki et al., 2014; Marrie, Elliott, et al., 2015; Thormann et al., 2016); prolonged diagnostic delays, increased lesion burden in MRI, and advanced brain atrophy have also been related to CVD and their risk factors (Kappus et al., 2016; Thormann, Sørensen, Koch-Henriksen, Laursen, et al., 2017). In our data, the risks for ischemic stroke and intracranial hemorrhages were elevated. Similar findings have been reported from Denmark and Canada as well (Christiansen et al., 2010; Marrie, Fisk, et al., 2016).

Despite the reduction of general mortality in coronary artery disease (Vartiainen, 2018), our findings point to elevated risks of CVD among Finnish MS patients. The treatment of risk factors may be neglected, and prolonged diagnostic delays may exist in this patient population. However, based on hospital records in our data, there was no increased OR for risk factors of CVDs, such as hyperlipidemia, hypertension, or other cardiac disorders. These factors are not always listed in the diagnoses in hospital patient records, as they are mainly treated in primary health care and are probably underestimated in our data. The only factor with higher OR for such diseases was type I diabetes mellitus. Lifestyle factors are important, and efficient primary prevention of vascular risk factors should belong to the care of the MS population.

The observation of elevated type 1 diabetes risk in our MS population is surprising and interesting. The incidence of type 1 diabetes in Finland is the highest in the world, peaking at $64.2/10^5$ in 2005 and stabilizing after that (Harjutsalo et al., 2013). Genetic predisposition is significant, and the strongest predisposing effects are related to haplotypes DR4-DQ8 and DR3-DQ2 with a synergistic manner, while DR15-DQ6 is reportedly protective against the disease (Taka et al., 2023). Environmental factors are suggested to play a role as well, one of which is vitamin D deficiency (Knip & Simell, 2012). The reason, which makes the observation of our study interesting, is that haplotype DR15-DQ6 has been shown to predispose for MS in the Finnish population (Laaksonen et al., 2002). In the future, this observation would be an interesting topic for further investigation.

6.1.4 End of life, causes, and places of death

The mortality of MS patients is nearly three times higher than in controls (Brønnum-Hansen et al., 2004; Lunde et al., 2017; Manouchehrinia et al., 2016; Sumelahti et al., 2010). The main causes of death are respiratory infections (Sumelahti et al., 2010). Aggravating disability causes immobility, which leads to an increased risk of infections. Both infections and disability set the demand to the place of care, and there is a risk for unplanned hospitalizations later in life. Although it is a known fact that MS is a progressive disease, advanced care planning for later stages has been scarce (Cottrell et al., 2020). Formerly, palliative care has mainly concerned cancer patients. Recent publications have pointed out that familiarizing both patients and caregivers with the concept of an advanced care plan (ACP) and palliative care (PC) in MS is beneficial (Strupp et al., 2016).

Studies concerning the period before death in MS patients are scarce, while mortality and causes of death have been studied more often. Few surveys on palliative care and advanced care planning in the MS population have been published within the latest decade (Cottrell et al., 2020; Solari et al., 2018; Strupp et al., 2016). The European Academy of Neurology has recently published a guideline on the palliative care of people with severe MS (Solari et al., 2020).

Our aim was to investigate factors related to the end of life among Finnish MS patients, including health care needs, disability, place, and causes of death. Deaths in our data occurred between 1970 and 2010. The increased risk of infection-related hospitalization and high infection-related mortality was also true in our data and concerned both younger and older patients. Most deaths took place at hospitals, and many decedents had a severe disability, which raises doubts about unplanned hospitalization and lack of advanced care planning. Our results highlight the need to recognize the urgency for PC and, before that, conduct ACP in time, both of which have been shown to be beneficial in the MS population (Seeber et al., 2019; Veronese et al., 2017).

The concept of ACP is not familiar to neurologists, nor to many general practitioners, which raises the need for both professionals and patients to become familiar. Another close topic is an early referral to palliative care, which has been shown to be beneficial in MS patients (Qureshi et al., 2019; Rosenwax et al., 2015; Spilsbury et al., 2017). From a general practitioner's point of view, MS is quite rare and may feel challenging to treat. For someone who is not familiar with the disease and its prognosis, it may feel better to refer the patient to specialized care. On the other hand, the core of palliative care remains the same, regardless of the disease

that led to it and is probably a more familiar concept overall in primary health care wards than in secondary or tertiary hospital wards.

Prior studies have shown that the leading causes of death among MS patients are infections mainly of the respiratory and urinary tract. Reported risks for cardiovascular causes and cancers have varied. In our data, the main causes of death were respiratory infections, followed by MS and cardiovascular causes. The causes of death in both our studies is distributed similarly to previous reports. In younger decedents, MS was not among the causes of death, whereas cardiovascular causes were more pronounced in the older age group. The mean age at death in our study was 57 years, lower than the 74 years in Canada and 65 years in the UK (Harding et al., 2020; Hirst et al., 2008). Differences may partly be explained by careful case ascertainment and high inclusion in our study.

Mortality is a complex outcome of many factors during the lifespan of a person. For example, as a socioeconomic factor, there is divorce: MS has been associated with a higher risk of divorce among men (Landfeldt et al., 2018; Pfleger et al., 2010), and divorce increases mortality, especially among men (Metsä-Simola & Martikainen, 2013; Sbarra et al., 2011). It is impossible to find all the potential factors affecting mortality within the limits of an observative survey like ours. However, it is evident that the effect of known comorbid risk factors is reflected in the distribution of CODs, such as cardio- and cerebrovascular diseases, which have been shown to reduce survival among MS patients also. Likewise, the accumulation of disability at the late stages of MS is reflected in place of death, which was a hospital ward for most of the decedents in our data. Of course, this is not unique to MS; among diseases with long trajectories, the place of death is quite often a hospital ward.

There are many differences in the aforementioned COD studies that hamper comparisons, such as different methods used, different case ascertainment, and manners of recording other diagnoses in patient records and death certificates. There are also differences between countries and even between physicians in determining causes of death. In our data, MS was recorded as ICOD in 11.5% of certificates, which is less than the previously reported 50–56% in other studies (Lunde et al., 2017; Smestad et al., 2009), except for 9% in Wales (Hirst et al., 2008). As an UCOD in our data, MS was recorded in 57.5% of certificates, which is slightly higher than in previous reports, where the occurrence has varied between 34–56% (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Hirst et al., 2008; Smestad et al., 2009).

6.2 Strengths and limitations

A strength of the data in our surveys is a confirmed MS diagnosis in study cohorts and long-term follow-up in neurology departments in Finland where diagnostic methods and criteria are used uniformly. Based on these factors, we believe we have reached almost all diagnosed MS cases in the area, and the results can be considered reliable. The investigations and diagnosis of MS are practically always made in a neurology unit of a central or university hospital, where treatment and regular follow-up visits take place as well. Diagnoses are made with the guidance of national Current Care Guidelines, which are based on international recommendations. There have not been major changes in the populational level during the study period or in the development of major differences between the study areas. Proportions of DMT cases can be considered reliable, as medications are prescribed by neurologists, either paid for by hospitals or fully reimbursed by the Finnish Social Insurance Institution. Also, every case was scrutinized by hand to meet diagnostic criteria and to assess disease courses and disability.

Linkage to mortality statistics in Statistics Finland is based on personal identification numbers, which every Finnish citizen has had since the 1960s (Digital and Population Data Services Agency, accessed 1.12.2023). When a Finnish person dies, the information is sent into the Population Data Services Agency, and a death record written by a physician is sent to Statistics Finland, where death records are archived. Statistics Finland also creates and updates mortality statistics.

Some factors limit the reliability of temporal and regional comparisons of prevalence and incidence. The longest follow-ups in our study are up to 60 years, as the first diagnoses were made in the 1950s. Changing diagnostic criteria over decades is a potential source of bias in a study with long follow-ups, limiting comparability. We aimed to tackle this risk of bias retrospectively by making sure that all cases included fulfilled one criterion, the clinically or laboratory-supported definite MS by Poser. This led to the exclusion of a few of the oldest cases, which did not have adequate documented evidence for diagnosis. In another incidence study from this data, a comparison was made with McDonald criteria for the cohort of 2000 to 2010, and there were no major differences in the incidence results between the two diagnostic criteria. One regional factor hampering comparisons is that the population in Pirkanmaa is younger than in Seinäjoki and Vaasa. Also, the two latter areas are less urbanized than Pirkanmaa, which is also a region with a migration gain.

One limitation is the assessment of disability. In the patient records, especially among the majority of those using DMT, EDSS was mentioned. However, in nearly

a quarter of patients, the EDSS value here was based on the description in the records. Both the information provided and the interpretation of the author may be susceptible to bias. To minimize the effect of such bias, and due to the relatively small number of cases in each step of the twenty-step scale, we categorized disability into three classes, in a similar manner that has been used previously (Solari et al., 2020), which gives a good perception of the distribution of disability.

As we utilized the patient records, we did not have potentially important information on patients' lifestyles and socioeconomic factors. Living conditions, socioeconomic status and its changes, education, and need for help and support are scarcely mentioned in the patient records. Smoking habits, obesity, hypertension, lipid-lowering medications, use of vitamin D supplements, and other lifestyle factors were also reported randomly, so there are no possibilities to study their effects in terms of administrative data.

6.3 Clinical implications and suggestions for future research

Epidemiological studies provide background knowledge when assessments of future care needs are being conducted. MS is a life-long disease, the number of MS patients is increasing and many are living longer with their disease. Descriptions of disability give a perspective of their need for help. Based on our data, it seems that the number of PPMS cases with the most severe disability is decreasing. On the other hand, due to increased prevalence, we can expect that the number of RRMS cases with a disability is going to increase with time, as patients are aging. Hence, it can be assumed, that the need for rehabilitation and other forms of help and care is going to increase as well.

Comorbid conditions impact the prognosis of MS patients, as our results also show. In the health care visits of MS patients, attention should be paid especially to screening through vascular risk factors and thorough primary prevention. Increasing disability increases the risk of immobility, which is a risk factor for CVD and infections. It is important to encourage MS patients to stay physically active, with the assistance of professionals, such as physical therapists, if necessary.

Expectations for advantage in survival and performance are present in the era of DMTs. The proportion of patients with moderate to severe disability over the long disease trajectory is not expected to be abolished. Therefore, advanced care planning and palliative care should be part of the treatment plans of these patients. According to palliative care guidelines, the need for APC should be triggered when EDSS 6 is

reached to avoid unplanned hospitalizations and to discuss plans with patients and their close ones in advance. Palliative care has been shown to have several advantages in progressive neurological diseases as well, such as better pain management, quality of life, and less aggressive care in the days before death.

In the future, temporal survival trends from our areas of high risk would provide important insights, as current international reports have been conflicting. Also, the effects of efficacious medications on survival, disability, and disease progression would be important topics of research in the future, as the results presented in this thesis describe the situation before wider use of high-efficacy treatments. The area of Western Finland is historically unique in the field of MS research, and of course, updating incidence and prevalence from this area is an important topic as well. In future epidemiological research, the new national Finnish MS database is a valuable source of data and offers new possibilities to determine epidemiological figures throughout the nation.

7 CONCLUSIONS

The main aim of this thesis was to describe the epidemiological characteristics of MS in Western Finland. Incidence and prevalence trends were assessed, along with disability and comorbidities related to survival. End of life, places, and MS patients' causes of death were described. Based on the results of this thesis, the following conclusions can be drawn.

1. The overall incidence/10^5 in Seinäjoki in 1981–2010 was twofold compared to Pirkanmaa, 12.5 and 6.7, respectively, and higher than 8.3 in Vaasa. There was a more than twofold increase from 1981–1990 to 1991–2000 among women in Seinäjoki and Vaasa, and a stabilizing trend from 1991–2000 to 2000–2010. Among men in these two counties, the incidence increased from 1981–1990 to 1990–2000, after which it decreased. In Pirkanmaa, there was a smaller yet increasing trend through the whole study period in both genders.

2. The ESP2013 standardized prevalence/10^5 increased by 45% from 133 in 2000 to 192 in 2010 in the areas of Pirkanmaa, Seinäjoki, and Vaasa. The increase was most notable among women (58%) from 176 to 277. Among men, the increase went from 91 to 119 (31%). RRMS prevalence increased by 60% up to 179 while the prevalence of PPMS decreased by 16% to 18. Increasing prevalence was seen in all three districts, most notably in Seinäjoki and Vaasa. The highest prevalence in 2010 was 372 among women in Seinäjoki. In the majority of cases, disability was mild. Severe disability was seen more often in the PPMS group.

3. CVDs significantly affected the survival of MS patients. The mean lifetime survival of MS patients in the whole cohort was 82.4 years, with CVD was 79.5 years, and without CVD was 85.4 years. The mean lifetime survival of age- and gender-matched controls was 85.6 years. The risk of cerebral infarction was significantly increased among MS patients by 50%, and the risk of intracranial hemorrhages was over twofold. In this data, no significant differences in CVD risk factors were seen between the MS and control population, apart from diabetes mellitus type I, for which the risk was

increased in the MS population. The risk for hospital-treated infection was high in the MS population.

4. The most common cause of death was infections; among them, respiratory ones were most frequent. Cardiovascular causes were mainly recorded in the age group 60 years and older and suicides in the age group less than 50 years. MS was most commonly mentioned as an underlying cause of death in 58% of cases. Most often MS patients perished in hospital wards. In most cases, disability was severe before death.

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9 REFERENCES

Abu-Raya, B., Michalski, C., Sadarangani, M., & Lavoie, P. M. (2020). Maternal Immunological Adaptation During Normal Pregnancy. *Frontiers in Immunology*, *11*, 575197. https://doi.org/10.3389/fimmu.2020.575197

Ahlgren, C., Odén, A., & Lycke, J. (2011). High nationwide prevalence of multiple sclerosis in Sweden. *Multiple Sclerosis Journal*, *17*(8), 901–908. https://doi.org/10.1177/1352458511403794

Ahlgren, C., Odén, A., & Lycke, J. (2014). High nationwide incidence of multiple sclerosis in Sweden. *PloS One*, *9*(9), e108599–e108599. https://doi.org/10.1371/journal.pone.0108599

Airas, L. (2015). Hormonal and gender-related immune changes in multiple sclerosis. *Acta Neurologica Scandinavica*, *132*(199), 62–70. https://doi.org/10.1111/ane.12433

Åivo, J., Kurki, S., Sumelahti, M.-L., Hänninen, K., Ruutiainen, J., & Soilu-Hänninen, M. (2017). Risk of osteoporotic fractures in multiple sclerosis patients in southwest Finland. *Acta Neurologica Scandinavica*, *135*(5), 516–521. https://doi.org/10.1111/ane.12623

AlJumah, M., Bunyan, R., Al Otaibi, H., Al Towaijri, G., Karim, A., Al Malik, Y., Kalakatawi, M., Alrajeh, S., Al Mejally, M., Algahtani, H., Almubarak, A., Cupler, E., Alawi, S., Qureshi, S., Nahrir, S., Almalki, A., Alhazzani, A., Althubaiti, I., Alzahrani, N., … Al-Jedai, A. (2020). Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. *BMC Neurology*, *20*(1), 49. https://doi.org/10.1186/s12883-020-1629-3

Alla, S., Pearson, J. F., Taylor, B. V, Miller, D. H., Clarke, G., Richardson, A., Willoughby, E., Abernethy, D. A., Sabel, C. E., & Mason, D. F. (2016). Disability profile of multiple sclerosis in New Zealand. *Journal of Clinical Neuroscience*, *28*, 97–101. https://doi.org/10.1016/j.jocn.2015.09.020

Almasi-Hashiani, A., Sahraian, M. A., & Eskandarieh, S. (2020). Evidence of an increased prevalence of multiple sclerosis: a population-based study of Tehran registry during 1999–2018. *BMC Neurology*, *20*(1), 169. https://doi.org/10.1186/s12883-020-01747-8

Aloisi, F., Giovannoni, G., & Salvetti, M. (2023). Epstein-Barr virus as a cause of multiple sclerosis: opportunities for prevention and therapy. *The Lancet Neurology*, *22*(4), 338–349. https://doi.org/10.1016/S1474-4422(22)00471-9

Alonso, A., & Hernán, M. A. (2008). Temporal trends in the incidence of multiple sclerosis. *Neurology*, *71*(2), 129 LP – 135. https://doi.org/10.1212/01.wnl.0000316802.35974.34

Alonso, A., Jick, S. S., Olek, M. J., & Hernán, M. A. (2007). Incidence of multiple sclerosis in the United Kingdom. *Journal of Neurology*, *254*(12), 1736–1741. https://doi.org/10.1007/s00415-007-0602-z

Alroughani, R., AlHamdan, F., Shuaibi, S., Ahmed, S. F., Behbehani, R., Lamdhade, S., & Al-Hashel, J. (2019). The prevalence of multiple sclerosis continues to increase in Kuwait. *Multiple Sclerosis and Related Disorders*, *32*, 74–76. https://doi.org/https://doi.org/10.1016/j.msard.2019.04.033

Angeloni, B., Bigi, R., Bellucci, G., Mechelli, R., Ballerini, C., Romano, C., Morena, E., Pellicciari, G., Reniè, R., Rinaldi, V., Buscarinu, M. C., Romano, S., Ristori, G., & Salvetti, M. (2021). A Case of Double Standard: Sex Differences in Multiple Sclerosis Risk Factors. *International Journal of Molecular Sciences*, *22*(7), 3696. https://doi.org/10.3390/ijms22073696

Anna Nicholls. (2020, August 26). *The standardised mortality ratio and how to calculate it*. Cochrane UK.

Arneth, B. (2020). Multiple Sclerosis and Smoking. *The American Journal of Medicine*, *133*(7), 783–788. https://doi.org/https://doi.org/10.1016/j.amjmed.2020.03.008

Ascherio, A. (2013). Environmental factors in multiple sclerosis. *Expert Review of Neurotherapeutics*, *13*(12 Suppl), 3–9. https://doi.org/10.1586/14737175.2013.865866

Ascherio, A., & Munger, K. L. (2010). Epstein–Barr Virus Infection and Multiple Sclerosis: A Review. *Journal of Neuroimmune Pharmacology*, *5*(3), 271–277. https://doi.org/10.1007/s11481-010-9201-3

Balasa, R., Barcutean, L., Balasa, A., Motataianu, A., Roman-Filip, C., & Manu, D. (2020). The action of TH17 cells on blood brain barrier in multiple sclerosis and experimental autoimmune encephalomyelitis. *Human Immunology*, *81*(5), 237–243. https://doi.org/https://doi.org/10.1016/j.humimm.2020.02.009

Balasa, R., Barcutean, L., Mosora, O., & Manu, D. (2021). Reviewing the Significance of Blood–Brain Barrier Disruption in Multiple Sclerosis Pathology and Treatment. *International Journal of Molecular Sciences*, *22*(16). https://doi.org/10.3390/ijms22168370

Barkhof, F., Filippi, M., Miller, D. H., Scheltens, P., Campi, A., Polman, C. H., Comi, G., Adèr, H. J., Losseff, N., & Valk, J. (1997). Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain : A Journal of Neurology*, *120 (Pt 1*, 2059–2069. https://doi.org/10.1093/brain/120.11.2059

Bar-Or, A., Pender, M. P., Khanna, R., Steinman, L., Hartung, H.-P., Maniar, T., Croze, E., Aftab, B. T., Giovannoni, G., & Joshi, M. A. (2020). Epstein-Barr Virus in Multiple Sclerosis: Theory and Emerging Immunotherapies. *Trends in Molecular Medicine*, *26*(3), 296–310. https://doi.org/10.1016/j.molmed.2019.11.003

Bebo, B., Cintina, I., LaRocca, N., Ritter, L., Talente, B., Hartung, D., Ngorsuraches, S., Wallin, M., & Yang, G. (2022). The Economic Burden of Multiple Sclerosis in the United States. *Neurology*, *98*(18), e1810. https://doi.org/10.1212/WNL.0000000000200150

Benkert, P., Meier, S., Schaedelin, S., Manouchehrinia, A., Yaldizli, Ö., Maceski, A., Oechtering, J., Achtnichts, L., Conen, D., Derfuss, T., Lalive, P. H., Mueller, C., Müller, S., Naegelin, Y., Oksenberg, J. R., Pot, C., Salmen, A., Willemse, E., Kockum, I., … Zecca, C. (2022). Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study. *The Lancet Neurology*, *21*(3), 246–257. https://doi.org/10.1016/S1474-4422(22)00009-6

Bentzen, J., Meulengracht Flachs, E., Stenager, E., Brønnum-Hansen, H., & Koch-Henriksen, N. (2010). Prevalence of multiple sclerosis in Denmark 1950—2005. *Multiple Sclerosis Journal*, *16*(5), 520–525. https://doi.org/10.1177/1352458510364197

Bergamaschi, R., Monti, M. C., Trivelli, L., Introcaso, V. P., Mallucci, G., Borrelli, P., Gerosa, L., & Montomoli, C. (2020). Increased prevalence of multiple sclerosis and clusters of different disease risk in Northern Italy. *Neurological Sciences*, *41*(5), 1089–1095. https://doi.org/10.1007/s10072-019-04205-7

Bezzini, D., Ulivelli, M., Gualdani, E., Razzanelli, M., Ferretti, F., Meucci, G., Francesconi, P., & Battaglia, M. A. (2020). Increasing prevalence of multiple sclerosis in Tuscany, Italy. *Neurological Sciences*, *41*(2), 397–402. https://doi.org/10.1007/s10072-019-04090-0

Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., Elledge, S. J., Niebuhr, D. W., Scher, A. I., Munger, K. L., & Ascherio, A. (2022). Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*, *375*(6578), 296–301. https://doi.org/10.1126/science.abj8222

Booth, D. R., Heard, R. N., Stewart, G. J., Goris, A., Dobosi, R., Dubois, B., Lorentzen, Å. R., Celius, E. G., Harbo, H. F., Spurkland, A., Olsson, T., Kockum, I., Link, J., Hillert, J., Ban, M., Baker, A., Sawcer, S., Compston, A., Mihalova, T., … (IMSGC), I. M. S. G. C. (2009). The expanding genetic overlap between multiple sclerosis and type I diabetes. *Genes & Immunity*, *10*(1), 11–14. https://doi.org/10.1038/gene.2008.83

Bossart, J., Kamm, C. P., Kaufmann, M., Stanikić, M., Puhan, M. A., Kesselring, J., Zecca, C., Gobbi, C., Rapold, I., Kurmann, R., Ammann, S., & von Wyl, V.

(2022). Real-world disease-modifying therapy usage in persons with relapsing-remitting multiple sclerosis: Cross-sectional data from the Swiss Multiple Sclerosis Registry. *Multiple Sclerosis and Related Disorders*, *60*. https://doi.org/10.1016/j.msard.2022.103706

Brasanac, J., Ramien, C., Gamradt, S., Taenzer, A., Glau, L., Ritter, K., Patas, K., Agorastos, A., Wiedemann, K., Demiralay, C., Fischer, F., Otte, C., Bellmann-Strobl, J., Friese, M. A., Tolosa, E., Paul, F., Heesen, C., Weygandt, M., & Gold, S. M. (2022). Immune signature of multiple sclerosis-associated depression. *Brain, Behavior, and Immunity*, *100*, 174–182. https://doi.org/https://doi.org/10.1016/j.bbi.2021.11.022

Brønnum-Hansen, H., Koch-Henriksen, N., & Stenager, E. (2004). Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain*, *127*(4), 844–850. https://doi.org/10.1093/brain/awh104

Burkill, S., Montgomery, S., Hajiebrahimi, M., Hillert, J., Olsson, T., & Bahmanyar, S. (2017). Mortality trends for multiple sclerosis patients in Sweden from 1968 to 2012. *Neurology*, *89*(6), 555–562. https://doi.org/10.1212/WNL.0000000000004216

Campbell, J. A., Simpson, S., Ahmad, H., Taylor, B. V, van der Mei, I., & Palmer, A. J. (2019). Change in multiple sclerosis prevalence over time in Australia 2010–2017 utilising disease-modifying therapy prescription data. *Multiple Sclerosis Journal*, *26*(11), 1315–1328. https://doi.org/10.1177/1352458519861270

Canto, E., & Oksenberg, J. R. (2018). Multiple sclerosis genetics. *Multiple Sclerosis Journal*, *24*(1), 75–79. https://doi.org/10.1177/1352458517737371

Carotenuto, A., Cacciaguerra, L., Pagani, E., Preziosa, P., Filippi, M., & Rocca, M. A. (2022). Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. *Brain*, *145*(8), 2785–2795. https://doi.org/10.1093/brain/awab454

Català-Senent, J. F., Andreu, Z., Hidalgo, M. R., Soler-Sáez, I., Roig, F. J., Yanguas-Casás, N., Neva-Alejo, A., López-Cerdán, A., de la Iglesia-Vayá, M., Stranger, B. E., & García-García, F. (2023). A deep transcriptome meta-analysis reveals sex differences in multiple sclerosis. *Neurobiology of Disease*, *181*, 106113. https://doi.org/https://doi.org/10.1016/j.nbd.2023.106113

Centers for Disease Control and Prevention. (2023, May 31). *Incidence Rate Example*.

Chou, I. J., Kuo, C. F., Tanasescu, R., Tench, C. R., Tiley, C. G., Constantinescu, C. S., & Whitehouse, W. P. (2020). Comorbidity in multiple sclerosis: its temporal relationships with disease onset and dose effect on mortality. *European Journal of Neurology*, *27*(1), 105–112. https://doi.org/10.1111/ene.14040

Christiansen, C. F., Christensen, S., Farkas, D. K., Miret, M., Sørensen, H. T., & Pedersen, L. (2010). Risk of Arterial Cardiovascular Diseases in Patients with

Multiple Sclerosis: A Population-Based Cohort Study. *Neuroepidemiology*, *35*(4), 267–274. https://doi.org/10.1159/000320245

Chruzander, C., Johansson, S., Gottberg, K., Einarsson, U., Fredrikson, S., Holmqvist, L. W., & Ytterberg, C. (2013). A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: Changes in disability and the value of different factors in predicting disability and mortality. *Journal of the Neurological Sciences*, *332*(1), 121–127. https://doi.org/10.1016/j.jns.2013.07.003

Cobo-Calvo, A., Tur, C., Otero-Romero, S., Carbonell-Mirabent, P., Ruiz, M., Pappolla, A., Alvarez, J. V., Vidal-Jordana, A., Arrambide, G., Castilló, J., Galan, I., Barranco, M. R., Midaglia, L. soledad, Nos, C., Acevedo, B. R., Torres, A. Z. de, Mongay, N., Rio, J., Comabella, M., … Montalban, X. (2023). Association of Very Early Treatment Initiation With the Risk of Long-Term Disability in Patients With a First Demyelinating Event. *Neurology*, 10.1212/WNL.0000000000207664. https://doi.org/10.1212/WNL.0000000000207664

Collaborators, G. B. D. 2016 M. S. (2019). Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology*, *18*(3), 269–285. https://doi.org/10.1016/S1474-4422(18)30443-5

Confavreux, C., & Vukusic, S. (2006). Natural history of multiple sclerosis: a unifying concept. *Brain*, *129*(3), 606–616. https://doi.org/10.1093/brain/awl007

Correale, J., & Gaitan, M. I. (2015). Multiple sclerosis and environmental factors: the role of vitamin D, parasites, and Epstein–Barr virus infection. *Acta Neurologica Scandinavica*, *132*, 46–55.

Cottrell, L., Economos, G., Evans, C., Silber, E., Burman, R., Nicholas, R., Farsides, B., Ashford, S., & Koffman, J. S. (2020). A realist review of advance care planning for people with multiple sclerosis and their families. *PLOS ONE*, *15*(10), e0240815. https://doi.org/10.1371/journal.pone.0240815

Cree, B. A. C., Arnold, D. L., Chataway, J., Chitnis, T., Fox, R. J., Ramajo, A. P., Murphy, N., & Lassmann, H. (2021). Secondary Progressive Multiple Sclerosis. *Neurology*, *97*(8), 378. https://doi.org/10.1212/WNL.0000000000012323

Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Neurology. (2020, January 23). *MS-tauti*. The Finnish Medical Society Duodecim. www.kaypahoito.fi

Cutter, G. R., Zimmerman, J., Salter, A. R., Knappertz, V., Suarez, G., Waterbor, J., Howard, V. J., & Marrie, R. A. (2015). Causes of death among persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *4*(5), 484–490. https://doi.org/https://doi.org/10.1016/j.msard.2015.07.008

Dai, X., Gakidou, E., & Lopez, A. D. (2022). Evolution of the global smoking epidemic over the past half century: strengthening the evidence base for policy action. *Tobacco Control*, *31*(2), 129. https://doi.org/10.1136/tobaccocontrol-2021-056535

De Stefano, N., Airas, L., Grigoriadis, N., Mattle, H. P., O'Riordan, J., Oreja-Guevara, C., Sellebjerg, F., Stankoff, B., Walczak, A., Wiendl, H., & Kieseier, B. C. (2014). Clinical Relevance of Brain Volume Measures in Multiple Sclerosis. *CNS Drugs*, *28*(2), 147–156. https://doi.org/10.1007/s40263-014-0140-z

De Stefano, N., Giorgio, A., Battaglini, M., Rovaris, M., Sormani, M. P., Barkhof, F., Korteweg, T., Enzinger, C., Fazekas, F., Calabrese, M., Dinacci, D., Tedeschi, G., Gass, A., Montalban, X., Rovira, A., Thompson, A., Comi, G., Miller, D. H., & Filippi, M. (2010). Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. *Neurology*, *74*(23), 1868 LP – 1876. https://doi.org/10.1212/WNL.0b013e3181e24136

Deisenhammer, F., Zetterberg, H., Fitzner, B., & Zettl, U. K. (2019). The Cerebrospinal Fluid in Multiple Sclerosis. *Frontiers in Immunology*, *10*, 726. https://doi.org/10.3389/fimmu.2019.00726

D'haeseleer, M., Cambron, M., Vanopdenbosch, L., & De Keyser, J. (2011). Vascular aspects of multiple sclerosis. *The Lancet. Neurology*, *10*(7), 657–666. https://doi.org/10.1016/S1474-4422(11)70105-3

Di Cesare, M., Sorić, M., Bovet, P., Miranda, J. J., Bhutta, Z., Stevens, G. A., Laxmaiah, A., Kengne, A.-P., & Bentham, J. (2019). The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. *BMC Medicine*, *17*(1), 212. https://doi.org/10.1186/s12916-019-1449-8

Digital and population data services agency. (n.d.). *The personal identity code*.

