Socioeconomic factors in multiple sclerosis

Thesis for the degree of Philosophiae Doctor (PhD)

Heidi Øyen Flemmen

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Institute of Clinical Medicine

Faculty of Medicine

University of Oslo

Department of Neurology

Telemark Hospital Trust

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Skien, December 2022

Heidi Øyen Flemmen

ABBREVIATIONS

AHSCT	Autologous haematopoietic stem cell transplantation
BBB	Blood-brain barrier
BOT	Buskerud Oslo Telemark
CI	Confidence interval
CIS	Clinical isolated syndrome
CSF	Cerebrospinal fluid
DIT	Dissemination in time
DIS	Dissemination in space
DMT	Disease modifying treatment
EAN	European Academy of Neurology
EBV	Epstein - Barr virus
ECTRIMS	European Committee of Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
Gd	Gadolinium
ICD	International Classification of Diseases
IgG	Immunoglobulin G
IgG index	CSF IgG: serum IgG/CSF albumin: serum albumin
IM	Infectious mononucleosis
IQR	Interquartile range
LP	Lumbar puncture
MAGNIMS	Magnetic resonance Imaging in Multiple Sclerosis
MS	Multiple sclerosis
MSSS	Multiple Sclerosis Severity Score
MRI	Magnetic Resonance Imaging
NEDA	No Evidence of Disease Activity
NfL	Neurofilament Light chain
OCB	Oligo-clonal bands

OR	Odds ratio
OUS	Oslo University Hospital
RMS	Relapsing multiple sclerosis
PIRA	Progression Independent of Relapse Activity
PML	Progressive multifocal leukoencpehalopathy
PMS	Progressive multiple sclerosis
PPMS	Primary progressive multiple sclerosis
pwMS	People with multiple sclerosis
RAW	Relapse-associated Worsening
SD	Standard deviation
SES	Socioeconomic status
SN	Statistics Norway
SPMS	Secondary progressive multiple sclerosis
STHF	Sykehuset Telemark Helse Foretak (Telemark Hospital Trust)
VVHF	Vestre Viken Helse Foretak (Vestre Viken Hospital Trust)

1. THESIS SUMMARY

The overall aim of this project was to evaluate the impact of socioeconomic factors on different aspects of multiple sclerosis (MS). There is substantial evidence that individuals with low socioeconomic status (SES) have poorer health conditions in general, compared to those with higher SES. This is also seen in welfare states traditionally marked by commitment to social equality, such as the Nordic countries. MS occurs with greater frequency in high-income nations, and some studies have concluded that there is a tendency for higher susceptibility to MS in households of greater affluence. The evidence for a social gradient in risk for MS in a multinational review is however inconsistent. The influence of socioeconomic status on progression in MS is sparsely investigated. To identify potential risk factors for disease severity and progression is of great importance in the treatment of MS. Several studies report an impact of socioeconomic factors on access to disease modifying treatment (DMT) in MS, with a trend of less access to more deprived persons.

The first paper aimed to explore the trends in prevalence and incidence of multiple sclerosis (MS) in Telemark county, Norway, over the past two decades, with focus on differences between rural and urban areas. We found a prevalence of MS in Telemark among the highest ever reported in Norway, consistent with an increasing incidence in the county over the past twenty years. We also found a higher prevalence in the rural areas that is unlikely to be explained by possible risk factors like latitude, exposure to sunlight and diet.

For paper II and III we used an MS registry of a near complete and geographically well-defined population, combined with data from Statistics Norway. In paper II we found higher maternal level of education in people with MS' (pwMS) adolescence associated with less pronounced disease progression. High maternal education was also associated with younger age and lower EDSS at disease onset, as well as shorter time from onset to diagnosis. Paper III confirmed that socioeconomic factors had some impact on access to disease modifying treatment (DMT). People with the highest levels of education were more likely to be ever treated with a DMT. However, when analysing access to high efficacy DMT as a first drug, a strategy that has been focused in the updated national treatment strategies, we did not find that deprived pwMS had less access. Access to high efficacy treatment was determined by disease severity, independent of the SES. We concluded that since 2012, the pwMS in this Norwegian cohort are treated equally with DMT in terms of different measures of socioeconomic position.

Sammendrag på norsk

Målsettingen med denne avhandlingen var å undersøke sosioøkonomiske faktorers påvirkning på ulike aspekter av multippel sklerose (MS). Det er kjent at personer med lavere sosioøkonomisk status (SØS) har dårligere helse for en lang rekke tilstander sammenliknet med personer med høyere SØS. Dette overordnede mønsteret observeres også i velferdsnasjoner der samfunnsstrukturen bygges på et ønske om sosial likhet, som i de Nordiske landene. På verdensbasis er det størst forekomst av MS i høy-inntektsland. Dette har ført til en oppfatning at det kan være høyere risiko for å utvikle MS hos personer med høyere SØS. Studier som er kommet gjennom senere år, har dog vist at denne trenden ikke er helt entydig. Betydningen av SØS på sykdomsprogresjon ved MS er lite undersøkt, men resultater som foreligger, viser at lavere SØS gir økt risiko for raskere progresjon. Flere studier har vist at sosioøkonomiske faktorer også spiller inn på tilgangen til sykdomsmodifiserende behandling ved MS. Trenden er at personer med lavere SØS har dårligere tilgang på behandling.

I første artikkel så vi på utviklingen av forekomst (prevalens og insidens) av MS i Telemark fylke, Norge, over de siste to tiårene. Resultatet viste at forekomsten av MS i Telemark var blant de høyeste noensinne rapportert i Norge. Vi sammenliknet MS-forekomst mellom urbane og rurale områder av fylket, og fant en høyere forekomst i bygde-kommunene i Telemark. Dette kan ikke forklares av de kjente risikofaktorene for MS, som vanligvis brukes som forklaring på prevalensforskjeller, som alderssammensetning, breddegrad, tilgang på sollys eller diett.

I andre og tredje artikkel har vi benyttet et nyopprettet MS register fra Buskerud, Oslo og Telemark («BOT-MS») med tilnærmet komplett dekningsgrad. Vi har kombinert funn fra sykejournaler med opplysninger fra Statistisk Sentralbyrå. I andre artikkel viste vi at personer som vokser opp med mødre med et høyt utdanningsnivå, har mindre uttalt sykdomsprogresjon for MS. Høy utdanning hos mødre var også assosiert med yngre alder, lavere sykdomsbyrde ved debut og kortere tid fra første symptom til diagnose. I tredje artikkel viste vi at sosioøkonomiske faktorer til en viss grad påvirket tilgangen til sykdomsmodifiserende behandling ved MS da dette ble tilgjengelig på slutten av 90-tallet, siden personer med høyere utdanning i litt større grad var behandlet. I de senere årene er nasjonale behandlingsstrategier fokusert på at personer med MS bør tilbys høy-effektiv sykdomsmodifiserende behandling fra start. Vi fant ingen sammenheng mellom SØS og tilgang på slik høy-effektiv behandling. Vi fant derimot at personer med alvorligere sykdomstegn har større sannsynlighet for å starte tidlig med høy-effektiv behandling. Vi konkluderte med at i tiden etter 2012 er det ingen forskjell i tilgangen på sykdomsmodifiserende behandling mellom personer med ulik sosioøkonomisk bakgrunn.

2. LIST OF PUBLICATIONS INCLUDED

I. **Prevalence of multiple sclerosis in rural and urban district in Telemark county, Norway**, (HØ Flemmen, CS Simonsen, P Berg-Hansen, SM Moen, H Kersten, K Heldal, EG Celius), Multiple Sclerosis and Related Disorders, 2020.

II. **Maternal education has significant influence on progression in multiple sclerosis**, (HØ Flemmen, CS Simonsen, L Broch, C Brunborg, P Berg-Hansen, SM Moen, H Kersten, EG Celius), Multiple Sclerosis and Related Disorder, 2021.

III. **The influence of socioeconomic factors on access to disease modifying treatment in a Norwegian multiple sclerosis cohort**, (HØ Flemmen, CS Simonsen, L Broch, C Brunborg, P Berg-Hansen, SM Moen, H Kersten, EG Celius), Multiple Sclerosis and Related Disorder, 2022.

3. INTRODUCTION AND BACKGROUND

Multiple sclerosis (MS) is a common diagnosis in neurology. MS is a chronic disease, affecting more than 2.8 million people world-wide. Onset is usually in younger age, and 2 out of 3 people with MS (pwMS) are female. In the past two decades, there has been a paradigm shift in the treatment of MS with the introduction of the disease modifying treatments (DMT), corresponding to an observed improvement of prognosis. Regardless, the disease still develops and progresses differently in people affected, and response to treatment also varies. There are a number of risk factors for both disease susceptibility and progression. The influence of socioeconomic factors in health in general and specifically in MS, is particularly interesting.

3.1. History of MS

The search for the origin of a disease is most likely rooted in a desire to put the ongoing work into a context. Neurology, in particular, is a field in which history has seen phases from observation, via systematization, to characterization of specific diagnostic entities. There is an unwritten rule among neurologists always to seek the eldest story confirming the disease of interest, and MS researchers do not deviate from this trend. There are several descriptions, from many centuries back, with named, and partly famous persons, who have expressed certain symptoms and characteristics which we today can recognize as MS. One of the very first, is the description of Dutch Lidwina of Schiedam (1380-1433) who experienced various neurological symptoms during the course of her life (Medaer, 1979). Another is the description of Augustus d'Esté, an illegitimate grandson of King George III of England, on October 17th, 1827:

"At Florence I began to suffer from a confusion of sight: about the 6th of November the malady increased to the extent of my seeing all objects double. Each eye had its separate vision (…) I remained in this extreme state of weakness for about 21 days, during which period I fell down about 5 times (never fainting) from my legs not being strong enough to carry my body. I never once fainted or had any sort of fit: debility, extreme debility, was the only cause of my falling" (Murray, 2005).

There is also evidence of MS in older Nordic litterateur, like the written stories of the Icelandic bishop, Thorlak Thorhallsson (1133-1193), who had various symptoms from the nervous system that healed. In fact, it has even been argued that the Vikings' raids have spread the genetic susceptibility of the disease (Poser, 1994).

Through systematic observations and records, a phenomenon of people suffering from relapsing and progressive neurological disease appears. Several clinicians, pathologist and anatomists contributed to the definition of the disease. Among them, Robert Carswell in Scotland, who made the first

descriptions of disseminated plaques in the nervous system and published illustrations of these in his *Pathological Anatomy* in 1838. However, Carswell failed to provide any clinical description of the cases. A contributor to both the anatomical and clinical expression, was the German Friedrich von Frerichs, who provided a description of an affliction he called "*Hirnsklerose*" (brain sclerosis), consisting of a clinical presentation and confirmed by results from autopsies. Edmé Vulpian in Paris and Ernst Leyden in Berlin described cases with episodic neurological symptoms, including suggestion of a hereditary pattern. The disease-frame of MS crystallised at the end of the nineteenth century, but it is generally Jean–Martin Charcot who has been accredited the "discovery of MS". Charcot was impressed by the sclerosis in the scattered lesions and in 1868 at the Salpêtrière in Paris, he gave a series of lectures named "*sclérose en plaque disseminée"*. Charcot's framing of the disease of *sclerosis multiplex*, or MS, has since been a structure upon which further advances have been built (Murray, 2005, Murray, 2009).

The next five decades brought several confirmations and refinements of Charcot's clinical and pathological observations. James Dawson (1870-1927) published in 1916-1918 a monumental work exploring the nature of the underlying processes of multiple sclerosis. He described cellular changes, reviewed theories of aetiology and discussed in detail the theories of an inflammatory process. He was convinced there had to be a specific external agent causing the disease. Dawson referred to "shadow sclerosis", plaques that have a definite shape, and his name continues to be linked with the appearance of flame-like lesions radiating off the corpus callosum, later called "Dawson's fingers" when visible on brain magnetic resonance imaging (MRI) (Murray, 2005).

From the 1920s to the 1950s, the lack of a specific diagnostic test perpetuated the notion that MS was a condition that was difficult to diagnose. The most common differential diagnoses were neuro-syphilis and hysteria (Talley, 2005), and syphilis therapies were used for MS until the 1940s (Murray, 2005). The hypothesis that MS had an infectious origin persisted for many years, and as a consequence it was logical to test antibiotics as a therapy after the discovery of penicillin in the 1940s (Murray, 2009).

In 1951, Marius Haarr (1908-1999) published the first Norwegian doctoral thesis on multiple sclerosis, *Periphlebitis retinae in multiple sclerosis – a clinical examination*. He deduced that the findings of inflammatory infiltrates in the ocular fundus had the same explanation as the lesions in the brain in patients with MS (Holmoy and Jorstad, 2021). One year later, the first epidemiological study of MS in Norway was published by a Canadian, Roy L. Swank, in the New England Journal of Medicine. He postulated an association with farming, dairying and low seafood consumption in

inland areas of Norway as an explanation for the higher incidence of MS in the inland compared to the coastal areas (Swank et al., 1952).

The search for the cause of MS has been comprehensive and the pathogenesis is still not completely understood. The postulation of a possible hereditary component has led to large genetic projects (Patsopoulos et al., 2019, Beecham et al., 2013). Perhaps the most significant contribution in the development of the diagnostic process of MS, is the introduction of MRI, first described by Ian Young, London, in 1981 (Young et al., 1981).

The treatment of MS has evolved from widespread use of diets, herbs, hydrotherapy, suspension apparatus, vibration or different types of electrical therapy (Murray, 2005). In the 1960s corticosteroids were introduced to limit the severity of relapses. In the 1970s and 1980s a variety of immunosuppressant agents were used in different trials, but the concept of immunomodulation was not explored until the late 1980s (Lublin, 2005). The first therapy that was proven to be effective in altering the natural history of MS, was interferon beta-1b in 1993 (Paty and Li, 1993). Since then, numerous disease modifying treatments (DMT) have been developed. Over the past 25 years, the dominant treatment strategy has evolved from escalation therapy, where the people with MS (pwMS) is started on a low efficacy therapy and only escalated to higher efficacy upon disease activity, to early high efficacy therapy, using the more-effective drugs earlier to prevent progression (Filippi et al., 2018). There is a push towards offering most, if not all, newly diagnosed pwMS highly effective DMT at the time of diagnosis (Schmierer et al., 2021).

Naming a disease is important in order to raise awareness and shift the attention to recognising, diagnosing, preventing and treating the disease. MS is a well-defined and characterised disease, but the treatment era is young – and has only just begun.

3.2. Pathophysiology of MS

MS is a chronic inflammatory and neurodegenerative disorder of the central nervous system (CNS).

The target for the pathogenesis of MS, is the neuron and its surrounding myelin. The neuron consist of the nerve cell body with a long axon, responsible for transporting the nerve signals. See Figure 1. To protect the axon and promote the nerve signals, there is an isolating sheath of myelin around the axon, formed by the supporting cells, the oligodendrocytes. The myelin sheath is segmented in layers, interrupted by regular intervals (Snell, 1992). If the myelin is damaged or removed, the conduction of the nerve signal will be impaired, leading to varying degrees of clinical deficit.

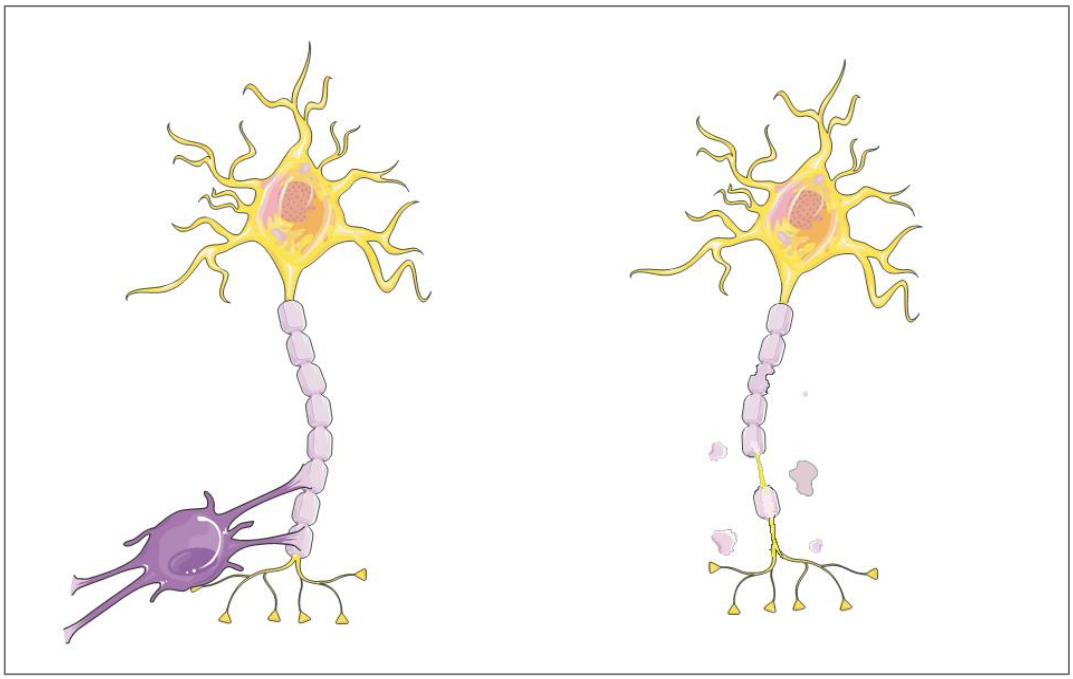


***Figure 1**: **Left:** a normal neuron with the axon myelinated from an oligodendrocyte. **Right:** a demyelinated axon. Illustration designed by use of Servier Medical art.*

The inflammatory process in MS is thought to be initiated by an activation of T-cells, involving an interplay between genetic and environmental factors (Grigoriadis et al., 2015). Pro-inflammatory cells then cross the blood-brain barrier (BBB), which has an increased permeability. The mechanism of the breakdown of the BBB is incompletely understood, but seems to involve pro-inflammatory cytokines produced by resident cells and endothelial cells (Filippi et al., 2018). Within the CNS, the T-cells respond to CNS antigens and are re-activated locally. A cascade of pro-inflammatory cytokines and chemokines, recruitment of additional inflammatory cells including cytotoxic T-cells, autoantibody producing B-cells, macrophages and microglia follow, and together they ultimately lead to demyelination and axonal loss (Grigoriadis et al., 2015, Garg and Smith, 2015).

The demyelination in MS is characterized by multifocal lesions, or “plaques”, and is considered the hallmark of MS pathology (Matthews et al., 2016). The typical “active lesion” with profound lymphocytic inflammation predominates in RRMS and consists mainly of CD8+ T-cells, while the component of CD4+ T-cells is relatively small (Lassmann et al., 2007). The B-cells (CD20+ B-cells) have in recent years been recognised as having a more important role as a contributor in MS pathology. The reactivated B-cells can induce complement-mediated damage to the myelin, and further activate the T-cells. Memory B-cells can also differentiate into plasma-cells in the cerebrospinal fluid (CSF) and are responsible for the production of oligo-clonal bands (Grigoriadis et al., 2015). Demyelination is followed by a varying degrees of axonal injury (Lassmann et al., 2007).

The demyelinated lesions in MS can occur anywhere in the CNS, including in the brain, spinal cord and optic nerve, although particularly in the white matter periventricular. The lesions evolve asynchronously and show different stages of inflammation and tissue responses, even within the same individual (Matthews et al., 2016). Cortical involvement can also occur in MS and may be due to cortical demyelination or actual neuronal loss (Garg and Smith, 2015). The anatomical location of the lesion is associated with specific clinical manifestations, but the overall lesion load only moderately corresponds with progression (Filippi et al., 2018).

The traditional concept of MS pathology consists of two stages, with an inflammatory, relapsing phase dominating early in the disease course and later developing into a non-inflammatory neurodegenerative phase. More recent pathological studies have shown that inflammation can be observed even in the terminal stages of MS (Grigoriadis et al., 2015).

3.3. Disease manifestations

3.3.1 Symptoms

The clinical presentation of MS is heterogeneous and the symptoms will depend on the location of the demyelinated lesions in the central nervous system. Table 1 presents common symptoms in MS. The symptoms usually have an acute or sub-acute onset, worsen over days and last for 2-4 weeks before a variable degree of remission occurs (Filippi et al., 2018).

The optic nerve is particularly vulnerable for demyelination and presents clinically as an optic neuritis (ON) with subacute monocular visual loss, reduced contrast acuity, painful eye movements and, eventually, reduced colour-vision (dyschromatopsia). ON is the initial clinical presentation in approximately 25 % of the pwMS, and about 70 % of the pwMS will experience an ON during the course of disease (Toosy et al., 2014, Filippi et al., 2018).

Sensory symptoms are the first symptoms in up to 43 % of the pwMS. The demyelinated lesions responsible for sensory symptoms are most often located in the brainstem or spinal cord (Filippi et al., 2018) and causes varying degrees of sensory abnormalities. A phenomenon associated with spinal cord lesions is the L'hermittes sign, which is the sensation of an electric shock radiating down the spine and into the limbs, trigged by flexion of the neck (McGinley et al., 2021).

Motor manifestations are the first symptom in 30-40 % of pwMS (Filippi et al., 2018) and are a result of demyelination in the pyramidal tracts of the CNS, in the hemispheres, the brainstem or the spinal cord. The symptoms include degrees of paresis and increased muscle tone or spasticity.

The cerebellum and brainstem will involve several symptoms and are present in up to 70 % of pwMS (Filippi et al., 2018). A special clinical presentation is the internuclear ophtalmoplegia (INO), which is an eye movement disorder resulting from a demyelination in the medial longitudinal fasciculus in the brainstem. The symptoms are unconjugated eye movements. The prevalence of INO in MS is up to 34 % when a proper investigation is performed (Nij Bijvank et al., 2019).

Bowel and bladder dysfunction are common in MS. Persons with medullary lesions more often experience these symptoms early in the disease course, but eventually they will affect up to 99 % of pwMS (Filippi et al., 2018).

Non-physical manifestations of the disease are increasingly being recognised and may be just as disabling as the physical manifestations for persons suffering from MS (Kobelt et al., 2017, Zwibel, 2009). Cognitive impairment can start in the early phases of the disease, affecting up to 40-70 % of the pwMS (Kobelt et al., 2017, Rocca et al., 2015). Fatigue is reported in 71-90 % of pwMS (Lerdal et al., 2007, Broch et al., 2021). There are many different types of pain in MS; dysesthesia, trigeminal neuralgia, back pain or pain following extensive spasticity, to name a few. Pain is estimated to occur in 29 % to 86 % of pwMS (Solaro et al., 2004). The prevalence of depression is higher in pwMS than in the general population, ranging from 4.3 % to 59.6 %. It is, however, difficult to quantify, as different studies uses different assessment tools. The depressive manifestations in MS are considered strongly related to other symptoms, like fatigue and pain (Solaro et al., 2018).

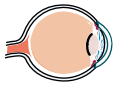
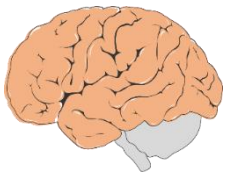
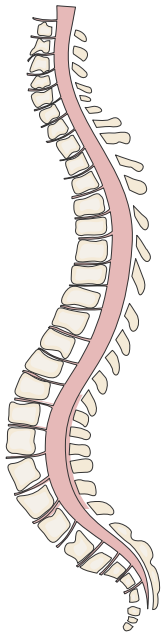
Location of demyelinated lesion(s) in CNS	Clinical presentation, references in text
Optic nerve 	Partial or complete visual loss in one eye Dyschromatopsia Painful eye movement Atypical: Bilateral affection
Brainstem and/or cerebellum 	Paresis of eye-movements Nystagmus Numbness of face Dysarthria, dysphagia Hearing loss Vertigo Ataxia or imbalance Internuclear opthalmoplegia (INO)
Cerebral hemispheres 	Hemisyndrome (Corticospinal tracts) ○ Hemisensory deficit ○ Hemiparesis Fatigue Cognitive symptoms Sleep disorders Affective disturbances
Spinal cord 	Myelitis Sensory (limbs and/or trunk): ○ Paresthesia ○ Numbness ○ Coldness ○ Tightness ○ Pain Motor deficit ○ Spastic paresis ○ Weakness Sphincter dysfunction ○ Urinary urgency, hesitancy, incontinence ○ Constipation, faecal incontinence Sexual dysfunction ○ Erectile dysfunction, impotence Clinical peculiarity: ○ L'hermittes phenomenon (transient electric feeling downward spine to limbs with flexion of the neck) ○ Uthoffs phenomenon (worsening of symptoms caused by increased temperature)

Table 1: Various symptoms of *MS, dependent on localization of the demyelinated lesion in the CNS. Illustration designed by use of Servier Medical art.*

3.3.2. Disease phenotypes

Traditionally, MS has been divided into a *relapsing remitting* (RRMS) and a *primary progressive* subtype (PPMS), depending on the characteristics of the initial disease. RRMS presents with waxing and waning of neurological symptoms and represent more than 80 % of pwMS in most investigated MS populations. PPMS has a progressive disease course without relapses, and consists of the remaining 15-20 % of the population. In the traditional course of the disease, a proportion of pwMS with a relapsing remitting subtype will enter a *secondary progressive* MS (SPMS). This is most often diagnosed in retrospect, after the initial relapsing remitting course has subsided and a steady deterioration of functional ability has lasted for at least six to twelve months (Ziemssen et al., 2020).

The main groups of relapsing remitting and progressive subtypes have been further divided several times, often as a consequence of the revisions of the diagnostic criteria (please see section 3.4.1). Some of the definitions have withstood the test of time, others have been rejected, such as the term "benign MS" (Oh et al., 2018). The 1996 definition of the four subgroups of relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS) and progressive relapsing MS (PRMS) have been widely used (Lublin and Reingold, 1996). The most comprehensive change was published by Lublin et al, after an initiative from the European Committee for treatment and research in multiple sclerosis (ECTRIMS) group in 2013. The key objective with this work was to clarify the phenotype descriptions, including *clinically isolated syndrome* (CIS) and *radiologically isolated syndrome* (RIS), as well as to add modifiers of basic phenotypes; active and not active disease. Activity is determined by clinical relapses and/or MRI activity. Progression is measured by clinical evaluation assessed at least annually. This definition softens the boundaries between relapsing and progressive disease (Lublin et al., 2014).

The *clinically isolated syndrome* (CIS) is recognized as the first clinical presentation of MS, meaning an episode with symptoms and findings attributed to demyelination that does not yet fulfil the criteria of dissemination in time (Lublin et al., 2014, Dobson and Giovannoni, 2019). The *radiologically isolated syndrome* (RIS) is described in the section of MS prodromes, please see section 3.6.1.2.

In the traditional view, there is a link between the pathophysiological process and the clinical features of MS. The phenotype becomes less inflammatory with age, with decreasing numbers of relapses and an increasing risk of developing progressive MS (Grigoriadis et al., 2015, Scalfari et al., 2016), see Figure 2.

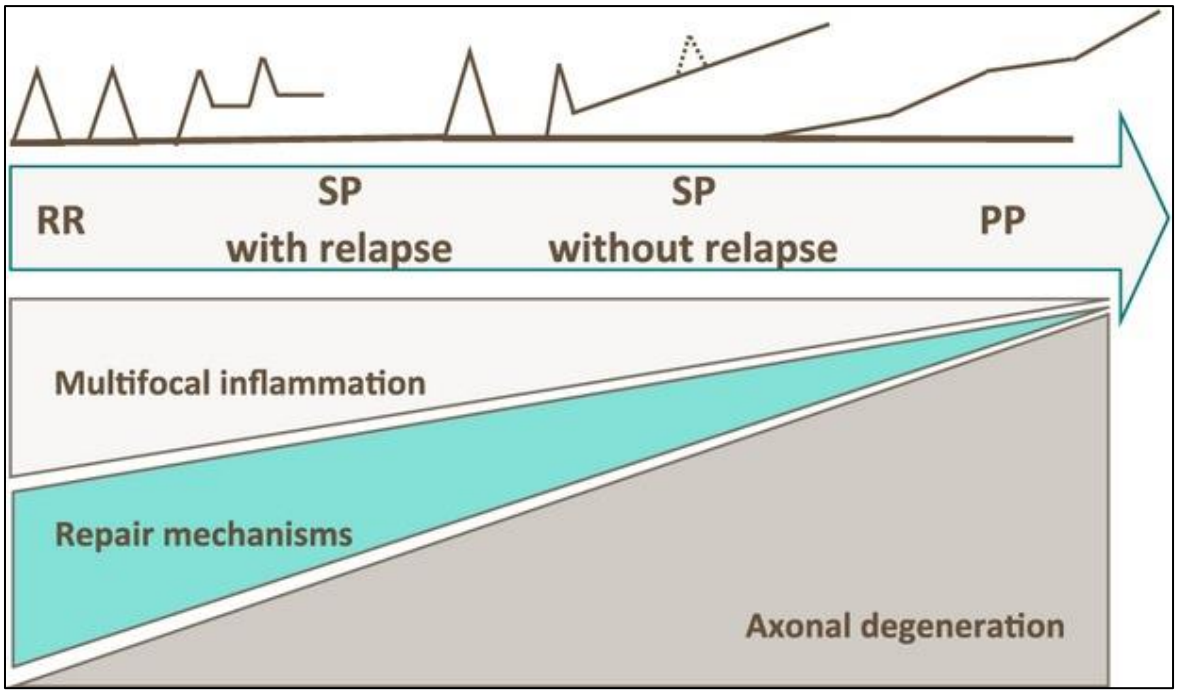


Figure 2: Balance between the pathophysiological mechanisms of MS and the subgroups of MS *(Grigoriadis et al., 2015). RR relapsing remitting, SP secondary progressive, PP primary progressive*. *Reprinted with permission of Jon Wiley and Sons copyright Clearance Centre.*

A recently published paper proposes a new way of describing the phenotypes in MS. The authors introduce the term *"smouldering MS"* implying a continuum between the relapsing and progressive stages of MS. They argue that *the real M*S is driven by a smouldering process accompanied by a superimposed inflammatory activity that represents the individual immune response to whatever is the underlying cause of the disease. The paper hypothesizes multiple pathological drivers of the smouldering MS, where demyelination is only one. Others include activation of innate or adaptive immune system, lifestyle factors and comorbidities, CNS infections and ageing mechanisms (Giovannoni et al., 2022). The terms *progression independent of relapse activity* (PIRA) and *relapse-associated worsening* (RAW) are also gaining traction in describing patterns for possible disease course and outcome (Kappos et al., 2020).