Dunmire, S. K., Hogquist, K. A., & Balfour, H. H. (2015). *Infectious Mononucleosis BT - Epstein Barr Virus Volume 1: One Herpes Virus: Many Diseases* (C. Münz, Ed.; pp. 211–240). Springer International Publishing. https://doi.org/10.1007/978-3-319-22822-8_9

Dunmire, S. K., Verghese, P. S., & Balfour, H. H. (2018). Primary Epstein-Barr virus infection. *Journal of Clinical Virology*, *102*, 84–92. https://doi.org/https://doi.org/10.1016/j.jcv.2018.03.001

Elíasdóttir, Ó., Kjartansson, Ó., & Olafsson, E. (2018). Prevalence of Multiple Sclerosis in Iceland. *Neuroepidemiology*, 50–56. https://doi.org/10.1159/000489472

Etemadifar, M., Nikanpour, Y., Neshatfar, A., Mansourian, M., & Fitzgerald, S. (2020). Incidence and prevalence of multiple sclerosis in persian gulf area: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders*, *40*. https://doi.org/10.1016/j.msard.2020.101959

Feinstein, A. R. (1970). THE PRE-THERAPEUTIC CLASSIFICATION OF CO-MORBIDITY IN CHRONIC DISEASE. *Journal of Chronic Diseases*, *23*(7), 455–468. https://doi.org/10.1016/0021-9681(70)90054-8

Filippi, M., Bar-Or, A., Piehl, F., Preziosa, P., Solari, A., Vukusic, S., & Rocca, M. A. (2018). Multiple sclerosis. *Nature Reviews Disease Primers*, *4*(1), 43. https://doi.org/10.1038/s41572-018-0041-4

Finnish Institute For Health and Welfare. (2023, May 31). *National Health Index 2019–2021*.

Fitzgerald, K. C., Munger, K. L., Köchert, K., Arnason, B. G. W., Comi, G., Cook, S., Goodin, D. S., Filippi, M., Hartung, H.-P., Jeffery, D. R., O'Connor, P., Suarez, G., Sandbrink, R., Kappos, L., Pohl, C., & Ascherio, A. (2015). Association of Vitamin D Levels With Multiple Sclerosis Activity and Progression in Patients Receiving Interferon Beta-1b. *JAMA Neurology*, *72*(12), 1458–1465. https://doi.org/10.1001/jamaneurol.2015.2742

Flemmen, H. Ø., Simonsen, C. S., Berg-Hansen, P., Moen, S. M., Kersten, H., Heldal, K., & Celius, E. G. (2020). Prevalence of multiple sclerosis in rural and urban districts in Telemark county, Norway. *Multiple Sclerosis and Related Disorders*, *45*, 102352. https://doi.org/10.1016/j.msard.2020.102352

Freedman, M. S., Thompson, E. J., Deisenhammer, F., Giovannoni, G., Grimsley, G., Keir, G., Öhman, S., Racke, M. K., Sharief, M., Sindic, C. J. M., Sellebjerg, F., & Tourtellotte, W. W. (2005). Recommended Standard of Cerebrospinal Fluid Analysis in the Diagnosis of Multiple Sclerosis: A Consensus Statement. *Archives of Neurology*, *62*(6), 865–870. https://doi.org/10.1001/archneur.62.6.865

Freeman, L., Longbrake, E. E., Coyle, P. K., Hendin, B., & Vollmer, T. (2022). High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing–Remitting Multiple Sclerosis. *CNS Drugs*, *36*(12), 1285–1299. https://doi.org/10.1007/s40263-022-00965-7

Goodin, D. S. (2009). The Causal Cascade to Multiple Sclerosis: A Model for MS Pathogenesis. *PLOS ONE*, *4*(2), e4565. https://doi.org/10.1371/journal.pone.0004565

Goodin, D. S., Khankhanian, P., Gourraud, P.-A., & Vince, N. (2021). The nature of genetic and environmental susceptibility to multiple sclerosis. *PloS One*, *16*(3), e0246157. https://doi.org/10.1371/journal.pone.0246157

Goodin, D. S., Khankhanian, P., Gourraud, P.-A., & Vince, N. (2023). Multiple sclerosis: Exploring the limits and implications of genetic and environmental susceptibility. *PLOS ONE*, *18*(6), e0285599-. https://doi.org/10.1371/journal.pone.0285599

Gourraud, P.-A., Harbo, H. F., Hauser, S. L., & Baranzini, S. E. (2012). The genetics of multiple sclerosis: an up-to-date review. *Immunological Reviews*, *248*(1), 87–103. https://doi.org/10.1111/j.1600-065X.2012.01134.x

Grytten, N., Torkildsen, Ø., & Myhr, K.-M. (2015). Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. *Acta Neurologica Scandinavica*, *132*(199), 29–36. https://doi.org/10.1111/ane.12428

Guerrero, B. L., & Sicotte, N. L. (2020). Microglia in Multiple Sclerosis: Friend or Foe? *Frontiers in Immunology*, *11*, 374. https://doi.org/10.3389/fimmu.2020.00374

Guerrero-García, J. de J., Carrera-Quintanar, L., López-Roa, R. I., Márquez-Aguirre, A. L., Rojas-Mayorquín, A. E., & Ortuño-Sahagún, D. (2016). Multiple Sclerosis and Obesity: Possible Roles of Adipokines. *Mediators of Inflammation*, *2016*, 4036232. https://doi.org/10.1155/2016/4036232

Harding, K., Zhu, F., Alotaibi, M., Duggan, T., Tremlett, H., & Kingwell, E. (2020). Multiple cause of death analysis in multiple sclerosis: A population-based study. *Neurology*, *94*(8), e820–e829. https://doi.org/10.1212/WNL.0000000000008907

Harjutsalo, V., Sund, R., Knip, M., & Groop, P.-H. (2013). Incidence of Type 1 Diabetes in Finland. *JAMA*, *310*(4), 427. https://doi.org/10.1001/jama.2013.8399

Hauser, S. L., & Cree, B. A. C. (2020). Treatment of Multiple Sclerosis: A Review. *The American Journal of Medicine*, *133*(12), 1380-1390.e2. https://doi.org/10.1016/j.amjmed.2020.05.049

Hawkes, C. H., Giovannoni, G., Lechner-Scott, J., & Levy, M. (2020). Is the incidence of multiple sclerosis really increasing? In *Multiple sclerosis and related disorders* (Vol. 45, p. 102527). https://doi.org/10.1016/j.msard.2020.102527

Heinonen, T., Castrén, E., Luukkaala, T., Mäkinen, K., Ruutiainen, J., & Kuusisto, H. (2020). The retirement rate due to multiple sclerosis has decreased since 1995– A retrospective study in a Finnish central hospital. *Multiple Sclerosis and Related Disorders*, *45*, 102360. https://doi.org/https://doi.org/10.1016/j.msard.2020.102360

Hirst, C., Swingler, R., Compston, D. A. S., Ben-Shlomo, Y., & Robertson, N. P. (2008). Survival and cause of death in multiple sclerosis: a prospective population-based study. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *79*(9), 1016 LP – 1021. https://doi.org/10.1136/jnnp.2007.127332

Hollenbach, J. A., & Oksenberg, J. R. (2015). The immunogenetics of multiple sclerosis: A comprehensive review. *Journal of Autoimmunity*, *64*, 13–25. https://doi.org/https://doi.org/10.1016/j.jaut.2015.06.010

Holmberg, M., Murtonen, A., Elovaara, I., & Sumelahti, M.-L. (2013). Increased Female MS Incidence and Differences in Gender-Specific Risk in Medium- and High-Risk Regions in Finland from 1981-2010. *Multiple Sclerosis International*, *2013*, 182516. https://doi.org/10.1155/2013/182516

Holten-Andersen, M. N., Haugen, J., Oma, I., & Strand, T. A. (2020). Vitamin D Status and Its Determinants in A Paediatric Population in Norway. *Nutrients*, *12*(5), 1385. https://doi.org/10.3390/nu12051385

Hong, Y., Tang, H. R., Ma, M., Chen, N., Xie, X., & He, L. (2019). Multiple sclerosis and stroke: a systematic review and meta-analysis. *BMC Neurology*, *19*(1), 139. https://doi.org/10.1186/s12883-019-1366-7

Houen, G., Trier, N. H., & Frederiksen, J. L. (2020). Epstein-Barr Virus and Multiple Sclerosis. *Frontiers in Immunology*, *11*, 587078. https://doi.org/10.3389/fimmu.2020.587078

International Multiple Sclerosis Genetics Consortium. A., P. N., E., B. S., Adam, S., Parisa, S., Chris, C., Garrett, W., H., B. A., Tojo, J., Joseph, R., S., V. I., Cristin, M., H., P. T., Aaron, B., Charles, W., Brendan, K., Maria, C., Phoebe, W., Ioannis-Pavlos, P., Allison, R., … L., D. J. P. (2019). Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*, *365*(6460), eaav7188. https://doi.org/10.1126/science.aav7188

Itkonen, S. T., Andersen, R., Björk, A. K., Brugård Konde, Å., Eneroth, H., Erkkola, M., Holvik, K., Madar, A. A., Meyer, H. E., Tetens, I., Torfadóttir, J. E., Thórisdóttir, B., & Lamberg-Allardt, C. J. E. (2020). Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. *Scandinavian Journal of Public Health*, *49*(6), 616–627. https://doi.org/10.1177/1403494819896878

Jadidi, E., Mohammadi, M., & Moradi, T. (2013). High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Multiple Sclerosis Journal*, *19*(10), 1336–1340. https://doi.org/10.1177/1352458513475833

Kalincik, T., Cutter, G., Spelman, T., Jokubaitis, V., Havrdova, E., Horakova, D., Trojano, M., Izquierdo, G., Girard, M., Duquette, P., Prat, A., Lugaresi, A., Grand'Maison, F., Grammond, P., Hupperts, R., Oreja-Guevara, C., Boz, C., Pucci, E., Bergamaschi, R., … Butzkueven, H. (2015). Defining reliable disability outcomes in multiple sclerosis. *Brain*, *138*(11), 3287–3298. https://doi.org/10.1093/brain/awv258

Kalincik, T., Vivek, V., Jokubaitis, V., Lechner-Scott, J., Trojano, M., Izquierdo, G., Lugaresi, A., Grand'Maison, F., Hupperts, R., Oreja-Guevara, C., Bergamaschi, R., Iuliano, G., Alroughani, R., Van Pesch, V., Amato, M. P., Slee, M., Verheul, F., Fernandez-Bolanos, R., Fiol, M., … Group, on behalf of the Msb. S. (2013). Sex as a determinant of relapse incidence and progressive

course of multiple sclerosis. *Brain*, *136*(12), 3609–3617. https://doi.org/10.1093/brain/awt281

Kamm, C. P., Uitdehaag, B. M., & Polman, C. H. (2014). Multiple sclerosis: current knowledge and future outlook. *European Neurology*, *72*(3–4), 132–141. https://doi.org/10.1159/000360528

Kampman, M. T., Aarseth, J. H., Grytten, N., Benjaminsen, E., Celius, E. G., Dahl, O. P., Holmøy, T., Løken-Amsrud, K., Midgard, R., Myhr, K.-M., Risberg, G., Vatne, A., & Torkildsen, Ø. (2013). Sex ratio of multiple sclerosis in persons born from 1930 to 1979 and its relation to latitude in Norway. *Journal of Neurology*, *260*(6), 1481–1488. https://doi.org/10.1007/s00415-012-6814-x

Kappos, L., Butzkueven, H., Wiendl, H., Spelman, T., Pellegrini, F., Chen, Y., Dong, Q., Koendgen, H., Belachew, S., & Trojano, M. (2017). Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. *Multiple Sclerosis Journal*, *24*(7), 963–973. https://doi.org/10.1177/1352458517709619

Kappus, N., Weinstock-Guttman, B., Hagemeier, J., Kennedy, C., Melia, R., Carl, E., Ramasamy, D. P., Cherneva, M., Durfee, J., Bergsland, N., Dwyer, M. G., Kolb, C., Hojnacki, D., Ramanathan, M., & Zivadinov, R. (2016). Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, *87*(2), 181–187. https://doi.org/10.1136/jnnp-2014-310051

Karampoor, S., Zahednasab, H., Ramagopalan, S., Mehrpour, M., Safarnejad Tameshkel, F., & Keyvani, H. (2016). 25-hydroxyvitamin D levels are associated with multiple sclerosis in Iran: A cross-sectional study. *Journal of Neuroimmunology*, *290*, 47–48. https://doi.org/https://doi.org/10.1016/j.jneuroim.2015.11.017

Kearns, P. K. A., Paton, M., O'Neill, M., Waters, C., Colville, S., McDonald, J., Young, I. J. B., Pugh, D., O'Riordan, J., Weller, B., MacDougall, N., Clemens, T., Dibben, C., Wilson, J. F., Castro, M. C., Ascherio, A., Chandran, S., & Connick, P. (2019). Regional variation in the incidence rate and sex ratio of multiple sclerosis in Scotland 2010-2017: findings from the Scottish Multiple Sclerosis Register. *Journal of Neurology*, *266*(10), 2376–2386. https://doi.org/10.1007/s00415-019-09413-x

Kieseier, B. C. (2011). The Mechanism of Action of Interferon-β in Relapsing Multiple Sclerosis. *CNS Drugs*, *25*(6), 491–502. https://doi.org/10.2165/11591110-000000000-00000

Kingwell, E., Leray, E., Zhu, F., Petkau, J., Edan, G., Oger, J., & Tremlett, H. (2019). Multiple sclerosis: effect of beta interferon treatment on survival. *Brain : A Journal of Neurology*, *142*(5), 1324–1333. https://doi.org/10.1093/brain/awz055

Kingwell, E., Marriott, J. J., Jetté, N., Pringsheim, T., Makhani, N., Morrow, S. A., Fisk, J. D., Evans, C., Béland, S. G., Kulaga, S., Dykeman, J., Wolfson, C., Koch, M. W., & Marrie, R. A. (2013). Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurology*, *13*, 128. https://doi.org/10.1186/1471-2377-13-128

Kingwell, E., van der Kop, M., Zhao, Y., Shirani, A., Zhu, F., Oger, J., & Tremlett, H. (2012). Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(1), 61–66. https://doi.org/10.1136/jnnp-2011-300616

Kingwell, E., Zhu, F., Evans, C., Duggan, T., Oger, J., & Tremlett, H. (2020). Causes that Contribute to the Excess Mortality Risk in Multiple Sclerosis: A Population-Based Study. *Neuroepidemiology*, *54*(2), 131–139. https://doi.org/10.1159/000504804

Kingwell, E., Zhu, F., Marrie, R. A., Fisk, J. D., Wolfson, C., Warren, S., Profetto-McGrath, J., Svenson, L. W., Jette, N., Bhan, V., Yu, B. N., Elliott, L., & Tremlett, H. (2015). High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991-2010). *Journal of Neurology*, *262*(10), 2352–2363. https://doi.org/10.1007/s00415-015-7842-0

Kinnunen, E. (1984). Multiple sclerosis in Finland: evidence of increasing frequency and uneven geographic distribution. *Neurology*, *34*(4), 457–461. https://doi.org/10.1212/wnl.34.4.457

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 Neurologica Scandinavica*, *67*(5), 255–262. https://doi.org/10.1111/j.1600-0404.1983.tb04574.x

Knip, M., & Simell, O. (2012). Environmental Triggers of Type 1 Diabetes. *Cold Spring Harbor Perspectives in Medicine*, *2*(7), a007690–a007690. https://doi.org/10.1101/cshperspect.a007690

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. *Journal of Neurology, Neurosurgery and Psychiatry*, *88*(8), 626. https://doi.org/http://dx.doi.org/10.1136/jnnp-2017-315907

Koch-Henriksen, N., & Magyari, M. (2021). Apparent changes in the epidemiology and severity of multiple sclerosis. *Nature Reviews Neurology*, *17*(11), 676–688. https://doi.org/10.1038/s41582-021-00556-y

Koch-Henriksen, N., & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet Neurology*, *9*(5), 520–532. https://doi.org/10.1016/S1474-4422(10)70064-8

Koch-Henriksen, N., & Sorensen, P. S. (2011). Why does the north–south gradient of incidence of multiple sclerosis seem to have disappeared on the Northern hemisphere? *Journal of the Neurological Sciences*, *311*(1), 58–63. https://doi.org/https://doi.org/10.1016/j.jns.2011.09.003

Koch-Henriksen, N., Thygesen, L. C., 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. https://doi.org/10.1212/WNL.0000000000005612

Korn, T. (2008). Pathophysiology of multiple sclerosis. *Journal of Neurology*, *255*(6), 2–6. https://doi.org/10.1007/s00415-008-6001-2

Kosmidou, M., Katsanos, A. H., Katsanos, K. H., Kyritsis, A. P., Tsivgoulis, G., Christodoulou, D., & Giannopoulos, S. (2017). Multiple sclerosis and inflammatory bowel diseases: a systematic review and meta-analysis. *Journal of Neurology*, *264*(2), 254–259.

Kowalec, K., McKay, K. A., Patten, S. B., Fisk, J. D., Evans, C., Tremlett, H., Marrie, R. A., & (ECoMS), C. T. in E. and I. of C. on M. S. (2017). Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study. *Neurology*, *89*(24), 2455–2461. https://doi.org/10.1212/WNL.0000000000004716

Krökki, O., Bloigu, R., Ansakorpi, H., Reunanen, M., & Remes, A. M. (2014). Neurological comorbidity and survival in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *3*(1), 72–77. https://doi.org/10.1016/j.msard.2013.06.006

Krökki, O., Bloigu, R., Reunanen, M., & Remes, A. M. (2011). Increasing incidence of multiple sclerosis in women in Northern Finland. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *17*(2), 133–138. https://doi.org/10.1177/1352458510384012

Kuhle, J., Kropshofer, H., Haering, D. A., Kundu, U., Meinert, R., Barro, C., Dahlke, F., Tomic, D., Leppert, D., & Kappos, L. (2019). Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. *Neurology*, *92*(10), e1007–e1015. https://doi.org/10.1212/WNL.0000000000007032

Kuhlmann, T., Moccia, M., Coetzee, T., Cohen, J. A., Correale, J., Graves, J., Marrie, R. A., Montalban, X., Yong, V. W., Thompson, A. J., Reich, D. S., Amato, M. P., Banwell, B., Barkhof, F., Chataway, J., Chitnis, T., Comi, G., Derfuss, T., Finlayson, M., … Waubant, E. (2023). Multiple sclerosis progression: time for a new mechanism-driven framework. *The Lancet Neurology*, *22*(1), 78–88. https://doi.org/10.1016/S1474-4422(22)00289-7

Kumar, G., & Axtell, R. C. (2023). Dual Role of B Cells in Multiple Sclerosis. *International Journal of Molecular Sciences*, *24*(3), 2336. https://doi.org/10.3390/ijms24032336

Kuokkanen, S., Gschwend, M., Rioux, J. D., Daly, M. J., Terwilliger, J. D., Tienari, P. J., Wikström, J., Palo, J., Stein, L. D., Hudson, T. J., Lander, E. S., & Peltonen, L. (1997). Genomewide Scan of Multiple Sclerosis in Finnish Multiplex Families. *The American Journal of Human Genetics*, *61*(6), 1379–1387. https://doi.org/10.1086/301637

Kurtzke, J. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–1452. https://doi.org/10.1212/wnl.33.11.1444.

Kurtzke, J. F. (1975). A REASSESSMENT OF THE DISTRIBUTION OF MULTIPLE SCLEROSIS. *Acta Neurologica Scandinavica*, *51*(2), 110–136. https://doi.org/https://doi.org/10.1111/j.1600-0404.1975.tb01364.x

Laaksonen, M., Pastinen, T., Sjöroos, M., Kuokkanen, S., Ruutiainen, J., Sumelahti, M.-L., Reijonen, H., Salonen, R., Wikström, J., Panelius, M., Partanen, J., Tienari, P. J., & Ilonen, J. (2002). HLA class II associated risk and protection against multiple sclerosis—a Finnish family study. *Journal of Neuroimmunology*, *122*(1), 140–145. https://doi.org/https://doi.org/10.1016/S0165-5728(01)00456-8

Lalive, P. H., Neuhaus, O., Benkhoucha, M., Burger, D., Hohlfeld, R., Zamvil, S. S., & Weber, M. S. (2011). Glatiramer Acetate in the Treatment of Multiple Sclerosis. *CNS Drugs*, *25*(5), 401–414. https://doi.org/10.2165/11588120-000000000-00000

Lalmohamed, A., Bazelier, M. T., Van Staa, T. P., Uitdehaag, B. M. J., Leufkens, H. G. M., De Boer, A., & De Vries, F. (2012). Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. *European Journal of Neurology*, *19*(7), 1007–1014. https://doi.org/https://doi.org/10.1111/j.1468-1331.2012.03668.x

Landfeldt, E., Castelo-Branco, A., Svedbom, A., Löfroth, E., Kavaliunas, A., & Hillert, J. (2018). The long-term impact of multiple sclerosis on the risk of divorce. *Multiple Sclerosis and Related Disorders*, *24*, 145–150. https://doi.org/10.1016/j.msard.2018.07.002

Landtblom, A.-M., Riise, T., & Kurtzke, J. F. (2005). Further considerations on the distribution of multiple sclerosis in Sweden. *Acta Neurologica Scandinavica*, *111*(4), 238–246. https://doi.org/https://doi.org/10.1111/j.1600-0404.2005.00395.x

Lane, J., Ng, H. S., Poyser, C., Lucas, R. M., & Tremlett, H. (2022). Multiple sclerosis incidence: A systematic review of change over time by geographical region. *Multiple Sclerosis and Related Disorders*, *63*. https://doi.org/10.1016/j.msard.2022.103932

Lassmann, H. (2014). Multiple sclerosis: Lessons from molecular neuropathology. *Experimental Neurology*, *262*, 2–7. https://doi.org/https://doi.org/10.1016/j.expneurol.2013.12.003

Lassmann, H. (2019). Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis . In *Frontiers in Immunology* (Vol. 9, p. 3116).

Lassmann, H., Brück, W., & Lucchinetti, C. F. (2007). The Immunopathology of Multiple Sclerosis: An Overview. *Brain Pathology*, *17*(2), 210–218. https://doi.org/https://doi.org/10.1111/j.1750-3639.2007.00064.x

Leray, E., Vukusic, S., Debouverie, M., Clanet, M., Brochet, B., Sèze, J. de, Zéphir, H., Defer, G., Lebrun-Frenay, C., Moreau, T., Clavelou, P., Pelletier, J., Berger, E., Cabre, P., Camdessanché, J.-P., Kalson-Ray, S., Confavreux, C., & Edan, G. (2015). Excess Mortality in Patients with Multiple Sclerosis Starts at 20 Years from Clinical Onset: Data from a Large-Scale French Observational Study. *PLOS ONE*, *10*(7), e0132033. https://doi.org/10.1371/journal.pone.0132033

Leray, E., Yaouanq, J., Le Page, E., Coustans, M., Laplaud, D., Oger, J., & Edan, G. (2010). Evidence for a two-stage disability progression in multiple sclerosis. *Brain : A Journal of Neurology*, *133*(Pt 7), 1900–1913. https://doi.org/10.1093/brain/awq076

Lerner, A., Jeremias, P., & Matthias, T. (2015). The World Incidence and Prevalence of Autoimmune Diseases is Increasing. *International Journal of Celiac Disease*, *3*(4), 151–155. http://pubs.sciepub.com/

Lorscheider, J., Buzzard, K., Jokubaitis, V., Spelman, T., Havrdova, E., Horakova, D., Trojano, M., Izquierdo, G., Girard, M., Duquette, P., Prat, A., Lugaresi, A., Grand'Maison, F., Grammond, P., Hupperts, R., Alroughani, R., Sola, P., Boz, C., Pucci, E., … Group, on behalf of the Msb. S. (2016). Defining secondary progressive multiple sclerosis. *Brain*, *139*(9), 2395–2405. https://doi.org/10.1093/brain/aww173

Lublin, F. D., Häring, D. A., Ganjgahi, H., Ocampo, A., Hatami, F., Čuklina, J., Aarden, P., Dahlke, F., Arnold, D. L., Wiendl, H., Chitnis, T., Nichols, T. E., Kieseier, B. C., & Bermel, R. A. (2022). How patients with multiple sclerosis acquire disability. *Brain*, *145*(9), 3147–3161. https://doi.org/10.1093/brain/awac016

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P. S., Thompson, A. J., Wolinsky, J. S., Balcer, L. J., Banwell, B., Barkhof, F., Bebo Jr, B., Calabresi, P. A., Clanet, M., Comi, G., Fox, R. J., Freedman, M. S., Goodman, A. D., Inglese, M., Kappos, L., … Polman, C. H. (2014). Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*, *83*(3), 278–286. https://doi.org/10.1212/WNL.0000000000000560

Lublin, F. D., Reingold, S. C., & Sclerosis*, N. M. S. S. (USA) A. C. on C. T. of N. A. in M. (1996). Defining the clinical course of multiple sclerosis. *Neurology*, *46*(4), 907. https://doi.org/10.1212/WNL.46.4.907

Lucas, R. M., Byrne, S. N., Correale, J., Ilschner, S., & Hart, P. H. (2015). Ultraviolet radiation, vitamin D and multiple sclerosis. *Neurodegenerative Disease Management*, *5*(5), 413–424. https://doi.org/10.2217/nmt.15.33

Lucchinetti, C. F., Popescu, B. F. G., Bunyan, R. F., Moll, N. M., Roemer, S. F., Lassmann, H., Brück, W., Parisi, J. E., Scheithauer, B. W., Giannini, C., Weigand, S. D., Mandrekar, J., & Ransohoff, R. M. (2011). Inflammatory Cortical Demyelination in Early Multiple Sclerosis. *New England Journal of Medicine*, *365*(23), 2188–2197. https://doi.org/10.1056/NEJMoa1100648

Lunde, H. M. B., Assmus, J., Myhr, K.-M., Bø, L., & Grytten, N. (2017). Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *88*(8), 621–625. https://doi.org/10.1136/jnnp-2016-315238

Magyari, M., Koch-Henriksen, N., Pfleger, C. C., & Sørensen, P. S. (2013). Reproduction and the risk of multiple sclerosis. *Multiple Sclerosis Journal*, *19*(12), 1604–1609. https://doi.org/10.1177/1352458513481397

Magyari, M., & Sorensen, P. S. (2020). Comorbidity in Multiple Sclerosis. *Frontiers in Neurology*, *11*, 851. https://doi.org/10.3389/fneur.2020.00851

Mäkitie, O. (2011). Muuttuiko mikään uusien D-vitamiini- suositusten myötä? *Lääketieteellinen Aikakauskirja Duodecim*, *127*(12), 1181–1183.