Pediatric onset MS

Pediatric onset MS (POMS) is generally defined as MS with an onset of symptoms before the age of 16 (sometimes before the age of 18) (Alroughani and Boyko, 2018). Between three and 10 % of pwMS experience their first symptoms before the age of 16, and less than 1% have symptoms onset before 10 years of age (Boiko et al., 2002). Children are less likely to develop progressive form of MS (Renoux et al., 2007).

3.4. Diagnosis of MS

3.4.1. Diagnostic criteria

The diagnostic criteria for MS has undergone multiple revisions leading to the current 2017 revision of the McDonald criteria (Thompson et al., 2018a). According to Gafson et al there have been six different attempts at defining diagnostic criteria before the start of the series of McDonalds criteria (Gafson et al., 2012):

Charcot started with an early attempt in 1868, using a triad of nystagmus, intention tremor and a scanning speech. In 1906 the Austrian neurologists Marburg revised the triad to include absent abdominal reflexes, pyramidal tract signs and Uthoff's phenomenon. The Allison and Millar criteria from 1954 differentiated cases into the concepts of early, probable and possible MS. In 1965, Schumacher led a panel with the task of providing a common definition of MS that could be utilised in medical trials. The Schumacher criteria required two or more episodes of neurological symptoms involving two or more locations within the CNS, thus establishing the concepts of dissemination in time (DIT) and dissemination in space (DIS) (Schumacher et al., 1965). These concepts have become the gold standard for epidemiological studies ever since. The following two sets of criteria; the McAlpine, Lumsden and Acheson criteria (1972) and the Rose criteria (1976) never quite gained on. Both of them were concerned with making subgroups of probable and possible MS. In 1983, Charles Poser and colleagues included results of CSF analysis and evoked potentials in the supplementary diagnostic criteria (Poser et al., 1983). The Poser criteria were widely used for nearly 20 years.

A panel led by Ian Mc Donald specifically addressed the need to include MRI results in the diagnostic work-up. The first version of the McDonald criteria came in 2001 (McDonald et al., 2001). The panel also created criteria for the diagnosis of primary progressive MS, which required the presence of oligo-clonal bands in the CSF. The McDonald criteria soon became the gold standard in the diagnosis of MS, and it was incorporated into most therapy trials. The first MRI guidelines were, however, not derived from reliable and clinically diagnosed cases of MS, but based on retrospective MRI findings in patients with clinical isolated syndrome (CIS) (Poser and Brinar, 2004). The second version from 2005 presented a more precise description of the criteria required to demonstrate dissemination in time. Abnormal CSF findings were no longer needed to diagnose progressive disease (Polman et al., 2005). The third revision was published in 2010 where information from the European Magnetic Resonance Imaging in MS (MAGNIMS) research group was included. The main goals of this revision were to make the criteria applicable to the Asian, Latin American and paediatric populations and to further clarify the criteria of dissemination in time (Polman et al., 2011). The fifth and so far last updated version is the 2017 McDonald criteria. They continue to apply primarily to patients experiencing a

CIS. For the first time, the presence of CSF specific oligo-clonal bands can considered as a substitute for dissemination in time, provided there is dissemination in space. This version also emphasizes need to exclude better explanation for the clinical presentation. Finally, they concluded that validation of the new criteria will still be needed in diverse populations, including persons from Asia, Latin America, the Middle East, Africa and other relatively less studied geographical locations, as well as patients with paediatric and late onset multiple sclerosis (Thompson et al., 2018a). The latest version did not change the diagnostic criteria for PPMS, with the exception of removing the distinction between symptomatic and asymptomatic lesions (Oh et al., 2018).

The evolution of the diagnostic criteria reflects the hope for a more reliable diagnostic process, with the aim of a more precise diagnosis. It is important to have insight into the development of diagnostic criteria for MS to be able to understand and discuss changes in prevalence rates and prognosis for the disease. The so-called Will Rogers phenomenon is relevant in this context, exemplified in a paper by Sormani et al (2008): When redefining persons from CIS to a confirmed MS, the prognosis for both the CIS group and the MS group will improve. When using the Poser criteria, the probability of reaching an EDSS ≥ 3 after one year was 11 % for CIS patients and 46 % for MS patients. When utilizing the 2005 McDonald criteria, which raised the proportion of definite MS in this cohort from 16 % (Poser criteria) to 44 % (McDonalds criteria), the probability of reaching EDSS ≥ 3 after one year was 7 % for CIS patients and 27 % for the MS patients (Sormani et al., 2008).

It is also noteworthy that the existing diagnostic criteria does not include other biomarkers than MRI and CSF specific oligo-clonal bands.

Table 2 presents the current diagnostic criteria for relapsing remitting MS and progressive MS at onset, according to the 2017 McDonald criteria. If the 2017 McDonald Criteria are fulfilled, and there is no better explanation for the clinical presentation, the diagnosis is MS (Thompson et al., 2018a, Thompson et al., 2018b).

Criteria for diagnosis of MS in patients with relapse at onset		
	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of MS
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of previous attack involving a lesion in distinct anatomical location)	None*
1 clinical attack	≥2	DIT demonstrated by additional clinical attack OR DIT demonstrated by MRI OR Presence of OCB
1 clinical attack	1	DIS demonstrated by additional clinical attack implicating another CNS site OR DIS demonstrated by MRI AND DIT demonstrated by MRI OR Presence of OCB
Criteria for diagnosis of MS in patients with progressive disease at onset		
• 1 year of disability progression, independent of relapse AND • 2 of the following: ○ ≥1 T2 hyperintense lesion characteristic of MS in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial ○ ≥ 2 T2 hyperintense lesions in spinal cord ○ Presence of OCB		

Table 2: Diagnostic criteria for a diagnosis of Multiple Sclerosis, McDonald 2017 *(Thompson et al., 2018a).*
** No additional tests are required to demonstrate DIS or DIT, however MRI should be obtain in all patients where MS is being considered.*
MRI: magnetic resonance imaging, DIT: dissemination in time, DIS: dissemination in space, OCB: oligo-clonal bands.

3.4.2. The practical diagnostic approach

There is no single diagnostic test for MS. The diagnosis is based on clinical presentation and supported by radiological imaging and laboratory tests. The different diagnostic criteria have changed over the years, as described in the previous section. The overall aim is, however, to demonstrate evidence for dissemination of disease characteristics in time and space (McGinley et al., 2021).

3.4.2.1. Clinical investigations

A detailed clinical history is important in elucidating previous episodes of neurological deficit, suspicious of MS, in addition to a thorough neurological examination. Clinical expertise is necessary to demonstrate and evaluate the diagnostic criteria – and to exclude other neurological conditions (Thompson et al., 2018b). According to the current diagnostic criteria (Table 2), the presence of DIS and DIT can be entirely based on clinical findings, with the evidence of two relapses in two distinct CNS locations (Oh et al., 2018).

The differential diagnoses must be thoroughly assessed, excluding "red-flags" suspicious of other diagnoses. One such "red flag" is a first relapse at older age, which is more likely to represent vascular disease. Another is the presence of comorbid systemic symptoms and signs, where other multisystem diseases, such as Sjøgrens and systemic lupus erythematosus, should be considered (Dobson and Giovannoni, 2019). See Table 3 listing differential diagnoses that may be considered, depending on signs and symptoms. Neuromyelitis optica spectrum disorders (NMO-SD) and anti-myelin oligodendrocyte glycoprotein associated disease (anti-MOG-AD) will be discussed in more detail in section 3.4.2.4.

3.4.2.2. Radiologically imaging - MRI

The most characteristic MRI findings in MS, are multifocal ovoid lesions in T2-weighted sequences (Filippi et al., 2018). The inflammation causes associated oedema, decreasing myelin content and local changes in tissue composition with glial scarring, all of which manifest as hyper-intense lesions. The localised breakdown of the blood brain barrier causes focal enhancement in acute lesions after the administration of intravenous gadolinium (Matthews et al., 2016). Most of the lesions are asymptomatic, with approximately 10 "asymptomatic" lesions visualised in MRI scans for every clinical relapse (Dobson and Giovannoni, 2019).

The MAGNIMS network produced modified MRI criteria for DIS in 2016. These criteria proposed an increase from the need to demonstrate lesions in two out of four locations (juxtacortical, periventricular, infratentorial, and spinal cord) to two out of five locations, by adding the optic nerve as a MS specific location. The revision also proposed to increase the number of periventricular lesions from one to at least three (Filippi et al., 2016). The 2017 revision of the McDonald criteria, however, did not use this specification on how to fulfil DIS and DIT. This disagreement has been followed by a number of studies concluding that the new diagnostic criteria from 2017 have a higher sensitivity, but lower specificity compared to the 2010 criteria in predicting clinically definite MS (Filippi et al., 2022, Brownlee et al., 2017).

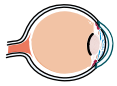
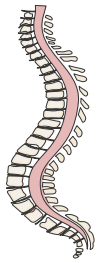
Symptoms of demyelination	Differential diagnosis
Optic neuritis 	▪ Neuromyelitis optica spectrum disorders (NMO-SD) ▪ Anti-myelin oligodendrocyte glycoprotein (anti-MOG) disease ▪ Ischemic events ▪ Non-arteritic ischemic optic neuritis (NEON) ▪ Leber's hereditary optic neuropathy
Brainstem and/or cerebellum 	▪ Ischemic events, stroke ▪ Space occupying lesion/tumor ▪ Vasculitis ▪ Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) ▪ Anti-myelin oligodendrocyte glycoprotein (anti-MOG) disease
Cerebral hemispheres /white matter lesions in MRI 	▪ Acute disseminated encephalomyelitis (ADEM) ▪ Hypoxic-ischemic vasculopaties, including stroke ▪ Migraine ▪ CNS vasculitis ▪ Sarcoidosis ▪ Fabry's disease (stroke events and vertigo) ▪ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Myelitis/myelopathy 	▪ Degenerative cervical spine disorder ▪ Postviral/postvaccinal/post-treatment inflammatory demyelination ▪ Other systemic autoimmune disorders, associated with medullary demyelination (RA, Sjøgren, SLE) ▪ Infectious myelitis (Lyme, HIV, other viruses) ▪ Ischemic/vascular event in spinal cord ▪ B12 or folat deficiency ▪ Neuromyelitis optica spectrum disorders (NMO-SD) ▪ Anti-myelin oligodendrocyte glycoprotein (anti-MOG) disease

***Table 3: Differential diagnoses of multiple sclerosis**, based on clinical experience and data from Dobson et al (2019) (Dobson and Giovannoni, 2019), Garg et al (2015) (Garg and Smith, 2015), Filippi et al (2018) (Filippi et al., 2018), Thompson et al 2018 (Thompson et al., 2018b).*

The MAGNIMS network, in cooperation with the Consortium of Multiple Sclerosis Centres (CMSC) and North American Imaging in Multiple Sclerosis Co-operative (NAIMS), published new recommendations, named the 2021 MAGNIUMS-CMSC-NAIMS consensus, on the use of MRI in pwMS. This consensus provides updated guidance on how and when to use MRI for diagnosis, prognosis and treatment monitoring in multiple sclerosis, including recommendations for protocols and the use of contrast agents (Wattjes et al., 2021).

In addition to the obvious role in diagnosing MS, MRI is widely used to monitor disease activity and treatment response, including recognition of treatment-related adverse effects, such as progressive multifocal leukoencephalopathy (PML) (Filippi et al., 2018). Traditionally, new MRI lesions or "active lesions" (gadolinium-enhancing), have been used to estimate disease activity (Dobson and Giovannoni, 2019). Finally, MRI can be used to measure axonal and neuronal loss associated with

brain atrophy in MS. Automated MRI-based methods to measure brain volume allow for longitudinal follow-up on brain atrophy (Matthews et al, 2016).

3.4.2.3. Laboratory tests - spinal fluid

A lumbar puncture (LP) is advised in all the diagnostic work-up for MS (Dobson and Giovannoni, 2019). The cerebrospinal fluid (CSF), collected in a LP, contains important information on the central nervous system. The routine analyses include quantification of cells, proteins and glucose, as well as electrophoresis using isoelectric focusing (IEF), looking for immunoglobulins in oligo-clonal patterns, or bands (OCB). In the 2017 revision of the McDonald diagnostic criteria, the presence of ≥ 2 CSF specific OCBs can be used in place of demonstrating dissemination in time (Thompson et al., 2018a). Finally, different specific antibody analyses can be performed, like borreliosis antibodies, or autoantibodies associated with the differential diagnosis in the neuromyelitis optica disorder spectrum, see section 3.4.2.4.

In Norway, there is a long-standing tradition of investigating almost all persons with symptoms suspicious of MS with a LP. However, the frequency of LPs differs greatly among countries and traditions. In surveys among neurologist, 87 % of physicians in Europe (Fernández et al., 2017), and only 15 % in the US (Tornatore et al., 2016) would perform a LP in a person with a history of CIS and MRI lesions. Approximately 95 % of pwMS in a Swedish cohort have OCB (Imrell et al., 2006) , and only 3% of pwMS in a cohort from the South-West of England were OCB negative (Joseph et al., 2009). Despite high sensitivity, the finding of OCBs in the CSF is not specific for MS, but can be seen in many inflammatory and non-inflammatory conditions (Awad et al., 2009).

Another analysis performed in the CSF, is the *IgG index*. This is a quantitative analysis of the relationship between IgG in CSF and serum, divided by the relationship of albumin in CSF and serum. Albumin is a smaller protein than IgG and crosses the BBB more easily (Simonsen et al., 2020b). The IgG index is elevated in about 70-90% of pwMS and is rarely abnormal in OCB negative patients (Awad et al., 2009). One advantage of the IgG index, is that the analysis is ready within a day and it is not rater-dependent, whereas the electrophoresis of OCB is more time and cost consuming. In a study on the CSF findings in the cohort used for all the publications included in this thesis, we found that 99.8% of patients with an elevated IgG index (above 0.8) had ≥2 OCBs in their CSF. This corresponds to a positive predictive value for OCB of 99.4 % and can be used as a proxy to OCB and thus, DIT (Simonsen et al., 2020b).

Blood-tests are often performed as a part of the routine work-up in the diagnostic process, mostly to be used for the evaluation of differential diagnoses (Oh et al., 2018).

3.4.2.4 Other inflammatory demyelinating diseases

Neuromyelitis optica spectrum disorders (NMO-SD)

Neuromyelitis optica (NMO) was first known as Devic disease, a clinical entity of optic neuritis and myelitis. NMO was first thought to be a variant of MS, but in 2004, a circulating IgG auto-antibody was reported in some of the patients, and the astrocyte water channel protein aquaporin 4 was identified as its target (Papadopoulos and Verkman, 2012). The most common symptoms, are optic neuritis or transverse myelitis (Pandit et al., 2015). NMO accounts for a small percentage of demyelinating disease in Caucasians, (1-2%) but a larger proportion in Asians (20-48%) (Levin et al., 2013). The term NMO spectrum disorders (NMO-SD) encompasses forms of NMO that do not satisfy the explicit diagnostic criteria of NMO, including the small proportion of patients with NMO who are sero-negative for aquaporin antibodies (Pandit et al., 2015).

Myelin-oligodendrocyte glycoprotein associated disease (MOGAD)

The myelin-oligodendrocyte glycoprotein (MOG) is responsible for a minor component of CNS myelin, expressed in the outer lamella of the myelin sheath. The detection of anti-MOG antibodies is associated with a distinct clinical phenotype in children and adults with CNS demyelination. The most commonly used term is MOG antibody associated disease (MOGAD) (Marignier et al., 2021). The reported frequencies of positive MOG antibodies vary from 0.3 % (Cobo-Calvo et al., 2020) to 6.5 % of all demyelinating syndromes in adults, and is higher in children (Kunchok et al., 2020). The most common clinical feature of MOGAD is optic neuritis, affecting up to 80 % of the patients, either at onset or during the disease course. Bilateral optic neuritis is seen in up to 40 %. Spinal cord involvement is seen in 30 % at onset and 50 % during the disease course, typically with involvement of the bladder or bowel (Marignier et al., 2021). Some of the people with positive MOG antibodies present as acute disseminated encephalomyelitis (ADEM), and in children with ADEM, the antibodies are discovered in up to 68 % (Rossor et al., 2020).

Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an umbrella term for non-infectious, acute inflammatory demyelinating events in the CNS (Pohl et al., 2016) . Population-based studies show an incidence of 0.23-0.4 per 100 000 children, the average age of onset being 3.6-7 years (Cole et al., 2019). The first descriptions of ADEM-like disorders were in association with infections, in particular smallpox and measles, and later associated with vaccines (Pohl et al., 2016). The aetiology of ADEM is unknown, but self-antigens with a molecular mimicry between viral sequences and myelin basic protein and MOG are thought to be a probable explanation (Cole et al., 2019). The presenting symptoms include a first polyfocal clinical CNS event with neurologic deficits, including encephalopathy with alternation in consciousness or behaviour. The MRI shows diffuse, poorly

demarcated, large lesions involving cerebral white matter (Cole et al., 2019, Pohl et al., 2016). The majority of people with ADEM will have a monophasic disease, but up to 36 % will experience another demyelinating event of some kind. Progression from ADEM to MS is, however, reported, with an incidence ranging from 0% to 17 % in studies with follow-up periods spanning several years (Cole et al., 2019).

3.4.3. Measures of disease severity and progression

There are a number of instruments that describe and quantify the clinical severity, disability and progression in MS. Three of the most common tools are the Expanded disability status scale (EDSS) (Kurtzke, 1983), the Multiple sclerosis functional composite (MSFC) (Cutter et al., 1999), and the Multiple sclerosis severity score (MSSS) (Roxburgh et al., 2005). These instruments are used as endpoints in clinical trials to assess the effectiveness of interventions.

3.4.3.1. EDSS

The EDSS is a clinician-administered assessment scale evaluating functional systems of the central nervous system. It was developed by John F. Kurtzke, using data on the natural history of MS, spanning some 30 years, in an American cohort of male World War II veterans (Kurtzke, 1983, Kurtzke, 2015). It consists of ordinal rating systems ranging from 0 (normal neurological status) to 10 (death due to MS), in 0.5 incremental intervals. See Figure 3. The neurological impairment is based on eight functional systems (FS); pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cognition and other. All the functional scores (except “other”) are ordinal scales from 0 to 5 (6), and the final EDSSS score is calculated on the basis of the sub-scores.

The lower scores of the scale (0-3.5) are mainly based on the result of the neurological examination and the functional scores, while values from 4 and up are mostly defined by walking ability. Typical milestones are EDSS 4; impaired walking ability, EDSS 6; the need of walking aid (cane or crutch) and EDSS 7, the need for a wheelchair to mobilise beyond five meters. The time between specific EDSS levels varies considerably (Zurawski et al., 2019).

The EDSS has been corroborated in numerous studies, though it is also the subject for criticism. Some functions, such as cognition, vision or upper limb function, are underrepresented (Meyer-Moock et al., 2014). Both inter- and intra-rater reliability (Cohen et al., 2021) as well as sensitivity to change are well-documented weaknesses, and should be taken into consideration when using the EDSS (Meyer-Moock et al., 2014). It is, however, the most widely used and the best-known instrument for assessing disease progression in clinical studies. The Neurostatus (D'Souza et al., 2017) is a

certification tool for physicians, which aims to improve reproducibility, practicability and quality of the EDSS in clinical MS research (Kappos et al., 2015), and is required for participation in most of the therapeutic trials in MS. The EDSS is shown in full in the appendix

Figure 3: EDSS with main steps*. Copy-right ©My-MS.org, reused with permission Image Licence D.*

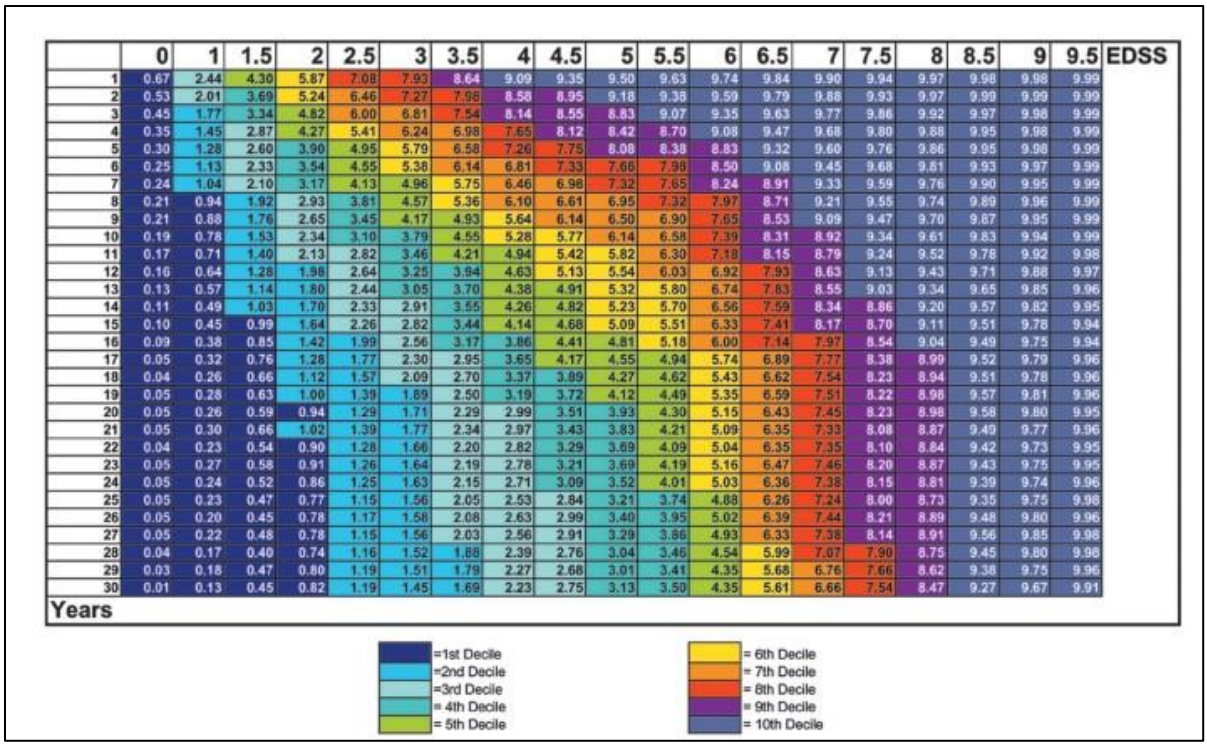
3.4.3.2. MSFC

The multiple sclerosis functional composite (MSFC) was developed by the (US) MS Society's Clinical Assessment Task Force as an additional clinical measure of MS disability progression (Meyer-Moock et al., 2014). The MSFC consists of three objective quantitative tests of neurological function, which are easy to administer. It includes the timed 25-foot walk test" (T25FT), which assesses leg function over a short distance, the "9-hole-PEG test" (9HPT), which measures arm function, and, finally, the "Paced Auditory Serial Addition test" (PSAT), which assesses cognition (Cutter et al., 1999). The main limitations of the MSFC is the individual's learning effect after repetitive testing (Meyer-Moock et al., 2014).

3.4.3.3. MSSS

The multiple sclerosis severity score (MSSS) adds disease duration to the EDSS score. It is based on databases from 11 countries (Europe and Australia). The MSSS corrects the EDSS for duration by comparing an individual's disability with the distribution of scores in cases with equivalent disease duration (Roxburgh et al., 2005). As a consequence, a similar MSSS score will be assigned to people who accrue severe disability over a longer period of time as people with moderate disability over a shorter period of time (Pachner and Steiner, 2009). See Figure 4.

A recent study concluded that incorporating the MSSS into the prediction models for treatment response improved the individual prognostic accuracy in MS (Kalincik et al., 2022).



	0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	EDSS
1	0.67	2.44	4.30	5.87	7.08	7.93	8.64	9.09	9.35	9.50	9.63	9.74	9.84	9.90	9.94	9.97	9.98	9.98	9.99	
2	0.53	2.01	3.69	5.24	6.46	7.27	7.98	8.58	8.95	9.18	9.38	9.59	9.79	9.88	9.93	9.97	9.99	9.99	9.99	
3	0.45	1.77	3.34	4.82	6.00	6.81	7.54	8.14	8.55	8.83	9.07	9.35	9.63	9.77	9.86	9.92	9.97	9.98	9.99	
4	0.35	1.45	2.87	4.27	5.41	6.24	6.98	7.65	8.12	8.42	8.70	9.08	9.47	9.68	9.80	9.88	9.95	9.98	9.99	
5	0.30	1.28	2.60	3.90	4.95	5.79	6.58	7.26	7.75	8.08	8.38	8.83	9.32	9.60	9.76	9.86	9.95	9.98	9.99	
6	0.25	1.13	2.33	3.54	4.55	5.38	6.14	6.81	7.33	7.66	7.98	8.50	9.08	9.45	9.68	9.81	9.93	9.97	9.99	
7	0.24	1.04	2.10	3.17	4.13	4.96	5.75	6.46	6.98	7.32	7.65	8.24	8.91	9.33	9.59	9.76	9.90	9.95	9.99	
8	0.21	0.94	1.92	2.93	3.81	4.57	5.36	6.10	6.61	6.95	7.32	7.97	8.71	9.21	9.55	9.74	9.89	9.96	9.99	
9	0.21	0.88	1.76	2.65	3.45	4.17	4.93	5.64	6.14	6.50	6.90	7.65	8.53	9.09	9.47	9.70	9.87	9.95	9.99	
10	0.19	0.78	1.53	2.34	3.10	3.79	4.55	5.28	5.77	6.14	6.58	7.39	8.31	8.92	9.34	9.61	9.83	9.94	9.99	
11	0.17	0.71	1.40	2.13	2.82	3.46	4.21	4.94	5.42	5.82	6.30	7.18	8.15	8.79	9.24	9.52	9.78	9.92	9.98	
12	0.16	0.64	1.28	1.98	2.64	3.25	3.94	4.63	5.13	5.54	6.03	6.92	7.93	8.63	9.13	9.43	9.71	9.88	9.97	
13	0.13	0.57	1.14	1.80	2.44	3.05	3.70	4.38	4.91	5.32	5.80	6.74	7.83	8.55	9.03	9.34	9.65	9.85	9.96	
14	0.11	0.49	1.03	1.70	2.33	2.91	3.55	4.26	4.82	5.23	5.70	6.56	7.59	8.34	8.86	9.20	9.57	9.82	9.95	
15	0.10	0.45	0.99	1.64	2.26	2.82	3.44	4.14	4.68	5.09	5.51	6.33	7.41	8.17	8.70	9.11	9.51	9.78	9.94	
16	0.09	0.38	0.85	1.42	1.99	2.56	3.17	3.86	4.41	4.81	5.18	6.00	7.14	7.97	8.54	9.04	9.49	9.75	9.94	
17	0.05	0.32	0.76	1.28	1.77	2.30	2.95	3.65	4.17	4.55	4.94	5.74	6.89	7.77	8.38	8.99	9.52	9.79	9.96	
18	0.04	0.26	0.66	1.12	1.57	2.09	2.70	3.37	3.89	4.27	4.62	5.43	6.62	7.54	8.23	8.94	9.51	9.78	9.96	
19	0.05	0.28	0.63	1.00	1.39	1.89	2.50	3.19	3.72	4.12	4.49	5.35	6.59	7.51	8.22	8.98	9.57	9.81	9.96	
20	0.05	0.26	0.59	0.94	1.29	1.71	2.29	2.99	3.51	3.93	4.30	5.15	6.43	7.45	8.23	8.98	9.58	9.80	9.95	
21	0.05	0.30	0.66	1.02	1.39	1.77	2.34	2.97	3.43	3.83	4.21	5.09	6.35	7.33	8.08	8.87	9.49	9.77	9.96	
22	0.04	0.23	0.54	0.90	1.28	1.66	2.20	2.82	3.29	3.69	4.09	5.04	6.35	7.35	8.10	8.84	9.42	9.73	9.95	
23	0.05	0.27	0.58	0.91	1.26	1.64	2.19	2.78	3.21	3.69	4.19	5.16	6.47	7.46	8.20	8.87	9.43	9.75	9.95	
24	0.05	0.24	0.52	0.86	1.25	1.63	2.15	2.71	3.09	3.52	4.01	5.03	6.36	7.38	8.15	8.81	9.39	9.74	9.96	
25	0.05	0.23	0.47	0.77	1.15	1.56	2.05	2.53	2.84	3.21	3.74	4.88	6.26	7.24	8.00	8.73	9.35	9.75	9.98	
26	0.05	0.20	0.45	0.78	1.17	1.58	2.08	2.63	2.99	3.40	3.95	5.02	6.39	7.44	8.21	8.89	9.48	9.80	9.96	
27	0.05	0.22	0.48	0.78	1.15	1.56	2.03	2.56	2.91	3.29	3.86	4.93	6.33	7.38	8.14	8.91	9.56	9.85	9.98	
28	0.04	0.17	0.40	0.74	1.16	1.52	1.88	2.39	2.76	3.04	3.46	4.54	5.99	7.07	7.90	8.75	9.45	9.80	9.98	
29	0.03	0.18	0.47	0.80	1.19	1.51	1.79	2.27	2.68	3.01	3.41	4.35	5.68	6.76	7.66	8.62	9.38	9.75	9.96	
30	0.01	0.13	0.45	0.82	1.19	1.45	1.69	2.23	2.75	3.13	3.50	4.35	5.61	6.66	7.54	8.47	9.27	9.67	9.91	

Years

Figure 4: Multiple sclerosis Severity Scores (MSSS). *Roxburgh et al Neurology 2005. Reprinted with permission from Copyright Clearance Centre's Rights Link.*

3.5. Epidemiology of MS

Epidemiology identifies the distribution of diseases, factors underlying their source and cause, and provides methods for control. Epidemiology requires an understanding of how political, social and scientific factors intersect to exacerbate disease risk. The field of epidemiology has evolved and adapted to changing public health needs. In addition to describing the distribution of the disease, the epidemiological studies of MS cover a wide range of topics, and have identified factors that may be related to the risk of developing MS, such as smoking, latitude, genetics and infectious processes.