Manouchehrinia, A., Tanasescu, R., Tench, C. R., & Constantinescu, C. S. (2016). Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. *Journal of Neurology, Neurosurgery, and Psychiatry*, *87*(3), 324–331. https://doi.org/10.1136/jnnp-2015-310361

Marrie, R. A., Cohen, J., Stuve, O., Trojano, M., Sørensen, P. S., Reingold, S., Cutter, G., & Reider, N. (2015). A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *21*(3), 263–281. https://doi.org/10.1177/1352458514564491

Marrie, R. A., Elliott, L., Marriott, J., Cossoy, M., Blanchard, J., Leung, S., & Yu, N. (2015). Effect of comorbidity on mortality in multiple sclerosis. *Neurology*, *85*(3), 240–247. https://doi.org/10.1212/WNL.0000000000001718

Marrie, R. A., Fisk, J. D., Fitzgerald, K., Kowalec, K., Maxwell, C., Rotstein, D., Salter, A., & Tremlett, H. (2023). Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Frontiers in Immunology*, *14*. https://www.frontiersin.org/articles/10.3389/fimmu.2023.1197195

Marrie, R. A., Fisk, J., Tremlett, H., Wolfson, C., Warren, S., Blanchard, J., Patten, S. B., & Sclerosis, C. T. in the E. and I. of C. on M. (2016). Differing trends in the incidence of vascular comorbidity in MS and the general population. *Neurology. Clinical Practice*, *6*(2), 120–128. https://doi.org/10.1212/CPJ.0000000000000230

Marrie, R. A., Garland, A., Schaffer, S. A., Fransoo, R., Leung, S., Yogendran, M., Kingwell, E., & Tremlett, H. (2019). Traditional risk factors may not explain increased incidence of myocardial infarction in MS. *Neurology*, *92*(14), e1624 LP-e1633. https://doi.org/10.1212/WNL.0000000000007251

Marrie, R. A., Leung, S., Yu, N., & Elliott, L. (2018). Lower prevalence of multiple sclerosis in First Nations Canadians. *Neurology. Clinical Practice*, *8*(1), 33–39. https://doi.org/10.1212/CPJ.0000000000000418

Marrie, R. A., Maxwell, C., Mahar, A., Ekuma, O., McClintock, C., Seitz, D., & Groome, P. (2021). Breast Cancer Survival in Multiple Sclerosis. *Neurology*, *97*(1), e13. https://doi.org/10.1212/WNL.0000000000012127

Marrie, R. A., Maxwell, C., Mahar, A., Ekuma, O., McClintock, C., Seitz, D., Webber, C., & Groome, P. A. (2021). Cancer Incidence and Mortality Rates in Multiple Sclerosis. *Neurology*, *96*(4), e501. https://doi.org/10.1212/WNL.0000000000011219

Marrie, R. A., Patten, S. B., Tremlett, H., Wolfson, C., Warren, S., Svenson, L. W., Jette, N., Fisk, J., & Sclerosis, C. T. in the E. and I. of C. on M. (2016). Sex differences in comorbidity at diagnosis of multiple sclerosis: A population-based study. *Neurology*, *86*(14), 1279–1286. https://doi.org/10.1212/WNL.0000000000002481

Marrie, R. A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Cutter, G., Reingold, S., & Sorensen, P. S. (2015). A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *21*(3), 318–331. https://doi.org/10.1177/1352458514564485

Marrie, R. A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Sorensen, P. S., Reingold, S. C., & Cutter, G. (2014). A systematic review of the incidence and prevalence of cancer in multiple sclerosis. *Multiple Sclerosis Journal*, *21*(3), 294–304. https://doi.org/10.1177/1352458514564489

Marrie, R. A., Reingold, S., Cohen, J., Stuve, O., Trojano, M., Sorensen, P. S., Cutter, G., & Reider, N. (2015). The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *21*(3), 305–317. https://doi.org/10.1177/1352458514564487

Marrie, R. A., Rudick, R., Horwitz, R., Cutter, G., Tyry, T., Campagnolo, D., & Vollmer, T. (2010). Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology*, *74*(13), 1041–1047. https://doi.org/10.1212/WNL.0b013e3181d6b125

Marrosu, M. G., Motzo, C., Murru, R., Lampis, R., Costa, G., Zavattari, P., Contu, D., Fadda, E., Cocco, E., & Cucca, F. (2004). The co-inheritance of type 1 diabetes and multiple sclerosis in Sardinia cannot be explained by genotype

variation in the HLA region alone. *Human Molecular Genetics*, *13*(23), 2919–2924. https://doi.org/10.1093/hmg/ddh319

Matsuura, E., Atzeni, F., Sarzi-Puttini, P., Turiel, M., Lopez, L. R., & Nurmohamed, M. T. (2014). Is atherosclerosis an autoimmune disease? *BMC Medicine*, *12*(1), 47. https://doi.org/10.1186/1741-7015-12-47

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H.-P., Lublin, F. D., McFarland, H. F., Paty, D. W., Polman, C. H., Reingold, S. C., Sandberg-Wollheim, M., Sibley, W., Thompson, A., Van Den Noort, S., Weinshenker, B. Y., & Wolinsky, J. S. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Annals of Neurology*, *50*(1), 121–127. https://doi.org/https://doi.org/10.1002/ana.1032

McKay, K. A., Tremlett, H., Fisk, J. D., Zhang, T., Patten, S. B., Kastrukoff, L., Campbell, T., Marrie, R. A., & Sclerosis, F. the C. T. in the E. and I. of C. on M. (2018). Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology*, *90*(15), e1316 LP-e1323. https://doi.org/10.1212/WNL.0000000000005302

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

Metsä-Simola, N., & Martikainen, P. (2013). The short-term and long-term effects of divorce on mortality risk in a large Finnish cohort, 1990–2003. *Population Studies*, *67*(1), 97–110. https://doi.org/10.1080/00324728.2012.746386

Miller, D. H., Weinshenker, B. G., Filippi, M., Banwell, B. L., Cohen, J. A., Freedman, M. S., Galetta, S. L., Hutchinson, M., Johnson, R. T., Kappos, L., Kira, J., Lublin, F. D., McFarland, H. F., Montalban, X., Panitch, H., Richert, J. R., Reingold, S. C., & Polman, C. H. (2008). Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *14*(9), 1157–1174. https://doi.org/10.1177/1352458508096878

Mirzaei, F., Michels, K. B., Munger, K., O'Reilly, E., Chitnis, T., Forman, M. R., Giovannucci, E., Rosner, B., & Ascherio, A. (2011). Gestational vitamin D and the risk of multiple sclerosis in offspring. *Annals of Neurology*, *70*(1), 30–40. https://doi.org/10.1002/ana.22456

Mokry, L. E., Ross, S., Timpson, N. J., Sawcer, S., Davey Smith, G., & Richards, J. B. (2016). Obesity and Multiple Sclerosis: A Mendelian Randomization Study. *PLoS Medicine*, *13*(6), e1002053–e1002053. https://doi.org/10.1371/journal.pmed.1002053

Moridi, T., Stawiarz, L., McKay, K. A., Ineichen, B. V, Ouellette, R., Ferreira, D., Muehlboeck, J.-S., Westman, E., Kockum, I., Olsson, T., Piehl, F., Hillert, J., Manouchehrinia, A., & Granberg, T. (2022). Association between brain

volume and disability over time in multiple sclerosis. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *8*(4), 20552173221144230. https://doi.org/10.1177/20552173221144230

MS International Federation. (2021). *Atlas of MS*. https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms

Munger, K. L., Åivo, J., Hongell, K., Soilu-Hänninen, M., Surcel, H.-M., & Ascherio, A. (2016). Vitamin D Status During Pregnancy and Risk of Multiple Sclerosis in Offspring of Women in the Finnish Maternity Cohort. *JAMA Neurology*, *73*(5), 515–519. https://doi.org/10.1001/jamaneurol.2015.4800

Munger, K. L., Bentzen, J., Laursen, B., Stenager, E., Koch-Henriksen, N., Sørensen, T. I. A., & Baker, J. L. (2013). Childhood body mass index and multiple sclerosis risk: a long-term cohort study. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *19*(10), 1323–1329. https://doi.org/10.1177/1352458513483889

Munger, K., Zhang, S. M., O'Reilly, E., Hernán, M. A., Olek, M., Willett, W., & Ascherio, A. (2004). Vitamin D intake and incidence of multiple sclerosis. *Neurology*, *62*, 60–65. https://doi.org/10.1212/01.WNL.0000101723.79681.38

Munk Nielsen, N., Corn, G., Frisch, M., Stenager, E., Koch-Henriksen, N., Wohlfahrt, J., Magyari, M., & Melbye, M. (2019). Multiple sclerosis among first- and second-generation immigrants in Denmark: a population-based cohort study. *Brain : A Journal of Neurology*, *142*(6), 1587–1597. https://doi.org/10.1093/brain/awz088

Murtonen, A., Kurki, S., Hänninen, K., Soilu-Hänninen, M., & Sumelahti, M.-L. (2018). Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections. *Multiple Sclerosis and Related Disorders*, *19*. https://doi.org/10.1016/j.msard.2017.10.019

Nälsén, C., Becker, W., Pearson, M., Ridefelt, P., Lindroos, A. K., Kotova, N., & Mattisson, I. (2020). Vitamin D status in children and adults in Sweden: dietary intake and 25-hydroxyvitamin D concentrations in children aged 10-12 years and adults aged 18-80 years. *Journal of Nutritional Science*, *9*, e47–e47. https://doi.org/10.1017/jns.2020.40

Nielsen, N. M., Harpsøe, M., Simonsen, J., Stenager, E., Magyari, M., Koch-Henriksen, N., Baker, J. L., Hjalgrim, H., Frisch, M., & Bager, P. (2017). Age at Menarche and Risk of Multiple Sclerosis: A Prospective Cohort Study Based on the Danish National Birth Cohort. *American Journal of Epidemiology*, *185*(8), 712–719. https://doi.org/10.1093/aje/kww160

Nielsen, N. M., Westergaard, T., Frisch, M., Rostgaard, K., Wohlfahrt, J., Koch-Henriksen, N., Melbye, M., & Hjalgrim, H. (2006). Type 1 Diabetes and Multiple Sclerosis: A Danish Population-Based Cohort Study. *Archives of Neurology*, *63*(7), 1001–1004. https://doi.org/10.1001/archneur.63.7.1001

Nielsen, N. M., Westergaard, T., Rostgaard, K., Frisch, M., Hjalgrim, H., Wohlfahrt, J., Koch-Henriksen, N., & Melbye, M. (2005). Familial Risk of Multiple Sclerosis: A Nationwide Cohort Study. *American Journal of Epidemiology*, *162*(8), 774–778. https://doi.org/10.1093/aje/kwi280

NIMH Information Resource Center. (n.d.). *What is Prevalence?*

Novakova, L., Zetterberg, H., Sundström, P., Axelsson, M., Khademi, M., Gunnarsson, M., Malmeström, C., Svenningsson, A., Olsson, T., Piehl, F., Blennow, K., & Lycke, J. (2017). Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. *Neurology*, *89*(22), 2230–2237. https://doi.org/10.1212/WNL.0000000000004683

Official Statistics Finland. (2023). *Tobacco statistics*. https://www.stat.fi/en/statistics/tupk

O'Gorman, C., Lin, R., Stankovich, J., & Broadley, S. A. (2013). Modelling Genetic Susceptibility to Multiple Sclerosis with Family Data. *Neuroepidemiology*, *40*(1), 1–12. https://doi.org/10.1159/000341902

Ortiz, G. G., Pacheco-Moisés, F. P., Macías-Islas, M. Á., Flores-Alvarado, L. J., Mireles-Ramírez, M. A., González-Renovato, E. D., Hernández-Navarro, V. E., Sánchez-López, A. L., & Alatorre-Jiménez, M. A. (2014). Role of the Blood–Brain Barrier in Multiple Sclerosis. *Archives of Medical Research*, *45*(8), 687–697. https://doi.org/https://doi.org/10.1016/j.arcmed.2014.11.013

Orton, S.-M., Herrera, B. M., Yee, I. M., Valdar, W., Ramagopalan, S. V, Sadovnick, A. D., & Ebers, G. C. (2006). Sex ratio of multiple sclerosis in Canada: a longitudinal study. *The Lancet Neurology*, *5*(11), 932–936. https://doi.org/https://doi.org/10.1016/S1474-4422(06)70581-6

Orton, S.-M., Wald, L., Confavreux, C., Vukusic, S., Krohn, J. P., Ramagopalan, S. V, Herrera, B. M., Sadovnick, A. D., & Ebers, G. C. (2011). Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology*, *76*(5), 425–431. https://doi.org/10.1212/WNL.0b013e31820a0a9f

Ostkamp, P., Salmen, A., Pignolet, B., Görlich, D., Andlauer, T. F. M., Schulte-Mecklenbeck, A., Gonzalez-Escamilla, G., Bucciarelli, F., Gennero, I., Breuer, J., Antony, G., Schneider-Hohendorf, T., Mykicki, N., Bayas, A., Then Bergh, F., Bittner, S., Hartung, H.-P., Friese, M. A., Linker, R. A., … Network, G. C. N. M. S. (KKNMS) and the B. (2021). Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(1), e2018457118. https://doi.org/10.1073/pnas.2018457118

Paavonen, T., Andersson, L. C., & Adlercreutz, H. (1981). Sex hormone regulation of in vitro immune response. Estradiol enhances human B cell maturation via inhibition of suppressor T cells in pokeweed mitogen-stimulated cultures. *Journal of Experimental Medicine*, *154*(6), 1935–1945. https://doi.org/10.1084/jem.154.6.1935

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. *Annals of Epidemiology*, *21*(7), 536–542. https://doi.org/10.1016/j.annepidem.2011.03.001

Palladino, R., Marrie, R. A., Majeed, A., & Chataway, J. (2020). Evaluating the Risk of Macrovascular Events and Mortality Among People With Multiple Sclerosis in England. *JAMA Neurology*, *77*(7), 820–828. https://doi.org/10.1001/jamaneurol.2020.0664

Pfleger, C. C. H., Flachs, E. M., & Koch-Henriksen, N. (2010). Social consequences of multiple sclerosis. Part 2. Divorce and separation: a historical prospective cohort study. *Multiple Sclerosis Journal*, *16*(7), 878–882. https://doi.org/10.1177/1352458510370978

Pirttisalo, A.-L., Soilu-Hänninen, M., & Sipilä, J. O. T. (2019). Multiple sclerosis epidemiology in Finland: Regional differences and high incidence. *Acta Neurologica Scandinavica*, *139*(4), 353–359. https://doi.org/10.1111/ane.13057

Pirttisalo, A.-L., Soilu-Hänninen, M., Sumelahti, M.-L., Krökki, O., Murtonen, A., Hänninen, K., & Sipilä, J. O. T. (2020). Changes in multiple sclerosis epidemiology in Finland over five decades. *Acta Neurologica Scandinavica*, *142*(3). https://doi.org/10.1111/ane.13295

Pitzalis, M., Zavattari, P., Murru, R., Deidda, E., Zoledziewska, M., Murru, D., Moi, L., Motzo, C., Orrù, V., Costa, G., Solla, E., Fadda, E., Schirru, L., Melis, M. C., Lai, M., Mancosu, C., Tranquilli, S., Cuccu, S., Rolesu, M., … Cucca, F. (2008). Genetic loci linked to Type 1 Diabetes and Multiple Sclerosis families in Sardinia. *BMC Medical Genetics*, *9*(1), 3. https://doi.org/10.1186/1471-2350-9-3

Polick, C. S., Rubenstein, D., Shah, S., Beckham, J. C., Calhoun, P. S., & Noonan, D. (2023). Addressing Smoking in Persons With Multiple Sclerosis: State of the Science and Need for a Targeted Intervention. *Nicotine & Tobacco Research*, ntad159. https://doi.org/10.1093/ntr/ntad159

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F. D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A. J., Waubant, E., Weinshenker, B., & Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*, *69*(2), 292–302. https://doi.org/https://doi.org/10.1002/ana.22366

Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H.-P., Kappos, L., Lublin, F. D., Metz, L. M., McFarland, H. F., O'Connor, P. W., Sandberg-Wollheim, M., Thompson, A. J., Weinshenker, B. G., & Wolinsky, J. S. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald

Criteria." *Annals of Neurology*, *58*(6), 840–846. https://doi.org/https://doi.org/10.1002/ana.20703

Ponsonby, A.-L., Lucas, R. M., van der Mei, I. A., Dear, K., Valery, P. C., Pender, M. P., Taylor, B. V, Kilpatrick, T. J., Coulthard, A., Chapman, C., Williams, D., McMichael, A. J., & Dwyer, T. (2012). Offspring number, pregnancy, and risk of a first clinical demyelinating event. *Neurology*, *78*(12), 867 LP – 874. https://doi.org/10.1212/WNL.0b013e31824c4648

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Silberberg, D. H., & Tourtellotte, W. W. (1983). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Annals of Neurology*, *13*(3), 227–231. https://doi.org/https://doi.org/10.1002/ana.410130302

Pucci, E., Giuliani, G., Solari, A., Simi, S., Minozzi, S., Di Pietrantonj, C., & Galea, I. (2011). Natalizumab for relapsing remitting multiple sclerosis. *Cochrane Database of Systematic Reviews*, *10*. https://doi.org/10.1002/14651858.CD007621.pub2

Purmonen, T., Hakkarainen, T., Tervomaa, M., & Ruutiainen, J. (2020). Impact of multiple sclerosis phenotypes on burden of disease in Finland. *Journal of Medical Economics*, *23*(2), 156–165. https://doi.org/10.1080/13696998.2019.1682004

Puthenparampil, M., Perini, P., Bergamaschi, R., Capobianco, M., Filippi, M., & Gallo, P. (2022). Multiple sclerosis epidemiological trends in Italy highlight the environmental risk factors. *Journal of Neurology*, *269*(4), 1817–1824. https://doi.org/10.1007/s00415-021-10782-5

Qureshi, D., Tanuseputro, P., Perez, R., Pond, G. R., & Seow, H.-Y. (2019). Early initiation of palliative care is associated with reduced late-life acute-hospital use: A population-based retrospective cohort study. *Palliative Medicine*, *33*(2), 150–159. https://doi.org/10.1177/0269216318815794

Ramagopalan, S. V, Heger, A., Berlanga, A. J., Maugeri, N. J., Lincoln, M. R., Burrell, A., Handunnetthi, L., Handel, A. E., Disanto, G., Orton, S.-M., Watson, C. T., Morahan, J. M., Giovannoni, G., Ponting, C. P., Ebers, G. C., & Knight, J. C. (2010). A ChIP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution. *Genome Research*, *20*(10), 1352–1360. https://doi.org/10.1101/gr.107920.110

Raulio, S., Tapanainen, H., Valsta, L., Jääskeläinen, T., Virtanen, S., & Erlund, I. (2021). FinRavinto 2017 -tuloksia: D-vitamiinin saanti ja seerumipitoisuus aikuisilla. *Lääkärilehti*, *76*(44), 2578–2584.

Ribbons, K., Lea, R., Tiedeman, C., Mackenzie, L., & Lechner-Scott, J. (2016). Ongoing increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: A 50-year study. *Multiple Sclerosis Journal*, *23*(8), 1063–1071. https://doi.org/10.1177/1352458516671819

Rinne, U., Panelius, M., Kivalo, E., Hokkanen, E., & Meurman, T. (1968). Multiple Sclerosis in Finland. *Acta Neurologica Scandinavica*, *44*, 631–642.

Río, J., Castilló, J., Rovira, A., Tintoré, M., Sastre-Garriga, J., Horga, A., Nos, C., Comabella, M., Aymerich, X., & Montalbán, X. (2009). Measures in the first year of therapy predict the response to interferon β in MS. *Multiple Sclerosis Journal*, *15*(7), 848–853. https://doi.org/10.1177/1352458509104591

Roifman, I., Beck, P. L., Anderson, T. J., Eisenberg, M. J., & Genest, J. (2011). Chronic Inflammatory Diseases and Cardiovascular Risk: A Systematic Review. *Canadian Journal of Cardiology*, *27*(2), 174–182. https://doi.org/10.1016/j.cjca.2010.12.040

Rojas, J. I., Patrucco, L., MIguez, J., Sinay, V., Cassara, F. P., Cáceres, F., Liguori, N. F., Saladino, M. L., Deri, N., Jaacks, G., Marcilla, M. P., Arrigoni, M. I., Correale, J., Fiol, M., Ysrraelit, M. C., Carrá, A., Curbelo, M. C., Martinez, A., Steinberg, J., … Cristiano, E. (2017). Gender ratio trends over time in multiple sclerosis patients from Argentina. *Journal of Clinical Neuroscience*, *38*, 84–86. https://doi.org/https://doi.org/10.1016/j.jocn.2016.12.030

Rosati, G. (2001). The prevalence of multiple sclerosis in the world: an update. *Neurological Sciences*, *22*(2), 117–139. https://doi.org/10.1007/s100720170011

Rosenwax, L., Spilsbury, K., Arendts, G., McNamara, B., & Semmens, J. (2015). Community-based palliative care is associated with reduced emergency department use by people with dementia in their last year of life: A retrospective cohort study. *Palliative Medicine*, *29*(8), 727–736. https://doi.org/10.1177/0269216315576309

Roshanisefat, H., Bahmanyar, S., Hillert, J., Olsson, T., & Montgomery, S. (2014). Multiple sclerosis clinical course and cardiovascular disease risk - Swedish cohort study. *European Journal of Neurology*, *21*(11), 1353-e88. https://doi.org/10.1111/ene.12518

Rosso, M., & Chitnis, T. (2020). Association Between Cigarette Smoking and Multiple Sclerosis: A Review. *JAMA Neurology*, *77*(2), 245–253. https://doi.org/10.1001/jamaneurol.2019.4271

Rotstein, D. L., Chen, H., Wilton, A. S., Kwong, J. C., Marrie, R. A., Gozdyra, P., Krysko, K. M., Kopp, A., Copes, R., & Tu, K. (2018). Temporal trends in multiple sclerosis prevalence and incidence in a large population. *Neurology*, *90*(16), e1435–e1441. https://doi.org/10.1212/WNL.0000000000005331

Rubicz, R., Yolken, R., Drigalenko, E., Carless, M. A., Dyer, T. D., Bauman, L., Melton, P. E., Kent Jr., J. W., Harley, J. B., Curran, J. E., Johnson, M. P., Cole, S. A., Almasy, L., Moses, E. K., Dhurandhar, N. V, Kraig, E., Blangero, J., Leach, C. T., & Göring, H. H. H. (2013). A Genome-Wide Integrative Genomic Study Localizes Genetic Factors Influencing Antibodies against Epstein-Barr Virus Nuclear Antigen 1 (EBNA-1). *PLOS Genetics*, *9*(1), e1003147.

Ruutiainen, J., Viita, A.-M., 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. *Journal of Medical Economics*, *19*(1), 21–33. https://doi.org/10.3111/13696998.2015.1086362

Sadovnick, A. D., Yee, I. M., Criscuoli, M., & DeLuca, G. C. (2021). Genes and environment in multiple sclerosis: Impact of temporal changes in the sex ratio on recurrence risks. *Multiple Sclerosis Journal*, 13524585211020220. https://doi.org/10.1177/13524585211020221

Salmela, E. (2012). *Genetic structure in Finland and Sweden: Aspects of population history and gene mapping*. University of Helsinki.

Salmela, E. (2023). Mistä suomalaisten perimä on peräisin? *Finnish Medical Journal Duodecim*, *139*(16), 1247–1255.

Sarasoja, T., Wikström, J., Paltamaa, J., Hakama, M., & Sumelahti, M.-L. (2004). Occurrence of multiple sclerosis in central Finland: a regional and temporal comparison during 30 years. *Acta Neurologica Scandinavica*, *110*(5), 331–336. https://doi.org/10.1111/j.1600-0404.2004.00326.x

Sbarra, D. A., Law, R. W., & Portley, R. M. (2011). Divorce and Death: A Meta-Analysis and Research Agenda for Clinical, Social, and Health Psychology. *Perspectives on Psychological Science*, *6*(5), 454–474. https://doi.org/10.1177/1745691611414724

Scalfari, A., Neuhaus, A., Daumer, M., Muraro, P. A., & Ebers, G. C. (2014). Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *85*(1), 67 LP – 75. https://doi.org/10.1136/jnnp-2012-304333

Schumacher, G. A., Beebe, G., Kibler, R. F., Kurland, L. T., Kurtzke, J. F., McDowell, F., Nagler, B., Sibley, W. A., Tourtellotte, W. W., & Willmon, T. L. (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. *Annals of the New York Academy of Sciences*, *122*(1), 552–568. https://doi.org/https://doi.org/10.1111/j.1749-6632.1965.tb20235.x

Seeber, A. A., Pols, A. J., Hijdra, A., Grupstra, H. F., Willems, D. L., & de Visser, M. (2019). Advance care planning in progressive neurological diseases: lessons from ALS. *BMC Palliative Care*, *18*(1), 50. https://doi.org/10.1186/s12904-019-0433-6

Serafini, B., Rosicarelli, B., Veroni, C., Mazzola, G. A., & Aloisi, F. (2019). Epstein-Barr Virus-Specific CD8 T Cells Selectively Infiltrate the Brain in Multiple Sclerosis and Interact Locally with Virus-Infected Cells: Clue for a Virus-Driven Immunopathological Mechanism. *Journal of Virology*, *93*(24), e00980-19. https://doi.org/10.1128/JVI.00980-19

Shemeikka, R., Rinne, H., Saares, A., Murto, J., & R, K. (2014). Alueelliset erot nuorten aikuisten terveydessä ja elintavoissa Suomessa 2012–2013. *Finnish Institute for Health and Welfare*. https://urn.fi/URN:ISBN:978-952-302-209-6

Simpson, S., Wang, W., Otahal, P., Blizzard, L., van der Mei, I. A. F., & Taylor, B. V. (2019). Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *90*(11), 1193 LP – 1200. https://doi.org/10.1136/jnnp-2018-320189

Smestad, C., Sandvik, L., & Celius, E. G. (2009). Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *15*(11), 1263–1270. https://doi.org/10.1177/1352458509107010

Solari, A., Giordano, A., Patti, F., Grasso, M. G., Confalonieri, P., Palmisano, L., Ponzio, M., Borreani, C., Rosato, R., Veronese, S., Zaratin, P., Battaglia, M. A., & Project, P. (2018). Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *24*(5), 663–674. https://doi.org/10.1177/1352458517704078

Solari, A., Giordano, A., Sastre-Garriga, J., Köpke, S., Rahn, A. C., Kleiter, I., Aleksovska, K., Battaglia, M. A., Bay, J., Copetti, M., Drulovic, J., Kooij, L., Mens, J., Meza Murillo, E. R., Milanov, I., Milo, R., Pekmezovic, T., Vosburgh, J., Silber, E., … Oliver, D. (2020). EAN guideline on palliative care of people with severe, progressive multiple sclerosis. *European Journal of Neurology*, *27*(8), 1510–1529. https://doi.org/10.1111/ene.14248

Sormani, M. P., & Bruzzi, P. (2013). MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *The Lancet. Neurology*, *12*(7), 669–676. https://doi.org/10.1016/S1474-4422(13)70103-0

Spilsbury, K., Rosenwax, L., Arendts, G., & Semmens, J. B. (2017). The impact of community-based palliative care on acute hospital use in the last year of life is modified by time to death, age and underlying cause of death. A population-based retrospective cohort study. *PloS One*, *12*(9), e0185275–e0185275. https://doi.org/10.1371/journal.pone.0185275

Statistics Finland. (2023). *Official Statistics of Finland (OSF): Population structure*.