3.5.1. Prevalence

The Atlas of MS is an open-source, global compendium of data on MS epidemiology. The reports contain epidemiological data at country, regional and global levels. The first edition was produced in 2008 in collaboration with the WHO. According to the most recent report, a total of 2.8 million people were estimated to live with MS worldwide in 2020, which gives a prevalence rate of $35.9/10^5$. When applying the same methodology as in the 2013 report, there is an estimated 30 % increase in prevalence from 2013 to 2020 (Walton et al., 2020). Figure 5 shows the worldwide prevalence of MS, by country, as shown by Filippi et al 2018.

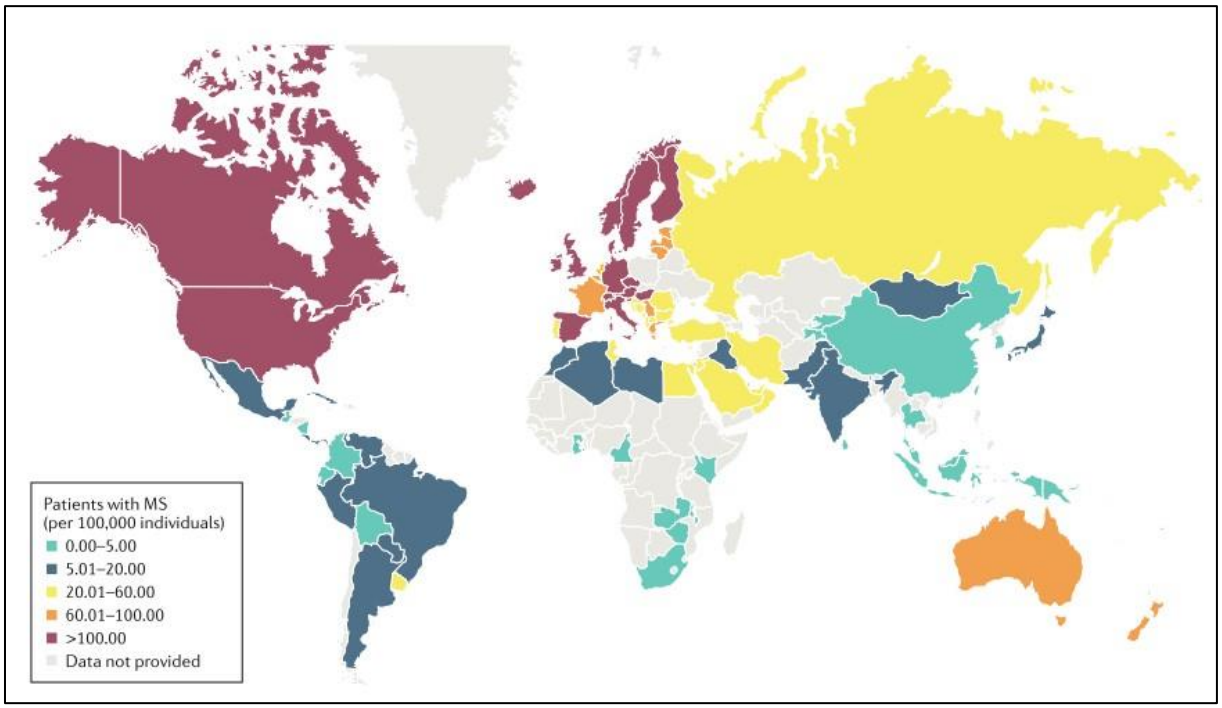


***Figure 5: Map showing geographical variation in MS prevalence per 100 000 population**. Countries without prevalence data are shown in grey. Reprinted with permission from Rights Link Copy Clearance Centre (Filippi et al., 2018).*

The prevalence of MS in Norway was $203/10^5$ in 2012, which is among the highest in the world (Berg-Hansen et al., 2014). Most of the Norwegian studies are based on single counties, though there is a clear trend of increasing prevalence (Gronlie et al., 2000, Dahl et al., 2004, Risberg et al., 2011,

Smestad et al., 2008, Vatne et al., 2011, Benjaminsen et al., 2014, Grytten et al., 2016, Simonsen et al., 2017, Lund et al., 2014) , see Table 4.

County	Prevalence		Incidence	
	Prevalence year	Prevalence per 10^5 population (95 % CI)	Period	Incidence per 10^5 population (95% CI)
Troms and Finnmark (Gronlie et al., 2000)	1993	73.0 (62.3-85.1)	1989-1992	4.3 (3.0-5.9)
Nord-Trøndelag (Dahl et al., 2004)	2000	163.6 (142.2-187.5)	1994-1998	5.3 (3.7-7.5)
Oppland (Risberg et al., 2011)	2002	174.4 (n.r.)	1999-2001	3.8 (2.4-5.9)
Vestfold (Lund et al., 2014)	2003	166.8 (n.r.)	1983-2002	4.5 (3.6-5.5)
Oslo (Smestad et al., 2008)	2006	148 (138-158)	2001-2005	6.6 (5.7-7.7)
Vest-Agder (Vatne et al., 2011)	2007	180 (161-202)	2001-2006	8.0 (4.6-14.2)
Nordland (Benjaminsen et al., 2014)	2010	182.4 (165.6-200.5)	2005-2009	10.7 (8.4-13.0)
Hordaland (Grytten et al., 2016)	2013	211.4 (198.3-224.2)	2003-2007	8.5 (7.3-9-7)
Buskerud (Simonsen et al., 2017)	2014	213.8 (196.4-231.1)	2003-2013	11.5 (10.2-12.7)
Møre and Romsdal (Willumsen et al., 2020)	2018	335.8 (314.1-358.5)	2015-2017	14.4 (11.9-17.3)

***Table 4: Reported prevalence and incidence in separate counties, Norway**. In counties with more than one publication, the last study is included. CI confidence interval, N.r. not reported.*

Prevalence is a function of incidence and survival time. The observed increase in MS prevalence may represent a true increase in disease burden, but it may also be a result of changes in the diagnostic criteria, earlier diagnosis (Lane et al., 2022), improved access to medical facilities (Filippi et al., 2018), and reduced mortality (Magyari and Sorensen, 2019).

The prevalence of paediatric MS is less investigated, but several studies indicate that at least 5 % of the MS population are paediatric patients (Alroughani and Boyko, 2018).

A striking characteristic of MS epidemiology, is the uneven distribution across the world. There is an established belief that higher latitudes correlates with increased prevalence of MS (Koch-Henriksen and Sorensen, 2010), both for the northern and southern hemispheres. This distribution has suggested an interplay between the genetics, environmental factors determined by geography and socioeconomic structure. This will be further discussed in section 3.5.6.

3.5.2. Incidence

According to the report from Atlas of MS, the availability and quality of incidence data are less reliable than the prevalence data. The pooled incidence rate across 75 reporting countries was 2.1 (95 % CI 2.09-2.12) per 100 000 persons/years (Walton et al., 2020). The lack of valid incidence studies is a problem. Prevalence rates are inflated by increased survival, and a true increase does not necessarily reflect a higher risk of the disease. The incidence is better suited to identify an increase in the population's MS risk, though not necessarily for detecting changes over time. As previously discussed, changes to the diagnostic criteria may contribute to apparent fluctuations in MS incidence rates. According to a recent systematic global review on incidence based on 42 regional estimates with consistent diagnostic criteria, the MS incidence rates significantly increased in 57 % (24/42), decreased in 21 % (9/42) and remained stable in 21% (9/42) of the studies. Only nine of these studies covered a substantial proportion of the country's population (more than one-third), and in these, there was no prominent trend in MS incidence over time (Lane et al., 2022). Several county-based epidemiological studies on incidence rates from different epochs have been performed in Norway, see Table 4. From the Norwegian studies investigating temporal changes in incidence, four studies showed an increase in MS incidence and two studies showed a decrease (Lane et al., 2022).

3.5.3. Age

The onset of MS usually occurs in young adulthood, between 20 and 40 years of age (Oh et al., 2018). As the incidence of MS peaks around 35 years of age and the prevalence peaks around 50, both incidence and prevalence rates will depend on the composition of the population studied (Koch-Henriksen and Sorensen, 2011). Between 3 and 10 % of persons with MS have disease onset before the age of 16, and less than 1% before the age of 10 (Boiko et al., 2002). Late onset MS (LOMS) is defined as MS with an onset after 50 years of age. In a study from Sweden, LOMS accounts for 4-9 % of pwMS (Song et al., 2019), while a study from Norway found that 25% of people diagnosed with MS after 2006 were diagnosed at 50 years of age and older (Simonsen et al., 2020a) . Figure 6 shows the age-distribution of the prevalent MS population in the Norwegian county of Buskerud, by phenotype.

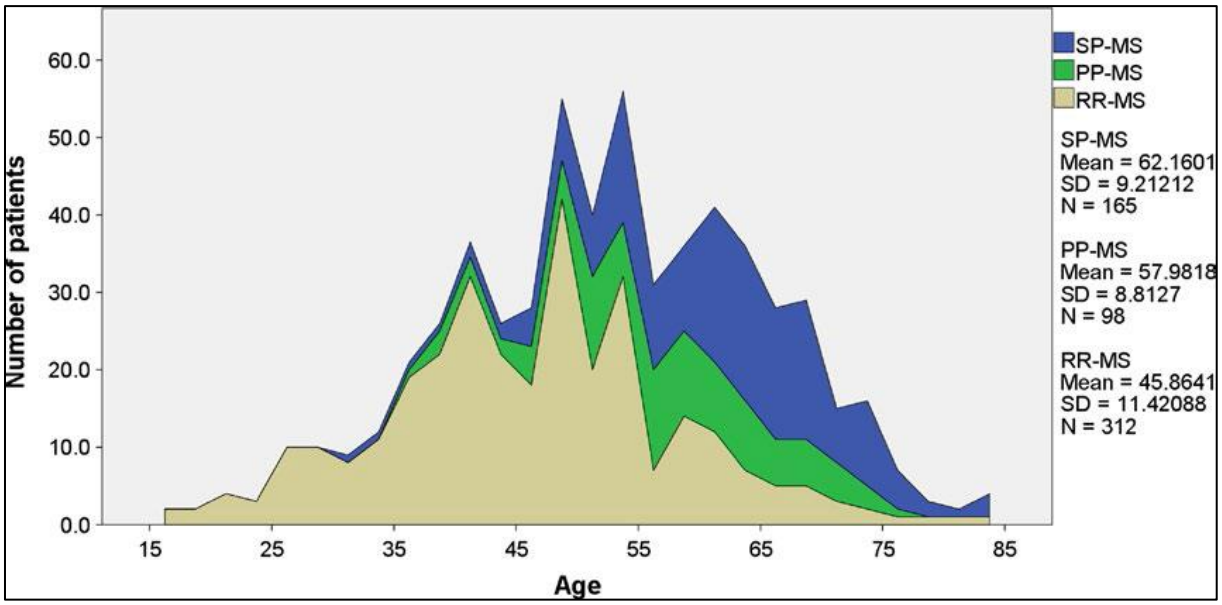


Figure 6: The distribution of MS phenotypes in the Norwegian county of Buskerud, by age*. (Simonsen et al., 2017). Reprinted with permission of Copyright Clearance Centre; Joh Wiley and son's license.*

3.5.4. Gender

There has been a steady increase in the female incidence of MS since the middle of the 20th century. Globally, females are twice as likely to have MS as males. This ratio is increasing and in some countries the ratio of women to men is as high as 4:1. However, the most often reported, and overall global result according to the Atlas of MS, is 30 % males and 70% females (Walton et al., 2020). The cumulative incidence rate for MS in Denmark has increased with 114 % in women, compare to a moderate increase of 30 % in men from 1950 until 2009. At the same time, the age at first pregnancy in Danish women has increased at exactly the same rate, indicating that fewer and postponed pregnancies may be a contributing factor (Koch-Henriksen et al., 2018). This phenomenon could, however, also indicate a reverse causality, since women with MS had an almost 50 % reduced birth rate in the last 5 years preceding the clinical onset of MS (Magyari et al., 2013). Another possible explanation is that women have become more inclined than men to seek medical assistance in case of subtle symptoms (Koch-Henriksen and Sorensen, 2011).

3.5.5. Ethnicity

The prevalence of MS is highest in individuals of European descent (Filippi et al., 2018). Recent incidence reports show an increasing rate of MS among African Americans compared to Caucasians. However individuals of Hispanic and Asian descent are less likely to develop MS (Amezcua and McCauley, 2020). A cohort study from the US, California, reported that African Americans had a 47 %

increased risk of MS, while Hispanics and Asians had a 50 % and 80 % lower risk, respectively, compared to white Americans (Langer-Gould et al., 2013). Migration may influence the trends in incidence, and increased migration from a country with a lower risk of MS might counteract the general tendency of increasing incidence. A Norwegian study on the prevalence of MS among first-generation immigrants found that the prevalence of MS in immigrants from European countries did not differ from the prevalence of the general population in Norway. Immigrants from Asia and Africa had a lower prevalence, except for immigrants from Iran, who had the same prevalence as the general population in Norway (Berg-Hansen et al., 2015).

3.5.6. Risk factors for disease onset in MS

In the search for an explanation why some individuals develop MS, several risk factors have been investigated throughout the years. Studies have found increasing evidence for some of these risk factors, while others have been rejected. Others again have received fluctuating research focus over the years. In their early epidemiological study of MS in Norway, for example, Swank and colleagues included dietary elements (Swank et al., 1952), whereas the impact of diet has been given less attention recently. Risk factors are most often a result of investigation of correlation. To find the true cause of a disease, one must evaluate causality. Causality implies that some individuals who develop MS after being exposed to a given risk factor would not have developed MS if they had not been exposed.

3.5.6.1. Genetics

Familial MS (FMS) is defined as a case of MS having at least one family member in the first, second or third degree or other more distant probands who is affected by MS. The prevalence of FMS was 12.4% in a systematic review by Harirchian et al. In other words, about one in eight pwMS have a family history of MS (Harirchian et al., 2018). The age-adjusted risk is higher for siblings (3%), children (2 %) and parents (2 %) than for second- and third degree family members. The recurrence in monozygotic twins is about 35 % (Compston and Coles, 2002). This suggests a genetic predisposition.

The first discovery of a genetic susceptibility in MS was detected within the human leucocyte antigen (HLA). The HLA gene encodes receptors that play an important role in regulation of the T-helper cell differentiation and regulation of the immune system (International Multiple Sclerosis Genetics et al., 2011). Over the last decade, genome-wide association studies (GWAS) have led to the discovery of more than 200 genetic loci that are associated with MS susceptibility, accounting for almost half of its heritability (Kim and Patsopoulos, 2022). Consequently, there are likely more genetic variants to be uncovered.

Multiple studies have also explored the association between genetic determinants and different clinical phenotypes (Harbo and Mero, 2012). Some genetic variants are associated with earlier age of onset (Briggs et al., 2018), and the pediatric onset MS has a higher genetic risk score burden compared to adult MS (Gianfrancesco et al., 2018). Increased comorbidity of other autoimmune diseases has long been observed in pwMS (Marrie, 2019a), and there is an increased risk of MS in persons with family members who have other autoimmune diseases. A common genetic background has been hypothesized, and large-scale GWAS have found increasing overlap of MS loci with that of other autoimmune diseases loci. Figure 7 shows genetic correlations across autoimmune diseases (Kim and Patsopoulos, 2022).

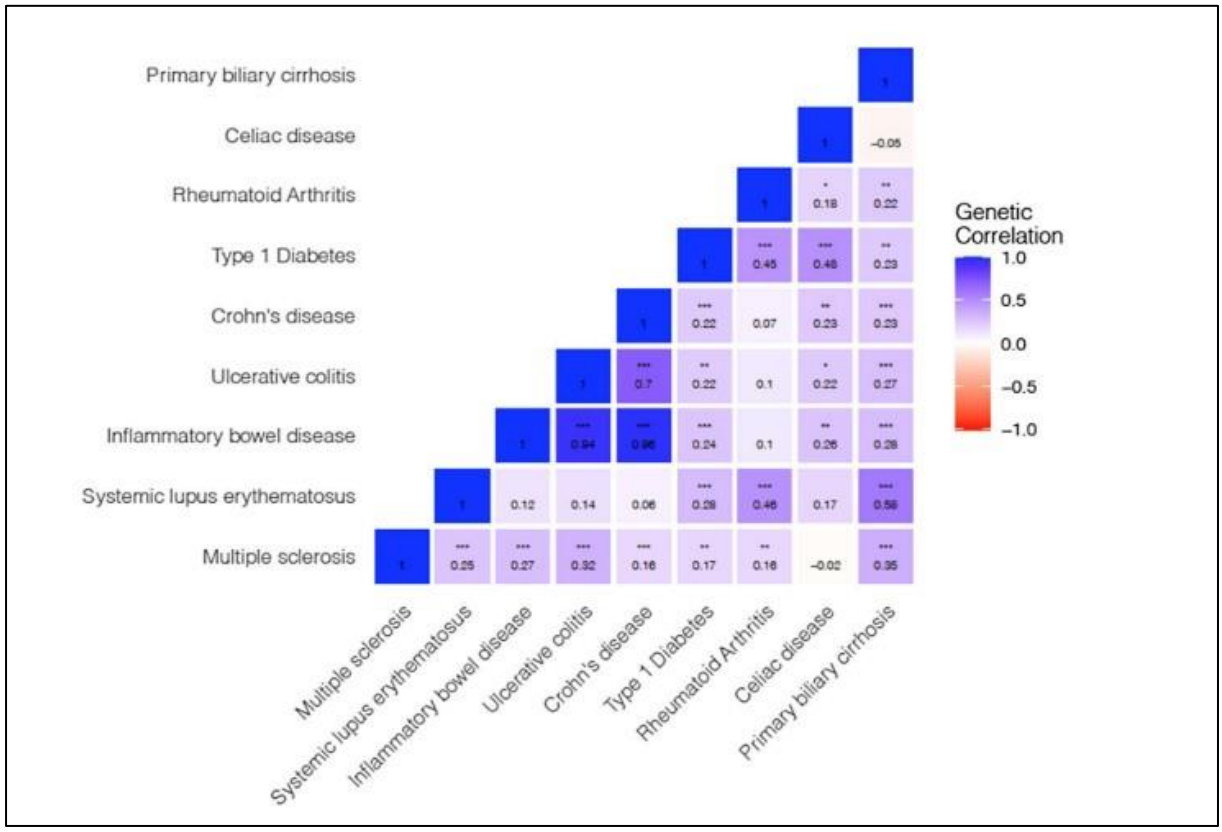


Figure 7: Genetic correlation across autoimmune diseases utilizing GWAS summary statistics*. An asterisk indicates nominal (p-value <0.05) significance, a double asterisk indicates p-value <0.01 and a triple asterisk indicates p-value <0.001. Reprinted with permission of Copyright Clearance Centre; Rights Link service (Kim and Patsopoulos, 2022).*

3.5.6.2. Latitude

The latitudinal effect on prevalence and incidence is broadly investigated in a meta-analysis performed by Koch-Henriksen et al in 2011 (Koch-Henriksen and Sorensen, 2011) and updated by Simpson et al in 2019 (Simpson et al., 2019). The latitudinal effect is modest in Europe and North America, while prevalence did not significantly vary with latitude in Australia and New Zealand. There

is apparently no latitudinal effect on incidence rates in the northern hemisphere, but it varies significantly with southern latitude in New Zealand and Australia. Koch-Henriksen emphasizes the difficulty in explaining the discrepancy in the latitudinal gradient in the southern and northern hemispheres, suggesting there may be strong environmental influences on the risk of MS (Koch-Henriksen and Sorensen, 2011). In Norway a lower prevalence in the Northern regions has previously been reported, possibly explained by a higher intake of dietary vitamin D in this region. However, a more complete case ascertainment in 2012 did not reveal any latitudinal effect in Norway. See Figure 8.

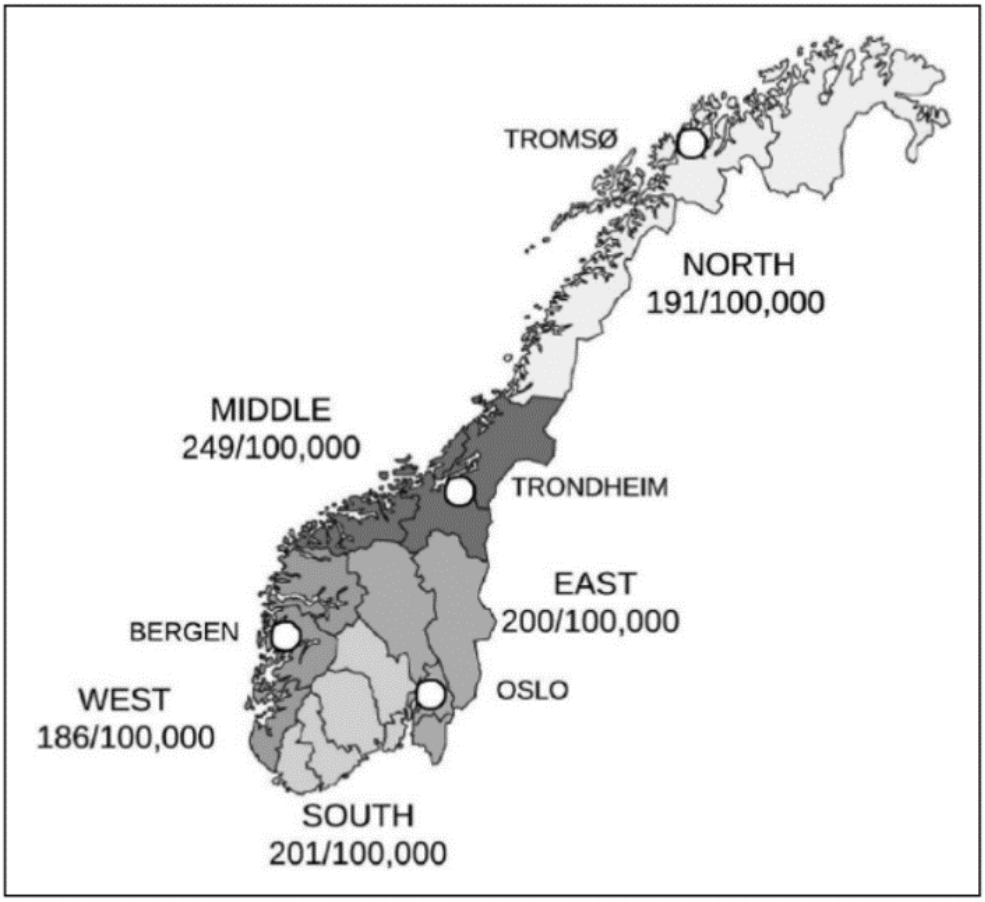


Figure 8: Map of Norway showing crude prevalence estimates in the five health regions, 2012. *Reprinted with permission of Sage Publishing copyright clearance centre (Berg-Hansen et al, 2014).*

3.5.6.3. Smoking

An association between smoking and the risk for MS has been found in several prospective investigations word-wide (Hernán et al., 2001, Riise et al., 2003), and the MS risk increases with smoking duration and intensity. Ascherio and colleagues concluded in a meta-analysis of four prospective studies that current smokers have a 40 % increased risk of MS, with a dose response effect ranging from 40 % in moderate smokers to 60 % in heavy smokers (Ascherio and Munger,

2016). How smoking is related to the increase in incidence of MS is still unclear, but several pathways have been suggested. A direct immunomodulatory effect of smoking is one theory, reinforced by the fact that several autoimmune diseases are more prevalent in smokers (like rheumatoid arteritis, systemic lupus erythematosus and psoriasis). Other theories include a direct effect on the blood-brain barrier as nicotine increases microvascular blood-flow and permeability (Hedström et al., 2009), and a toxic effect on the central nervous system from compounds in cigarette smoke (Rosso and Chitnis, 2020). The use of snuff, however, is not associated with an elevated risk for MS (Hedström et al., 2009), and this insight has led to a theory that these agents cause post-translational modifications via antigen presentation occurring in the lungs (Dobson and Giovannoni, 2019). There is also evidence that smoking may have an influence on the genetic risk of developing MS. In a Swedish population-based case-control study, the risk of developing MS in smokers with no genetic risk factors was 1.4. However, this increased to a factor of 2.8 in smokers with two genetic risk factors (human leucocyte antigen DRB1*15 and A*02) (Hedstrom et al., 2011).

3.5.6.4. Vitamin D

There is an established link between the intake of vitamin D and risk of MS, though the results are conflicting. Some prospective studies have shown that a higher intake of vitamin D is associated with a reduced risk of MS (Munger et al., 2004, Munger et al., 2006), while another prospective study did not find an association between MS and any dietary factors, including vitamin D (Rotstein et al., 2019). A Finnish study has shown an increase in the risk for MS in the offspring in women with insufficient vitamin D during pregnancy (Munger et al., 2016). This is further reinforced by the findings of a significantly elevated risk of MS risk in those born in April, and a reduced in risk in people born in October in the Northern hemisphere (Dobson et al., 2013, Grytten et al., 2013). However, a Swedish study has since concluded that there is no association between neonatal vitamin D levels and the future risk of MS (Ueda et al., 2014). One argument for a true association includes the pattern of MS prevalence according to latitude and solar radiation effects, which increase with a North or South latitude away from equator (Koch-Henriksen and Sorensen, 2010). In addition, we observe a correction of the prevalence of MS in second-generation immigrants (Berg-Hansen et al., 2015). There is also a beneficial role of both vitamin D and exposure to sunlight on the immunomodulatory mechanisms as the active form of vitamin D plays an essential role in activation and proliferation of immune cells and the production of specific antibody isotypes (Sintzel et al., 2018). Finally, the genes encoding different enzymes responsible for vitamin D metabolism also influence the risk of MS, such as abnormalities of the CYP24A1 gene, which encodes the enzyme responsible for initiating calcitriol degradation (active vitamin D) (Pierrot-Deseilligny and Souberbielle, 2017).

3.5.6.5. The Hygiene Hypothesis and the Epstein - Barr virus (EBV)

The “hygiene hypothesis” was proposed in the early 2000s. It postulates that the observed increase in autoimmune diseases in general is a result of an environment that is too clean and thus fails to appropriately stimulate, educate, and, consequently, regulate the immune system (Wasko et al., 2020). As a continuation of this theory, many argue that exposure to multiple infections in early childhood reduces the risk of MS by modulating the immune response (Ascherio and Munger, 2016).

The Epstein–Barr virus (EBV) causes a persistent, latent infection with periodic reactivations, immortalizing B lymphocytes and eliciting a strong T-cell response. It has been launched as a plausible cause of several autoimmune diseases (Ascherio and Munger, 2015). The role of EBV in development of MS originates from observational epidemiological studies, ecological studies and experimental laboratory based research. Approximately 95 % of the general population has been infected by EBV (Bjornevik et al., 2022) and the virus persist latently in the memory B cell pool throughout life (Owens and Bennett, 2012). In developing countries, infections with common viruses, such as EBV, occur in early childhood, and the prevalence of EBV sero-positivity is over 90 % by the age of 4. In contrast, many children escape EBV infection until adolescence in more developed countries (Ascherio and Munger, 2016). The EBV infection in early life less commonly causes symptomatic infectious mononucleosis (IM). A link between EBV and MS was first proposed due to the similarities in IM and MS epidemiology in terms of age, socioeconomic status and geographical distribution (Ascherio and Munger, 2007). There is consistent evidence that people with MS are more likely to report past infectious mononucleosis (IM) than unaffected controls (Lucas et al., 2011) and a meta-analysis found a two-fold risk of developing MS in persons reporting IM in adolescence (Handel et al., 2010).

The influence of EBV on development of MS has been investigated for many years, and different meta-analysis have found a 4.5 to 16-fold increased risk of MS (Laurence and Benito-Leon, 2017). Bjørnevik et al published a paper on the risk of EBV in Science in 2022. They found a 32-fold increased risk of MS after infection with EBV when investigating repeated serum samples from more than 10 million young adults on active duty in the US military. Only 35/801 of those who later developed MS were EBV negative in the baseline sample, and all but one of these became infected and seroconverted before the onset of MS. See Figure 9. The median time from the first EBV positive sample to MS onset was 5 years (range 0-10 years). These results are supported by the finding of elevated levels of serum neurofilament light chain, a biomarker of neuro-axonal degeneration, following EBV seroconversion (Bjornevik et al., 2022).

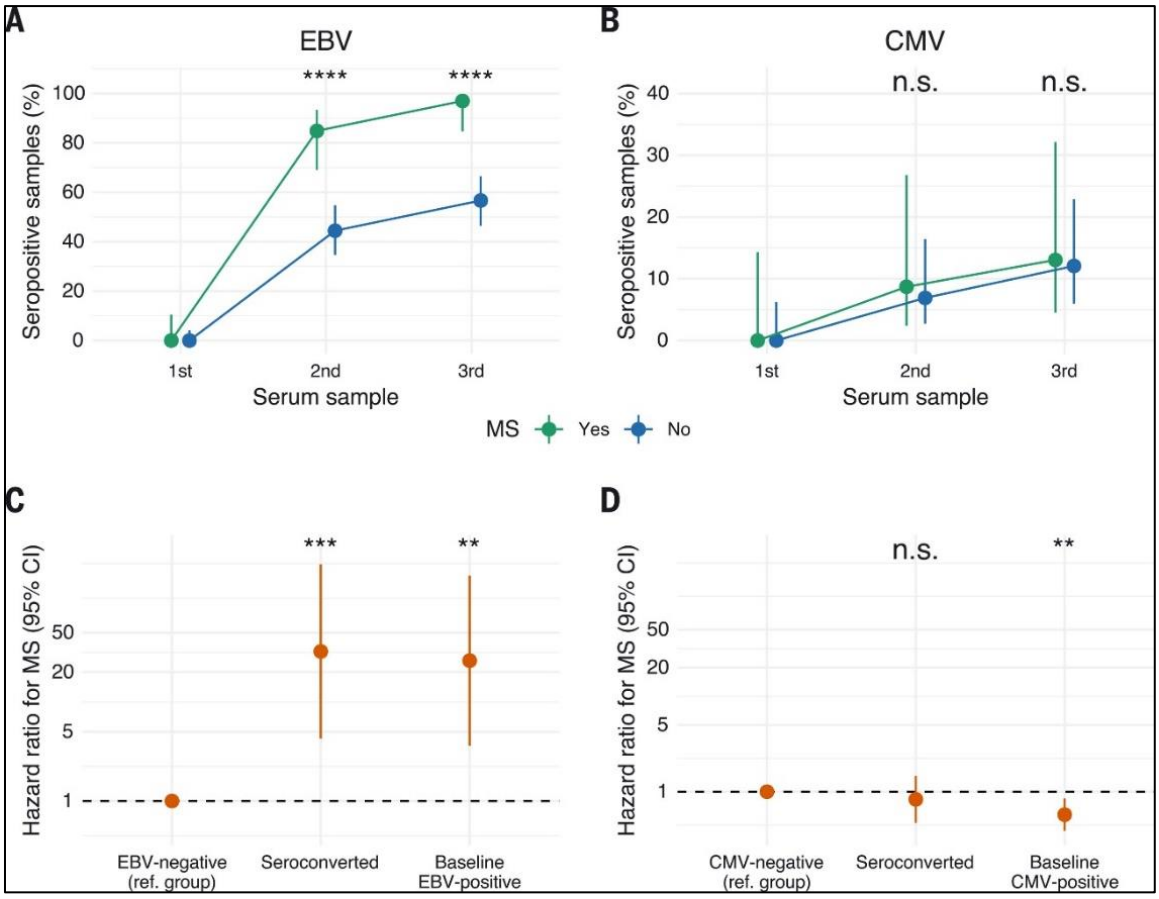


Figure 9: EBV infection precedes MS onset and is associated with markedly higher disease risk*. (A) Proportion of individuals EBV negative at baseline, positive at second and third sample (B) Proportion of individuals CMV negative at baseline, positive at second and third sample (C) Risk ratio for MS according to EBV status (D) Risk ratio for MS according to CMV status. Reprinted with permission of Copyright Clearance Centre, American association of the Advancement of Science (Bjørnevik et al 2022).*

Past IM also appears to modify the MS risk associated with the major susceptibility gene HLA-DRB1*15. There is a 10-fold increased risk of MS in persons who are DRB1*15 positive and have a history of IM compared to those who are DRB1*15 negative and no history of IM (Lucas et al., 2011, Nielsen et al., 2009).

The mechanisms underlying the linking of EBV infection to MS remain unclear. One possibility is that EBV-infected B-cells infiltrate the brain and elicit a cytotoxic T-lymphocyte response, damaging the surrounding brain tissue. This theory has been supported by post-mortem brain tissue from MS cases (Ascherio and Munger, 2010, Serafini et al., 2007). These findings have since been deemed inconclusive, as the presence of EBV-positive cells in MS lesions does not prove that these cells have a causal role. Another theory is that infected B cells, in addition to activating EBV-specific T cells, promote inflammation by releasing Epstein–Barr virus-encoded small RNAs (EBERs) that bind

to the specific receptors, resulting in activation of innate immunity and interferon-α production (Ascherio and Munger, 2015).

Other viruses have been investigated as possible risk factors, such as cytomegalovirus, human herpesvirus 6 (HHV-6), herpes simplex virus type 1 (HSV-1), varicella zoster, mumps, measles and rubella. So far, studies on serology have shown an inconsistent association or no association at all between these viruses and MS (Ascherio and Munger, 2007, Laurence and Benito-Leon, 2017, Bjornevik et al., 2022, Langer-Gould et al., 2017). See Figure 9 for results of a non-significant association of cytomegalovirus (CMV) and risk of MS (Bjornevik et al., 2022).

3.5.6.6. Obesity

Epidemiological data shows that obesity in early life appears to be strongly associated with a higher risk of MS. There is a two-fold increased risk of developing MS for subjects whose body mass index (BMI) exceeds 27 kg/m^2 (or 30 kg/m^2) compared to normal weight subjects (Hedström et al., 2012, Munger et al., 2009). The most critical period seems to be during adolescence and not during childhood (Hedstrom et al., 2016). Follow-up Mendelian randomization studies, that avoid bias, show that genetic determinants for a high BMI are associated with an increased risk of MS. This is further a genetic support for a causal effect of obesity, also in younger age (childhood), on MS susceptibility (Harroud et al., 2021). The association of childhood BMI and risk for MS seems stronger for girls (Munger et al., 2013). A Norwegian-Italian study on body size and the risk of MS found an association present for at least 15 years prior to diagnosis in Norway, but there were no significant associations in the Italian part of the cohort (Wesnes et al., 2015). Partly overlapping pathways have been suggested as an explanation for the association between obesity and MS. These include adipocyte hyperplasia, characterized by a “low-grade” inflammation and occurrence of high levels of pro-inflammatory mediators produces in fat tissue (Schreiner and Genes, 2021), and decreased bioavailability of vitamin D seen in obese people (Pereira-Santos et al., 2015, Alfredsson and Olsson, 2019).

3.5.6.7. Socioeconomic factors

The influence of socioeconomic factors on the risk of MS will be discussed in chapter 3.8.4.1.

3.6. Disease course

The natural history of MS includes the characteristics of the disease from the first symptom of a demyelinating disease, often years before the diagnosis, to the time of diagnosis and trough the more progressive, end-stage phases of the disease.

3.6.1. Prodromes of multiple sclerosis

A prodrome is defined as signs and symptoms that precede the onset of typical signs and symptoms of the disease. There is increasing focus on the MS prodrome and several studies have attempted to describe the prodromal phase of the disease (Makhani and Tremlett, 2021, Wijnands et al., 2019, Tremlett and Marrie, 2021). The understanding of the prodromal phase of MS, as for any disease, is of importance in order to recognize potential preventive measures (Marrie, 2019b).

3.6.1.1. Clinical features of the MS prodrome

Several lines of evidence show that people who go on to develop MS change their health-related behavior in the years leading up to the diagnosis. Compared to controls, people who go on to develop MS see their general practitioner more often, have a higher frequency of hospital visits, more prescriptions and an elevated mental health burden. In addition, they experience more non-specific symptoms, ranging from pain to gastrointestinal and genito-urinal symptoms compared to age- and sex-matched controls (Wijnands et al., 2019, Disanto et al., 2018, Makhani and Tremlett, 2021). A Norwegian study demonstrated reduced performance on intelligence tests at conscription compared to peers up to two years before onset of MS symptoms (Cortese et al., 2016). However, another study from Norway did not find a significant differences in grades between graduates from upper secondary school who later developed MS and matched controls. There were, however, non-significant tendencies of more days of absence in the group who later went on to develop MS (Simonsen et al., 2021b). The recognition of prodromal health behaviour also emphasises the need for re-evaluating whether presumed risk factors for MS could, in fact, be prodromal features. One example is the earlier thought that fewer pregnancies and use of oral contraceptives could increase a woman's risk of developing MS (Runmarker and Andersen, 1995). More female cases than controls had no or few childbirths before clinical onset of MS in a Danish case- control study (Magyari et al., 2013) suggesting reverse causation as a plausible explanation; the prodromal phase of MS might change the behaviour of these women as an reaction to their health concerns (Makhani and Tremlett, 2021).

3.6.1.2. Biomarkers of the MS prodrome

Neurofilaments are seen as markers of neuro-axonal damage. In a nested case-control study among US military personnel, serum neurofilaments light chain (sNfL) levels were higher in cases who later

developed MS compared to matched controls in samples drawn a median of 6 years before the first clinical onset of MS. The difference between sNfL levels in people who developed MS and those of controls increased as the interval between serum testing and clinical onset decreased. (Bjornevik et al., 2020). The use of sNfL has not yet been incorporated into routine clinical practice, and there is a need for more knowledge before it can be used to measure clinical responsiveness on an individual basis (Thebault et al., 2021).

Radiologically isolated syndrome (RIS) is defined as an incidental MRI finding of lesions characteristic of MS. The lesions are highly suggestive of demyelinating pathology based on location and morphology. This concept was first outlined by Okuda et al in 2009, including suggestions of diagnostic criteria for a diagnosis of RIS (Okuda et al., 2009). The major motivation for performing a cerebral MRI is headache (Lebrun et al., 2014) and the detection of the hyper-intensive lesions may be an unintended consequence of the examination. The exact prevalence of RIS is unknown, but a review of different studies concluded that the prevalence is 0.06-0.07% (Granberg et al., 2013). (Granberg et al., 2013). A North American study suggests that the prevalence of RIS is even higher. When using the Okuda criteria for RIS, they found RIS in 2.4 % of persons without CNS pathology, and in 2.9 % of healthy subjects with a first- second or third degree relative with MS (Gabelic et al., 2014). The risk of misclassification is present, and one study found that 8 % (of 220 persons) referred to a neurologist with proposed RIS actually had this diagnosis. It is, however, worth noting that at six months, 35.4 % in this cohort had a diagnosis of MS according to the 2010 McDonald criteria (Lebrun et al., 2014). In a longitudinal cohort study of persons with RIS, a cumulative probability of a first clinical event of MS at 10 years was 51.2 %. Age, oligo-clonal bands in cerebrospinal fluid, infra-tentorial lesions and the presence of gadolinium-enhancing lesions were associated with a higher risk (Lebrun-Frenay et al., 2020). Even in this, potentially, early stage of the disease, there is evidence of end-organ damage. Persons with RIS have significant cognitive impairment similar to persons with established MS (Amato et al., 2012).

3.6.2. Natural history of MS

Over the last decades, there have been several studies on the natural history of MS. The studies typically follow cohorts of pwMS over extended periods of time. The results from such studies are in particular valuable when advising pwMS on prognosis and treatment choice (Tremlett et al., 2010). EDSS is the scale traditionally used for evaluating functional systems of the central nervous system in MS, described in section 3.4.3.1.

In a 1977 study by Kurtzke et al on series of cases of MS in the US Army in World War II, 20 % of the patients were considered to have “benign” disease (Disability Status Score (DSS) 0-2) after 10 to 15 years of disease, whereas 50 % had “severe” disease (DSS score ≥ 6, including deaths) (Kurtzke et al., 1977). Over the years, the time from onset of the disease to EDSS 6 (the point when a pwMS is dependent on a cane or crutch for walking), is one of the most commonly used milestones.

In Weinshenker’s study from Ontario and London (1972-1984) the median time to EDSS 6 from onset was approximately 15 years (Weinshenker et al., 1989, Weinshenker, 1994). The time to EDSS 6 has since then improved. In a study from Tremlett et al in Canada, the time to EDSS was 27.9 years (Tremlett et al., 2006). In a Norwegian study from 2020, the mean time from onset to EDSS 6 was 29.8 years. When analysed in sub-groups by years for diagnosis, the time to EDSS estimated in models, showed a significant increase, from 31.5 years in the cohort diagnosed 2003-2007, to 42.8 years for the cohort diagnosed from 2013-2017 (Simonsen et al., 2020a). This may be due to disease modifying treatments, earlier diagnosis, changes in the diagnostic criteria and the characteristic of the cohorts other than gender and age. During the past decade, the entire course of MS appears to be milder probably due to a complex interplay of several factors (Simonsen et al., 2020a, Sorensen et al., 2020). Figure 10 shows the proportion of pwMS reaching EDSS 3 according to the era in which the diagnosis took place, as presented in a publication by Sørensen et al in Brain, 2020.

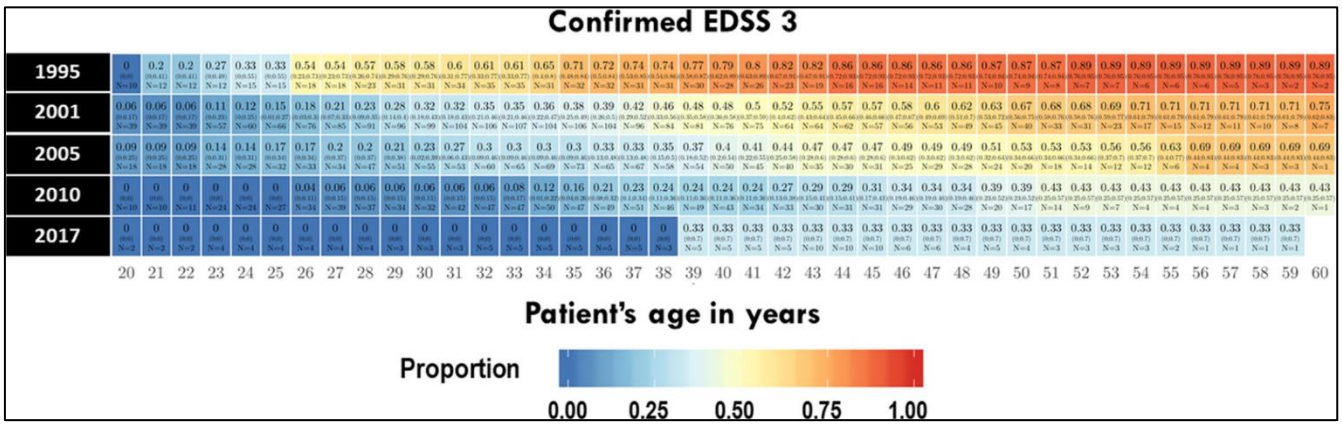


Figure 10: Kaplan-Meier heat map presenting the proportion of patients (with 95 % confidence interval) reaching EDSS 3 at a given age according to the era in which the diagnosis took place. *Reprinted with permission of Copyright Clearance Centre, Right Link* (Sorensen et al., 2020).

The development of secondary progressive MS has traditionally been reported to occur 10-15 years from RRMS onset (Dobson and Giovannoni, 2019) . There is a lack of clear diagnostic criteria for when a person has developed SPMS. Some of the variables significantly associated with being classified as having *early* SPMS is the presence of motor symptoms, ataxia or coordination symptoms,

increasing age and a high number of T2 lesions. The presence of paraesthesia or other sensory symptoms is not (Ziemssen et al., 2020).

3.6.3. Prognostic factors for expected disease course

MS is a chronic condition, but the individual course of the disease is highly variable. Through natural history studies on different MS cohorts, risk factors that predict the evolution from a clinically isolated syndrome (CIS) to definite MS, and the risk of disability accumulation, have been identified (Confavreux et al., 2003, Langer-Gould et al., 2006, Scalfari et al., 2010, Tutuncu et al., 2013, Kuhle et al., 2015, Tintore et al., 2015, Scalfari et al., 2016, Sorensen et al., 2020).

3.6.3.1. Risk of conversion to clinical definite MS (CDMS)

There has been a focus on identifying risk factors for people diagnosed with CIS to convert to clinical definite MS (CDMS). In a Spanish study, Tintore et al showed that the risk of conversion to CDMS did not differ between genders. Younger age at onset was, however, associated with a greater risk of CDMS. Conversely, there was a lower risk of conversion in people with optic neuritis as their first symptom. The strongest predictor for conversion was the number of MRI lesions as more than 10 lesions increased the risk with a hazard ratio of 11.3 (6.7-19.3). The presence of oligo-clonal bands in the CSF was also positively associated with conversion to CDMS, with a hazard ratio of 2.9 (1.4-6.0) (Tintore et al., 2015).

In a large, international, multicenter study, Kuhle et al confirmed that MRI lesion load, the presence of oligo-clonal bands in the CSF and younger age are the strongest independent predictors of conversion to CDMS. A role for vitamin D-level has also been suggested, but this needs further investigation (Kuhle et al., 2015).

3.6.3.2. Risk factors for disability progression

Male *gender* has traditionally been reported as a risk factor for poorer outcome of RRMS. The median time from the onset of a both RRMS and a PMS to different hallmarks of disease severity, such as EDSS 4,6 and 7, is significantly longer in females than in males (Confavreux et al., 2003). The evidence for the contribution of gender is, however, mixed, and in a review by Langer-Gould et al, 5 out of 10 included studies found no effect on progression by gender (Langer-Gould et al., 2006).

The risk of disease progression increases with a higher *age* at onset. (Langer-Gould et al., 2006). The frequency of early relapses are thought to be a predictor of long-term outcome, but frequency of relapses after year two does not appear to predict outcome any further (Scalfari et al., 2010). According to a study by Scalfari et al there is not a significant correlation between age at onset and

the number of early relapses. On the other hand, being older at onset is correlated with a significantly lower number of late relapses, in addition to a lower number of total relapses before the onset of disease progression. Scalfari concluded that the age of entering a progressive phase did not influence the rate of disability accumulation (Scalfari et al., 2016).

The *initial manifestation* of the diseases also seem to have an influence on progression, with a longer time to EDSS 6 when the onset symptom is optic neuritis compared to pyramidal symptoms (Confavreux et al., 2003). Optic neuritis as a first symptom is also seen as a low impact prognostic factor for reaching an EDSS of 3.0 (Tintore et al., 2015). Sphincter problems, incomplete recovery from the first relapse and a short interval between the first and second relapse are also associated with a poorer prognosis (Langer-Gould et al., 2006).

A significant association between *genes* and disease progression (measured by MSSS) has not been found, suggesting that the genetic contribution to MS affects the disease initiation, but not the disease progression (Kim and Patsopoulos, 2022). However, there are identified variations in specific genes associated with an increase relapse rate (Vandebergh et al., 2021) and higher degree of atrophy in subcortical grey matter (Isobe et al., 2016). This could indicate a predisposition for a more aggressive progression.

The *neurofilament light chain* is expressed in neurons and released into the extracellular space when an axon is damaged (Teunissen and Khalil, 2012). An elevated concentrations of serum neurofilament light chain (sNfL) in pwMS is associated with an increased risk of relapses and a higher disability score in general (Hakansson et al., 2017, Barro et al., 2018). A study by Brune et al concluded that pwMS with elevated sNfL concentrations have an increased risk of disease worsening after a median of 2 years, with a 2.8 fold increased risk of disease worsening, a 4.0 fold increased risk of new T2 lesions and a 3.3 fold increased risk of relapse activity. There was, however, no statistically significant risk of EDSS progression (Brune et al., 2022).

Many of the factors identified as risk factors for developing MS (see section 3.5.6) are also factors that impact the course of the disease and progression. Several studies have reported an immunomodulatory effect of *vitamin D* on the immune response, and cohort studies have shown that increasing serum 25 (OH) D vitamin levels is associated with low disease activity in CIS and RRMS (Smolders et al., 2019). However, a meta-analysis concluded that vitamin D appeared to have no therapeutic effect on the EDSS or the annualised relapse rate in pwMS (Zheng et al., 2018). Several studies have explored the association between *smoking* and MS progression, and the majority have shown an adverse effect of smoking on the MS disease severity and progression (Hedström, 2020).

There is also evidence for a dose-response effect of smoking on the EDSS and the MSSS (Manouchehrinia et al., 2013).

3.6.4. Impact of comorbidity

The definition of comorbidity usually refers to the total burden of chronic illness other than the "index disease", a condition distinct from the complications of the index disease (Marrie, 2019a). The prevalence of comorbidity is high in MS, particularly mood disorders, other autoimmune conditions and cardiovascular diseases (Marrie et al., 2015). Migraine, restless legs syndrome and epilepsy are all increased in pwMS compared to control populations (Hauer et al., 2021). The cancers with the highest prevalence in pwMS were cervical, breast and digestive system cancers, according to a systematic review by Marrie et al (Marrie et al., 2015). In a Norwegian cohort, 97.5 % of pwMS had a comorbid condition. The overall cancer proportion in this cohort (Nordland county) was 6.4 %, compared to 5 % in the Norwegian population. Higher proportions of inflammatory bowel disease and epilepsy were also found (Benjaminsen et al., 2021). A study from the Norwegian Multiple Sclerosis registry found that the overall risk of cancer was higher among pwMS than controls, with a hazard risk for cancer in pwMS of 1.14 (95 % confidence interval 1.05-1.23) (Grytten et al., 2020). However, recent review studies have not found an increase in the overall risk of malignancy in pwMS, though there may be a risk associated with some DMTs (Magyari and Sorensen, 2020). The increasing age of the prevalent pwMS population will also increase the risk of comorbidities (Ostolaza et al., 2021).

Apart from the obvious influence on the quality of life, comorbidities may also adversely influence the disease course and progression of MS. In a retrospective cohort study there was an annual increase in the EDSS of 0.18 points for every physical comorbidity (Zhang et al., 2018). A Canadian study found that people with RRMS who had three or more comorbidities, had a significantly increased relapse rate over 2 years (Kowalec et al., 2017).

Coexisting comorbidities also raise challenges concerning immunomodulatory treatments of MS (Marrie et al., 2015, Magyari and Sorensen, 2020). There is an association between comorbidity and the initiation of a DMT, with anxiety and ischemic heart disease associated with less initiation of DMTs. The number of comorbidities, on the other hand, is not associated with the choice of DMT when comparing betainferon and glatiramer acetat (Zhang et al., 2016). The use of DMTs may also increase the risk of developing certain comorbidities. There is an increased risk of cardiac events in people treated with fingolimod (Akbulak et al., 2018), autoimmune thyroid disease is a common side

effect of alemtuzumab (Khalilidehkordi et al., 2017) and rituximab may induce colitis (Bhalme et al., 2012).

3.6.5. Mortality

A number of studies have reported a higher mortality in pwMS than in corresponding populations (Scalfari et al., 2013). However, MS in itself is not a lethal disease. The premature death seen with MS is most likely due to complications, such as infections or respiration failure (Koch-Henriksen et al., 1998, Scalfari et al., 2013). In an early study on world war two veterans, 17 % of pwMS had died 15 years after disease onset (Kurtzke et al., 1977). A Norwegian study from 2009 showed a median survival of 35 years after MS onset (95 % confidence interval 33-37) (Smestad et al., 2009). In this Norwegian cohort, MS was defined as the cause of death in approximately 50 % of death certificates (Lunde et al., 2017, Smestad et al., 2009). Smestad et al concluded that infections were, most likely, the main cause of death in pwMS, though the frequency was underestimated due to misleading information on death certificates (Smestad et al., 2009). A Canadian study investigating death certificates where MS was mentioned found that respiratory infection was the most common cause of death, with other infections, including sepsis, in second (Harding et al., 2020). The suicide rate in pwMS is elevated, with the suicidal mortality ratio approximately twice that of the general populations (Feinstein and Pavisian, 2017).

The standardised mortality ratio (SMR) is a measure of mortality relative to the general population. A Norwegian 60-year longitudinal population study found a SMR of 2.4 in RRMS and 3.9 in PPMS. Using the year for disease onset, the SMR has decreased significantly from 3.1 for onset between 1953 and 1974, to 0.8 for onset between 1997 and 2012 (Lunde et al., 2017). A decrease in mortality was also shown in a Danish cohort, with the authors concluding that the decline in excess mortality started decades before DMTs for MS became available (Koch-Henriksen et al., 2017). The reasons for this reduction may be that better living conditions and better welfare for chronically ill people. It could also be the result of a change in the MS cohort, with an increasing female incidence and more benign cases diagnosed (Grytten, 2017, Koch-Henriksen et al., 2017).

3.7. Treatment and management of MS

3.7.1. Treatment of relapses

The most commonly used treatment in acute MS relapses, is administration of a high-dose intravenous corticosteroid. Current protocols typically recommend 3-5 days of methylprednisolone (Filippi et al., 2018). Trials report a benefit in speed of relapse recovery compared to placebo (Sellebjerg et al., 2005). Evidence does not support any major differences in clinical effect of methylprednisolone treatment given intravenously versus orally (Sellebjerg et al., 2005), though long-term oral corticosteroid treatment is associated with more side-effects. Relapse treatment with corticosteroids has, however, no influence on the occurrence of new relapses or long-term disability (Myhr and Mellgren, 2009). Relapses that do not respond to corticosteroid treatment, may be treated with plasma exchange or intravenous immunoglobulins (IVIG) (Filippi et al., 2018, McGinley et al., 2021). A study on plasma-exchange in persons with steroid refractory demyelination showed moderate to marked functional neurological improvement within 6 months following treatment, though this was less effective for people with a progressive MS (Magaña et al., 2011). There were no significant differences in the EDSS score improvement in a study comparing IVIG with methylprednisolone in acute MS relapses. IVIG is therefore recommended for people without response to methylprednisolone, or in severe cases where methylprednisolone or plasma exchange is contraindicated (Elovaara et al., 2011).

3.7.2. Disease modifying treatment

The improved understanding of the neurobiological and immunological disease processes underlying MS has led to the development of many new treatments that can substantially reduce disease activity in many patients, and at least partially delay disease progression.

The primary mechanism of action of all available DMTs to date, is to diminish neuro-inflammation. Table 5 gives short descriptions on the mechanisms of action for each available DMTs and Figure 11 presents an overview of the DMTs. More generally, the mechanism of action can be grouped into five groups according to treatment targets:

1. **General anti-inflammatory effects (interferons, glatiramer acetat, teriflunomide, dimetylfumarat).**

This group of DMTs have pleiotropic effects by producing mild, but persistent attenuation of the pro-inflammatory lymphocytes or by down-regulating T-cell activation (Mehta et al., 2019).

2. Preventing egress of lymphocytes from lymph nodes (S1P modulators)

The myelin-reactive lymphocytes undergo crucial activation steps in the lymph nodes. Migration of activated lymphocytes is mediated via sphingosine 1-phosphate (S1P) receptors. S1P modulators, like fingolimod, ozanimod, ponesimod and siponimod, prevent the egress of these lymphocytes, with a consequently fall of lymphocytes in peripheral blood (Bierhansl et al., 2022) .

3. Preventing lymphocytes entry to CNS (natalizumab)

The breakdown of the blood-brain barrier (BBB) is an early hallmark in MS, visualised on MRI by contrast enhancement. The entrance of inflammatory cells through the BBB is tightly regulated in the normal brain. In MS, the autoreactive leucocytes enter the CNS after peripheral activation of cellular migration molecules. Natalizumab is an antibody targeting the leucocyte ligand α4β and impairs the adhesion of leucocytes to the vascular cell adhesion molecule 1 (VCAM1) (Bierhansl et al., 2022).