Strupp, J., Voltz, R., & Golla, H. (2016). Opening locked doors: Integrating a palliative care approach into the management of patients with severe multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *22*(1), 13–18. https://doi.org/10.1177/1352458515608262

Sumelahti, M. L., Tienari, P. J., Wikström, J., Palo, J., & Hakama, M. (2001). Increasing prevalence of multiple sclerosis in Finland. *Acta Neurologica Scandinavica*, *103*(3), 153–158. https://doi.org/10.1034/j.1600-0404.2001.103003153.x

Sumelahti, M. L., Tienari, P. J., Wikström, J., Salminen, T. M., & Hakama, M. (2002). Survival of multiple sclerosis in Finland between 1964 and 1993. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *8*(4), 350–355. https://doi.org/10.1191/1352458502ms811oa

Sumelahti, M.-L., Hakama, M., Elovaara, I., & Pukkala, E. (2010). Causes of death among patients with multiple sclerosis. *Multiple Sclerosis Journal*, *16*(12), 1437–1442. https://doi.org/10.1177/1352458510379244

Sumelahti, M.-L., Holmberg, M. H. A., 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. *Multiple Sclerosis International*, *2014*, 186950. https://doi.org/10.1155/2014/186950

Sumelahti, M.-L., Tienari, P. J., Hakama, M., & Wikström, J. (2003). Multiple sclerosis in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*(1), 25–28. https://doi.org/10.1136/jnnp.74.1.25

Sumelahti, M.-L., Tienari, P. J., Wikstrom, 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. https://libproxy.tuni.fi/login?url=https://www.proquest.com/scholarly-journals/regional-temporal-variation-incidence-multiple/docview/232975951/se-2?accountid=14242

Svenningsson, A., Salzer, J., Vågberg, M., Sundström, P., & Svenningsson, A. (2015). Increasing prevalence of multiple sclerosis in Västerbotten County of Sweden. *Acta Neurologica Scandinavica*, *132*(6), 389–394. https://doi.org/10.1111/ane.12408

Taka, A.-M., But, A., Lempainen, J., Vatanen, T., Härkönen, T., Ilonen, J., & Knip, M. (2023). Finnish children carrying the high-risk HLA genotype have a 45-fold increased risk of type 1 diabetes compared to peers with neutral or protective genotypes. *Diabetes Research and Clinical Practice*, *197*. https://doi.org/10.1016/j.diabres.2023.110256

Taylor, B. V, Pearson, J. F., Clarke, G., Mason, D. F., Abernethy, D. A., Willoughby, E., & Sabel, C. (2010). MS prevalence in New Zealand, an ethnically and latitudinally diverse country. *Multiple Sclerosis Journal*, *16*(12), 1422–1431. https://doi.org/10.1177/1352458510379614

Tedeholm, H., Lycke, J., Skoog, B., Lisovskaja, V., Hillert, J., Dahle, C., Fagius, J., Fredrikson, S., Landtblom, A.-M., Malmeström, C., Martin, C., Piehl, F., Runmarker, B., Stawiarz, L., Vrethem, M., Nerman, O., & Andersen, O. (2012). Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. *Multiple Sclerosis Journal*, *19*(6), 765–774. https://doi.org/10.1177/1352458512463764

Tettey, P., Simpson, S. J., Taylor, B. V, & van der Mei, I. A. F. (2015). The co-occurrence of multiple sclerosis and type 1 diabetes: shared aetiologic features and clinical implication for MS aetiology. *Journal of the Neurological Sciences*, *348*(1–2), 126–131. https://doi.org/10.1016/j.jns.2014.11.019

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet. Neurology*, *17*(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2

Thompson, A. J., Baranzini, S. E., Geurts, J., Hemmer, B., & Ciccarelli, O. (2018). Multiple sclerosis. *The Lancet*, *391*(10130), 1622–1636. https://doi.org/https://doi.org/10.1016/S0140-6736(18)30481-1

Thormann, A., Magyari, M., Koch-Henriksen, N., Laursen, B., & Sørensen, P. S. (2016). Vascular comorbidities in multiple sclerosis: a nationwide study from Denmark. *Journal of Neurology*, *263*(12), 2484–2493. https://doi.org/10.1007/s00415-016-8295-9

Thormann, A., Sørensen, P. S., Koch-Henriksen, N., Laursen, B., & Magyari, M. (2017). Comorbidity in multiple sclerosis is associated with diagnostic delays and increased mortality. *Neurology*, *89*(16), 1668–1675. https://doi.org/10.1212/WNL.0000000000004508

Thormann, A., Sørensen, P. S., Koch-Henriksen, N., Thygesen, L. C., Laursen, B., & Magyari, M. (2017). Chronic comorbidity in multiple sclerosis is associated with lower incomes and dissolved intimate relationships. *European Journal of Neurology*, *24*(6), 825–834. https://doi.org/10.1111/ene.13297

Tienari, P. J., Sumelahti, M.-L., Rantamäki, T., & Wikström, J. (2004). Multiple sclerosis in western Finland: evidence for a founder effect. *Clinical Neurology and Neurosurgery*, *106*(3), 175–179. https://doi.org/https://doi.org/10.1016/j.clineuro.2004.02.009

Trojano, M., Lucchese, G., Graziano, G., Taylor, B. V, Simpson Jr, S., Lepore, V., Grand'Maison, F., Duquette, P., Izquierdo, G., Grammond, P., Amato, M. P., Bergamaschi, R., Giuliani, G., Boz, C., Hupperts, R., Van Pesch, V., Lechner-Scott, J., Cristiano, E., Fiol, M., … Butzkueven, H. (2012). Geographical Variations in Sex Ratio Trends over Time in Multiple Sclerosis. *PLOS ONE*, *7*(10), e48078. https://doi.org/10.1371/journal.pone.0048078

University of California, Cree, B. A. C., Hollenbach, J. A., Bove, R., Kirkish, G., Sacco, S., Caverzasi, E., Bischof, A., Gundel, T., Zhu, A. H., Papinutto, N., Stern, W. A., Bevan, C., Romeo, A., Goodin, D. S., Gelfand, J. M., Graves, J., Green, A. J., Wilson, M. R., … Hauser, S. L. (2019). Silent progression in disease activity–free relapsing multiple sclerosis. *Annals of Neurology*, *85*(5), 653–666. https://doi.org/https://doi.org/10.1002/ana.25463

Urru, S. A. M., Antonelli, A., & Sechi, G. M. (2019). Prevalence of multiple sclerosis in Sardinia: A systematic cross-sectional multi-source survey. *Multiple Sclerosis Journal*, *26*(3), 372–380. https://doi.org/10.1177/1352458519828600

van den Elsen, P. J., van Eggermond, M. C. J. A., Puentes, F., van der Valk, P., Baker, D., & Amor, S. (2014). The epigenetics of multiple sclerosis and other related disorders. *Multiple Sclerosis and Related Disorders*, *3*(2), 163–175. https://doi.org/10.1016/j.msard.2013.08.007

Vandebergh, M., & Goris, A. (2020). Smoking and multiple sclerosis risk: a Mendelian randomization study. *Journal of Neurology*, *267*(10), 3083–3091. https://doi.org/10.1007/s00415-020-09980-4

Varhaug, K. N., Torkildsen, Ø., Myhr, K.-M., & Vedeler, C. A. (2019). Neurofilament Light Chain as a Biomarker in Multiple Sclerosis. *Frontiers in Neurology*, *10*, 338. https://doi.org/10.3389/fneur.2019.00338

Vartiainen, E. (2018). The North Karelia Project: Cardiovascular disease prevention in Finland. *Global Cardiology Science & Practice*, *2018*(2), 13. https://doi.org/10.21542/gcsp.2018.13

Veronese, S., Gallo, G., Valle, A., Cugno, C., Chiò, A., Calvo, A., Cavalla, P., Zibetti, M., Rivoiro, C., & Oliver, D. J. (2017). Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: NE-PAL, a pilot randomised controlled study. *BMJ Supportive &Amp; Palliative Care*, *7*(2), 164 LP – 172. https://doi.org/10.1136/bmjspcare-2014-000788

Veroni, C., & Aloisi, F. (2021). The CD8 T Cell-Epstein-Barr Virus-B Cell Trialogue: A Central Issue in Multiple Sclerosis Pathogenesis. *Frontiers in Immunology*, *12*. https://www.frontiersin.org/articles/10.3389/fimmu.2021.665718

Visser, E. M., Wilde, K., Wilson, J. F., Yong, K. K., & Counsell, C. E. (2012). A new prevalence study of multiple sclerosis in Orkney, Shetland and Aberdeen city. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *83*(7), 719 LP – 724. https://doi.org/10.1136/jnnp-2011-301546

Visser, E., Milne, D., Collacott, I., McLernon, D., Counsell, C., & Vickers, M. (2014). The epidemiology of infectious mononucleosis in Northern Scotland: a decreasing incidence and winter peak. *BMC Infectious Diseases*, *14*(1), 151. https://doi.org/10.1186/1471-2334-14-151

Voskuhl, R. R. (2020). The effect of sex on multiple sclerosis risk and disease progression. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *26*(5), 554–560. https://doi.org/10.1177/1352458519892491

Voskuhl, R. R., Patel, K., Paul, F., Gold, S. M., Scheel, M., Kuchling, J., Cooper, G., Asseyer, S., Chien, C., Brandt, A. U., Meyer, C. E., & MacKenzie-Graham, A. (2020). Sex differences in brain atrophy in multiple sclerosis. *Biology of Sex Differences*, *11*(1), 49. https://doi.org/10.1186/s13293-020-00326-3

Vuorela, N., Saha, M.-T., & Salo, M. K. (2011). Change in prevalence of overweight and obesity in Finnish children – comparison between 1974 and 2001. *Acta Paediatrica*, *100*(1), 109–115. https://doi.org/https://doi.org/10.1111/j.1651-2227.2010.01980.x

Wallin, M. T., Culpepper, W. J., Campbell, J. D., Nelson, L. M., Langer-Gould, A., Marrie, R. A., Cutter, G. R., Kaye, W. E., Wagner, L., Tremlett, H., Buka, S. L., Dilokthornsakul, P., Topol, B., Chen, L. H., & LaRocca, N. G. (2019). The prevalence of MS in the United States. *Neurology*, *92*(10), e1029 LP-e1040. https://doi.org/10.1212/WNL.0000000000007035

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., Robertson, N., La Rocca, N., Uitdehaag, B., van der Mei, I., Wallin, M., Helme, A., Angood Napier, C., Rijke, N., & Baneke, P. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *26*(14), 1816–1821. https://doi.org/10.1177/1352458520970841

Wändell, P., Fredrikson, S., Carlsson, A. C., Li, X., Sundquist, J., & Sundquist, K. (2020). Multiple sclerosis among first- and second-generation immigrant groups in Sweden. *Acta Neurologica Scandinavica*, *142*(4), 339–349. https://doi.org/10.1111/ane.13314

Wattjes, M. P., Steenwijk, M. D., & Stangel, M. (2015). MRI in the Diagnosis and Monitoring of Multiple Sclerosis: An Update. *Clinical Neuroradiology*, *25*(2), 157–165. https://doi.org/10.1007/s00062-015-0430-y

Weinstock-Guttman, B., Sormani, M. P., & Repovic, P. (2022). Predicting Long-term Disability in Multiple Sclerosis: A Narrative Review of Current Evidence and Future Directions. *International Journal of MS Care*, *24*(4), 184–188. https://doi.org/10.7224/1537-2073.2020-114

Wens, I., Dalgas, U., Stenager, E., & Eijnde, B. O. (2013). Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis – a systematic review. *Multiple Sclerosis Journal*, *19*(12), 1556–1564. https://doi.org/10.1177/1352458513504252

Westerlind, H., Boström, I., Stawiarz, L., Landtblom, A.-M., Almqvist, C., & Hillert, J. (2014). New data identify an increasing sex ratio of multiple sclerosis in Sweden. *Multiple Sclerosis Journal*, *20*(12), 1578–1583. https://doi.org/10.1177/1352458514530021

Westerlind, H., Ramanujam, R., Uvehag, D., Kuja-Halkola, R., Boman, M., Bottai, M., Lichtenstein, P., & Hillert, J. (2014). Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. *Brain : A Journal of Neurology*, *137*(Pt 3), 770–778. https://doi.org/10.1093/brain/awt356

Whitacre, C. C., Reingold, S. C., & O'Looney, P. A. (1999). A Gender Gap in Autoimmunity. *Science*, *283*(5406), 1277–1278.

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 Neurologica Scandinavica*, *51*(2), 85–98. https://doi.org/10.1111/j.1600-0404.1975.tb01362.x

Wucherpfennig, K. W., & Strominger, J. L. (1995). Molecular mimicry in T cell-mediated autoimmunity: Viral peptides activate human T cell clones specific for myelin basic protein. *Cell*, *80*(5), 695–705. https://doi.org/10.1016/0092-8674(95)90348-8

Xu, Y., Hiyoshi, A., Smith, K. A., Piehl, F., Olsson, T., Fall, K., & Montgomery, S. (2021). Association of Infectious Mononucleosis in Childhood and Adolescence With Risk for a Subsequent Multiple Sclerosis Diagnosis Among Siblings. *JAMA Network Open*, *4*(10), e2124932–e2124932. https://doi.org/10.1001/jamanetworkopen.2021.24932

Ysrraelit, M. C., & Correale, J. (2019). Impact of sex hormones on immune function and multiple sclerosis development. *Immunology*, *156*(1), 9–22. https://doi.org/10.1111/imm.13004

Zhang, T., Tremlett, H., Leung, S., Zhu, F., Kingwell, E., Fisk, J. D., Bhan, V., Campbell, T. L., Stadnyk, K., & Yu, B. N. (2016). Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis. *Neurology*, *86*(14), 1287–1295.

Zhang, Y., Salter, A., Jin, S., Culpepper, W. J., Cutter, G. R., Wallin, M., & Stuve, O. (2021). Disease-modifying therapy prescription patterns in people with multiple sclerosis by age. *Therapeutic Advances in Neurological Disorders*, *14*, 17562864211006500. https://doi.org/10.1177/17562864211006499

Zrzavy, T., Hametner, S., Wimmer, I., Butovsky, O., Weiner, H. L., & Lassmann, H. (2017). Loss of "homeostatic" microglia and patterns of their activation in active multiple sclerosis. *Brain : A Journal of Neurology*, *140*(7), 1900–1913. https://doi.org/10.1093/brain/awx113

ORIGINAL PUBLICATIONS

PUBLICATION I

Increased Female MS Incidence and Differences in Gender-Specific Risk in Medium- and High-Risk Regions in Finland from 1981–2010

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Review Article

Increased Female MS Incidence and Differences in Gender-Specific Risk in Medium- and High-Risk Regions in Finland from 1981–2010

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Background. MS incidence has increased among females, suggesting the presence of environmental effect. *Object*. Regional differences and temporal changes in gender-specific MS incidence were studied in Finland. *Methods*. Cases from Jan 1, 1981 to Dec 31, 2010 in Pirkanmaa, Seinäjoki and Vaasa districts were included. The standardized incidence rates (SIR), incidences per 10^5 person years with 95% confidence intervals (CI), and female-to-male ratios (F/M) were determined by district. *Results*. 1617 cases were included. Compared to Pirkanmaa, the MS risk was 1.9-fold (95% CI: 1.7–2.0) greater in Seinäjoki and 1.2-fold (95% CI: 1.1–1.4) in Vaasa, and the risk was high for both genders. The incidence trend stabilized in Seinäjoki and Vaasa, accompanied by an increase in the F/M ratio. A steady increase in Pirkanmaa was accompanied by a high F/M ratio. *Conclusion*. A high female preponderance accompanied a general increase in incidence since the 1990s, suggesting the influence of environmental factors. In high-risk districts, increased MS risk prevailed in both genders. High risk reflects both genetic and environmental effects. These effects may be shared with autoimmune diseases such as type 1 diabetes mellitus; the incidence of which follows MS in Finland. Population-based case-control studies are needed to identify these factor effects.

1. Introduction

MS incidence has increased, particularly among females [1–4], indicating the influence of environmental factors. The integration of magnetic resonance imaging (MRI) in diagnostic criteria since the 1990s and progress in immunomodulatory drug treatments have contributed to these increasing rates [5, 6].

Epidemiologically, MS is characterized by an uneven geographical distribution [7]. Studies performed since 1964 confirm this observation in Finland [8–10], which is located in Northern Europe between the latitudes 60 and 70°N. High-risk areas in the western districts, Seinäjoki and Vaasa, are characterized by an irregular incidence pattern, and an increased male risk was observed in Seinäjoki in 1979–1993 [10].

We aimed to analyze the gender-specific incidence in high- and medium-risk areas in 1981–2010 to make inferences on the etiological factors correlated with high-risk groups. The incidence in the former medium-risk area Pirkanmaa [8] is studied for the first time. Incidence is regarded as the most important indicator of disease frequency, and changes in incidence reflect environmental factors in genetically stable populations.

2. Materials and Methods

The districts examined in this study are shown in Figure 1. The total population in 2010 was 850630 [11]. The Pirkanmaa Central Hospital (population 485911) is one of five University hospitals in Finland. The Seinäjoki and Vaasa Central Hospitals serve populations of 198469 and 166250, respectively [11]. Both Seinäjoki and Vaasa are mainly rural districts, while Pirkanmaa is more urbanized, which is reflected in the age-structure and distribution of its populations.

From 1981 to 2010, the population increased by 19% in Pirkanmaa and 9% in Vaasa, while a 2% decrease was

reported in Seinäjoki. A 21% decrease in the age group 0–39 years was observed in Seinäjoki and Vaasa [11].

Neurological services were evenly distributed between the district hospitals. MS is diagnosed by neurologists in central or university hospitals in Finland [10]. CSF is a routine examination in MS diagnostics. MRI scans have been used in diagnostics from 1990 in Pirkanmaa and 1993 in Seinäjoki and Vaasa.

The National Institute for Health and Welfare and the local ethical standards committee approved the retrospective examination of identified patient records in the hospitals in this study.

Patients with multiple sclerosis in the health care districts of Pirkanmaa, Seinäjoki and Vaasa, including Jacobstad, were recruited from hospital registries from January 1, 1981 to December 31, 2010 according to multiple sclerosis or morbus demyelinans diagnoses and optic- or retrobulbar neuritis (340, 341, and 377 in the *International Classification of Diseases*, ICD versions 8 and 9, G35, G37, and H46 in ICD-10). The patient records were then examined by the authors (Markus Holmberg, Annukka Murtonen, and Marja-Liisa Sumelahti). Patient information was collected on the date, and the quality of the first symptoms and clinical findings were recorded. Confirmatory positive results at the time of diagnosis were obtained from patient records for MRI, cerebrospinal fluid (CSF), and evoked potentials (EP). The dates of the follow-up MRI results were also recorded. Patient cases were included in the analyses when fulfilling the criteria of clinically (CD) or laboratory supported definite (LSD) MS as previously described by Poser [12] during January 1, 1981 to December 31, 2010, and when the patients resided in the study districts at the year of diagnosis. The patient's residence was updated using a personalized identification number and the year of diagnosis at Statistics Finland.

The age-adjusted and gender-specific incidence per 10^5 person-years was calculated from January 1, 1981 to December 31, 2010 for three 10-year-periods (1981–1990, 1991–2000, and 2001–2010) with a 95% confidence interval (CI) by district. The incidence of the 5-year-periods did not change our overall conclusions (data not shown). Furthermore, to avoid chance variation, we used 10-year-periods in our calculations. Due to the small number of cases in the age-specific strata, indirect standardization [13] was used to study regional risk during 1981–2010. In this study, the standard population used was the Pirkanmaa population. The incidence rates in Pirkanmaa from 1981 to 2010 in each 10-year-age group were used to calculate the expected numbers of cases for both the Seinäjoki and Vaasa populations. The resulting expected number of cases was then compared to the actual observed numbers of cases in Seinäjoki and Vaasa, resulting in the standardized incidence rate (SIR), which was the ratio of observed and expected cases. The total and gender-specific SIRs with a 95% CI are presented.

3. Results

The patient characteristics of 1617 cases is shown in Table 1. The onset symptoms were evenly distributed (the district-specific figures are not shown), as were the total F/M ratio

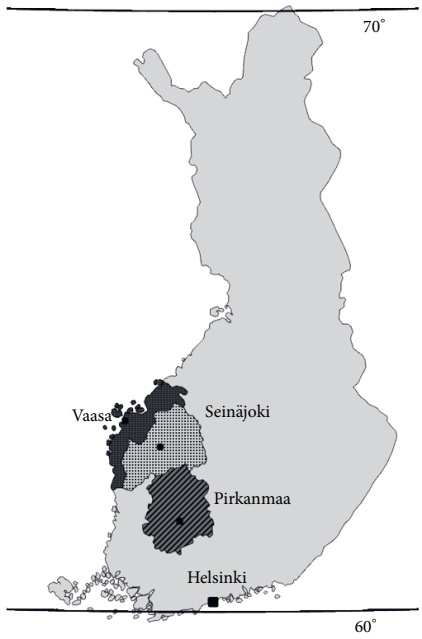

Figure 1: Map of Finland. Finland lies in Scandinavia, North Europe between latitudes 60–70°N. Gulf of Bothnia in northern most part of Baltic Sea limits the west coast. The total population was 5.4 million in 2010. The University Hospital District of Tampere is demarcated, and location of central hospitals and hospital districts in Pirkanmaa (oblique lines), Seinäjoki (dots), and Vaasa (dark grey) are pointed in the map.

(2.2), median age at onset (32.0), and age at diagnosis (37.0 years). The median diagnostic delay decreased from 4.0 years to 2.0 years (Chi-square test $P < 0.001$) during the study periods. Paraclinical studies in 10-year-periods are shown in Table 2. The CSF (including either the IgG index, immunoelectrophoresis, or both) was performed in 89–92% of the cases. The decreasing use of evoked potentials (27% to 19%) and the increasing use of MRI (36% to 98%) was observed during the follow-up evaluation. The second scan, which was used to study dissemination in time and space in 65% of the cases, was performed during the next 18 months after the first scan in 58% of the cases, 94% of which were positive for MS. The delay to the first MRI from the date of onset of symptoms was significantly decreased during the follow-up evaluation (Figure 2).

From January 1, 1981 to December 31, 2010, the age-adjusted incidence was 6.7×10^5 (95% CI: 6.2–7.2) in Pirkanmaa, 12.5×10^5 (95% CI: 11.5–13.5) in Seinäjoki, and 8.3×10^5 (95% CI: 7.4–9.2) in Vaasa. The SIR was 1.9 (95% CI: 1.7–2.0) in Seinäjoki and 1.2 (95% CI: 1.1–1.4) in Vaasa, compared to Pirkanmaa (SIR 1.0).

The incidence for 10-year-periods (1981–1990, 1991–2000, and 2001–2010) is shown in Table 3. A steady increase in Pirkanmaa (from 5.1 to 8.2) and a two-fold increase in both

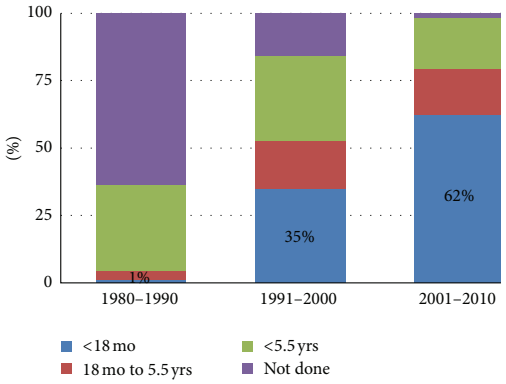

Figure 2: Percentage of performed MRI scans by time from disease onset among MS cases diagnosed between 1981 and 2010.

Table 1: Characteristics of MS cases in Pirkanmaa, Seinäjoki, and Vaasa during the period 1981–2010.

Number of cases, *n* (%)	
Total	1617
Male	512 (32)
Female	1105 (68)
F/M	2.2
Diagnosis using Poser, *n* (%)	
CDMS	60 (4)
CDMS + paraclinical	1223 (75)
LSDMS	75 (5)
LSDMS + paraclinical	259 (16)
Age, years	
At onset, median	32
At the time of diagnosis, median	37
Diagnostic delay, years	
Mean	4.6
Median	2.0
First symptoms by anatomic level, %	
Brainstem/cerebellum	25
Visual tract	22
Sensory	22
Medullary	19
Pyramidal tract above medulla	5
Other/UN	4
Multiple	3

Seinäjoki (from 7.1 to 14.7) and Vaasa (from 5.7 to 11.7) were observed. The female incidence was significantly higher in all age groups and in all districts. The male incidence decreased during the last decade in Vaasa and Seinäjoki. The F/M ratios remained stable in Pirkanmaa (2.5, 2.1, 2.2) and increased 1.3-fold (1.8, 1.9, and 2.3) in Seinäjoki and 1.6-fold (1.8, 2.1, and 2.8) in Vaasa.

The F/M ratios in the 10-year-age groups according to district are shown in Figure 3. The highest F/M ratio of 3.5 was

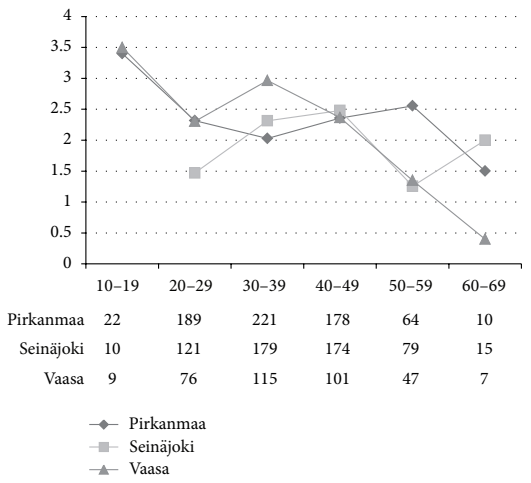

Figure 3: F/M-ratio by total number in 10-year-age groups among cases diagnosed during 1981–2010 in hospital districts of Pirkanmaa, Seinäjoki, and Vaasa. There were no men in the 10–19 group in Seinäjoki.

observed in the 10–19-year-age group. In Pirkanmaa, the ratio subsequently remained stable, whereas peaks were observed in Seinäjoki (age group: 30–49-years) and Vaasa (age group: 30–39-years).

Female risk values in Seinäjoki (SIR 1.8, 95% CI: 1.7–2.0) and Vaasa (1.5, 95% CI: 1.3–1.7) were similar and the age-specific incidence peaked at 30–39 years (Figure 4). Male risk in Seinäjoki was 2-fold compared to Pirkanmaa (SIR 2.00, 95% CI: 1.7–2.3) and the incidence was high in the large age group (20–59 year olds). In Vaasa, male risk (1.4, 95% CI: 1.2–1.7) peaked in the older age groups.

4. Discussion

Regional differences in MS epidemiology were among the earliest observations made in Finland [8–10]. Earlier observations on high-risk MS in Seinäjoki have also been confirmed here, because the 30-year-incidence rate of $12.5/10^5$ person-years in 2010 is the highest reported [8, 10]. The incidence was 8.3 and 6.7 in Vaasa and Pirkanmaa, respectively. However, the regional MS risk in Seinäjoki remains nearly two-fold (SIR 1.9) compared to Vaasa (1.2) and Pirkanmaa (1.0) in Finland. The southern and urbanized Uusimaa district, which locates the capital city Helsinki, and Pirkanmaa (formerly Häme) are regarded as regions with similar and standard MS risk in Finland [8, 10]. This perception holds true, because an incidence of 5.1 in Uusimaa was reported in 1993 [10], which was similar to the rate of 5.1 in Pirkanmaa in 1981–1990.

Consistent with these findings, contemporary studies performed in Ireland and Wales [2, 14] revealed an approximately 1.5-fold increase in the F/M ratio, observed also in

Table 2: Paraclinical test results among cases with definite MS diagnosis by 10-year periods from 1981–2010.

Hospital district	1981–1990				1991–2000				2001–2010			
	Cases	CSF	EP	MRI	Cases	CSF	EP	MRI	Cases	CSF	EP	MRI
Pirkanmaa	167	152	88	72	219	209	98	199	298	282	50	292
Percentage performed		91%	53%	43%		95%	45%	91%		95%	17%	98%
Positive findings (%)		150 (99%)	73 (83%)	67 (93%)		192 (92%)	79 (81%)	176 (88%)		255 (90%)	38 (76%)	267 (91%)
Seinäjoki	123	106	7	36	237	215	69	189	218	200	70	213
Percentage performed		86%	6%	29%		91%	29%	80%		92%	32%	98%
Positive findings (%)		97 (92%)	5 (71%)	32 (89%)		194 (90%)	48 (70%)	176 (93%)		173 (87%)	50 (71%)	196 (92%)
Vaasa	70	63	1	21	142	126	9	117	143	126	6	140
Percentage performed		90%	1%	30%		89%	6%	82%		88%	4%	98%
Positive findings (%)		55 (87%)	1 (100%)	21 (100%)		103 (82%)	6 (67%)	109 (93%)		102 (81%)	5 (83%)	129 (92%)
Total	360	321	96	129	598	550	176	505	659	608	126	645
Percentage performed		89%	27%	36%		92%	29%	84%		92%	19%	98%
Positive findings (%)		302 (94%)	79 (82%)	120 (93%)		489 (89%)	133 (76%)	461 (91%)		530 (87%)	93 (74%)	592 (92%)

CFS: cerebrospinal fluid, Ep: evoked potential, and MRI: magnetic resonance imaging.

Table 3: Incidence of MS during the three decades examined in Pirkanmaa, Seinäjoki, and Vaasa.

Period	1981–1990			1991–2000			2001–2010		
District	Inc/10^5	95% CI	*N*	Inc/10^5	95% CI	*N*	Inc/10^5	95% CI	*N*
Pirkanmaa									
Males	3.0	(2.2–3.8)	48	4.1	(3.1–5.1)	70	5.1	(4.1–6.1)	92
Females	7.1	(5.8–8.4)	119	8.8	(7.4–10.2)	149	11.5	(9.9–13.1)	206
Total	5.1	(4.3–5.9)	167	6.5	(5.4–7.4)	219	8.2	(7.3–9.1)	298
Seinäjoki									
Males	5.0	(3.5–6.5)	44	10.5	(8.2–12.8)	83	8.6	(6.5–10.7)	66
Females	9.2	(7.2–11.2)	79	20.3	(17.1–23.5)	154	21.0	(17.7–24.3)	152
Total	7.1	(5.8–8.4)	123	15.3	(13.4–17.2)	237	14.7	(12.7–16.7)	218
Vaasa									
Males	4.1	(2.5–5.7)	25	7.4	(6.3–8.5)	46	6.0	(4.6–7.4)	38
Females	7.4	(5.2–9.6)	45	16.0	(14.4–17.6)	96	17.6	(14.2–21.0)	105
Total	5.7	(4.4–7.1)	70	11.7	(10.7–12.7)	142	11.7	(9.8–13.6)	143

this study in districts of Seinäjoki and Vaasa from 1981–2010. Ratios of 2.3 in Seinäjoki and 2.8 in Vaasa in 2010 exceeded the corresponding ratios of 1.6 and 2.2 in an earlier study from 1979–1993 [10]. However, the ratio in Pirkanmaa remained stable, which was consistent with other previous studies [15, 16].

MS affects women during their most active years of life. In this study, we showed the highest F/M ratio of 3.5 in the 10–19-year-age group, where the total incidence remains low. The female preponderance remained high in the 20–59-year-age group. Thus, the high F/M ratio in the youngest age group may indicate the presence of risk factors affecting this female subpopulation, independent of a geographically associated risk.

The local risk of multiple sclerosis in Seinäjoki may be explained by genetic factors because HLA characterization has demonstrated increased frequencies for B7, B12, and DR2 among both patients and their healthy relatives [17]. The patients' families were subsequently examined for the myelin basic protein (MBP) gene on chromosome 18, which is a candidate gene involved in multiple sclerosis. Genetic linkage and association analyses suggested that a genetic predisposition to multiple sclerosis was closely linked to the MBP gene in this population [18]. Despite this finding, the genetic background was similar in rural areas of partially Swedish-speaking Vaasa, Finnish-speaking Seinäjoki, and the more urbanized Pirkanmaa [19–21].

Risk among males was increased in Seinäjoki despite the presence of a declining male incidence. The SIR for males remained 2-fold (2.0, 95% CI: 1.7–2.3), with an SIR of 2.8 (95% CI: 2.3–3.5) reported in an earlier study in 1979-93 [10]. Although the SIRs for males in both Seinäjoki and Vaasa (1.4) were higher compared to Pirkanmaa, they did not differ from the female ratios. Given that the populations examined were genetically homogeneous and stable and that the genetic changes in these populations were slow, the gender-specific incidence trends observed in this study indicated that environmental factors affecting the increased male MS risk in high-risk districts were less powerful than factors affecting the increasing female preponderance in the 1990s. According

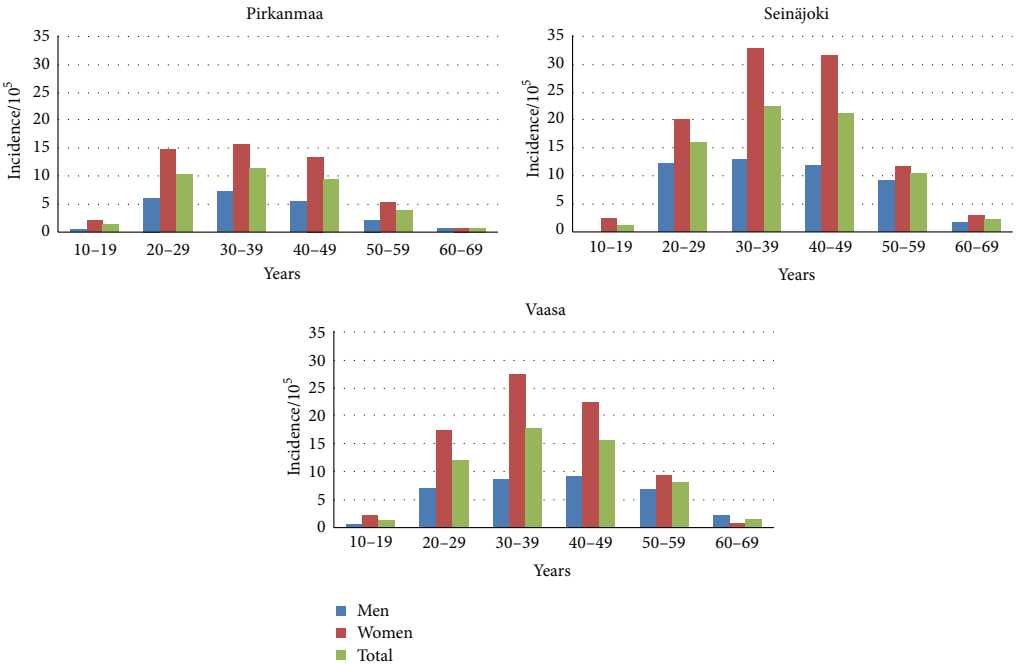

Figure 4: Incidence of MS in the 10-year-age groups in Pirkanmaa, Seinäjoki, and Vaasa hospital districts during the period 1981–2010.

to this observation, the factors affecting males and females may be different in general, and some of these factors may act temporally and locally.

The common awareness of MS and the availability of MRI from 1993 in all districts, together with revised criteria and justified early DMT start in RRMS have also precipitated MS diagnosis in Finland [22, 23]. The diagnostic evaluation performed in this study was on the basis of the International and National Current Care Guidelines [24–26]. Due to a highly centralized health care system, we were able to obtain full coverage of the MS patients in this population-based study. The diagnosis-based incidence was used to avoid proportional incidence and underestimated risk, in addition to problems with recognition and the definition of the historical and often arbitrary onset symptoms in long-term follow-up evaluations [10]. We included definite MS cases to consolidate regional and temporal comparisons. Active CSF sampling in Finland promoted the application of Poser criteria [12], in which a positive finding is essential. CSF s considered fundamental in differential diagnostics for MS [27]. Because purely clinical diagnoses were nearly nonexistent in 2001–2010, diagnostic specificity may be considered high in this cohort. However, the number of cases was fairly low, and the population in central parts of the country was younger compared to Seinäjoki and Vaasa, which was among the factors that may confound a regional and temporal comparison of incidence [11]. Thus, because small numbers were generally present in the age- and gender-specific strata, we decided to use indirect standardization in the risk calculations performed in this study [13].

We observed a significant decrease in the diagnostic delay, which was consistent with rapid MR imaging after the first symptoms in 2001–2010 in each district. Despite this finding, the incidence during the last ten-year period in both Vaasa and Seinäjoki showed a stabilization after a two-fold increase in 1981–2000. In 1981–2010, the population at risk in the 10–39-year-age groups decreased to 11% and 26% in Vaasa and Seinäjoki, respectively. The number of MS cases in 2001–2010 decreased by 21% in both Seinäjoki (a decrease from 122 to 96 patients) and Vaasa (from 80 to 63 patients), which was observed in males and caused the recent stabilization and observed incidence decline. In Pirkanmaa, the population only decreased by 3% and the number of new MS cases increased by 23% (from 130 to 168 patients), which was accompanied by a steadily increasing trend. Despite these recent differences in population structure, the current sources of livelihood were similar in the districts, including those of the Swedish-speaking population (22%) in the Vaasa district, which may indicate that the environmental risk factors may be connected to changes and differences in lifestyle.

In conclusion, Seinäjoki and Vaasa represented high MS risk areas, where risk was observed to be high among females, peaking in the youngest age group, and among males in a large age group. However, high risk in general reflects both genetic and environmental effects. These effects may also be shared among other autoimmune diseases, such as type 1

diabetes mellitus, which predominantly affects males. The incidence of type 1 diabetes mellitus closely follows MS, both geographically and temporally, in Finland [28]. Thus, population-based case control studies are required to further characterize these factor effects, which may include a role for Vitamin D, several lifestyle factors (including smoking, obesity, and hormone replacement therapy), and later childbirth among females.

Conflict of Interests

The authors declare that there was no conflict of interest.

Acknowledgment

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References

[1] N. Koch-Henriksen and P. S. Sørensen, "The changing demographic pattern of multiple sclerosis epidemiology," *The Lancet Neurology*, vol. 9, no. 5, pp. 520–532, 2010.

[2] O. M. Gray, G. V. McDonnell, and S. A. Hawkins, "Factors in the rising prevalence of multiple sclerosis in the North-East of Ireland," *Multiple Sclerosis*, vol. 14, no. 7, pp. 880–886, 2008.

[3] S. Simpson Jr., L. Blizzard, P. Otahal, I. van der Mei, and B. Taylor, "Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 10, pp. 1132–1141, 2011.

[4] A. Alonso and M. A. Hernán, "Temporal trends in the incidence of multiple sclerosis: a systematic review," *Neurology*, vol. 71, no. 2, pp. 129–135, 2008.

[5] M. Tintoré, A. Rovira, J. Río et al., "New diagnostic criteria for multiple sclerosis: application in first demyelinating episode," *Neurology*, vol. 60, no. 1, pp. 27–30, 2003.

[6] M. Filippi and M. A. Rocca, "MR imaging of multiple sclerosis," *Radiology*, vol. 259, no. 3, pp. 659–681, 2011.

[7] A. Compston, "Genetic epidemiology of multiple sclerosis," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 62, no. 6, pp. 553–561, 1997.

[8] J. Wikström, "Studies on the clustering of multiple sclerosis in Finland. II: microepidemiology in one high risk county with special reference to familial cases," *Acta Neurologica Scandinavica*, vol. 51, no. 3, pp. 173–183, 1975.

[9] E. Kinnunen, "Multiple sclerosis in Finland: evidence of increasing frequency and uneven geographic distribution," *Neurology*, vol. 34, no. 4, pp. 457–461, 1984.

[10] M. L. Sumelahti, P. J. Tienari, J. Wikström, J. Palo, and M. Hakama, "Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979–1993," *Neuroepidemiology*, vol. 19, no. 2, pp. 67–75, 2000.

[11] Statistics Finland, 2010, http://www.stat.fi/tup/suoluk/suoluk_vaesto.html#bruttokansantuote.

[12] C. M. Poser, D. W. Paty, L. Scheinberg et al., "New diagnostic criteria for multiple sclerosis: guidelines for research protocols," *Annals of Neurology*, vol. 13, no. 3, pp. 227–231, 1983.

[13] P. Armitage and G. Berry, "Standardization," in *Statistical Methods in Medical Research*, P. Armitage and G. Berry, Eds., pp. 436–443, Blackwell Science, Oxford, UK, 1994.

[14] C. Hirst, G. Ingram, T. Pickersgill, R. Swingler, D. A. S. Compston, and N. P. Robertson, "Increasing prevalence and incidence of multiple sclerosis in South East Wales," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 80, no. 4, pp. 386–391, 2009.

[15] S. M. Orton, B. M. Herrera, I. M. Yee et al., "Sex ratio of multiple sclerosis in Canada: a longitudinal study," *The Lancet Neurology*, vol. 5, no. 11, pp. 932–936, 2006.

[16] E. G. Celius and C. Smestad, "Change in sex ratio, disease course and age at diagnosis in Oslo MS patients through seven de cades," *Acta Neurologica Scandinavica*, no. 189, pp. 27–29, 2009.

[17] E. Kinnunen, S. Koskimies, A. Lagerstedt, and J. Wikstrom, "Histocompatibility antigens in familial multiple sclerosis in a high-risk area of the disease," *Journal of the Neurological Sciences*, vol. 65, no. 2, pp. 147–155, 1984.

[18] P. J. Tienari, J. Wikström, A. Sajantila, J. Palo, and L. Peltonen, "Genetic susceptibility to multiple sclerosis linked to myelin basic protein gene," *The Lancet*, vol. 340, no. 8826, pp. 987–991, 1992.

[19] H. R. Nevanlinna, "The Finnish population structure. A genetic and genealogical study," *Hereditas*, vol. 71, no. 2, pp. 195–236, 1972.

[20] E. Salmela, T. Lappalainen, I. Fransson et al., "Genome-wide analysis of single nucleotide polymorphisms uncovers population structure in Northern Europe," *PLoS ONE*, vol. 3, no. 10, Article ID e3519, 2008.

[21] U. Hannelius, E. Salmela, T. Lappalainen et al., "Population substructure in Finland and Sweden revealed by the use of spatial coordinates and a small number of unlinked autosomal SNPs," *BMC Genetics*, vol. 9, article 54, 2008.

[22] W. I. McDonald, A. Compston, G. Edan et al., "Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis," *Annals of Neurology*, vol. 50, no. 1, pp. 121–127, 2001.

[23] C. H. Polman, S. C. Reingold, G. Edan et al., "Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald criteria'," *Annals of Neurology*, vol. 58, no. 6, pp. 840–846, 2005.

[24] D. S. Goodin, E. M. Frohman, G. P. Garmany Jr. et al., "Disease modifying therapies in multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American academy of neurology and the MS council for clinical practice guidelines," *Neurology*, vol. 58, no. 2, pp. 169–178, 2002.

[25] "NICE guideline for management of multiple sclerosis," 2003, http://www.nice.org/.

[26] Working Group Appointed by the Finnish Medical Society Duodecim and the Finnish Neurological Society, "Current care guideline: multiple sclerosis," The Finnish Medical Society Duodecim and the Finnish Neurological Society, 2009 and 2012.

[27] M. S. Freedman, E. J. Thompson, F. Deisenhammer et al., "Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement," *Archives of Neurology*, vol. 62, no. 6, pp. 865–870, 2005.

[28] G. Soltesz, C. C. Patterson, and G. Dahlquist, "Worldwide childhood type 1 diabetes incidence—what can we learn from epidemiology?" *Pediatric Diabetes*, vol. 8, no. 6, pp. 6–14, 2007.

PUBLICATION II

Multiple sclerosis prevalence in 2000 and 2010 in Western Finland

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ORIGINAL ARTICLE

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Multiple sclerosis prevalence in 2000 and 2010 in Western Finland

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Objective: To study ten-year change in MS prevalence in the Province of Western Finland in Tampere University Hospital District located in 62.7°N, 23.7°E.

Methods: Age-standardized prevalence/10^5 by using direct standardization in European Standard Population (ESP2013) and crude prevalence/10^5 with 95% confidence interval (95% CI) were assessed among resident MS cases fulfilling Poser criteria by sex and disease course in 31.12.2000 and 31.12.2010. MS-related disability and disease-modifying treatment (DMT) use were estimated in 31.12.2010.

Results: Crude prevalence increased 49% from 129/10^5 (95% CI 121-137) in 2000 (N 1080) to 196/10^5 (187-203) in 2010 (N 1666). Age-standardized prevalence increased 45% from 133/10^5 (127-140) to 192/10^5 (184-200) and peaked in 40- to 49-year age-group. Age-standardized prevalence increased 58% among women from 176/10^5 (171-176) to 277/10^5 (270-284) and 31% among men from 91/10^5 (87-95) to 119/10^5 (115-124). Increase in RRMS was 61% from 111/10^5 (105-117) to 179/10^5 (171-186), and decrease in PPMS was 14% from 21/10^5 (19-24) to 18/10^5 (15-21).

In 2010 among the 52% RRMS cases on DMT, MS-related disability was mild in 50%. In total, cohort disability was mild in 46%, moderate to severe in 47%, and information was not available in 14%.

Conclusion: A significant increase in prevalence was observed in Western Finland. Increase was higher among women and in relapsing-remitting onset MS. Disability showed age- and disease course-specific variation.

KEYWORDS
disease course, epidemiology, multiple sclerosis, prevalence, sex

1 | INTRODUCTION

Epidemiological observations in multiple sclerosis (MS) have consistently pointed at globally increasing prevalence.[1,2] At the same time, MS mortality has decreased, and analyses on incidence have shown both stability and increase.[2-5] The highest age-standardized estimates have been observed in northern latitudes where prevalence among women and in relapsing-remitting MS is high. The relationship between socioeconomic determinants and increase in MS occurrence is observed, occurrence being higher in areas of higher socioeconomic level.[6] The case ascertainment and diagnostic criteria used in contemporary cohorts are today fairly comparable, but differences in population composition and population ethnic background, data sources, and follow-up times are among the causes that hamper the direct comparisons.

Finland is located between latitudes 60° and 70°N, and longitudes 20° and 32°E, and it is one of the world's northernmost countries. Epidemiological data updated in 2016 showed a high nationwide MS crude prevalence estimate of 180-200/10^5 and east-west gradient.[7,8] Incidence trends from 1981 to 2010 in the Province of Western Finland in Tampere University Hospital District showed a significant increase among women and opposite trends

in increasing relapsing-remitting onset MS (RRMS) and decreasing primary progressive (PPMS).[9] These trends differed from a tandem increase in RRMS and PPMS reported in a Finnish MS cohort from 1979 to 1993.[10]

We aim to study prevalence in 2000 and 2010 in the Province of Western Finland in Tampere University Hospital District and evaluate the impact of the observed incidence trends. In order to understand the present and future healthcare needs in MS, we aim to focus on disease course- and age-specific changes, disability status, and disease-modifying treatment (DMT) use in the prevalence cohort in 2010.

2 | MATERIALS AND METHODS

After the National Institute for Health and Welfare and local ethical standards committee approval, a retrospective search from hospital administrative registries for diagnoses multiple sclerosis or morbus demyelinans and optic- or retrobulbar neuritis (340, 341, and 377 in the International Classification of Diseases, ICD versions 8 and 9, G35, G37, and H46 in ICD10) up to 31.12.2010 was accomplished in three central hospital districts belonging to Tampere University Hospital District in the Province of Western Finland, shown in Figure 1. The catchment area located in 62.7°N, 23.7°E includes the high-risk areas in coastal hospital districts of Vaasa and Seinäjoki, and the more centrally located Pirkanmaa. The genetic and socioeconomic background in the districts is similar both in rural areas of partially Swedish-speaking Vaasa, Finnish-speaking Seinäjoki, and in the more urbanized Pirkanmaa.[11,12]

Altogether 2131 cases with searched ICD diagnoses were identified from 1950s up to end of follow-up in 31.12.2010. Retrospective and longitudinal follow-up up to 31.12.2010 involved data collection from patient documents for time point of initial MS symptoms, symptoms and disability progression during the follow-up, diagnostic procedures including cerebrospinal fluid examination, evoked potential and magnetic resonance imaging (MRI) dates and results. Information was scrutinized from patient records from first and successive neurological hospital visits up to 31.12.2010 by authors and MD Markus Holmberg. Cases were reassessed by authors to meet the inclusion criteria for a confirmed diagnosis by Poser at prevalence dates 31.12.2000 and 31.12.2010, including laboratory-supported and clinically definite MS cases.[13] Disease course at onset was categorized into relapsing-remitting MS (RRMS), including later secondary progressive MS cases, and primary progressive at onset (PPMS). The classification of disease course first done by a treating neurologist was re-evaluated by authors to meet the criteria by Lublin and Reingold.[14]

Inclusion criteria for prevalence assessments were residency in the study district and a confirmed MS diagnosis by definite Poser criteria[13] at prevalence dates in 31.12.2000 (N 1080) and 31.12.2010 (N 1666). Date of death and residency at prevalence dates were updated by personalized identification number at Finnish Population Register Center.

Disability status in 31.12.2010 was evaluated. Assessment based on neurological examination at yearly clinical visits including visits in ± one-year window. Disability categorization into mild, moderate, or severe was based on given Expanded Disability Status Scale (EDSS)[15] value or description of disability in patient document based on status signs, patient-reported symptoms, and symptomatic treatment shown in the patient record. In case there was no description of handicap at any central nervous system level or any symptoms that needed treatment or rehabilitation, or when the described symptoms and signs could be graded as mild, we categorized patient into a mild disability group, corresponding to EDSS grades <3.0. Categorization to moderate disability group concerned cases with a reported handicap in several functions, corresponding EDSS grades 3.0-5.5. Severe disability group here included cases with a significant handicap, shortened walking distance, and a regular use of a walking aid, corresponding EDSS 6.0 or greater.

In 2010, information on disability was available in 86%, 1432/1666. Among these, EDSS value was given in 61.2%, 876/1432 cases. In 556 cases, disability assessment based on a detailed description in patient record. Altogether 234/1666 cases (14.4%) were lost from yearly hospital follow-up in 2010, and information on disability was not available; of them, 47 were PPMS and 187 RRMS cases. Information was available in 94.6% for RRMS cases on active DMT (790/835) in 2010.

Use of disease-modifying immunomodulatory treatments (DMT) was assessed in 31.12.2010 among RRMS cases and based on longitudinal information in patient record. We did not include information on earlier treatments or if treatment was stopped before 31.12.2010. In 2010, a total of 835/1432 RRMS cases were actively using DMTs. Use of injectable DMTs started in 1990s in Finland, and patients on any immunomodulatory medication are followed in hospital neurological clinics. Injectable treatments are reimbursed by Finnish Social Insurance Institution.

Age-standardized total and sex-specific prevalence per 10^5 with 95% confidence interval (95% CI) were calculated by using a direct method in European standard population in 2013 (ESP2013), where standard population is based on geographical area given in Eurostat report.[16] Population statistics from Statistics Finland (www.stat.fi) was used to study crude total, sex-, and disease course-specific prevalence per 10^5 with 95% CI. Demographic comparisons of cases in the 2000 and 2010 prevalence cohorts were calculated, and the significance of each comparison was assessed with suitable statistical tests (eg, chi-squared, one-way ANOVA, independent samples *t* test); significance was given by using *P* values <.05. STROBE checklist was used. Statistical analyses were made with SPSS for Mac version 25.

3 | RESULTS

The catchment area in the Tampere University Hospital District in Western Finland located 62.7°N and 23.7°E is shown in Figure 1.

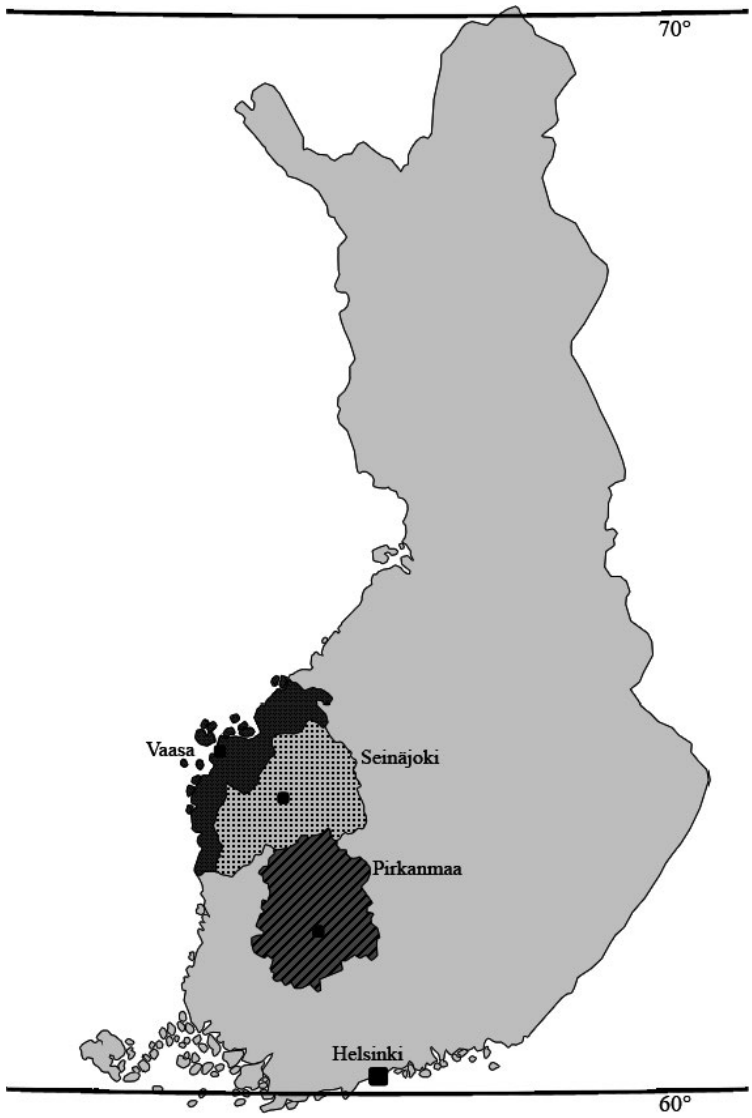

FIGURE 1 Map of Finland. Finland lies in Scandinavia, North Europe between latitudes 60-70°N. Gulf of Bothnia in northernmost part of Baltic Sea limits the west coast. Western district locates in 62.7°N, 23.7°E and belongs to Tampere University Hospital District. Location of three hospitals in Pirkanmaa (oblique lines), Seinäjoki (dots), and Vaasa (dark gray) are pointed in the map

In 31.12.2000 inclusion criteria for prevalence were met by a total of 1080 MS cases, 718 women and 362 men (F/M 2.0) in a population of 836 596. In 31.12.2010, a total of 1666 cases, 1150 women and 516 men (F/M 2.2), were included in a population of 875 875. The detailed demographics of cases in 2000 and 2010 are given in Table 1. Mean diagnostic delay (time to diagnosis from onset symptoms) remained stable ($P > .05$). Female vs. male ratio increased from 2.0 to 2.2. Mean age and disease duration were lower in RRMS group as compared to PPMS ($P < .05$) at both time points.

Total age-standardized prevalence (ESP2013) increased 44.5% from 133.0/10^5 (95% CI 126.7-139.7) in 2000 (N 1080) to 192.2 (184.3-200.2) in 2010 (N 1666). Increase was 57.5% among women from 175.9 (170.6-175.9) to 277.0 (270.4-283.6) and 30.8% from 91.0 (87.4-94.8) to 119.0 (114.6-123.5) among men. (Figure 2.) Total age-standardized prevalence in 10-year age-groups peaked in 50-59 years in 2000 and in 40-49 years in 2010; this was also true among men but the peak prevalence among women in age-group 40-49 years remained unchanged (Figure 3).

Total age-standardized prevalence in RRMS increased 60.4% from 111.3 (105.4-117.1) in 2000 (N 906) to 178.5 (171.0-186.0) in 2010 (N 1490). In PPMS, decrease was 15.9% from 21.4 (18.8-24.0) in 2000 (N 174) to 18.0 (15.4-20.6) in 2010 (N 176).

Crude prevalence increased 51.4% from 129.1 (121.4-136.8) in 2000 to 195.5 (186.5-202.5) in 2010. The 66.3% increase among women from 156.1 (131.5-180.7) to 259.6 (244.6-274.6) was >50.5% increase among men from 79.2 (61.0-97.4) to 119.2 (108.9-129.5).

TABLE 1 Demographic features in MS prevalence cohorts by disease course at end of follow-up in 31.12.2000 and 31.12.2010

	31.12.2000				31.12.2010			
	RRMS	PPMS	*P*	Total	RRMS	PPMS	*P*	Total
Total N (%)	906 (84%)	174 (16%)		1080 (100%)	1490 (89%)	176 (11%)		1666 (100%)
Women	618 (86%)	100 (14%)		718 (100%)	1046 (91%)	104 (9%)		1150 (100%)
Men	288 (80%)	74 (20%)		362 (100%)	444 (86%)	72 (14%)		516 (100%)
F/M	2.2	1.3		2.0	2.4	1.4		2.2
Mean age (SD), y	48.0 (12.3)	56.6 (11.1)	<.001	49.6 (12.6)	48.8 (13.8)	62.4 (10.9)	<.001	50.2 (14.2)
Disease duration, mean (SD), y	11.7 (9.3)	15.8 (11.1)	<.001	12.5 (9.8)	12.8 (10.1)	19.0 (11.9)	<.001	13.5 (10.5)
Age at diagnosis, mean (SD), y	36.6 (10.1)	41.1 (9.6)	<.001	37.3 (10.2)	35.9 (10.3)	43.4 (10.4)	<.001	36.7 (10.5)
Diagnostic delay, mean (SD), y	4.5 (5.7)	4.0 (4.9)	.2	4.4 (5.6)	3.9 (5.7)	4.1 (5.5)	.7	3.9 (5.7)

Abbreviations: F/M, female to male ratio; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

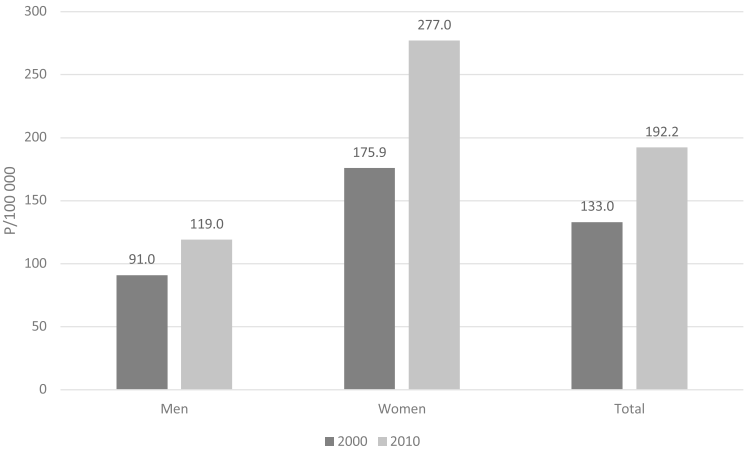

FIGURE 2 Total and sex-specific age-standardized prevalence in 2000 and 2010

Crude prevalence in RRMS increased 59.4% from 106.7 (99.7-113.7) to 170.1 (161.5-178.8) and differed from the trend (decrease 3.4%) in PPMS from 20.8 (17.7-23.9) to 20.1 (17.1-23.1). Age- and sex-specific prevalence estimates in 2000 and 2010 are presented as a Table S1.

In 31.12.2010, the number of resident MS cases in three hospital districts was 762 (47.5%) in Pirkanmaa (population 511 156), 560 cases (33.6%) in Seinäjoki (198 469), and 356 cases (21.4%) in Vaasa (166 250). The age-standardized prevalence (ESP2013) was 275.6 (267.6-283.5) in Seinäjoki, 226.1 (202.1-250.2) in Vaasa, and 149.3 (120.9-177.8) in Pirkanmaa.

In 2010, the mean and median calendar year of MS diagnoses were 1996 and 1999. Mean age at follow-up was 50.2 years, and mean disease duration was 13.5 years. Mean age in PPMS cohort (N 176) was significantly higher ($P < .001$) 62.4 years (SD 10.9) as compared to RRMS cohort (N 1490), 48.8 years (SD 13.8). Same was true for disease duration, 19.0 years (11.9) and 12.8 years (10.1), respectively ($P < .001$).

Disability distribution in 31.12.2010 in total cohort showed a mild disability in 46% of cases, which was significantly higher percentage than the 16% in moderate, 23% in severe, and 14% with missing disability evaluation, $P < .001$. Distribution by disease course is shown in Figure 4. Disease course-specific distribution pointed at a mild disability among the majority of RRMS cases in 52% and severe disability among PPMS cases in 44%. Disability evaluation was not available in 14%, and these cases represented older age-groups and a long disease duration: the mean age was 60.7 years (SD 11.9) in RRMS (N 187) and 66.6 years (11.0) in PPMS, and the disease duration was 20.7 years (11.5) and 21.8 (13.6) years, respectively.

In 31.12.2010, a total of 835/1490 RRMS cases (56%) were actively using DMT, mainly injectable medications (51.6%). Treated RRMS patients showed a mild disability (corresponding to EDSS 0-2.5) in 50% (421/835) and mainly in the youngest age-group <31 years, shown in Figure 5. DMTs were any subcutaneous or intramuscular injectable in 753/835 (90.2%), natalizumab in seven, and other immunosuppressing medication in 17 case. Fifty-nine cases were participating in randomized clinical trials. EDSS value in 2010 was given in 94.6%, and disability evaluation was missing 5.4% (45 cases). Disability increased in older age-groups, and moderate or

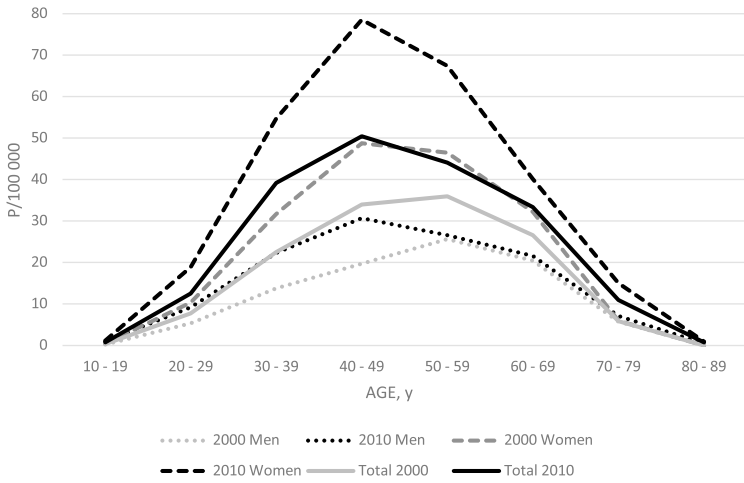

FIGURE 3 Age-standardized prevalence in ten-year age-groups in 2000 and 2010

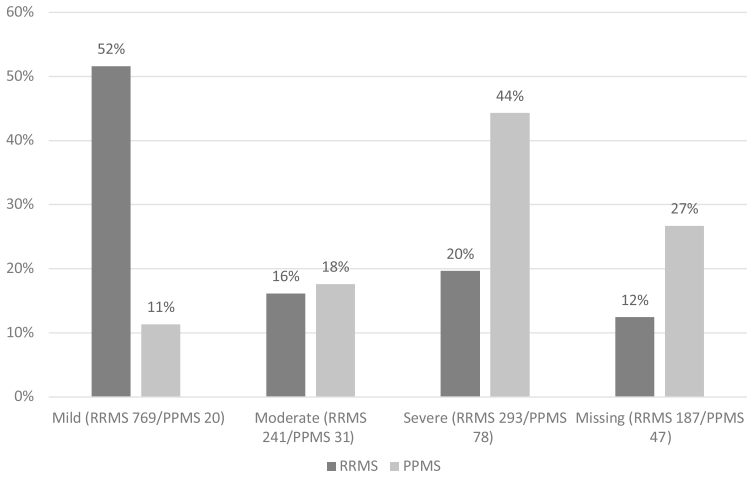

FIGURE 4 Number and distribution of RRMS (1490) and PPMS (176) cases by disability status in 2010

severe disability was observed in 369/835 (45%). Disability distribution showed no sex difference (Chi-squared $P = .58$).