4. Affecting proliferation of lymphocytes DNA (cladribine)

Another approach to prevent neuro-inflammation, is by inhibiting lymphocyte-specific signalling cascades (Bierhansl et al., 2022). The effect of pulsed cladribine is an inhibition of DNA synthesis and repair, and subsequent apoptosis of the T-cells. The accumulation of cladribine nucleotide produces a rapid and sustained reduction in CD4+ and CD8+ cells, a more transient effects on CD 19+ B-cells and a relative sparing of other immune cells (Giovannoni et al., 2010).

5. Affecting specific lymphocytes, inducing cell-deaths (anti CD20 and anti CD25)

As opposite to non-specific immune suppressants, the depletion of selected immune cell populations is a more specific target. Different antibodies attack different surface-molecules on immune cells. The anti-CD 20 antibodies, such as rituximab and ocrelizumab, deplete most of the B lymphocytes lineage and a small population of T-cells. Anti-CD52 therapy, like alemtuzumab, targets a pan-lymphocyte cell-surface molecule and removes almost all lymphocytes (Bierhansl et al., 2022).

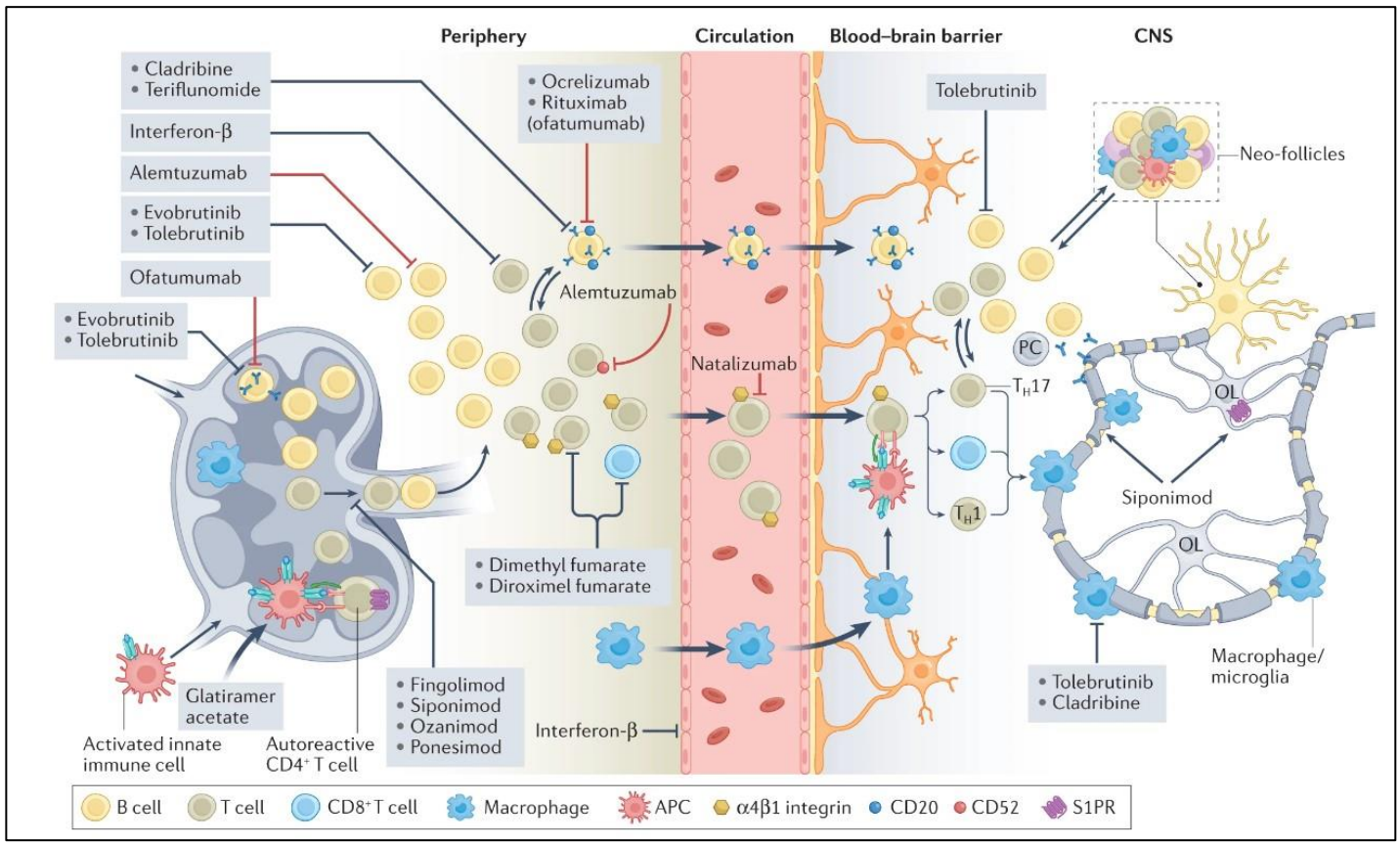


***Figure 11**: Overview of the immunopathogenesis and targets of available disease-modifying treatments in MS. APC antigen presenting cell, OL oligodendrocyte, S1PR sphingosine 1-phsophate receptor, T_H cell T helper cell. Reprinted with permission of Copyright Clearance Center, Springer Nature (Bierhansl et al., 2022)*.

Table 5 presents all the available DMTs for RRMS in Norway, as of November 1st 2022.

The reduction in annualised relapse rate has been used as a measure of treatment efficacy in most studies. However, it is important to emphasise that the comparator has also changed, from placebo to an active treatment (interferon beta or teriflunomide). The impact on the MRI lesion burden is difficult to compare across studies, as the measures of activity – or absence of activity – differ. The earlier studies merely used a reduction in the number of new or enlarged T2 lesions as a marker of efficacy, while gadolinium enhancement is weighted more heavily in later studies. In the recent years the total volume loss has been used more frequently.

Generic name *Trade name in Norway, adm.*	**Year EMA approval** *Study, comparator*	**Reduction annualized relapse rate %**	**Relative reduction MRI lesions**	**Most common or significant side effects**	**Mechanism of action**
MODERAT EFFICACY DISEASE-MODIFYING TREATMENTS					
Interferon β-1a *Betaferon® sc x 1* *Rebif®sc x3/w* *Avonex®im/w* *Plegridy®imx2/w*	1995 *PRISMS, placebo(Paty and Li-Kroeger, 1993)* 1998 1997 2014	33%	n.a.	influenza-like symptoms, injection site reaction, abnormal LFT	Reduces antigen presentation and T-cell proliferation, alters cytokine expression, restores suppressor function
Glatiramer acetat *Copaxone® sc x 1*	2000 CMSSG(Johnson et al., 1995) placebo	29%	n.a.	injection site reaction, flushing reaction	Activates anti-inflammatory lymphocytes, crosses BBB
Teriflunomide *Aubagio® po x 1*	2013 *TEMSO(O'Connor et al., 2011), placebo*	32%	67%**	hair loss, GI symptoms	Inhibits proliferation of B and T cell, induces anti-inflammatory cytokines
Dimethylfumarat *Tecfidera® po x 2*	2014 *DEFINE(Gold et al., 2012), placebo*	53%	85%*	flushing reaction, GI symptoms, lymphopenia, abnormal LFT	Reducing release of inflammatory cytokines, antioxidant effect
HIGH EFFICACY DISEASE-MODIFYING TREATMENT					
Natalizumab *Tysabri® iv/4w*	2006 *AFFIRM(Polman et al., 2006), placebo*	68%	83%*	PML, Infusion-reaction	Humanized MAB, block α-integrin, inhibits lymphocyte entry through BBB
Fingolimod *Gilenya® po x 1* *Fingolimod®pox1*	2011 *FREEDOMS(Kappos et al., 2010), placebo*	54%	63 %*	arrhythmia, lymphopenia, abnormal LFT, macular oedema	S1P-modulator, prevents egress of lymphocytes from lymph nodes
Alemtuzumab *Lemtrada® iv 8 days over 2 years*	2013 *CARE MS I,II(Cohen et al., 2012), Interferon β*	52%	n.s.*	infusion reactions, secondary autoimmunity, leukopenia	Humanized MAB, anti-CD52
Cladribine *Mavenclad® po 10 d yr 1 and yr 2*	2017, *CLARITY(Giovannoni et al., 2010), Placebo*	58%	74% ***	lymphopenia, infections (herpes zoster)	Purine analog, affects proliferating lymphocyte DNA, inducing cell death
Ozanimod *Zeposia® po x 1*	2020 *SUNBEAM(Comi et al., 2019)* *Interferon β*	52 %	52%*	lymphopenia, abnormal LFT	S1P-modulator, prevents egress of lymphocytes from lymph nodes
Ponesimod *Ponvory® po x 1*	2021 *OPTIMUM(Kappos et al., 2021), teriflunomide*	31%	42% ***	lymphopenia, abnormal LFT	S1P-modulator, prevents egress of lymphocytes from lymph nodes
OFF-LABEL THERAPIES					
Rituximab *Rixathon® iv/ 6 months*	Not approved for MS			infusion reactions, opportunistic infections, hypogammaglobulinemia	Chimeric MAB, anti CD20

Table 5: Disease modifying treatment *available and financed by the public health care system in Norway, as of April 1st 2022. EMA European Medicines Agency, MRI Magnetic Resonance Imaging, sc subcutaneous, iv intravenous, im intramuscular, po per oral, d day, w week, yr year,LFT liver function test, MAB monoclonal antibody, GI gastrointestinal, PML progressive multifocal leukoencephalopathy, BBB blood brain barrier, na not available result*

 # The interferon ϐ group exemplified by the first study PRISM – later studies with similar results of efficacy
** Reduction in new or enlarged T2 lesions on MRI during follow-up.*
*** Reduction in total lesion volume on MRI during follow up*
**** Reduction in new T1 gd+ lesions or new or enlarging T2 lesions*

3.7.3. Autologous haematopoetic stem cell transplantation (AHSCT)

The first attempt of stem cell transplantation in the treatment of MS was performed in 1995 on 15 people with progressive MS. Significant improvement in the EDSS was observed in seven of the 15 participants, though the median follow-up time was only six months (Fassas et al., 1997). Over the years, increasing evidence that AHSCT is a very effective treatment, in particular for highly aggressive RRMS, has emerged. However, there has been a lack of larger randomized studies (Burman et al., 2014).

The AHSCT is meant to eliminate autoreactive lymphocytes and restart or reconstitute a new immune system in a non-inflammatory environment (Burt et al., 2019). The protocols used for AHSCT are divergent. Most start with stimulation of hematopoietic stem cells to enter the peripheral blood, followed by collection of stemcells and treatment with a conditioning cytostatic, before re-transplantation of the autologous stem cells.

An observational study from Sweden have identified a 5 years relapse-free survival of 87 % and no mortality in the group of 48 people. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%) (Burman et al., 2014). In a study from the US, Burt and colleagues randomized pwMS to receive either HSCT or a DMT. Disease progression occurred in three pwMS in the HSCT groups and 34 pwMS in the DMT groups (Burt et al., 2019). However, there were multiple DMT used, ranging from the interferons to natalizumab. In Norway, AHSCT is primarily offered to people with a highly aggressive MS, despite use of a high efficacy DMT.

A recently published observational study, which included 104 people with RRMS treated with AHSCT in Norway and Sweden from 2011 to 2021, did not show any cases of treatment related mortality. The last DMT used prior to AHSCT did not affect the occurrence of secondary autoimmunity, severe infections or prolonged hospitalization (Kvistad et al., 2022).

3.7.4. Therapeutic strategies and therapeutic goals

The treatment era for MS began in 1993, when the effect of the first DMT was proven (Paty and Li-Kroeger, 1993). Over the past few years, the growing armamentarium of therapies has introduced several new options for the affected person, making individualized medicine possible in the treatment of MS. Both the European Federation of Neurological Societies (EFNS), later the European Academy of Neurology (EAN), and the European Committee for treatment and research in multiple sclerosis (ECTRIMS) have published detailed and updated recommendations on different treatments in MS over the years (Sellebjerg et al., 2005, Montalban et al., 2018b). Many countries have their own national strategy for treatment in MS. In Norway, the latest version was published in September 2022, which, for the first time, recommended early initiation of high-efficacy DMT as the first line therapy (Norwegian Directorate of Health, 2017).

3.7.3.1. Therapeutic strategies

As the array of DMTs grew, so did the need for a treatment strategy. One of the main concerns has been that the DMTs with the highest efficacy are associated with more complex safety profiles, monitoring requirements and the need for hospital or day unit admission (Harding et al., 2019a). There has been focus on understanding and using the benefit versus risk profiles of the different therapies, to ensure personalized and safe treatment for each individual pwMS. Different MS management strategies have emerged, among them sequential monotherapy, escalation therapy, induction therapy and maintenance therapy (Comi et al., 2017).

The *sequential monotherapy* implies that, after starting a first DMT, the pwMS must be monitored for tolerability, adherence and safety, as well as signs of clinical or MRI activity. As long as there are no signs of disease activity or significant adverse events, the therapy is continued. If experiencing a breakthrough relapse or MRI activity, treatment escalation is possible/an option. If the problem is side effects, the rationale is to try a DMT with a different mechanism of action, even if the efficacy is similar (Wingerchuk and Carter, 2014).

The *escalation therapy* strategy aims to use the DMT with the least amount of side effects, with subsequently escalation to more efficacious therapies in the event of disease activity (Harding et al., 2019a).

The *induction* therapy means using high active immunotherapy from the beginning, in the hopes of postponing or preventing outcome of a degenerative SPMS course (Wingerchuk and Carter, 2014). The induction strategy is also referred to as early intensive treatment (EIT) (Iaffaldano et al., 2021).

For some years, the recommendation was that the amount of disease activity at baseline should dictate whether to choose an escalation or an induction strategy. For people with highly active disease at baseline, or a rapidly evolving severe disease, the more effective treatments were recommended as the initial therapy (Ziemssen et al., 2016).

There is increasing evidence for an early, intensive treatment strategy for a better patient outcome (Simonsen et al., 2021a, Spelman et al., 2021, Iaffaldano et al., 2021, Harding et al., 2019a, Brown et al., 2019, He et al., 2020). Studies have shown that pwMS want to discuss progression and likely prognosis with their neurologist (Celius et al., 2021). Several clinical support-tools have been developed (Ziemssen et al., 2022). The increasing complexity and focus on decision-making has brought the pwMS' own preferences on administration, pregnancy plans, expected side effects and comorbitidy to the forefront (Wingerchuk and Carter, 2014). There is increasing focus on *shared decision making* process, where the neurologist and the pwMS should consider all appropriate DMTs together (Giovannoni et al., 2016, Hobart et al., 2022). Figure 12 is an illustration of the shared decision making process.

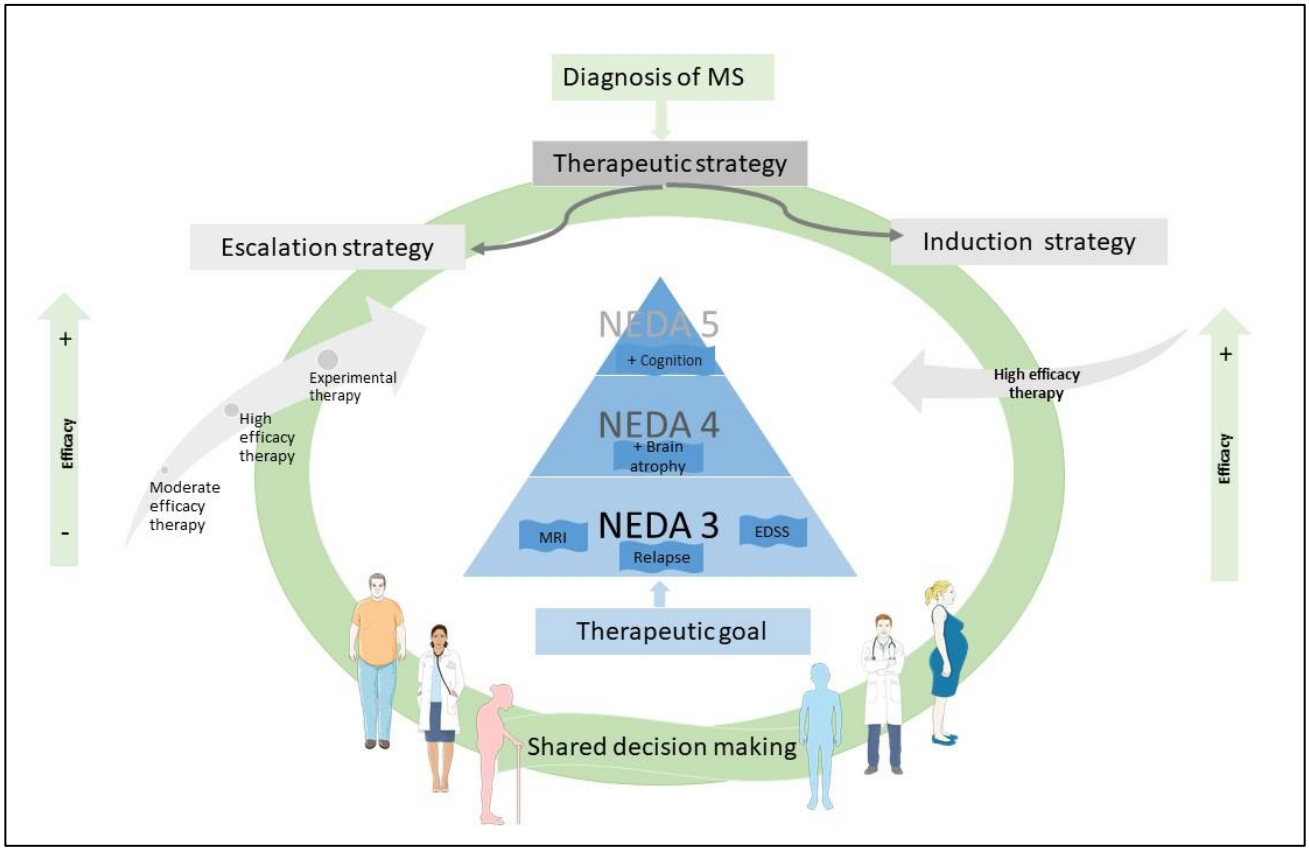


***Figure 12**: **Shared decision making in therapeutic strategy and therapeutic goal**. Illustration designed by use of Servier Medical art. NEDA = No evidence of disease activity, MRI = Magnetic Resonance Imaging, EDSS= expanded disability status scale.*

3.7.3.2. Therapeutic goal

There is an ongoing discussion around which outcome measure is best suited as a therapeutic goal for disease modifying treatment in MS. Early treatment efficacy studies have used relapses, EDSS progression or MRI results as outcome measures. The concept of "absence of disease activity", a combination of all of the above, was first introduced by Havrdova et al in 2009 (Havrdova et al., 2009). At a conference at the Cleveland Clinic in 2012, the concept was renamed "No evident disease activity" (NEDA) and suggested as a treatment goal in MS (Giovannoni et al., 2018). The first definitions of NEDA used clinical and MRI criteria as measurements. Using combined endpoints to define NEDA has become increasingly common (Giovannoni et al., 2017). NEDA-3 was defined as the absence of relapses, disability progression and MRI activity (Comi et al., 2017). NEDA-4 includes no brain volume loss (Kappos et al., 2016) and involvement of neuropsychological parameters and patient related outcomes have been suggested to expand the NEDA concept further (Stangel et al., 2015).

The goal of "no MRI activity" has recently been suggested as being too strict. According to the MAGNIMS score, pwMS with less than three new T2 lesions on MRI in the absence of relapses, have a very low risk of disability worsening in the following 2-3 years (Sormani et al., 2016). This threshold, defined as minimal evidence of disease activity (MEDA) has been suggested as a more realistic goal (Prosperini et al., 2020).

3.7.5. Future perspectives for disease modifying treatments

On clinical trials.gov, almost 2000 studies have been registered as interventional, clinical trials for MS. One promising agent in the treatment of MS, is the Brutons tyrosine kinase (BTK) inhibitor. Phase II trials have been published and at least seven ongoing trials (according to clinical trials.com) are investigating the efficacy in both progressive and relapsing MS. BTK regulates the function of B-cells and myeloid cells, and selective inhibitors have been shown to inhibit B-cell activation both in vitro and in vivo.

There has also been progress in identifying therapeutic agents with potential neuroprotective or remyelinating effects (Filippi et al., 2018). This has led to research beyond the immune cells, to multiple glial cell types in general, and the oligodendrocytes in particular. The oligodendrocyte progenitor/precursors cell (OPC) needs to be recruited to the zone of myelin loss and undergo differentiation to become a myelin producing cell (Bierhansl et al., 2022). Different phase II studies have shown varying results. One of the best known targets is the histamine and muscarine receptor

system, and clemastine, a histamine H1 receptor antagonist, are shown to induce differentiation of OPCs (Green et al., 2017) .

3.7.6. Treatment of progressive MS

The disease modifying treatments in MS act primarily on the inflammatory activity (Filippi et al., 2018)) and treatments available for progressive MS, which includes both PPMS and SPMS, are limited. Several therapies have been tested in progressive MS, though, unfortunately most of these have been unsuccessful (Baldassari and Fox, 2018). Fingolimod has been tested in PPMS (Lublin et al., 2016) and natalizumab has been tested in SPMS (Kapoor et al., 2018), and none of them demonstrated superiority over placebo. A double-blind placebo-controlled, multicentre trial on rituximab in PPMS did suggest that selective B-cell depletion may affect disease progression in younger patients, though time to disease progression was not significant different (Hawker et al., 2009). The phase III trial comparing ocrelizumab with placebo in the treatment of PPMS showed lower rates of clinical and MRI progression in the ocrelizumab treated group (Montalban et al., 2017). This lead to the first approval of a DMT for PPMS. It is important to notice that this study excluded pwMS over 55 years of age and those with disease duration of more than 10-15 years and an EDSS more than 5. A substantial proportion of the participants had gadolinium enhancing lesions on MRI (Baldassari and Fox, 2018), suggesting that earlier phases of PPMS might be more responsive to treatment (Filippi et al., 2018). The understanding of the progressive disease course is, however, incomplete, and the concept of neuroprotection and remyelinisation are potential targets for future research and treatments in progressive MS (Baldassari and Fox, 2018).

3.7.6. Symptomatic treatment of MS

A symptomatic treatment of MS refers to the physical and pharmaceutical efforts to mitigate different symptoms that occur as a result of the CNS damage in the disease (Dobson and Giovannoni, 2019). These treatments are most often not MS-specific, and the evidence for different treatments in pwMS are, in general, weak. Only two symptomatic treatments have been tested more extensivly in persons with MS; fampiridine for walking ability, and cannabinoids for the treatment of spasistity (Filippi et al., 2018) . There are, however, many possible agents that have a potential effect on different symptoms, including urinary incontinence, neuropathic pain, spasticity and neuropsychiatric symptoms. The treatment options must be based on an individual evaluation. The pwMS should be followed by a multidisciplinary team throughout the entire disease course (Soelberg Sorensen et al., 2019).

3.7.7. Physical activity and exercise

Meta-analyses and systematic reviews of randomized controlled trials have demonstrated the benefits of physical activity, both in the prognosis and the quality of life in pwMS (Motl and Sandroff, 2015, Motl et al., 2017). The benefits of exercise was first established as an effective treatment of symptoms, known as tertiary prevention in MS (Dalgas et al., 2019). Studies find that exercise has a positive impact on symptoms, such as fatigue, pain, cognition, strength and walking disability (Dalgas et al., 2019). More recent studies have also suggested that exercise impacts the pathological hallmarks of MS, demyelination and axonal injury (Souza et al., 2017) and also has a disease modifying effect on the disease (Dalgas et al., 2019). There has been a traditional concern that training may trigger the onset of relapse or worsening of neurological symptoms in MS, but a systematic review by Pilutti et al did not find any association between exercise and risk of relapses or adverse effects (Pilutti et al., 2014). The Consortium of Multiple sclerosis Centers has, based on current evidence and expert opinion, strongly recommended that healthcare providers endorse and promote the benefit of exercise and a positive lifestyle, including physical activity, in every pwMS (Kalb et al., 2020).

3.8. Socioeconomic factors

3.8.1. History of research of inequality in health

The impact of socio-economic differences as risk factors for disease was not a major focus in epidemiological research until the 1970s. There are, however, some exceptions in historical medical writings, like the work of the Italian doctor and academic Ramazzini, who, more than three centuries ago, in 1713, described an association between the workplace and health problems. Among other findings, he noticed an unusually high frequency of breast cancer in Catholic nuns (Franco, 2012).


DE
MORBIS
ARTIFICUM
BERNARDINI RAMAZZINI
IN PATAVINO GYMNASIO
PRACTICAE MEDICINAE PROFESSORIS
PRIMARII
DIATRIBA
MUTINAE OLIM EDITA.
Nunc secundo supplementis ejusdem
auctoris,
AC DISSERTATIO
DE
SACRARUM VIRGINUM
VALETUDINE TUENDA.
PATAVII. M.DCC.XIII.
Per Jo. Baptistam Conzattum.
SUPERIOR. PERMISSU, AC PRIVIL.

CAPUT XX.

Figure 13. Front page of the 1713 editio princeps of De Morbis Artificum Diatriba and of Chapter XX De Nutricum Morbis *(Franco, 2012).*

Another exception is the surgeon Percivall Pott, who reported a cluster of scrotal cancer among British chimney sweepers in the mid-18th century. He described the chimney sweepers' background; "*they are most frequently treated with great brutality, and almost starved with cold and hunger*" and blamed these working-conditions for the development of cancer (Brown and Thornton, 1957). In the mid-19th century, the Norwegian social researcher and priest, Eilert Sundt, wrote about the conditions of the poor in the Norwegian capital, Christiana. In his book, he established a connection between illness and poverty as a class phenomenon, and to some extent, he called for action to prevent further development of differences in health (Sundt, 1870).

A growing public interest in socio-economic conditions and health appeared in the first half of the 19th century, especially in Britain. From 1851, occupational death rates were reported around the time of each decennial census. The mortality statistics were published on geographical localities, using "healthy districts" as a proxy for the higher social classes, who had significantly longer life expectancy. The trend continued into the first half of the 20th century, where the research from

Richard Titmuss on class-based mortality trends particularly influenced the field. He documented that the disparity in infant mortality rates between the upper- and lower classes continued to increase from 1910 to 1930 (Macintyre, 1997). In the early 1950s, the British researchers Doll and Hill demonstrated that smokers had a higher risk of lung cancer, with an association between the risk and the amount of smoking (Doll and Hill, 1956). The American Framingham-study, founded in 1948, showed a correlation between blood pressure, cholesterol levels and cardiovascular disease, introducing a theory of compound causalities within social classes. This work, in many ways, represented the start of a risk factor approach for understanding the socially-dependent distribution of diseases (Giroux, 2012). The obvious findings of inequalities in health, the growing understanding of determinants of health and the importance of measurement when monitoring lifestyle factors, gained increasing health policy significance. This lead to new, major epidemiological research in Europe, such as The Black report and the Whitehall studies.

The Black report

In the late 1970s, the United Kingdom's Department of Health and Social Security formed the "Research Working Group on Inequalities in Health" and selected Sir Douglas Black as its chair. The committees' report was published in 1980, known as "The Black report". The report described how disease and death were unequally distributed among the population of Britain. In particular, the report documented how these inequalities had been widening over the last decades. The report highlighted inequality in education, housing, diet, employment and working conditions as an explanation for the differences (Gray, 1982). The report gave recommendations for further research and policy, emphasizing the need for improving education and a comprehensive anti-poverty strategy (Macintyre, 1997). The report was, however, presented for the Thatcher government, which had taken power in United Kingdom in 1979, and not for the Labour government, who had commissioned the report (Strand and Næss, 2007). The conservative Thatcher-government did not fully recognize the recommendations and the report suffered from attempts at restricting its publication (Blane, 1985). However, The Black report led to increased attention and research activity on social inequality in Britain and several other European countries. One example is the extensive research from the Whitehall studies of Geoffrey Rose and Michael Marmot (Thelle, 2015)

The Whitehall studies

The Whitehall study started in 1967 where more than 17 000 civil servants were classified according to their employment grade, and death certificates were recorded over 10 years. The results showed a steep inverse relationship between employment grade and mortality. Civil servants in the lowest grade had three times the mortality rate from coronary heart disease, and a range of other causes, compared to administrators. Even though smoking was found to be more common in the lower

grades, this could only account for a part of the mortality differences, suggesting that other factors were also involved (Marmot et al., 1984). The second Whitehall study investigated a new cohort of civil servants, men and women, between 1985 and 1988. The results showed no diminution in social class difference on morbidity in the 20 years separating the two studies. The Whitehall II study concluded that healthy behavior should be encouraged across the whole of society, but with extra attention on the social environment and the consequences of income inequality (Marmot et al., 1991).