4 | DISCUSSION

The ten-year increase in MS age-standardized prevalence in Western Finland showed a statistically significant 32% increase from 2000 to 2010. The 192/10[5] age-standardized prevalence in 2010 is high in global comparison and corresponds to prevalence in other Nordic areas and the recent estimate in Finland.[2,8] Increase concerned both sexes, and the female versus male ratio varied only slightly from 2.0 to 2.2. The significant increase in RRMS prevalence contrasted the stable trend in PPMS. Prevalence increased in all age-groups and peaked in age-group 40-49 years in 2010.

The relative effects of changes in MS survival and incidence are reflected in prevalence. As the recent incidence and sex difference seem to have stabilized[3] and the global trends in mortality have decreased,[2] the general increase in prevalence is largely explained by increasing survival in MS population,[17] which may largely explain for the ten-year change also in our data. The incidence up to 2010 in the three hospital districts under study has earlier shown high female versus male ratios and both increase (in Pirkanmaa) and stability (in Seinäjoki and Vaasa) in total trends.[18] The earlier reported concurrent standardized mortality ratios up to 2006 in a Finnish cohort (including Seinäjoki, Vaasa, and southern Uusimaa districts) diagnosed from 1964 to 1993 were shown to be higher among women as compared to men.[19] The relative impact of both sex-specific incidence change and the sex-specific mortality risk may be reflected in the age-specific standardized prevalence change, where peak among women remained in the 40 to 49-year group, but moved from 50-59 years to 40-49 years among men.

In this study, we examined demographic trends which may have impacted the prevalence proportions at two time points. Decrease

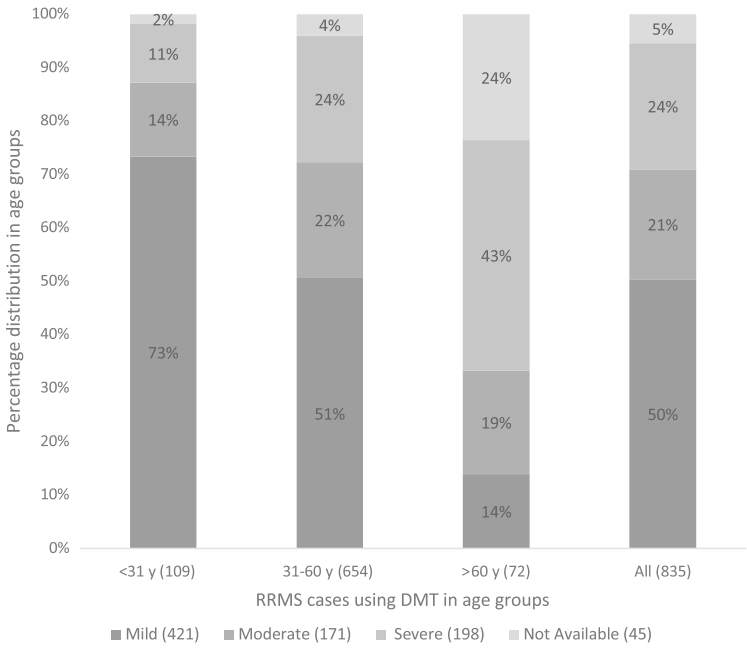

FIGURE 5 Distribution of cases in 2010 on active disease-modifying treatment (DMT) in three age-groups by disability status. Evaluation of disability was not available in 45 cases in 2010

in mean age at diagnosis was less than one year after an interval of 10 years. There was only a modest increase both in the mean disease duration from 12.6 to 13.5 years and in the mean age from 49.6 to 50.2 years, corresponding to the stability in age-specific trend. The identified demographic differences in the two cohorts concerned the increased mean disease duration from 15.8 to 19 years and mean age from 56.6 to 62.3 years in PPMS. The respective change in RRMS group was smaller, duration from 11.7 to 12.8 years and mean age from 47.9 to 48.8 years. These demographic changes in disease course groups reflect the longevity effect. However, the impact of concurrent incidence changes from 1981 to 2010 in the same catchment area is to be considered, as we have reported a statistically significant increase in RRMS from 4.2 (95% CI 3.7-4.6) to 9.7 (8.9-10.5)/10^5 and a drop in PPMS from 1.2 (0.9-1.4) to 0.7 (0.5-0.7), which differences however stabilized during the last study decade.[9] These trends differed from the observation in a Finnish cohort diagnosed in 1979-1993, where a tandem increase in RRMS and PPMS was shown.[10] Differences between results in the two incidence studies may be explained by improvements in MS diagnostics, the common awareness and importance of early diagnosis and treatment start. The resulting disease course-specific prevalence trends in 2000 and 2010 differed, likely reflecting impact of both survival and incidence. The impact of factors related to case ascertainment and diagnostic accuracy seems to have stabilized recently, since there was no remarkable change in age at diagnosis or diagnostic delay in the 2000 and 2010 prevalence cohorts. The impact of longevity effect and incidence has resulted in a high mean age in PPMS, over 60 years, being 49 years in RRMS in 2010. MS-related disease burden was higher in PPMS subgroups, based on a proportion of cases with a confirmed severe disability. The long follow-up from 1950s to 2010 and inclusion of secondary progressive cases into relapsing-remitting onset MS category are the likely factors explaining for the variability of disability distribution in RRMS. The highest proportion of cases with a low disability was observed among the youngest RRMS cases who were using disease-modifying treatments in 2010.

Estimates for DMT use in MS cohorts are generally scarce. Injectable DMTs, available from 1990s, were used in more than half (52%) among the RRMS cases in our 2010 cohort. The 76% of all cases on current treatment were included in a mild disability group in age-group <31 years, which was significantly higher as compared to reported 51% in largest age-group of 31-60 years, result concerning both sexes. However, altogether 45% of cases on treatment showed a moderate-to-severe disability and more so in older age-groups. We did not include cases who had stopped medication before follow-up in 2010 and the estimate for DMT use as given here is a rough point estimate and in dynamic change. The results on disability in our total and RRMS cohorts indicate both burden related to quality of life, long-term treatment costs, and employment, as well as a need for rehabilitation services in a wide age-group of MS patients.[20,21]

The limitation for comparability of data concerns the changing diagnostic criteria and diagnostic methods in long follow-up studies such as in our study. The first diagnosed cases in our data from 1950s to 1990s were diagnosed in the clinics mainly by using Schumacher criteria.[22] During the follow-up, these criteria were substituted by Poser criteria[13] in 1990s and the McDonald criteria in 2000s.[23] Active cerebrospinal fluid sampling and examination using both IgG index and oligoclonal bands as well as active use of MRI, including gadolinium enhancement from 1990s, promoted the retrospective application of Poser criteria in our data. Cases in our study cohorts were re-evaluated to fulfill the laboratory-supported or clinically

definite MS by Poser criteria, and this led to exclusion of cases especially in older age-groups where patient documents did not show sufficient evidence for a definite diagnosis.

By using the definite Poser inclusion criteria, our effort was to control for the risk for diagnostic bias and ascertain for the validity of case ascertainment in this study cohort covering a long follow-up of cases from 1950s.

Another limitation in our inferences concerns the disability assessment. Today EDSS is implemented in MS follow-up information in neurological clinics, and also, in our data EDSS was given in a majority of cases on active follow-up. Disability assessment in almost quarter of cases was however based on status description and thus susceptible to biases, both in terms of the level of detail provided in the record and the authors' interpretation of this. We categorized disability in three severity categories, based on both given EDSS and descriptive assessment. Such categorization into mild, moderate, and severe disability is also used elsewhere, and we believe that it gives a clear enough perception of disability.[2] Disability information in 2010 was not available in 14%. In this group, a progressed disability is likely, as a truly benign disease course is rare and patients are shown to live at an average almost 20 years with moderate and 30 years with severe disability, as was reported in a Swedish study.[24,25] In spite of the shortcoming, the convincing trend for progressive nature in MS by age was observed in RRMS group for cases on DMT, where disability information was available in 95%.

Strength in this population-based study is a confirmed diagnosis and a long follow-up in neurological clinics, and a stable ethnic and socioeconomic background[12] of the study population in a large population and catchment area. Data on death dates and residence are based on national data sources by using a personalized identity code given to Finnish residents. This information is reliable, and it was available for all cases. MS patients in Finland in almost 100% are diagnosed and treated in publicly funded central or University Hospital neurological clinics. Comparable medical standards in the hospitals enable us to draw inferences on regional trend. Our data source is reliable, and it is based on hospital discharge ICD diagnoses. We were able to scrutinize information for neurological follow-up visits from patient records and evaluate the demographics, disease course, and disease-modifying treatment use. Description on patients' disability was available in a majority of cases. This and the follow-up in case of disease-modifying treatment use are almost complete. Medication is either payed by hospitals or reimbursed by Finnish Social Insurance Institution. Reimbursement is 100% in case of injectable DMTs, which were mainly used during the follow-up here. Based on the availability of reimbursed treatments and the active follow-up, the proportion of treated cases may be regarded reliable.

A special epidemiological feature in Finland observed already in 1970s concerns the regionally high MS prevalence in coastal parts of Western and South-Western Finland.[26] The difference between South-Western and Eastern Districts shown already in 1970s[26] prevailed in a study in 2016, where a 5-year follow-up from 2012 to 2016 showed age-standardized rates 280/10^5 (95% CI 264-296) and 168/10^5 (95% CI 148-190), respectively.[7] Difference between coastal and inland districts was shown to prevail also in our data. These results point at regional high MS risk in the western coast of Finland. The rates in a large region in Western Finland as shown here in 2010 corroborate the concurrent rates in other Scandinavian countries, such as the nationwide prevalence 188.9/10^5 reported in 2008 in Sweden,[27] crude nationwide prevalence 208/10^5 in 2013 in Norway,[28] 154.5 /10^5 in 2005 in Denmark,[29] and 167.1/10^5 in 2007 in Iceland.[30] Although no exact nationwide prevalence estimation exists in Finland, results here and in a recent report based on a national register information point at a globally high nationwide prevalence of 180-200/10^5.[8]

Early observations in geographical variation in MS occurrence, such as has been observed in Finland and scandinavian countries, suggest that local environmental risk factors could be related to dietary and life style factors.[31,32]

5 | CONCLUSION

We report a high and increased MS prevalence from 2000 to 2010 in Western Finland in concordance with recent prevalence data concerning Finland and other high-risk areas. A majority of cases in 2010 showed a relapsing-remitting onset course and a mild disability. Moderate-to-severe disability was high in older age-groups and in PPMS. Variable occupational and healthcare needs in MS population are expected to increase, and this should be considered in social and healthcare resource planning.[33]

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CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Melcon MO, Correale J, Melcon CM. Is it time for a new global classification of multiple sclerosis? *J Neurol Sci*. 2014;344:171-181.
2. Wallin M, Culpepper W, Campbell J, et al. The prevalence of MS in United States. A population-based estimate using health claims data. *Neurology*. 2019;92:e1029-e1040.
3. Rotstein DL, Chen H, Wilton AS, et al. Temporal trends in multiple sclerosis prevalence and incidence in a large population. *Neurology*. 2018;90:e1435-e1441.
4. Koch-Henriksen N, Thygesen LC, Stenager E, Laursen B, Magyari M. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. *Neurology*. 2018;90:e1954-e1963.

5. Grytten N, Aarseth JH, Lunde HM, et al. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. *J Neurol Neurosurg Psychiatry*. 2016;87:100-105.
6. Pakdel M, Karin Hedström A, Bidkhori M, et al. Do socioeconomic factors affect the prevalence of multiple sclerosis in Iran? *Acta Neurol Scand*. 2019;140(5):328-335.
7. Pirttisalo AL, Soilu-Hänninen M, Sipilä JOT. Multiple sclerosis epidemiology in Finland: regional differences and high incidence. *Acta Neurol Scand*. 2019;139:353-359.
8. Laakso SM, Viitala M, Kuusisto H, et al. Multiple sclerosis in Finland 2018-Data from the national register. *Acta Neurol Scand*. 2019;140(5):303-311.
9. Sumelahti M-L, Holmberg MHA, Murtonen A, Huhtala H, Elovaara I. Increasing incidence in relapsing-remitting MS and high rates among young women in Finland: a thirty-year follow-up. *Mult Scler Int*. 2014;2014:1-8.
10. Sumelahti ML, Tienari PJ, Hakama M, et al. Multiple sclerosis in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses. *J Neurol Neurosurg Psychiatry*. 2003;74:25-28.
11. Nevanlinna HR. The Finnish population structure. A genetic and genealogical study. *Hereditas*. 1972;71:195-236.
12. Hannelius U, Salmela E, Lappalainen T. Population substructure in Finland and Sweden revealed by the use of spatial coordinates and a small number of unlinked autosomal SNPs. *BMC Genet*. 2008;9:54.
13. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol*. 1983;13:227-231.
14. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results from an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials on New Agents in Multiple Sclerosis. *Neurology*. 1996;46:907-911.
15. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
16. Pace M, Lanzieri G, Glickman M, et al. Revision of the European Standard Population. Methodologies and Working papers. Eurostat2013.
17. Lunde HMB, Assmus J, Myhr K-M, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry*. 2017;88:621-625.
18. Holmberg M, Murtonen A, Elovaara I, Sumelahti M-L. 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;2013:1-6.
19. Sumelahti M-L, Hakama M, Elovaara I, Pukkala E. Causes of death among patients with multiple sclerosis. *Mult Scler J*. 2010;16(12):1437-1442.
20. Prescott JD, Factor S, Pill M, Levi GW. Descriptive analysis of the direct medical costs of multiple sclerosis in 2004 using administrative claims in a large nationwide database. *J Manag Care Pharm*. 2007;13:44-52.
21. Raggi A, Covelli V, Schiavolin S, et al. Work-related problems in multiple sclerosis: a literature review on its associates and determinants. *Disabil Rehabil*. 2016;38:936-944.
22. Schumacher GA, Beebe G, Kibler RF, et al. 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*. 1965;122:552-568.
23. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol*. 2001;50:121-127.
24. Hirst C, Ingram G, Swingler R, Compston DA, Pickersgill T, Robertson NP. Change in disability in patients with multiple sclerosis: a 20-year prospective population-based analysis. *J Neurol Neurosurg Psychiatry*. 2008;79:1137-1143.
25. Manouchehrinia A, Beiki O, Hillert J. Clinical course of multiple sclerosis: a nationwide cohort study. *Mult Scler*. 2017;23:1488-1495.
26. Wikström J, Palo J. Studies on the clustering of multiple sclerosis in Finland I: comparison between the domiciles and places of birth in selected subpopulations. *Acta Neurol Scand*. 1975;51:85-98.
27. Ahlgren C, Odén A, Lycke J. High nationwide prevalence of multiple sclerosis in Sweden. *Mult Scler*. 2011;17:901-908.
28. Grytten N, Torkildsen Ø, Myhr KM. Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. *Acta Neurol Scand*. 2015;132:29-36.
29. Bentzen J, Flachs EM, Stenager E, et al. Prevalence of multiple sclerosis in Denmark 1950–2005. *Mult Scler*. 2010;16:520-525.
30. Elíasdóttir Ó, Kjartansson Ó, Olafsson E. Prevalence of Multiple Sclerosis in Iceland. *Neuroepidemiology*. 2018;51:50-56.
31. Bihrmann K, Nielsen NM, Magyari M, Koch-Henriksen N, Nordsborg RB, Ersbøll AK. Small-scale geographical variation in multiple sclerosis: A case-control study using Danish register data 1971–2013. *Mult Scler Relat Disord*. 2018;23:40-45.
32. Swank R, Lerstad O, Strom A, Backer J. Multiple sclerosis in rural Norway — its geographic and occupational incidence in relation to nutrition. *N Engl J Med*. 1952;246:721-728.
33. Koch-Henriksen N, Stenager E, Brønnum-Hansen H. Studies based on the Danish Multiple Sclerosis Registry. *Scand J Public Health*. 2011;39:180-184.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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PUBLICATION III

Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections

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Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections

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ABSTRACT

Background: Survival in MS has increased during the era of disease modifying therapies, but life expectancy in MS patients is still reduced by several years. Increased risk for common comorbidities related to brain health, such as risk for circulatory diseases have been reported in MS and could affect survival. In this paper, we studied age- and gender adjusted risks for circulatory diseases and related disorders, and their impact on overall MS survival in population of Southwest Finland.

Materials and methods: The ICD-10 codes for hospital visits were searched from the administrative data pool from 1.1.2004 up to 31.12.2012 for the resident MS and control cases at the Hospital District of Southwest Finland. The MS population under study consisted of prevalent cases in 1.1.2004 and new cases from 1.1.2004 followed up to death or 31.12.2012. Patient documents were scrutinized to confirm the MS diagnosis (G 35) by the McDonald´s criteria and to confirm the diagnoses and causes of death for the cerebro- and cardiovascular diagnoses under study. The randomly chosen 10-fold control population was matched by birth year and gender to calculate the coincident risks (odds ratio, OR) with 95% confidence intervals (95% CI) and another separate control population from the same patient pool was used to verify the stability of the results. P-values were calculated using Pearson's $\chi 2$ test. The Kaplan- Meier analysis log rank test was applied to study survival.

Results: During the follow-up 1074 confirmed MS cases were treated in the hospital district, including the deceased cases after 1.1.2004 (5.9%). The probability of survival was 82.4 years among MS and 85.6 years among the control cases, log rank $p < 0.001$. The survival disadvantage within MS was associated with comorbidity for circulatory disease codes in ICD −10: I06-I71, log rank $p < 0.001$. The specific risk for ischemic and haemorrhagic stroke was significant with high OR of 1.49 (95% CI 1.03- 2.35) and 2.5 (1.24–5.06) respectively. The two-fold risk for type 1 diabetes in MS was significant, OR 2.1 (1.3–3.36). The main causes of death among the MS cases were infections and the coincident high risk for several infections was significant. There was no difference in the risk for acute myocardial infarct, transient ischemic attack, atrial fibrillation, hypertension, or obesity in comparison with the control cases.

Conclusions: Given the high risk for stroke in this MS population and the observed complexity among the coincident common risk factors for circulatory diseases, the high risk for type 1 diabetes and common infections raise a need to recognize patients at risk with these conditions and with the other known risk factors such as metabolic syndrome and smoking. The survival disadvantage related to circulatory diseases observed in general population is true also in MS and should be recognized to reduce the burden of disease and premature mortality in MS.

1. Introduction

Multiple sclerosis (MS) is a progressive autoimmune disease causing disability and premature mortality. Pathologically MS is characterized by inflammation, demyelination and neurodegeneration in the central nervous system (CNS) Hauser and Goodwin (2008).Other mechanisms in CNS include changes in vascular perfusion, activation of microglia and intracerebral vascular changes like blood-brain barrier leakage (Cramer et al., 2013; Wuerfel et al., 2007).

Autoimmune disorders, infections and circulatory diseases are

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common in MS population (Montgomery et al., 2013; Christiansen et al., 2010; Berkovich et al., 2011). Several disorders in these disease groups affect brain and the nervous system in MS, such as cardio- and cerebrovascular diseases, hypertension and diabetes Marrie et al. (2015a).

There is a risk for premature mortality in MS (Sumelahti et al., 2010; Kingwell et al., 2012) and the major cause of death are infections. It is increasingly recognized that the common causes of death observed in general population are present also in MS, such as cardiovascular causes and stroke (Sumelahti et al., 2010; Kingwell et al., 2012; Krökki et al., 2014; Bronnum-Hansen et al., 2004). At the same time findings regarding the prevalence of several vascular comorbidities in MS are conflicting (Marrie et al., 2015b). An almost two-fold increased risk for cerebrovascular comorbidity and a significant risk for cardiovascular comorbidity after MS onset has been recently reported (Thormann et al., 2016). This observation has raised a question of converging causal pathways of the coexisting diseases and a need to study the effects in a broader spectrum of comorbidities in MS. Vascular aspects in MS are thus recognized and the reported risk may be explained on basis of the inflammatory and vascular mechanisms present in both MS and circulatory diseases, in addition to suspected effect of shared genetic and life-style risk factors. (D'haeseleer et al., 2011; Wang et al., 2016)

Our study bases on these observations and hypotheses. We studied the age- and gender adjusted risk for circulatory diseases in an MS population diagnosed and followed-up in a large university hospital district in Southwest Finland. We focused on ischemic cerebro- and cardiovascular diseases and related disorders, diabetes and acute and chronic infections. An established public health care system and population registers in Finland form a reliable basis in our survey. By access to administrative and patient specific data from the Hospital District of Southwest Finland we studied the coincident risk and survival effect for circulatory diseases and related comorbidities in MS, to assess the need of preventive actions and practical treatment strategies.

2. Materials and methods

This study was registered and approved by the Turku Clinical Research Center, Finland. Ethical committee approval was obtained from the joint Ethics Committee of the Tampere University and Pirkanmaa Hospital District, Finland.

For data mining, we used the administrative Clinical Data Repository of the University Hospital of Turku containing electronic health records at the Hospital District of Southwest Finland. These are collected directly and retrospectively monthly from the operational patient data systems from the central and university hospitals of the region by using ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for 2016) from 1.1.2004 to 31.12.2012.

All resident cases with MS (ICD-10 code G35) were included. The catchment of data concerned both alive and deceased MS patients followed from 1.1.2004. Case ascertainment followed the initial data mining by scrutiny of each patient document by author K.H. to meet the study inclusion criteria of definite MS by McDonald criteria (Polman et al., 2011). Patient documents of the confirmed MS cases with diagnoses for cardiac (acute myocardial infarct I21), ischemic stroke (cerebral infarct, I62) and other vascular diseases of the brain were next scrutinized by the authors (M-L.S, A.M, M.S-H) for diagnostic ascertainment, including information on paraclinical diagnostics (date and results of brain CT or MRI scans, ECG and specific laboratory results). The ICD codes for causes of death among the deceased MS cases were collected from the patient records.

Comorbidities diagnosed both before and after the date of diagnosis of definite MS were included in the analysis.

Confirmed MS cases in this nested case control study were gender- and age matched to controls drawn from the same population cohort. A 10-fold gender- and age (based on birth year) - matched control population was randomly chosen from the CDR patient pool and another separate age- and gender-matched 10-fold control population was used to verify the stability of the results in the district.

All ICD-10 codes for each hospital visit were available for MS and control cases residing in the catchment area from 1.1.2004 to 31.12.2012. We collected data for ICD codes I06-I71 in Diseases of Circulatory Disease group, Chapter IX, I00-I71 and for other specific diagnoses under the study irrespective of time or age at each diagnosis. Dates of death were available from CDR.

2.1. Statistical analyses

Kaplan-Meier (KM) survival analysis was applied to study the mean survival times. A separate KM analysis was performed to study the effect of CD morbidity (I00-I71 codes). Significance was assessed by log-rank test.

The odds ratios, OR's, were calculated with 95% confidence intervals (95% CI) and p-values were calculated using Pearson's χ^2 test. All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R Statistics version 3.0.2 with standard packages.

3. Results

A total of 1074 confirmed MS cases, 315 men and 759 women, were identified in a population of 472 139. The distribution of prevalent cases in 2004 and new incident cases from 2004 to 2012 by sex and age at entry is shown in Table 1. The date of entry is the first hospital visit due to any cause.

During the follow-up death in MS occurred in 5.9% (n 70, 34 women and 36 men). The main cause of death was infections (n 38, 54.3%). Other specific causes in the circulatory diseases group (n 5, 7.1%) were one case of acute myocardial infarct, four cases of ischemic stroke and one case of subarachnoid haemorrhage. Causes in other disease groups were respiratory insufficiency (n 6, 8.6%), cancer (n 3, 4.3%) and intoxication (n 2, 2.9%). The rest of the death causes represented other causes of death (n 16, 22.9%).

The mean survival time in MS was 82.4 years compared to 85.6 years in the age and gender matched control population, difference was statistically significant (KM log rank $p < 0.001$), KM curve shown in Fig. 1.

The MS prevalence in 31.12.2012 was 212.6 / 10^5 (95% CI 199.5–225.8), 121.4 (114.5–128.4) for men and 258.3 (247.9–268.6) for women (Åivo et al., 2016).

The diagnosed concomitant circulatory system diseases in ICD I06-I71 at any point of disease trajectory including death during the follow-up in 2004–2012 were included in the second KM analysis shown in

Table 1
Number, mean age and standard deviation (years) at enrollment from 1.1.2004 to 31.12.2012 among the 1074 MS cases (ICD-10 G35) by gender in the Hospital District of Southwest Finland.

Female			Male			
Year of entry	Mean age	Std dev	Year of entry	Mean age	Std dev	Number of Cases
2004	44.6	12.0	2004	47.7	13.8	111
2005	46.8	13.2	2005	50.3	14.1	53
2006	44.4	12.7	2006	48.2	14.4	34
2007	42.6	14.3	2007	49.2	14.5	26
2008	45.4	15.7	2008	42.7	13.1	33
2009	44.9	17.6	2009	45.1	13.9	18
2010	48.7	14.2	2010	49.1	15.1	14
2011	41.9	14.5	2011	45.9	15.1	16
2012	45.9	18.5	2012	49.6	18.6	10
Total	44.9	13.8	Total	47.5	14.1	315

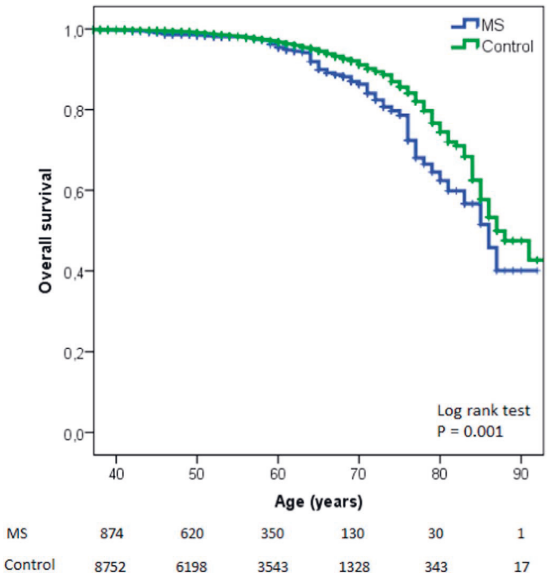

Fig. 1. Kaplan-Meier survival curve from birth up to end of follow-up or at the point of death due to any cause for MS and age- and gender matched control cases. MS cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. The numbers below refer to the number of cases in each group that are still part of the follow-up at that time and have not experienced an event.

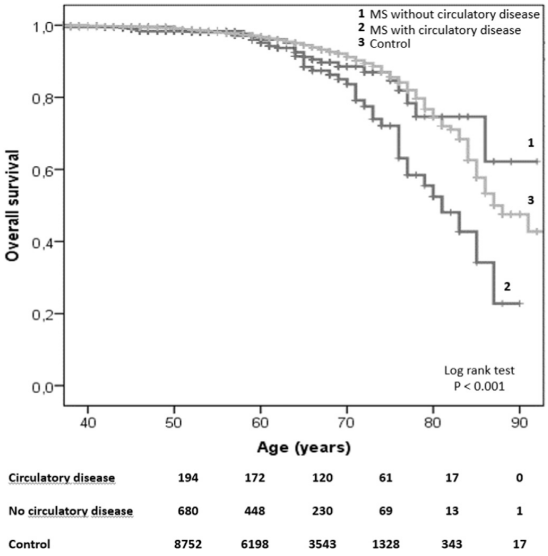

Fig. 2. Kaplan-Meier survival curve for MS cases with and without circulatory disease diagnosis and for the age- and gender matched controls from birth up to end of follow-up or at the point of death due to any cause. Cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. The numbers below refer to the number of cases in each group that are still part of the follow-up at that time and have not experienced an event.

Fig. 2. The risk related to circulatory disease diagnoses in MS was statistically significant, log rank $p < 0.001$: the mean survival time among MS cases with circulatory diseases was 79.5 years and without circulatory diseases 85.4 years. Survival among controls was 85.6 years.

Table 2
The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for the diagnosed and confirmed cases in acute myocardial infarct, cerebral infarct and other vascular disease of the brain for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD-10 code	Disease	MS (n)	%	Controls (n)	%	OR	95% CI
I21	Acute myocardial infarct	18	1.7	121	1.1	1.49	0.91–2.43
I63	Cerebral infarct	25	2.3	161	1.5	1.55	1.03–2.35
I67	Other vascular disease of the brain	9	0.8	36	0.3	2.50	1.24–5.06

The odds ratios (OR) concerning MS and control cases in specific circulatory diseases ICD- groups I06-I71 (n = 340) are shown in the additional data.

The number of MS, age- and gender matched control cases and OR's for specific circulatory diseases diagnoses are presented in Table 2. An almost 50% greater risk for ischemic cerebral infarct in MS (n 25), OR 1.49 (95% CI 1.03–2.35), was statistically significant. A statistically significant and over two-fold risk was observed also for other strokes (n 9) including both subarachnoid and intracerebral haemorrhages: OR 2.5 (1.24–5.06). Acute myocardial infarct (n 18, 1.85%) showed no increased risk in MS, OR was 1.49 (0.91–2.43). Diagnoses with other cerebrovascular diseases by code I67 (n 9) and sequelae of cerebrovascular disease I69 (n 18) may overlap the acute stroke diagnoses why they were assessed separately. Respective OR's were high, 2.5 (1.24–5.06) and 1.73 (1.06–2.83).

Ischemic stroke (cerebral infarct, I63) was confirmed either as a comorbid diagnosis (n 21) or an immediate cause of death (n 4). Case ascertainment was based on findings in CT scan or MRI in 92% (23/25 cases), location was mainly parietal in middle artery region (n 11), posterior (n 6) and subcortical (n 6). Female to male ratio was 0.79 (11/13 cases). Mean age at cerebral infarct was 69.5 years, median 69 years (SD 10.58), 71.6/71 years (SD 9.93) for women and 67.86/67.5 years (SD 11.15) for men (χ^2 p = 0.23, statistically nonsignificant). All cases in I67 (subarachnoid and intracerebral haemorrhage) were radiologically confirmed. Diagnosis of acute myocardial infarct based on ECG and blood tests.

The number of MS, age- and gender matched control cases and OR's for common circulatory disease related risk factors are presented in Table 3. Type 1 diabetes showed a two-fold risk, OR 2.1 (1.3–3.36). A statistically nonsignificant risk was observed for type 2 diabetes, transient ischemic attack (TIA), atrial fibrillation, other cardiac arrhythmia,

Table 3
The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for the common circulatory diseases diagnosed in hospitals for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD-10 code	Disease	MS	%	Controls	%	OR	95% CI
G45	TIA	12	1.1	136	1.3	0.88	0.49–1.59
I48	Atrial or fibrillation or flutter	18	1.7	350	3.3	0.51	0.33–0.81
I49	Other cardiac arrythmia	18	1.7	189	1.8	0.95	0.59–1.54
I10	Essential hypertension	93	8.7	1034	9.6	0.90	0.74–1.10
I70	Atherosclerosis	12	1.1	102	1.0	1.18	0.65–2.13
E10	Type I diabetes mellitus	20	1.9	95	0.9	2.11	1.32–3.36
E11	Type II diabetes mellitus	39	3.6	391	3.6	1.00	0.72–1.38
E78	Hyperlipidemia	17	1.2	336	3.1	0.51	0.32–0.81
E66	Obesity	21	2.0	328	3.1	0.64	0.42–0.99

Table 4
The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for common acute and chronic infections diagnosed in hospital for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD −10 code	Disease	MS (n)	%	Controls (n)	%	OR	95% CI
N10	Acute pyelonephritis	88	8.2	116	1.1	7.59	6.01–9.57
J22	Unspecified acute lower respiratory infection	7	0.7	10	0.1	7.0	3.06–16.03
N30	Cystitis	81	7.5	116	1.1	6.98	5.48–8.89
J41	Simple and mucopurulent chronic bronchitis	4	0.4	7	0.1	5.71	1.93–16.92
A41	Other sepsis	29	2.7	62	0.6	4.68	3.14–6.97
J18	Pneumonia, unspecified organism	100	9.3	297	2.8	3.37	2.73–4.15
K02	Dental caries	25	2.3	90	0.8	2.78	1.82–4.24
J20	Acute bronchitis	25	2.3	102	0.95	2.45	1.61–3.73
K05	Gingivitis and periodontal diseases	23	2.1	101	0.94	2.28	1.47–3.53
A04	Other bacterial intestinal infections	14	1.3	62	0.6	2.26	1.29–3.96
K08	Other disorders of teeth and supporting structures	18	1.7	86	0.8	2.09	1.28–3.43
L02	Cutaneous abscess, furuncle and carbuncle	15	1.4	77	0.7	1.95	1.13–3.35
A09	Infectious gastroenteritis and colitis, unspecified	29	2.7	164	1.5	1.77	1.20–2.60
J06	Acute upper respiratory infections of multiple and unspecified sites	41	3.8	237	2.2	1.73	1.25–2.39

hypertension, hyperlipidaemia and obesity in MS.

The number of MS, age- and gender matched control cases and OR's for a number of acute and chronic infections are presented in Table 4. with detailed results. The coincident risk for the hospital treated infections showed an increased risk for urinary, respiratory and periodontal infections in MS.

4. Discussion

The lower mean survival time of 82.4 years in MS compared to 85.6 years in the control population was statistically significant. However, life expectancy was reduced much less than in earlier studies showing 6–7 years shorter life expectancy in MS (Sumelahti et al., 2010; Kingwell et al., 2012; Lunde et al., 2017). This supports improved survival in patient cohorts from the era of disease modifying therapies and is in line with the recent study from Norway showing a near normal standardised mortality ratio in the patient cohort monitored from 1997 to 2012 (Lunde et al., 2017).

The high mortality of cerebrovascular diseases in the Finnish general population (Causes of death, 2012) was here shown to concern also the MS population. Result supports the Danish study (Christiansen et al., 2010) and corroborates survival disadvantage reported for cerebrovascular diseases among MS patients (Krökki et al., 2014; Bronnum-Hansen et al., 2004; Marrie et al., 2015b; Thormann et al., 2016). Survival disadvantage related to circulatory disease comorbidity was significant in our study. The mean survival time was lower for MS cases with any circulatory diseases related diagnosis in ICD-10 I06-I71 group, 79.5 years, in comparison with the 85.4 years in MS patients without it. The specific risk for the common risk factors for these diseases, such as hypertension, hyperlipidaemia or cardiac disorders and arrhythmias, were low also in our MS population (Marrie et al., 2012) along with other risk factors for ischemic stroke, except for type 1 diabetes.

MS patients were followed up during a 9-year period in 2004–2012. The catchment area in the Hospital District of Southwest Finland represents a high-risk region of MS, where prevalence was $212/10^5$ in 2012 Åivo et al. (2016). MS cohort originated from an administrative database and after confirmation of MS diagnosis 9.6% of cases were excluded, which amount is similar to other reports using administrative catchment (Christiansen et al., 2010; Marrie et al., 2012). Patient records were examined for confirmation of MS, ischemic brain and myocardial infarcts and for causes of death, why we believe to have reliable data for the statistical assessment concerning these diagnoses. The diagnosis of type 1 diabetes was considered reliable in this population due to regular hospital controls.

Strength of our study is the public health care system, where health care is available for all Finnish citizen and an equal treatment practice is followed. The national and hospital registers in Finland base on personalized identification code and are regarded reliable. The administrative health registry covers almost the entire population of the study region and provides objective data avoiding bias related to patient recall. MS is diagnosed and treated by neurologist in central and university hospitals why we believe to have a representative sample of MS patients from a large hospital district. A 10-fold sample of the general non-MS population ensure that study observations reflect general patterns of co-occurrence of health problems among MS patients, which may not be accurate in small clinical samples, due to sampling, or referral biases.

We observed an increased risk for circulatory diseases in MS population as compared to age- and sex matched control population during the follow-up. Evidence that autoimmunity may play an essential role in the pathogenesis of atherosclerosis (Matsuura et al., 2014) is supported by reports on increased risk for cerebro- and cardiovascular disorders in several immune-mediated diseases, such as MS (Capkun et al., 2015), rheumatoid arthritis (Nurmohamed, Dec et al., 2015; Meissner et al., 2017) and type 1 diabetes (O'Donnell et al., 2016). These results suggest that these inflammatory diseases may share pathological links with cerebrovascular diseases. However, although inflammation is shown to contribute to stroke risk (Dregan et al., 2017), other typical risk factors may be absent in MS (O'Donnell et al., 2016; Wens et al., 2013). This view was supported by observations in our data, as other common cerebrovascular risk factors, such as TIA, atrial fibrillation and other arrhythmias, showed no increased risk, nor was there any risk for secondary hypertension, hyperlipidaemia or obesity. Result differs from observations in rheumatoid arthritis and type 1 diabetes populations, where several common risk factors exist, but corroborates observations in other MS populations where prevalence of diabetes, hypertension, and hyperlipidaemia have been similar to rates in general population Marrie et al. (2012).

Given the observation of increased risk for stroke, which is diagnosed in hospital, and the low comorbidity for some of the most common vascular disease risk factors, our results are discordant but in accordance with other studies Marrie et al. (2012). Limitation in our study population however concerns the catchment of these risk diagnoses from the tertiary care hospital data, as most of these conditions are recognized and treated mainly in the primary care. It also remains unknown to what content the observed circulatory disease risk is related to metabolic syndrome in MS, a question which has remained open also in other studies addressing this relation and the increased risk of obesity or changes in body composition, hypertension, dyslipidaemia or type II diabetes in MS (Wens et al., 2013). Although administrative data are considered a valid means of tracking diabetes, hypertension, and hyperlipidaemia in MS (Wens et al., 2013) the so far inconclusive results from hospital data regarding common circulatory disease risk

factors in MS as shown here could be elaborated by linkage to other databases and primary care data.

Respiratory infections were the major cause of death and the high rates of acute and chronic respiratory, urinary and periodontal infections were present also in our MS cohort (Sumelahti et al., 2010; Bronnum-Hansen et al., 2004; Sheu and Lin, 2013). Acute and chronic infectious diseases are related to risk of stroke (Lindsberg and Grau, 2003) and infections may be a specific risk factor in MS population. There is a connection between the immunological and vascular factors (Caprio et al., 2016), which supports the suggested hypothesis on the shared inflammatory mechanisms in MS and ischemic stroke (Claudio et al., 1995). The control of inflammation and infections appear as important modifiable factors in MS related circulatory disease risk. Evidence from observational studies shows that vaccination against influenza is associated with a reduced risk of stroke, myocardial infarction and all-cause mortality Urbanek et al. (2010). The preventive seasonal and H1N1 vaccines are safe and efficacious also among MS patients, nor is there any reduced response to vaccination against influenza associated to majority of immunomodulatory drugs used in MS Auriel et al. (2012).

The independent coincident relative risk for type 1 diabetes in our MS population was high and corroborates results in other studies (Fromont et al., 2013). In Finland, the incidence of both type 1 diabetes and MS are high (Karvonen et al., 2000). The autoimmune pathogenesis of MS and type 1 diabetes (Berkovich et al., 2011) as well as socioeconomic, environmental and latitude correlated factors may contribute to the predisposition of these immune-mediated diseases. The global and steep increase in both type 1 and 2 diabetes (World Health Organisation, 2016) and MS incidences recorded in the last half of the 1990's may be a serious signal of unhealthy changes in the environment and life style. These may affect the penetrance of disease susceptibility genes in autoimmune diseases and may also be involved in the high circulatory disease risk observed in MS and type 1 diabetes in Finland. The modifiable risk factors in type 1 diabetes, MS and circulatory diseases include childhood obesity and smoking Ponsonby et al. (2013).

MS patients today expect a longer survival. The long disease trajectory combines an increased risk for comorbidities common in the general population, as shown here for ischemic stroke risk along with other studies. Consistent with other reports, limitation for information regarding circulatory disease mortality related life-style factors here concerns the lack of socioeconomic and lifestyle information in MS cohorts. At the moment, we have no information on the changes in occupational status, medication, weight, serum lipid status or on individual lifestyle factors such as smoking, dietary habits, physical activity or health behaviour in general, but evidence on accumulating comorbidity risk in MS supports the importance of dealing with these factors. Life style interventions are justifiable as the key findings in comorbidity studies in MS have been association of life-style related type 2 diabetes, hypertension, dyslipidaemia or peripheral vascular disease at any point in the disease course with a greater progression in disability Marrie et al. (2012). These factors may add to complex risk for circulatory diseases in MS and have implications for prevention and treatment in the recognized risk groups. Disadvantages in administrative databases such as ours include the lack of structured data on life style factors. We expect to expand the information in our databases in the future with the application of text mining tools to patient reports and linkage to other governmental health registries such as the medication reimbursement registry of social insurance institution of Finland.

The immortal time bias is a limitation for inferences in cohort and case-control study designs, however a nested case-control analysis as chosen here, and matching by age and sex, may be much less susceptible to selection bias than the other approaches since controls are known to represent the source population that gave rise to the cases and the analysis can include all the cases from the source population Lévesque et al. (2010). This analytical technique has not only been shown to provide an unbiased estimate of the hazard ratio that would be obtained from a traditional time to event analysis of the full cohort (Liddell et al., 1977; Breslow and Day, 1987; Suissa, 2005) and its inherent time dependent nature means that it is also free of immortal time bias.

In conclusion, the overall survival advantage in MS was related to lack of circulatory disease diagnoses at any point during the follow-up. Further knowledge on influences of comorbidities on the course and outcome of MS is important for better clinical care and optimized life style interventions in the individual patients.

Disclose

Authors have nothing to disclose.

Conflict of interest

Authors report no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2017.10.019.

References

Åivo, J., Kurki, S., Sumelahti, M.-, Hänninen, K., Ruutiainen, J., Soilu-Hänninen, M., 2016. Risk of osteoporotic fractures in multiple sclerosis patients in southwest Finland. Acta Neurol. Scand (ePub ahead of print22 Jun).

Auriel, E., Gadoth, A.F., Regev, K.F., Karni, A., 2012. Seasonal and H1N1v influenza vaccines in MS: safety and compliance. J. Neurol. Sci. 314, 102–103.

Berkovich, R., Subhani, D., Steinman, L., 2011. Autoimmune comorbid conditions in multiple sclerosis. US Neurol. 7, 132–138.

Breslow, N.E., Day, N.E. (Eds.), 1987. Fitting Models to Continuous Data. Statistical Methods in Cancer Research. Vol. 2. The Design and Analysis of Cohort Studies 2. IARC Scientific Publications, pp. 178–229.

Bronnum-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.

Capkun, G., Dahlke, F., Lahoz, R., et al., 2015. Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: an observational study using the US department of defense administrative claims database. Mult. Scler. Relat. Disord. 4, 546–554.

Caprio, M.G., Russo, C., Giugliano, A., et al., 2016. Vascular disease in patients with multiple sclerosis: a review. Vasc. Med Surg. 4, 2. http://dx.doi.org/10.4172/2329-6925.1000259.

Causes of death, Statistics Finland. ⟨http://www.stat.fi/til/ksyyt/2012/ksyyt_2012_2013-12-30_tie_001_en.html⟩.

Christiansen, C.F., Christensen, S., Farkas, D.K., Miret, M., Sorensen, H.T., Pedersen, L., 2010. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 35, 267–274.

Claudio, L., Fau, R.C., Brosnan, C.F., 1995. Evidence of persistent blood-brain barrier abnormalities in chronic-progressive multiple sclerosis. Acta Neuropathol. 90, 228–238.

Cramer, S.P., Simonsen, H., Frederiksen, J.L., Rostrup, E., Larsson, H.B.W., 2013. Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI. Neuroimage Clin. 10, 182–189.

D'haeseleer, M., Cambron, M., Vanopdenbosch, L., De Keyser, J., 2011. Vascular aspects of multiple sclerosis. Lancet Neurol. 10, 657–666.

Dregan, A., Chowienczyk, P., Molokhia, M., 2017. Cardiovascular and type 2 diabetes morbidity and all-cause mortality among diverse chronic inflammatory disorders. Heart. http://dx.doi.org/10.1136/heartjnl-2017-311214. (Epub ahead of print).

Fromont, A., Binquet, C., Rollot, F., Despalins, R., Well, A., Clerc, L., et al., 2013. Comorbidities at multiple sclerosis diagnosis. J. Neurol. 260, 2629–2637.

Hauser, S.L., Goodwin, D.S., 2008. Multiple sclerosis and other demyelinating diseases. In: Fauci, A.S., Braunwald, E., Kasper, D.L., Hauser, S.L. (Eds.), Harrison's Principles of Internal Medicine, 17th ed. McGraw-Hill Medical, New York, pp. 2611–2621.

Karvonen, M., Viik-Kajander, M., Moltchanova, E., Libman, I., LaPorte, R., Tuomilehto, J., 2000. Incidence of childhood type 1 diabetes worldwide. diabetes mondiale (DiaMond) project group. Diabetes care. 23, 1516–1526.

Kingwell, E., van der Kop, M.F., Zhao, Y.F., et al., 2012. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J. Neurol. Neurosurg. Psychiatry 83, 61–66.

Krökki, O., Bloigu, R., Ansakorpi, H., Reunanen, M., Remes, A.M., 2014. Neurological comorbidity and survival in multiple sclerosis. Mult. Scler. Relat. Disord. 3, 72–77.

Lévesque, L.E., Hanley, J.A., Kezouh, A., Suissa, S., 2010. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 340, b5087.

Liddell, F.D.K., McDonald, J.C., Thomas, D.C., 1977. Methods of cohort analysis:

appraisal by application to asbestos mining. J. R. Stat. Soc. Ser. A 140, 469–491.
Lindsberg, P.J., Grau, A.J., 2003. Inflammation and infections as risk factors for ischemic stroke. Stroke 2518–2532.
Lunde, H.M.B., Assmus, J., Myhr, K.M., et al., 2017. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J. Neurol. Neurosurg. Psychiatry. http://dx.doi.org/10.1136/jnnp-2016-315238.
Marrie, R.A., Yu, B.N., Leung, S., et al., 2012. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult. Scler. 18, 1310–1319.
Marrie, R.A., Cohen, J., Stuve, O.A., et al., 2015a. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult. Scler. 21 (3), 263–281. http://dx.doi.org/10.1177/1352458514564491. (Epub 2015 Jan 26).
Marrie, R.A., Reider, N., Cohen, J., et al., 2015b. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult. Scler. 21 (3), 318–331. http://dx.doi.org/10.1177/1352458514564485. (Epub 2014 Dec 22).
Matsuura, E., Atzeni, F., Sarzi-Puttini, P., et al., 2014. Is atherosclerosis an autoimmune disease? BMC Med. 12, 47.
Meissner, Y., Richter, A., Manger, B., et al., 2017. Serious adverse events and the risk of stroke in patients with rheumatoid arthritis: results from the German RABBIT cohort. Ann. Rheum. Dis. http://dx.doi.org/10.1136/annrheumdis-2017-211209.
Montgomery, S., Hillert, J., Bahmanyar, S., 2013. Hospital admission due to infections in multiple sclerosis patients. Eur. J. Neurol. 20, 1153–1160.
Nurmohamed, M.T., Heslinga, M., Kitas, G.D., 2015. Cardiovascular comorbidity in rheumatic diseases. Nat. Rev. Rheumatol. 11 (12), 693–704.
O'Donnell, M.J., Chin, S.L., Rangarajan, S., et al., 2016. INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 388 (10046), 761–775. http://dx.doi.org/10.1016/S0140-6736(16)30506-2. (Epub2016 Jul 16).
Polman, C., Reingold, S., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69, 292–302.
Ponsonby, A.L., Lucas, R.M., Dear, K., van der Mei, I., Taylor, B., Chapman, C., et al., 2013. The physical anthropometry, lifestyle habits and blood pressure of people presenting with a first clinical demyelinating event compared to controls: the ausimmune study. Mult. Scler. 19, 1717–1725.
Sheu, J., Lin, H., 2013. Association between multiple sclerosis and chronic periodontitis: a population-based pilot study. Eur. J. Neurol. 20, 1053–1059.
Suissa, S., 2005. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom, B.L. (Ed.), Pharmacoepidemiology, 4th ed. John Wiley, pp. 811–829.
Sumelahti, M.L., Hakama, M., Elovaara, I., Pukkala, E., 2010. Causes of death among patients with multiple sclerosis. Mult. Scler. 16, 1437–1442.
Thormann, A., Magyari, M., Koch-Henriksen, N., Laursen, B., Sørensen, P.S., 2016. Vascular comorbidities in multiple sclerosis: a nationwide study from Denmark. J. Neurol. 263 (12), 2484–2493 (Epub 2016 Oct 3).
Urbanek, C., Palm, F., Grau, A.J., 2010. Influenza and stroke risk: a key target not to be missed? Infect. Disord. Drug Targets 10 (2), 122–131.
Wang, Y., Bos, S.D., Harbo, H.F., Thompson, W.K., Schork, A.J., Bettella, F., et al., 2016. Genetic overlap between multiple sclerosis and several cardiovascular disease risk factors. Mult. Scler. 22, 1783–1793.
Wens, I., Dalgas, U., Stenager, E., Eijnde, B.O., 2013. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis - a systematic review. Mult. Scler. 19, 1556–1564.
World Health Organisation, 2016. Global report on diabetes, Geneva.
Wuerfel, J., Paul, F., Zipp, F., 2007. Cerebral blood perfusion changes in multiple sclerosis. J. Neurol. Sci. 259, 16–20.

PUBLICATION IV

End of life in multiple sclerosis: Disability, causes and place of death among cases diagnosed from 1981 to 2010 in Pirkanmaa hospital district in Western Finland

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End of life in multiple sclerosis: Disability, causes and place of death among cases diagnosed from 1981 to 2010 in Pirkanmaa hospital district in Western Finland

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ABSTRACT

Background: Mortality risk and causes of death have been widely studied in MS. Surveys on conditions related to approaching death have not been conducted before in Finland.
Objective: Our aim was to sort out the possible needs for end of life (EOL) care in MS by examining causes, place of death and level of hospitalization by age and MS related disability before approaching death.
Materials: Data included information for MS patients diagnosed from 1981 to 2010 in a Finnish university hospital district. Information on place and causes of death and care prior to death was based on death certificates from Statistics Finland. Decedents initial disease course, disease modifying treatment (DMT) use and MS related disability status by using EDSS were achieved from hospital records.
Results: Data included 113 decedents. Level of disability showed EDSS 6.0 or higher in 54% of the patients. In relapsing onset MS (N 93, 80%) DMTs were used in 11%. Infections, respiratory or other, were the main immediate cause of death (51.3%, n 58) among cases with varying disability. Central or university hospital (42.5%) or community hospital ward (28.3%) were places of death in majority of cases and nursing home (13.3%), home (9.7%) or hospice (3.7%) less often. Place of death did not significantly differ between age-groups (Chi square $p = 0.86$). Mean age at death was 57 years (range 28–90, SD 13.86). Cardiovascular causes of death were reported mainly in age group 60 years or more and suicide in age group younger than 50 years.
Conclusion: The level of hospitalization was high at end of life in all age-groups. High MS related disability and immobility among decedents likely relates to infections as the most common cause of death. Along with our and earlier surveys in this field, we showed that places of death and level of disability before death share similarities in both younger and older age groups highlighting the need of palliative care and end of life care plans in all MS patients with triggers of poor survival. The recently published consensus definition featuring palliative care guideline in MS is aimed at improving end of life care in MS. Our results point at need for future studies in order to assess the impact of palliative care treatment guidelines in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system, starting in early adulthood and affecting 2.3 million people worldwide. Initial disease course is relapsing-remitting (RRMS) in a majority of cases (Scalfari et al., 2014).

At its later stage MS may show a progressive and debilitating course (Leray et al., 2010), accompanied by heterogenous neurological symptoms of varying severity, that cause decrease in quality of life (Kobelt et al., 2006; Ruutiainen et al., 2016), early retirement (Pfleger et al., 2010) and higher mortality ratios as compared to general population (Brønnum-Hansen et al., 2004; Hirst et al., 2008; Lunde et al., 2017; Smestad et al., 2009; Sumelahti et al., 2010). Surveys point that there is an increased risk of infection-related hospitalizations (Pirttisalo et al., 2020) and infection related mortality in MS (Lalmohamed et al., 2012; Montgomery et al., 2013; Nelson et al., 2015).

There is increasing understanding on circumstances and complex patterns that contribute to death due to MS (Harding et al., 2020). Also, the complex conditions related to advanced disability and immobility (Harding et al., 2020) point at need for individual advanced care

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planning in MS (Davies et al., 2016; Sleeman et al., 2013; Strupp et al., 2014). The recently published guidelines for palliative care (PC) of people with severe, progressive multiple sclerosis and studies up to 2017 present evidence-based recommendations for several MS related symptoms (Solari et al., 2020). However, publications or trials are lacking for recommendations in several common symptoms, for example respiratory or swallowing difficulties.

In this study we aim to study the reported conditions related to approaching death in MS by using data from death certificates and hospital patient records among deceased cases in MS cohort diagnosed from 1981 to 2010 at the university health care district Pirkanmaa in Western Finland. We aim to study the immediate and other causes of death by age and MS related disability level in relation to patients´ need for end of life hospital care and place of death.

2. Material and methods

2.1. Data collection

This is a retrospective observational study including confirmed MS patients from 1.1.1981 to 31.12.2010 with a death certificate at University Hospital District of Tampere in Pirkanmaa. The end of follow-up is 31.12.2010. The examination of identified patient records at hospitals and the linkage to Statistics Finland and the Population Register Centre's Population Information System for deaths were approved by The National Institute for Health and Welfare and The Ethics Committee of the Tampere University Hospital District.

Data in this study includes deceased incident MS cases, a detailed description of the catchment population is reported earlier (Holmberg et al., 2013). Cases with ICD-code of multiple sclerosis (codes 340, 341, 377, G35 in the International Classification of Disease, versions 8 to 10) from January 1, 1981, to December 31, 2010, were first identified from administrative registries in hospitals belonging to the University Hospital district of Tampere in Pirkanmaa. Patients who fulfilled the criteria of definite MS at the timepoint of diagnosis were included (McDonald et al., 2001; Polman et al., 2005; Poser et al., 1983).

All included cases had a confirmed MS diagnosis and a Finnish death certificate. If a patient had visited other neurologist in Finland or abroad, information on this was detectable in the patient record. We were able to control for patient information available from all hospitals in the catchment area based on personal identification code of cases.

Linkage of the MS cohort to the Statistics Finland death database from 1 January 1981 until 31 December 2010 was done automatically by using the patient's personal identity code as the key. All residents of Finland have since 1 January 1967 had this unique personal identity code. This code is used in all main registers in Finland and allows reliable computerized record linkages.

2.2. Death certificate process in finland

Any health care unit or licensed physician must immediately report any decease and causes of death to Population Register centre of Finland and National Institute for Health and Welfare, where reports are sent onwards to Statistics Finland. This certificate is on paper form up to 2014 and electronic from 2015. Approximately 80% of all death certificates are issued by the attending physician. A forensic autopsy is performed in 20% of the cases (Korpisaari, 2016).

Statistics Finland maintains Finnish residents' death certificate archives from where death certificate data or copies of death certificates are released for purposes defined by law. Since 1996, the statistics have been compiled based on the 10th revision of the International Classification of Diseases (ICD-10). Between 1987 and 1995, the data were classified using the national classification of diseases 1987 and from 1969 to 1986, the international classification ICD-8 was in use.

Death certificate contains data of the deceased, including sex, age, timepoint and causes of death by immediate, intermediate, and underlying causes, other notable diseases, injuries and contributing factors to death, manner, and place of death. The medical case history during the EOL is reported in these certificates in a form of epicrisis.

2.3. Methods

Death certificates (N 113 in paper form) were scrutinized by authors (AM, MLS). For purposes in this study information was included for the timepoint, place and causes of death by immediate, intermediate, and underlying causes. Data from epicrisis was collected for the final institution of care, disability, contributing diseases and treatments at end of life.

Hospital records were scrutinized (AM, MLS) to collect demographic information for birth year, initial disease course (relapsing-remitting, RRMS or primary progressive, PPMS) (Lublin et al., 2014), MS duration from diagnosis, any exposure to disease modifying treatments (DMT) and last assessment of disability. Disability status at last evaluation was based on given Expanded Disability Status Scale (EDSS) value (Kurtzke, 1983) or description of disability in patient document based on status signs, patient reported symptoms and symptomatic treatment shown in the patient record. Disability categorization into mild, moderate, or severe was used in a similar manner than in our previous prevalence study (Murtonen and Sumelahti, 2020). In case there was no description of handicap at any central nervous system level or any symptoms that needed treatment or rehabilitation, or when the described symptoms and signs could be graded as mild, we categorized patient into a mild disability group, corresponding to EDSS grades < 3.0. Categorization to moderate disability group concerned cases with a reported handicap in several functions, corresponding EDSS grades 3.0–5.5. Severe disability group here included cases with a significant handicap, constant bilateral support required to walk 20 m without resting, corresponding EDSS 6.0 or greater (Solari et al., 2020).

2.3.1. Statistical methods

Statistical analyses were conducted with SPSS version 26. Descriptive statistics, distributions and appropriate tests for significance were used: T-tests to compare two independent groups with a single variable and Chi-Square when there were several categories.

3. Results

During the 30-year follow-up from 1981 to 2010 among 684 confirmed MS cases from the catchment area, a total of 113 cases with death records were scrutinized. Mean age at MS onset was 36.2 years (min 15, max 62, SD 11.2). Mean age at death was 57.4 years (min 28, max 90, SD 13.86). Women (N 63) were slightly older at death, mean 59 years, than men (N 50) 57 years, difference was not significant (T-test $p = 0.244$). Initial disease course was RRMS in 90 (79.6%) and PPMS in 23 (20.4%) cases. Half of the mortality cohort were working aged and reported a marital status, while half were single, divorced or widows. Majority had children.

Distribution of immediate causes and places of death in three age-groups are shown in Table 1. As immediate cause of death MS was recorded in 13 (11.5%) cases. Infections were recorded in a majority of 58 (51.3%) cases. Infections were mainly respiratory in 52 cases (46.0%), gastrointestinal and urinary infections in 2 (1.8%) and sepsis with unknown focus in 4 (3.5%). Cardiovascular causes in 10 cases (11%) were mainly seen in the oldest age group (60 years or older) and suicide in three cases (2.7%) in the youngest group. Group differences by immediate causes of death in age-groups were statistically significant (Chi square $p = 0.006$).