The recent years

Over the past decades, there has been a change in the way we understand the differences in health between individuals. Some theories aim to explain the association between social class and health differences beyond life style factors like smoking, living conditions and eating habits. The British economist, Richard Wilkinson, formulated his theory on health inequalities and income standards in 1966 (Wilkinson, 1997). He used empirical data from several industrial countries to show that the larger the differences between social classes in a country, the higher the differences in the average mortality rate. He argued that an egalitarian society is more important than individual factors for measures of health. Furthermore, he stated that increased differences in income between individuals in a society will increase the differences in health, independent of the absolute level of the economic situation in the society (Thelle, 2015). It follows that political efforts to optimize public health must involve changing the focus from an individual level to a community level

3.8.2. Inequality of health in Norway

Statistics Norway has published a report based on a Medline search for publications indexed with the keywords “social inequalities and mortality”. This report identified only four studies on the topic from Norway before 1970 (Strand and Næss, 2007). One of the exceptions is the study by Trygve Gjestland on untreated syphilis. To investigate the mortality of syphilis, Gjestland did a regional study on the mortality of the inhabitants in Oslo. He compared the population in the western and eastern part of the city. The results showed an excess mortality among the residents of the eastern parishes, in both sexes, in all the 10-year periods between 1890 and 1940. The excess mortality in the eastern population ranged between 25 and 38 percent in females, and between 16 and 27 percent in males (Gjestland, 1955). In absolute numbers, this is the equivalence of a five year lower life expectancy among women living in the eastern part of Oslo, compared to the western part. For men, this difference was three years (Gjestland, 1955, Sandvik and Lie, 2016).

The painting below, named *Albertine to See the Police Surgeon*, was painted by the Norwegian artist Christian Krogh, known for focusing on the conditions of the poor people of Oslo. In the painting, the prostitute, Albertine, is being examined for syphilis, as witnessed by a shocked citizenry.

***Figure 14**: **Albertine to See the Police Surgeon** (Albertine i politilægens venteværelse), painted by Christian Krogh 1885-1887. Downloaded from Nasjonalmuseet.no, no restrictions (Creative commons – attribution CC-BY)*

Gjestland continued his work with a second mortality report from 1971-1980. Despite considerable improvement in the levels of living and health in the Norwegian population in the post-war years, the differences in mortality in the latter period was the same as the previous. In other words, the men in Oslo east had a 3.3 years shorter life expectancy than men in Oslo west (Gjestland T, 1988). In 1997, a Dutch group, led by professor Mackenbach, presented their comparative research in Lancet showing that health inequality in the northern countries of Europe, traditionally viewed as more egalitarian, was at the same level as that of other European countries. For men's perceived general health, inequalities by level of education in Norway were larger than that of Switzerland and Spain. Sweden and Norway had larger relative inequalities in health than most other countries when using a score for morbidity versus mortality (Mackenbach et al., 1997). This finding gave rise to a debate around the paradox that health inequalities had persisted despite the rise of the welfare state (Mackenbach, 2017). According to Statistics Norway, the differences in life-expectancy is now even larger between Oslo west and Oslo east, with 8.8 years for men and 6.9 years for women in 2011. (Berntsen 2013).

The official Norwegian research regarding inequality in health is dominated by reports. Statistics Norway has mapped the Norwegian population's standard of living over many decades. In 1973 the first so called "Standard of living" survey (Norwegian: "Levekårsundersøkelsen") was published. In the period of from 1998 to 2012, the Statistics Norway conducted regular cross-sectional surveys to map income and living conditions, with health being the main focus every third year. From 2015, the survey has been coordinated with the European Union Survey on Income and Living Conditions (EU-SILC), performed by Eurostat. The purpose of this survey is to follow the health in the Norwegian population, including health related behaviour, own perception of health and the use of health services (Isungset MA, 2017).

The Norwegian Institute of Public Health has had an increasing focus on social inequality. The Public Health Reports have been published in 2010, 2014, 2018 and 2021, describing the health status in Norway. The report from 2018 emphasizes the inequality in health with regards to life expectancy for different educational levels, and also according to the distribution of smoking and overweight (Norwegian Institute of Public Health, 2018).

The Norwegian government has also acknowledged the increasing evidence for health inequalities. From the 1990's, the government work was mainly dominated by commissioning reports, like the Norwegian Official Reports (Norwegian: "Norsk offentlig utredning; NOU") and the Reports to the Storting/White paper (Norwegian:"Stortingsmelding"). The reports have reached varied attention in media and politics. In 2007, the Department of Health launched a National strategy to reduce health inequality (Report No. 20 to the Storting, 2006-2007). The aim is clear, we are waiting for the results.

3.8.3. The concept socioeconomic status

Socioeconomic status (SES) has emerged as an important "exposure" with significant health consequences. SES can be defined as the position of an individual on the socioeconomic scale in relation to others. This position is determined by a combination of social and economic factors, such as income, amount and kind of education, type and prestige of occupation, place of residence, and—in some societies or parts of society—ethnic origin or religious background (Definition by American psychological Association's Dictionary of psychology). Individuals with a lower SES are more likely to suffer increased morbidity and mortality across a wide range of diseases (Marmot, 2005, Norwegian Institute of Public Health, 2010, Kivimaki et al., 2020). We know that health-related behavior, such as smoking, level of physical activity and nutritional standards are influenced by SES, to a great extent (Report No. 20 to the Storting, 2006-2007). Smoking and physical inactivity are more common in groups with lower levels of education (Veenstra, 2009). In addition, SES comprises a variety of other

environmental factors, such as housing facilities and hygienic standards. One hypothesis suggests that a low SES is related to a more pro-inflammatory phenotype, in which deprived people are more susceptible to the inflammatory response and development of disease (Loucks et al., 2010). A recurring question in the studies of health inequalities is whether health is a result of the socioeconomic position, or vice versa (Norwegian Directorate of Health Circular IS-1573, 2008).

Measures of SES

There is no single best indicator of socioeconomic position or - status. There are several indicators measuring different aspects of socioeconomic stratifications, many of which are related. Some indicators are more relevant to different health outcomes than others, and they will contribute differently at different stages of life. When choosing an SES measure, the research question must be considered carefully, including reflecting of whether SES is the exposure of interest, or merely a confounding factors (Braveman et al., 2005). Galobardes and colleges published a glossary in the Journal of Epidemiological Community Health in 2006, listing different indicators of socioeconomic position used in health research (Galobardes et al., 2006a, Galobardes et al., 2006b). Table 6 lists the most commonly used measures of SES on individual level used in health-related research. This information is based on Galobardes publications, as well as my own experience through reviewing the literature.

In several countries, an index has been developed to be used as a measure of relative deprivation. These indices are area level measures. One example is the English Indices of Deprivation (EID). The EID combines several domains, including income, employment, education, crime and housing into one measure for socioeconomic status (Noble S, 2019). Another example is the European deprivation Index (EDI). The EDI is an aggregates score of relative deprivation, which can be calculated for each European country at a small area level, using data from the European Union Statistics on Income and Living Conditions: EU-SILC (Launoy et al., 2018).

Health literacy

The concept health literacy has reached increased focus in the work for understanding the differences in health status, and the concept is used in a wide spectre of conditions (Nutbeam and Lloyd, 2021). Health literacy is a construct that includes the capacities of people to meet the complex demands of health. An integrated definition of the concept is proposed by Sørensen et al. They state that health literacy is *"the knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgments and take decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve quality of life throughout the course of life*" (Sorensen et al., 2015).

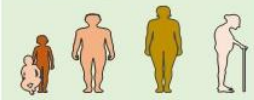
Measurements of SES	Level of influence in life course	Strengths	Limitations
 **Education** • Years of education (continuous) • Educational achievements (categorical) • Parental education (categorical)	 	• Captures transition from parents to own SES • Express of knowledge and skills, health literacy	• Levels will vary for different birth cohorts • Changes in opportunities for women and minority groups • Possible influence of illness in early ages
 **Income** • Individual income • Household income		• Best single indicator material living standards • Possible to standardize (e.g. EU standard) • Relative indicator establishing levels of poverty	• Sensitive information (non-response) • Changes on short time basis • Gender differences
 **Household amenities** • Number of rooms, books • Access to cars, pc, water, hygiene • Centrality index (rural vs urban)		• Different measures associated with specific mechanism	• Specific to temporal and geographical context
 **Occupation** • Classifications of work		• Reflects the persons place in society • Expression of network	• Different meaning for different historical cohorts • Gender differences • Currently unemployed are not considered

Table 6: Different measures of socioeconomic position on an individual basis*. Summarized overview of the most important and mostly used measurements of socioeconomic status (SES), based on the publication by Galobardes et al (Galobardes et al., 2006b) and own experience and opinion.*

3.8.4. The impact of socioeconomic status in MS

Socioeconomic status has emerged as an important factor for evaluating many aspects of MS. In this thesis, the focus has been on the influence of SES on the risk for developing MS, the disease progression and access to treatment. During this work, the author has performed several searches in pubmed.ncbi.nlm.nih.gov for "socioeconomy AND MS" to gain knowledge into the main findings of previous works in this field. The results are presented in tables in the next subchapters. There is also an increasing numbers of publications on the socioeconomic *consequences* of MS. This is considered beyond the scope of this work and not included in the thesis.

3.8.4.1. SES and susceptibility for MS

Internationally, MS occurs with greater frequency in high-income nations (Buchter et al., 2012). In individual countries, studies have found a tendency of higher susceptibility of MS in households of greater affluence (Montgomery et al., 2004). In epidemiological studies of MS in US veterans, higher socioeconomic class, rather than urban or rural residency, was associated with an increased risk of MS (Kurtzke and Page, 1997). However, the evidence is inconsistent (Goulden et al., 2015), with

some studies finding no social gradient, or even the opposite association (Nielsen et al., 2013). In Norway, one study showed an inverse relationship between higher education and the risk of MS (Riise et al., 2011). This study is based on the patient's own level of education, but since MS mostly affects younger people, the disease itself can affect the individual's educational level (Flensner, 2013). A study by Cortese et al showed that young men who later developed MS, scored lower on cognitive testing at the age of 18 compared to men who did not develop MS (Cortese et al., 2016). This implies that the disease affect the people for years before onset of symptoms that trigger a diagnosis, and may consequently affect the level of education. On the other hand, a recently published Norwegian study by Simonsen et al on absence and grades in upper secondary school concluded that there were no significant differences between the cohort who later developed MS and matched controls (Simonsen et al., 2021b).

Table 7 shows the results of the main studies on socioeconomic status and MS susceptibility.

In addition, the variations in the geographical distribution of MS (Marrie, 2004) may be associated with SES, as SES is, to some extent, influenced by place of residency. In Norway, studies have shown similar prevalence rates of MS in the Southern and Northern regions, whereas there is a higher prevalence in the Middle region (Berg-Hansen et al., 2014). There are documented differences in health and health-related lifestyle in the different regions of Norway (Borgan, 2009). There is also some evidence of a higher prevalence of MS among urban rather than rural residents (Kotzamani et al., 2012, Daltrozzo et al., 2018, Lowis, 1990, Beebe et al., 1967). This pattern has, however, mainly been linked to lower access to specialist services in rural areas (Roddam et al., 2019).

3.8.4.2. SES and MS progression

There is an increasing focus on the possible impact of SES on disease progression. Table 8 presents the main findings.

In a wider definition of SES, racial/ethnic differences are likely to reflect unmeasured socioeconomic differences (Braveman et al., 2005). There is a more aggressive disease course in non-western immigrants with MS compared to native Norwegians and immigrants from western countries. Immigrants from the Middle East seem to have a significantly higher prevalence of MS compared to other non-western immigrants (Berg-Hansen et al., 2015). International studies have shown poorer quality of health care in ethnic minorities compared to the majority population (Eike et al., 2010), and Norwegian statistical analyses show that immigrants with a higher SES have better health in general (Blom, 2010). We have, however, not focused any further on ethnical differences in this thesis.

Publication	Cases, controls, main measures	Main findings
(Moghaddam et al., 2021) BMC Neurol. 2021	Global estimates of MS SES: Prosperity and human development indices (PI and HDI)	Developed countries had significantly higher prevalence and incidence than developing countries
(Dobson et al., 2020) Ann Neurol 2020	Nested case-control, > 1 million individuals from primary care records; United Kingdom SES: Index of Multiple Deprivation (IMD)	Increase in MS odds in the least deprived quintile
(Pakdel et al., 2019) Acta Neurol Scand 2019	SES: Statistical Centre of Iran; demographic, income, education, Iran	Higher prevalence of MS in provinces with higher SES
(Abdollahpour et al., 2018) Mult Scler Rel Disord 2018	Population-based incident case-control (n = 575, controls 1057), Iran SES: Parental education, household SES in adolescence (telephon interview)	Parental level of education not associated with MS Adolescence SES insignificant associated increased risk
(Bjornevik et al., 2017) Mult Scler 2017	Norwegian MS registries and prevalence studies, siblings and parents N = 4494, controls 9193 SES: Level of education	Level of education inversely associated with MS risk
(Bjornevik et al., 2016) Mult Scler 2016	Case-controlstudy (EnvIMS), n =953 (1717 controls), Norway SES: Self-reported level of education, exposure to putative environmental risk factors (smoke, cod liver oil, body size, IM)	Higher level of education associated with decreased MS risk
(Goulden et al., 2016b) Eur J Neurol. 2016	Multinational case-control study (EnvIMS), n = 2144 (3859 controls), Norway, Canada and Italy SES: Self-reported parental level of education	No consistent association between parental SES and MS risk
(Briggs et al., 2014) J Epidemiol Community Health, 2014	MS cases (n = 1643) and controls, California, USA SES: Childhood SES (parental level of education, household facilities), adulthoos level of education	Adverse SES during life course associated with MS risk
(Magyari et al., 2014) Mult Scler Rel Disord 2014	National MS registry, Denmark n= 1403, 35 045 controls SES: Level of education, household conditions	Level of education, housing conditions in youth did not influence risk of MS
(Nielsen et al., 2013) Am J Epidemiol 2013	National cohort, Denmark, 1.5 million SES: Childhood SES; annual household income, level of education	No strong association, tendency towards reduced risk in highly educated parents, particularly mothers
(Riise et al., 2011) Mult Scler 2010	Cohort of offshore workers and general working population (n=394 705); Norway	Lower level of education associated with increased MS risk
(Hammond et al., 1996) J Neurol Neurosurg Psychiatry, 1996	MS cases, n = 2307, Australia SES: Level of education MS prevalence calculated by level of education, adjusted for age	Significant higher frequency of MS in those who achieved higher level of education
(Goulden et al., 2015) Eur J Neurol 2015	**Review, 21 studies from 13 countries** Italy, USA (2), Mexico, Israel	Risk of MS: 5 association with high SES
	USA (Briggs et al), Canada, Norway (Riise et al)	3 association with low SES
	USA (2), Israel, France, Spain (2); Denmark (3), Greece, Cuba, Finland, UK	13 no association

Table 7: Socioeconomic status (SES) and susceptibility for MS.

Publication	Cases, controls, main measures	Main findings
SES AND DISEASE PROGRESSION IN MS		
(Abbatemarco et al., 2022) Mult Scler Rel Disord 2022	n = 2921, Cleveland USA SES: Area deprivation index (ADI) MS: upper and lower extremity function and cognitive function	Socioeconomic disadvantage associated with disability accrual
(Boorgu et al., 2022) Mult Scler Relat Disord 2022	n=1316, USA SES: Area deprivation index (ADI), household income MS: patient-reported outcome measures	Lower SES associated with worse neurological outcomes
(Vasileiou et al., 2021) Brain 2021	n=789, USA SES: Neighborhood-level SES MS: Optical coherence tomography	Lower neighborhood level SES associated with faster retinal atrophy
(Gray-Roncal et al., 2021) Neurology 2021	n = 8744, USA SES: Neighborhood-level SES, black American (BA) white (WA) MS: Self-reported disability, MRI, walking speed, cognitive tests	Greater disease burden in BA relative to WA despite adjustment for SES
(Calocer et al., 2020) Mult Scler Rel Disord 2020	n=4498, France SES: European Deprivation Index (EDI) MS: EDSS 4 and EDSS 6	Socioeconomic deprivation significantly associated with risk of reaching EDSS 4 and 6
(Harding et al., 2019b) Neurology 2019	n=3113, Canada and United Kingdom SES: Neighborhood-level SES MS: EDSS 4 and EDSS 6	Lower neighborhood level SES associated with a higher risk of disability progression
(D'Hooghe M et al., 2016) Acta Neurol Scand 2016	n= 1372, Belgium SES: Self-reported level of education MS: EDSS 6	Highest level of education reduced risk of reaching EDSS 6

Table 8: Socioeconomic status (SES) and disease progression in MS*. EDSS: Expanded Disability Status Scale*

3.8.4.3. SES and access to treatment in MS

The choice of a suitable DMT for each pwMS is complex (Montalban et al., 2018a, Rae-Grant et al., 2018), with accumulating evidence of inequalities in access to treatment (Browne et al., 2014). An American survey confirms that a substantial fraction of pwMS face financial and health plan-related barriers to obtaining expensive DMTs (Iezzoni et al., 2008), and the rising cost of drugs adversely affects the access to treatment (Wang et al., 2016). Even in high-income countries, where the cost of all treatments is fully reimbursed, access to therapies varies widely (Giovannoni et al., 2016). Table 9 present the main studies investigation SES' influence on access to treatment. The results are divergent.

Publication	Cases, controls, main measures	Main findings
(Das et al., 2022) Mult Scler Relat Disord 2022	n = 1449, United Kingdom SES: Index of Multiple Deprivation (IMD) MS: Access to DMT	Participant who lived in more deprived areas were less likely to receive DMT
(Gomez-Figueroa et al., 2021) Mult Scler Relat Disord 2021	n=974, Mexico SES: Mexican deprivation criteria MS: EDSS, MS phenotype, DMT	Lower SES associated with higher disability, higher proportion of SPMS and higher proportion not receiving any DMT
(Reyes et al., 2020) Mult Scler Relat Disord 2020	n = 633 United Kingdom SES: Income and education, Index of Multiple Deprivation (IMD) MS: Moderate, high or very-high efficacy DMT	SES not predictive of DMT prescribing patterns
(Calocer et al., 2018) PLoS One 2018	n = 733, France SES: European Deprivation Index MS: Time between first and second line DMT	Higher SES facilitate access to a second-line DMT few years after first-line DMT exposure
(Owens et al., 2013) Eur J Health Econ 2013	n = not reported, United Kingdom SES: Index of Multiple Deprivation (IMD) MS: Access to DMT	People from more deprived areas were less likely to have been prescribed DMTs

Table 9: Socioeconomic status (SES) and access to disease modifying treatment (DMT) in MS

In a review by Roddam et al from 2019, six studies that consider SES and access to treatment were identified (Roddam et al., 2019). In Table 9, only one of these studies are included (Owens et al., 2013), as the others use race, gender and age as the only measures of SES. The remaining five studies include a study by Buchanan et al evaluating the influence of race on drug prescription. They concluded that the proportion of Latino people with MS who had never used DMTs (12.3%), is higher than for Caucasians (11.1%) and African Americans (8.5%). This study did, however, only include the first line injectable DMTs (Buchanan et al., 2010). Three of the studies explored the relationship between gender and DMTs: A study from Spain (Ribes Garcia et al., 2016) and a study from US (Avasarala et al., 2007) both reported higher degrees of DMT prescription in female compared to male pwMS, while a study from Germany (Windt et al., 2013) did not find any gender differences. Finally, the review included the study from Iezzoni et al, reporting that younger pwMS were more likely to receive DMTs (Iezzoni et al., 2008).

4. AIMS

The overall aim of this thesis was to evaluate how socioeconomic factors influence different aspects of the diagnosis of multiple sclerosis in a well-defined cohort in the South East of Norway. The greater goal was to identify socioeconomic factors influencing access to health care in general, and disease-modifying treatment in particular.

The specific aims for each included paper were:

Paper I:

To explore the trends in incidence and prevalence of multiple sclerosis in Telemark, Norway, using centrality of municipality as one measure of socioeconomic status.

Paper II:

To investigate how socioeconomic factors, in both adolescence and at present, influence disease progression, measured by changes in EDSS, time to EDSS 6 and current MSSS.

Paper III:

To examine whether socioeconomic factors have an influence on the access to disease modifying treatment in MS, with a particular focus on access to high efficacy treatment as the initial drug.

5. SUMMARY OF THE PAPERS

5.1. Paper I

Prevalence of multiple sclerosis in rural and urban districts in Telemark County, Norway

Several studies in past decades have described the prevalence of MS in different counties in Norway. In the very first such investigation, performed by Swank in 1952, Telemark was marked as a high incidence area. The author postulated a hypothesis of an association between farming and low seafood consumption in inland areas, including Telemark, and a high incidence of MS. In 2012, a nationwide study from Norway estimated the prevalence in Telemark to be $194/10^5$, but Telemark was never independently investigated. In our study, we aimed at investigate incidence and prevalence in Telemark. To highlight possible socioeconomic differences, we decided to use place of residency as a proxy for socioeconomic status. This was done by referencing an index from the Norwegian Government, the so-called Centrality index, to identify the centrality of the different municipalities in Telemark.

The crude adjusted prevalence of MS in Telemark for January 1st 1999, 2009 and 2019 were $105.8/10^5$ (95 % CI 90.1-121.5), $177.7/10^5$ (95 % CI 157.6-197.9), and $260.6/10^5$(95 % CI 236.6-284.6), respectively. We calculated incidence per five-year periods and found that the yearly incidence rate increased, although not significantly, from $8.4/10^5$ (95 % CI 4.0-12.8) in the period 1999-2003, to $14.4/10^5$ (95 % CI 8.7-20.0) in the period 2014-2018.

We found a higher adjusted prevalence for persons living in rural areas (centrality indices 5 and 6); $316.2/10^5$ (95 %CI 247.3-385.1) compared to those living in the most urban areas (centrality index 3); $250.4/10^5$ (95 % CI 220.6-280.7). When analysing gender-specific prevalence, we found this pattern to be only significant for the female population. Overall, there were no significant differences in mean age for the whole study population, or females specifically, when comparing those residing in rural versus urban areas.

We concluded that the prevalence of MS in Telemark is among the highest ever reported in Norway. The even higher prevalence in the rural areas is unlikely to be explained by possible risk factors like latitude, exposure to sunlight and diet. There are, however, some lifestyle factors are associated with residency in Norway that might shed light on the subject. Among them is the proportion of smokers, which is higher in rural (15 % daily smokers) versus urban (11 % daily smokers) areas of Norway, where smoking is a known risk factor for MS. The level of education in the general population is also lower in rural areas. These two factors, indirectly and directly measures of socioeconomic status, may explain some of the differences in prevalence.

5.2. Paper II

Maternal education has significant influence on progression in multiple sclerosis

The existing documentation of the association between socioeconomic factors and disease progression in MS are limited. The aim of this study was therefore to investigate how socioeconomic status influences disease progression in MS in a Norwegian cohort. We chose variables from the affected people's adolescence to compensate for the fact that MS is affecting young people with a possible influence of their capacity for educational achievements, one of the most powerful socioeconomic factors.

We used the BOT-MS registry, combined with data from annually performed censuses from Statistics Norway, to determine parental level of education and the municipality of residency when the pwMS turned 16, as well as the pwMS' own level of education and municipality on the prevalence date. We calculated MSSS on the prevalence date, change in EDSS five years from diagnosis, and registered time to EDSS 6 as markers for disease progression.

Of the 1598 included pwMS, 662 had an EDSS registered 5 years after the diagnosis. We found a significantly higher degree of disease progression in patients whose maternal level of education was limited to primary school. PwMS whose mothers completed a graduate level of education more often displayed improvement in EDSS by year five. The association with paternal level of education showed a similar pattern, without reaching statistical significance.

Within a prevalence date of 01/01/2019, 308 of the pwMS had reached EDSS 6. Only 15 of these had mothers with a graduate level of education. Median time to EDSS 6 was 28.0 years (95 % CI 22.7-33.3) when the maternal the level of education was primary school and 39.0 years (95 % CI 35.4-42.6) when the maternal level of education was secondary school. When analysing time to EDSS 6 for paternal level of education, we found the same pattern, but no significant differences.

We evaluated the socioeconomic factors' influence on MSSS at prevalence date by performing a regression analysis. In the final regression model, we found younger age at diagnosis, female sex, use of DMTs and the patients' level of education as significant reducing coefficients for the prediction of MSSS. The only variable from adolescence significantly included in the final model was maternal level of education at age 16, but in return, this variable influences MSSS at the same level as DMT.

The strong association of parental (maternal) level of education with disease progression is likely complex. Health related behaviours (health literacy) are adapted from parents in childhood, among

them smoking, a known risk factor of MS, and these impact the outcome. To explore alternative explanations for the impact of education, we divided the population into groups by parental educational level and found that age of onset, age at diagnosis and time from onset to diagnosis are significantly lower for the PwMS whose parents had a graduate level of education. A possible, more complex explanation may be that parents with a high level of education teach their children more relevant health related behaviour. This may also involve encouraging early contact with the health care system for a diagnostic clarification of symptoms. In MS, an early diagnosis, followed by the start of DMT, has a significant impact on the disease progression.

5.3. Paper III

The influence of socioeconomic factors on access to disease modifying treatment in a Norwegian multiple sclerosis cohort

Several studies report an impact by socioeconomic factors on access to disease modifying treatment (DMT) for multiple sclerosis (MS), with a trend of less access available to more deprived persons. Our aim for this study was to investigate if the disease modifying treatment of MS is distributed equally regardless of socioeconomic status in a Norwegian cohort.

We used the BOT registry for information on disease development and the administration of DMT. The EDSS at diagnosis was divided into three subgroups by score: 0-1.5, 2-2.5 and ≥3. DMTs were divided into moderate efficacy DMTs (interferons, glatiramer acetate, teriflunomide and dimethyl-fumarate) and high efficacy DMTs (natalizumab, fingolimod, alemtuzumab, rituximab and cladribine). We used data from Statistics Norway's annually performed censuses to determine the parental level of education and municipality of residency at the pwMS' age 16, as well as their current level of education, home municipality at the prevalence date, birth country, marital status and household income. The questionnaire provided data on smoking, other autoimmune diseases, self-perceived SES and self-perceived health. We excluded from the BOT database all participants with primary progressive MS as there were no DMT available for this group in Norway as of January 2018. We have further divided the population by diagnosis before or after 2006, because the first high efficacy DMT, natalizumab, was introduced in 2006, and the population diagnosed within the last six-year period (2012-2017) was used to evaluate the most recent treatment patterns.

Of the 1314 included pwMS, 902 had been treated with DMT, while 412 had not.

In the total population, the ever-treated subgroup is younger at onset, diagnosis and present. Moreover, it had a shorter time from onset to diagnosis and is characterised by a lower EDSS at

diagnosis and at present compared with those never treated with a DMT. The treated subgroup was also better educated, had better educated parents and scored significantly higher on self-perceived health, while the never-treated group reported more additional autoimmune diseases and were more frequently “widowed” or “divorced”. We did not, however, find any significant difference in the centrality of municipality, self-reported SES, median household income, smoking status or country of origin.

In a comparison of those pwMS treated with a high efficacy DMT as a first drug with those not, the high efficacy treated group was younger at prevalence date, but not at onset or diagnosis, and the EDSS was 0.5 points higher. There is moreover an inverse impact by the level of education, where the pwMS with the lowest degree of educational achievements have a higher proportion of high efficacy treatment as a first drug, and the median household income is significantly lower in the subgroup with high efficacy DMT as a first treatment.

The level of the pwMS’ or their parents’ education did not significantly influence the odds ratio (OR) of receiving a high efficacy treatment as a first drug. There was, however, a significantly lower OR for high efficacy treatment as the first drug with increasing quartiles of median household income. Finally, the group with EDSS 3 or higher at diagnosis had a significantly higher OR for high efficacy treatment as the first drug compared to those with EDSS 0-1.5. Nevertheless, none of the above differences persisted when analysing the subgroup diagnosed within the last six years.

We concluded this study by determining that there has been a change over time to a current pattern, where pwMS are treated broadly equally in terms of socioeconomic position.

6. MATERIAL AND METHODS

6.1 Study population

The population included in this study was collected from three former counties in the South-East of Norway: Oslo, Buskerud and Telemark.

6.1.1. Description of the geographic area and background population

Norway is one of the Scandinavian countries in Northern Europe. The country stretches from 58 degrees to 71 degrees north. It borders to Sweden, Finland and Russia to the east, and has a long coastline in the west, with a coastal perimeter of 2650 kilometres formed along the Skagerrak, the North Sea, the Norwegian Sea and the Barents Sea. Norway is administratively and politically subdivided into two levels: Counties and municipalities. Norway was until 2018 divided into 19 counties, but changes to this structure, involving two of the counties included in this population, were made in the years 2018-2020, namely Buskerud (a part of Viken county as of 01.01.20) and Telemark (a part of Vestfold and Telemark county as of 01.01.20). See Figure 15, map of Norway with the three included counties marked in red.

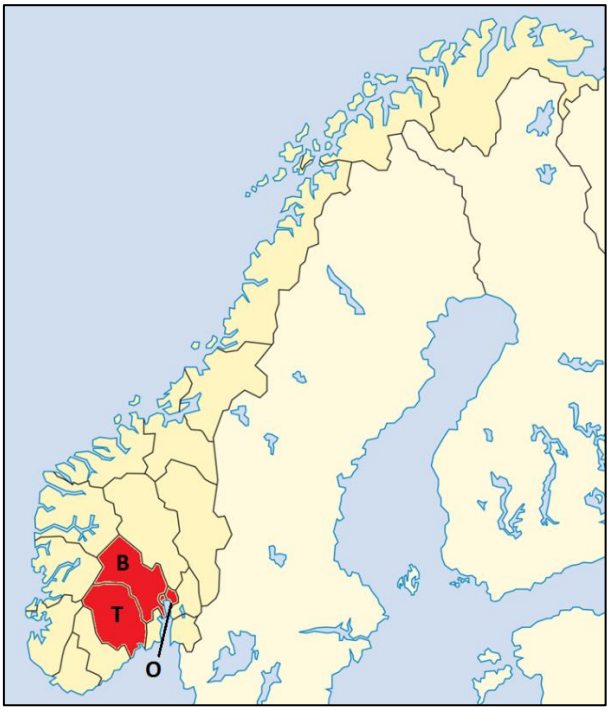


***Figure 15: The three included counties in BOT-MS**, adapted from an original map courtesy of Kartverket. B = Buskerud, O = Oslo, T = Telemark.* Figure reused with permission from Cecilia Smith-Simonsen's thesis: The contemporary MS patient (University of Oslo, 2022) (Simonsen, 2021)

A large part of Norway is dominated by mountains or high terrain, but there is also a great variety of natural features, most noticeable the fjords. Oslo is situated at the north end of the north-south

ranging Oslofjord and is the capital of Norway. Both Buskerud and Telemark border the Oslofjord in the east, and Buskerud is north of Telemark. Buskerud and Telemark extend from the coastline of the Oslofjord to the Hardanger plateau in west, 1200 metres above sea level. Because of Norway's high range of latitude, there are large seasonal variations in daylight. The counties of Oslo, Buskerud and Telemark have, however, generally the same climate and daylight variations, with warmer summers and colder winters.

The population sizes and extent of land areas in each included county are shown in Table 10. The largest city in Buskerud is Drammen with a population of 117 510 inhabitants, which is the fifth largest city in Norway. The largest city in Telemark is Skien, which together with the twin city Porsgrunn includes 92 753 inhabitants, the seventh largest in Norway.

Population and area, 01.01.2019				
	Norway	Buskerud	Oslo	Telemark
Population	5 328 212	283 148	681 067	173 318
Area (km^2)	323 805	14 912	454	15 298
Population per km^2 land area	18	21	1 597	13

Table 10: Population and land areas of Norway, Buskerud, Oslo and Telemark 01.01.2019. *Source:* Population and area (M) 2007 – 2022 (Statistics Norway, 2019d).

6.1.2. Socioeconomic status in Norway

The Norwegian Welfare society has been a success for decades. The creation of a welfare state, with equal opportunities and a good standard of living for all, was attained via a comprehensive public education system and health service, which have been key features of the government for many years. The development of a welfare state accelerated after World War II, with the establishment of the national insurance scheme in 1967 as an important milestone. The Norwegian state income is mainly derived from natural resources. Initially a shipping nation with timber and fish as its key export, this gave way to hydropower and subsequently the discovery of oil and gas deposits on the Norwegian continental shelf. Norway has converted these major natural resources into one of the world's largest sovereign wealth funds. Gross domestic product (GDP) is a standard measure of the added value created through the production of goods and services in a country during a specified period. Norway has one of the highest GDP per capita in the world according to the Organisation for Economic Cooperation and Development (OECD) (Report No. 13 to the Storting (2020-2021), 2021).

The OECD's "Better-life" index compares well-being across countries based on 11 topics the OECD has identified as essential, including material living conditions and quality of life. Norway performs

well in many dimensions of well-being relative to other countries and outperforms the average in environmental quality, social connections, life satisfaction and work-life balance (Organisation for Economic Co-operation and Development, 2020b)

Education:

Higher education in Norway is offered by a range of seven universities, five specialised colleges, 25 university colleges as well as a range of private colleges. Education follows the Bologna Process involving bachelor's (3 years), master's (2 years) and PhD (3 years) degrees. Acceptance is offered after finishing upper secondary school with general study competence. Public education is virtually free in Norway. In Norway, 82% of adults aged 25-64 have completed upper secondary education**,** higher than the OECD average of 79% (Organisation for Economic Co-operation and Development, 2020b). The level of education in Norway and the three counties of Buskerud, Oslo and Telemark are shown in Table 11.

Employment:

In terms of employment, about 75% of people in Norway aged 15 to 64 have a paid job, above the OECD employment average of 66% (Organisation for Economic Co-operation and Development, 2020b). The unemployment rate in Norway and the three counties of Buskerud, Oslo and Telemark are shown in Table 11.

Education, employment status and income, 01.01.2019				
	Norway	Buskerud	Oslo	Telemark
Level of education (≥16 years of age), proportion (%) *				
Primary (9 years)	23.9	28.2	20.9	28.7
Secondary (10-12 years)	33.7	41.4	27.8	44.3
Graduate (more than 12 years)	42.4	30.4	51.3	27.0
Proportion unemployed of labour force, men/women (%) **	2.3/2.8	2.7/2.5	3.0/2.6	3.3/2.7
Household median income after tax (NOK)***	540 000	544 000	493 000	517 000

Table 11: Level of education, proportion of unemployed and household income in Norway and the three counties of Buskerud, Oslo and Telemark as of 2019.

*Source: Data from Statistics Norway, as used in paper II.

**Source: The Norwegian Labour and Welfare Administration (NAV) (The Norwegian Labour and Welfare Administration, 2019)

*** Source: Household income, by type of household. Number of households and median (M) (UD) 2005 – 2020 (Statistics Norway, 2019b).

Income:

The Norwegian standard of income is in general high compared to other countries. The report "How's life" from OECD compares the average income in Norway to the average from all OECD countries, as shown in Table 12. The report concludes that in Norway, wage inequality is low, which, combined with high labour-force participation and redistribution through the tax and benefit system, results in an egalitarian distribution of net household income (Organisation for Economic Co-operation and Development, 2020b).

Key findings on income, Norway versus OECD, 2020		
	Norway	Average OECD countries
Average income (USD)	55 780	49 165
Expected loss of earning, if unemployed (%)	2.8	5.1
Average household income per capita* (USD)	39 144	30 490
Average household net wealth ** (USD)	268 358	323 960

Table 12: Key findings income Norway versus average OECD countries. USD: United States Dollar.
***** The amount of money that a household earns each year after taxes and transfer.
** The total value of a household's financial and non-financial worth (Organisation for Economic Co-operation and Development, 2020b, Organisation for Economic Co-operation and Development, 2020a).

The differences in median household income in the three counties of Buskerud, Oslo and Telemark, as well as Norway in general, are listed in Table 11. Income inequality in an area or a country is typically measured using indicators such as the Gini coefficient. The Gini coefficient is based on the comparison of cumulative proportions of the population against the cumulative proportions of income they receive, and it ranges between 0, in the case of perfect equality, and 1, in the case of perfect inequality. In Norway, the Gini coefficient was 0.259 in 2019, which is one of the lowest worldwide, according to the OECD's, Income inequality indicator (Organisation for Economic Co-operation and Development, 2021)

Statistics Norway also presents Gini coefficients for the different counties of Norway, listed below:

- Oslo 0.314
- Buskerud 0.244
- Telemark 0.228

Source: Measures of income dispersion. Household equivalent income (EU-scale) between persons Statbank Norway (Statistics Norway, 2019c).

Health:

Public health care is free in Norway, after an annual charge of around 2000 NOK for all inhabitants over 16 years of age. Every inhabitant has a general practitioner as their primary physician ("fastlege"). There are University hospitals in five cities (Oslo, Bergen, Trondheim, Stavanger and Tromsø), and there are regional hospitals in each (former) county. In total, there are 18 departments of neurology (all counties but Finnmark) and 475 neurologists in Norway as of 01.01.2020 (Dietrichs E, 2020). Persons in need of a neurological consultation will be referred to a neurological department or one of very few neurologists in private practice in Norway. The Norwegian health care system provides disease-modifying treatments for MS free of charge for the pwMS.

The Norwegian Institute of Public Health presents yearly health profiles from each municipality and county. The data resources for these profiles are a number of high quality health registries in Norway. Table 13 presents a collection of some health statistics for the three counties included in this study, as well as for the country as a whole.

Measures of Public health, 2019				
	Norway	Buskerud	Oslo	Telemark
Proportion of children, 0-17 years (%)	21.3	21.1	19.6	20.1
Proportion of one-person households (%)	25.4	25.2	33.5	26.0
Proportion of those completing upper secondary school or higher education, 30-39 years (%)	80	77	84	76
Proportion of low income households (0-17 years)* (%)	9.2	10.0	13.0	13.0
Proportion of daily smokers 16-44 years (%)	7.6	9.8	6.1	12.0
Proportion of daily smokers 45-74 years (%)	15.0	15.0	12.0	20.0
Life expectancy men (age in years)	80.1	80.0	80.0	79.4
Life expectancy women (age in years)	83.9	83.8	83.8	83.2
Educational difference life expectancy **	5.0	5.1	5.2	5.4

Table 13: Indicators of public health in 2019, Norway, Buskerud, Oslo and Telemark.
Source: "Health profiles" 2019 Public health profiles - a summary of health data for each municipality (Norwegian Institute of Public Health, 2019).
**2017, children living in households with an income below 60% of the national median, and gross financial capital under 1G*
***2002-2016, assessed according to the difference in life expectancy at 30, between those with lower secondary school as the highest education and those with upper secondary school or higher education.*

Immigration

The number of immigrants to Norway has increased over the last five decades. In 2010, 9.5 % of the Norwegian population were immigrants, increasing to 15.1 % in 2022. When including Norwegian-born to immigrant parents, these numbers are respectively 11.4 % and 18.9 %. Table 14 shows the share of immigrants and Norwegian born to immigrants in 2019 in Norway, Buskerud, Oslo and Telemark.

Immigrants in percent of population, 01.01.2019				
	Norway	Buskerud	Oslo	Telemark
Immigrants, per cent of population	14.4	16.0	25.2	11.3
Immigrants and Norwegian-born to immigrant parents, percent of population	17.7	20.1	33.4	13.7
Immigrants and Norwegian-born to immigrant parents from EU, UK, USA, Canada, Australia and New Zealand, percent of population	7.3	8.6	10.2	5.1

Table 14: Immigrants and Norwegian-born to immigrant parents in Norway, Buskerud, Oslo and Telemark 01.01.2019. *Source:* Immigrants and Norwegian-born to immigrant parents by immigration category, country background and percentages of the population (M) 2010 - 2022. Statbank Norway (Statistics Norway, 2019a).

6.1.3. The BOT-MS registry

The Norwegian MS registry was established in 2001 under a licence issued by the Norwegian data Protection Authority. The National MS registry is based at the Norwegian National Advisory Unit on Multiple Sclerosis at Haukeland University Hospital in Bergen, on the west coast of Norway. It is funded by grants from the Ministry of Health and Care services. The purpose of the MS Registry is to monitor the occurrence of MS in order to uncover geographical differences and any changes over time in Norway. The data registered include demographic data, clinical data and treatment data. However, the inclusion rates have varied considerably across the country, and not until very recently has the coverage been satisfying. In 2017, approximately 50 % of persons with MS in Norway were registered in the National MS registry, and in 2021 the estimate was 83 %, 96 % of them newly diagnosed (Norwegian MS registry, annual report, 2017 and 2021).

The data used in this thesis is included in the so-called BOT-MS registry. BOT is an acronym for the three counties included in the study population: Buskerud – Oslo – Telemark. The creation of the register used for this thesis (the BOT-MS registry), starting in 2017, was intended to compensate for the poor degree of coverage in the National Registry. Subsequently, we have entered most of the data collected in BOT MS registry into the National Registry.

This thesis is the second of three planned PhDs stemming from the BOT MS registry, see Figure 16.

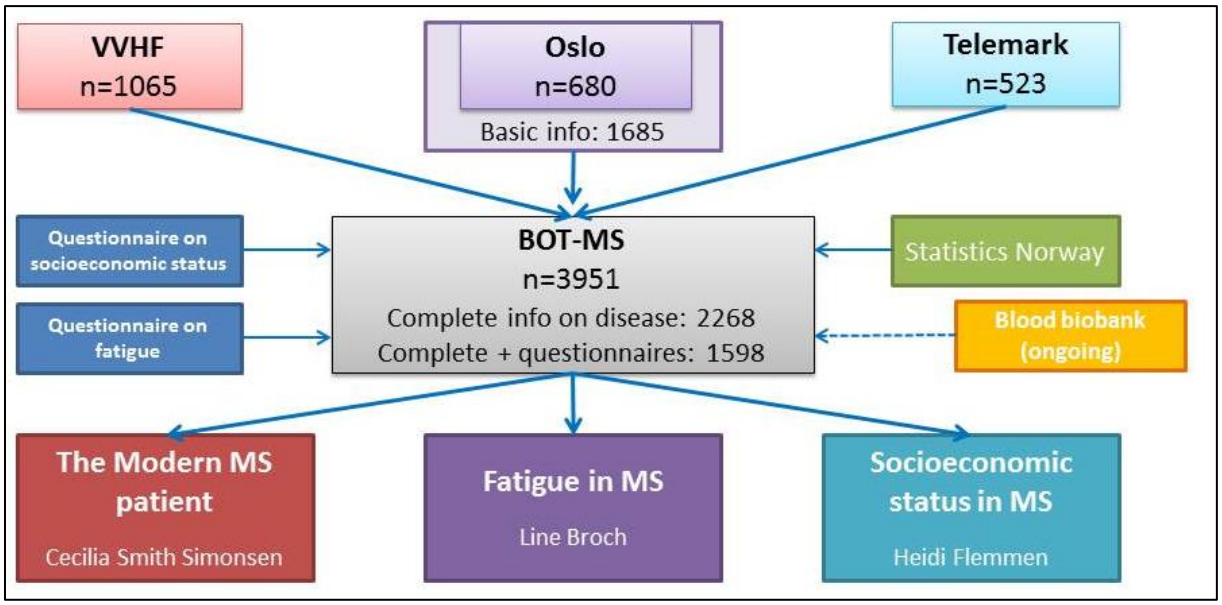


Figure 16: Overview of the BOT-MS projects. *Figure reused with permission from Cecilia Smith-Simonsen's thesis: The contemporary MS patient (University of Oslo, 2022) (Simonsen, 2021)*

6.1.4. Selection of population

To identify all persons with MS in the counties of Buskerud, Oslo and Telemark, we did systematic searches in the electronic patient records from the Vestre Viken Hospital Trust (in Buskerud), Oslo University Hospital, and the Telemark Hospital Trust. In addition to the population of Buskerud, Vestre Viken Hospital Trust serves a small part of the population in the northern regions of the neighbouring county of Vestfold, as well as a part of the south-western suburbs of Oslo (Asker and Bærum). In Oslo, there are two hospitals serving the MS population. The Oslo University Hospital (OUS) serves the central and western parts of Oslo, while Akershus University Hospital (AHUS) serves the northern parts of the city. We have only included patients from the OUS, and the Oslo population is therefore incomplete. There are a few private neurological practices in the counties. In Buskerud and Telemark, however, none of them treat pwMS, thus we believe we can claim that the included populations from these two counties are complete.

We used the International Classification of Diseases (ICD)-10 (World Health Organization (WHO), 1993) diagnosis G35 for the primary search. The search was performed in March 2017 and again in January 2018. Telemark Hospital Trust started using the electronic patient record system in 1993. Since the ICD-10 code system started in 1999, we used an additional search for the ICD-9 code (World Health Organization (WHO), 1978) diagnosis 340 (MS) to include all persons available. All pwMS were diagnosed according to the prevailing diagnostic criteria of the time. We stopped inclusion on 01.01.2018, except for persons from Telemark hospital, where we for the prevalence study continued until 01.01.2019.

6.2. Data collection, disease-specific variables

All medical journals were examined by the three neurologists with a special interest in MS and the ongoing PhD-projects, as shown in Figure 16. All three researchers have performed a level C Neurostatus certification (D'Souza et al., 2017) for the EDSS-scoring.

We used the already existing database from professor Celius' original Oslo MS registry as a starting point. This database has been added to by both herself and two previous PhD-students. The variables were thoroughly re-evaluated and discussed in advance, and we prepared a user manual to ensure a uniform retrieval and registration of data. Data were recorded in EpiData and later converted to SPSS for the statistical analysis.

The following disease specific variables have been collected:

1. Baseline information
- Demographics: Gender, date of birth, ethnicity, heredity, county/postal code, year of death
- Disease onset: Month and year, symptoms (Kurtzke), multiple symptoms
- Details of diagnosis:
    - Time (month and year)
    - Hospital
    - Phenotype (RR, SP, PP)
    - Diagnostic criteria used
    - Number of relapses before diagnosis
    - Supplemental investigations: MRI VEP, lumbar puncture (time and results)
    - EDSS at diagnosis
- Other autoimmune diseases, smoking, snuff, NAB, JCV index

2. Disease modifying treatments (DMTs)
    - Name of DMT
    - Onset DMT (month and year)
    - Delay, cause if any
    - Compliance
    - Discontinued, date if discontinued, cause if discontinued
3. Relapses
    - Time (month and year)
    - Treatment with steroids (yes or no)

4. EDSS at follow-up – as many as available
    - Time (month and year)
    - EDSS score – marked with validity
        i. Full EDSS in medical record
        ii. Estimated from file
        iii. Reported stable

    - More than three months since last relapse onset
5. MRI follow-up
    - Time (month and year)
    - Number of new brain lesions and Gd + lesions
    - Atrophy
    - Number of new spinal lesions and Gd+ spinal lesions

Disease modifying treatment (DMT):
When appropriate, we grouped the DMTs into moderate efficacy or high efficacy DMTs, as follows:

- Moderate efficacy DMTs: interferons, glatiramer acetate, teriflunomide and dimethyl-fumarate
- High efficacy DMTs: natalizumab, fingolimod, alemtuzumab, rituximab and cladribine

6.3. Data collection, socioeconomic variables

For an evaluation of the socioeconomic position of the included population, we collected information through a questionnaire and by linking with data from Statistics Norway.

6.3.1. The BOT-MS questionnaire

We created a BOT-MS questionnaire by re-evaluating a formerly used questionnaire, removing some, and adding other, questions, the latter more specific for mapping socioeconomic position. The questions were, when appropriate, retrieved from earlier validated questionnaires (Gustavsen et al., 2014), but there is no previous use of this specific composition of questions. The main questions included educational-, occupational- and marital status; parents' educational level; health-and lifestyle-factors; and patients' own perception of health and position in society. For women we included questions on menarche, menopause, pregnancy and lactation. We also added questions to be used in a wider definition of socioeconomic position when asking for the number of books in actual and childhood housing and mapping the so-called Norwegian cultural barometer, showing engament in different cultural activities last 12 months. Altogether, the questionnaire consisted of 44 questions (37 questions for men).

The questionnaire is presented in full-text in the Appendix, as well as summarised including the following variables:

- Gender, date of birth, birth country of person, parents and grandparents
- Marital status, number of siblings, number of children
- Level of education for person and parents
- Attachment to employment and classification of past or present work

- Self-perceived health (5-point scale)
- Height and weight
- Past or present autoimmune comorbidity
- History of mononucleosis
- History of severe infectious diseases
- Completion of national vaccination program
- Smoking and snuff habits, including exposure of second-hand smoking
- Alcohol habits
- Place of residence in childhood (municipality)
- Exposure of household animals
- Number of books in childhood and present home
- Use of cultural activities last 12 months (Cultural barometer)
- Self-perceived socioeconomic status by the 10-step MacArthur scale (Adler et al., 2000)
- For women: Age of menarche, menopause, pregnancy, childbirths and history of lactation

Validation of the BOT-questionnaire:

We validated the composition of the questionnaire in terms of reliability (test-retest and internal consistency) and concurrent validity. The validity test was performed on 39 pwMS and 39 healthy controls who were enrolled in November and December 2016. The questionnaire was completed twice, 4-6 weeks apart. We estimated the test-retest results by Cohen's kappa, internal consistency by Cronbach's alpha and concurrent validity by correlation coefficient. The results are published in an ECTRIMS paper (ECTRIMS Online Library. Flemmen H. 09/12/19; 279125; P765). The validation of the questionnaire led to some minor changes. Thus, we believe we can claim that the BOT-MS questionnaire is a reliable instrument for collecting data regarding socioeconomic information in patients with MS.

Administration of questionnaire:

The questionnaire was sent to all pwMS alive and resident in Norway that were identified through the systematic search in medical records. Together with the BOT-questionnaire, we also sent out a questionnaire for mapping symptoms of fatigue and affective disorders (the Fatigue Scale for Motor and Cognitive Functions (FSMC) and the Hospital Anxiety and Depression Scale (HADS).

The questionnaires were sent out from September to December 2017, and a reminder was sent out to non-responders in April and May 2018. The questionnaires were returned together with a written consent for use. Out of the 2512 persons eligible for participation, we received consent from 1598 (64 %), where 25 of these did not fill in the questionnaire. See Figure 17 for a flowchart of the BOT MS registry.

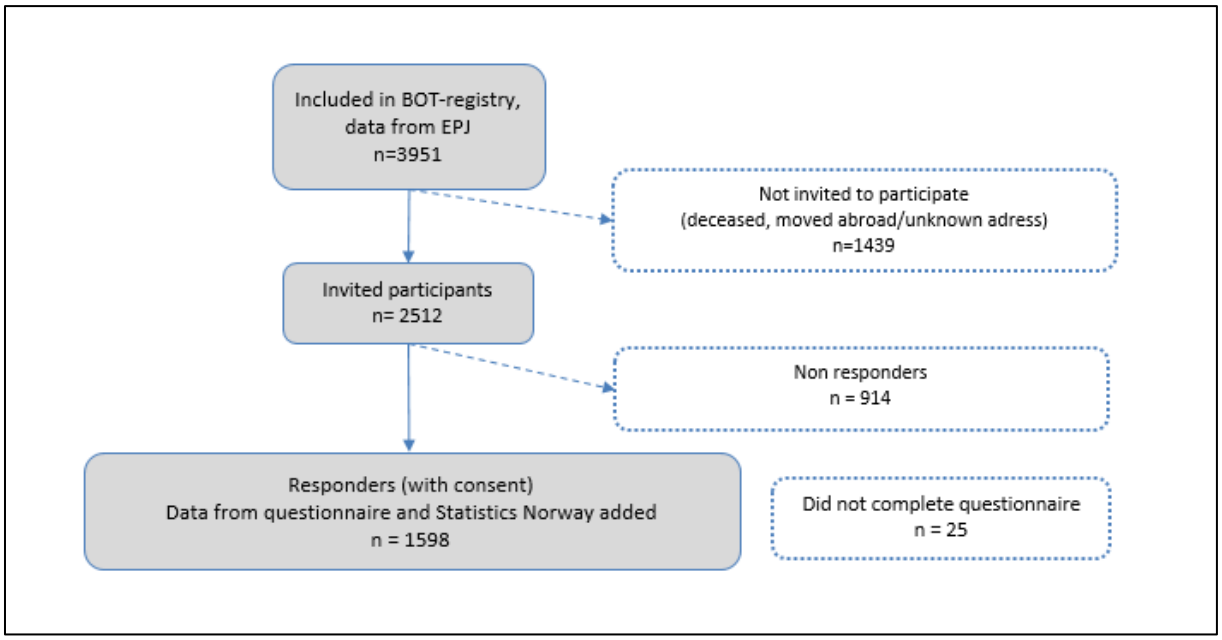


***Figure 17**: **Flowchart of the BOT-MS registry.** EPJ: Electronic patient journal*

6.3.2. Statistics Norway

Statistics Norway is the national statistical institute of Norway, established in 1876, ad the main producer of official statistics in the country. The combination of our clinical data and variables from these official statistics is possible through a unique identity number for each person in Norway.

We applied for data from Statistics Norway in September 2019. The agreement was signed in December 2019 (SSB-reference: 19/1681), and we received the de-identified data on January 28th and February 12th 2020.

The following variables have been delivered from Statistics Norway

- Place of birth (country and municipality)
- Country of origin for person, parents and grandparents
- If immigrated: Category for immigration to Norway
- Municipality for residency, yearly 1975-2019
- Municipality for residency at 16 years of age
- Birth-year mother and father, number of maternal siblings
- Number of children, with birth year
- Marital status, yearly 1975-2019
- Level of education, yearly 1970-2018
- Level of education for mother, father and parents combined at a person's 16th year
- Status of work, sick leave and disability pension, yearly 1992-2019
- Income after tax and household income, yearly 2004-2017
- Number of days of absenteeism and grades, secondary school

In November 2020 we received data from Statistics Norway describing details concerning the level of education of the background population in the three counties of Buskerud, Oslo and Telemark along with their parental level of education. In December 2020 we also applied for data from a matched control group, matched for sex, education and municipality of residence at age 16. We received the control data on February 12th 2021.

6.3.3. The socioeconomic variables with subgroups

Some of the variables were rearranged to make them suitable for analysis.

Level of education:

The level of education is divided into groups according to the total number of years in the Norwegian education system. The most commonly used categories are primary, secondary and graduate level of education. In Norway, primary school involved 7 years of education until 1969, when it was extended to 9 years. From 1997, the age for starting primary school was reduced from 7 to 6 years old. This led to primary school now lasting 10 years.

Secondary school lasts for three years with different fields of education. These are all grouped together, according to years of education.

In the data deliverance from Statistics Norway, the level of education was subdivided:

- primary school (0-10 years)
- secondary school (10-13 years) and
- lower graduate education, defined as 1-4 years after secondary school, and
- higher graduate education, defined as more than 4 years after secondary school

We have also used the level of parental education, both maternal and paternal separately, and parental level of education combined. The combined variable is according to a definition given by Statistics Norway and labelled by the highest level of education both parents have achieved.

In the preparation of the socioeconomic variables for analysis, we found that when using level of education with four categories (primary, secondary, graduate 0-4 years and graduate more than 4 years), the number of individuals were less than 5 in a few of the contingency table cells when separating maternal and paternal level of education. We consequently regrouped the level of education into three categories (primary, secondary and graduate) for paper 2. In paper 3 we chose to use the combined parental level of education with all four subgroups.

Centrality index:

The Norwegian government has developed an index characterising the different municipalities by centrality. The index comprises information on the number of service functions (including health care) and work places a resident can reach within 90 minutes by car. Added up, this gives each municipality a value from 1 to 6, where 1 denotes the most central areas and 6 the most rural (Høydahl, 2017).

We recoded the variables of residency given from Statistics Norway according to the centrality index, both for the residency at 01.01.2018 and for the variable residency at 16 years of age.

We divided the centrality indices into three groups; Centrality index 1 and 2, labelled this as urban areas; Centrality index 3 and 4, labelled as suburban areas; and Centrality index 5 and 6, labelled as rural areas.

In the county of Telemark, there are no municipality with Centrality index 1 or 2. However, the cities in Telemark has a Centrality index 3. In paper I we consequently labelled the municipalities with Centrality index 3 as urban areas; Centrality index 4 as suburban areas; and Centrality index 5 and 6, as rural areas.

Smoking:

The smoking variable was dichotomised into yes or no, where yes included both the answers “yes, daily smoking” and “yes, smoking now and then”.

Country of origin:

Birth country is sub-grouped as follows:

- Norway,
- Western countries (The rest of Europe, US, Canada, New Zealand and Australia) and
- Non-Western countries (Africa, Asia and South America).

Household income:

Household income is calculated as after tax income per consumption unit, corrected for differences in household size. The correction is performed by Statistics Norway using the European Union equivalence scale. This scale assigns a value of 1 to the household head, 0.5 to each additional member and 0.3 to each child under the age of 17. We have converted the results from Norwegian currency to Euro, using the exchange-rate nearest the prevalence date of 01.01.18. Household

income was considered a continuous variable, presented as a median and interquartile range when appropriate. When used in regression analysis, we rearranged the results in quartiles.

Marital status:
Marital status is presented as married, widowed, divorced or other, the latter including both single living persons and persons in cohabitation.

Self-perceived overall health-status:
Self-perceived overall health status was measured using a single-item question characterising the subjective perception of physical health within five possible responses: excellent, very good, good, fair and poor. We grouped the last two categories, fair and poor, together.

Self-reported socioeconomic status:
The Mac-Arthur scale is a 10-step scale where the respondent is asked to rate their subjective social status with the following instructions: Think of a ladder (diagram of a ladder is shown in the questionnaire) as representing where people stand in our society. At the top step (step 10) are the people who are best off with the best jobs, the most money and the highest education. At the lowest step (step 1) are the people who are worst off, those who have the least money, the lowest education, and the worst jobs or no jobs (Adler et al., 2000). We sub-grouped the self-perceived SES into three steps: low (Steps 1-3), medium (Steps 4-7) and high (Steps 8-10).