MS as an underlying cause of death (not shown) was recorded in 65 death certificates (57.5%). Other underlying causes were infection in 5, cancer in 13, vascular cause in 19, gastrointestinal cause, other neurological disorder, trauma, and suicide altogether in 14 cases.

Overall, ICD codes for MS were mentioned in 92% of death

Table 1
Characteristics in the study cohort.

	Agegroups, n (%) 0–49 years	50–59 years	60 and over	Total	%
N (%)	34 (30.1)	33 (29.2)	46 (40.7)	113	
Mean age at death (SD) years	41.3 (6.1)	55.1 (2.3)	71.0 (7.6)	57.4	
Mean duration of MS (SD) years	10.9 (5.2)	15.7 (7.2)	21.1 (8.7)	16.5 (8.5)	
Disability (N,%)					
EDSS < 3.0	7 (28)	7 (28)	11 (44)	25 (100)	22.1%
EDSS 3.0–5.5	8 (38.1)	5 (23.8)	8 (38.1)	21 (100)	18.6%
EDSS 6.0 or greater	19 (31.1)	18 (29.5)	24 (39.3)	61 (100)	54.0%
Immediate cause of death (N)					
Infection	16	22	20	58	51.3%
MS	4	5	4	13	11.5%
Cardiovascular	2	0	10	12	10.6%
Cancer	3	2	5	10	8.8%
Accident	3	0	2	5	4.4%
Pulmonary embolism	3	2	0	5	4.4%
Cerebrovascular	0	0	4	4	3.5%
Gastrointestinal	0	2	0	3	2.7%
Suicide	3	0	0	3	2.7%
Place of death (N)					
Central or university hospital ward	17	15	16	48	42.5%
Community hospital ward	6	14	12	32	28.3%
Nursing home	1	0	14	15	13.3%
Home	6	3	2	11	9.7%
Hospice	2	1	1	4	3.5%
Other	2	0	1	3	2.7%

certificates. MS was not shown for 9/113 (7.96%) decedents, where mean age of death was 46.8 years and immediate causes of death were accident or suicide (N 3), acute myocardial infarction (N 3), pulmonary embolism (N1) and cancer (N1).

Do Not Resuscitate (DNR) statement was mentioned in 5/113 cases (4.4%) in the death certificate.

The place of death was central or university (42.5%) or community hospital ward (28.3%), while nursing home (13.3%), home (9.7%) and hospice care (3.7%) represented a minority. No significant difference between place of death existed by age-groups (Chi square $p = 0.86$). Place of death by immediate cause of death is shown in Fig. 1.

Information on the latest hospital recorded disability status at the neurological or other clinic before death was compared with information available in the death record. Based on this information disability before death was mild in 22.1%, (corresponding to EDSS < 3.0, N 25), moderate in 18.6% (corresponding EDSS 3.0–5.5, N 21) and severe in 54% (corresponding EDSS 6.0 or more, N 61). In 5.3% information on disability was not available (not classified, NC, N 6). Distribution of disability using this classification was similar in the three age-groups (<50 years, 50−59 years, 60> years) (Chi-square $p = 0.72$), by initial disease course (RRMS, PPMS) ($p = 0.42$) and by sex ($p = 0.56$), showing statistically nonsignificant differences. Disability distribution by cause of death is shown in Fig. 2 and in by initial disease course in Fig. 3.

4. Discussion

In this MS cohort, care of dying patients and deaths took place mainly at hospital wards. MS related disability was high among majority of decedents and the main immediate cause of death were respiratory infections in all age groups. Result in our report supports earlier observations that MS patients with a severe, progressive disease die in hospital rather than at home (Campbell et al., 2010; Lunde et al., 2017) and confirms the observation on increased risk of infection-related hospitalizations and infection related mortality in MS (Lalmohamed et al., 2012; Montgomery et al., 2013; Nelson et al., 2015). Along with results in earlier surveys, we showed here that this concerns patients in both young age-groups, where end of life care plans are not usually necessitated, and also in older age groups, where slow disease progression may disperse observation of the triggers for palliative care.

The level of hospitalization was high, as almost half (42.5%) of all deaths took place at central or university hospital ward, where the main causes of death were respiratory infections. Majority of reported deaths in all age-groups during the follow-up took place at any health care institutions. Among the four decedents in hospice care, MS and cancer were reported as causes of death. Deaths that took place outside health care institutions related to acute vascular diseases, suicide, and accidents.

This is the first Finnish survey on characteristics of dying MS patients

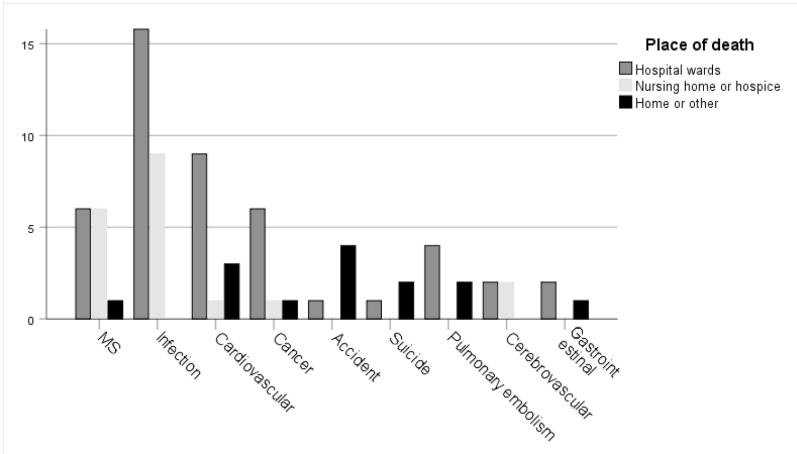

Fig. 1. Place of death by immediate causes of death. Number of cases treated for infections in hospital wards is 49.

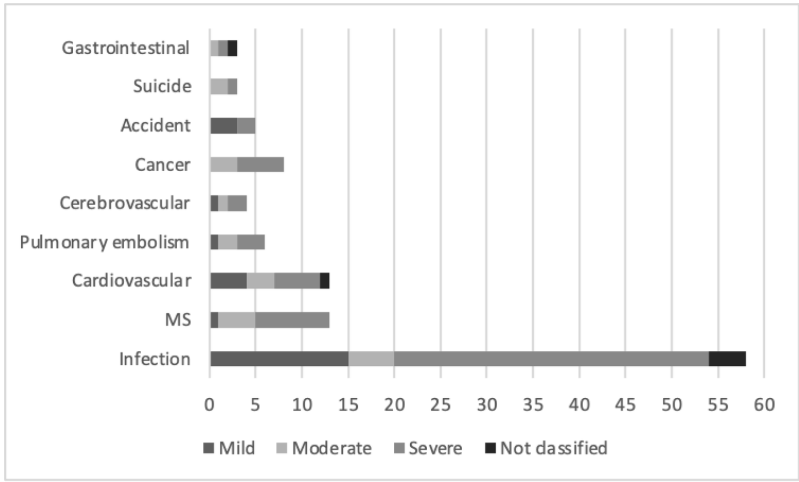

Fig. 2. Distribution of disability before care period prior to death by immediate cause of death.

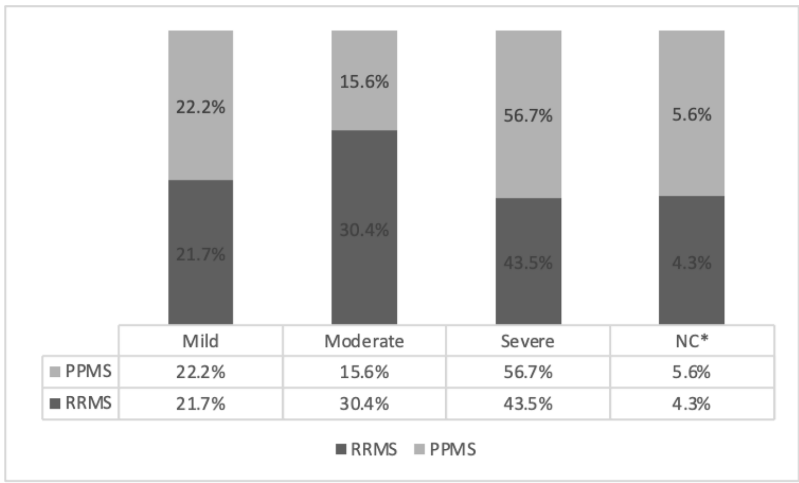

Fig. 3. Disability distribution before care period prior to death by disease course.

covering a long follow up for 30 years in a cohort of 113 decedents. During the follow up the structure of health care system by large has remained unchanged, and facilities are comparable to those in other Scandinavian and North European countries. Finland offers its residents a universal healthcare, which consists of a highly decentralized three-level publicly funded healthcare system and a much smaller private sector. The diagnosis of MS is practically always confirmed in public health care neurology clinics, where regular control visits also take place. The death certificate procedure has been described earlier in this report and it follows the international standards (World Health Organization, 1979).

In our data the ICD code for MS was mentioned in 92% of death certificates, rate being somewhat higher than reported elsewhere, 80–90% (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Harding et al., 2020). MS as an immediate cause of death was recorded in 11.5% of decedents, which was similar to previously reported 9% (Hirst et al., 2008). As an underlying cause of death MS was mentioned in 57.5% of records, being similar or a bit higher than reported previously, 34–56% (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Hirst et al., 2008; Smestad et al., 2009).

Mean age at death, 57.4 years, was lower than reported in two previous studies: 74.5 years (Harding et al., 2020) and 65.3 years (Hirst et al., 2008). In our data the mean age of death was lowest (not shown in results, 46.8 years) among cases with a missing MS ICD code. High inclusion rate of diagnosed cases in this set of data could be among explanations for the observed low mean age of death. However, the standardized mortality rate (SMR) of 2.8 reported in several populations is true also in Finland (Brønnum-Hansen et al., 2004; Lunde et al., 2017; Sumelahti et al., 2010). In line with earlier reports, infections (51.3%) were the main cause of death here in our cohort, followed by cardiovascular causes (10.6%) (Brønnum-Hansen et al., 2004; Harding et al., 2020; Hirst et al., 2008; Smestad et al., 2009).

We believe to have a full coverage of MS cases and their disease course in the study district (Holmberg et al., 2013; Murtonen and

Sumelahti, 2020). The cohort was followed retrospectively from disease onset by using hospital records. The earlier reported high MS mortality and distribution of causes of death in other Finnish districts (Sumelahti et al., 2010) and our present data on causes of death from Pirkanmaa district are similar to results in other medium-to high MS risk areas (Cutter et al., 2015; Lalmohamed et al., 2012; Lunde et al., 2017; Sumelahti et al., 2010), why we believe that our results here are reliable for comparisons.

Exploration of determinants of place of death is important for public health policy, which aims at improving the quality of end of life care. Our aim here was to assess the characteristics of MS patients approaching death, and specify their place of death by healthcare level, which is supposed to relate to the complexity of the medical needs as well as the skills and specialties of the providers. This information and causes of death were based on death certificates and hospital patient records and information was sorted out to evaluate the possible needs and unmet needs for end of life care in MS. Much of the information for the purposes in this study was available from these sources (Davies et al., 2016). The domains for specific symptoms at advanced stages of MS, or information on patients´ living conditions, changes in social or working status and need for medical care and support, along with differences in caregiver roles were not available from the sources used in this study. In our hospital record data, the specific MS symptoms such as fatique, cognitive symptoms, pain, spasticity, bladder symptoms, dysphagia, dyspnea or other respiratory symptoms prior to the dying phase, were randomly reported. During the care period prior to death recordings of recurrent infections, aspiration pneumonia and description for respiratory insufficiency were found in the epicrisis in the death certificate. However, the specific triggers in order to evaluate the applicable healthcare level for patients approaching death were randomly reported in hospital records, and information is thus deficient for research purposes. We also lacked some information on patients´ sociodemographic status. This information in some studies has shown to be associated with cause and place of death, and includes factors such as age and marital status, and degree of urbanization and healthcare system, while social status plays lesser role (Gomes and Higginson, 2006; Houttekier et al., 2011).

Use of more structured information is thus needed in future studies. In addition, national registers in Finland, such as the Care Register for Healthcare informing about hospital admissions, National Health Insurance registry providing information on retirement, rehabilitation and other health related support and data from Finnish MS patient Register will be useful sources in future register-based studies.

This research is subject to several limitations mentioned above, such as lack of detailed information on specific symptoms and need of care. However, despite these shortcomings, disability status and information on ambulation were described in majority of hospital records and death certificates. Although information on disability or the EDSS score offer a limited description on need of care, increased disability seems to be a solid indicator for a permanently advanced disability and immobility in MS. In our cohort over half of decedents showed a severe disability before death up to end of follow-up in 2010, while mild and moderate disability were shown in the rest of the cases. As no uniform definition for progressive, severe MS exists, we used the definition used in EAN guideline, where severe MS was assessed when a constant bilateral support required to walk 20 m without resting corresponding to EDSS$>$ 6.0 or higher (Solari et al., 2020). This classification has been used earlier also in the prevalence study in Western Finland in 2010, including the catchment area in this study (Murtonen and Sumelahti, 2020). The disability status was moderate or severe among almost half of the prevalent cases, where mean age was 50.2 years. Such information on disability from prevalence cohorts could be useful for future health care planning (Murtonen and Sumelahti, 2020).

In our data severe disability was observed in both RRMS and PPMS, nor were there differences by immediate causes of death or place of death by disease course. The severe disability in 44% in RRMS is explained by development of secondary progressive course, generally shown in 40% after 15 years in relapsing–remitting disease (Scalfari et al., 2014). The DMT effect may be considered minor as only 11% among deceased RRMS patients had used DMTs. It may be expected that increasing use of available immunomodulatory treatments, such as DMTs, may suppress inflammation, prolong patients' performance and time to retirement (Heinonen et al., 2020) but it is unknown how these effects are reflected over the entire disease trajectory. Considering the high number of aging treatment naïve MS patients in many current MS cohorts, the awareness of risk factors and progressive symptoms in all disease course groups remains important. Information on the common risk factors may be derived from the earlier reported causes of death in progressive MS, which include infections, such as aspiration pneumonia or urinary tract infections, and complications of falls and fractures, and sepsis secondary to pressure ulcers (Hirst et al., 2008; Sumelahti et al., 2010).

A good proportion of decedents in our cohort had died in hospital settings in spite of a progressed disability which raises the question of unplanned hospitalizations (Seeber et al., 2019; Veronese et al., 2017). At present we do not know how MS patients engage in the process of decision-making, but it is suspected that also in our cohort there is a need for increasing awareness of advance care planning (ACP), supported by reported benefits and the generally low use in neurological diseases (Higginson et al., 2009; Hussain et al., 2018; Seeber et al., 2019). In recent studies contexts and mechanisms underpinning engagement in ACP have been identified in MS, indicating the crucial role of health care professionals and communication throughout the whole course of progressive disease (Seeber et al., 2019; Solari et al., 2018; Veronese et al., 2017). Similar to benefits in ACP, early referral to PC has shown advantages such as better pain management, quality of life, less aggressive EOL care and reduced late-life acute-hospital use (Qureshi et al., 2019; Rosenwax et al., 2015; Spilsbury et al., 2017). PC is a fairly new concept in MS (Solari et al., 2020; Strupp et al., 2016, 2014). The qualifications have only recently been assessed in 2016 by Strupp J et al. (Strupp et al., 2016) indicating benefits in severe MS (Higginson et al., 2009). General triggers for need of PC relate to common symptoms in progressing MS such as deteriorating physical function, weight loss, dysphagia and recurrent infections and aspiration pneumonia (Hussain et al., 2018). Effectiveness of PC among late stage MS patients is expected to be similar than in other neurological diseases (Strupp et al., 2014). In 2014 the Delphi study group reached consensus that specialized PC in MS should begin once the disease has progressed up to EDSS $>$ 6 and nursing care required, and a specialized PC should be consulted when the need exists for communication about disease progression, psychological support, relatives support and pain medication (Strupp et al., 2014). This common lack of integration of PC in EOL may call for a need for standardized referral criteria (Ahmed et al., 2004) and a more widespread empowerment (Westerlund et al., 2018).

4.1. Limitations

As discussed above, this study is subject to several limitations. Detailed information concerning symptoms, all medications and need of care during the days prior to death is lacking in hospital patient records or death certificates. Similarly, information on living conditions, social status, or specific triggers to evaluate the appropriate place of care for patients approaching death were not available or reported randomly. Same is true for detailed information about MS-symptoms and disability among those decedents, whose MS was progressed and were mainly treated in primary health care. Information of possible DNR-statement may as well be lacking from our sources of information. However, in majority of cases there was enough information to categorize the disability into one of the three EDSS-classes discussed above.

5. Conclusions

High disability, hospital deaths and infections were common characteristics of the dying MS patients in all age groups in this cohort. Our results thus reflect the need for better integration of advanced care planning on the comprehensive care of MS patients showing severe disease progression. Our results also point need for future studies in order to assess the impact of palliative care treatment guidelines in MS (Strupp et al., 2016).

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Credit author statement

Annukka Murtonen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing

Juho Lehto: Conceptualization, Writing – Original Draft, Writing – Review & Editing

Marja-Liisa Sumelahti: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration, Funding acquisition

Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ahmed, N., Bestall, J.C., Ahmedzai, S.H., Payne, S.A., Clark, D., Noble, B., 2004. Systematic review of the problems and issues of accessing specialist palliative care by patients, carers and health and social care professionals. Palliat. Med. 18, 525–542. https://doi.org/10.1191/0269216304pm921oa.

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. https://doi.org/10.1093/brain/awh104.

Campbell, C.W., Jones, E.J.S., Merrills, J., 2010. Palliative and end-of-life care in advanced Parkinson's disease and multiple sclerosis. Clin. Med. 10, 290–292. https://doi.org/10.7861/clinmedicine.10-3-290.

Cutter, G.R., Zimmerman, J., Salter, A.R., Knappertz, V., Suarez, G., Waterbor, J., Howard, V.J., Marrie, R.A., 2015. Causes of death among persons with multiple sclerosis. Mult. Scler. Relat. Disord. 4, 484–490. https://doi.org/10.1016/j.msard.2015.07.008.

Davies, J.M., Gao, W., Sleeman, K.E., Lindsey, K., Murtagh, F.E., Teno, J.M., Deliens, L., Wee, B., Higginson, I.J., Verne, J., 2016. Using routine data to improve palliative and end of life care. BMJ Support. & Palliat. Care 6. https://doi.org/10.1136/bmjspcare-2015-000994, 257 LP –262.

Gomes, B., Higginson, I.J., 2006. Factors influencing death at home in terminally ill patients with cancer: systematic review. BMJ 332, 515–521. https://doi.org/10.1136/bmj.38740.614954.55.

Harding, K., Zhu, F., Alotaibi, M., Duggan, T., Tremlett, H., Kingwell, E., 2020. Multiple cause of death analysis in multiple sclerosis: a population-based study. Neurology 94, e820–e829. https://doi.org/10.1212/WNL.0000000000008907.

Heinonen, T., Castrén, E., Luukkaala, T., Mäkinen, K., Ruutiainen, J., Kuusisto, H., 2020. The retirement rate due to multiple sclerosis has decreased since 1995– A retrospective study in a Finnish central hospital. Mult. Scler. Relat. Disord. 45, 102360 https://doi.org/10.1016/j.msard.2020.102360.

Higginson, I.J., McCrone, P., Hart, S.R., Burman, R., Silber, E., Edmonds, P.M., 2009. Is Short-Term Palliative Care Cost-Effective in Multiple Sclerosis? A Randomized Phase II Trial. J. Pain Symptom Manage. 38, 816–826. https://doi.org/10.1016/j.jpainsymman.2009.07.002.

Hirst, C., Swingler, R., Compston, D.A.S., Ben-Shlomo, Y., Robertson, N.P., 2008. Survival and cause of death in multiple sclerosis: a prospective population-based study. J. Neurol. Neurosurg. & Psychiatry 79. https://doi.org/10.1136/jnnp.2007.127332, 1016 LP –1021.

Holmberg, M., Murtonen, A., Elovaara, I., Sumelahti, M.-L., 2013. Increased Female MS Incidence and Differences in Gender-Specific Risk in Medium- and High-Risk Regions in Finland from 1981 to 2010. Mult. Scler. Int. 2013, 182516 https://doi.org/10.1155/2013/182516.

Houttekier, D., Cohen, J., Surkyn, J., Deliens, L., 2011. Study of recent and future trends in place of death in Belgium using death certificate data: a shift from hospitals to care homes. BMC Public Health 11 (228). https://doi.org/10.1186/1471-2458-11-228.

Hussain, J., Allgar, V., Oliver, D., 2018. Palliative care triggers in progressive neurodegenerative conditions: an evaluation using a multi-centre retrospective case record review and principal component analysis. Palliat. Med. 32, 716–725. https://doi.org/10.1177/0269216318755884.

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, 918–926. https://doi.org/10.1136/jnnp.2006.090365.

Korpisaari, P., 2016. Electronic Death Certificate - Report Series of European Commission Grant Agreement. Finnish institute for Health and Welfare.

Kurtzke, J., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452. https://doi.org/10.1212/wnl.33.11.1444.

Lalmohamed, A., Bazelier, M.T., Van Staa, T.P., Uitdehaag, B.M.J., Leufkens, H.G.M., De Boer, A., De Vries, F., 2012. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur. J. Neurol. 19, 1007–1014. https://doi.org/10.1111/j.1468-1331.2012.03668.x.

Leray, E., Yaouanq, J., Le Page, E., Coustans, M., Laplaud, D., Oger, J., Edan, G., 2010. Evidence for a two-stage disability progression in multiple sclerosis. Brain 133, 1900–1913. https://doi.org/10.1093/brain/awq076.

Lublin, F.D., Reingold, S.C., Cohen, J.A., Cutter, G.R., Sørensen, P.S., Thompson, A.J., Wolinsky, J.S., Balcer, L.J., Banwell, B., Barkhof, F., Bebo Jr,, B., Calabresi, P.A., Clanet, M., Comi, G., Fox, R.J., Freedman, M.S., Goodman, A.D., Inglese, M., Kappos, L., Kieseier, B.C., Lincoln, J.A., Lubetzki, C., Miller, A.E., Montalban, X., O'Connor, P.W., Petkau, J., Pozzilli, C., Rudick, R.A., Sormani, M.P., Stüve, O., Waubant, E., Polman, C.H., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83, 278–286. https://doi.org/10.1212/WNL.0000000000000560.

Lunde, H.M.B., Assmus, J., Myhr, K.-M., Bø, L., Grytten, N., 2017. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J. Neurol. Neurosurg. Psychiatry 88, 621–625. https://doi.org/10.1136/jnnp-2016-315238.

McDonald, W.I., Compston, A., Edan, G., Goodkin, D., Hartung, H.-P., Lublin, F.D., McFarland, H.F., Paty, D.W., Polman, C.H., Reingold, S.C., Sandberg-Wollheim, M., Sibley, W., Thompson, A., Van Den Noort, S., Weinshenker, B.Y., Wolinsky, J.S., 2001. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann. Neurol. 50, 121–127. https://doi.org/10.1002/ana.1032.

Montgomery, S., Hillert, J., Bahmanyar, S., 2013. Hospital admission due to infections in multiple sclerosis patients. Eur. J. Neurol. 20, 1153–1160. https://doi.org/10.1111/ene.12130.

Murtonen, A., Sumelahti, M.-L., 2020. Multiple sclerosis prevalence in 2000 and 2010 in Western Finland. Acta Neurol. Scand. 141 https://doi.org/10.1111/ane.13203.

Nelson, R.E., Xie, Y., DuVall, S.L., Butler, J., Kamauu, A.W.C., Knippenberg, K., Schuerch, M., Foskett, N., LaFleur, J., 2015. Multiple sclerosis and risk of infection-related hospitalization and death in US veterans. Int. J. MS Care 17, 221–230. https://doi.org/10.7224/1537-2073.2014-035.

Organization, W.H., 1979. Medical certification of cause of death : instructions for physicians on use of international form of medical certificate of cause of death.

Pfleger, C.C.H., Flachs, E.M., Koch-Henriksen, N., 2010. Social consequences of multiple sclerosis (1): early pension and temporary unemployment—A historical prospective cohort study. Mult. Scler. J. 16, 121–126. https://doi.org/10.1177/1352458509352196.

Pirttisalo, A.-L., Sipilä, J.O.T., Viitala, M., Soilu-Hänninen, M., 2020. Trends and characteristics of infection-related hospital admissions in multiple sclerosis patients in Southwest Finland in 2009-2018. Mult. Scler. Relat. Disord. 44, 102328 https://doi.org/10.1016/j.msard.2020.102328.

Polman, C.H., Reingold, S.C., Edan, G., Filippi, M., Hartung, H.-P., Kappos, L., Lublin, F. D., Metz, L.M., McFarland, H.F., O'Connor, P.W., Sandberg-Wollheim, M., Thompson, A.J., Weinshenker, B.G., Wolinsky, J.S., 2005. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria. Ann. Neurol. 58, 840–846. https://doi.org/10.1002/ana.20703.

Poser, C.M., Paty, D.W., Scheinberg, L., McDonald, W.I., Davis, F.A., Ebers, G.C., Johnson, K.P., Sibley, W.A., Silberberg, D.H., Tourtellotte, W.W., 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann. Neurol. 13, 227–231. https://doi.org/10.1002/ana.410130302.

Qureshi, D., Tanuseputro, P., Perez, R., Pond, G.R., Seow, H.-Y., 2019. Early initiation of palliative care is associated with reduced late-life acute-hospital use: a population-based retrospective cohort study. Palliat. Med. 33, 150–159. https://doi.org/10.1177/0269216318815794.

Rosenwax, L., Spilsbury, K., Arendts, G., McNamara, B., Semmens, J., 2015. Community-based palliative care is associated with reduced emergency department use by people with dementia in their last year of life: a retrospective cohort study. Palliat. Med. 29, 727–736. https://doi.org/10.1177/0269216315576309.

Ruutiainen, J., Viita, A.-M., 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, 21–33. https://doi.org/10.3111/13696998.2015.1086362.

Scalfari, A., Neuhaus, A., Daumer, M., Muraro, P.A., Ebers, G.C., 2014. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. J. Neurol. Neurosurg. & Psychiatry 85 (67). https://doi.org/10.1136/jnnp-2012-304333. LP –75.

Seeber, A.A., Pols, A.J., Hijdra, A., Grupstra, H.F., Willems, D.L., de Visser, M., 2019. Advance care planning in progressive neurological diseases: lessons from ALS. BMC Palliat. Care 18 (50). https://doi.org/10.1186/s12904-019-0433-6.

Sleeman, K.E., Ho, Y.K., Verne, J., Glickman, M., Silber, E., Gao, W., Higginson, I.J., 2013. Place of death, and its relation with underlying cause of death, in Parkinson's disease, motor neurone disease, and multiple sclerosis: a population-based study. Palliat. Med. 27, 840–846. https://doi.org/10.1177/0269216313490436.

Smestad, C., Sandvik, L., Celius, E.G., 2009. Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. Mult. Scler. 15, 1263–1270. https://doi.org/10.1177/1352458509107010.

Solari, A., Giordano, A., Patti, F., Grasso, M.G., Confalonieri, P., Palmisano, L., Ponzio, M., Borreani, C., Rosato, R., Veronese, S., Zaratin, P., Battaglia, M.A., Project, P., 2018. Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis. Mult. Scler. 24, 663–674. https://doi.org/10.1177/1352458517704078.

Solari, A., Giordano, A., Sastre-Garriga, J., Köpke, S., Rahn, A.C., Kleiter, I., Aleksovska, K., Battaglia, M.A., Bay, J., Copetti, M., Drulovic, J., Kooij, L., Mens, J., Meza Murillo, E.R., Milanov, I., Milo, R., Pekmezovic, T., Vosburgh, J., Silber, E., Veronese, S., Patti, F., Voltz, R., Oliver, D., 2020. EAN guideline on palliative care of people with severe, progressive multiple sclerosis. Eur. J. Neurol. 27, 1510–1529. https://doi.org/10.1111/ene.14248.

Spilsbury, K., Rosenwax, L., Arendts, G., Semmens, J.B., 2017. The impact of community-based palliative care on acute hospital use in the last year of life is modified by time to death, age and underlying cause of death. A population-based retrospective cohort study. PLoS ONE 12. https://doi.org/10.1371/journal.pone.0185275 e0185275–e0185275.

Strupp, J., Romotzky, V., Galushko, M., Golla, H., Voltz, R., 2014. Palliative care for severely affected patients with multiple sclerosis: when and why? Results of a Delphi survey of health care professionals. J. Palliat. Med. 17, 1128–1136. https://doi.org/10.1089/jpm.2013.0667.

Strupp, J., Voltz, R., Golla, H., 2016. Opening locked doors: integrating a palliative care approach into the management of patients with severe multiple sclerosis. Mult. Scler. 22, 13–18. https://doi.org/10.1177/1352458515608262.

Sumelahti, M.-L., Hakama, M., Elovaara, I., Pukkala, E., 2010. Causes of death among patients with multiple sclerosis. Mult. Scler. J. 16, 1437–1442. https://doi.org/10.1177/1352458510379244.

Veronese, S., Gallo, G., Valle, A., Cugno, C., Chiò, A., Calvo, A., Cavalla, P., Zibetti, M., Rivoiro, C., Oliver, D.J., 2017. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: NE-PAL, a pilot randomised controlled study. BMJ Support. & Palliat. Care 7. https://doi.org/10.1136/bmjspcare-2014-000788, 164 LP –172.

Westerlund, C., Tishelman, C., Benkel, I., Fürst, C.J., Molander, U., Rasmussen, B.H., Sauter, S., Lindqvist, O., 2018. Public awareness of palliative care in Sweden. Scand. J. Public Health 46, 478–487. https://doi.org/10.1177/1403494817751329.