6.4. Statistics

We used EpiData Entry software, version 4.0.2.49 (Epidata Association, Odense, Denmark) for data collection and transferred all data to IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). We cleaned the data, merged files and performed all statistical analysis in SPSS. The survival analysis in paper II and paper III were also performed in Stata 16 (Stata Statistical Software; Release 16. College Station, TX: StataCorp LLV), as the graphics in this program are perceived to be better for this purpose. We used Open-epi.com to perform the mid-P exact test to compare prevalences and the z-test for differences in proportion between the MS population and the background population.

Data are presented as means ± standard deviation, median and interquartile range (IQR), or numbers and percentages, depending on distribution.

We used contingency tables to display associations between different variables. Moreover, we tested associations between different variables to see if the distribution of individuals among the categories of one variable is independent of their distribution among the categories of the other in contingency tables.

Choice of test of associations (Kirkwood BR, 2003).

- We used the Pearson chi-square tests or the Fisher exact test when every variable was categorical. We used the chi square-test except when more than 20 % of the expected numbers were less than 5, in which case we preferred a Fischer exact test.
- To investigate differences in continuous variables between two groups, we used an independent sample t-test for normal distributed variables and a Mann-Whitney U test for very skewed continuous variables.
- To investigate differences in continuous variables between more than two groups, we used one-way analysis of variance (ANOVA) for normally distributed variables and a Kruskall-Wallis test for very skewed continuous variables (like the EDSS).

We have used regression models to analyse the impact of socioeconomic factors on progression and access to disease modifying treatment. We have furthermore used both linear regression and logistic regression models depending on the outcome. Linear regression is used to estimate the best-fitting straight line that describes the association between exposure variables and continuous outcome variables, whereas simple linear regression is used with only one exposure variable at time. In multiple regression models, we examine more than one exposure variable at the same time. The results of linear regressions are given in regression coefficient (β) with its standard error (SE). The logistic regression is a method to be used for the analysis of binary outcome variables, and the results are given in odds ratio (OR) with 95% confidence interval (Kirkwood BR, 2003).

Multicollinearity is a phenomenon in which two or more variables are strongly correlated to one another. This means that in a multiple regression model one variable can be linearly predicted from one of the other variables, which can lead to spurious findings. To avoid multicollinearity, all variables were checked using the Spearman coefficient before being entered in multiple regression models. We did not find significant multicollinearity, and the limit for it was set to a Spearman correlation coefficient ≥ 0.7 (Rothman, 2014).

Statistical significance was defined by $p < 0.05$.

6.4.1. Paper I

We calculated the crude prevalence of MS in Telemark, defined as the total number of MS cases living in the population of Telemark measured at three dates, 01.01. 1999, 01.01.2009, 01.01.2019. We used the number of MS cases in Telemark as the numerator, divided by the total population of Telemark, with the result given per 10^5. The crude annual incidence was defined as the number of persons diagnosed with definite MS or CIS, which was later converted into definite MS per year when residing in Telemark per 10^5 inhabitants. As the number of those diagnosed with MS per year is low, we used five-year intervals and calculated the mean yearly incidence in each five-year period. For this, we used the average population at risk during the corresponding five-year interval. Population data stratified by age and sex was obtained from Statistics Norway.

To be able to compare the results of prevalence and incidence calculations with results from other counties or countries, we have used the European standard population to control for different age distributions among populations. We used the latest European Standard population, revised in 2013 (Pace, 2013, Kirkwood BR, 2003). We adjusted the age-stratified population according to the European standard populations, and then recalculated the prevalence and incidence within each age-group and for the total population. Both results (original and adjusted) are presented in the publication.

Ninety-five percent confidence intervals (CI) for prevalence and incidence were calculated manually from the formula p ± 1,96 x SD, where SD is the standard deviation, given by the formula $\sqrt{p(1-p)/n}$, p being the crude prevalence or incidence, and n the number of persons participating.

We compared the demographic variables (age at onset, age at prevalence date and mean time from onset to diagnosis) in 2019 compared to 1999 using the independent sample t-test, as we considered the data normally distributed. To assess the significance of change in prevalence and incidence, and compare the prevalence in rural versus urban areas of Telemark, we used the mid-P exact test, as described in Rothman's Modern Epidemiology (Rothman et al., 2008), using OpenEpi.com.

6.4.2. Paper II

Here we used three different measures of disease progression to evaluate the impact of socioeconomic factors on disease progression.

1) Change in EDSS from diagnosis to year 5 after diagnosis
2) Time to EDSS 6
3) The MSSS at prevalence date

We then calculated the change in EDSS from time of diagnosis to EDSS year 5 after diagnosis by using the EDSS variable collected in the registry. If no EDSS was available in year 5, we used the EDSS at year 6 (213/768) or year 7 (81/768). We also labelled the different results in categories: an increase in EDSS by more than 2 points was labelled as “marked progression”; an increase by 1-2 points was labelled as “moderate progression”; a change by +/- 0.5 points was labelled as “stable disease”; and finally, a reduction in EDSS by 1 point or more was labelled as “improvement”. The time to EDSS 6 was calculated in all persons who had reached this milestone. The MSSS was manually calculated by using the EDSS at the prevalence date in 2018 and disease duration as described by Roxburgh et al. (Roxburgh et al., 2005). The MSSS is limited to 30 years with diagnosis and 251 of the pwMS had more than 30 years since diagnosis. For the individuals with 30-35 years since onset, we have used the MSSS at year 30 after diagnosis, and the 147 persons with more than 35 years of disease duration were excluded from this analysis.

The results were presented in contingency tables. Depending on the type of variable and distribution, we used the chi square test, independent sample t-test or one-way ANOVA to assess differences in variables between groups of change in EDSS year 5. When the result of the chi square test was significant for associations, we performed a post-hoc analysis where “stable disease” was used as a comparator for the two categories of progression (marked and moderate progression). As the distribution of EDSS was skewed, we used the Kruskal Wallis test to compare EDSS across subgroups.

The influence of socioeconomic variables on time to the milestone EDSS 6 were calculated by use of the Kaplan-Meier method. We used time from onset until the date of EDSS 6, date of emigration, time of death or time to prevalence date as the follow up time, selecting whichever event occurred first. The results are presented as mean time to EDSS 6 and a confidence interval.

For evaluation of the MSSS against socioeconomic variables at the prevalence date in 2018, we performed a univariate, then multivariable, and at last a final, model. The variables with a significant β coefficient in the univariate analysis were included in the multivariate analysis. In addition, we chose to include the centrality index (not significant in the univariate analysis). In this process, all the β-coefficients are adjusted for each other.

For the final model, we excluded one by one of the non-significant variables from the multivariable analysis, starting with the variable with the highest p-value. The final model excluded the centrality index, paternal level of education and second-hand smoking. The final model then included maternal level of education, age at diagnosis, receiving a DMT and current smoking as the significant contributors to the regression line. The results were presented as β-coefficients, SE and p-values

and explained variance (R^2). The R^2 expresses the percentage of the variance explained by the included socioeconomic variables (R^2 =0.11, 11%).

Factors strongly associated were not included in the multivariable analysis to avoid multicollinearity.

6.4.3. Paper III

In this paper, we evaluated socioeconomic variables impact on access to disease modifying treatment (DMT). We evaluated both access to DMT in general and access to high effective DMT as first treatment. We used contingency tables to present the results. Depending on type of variable and distribution, we used the chi square test, independent sample t-test or Mann Whitney test to assess differences in variables between the group ever treated and never treated with DMT.

When evaluating the access to high efficacy DMT as a first treatment, we divided the population by year of diagnosis, represented by two groups: diagnosed 2007-2017 and 2012-2017. We used the first time-period (2007-2017) because the first high efficacy DMT, natalizumab, was introduced in 2006. The period 2012-2017 was used to evaluate the most recent treatment patterns, as the first per oral high efficacy DTM, fingolimod, was introduced in 2011 and with that supplement, the choice between moderate and high efficacy treatment as first DMT is considered relevant. We used contingency tables to present the results. Depending on the type of variable and distribution, we used the chi square test, independent sample t-test, Mann Whitney test or Fisher exact test to assess differences in the socioeconomic variables between those groups treated with high efficacy as the first DMT and those not in both time periods.

We performed a multivariable binary logistic regression model to analyse the impact of socioeconomic variables on access to high efficacy DMT. The selection of which variables to include in the model was based on a discussion in the research group, emphasising the results of clinical knowledge and those of paper I and paper II. We included gender, age at onset and EDSS at diagnosis. As socioeconomic variables, we included the level of education of pwMS and their parents combined, the centrality index of the municipality in 2018, household income and self-perceived overall health status. Next, we calculated the OR after defining a reference variable for each.

The influence of socioeconomic variables on time for high efficacy treatment was analysed for all variables included in the regression analysis by use of the Kaplan-Meier method. The results are presented as median time for high efficacy treatment. We also used the Mantel-Haenszel test in order to test for linear trends concerning the proportion treated with DMT or that treated with highly efficacious DMT over time. The time to start DMT was tested by a linear regression.

7. METHODOLOGICAL CONSIDERATIONS

7.1. Study design

This project is built upon a real-world population-based registry. The data were recorded prospectively but collected retrospectively in the BOT-MS registry, as described in detail in previous chapters.

A cohort designates a group of people who share a common experience or condition (Rothman et al., 2008). In this project, the diagnosis of MS is the common condition for all participants. The data included in our study represent a real-world population where we follow disease courses in the selected MS-population over time. The use of real-world data is in general more extensive, available for long-term follow-up and most often more population-representative than clinical trials; however, the collection of real-world data is also subject to multiple classes of bias, which the following sections will focus on details (Kalincik and Butzkueven, 2016) .

The inclusion of participants in the BOT MS registry was completed on January 1st 2018. For paper I, we used three dates for evaluating the prevalence of MS in Telemark: January 1st in 1999, 2009 and 2019. For the latter, we additionally included persons with MS diagnosed in Telemark in 2018, up until January 1st 2019, resulting in three prevalence dates with ten years apart.

For paper I, we used the pwMS being followed by Telemark Hospital and/or those who were residents in Telemark at one or more of the three prevalence dates. Through an accurate review of the entire registry, including Buskerud and Oslo, we identified five persons diagnosed with MS, residing in Telemark, without any contact with Telemark Hospital. These were also included for the prevalence and incidence calculations. The county of Telemark only has one neurological department, and there were no private neurologists treating MS in Telemark on any of the prevalence dates. Telemark Hospital started using electronic patient records in 1993, which also supports the claim of a complete population during the entire period. For paper II and III, we have used the cohort of participants with a signed consent in order to include their data from Statistics Norway in the analysis.

7.2. Internal validity

The objective of most epidemiologic studies is to obtain a precise and valid estimate of the frequency of a disease, or the effect of an exposure on an outcome of the disease in the source population of the study. The internal validity is defined as the extent to which the observed results represent the

true description of the population studied and not due to methodological errors (Rothman et al., 2008).

To produce internal validity, the errors of the different estimates should be as small as possible. There are two types of errors in estimations, traditionally classified as either random or systematic errors. The random errors concern the difference between the observed and true values and will occur when measurements deviate from the true value, but are equally distributed around this value (Thelle, 2015). Systematic errors, on the other hand, are often referred to as biases, as the opposite to validity. Systematic errors occur if measurements always deviate in a certain direction away from the true value (Thelle, 2015). Random errors cannot be fully eliminated, but most systematic errors can be reduced. The systematic errors at risk in epidemiological studies are most often divided into three main categories: selection bias, information bias and confounders.

7.2.1. Selection bias

Selection bias results from a preferential inclusion of participant subpopulations into observational studies (Kalincik and Butzkueven, 2016). When the procedure used for the selection of subjects for the study influences the participation, there is a selection bias. The risk of selection bias is reduced by using a population-based cohort, like ours. The search for participants for our study was systematically performed; all persons with a registered diagnosis of MS, identified through the registered ICD diagnosis in the electronic records in the hospitals, were evaluated. The Norwegian Health care system is organised so that all disease-modifying treatments of MS are prescribed and financed by the public hospitals, which ensures a complete population. All Norwegian citizens have a national identity number that allows for the unique identification of persons and enables a life-time follow-up. We have included persons with a certain diagnosis of MS after prevailing diagnostic criteria and have excluded persons with a misdiagnosis of MS. All inclusions were made by three researchers with clinical experience in MS.

When collecting the data retrospectively, we are aware that the conditions for inclusion in the cohort are not permanent. The diagnostic criteria of MS have changed several times within recent decennials. The conditions in which persons with MS live have also changed over the years, especially the availability and access to disease-modifying treatments and the strategies for using them. Survival bias is a form of selection bias, and the loss to follow up through deaths will influence the long-time prognosis of the disease. There is therefore reason to believe that the persons leaving the cohort as dead may have had a more aggressive disease, whereas those available for follow-up are

less affected. We have tried to compensate for these facts through our choice of adapted statistical methods.

For paper I, we have used the complete cohort from Telemark and thus the risk of selection bias is close to negligible. For paper II and III, however, we have used only persons with a written consent for retrieving data from Statistics Norway. The call for participation was sent out by ordinary mail to all living persons identified as diagnosed with MS. As described in a previous section, the cohorts from the counties of Buskerud and Telemark are considered complete. However, the Oslo population is not complete. The selection of persons from Oslo was based on the Oslo MS-registry, but it was incomplete due to changes in the hospitals' catchment area in recent years. We therefore acknowledge there is a possible selection bias in the Oslo population. The population that consented to participate will, in general, also represent a possible selection of population. The response rate for participation in our study was close to 64% and we did not find any differences in disease characteristics between those who responded and those who did not (Broch et al., 2022). However, we have for obvious reasons not been able to compare the respondents to the non-respondents regarding the socioeconomic variables. It was earlier described that people with a higher level of education are more likely to participate in studies (Reinikainen et al., 2018). Nevertheless, we have compared the respondents to the background populations in the counties of Buskerud, Oslo and Telemark and found a similar level of education in our participating MS population compared to the general background population, including when the known correlation between parental and individual level of education (Weinberg et al., 2019) was taken into account. For the evaluation of socioeconomic variables, we do not suspect that any specific selection pattern had a considerable effect on the results.

For paper III, in which we evaluated the access to disease modifying treatment (DMT), we excluded people with primary progressive MS, as there were no DMT available for this group in Norway as of January 2018. We also chose to use only the participants diagnosed after 2006 for a specific analysis on time to access treatment, as this was the year for the registration of the first high efficacy DMT in Norway. These last two examples of selection from the population are based on medical experience and knowledge and cannot be accounted for as typical selection biases.

7.2.2. Information bias

The information used in an epidemiological study must be obtained as specifically as possible. Information bias is an expression of data inaccuracy and will occur if the measurements of exposures or outcomes are determined with substantial error (Kukull and Ganguli, 2012).

In our study, we have collected the data from the electronic patient journals retrospectively. This method obviously has a potential for information bias, as all clinical measurements may have been erroneous at the time they were written in the journals. This is one of the main disadvantages with using real-world data. To minimise the data inaccuracies, we created a manual for data inclusion to be used by the three researchers collecting data. All three researchers were grade C certified in Neurostatus (D'Souza et al., 2017) and worked part-time as clinicians with a special interest in MS. We have also used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Cuschieri, 2019) in order to be transparent about this weakness in the published papers.

For discrete variables, error in measurement is usually called classification error, or misclassification. Misclassification is subdivided into non-differential- and differential misclassification. Non-differential misclassification occurs when the data obtained is incorrect but does not depend on the values of other variables (the same error across groups), whereas differential misclassification occurs when the incorrectness of data varies across other variables or between groups.

Both non-differential- and differential misclassification errors may have occurred in our data collection, both in the clinical and socioeconomic variables.

Misclassification errors in the clinical measures

The extended disability status scale (EDSS) has several limitations and is assed with moderate intra-rater- and high interrater variability (Cohen et al., 2021). As a part of the collection of data, we have constructed an EDSS score when missing, if possible, the possibility to construct one is based on the description of clinical findings in journal records. We are aware of this bias; however, this should be considered non-differential, as it has appeared across all subgroups of patients. In the BOT-MS registry, we registered if the EDSS was scored by the physician responsible for the investigation at the time the record was written, or if it was constructed retrospectively based on the neurological examination. We have, however, for practical reasons not used these notifications in the analysis performed in the papers included in this project. We have also registered, but not used in the analysis for these three papers, if the EDSS was scored within 3 months after a relapse of the disease.

A potential differential error, in comparison, is the result of MRI-scans. We have relied on the reports from the local radiological departments, but are aware that the interpretation, especially regarding the MAGNIMS criteria (Wattjes et al., 2021), are used to varying degrees in the different departments and hospitals. However, the MRI data in the BOT-MS registry are not used in the papers included in this project.

Misclassification in the socioeconomic measures

In research including socioeconomic factors, information about a person's level of education is most often obtained by self-administered questionnaires. It is important to assess the validity of the variable, as the risk of incorrect answers is substantial, most often as respondents over-report their level of education. A study from Tromsø, Norway, has performed a validity test analysing the self-reported level of education against data recorded from Statistics Norway and they concluded that self-reported level of education in their population was adequately complete. However, a certain pattern of misclassification could be observed, with low correctness for those with a primary educational level. The sensitivity of self –reported level of education was highest among those with the highest level of education (Vo et al., 2022).

Level of education was for our study collected both by the questionnaire (self-reported) and from the data delivered by Statistics Norway (the "gold standard").

We have performed simple cross tables using the official level of education from Statistics Norway in the columns and the self-reported level of education in the rows. Only 40.7% of those with primary school as their highest achievement gave the "correct" answer in our BOT-questionnaire, whereas 96 % of those with the highest level of education self-reported accurately. See Table 15.

The strength of agreement for the overall results are analysed by weighted Kappa. The value of Kappa is rated 0.00-0.20 as "slight", 0.21-0.40 as "fair", 0.41-0.60 as "moderate", 0.61-0.80 as "good" and 0.81.1.00 as "very good" concerning strength of agreement (Landis and Koch, 1977).

Cross tabulation level of education, percent of self-reported versus the "gold-standard" recorded from Statistics Norway					
		Level of education recorded from Statistics Norway			
		Primary school	Secondary school	Graduate 14-17 years	Graduate ≥ 18 years
Self-reported level of education	Primary school	40.7	11.4	0.2	0
	Secondary school	48.5	65.2	2.3	0.5
	Graduate 14-17 years	5.5	21.9	67.1	4.0
	Graduate ≥ 18 years	0.6	1.5	30.4	95.5
	Total	100	100	100	100

Table 15: Percent of the self-reported level of education compared to the "gold-standard" level of education*. The cells with the correctly reported level of education are highlighted in grey. Strength of agreement is* ***good****, analysed by Kappa: 0.646 (95% confidence interval 0.621-0.672).*

When analysing the results of the self-reported parental level of education, we acknowledged the same pattern. However, there was an overall a more accurate indication of the primary level of

education, for both mothers and fathers. It is important to emphasise that the self-report of parental level of education is not time-specified (questionnaire: "What is the highest level of education of your mother/father"), whereas the variable from Statistics Norway specifies the level of education of parents when the patients were aged 16. Some of the misclassification in these results, presented in Tables 16 and 17, may therefore be explained by the fact that the parents increased their education after the person in question turned 16, although we do consider that most parents will have ended their education prior to their child turning 16.

Cross tabulation maternal level of education, percent patient-reported versus "gold-standard" recorded from Statistics Norway					
		Maternal level of education recorded from Statistics Norway			
		Primary school	Secondary school	Graduate 14-17 years	Graduate ≥ 18 years
Self-reported maternal level of education	Primary school	78.0	35.1	0	0
	Secondary school	18.4	47.7	4.8	3.4
	Graduate 14-17 years	3.4	15.5	65.4	10.3
	Graduate ≥ 18 years	0.2	1.6	29.8	86.2
	Total	100	100	100	100

Table 16: Percent of self-reported maternal level of education compared to the "gold-standard" level of education*. The cells with the correctly reported level of education are highlighted in grey. Strength of agreement is* ***moderate****, analysed by Kappa: 0.548 (95% confidence interval 0.514-0.581)*

Cross tabulation paternal level of education, percent patient-reported versus "gold-standard" recorded from Statistics Norway					
		Paternal level of education recorded from Statistics Norway			
		Primary school	Secondary school	Graduate 14-17 years	Graduate ≥ 18 years
Self-reported paternal level of education	Primary school	81.0	29.9	0	0
	Secondary school	15.8	43.0	8.6	0
	Graduate 14-17 years	2.5	23.4	64.4	11.5
	Graduate ≥ 18 years	0.7	3.8	27.0	88.5
	Total	100	100	100	100

Table 17: Percent of self-reported paternal level of education compared to the "gold-standard" level of education*. The cells with correctly reported paternal level of education are highlighted in grey. Strength of agreement is* ***good****, analysed by Kappa: 0.625 (95% confidence interval 0.595-0.654)*

All this considered, to reduce information bias, we used the level of education given by Statistics Norway. We would like to highlight this as an important strength of our study, as we avoided the differential misclassification error.

7.2.3. Confounders and colliders

Confounders are extraneous factors that may affect both the measure of exposure and the measure of effect in a study. A prerequisite for a variable to be classified as a confounder is that the confounder is associated with the exposure, but not a consequence of the exposure, and is independent of the effect or outcome(Thelle, 2015). Typical confounders include age, gender and ethnicity. *Colliding* is a situation where a variable (the collider) is a consequence of both associated factors (exposure and outcome) (Laake, 2015).

In paper I we adjusted all the prevalence and incidence calculations after the EU standard for correction of age (Pace, 2013), as different age-distributions in different populations is a potential confounder. This is important to do be able to compare the results with prevalence estimates from other populations.

In the prevalence calculations we have not included socioeconomic variables other than the centrality of residency. When investigating causality in different epidemiologic studies, socioeconomic factors are ideally controlled for as possible confounding factors. We did not adjust the prevalence for any other socioeconomic factors, although we realise that level of education in particular might be a factor that can influence the findings of different prevalence of MS in different areas. In Figure 18 we tried to illustrate the problem of determining this third factor, level of education, as confounding or colliding.

The hypothesis generated from paper I is that rural living will increase the risk of MS, as we found higher prevalence in these parts of the county of Telemark. People living in the rural areas of Telemark, as well as Norway in general, have a lower level of education than those living in the cities (source: Statistics Norway). Nevertheless, we also know that educational attainment might be disrupted due to MS (Flensner, 2013). We cannot, therefore, prove that a lower level of education in itself provides a higher risk for MS. To be emphasised in the discussion, this will probably depend on several factors, as health literacy in general, or smoking in particular, has an impact on the risk of MS. We have thus concluded that level of education is most probably a collider of the association between centrality of living and prevalence of MS, even though we recognise this is up for discussion in further investigation.

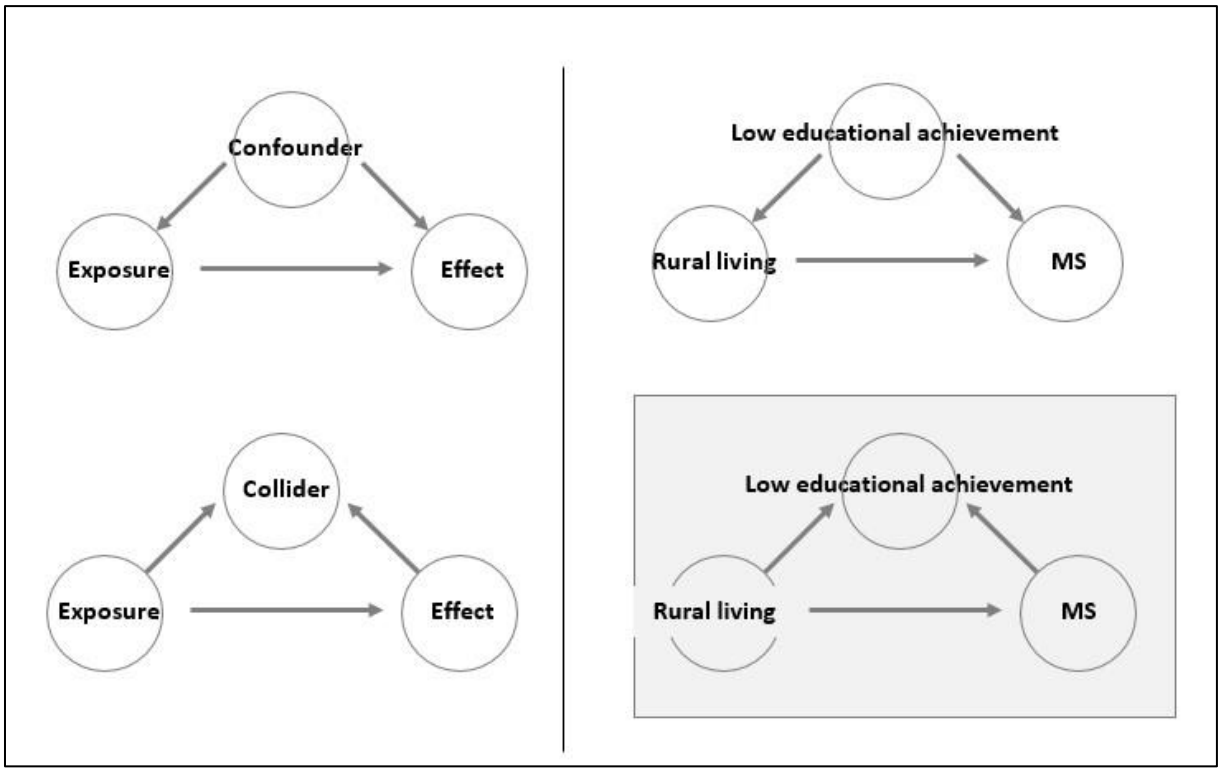


Figure 18: ***Left side:*** *theoretical illustration of the association between exposure and effect, and the consequence of a confounder (above) or collider (below).* ***Right side:*** *the illustrations investigating the association between rural living and MS, where low level of education is considered either a confounder or a collider. The most obvious model (collider) is highlighted in a grey frame.*

This knowledge from paper I has had an impact on the analysis performed in paper II and paper III. We decided to use parental level of education as a measure of socioeconomic position, as the participant's own level of education is more probably influenced by the disease itself.

The evaluation of the influence of different socioeconomic factors is complex. Many of the variables measuring socioeconomic status are interdependent. Examples of variables with an association are level of education and income, level of education and smoking, parental level of education and a person's own level of education, and income and self-perceived socioeconomic status. We considered using a model of directed acyclic graphs (DAG) to illustrate the possible connections between variables. However, as we used a prognostic/predictive strategy, meaning that priority was not given to specific hypotheses, we investigated if socioeconomic factors could predict progression or access to disease modifying treatments. Hence, we were not interested in studying potential confounders and effects, and we believe adding a DAG might be more confusing than enlightening.

7.3. Generalisability (external validity)

The generalisability of the results from an epidemiological study refers to what extent the results can be applied to a population outside the cohort. This is referred to as the external validity of the results.

We believe one of the strengths of this study is the broad recruitment of a study population. As described in previous sections, the three counties of Buskerud, Oslo and Telemark consist of a large spectrum of people, representing an especially wide range of socioeconomic status. As already addressed in the methods section, the Oslo population is not complete, which is a disadvantage with respect to generalisability. All the analyses of the socioeconomic factors that influence different aspects of MS are conducted on the total cohort, which includes all three counties, as we believe this will help balance this out.

The results from paper II and III are based on variables from those who consented to participate. This can represent a bias in the population, which in turn affects the generalisability. Out of the 2512 persons eligible for participation, we received consent from 1598 (64 %). Concerning this percentage, Rothman, who in his "Modern Epidemiology" questions the belief that a high response rate is a sign of high quality (Rothman et al., 2008). Rothman states (chap 24, page 497): "The specific threats depend on study design. For instance, loss of target population at recruitment into a cohort study does not threaten validity, but loss of follow-up of the recruited members can do so, because the rate of loss might differ by both disease and exposure". In this view, we believe we can argue that our data is of good quality, as the loss to follow-up is not a big issue, and the collection of validated census data from Statistics Norway is obtained from every included individual.

7.4. Choice of statistical method

We have chosen and performed statistical methods for each of the papers under the guidance of a statistician and epidemiologist. The statistical methods are described in detail in section 6.4.

In paper I we used classical statistical methods for estimating prevalence and incidence.

In paper II and III we performed varied statistical methods to analyse the possible impact of socioeconomic factors on different aspects of MS. The null-hypothesis in both papers is that there are no differences between groups, which means there is no influence by socioeconomic variables on the different outcome measures of disease progression and access to disease modifying treatments.

We have used a p-value < 0.05 as the limit for rejecting the null hypothesis. When evaluating the p-values, we can make two possible errors named type I and type II errors. The type I error is when the null hypothesis is rejected because the p-value is low, while the null hypothesis is in fact true. The type II error, on the other hand, is when the null hypothesis is accepted but the groups are in fact different (Thelle, 2015).

In papers II and III we initially investigated whether socioeconomic factors have an impact on disease progression and access to DMTs in persons with MS by performing multiple cross-tables. Additionally, the analyses were conducted within strata of time periods to check whether the results could possibly be affected by the introduction of the high efficacy DMT, resulting in some multiple testing. We are aware of that 1 in 20 positive tests with a significance level of 5 % could have occurred by chance alone. We agree there is a concern that when performing multiple tests, the probability of a spurious result is increased, and by this a type I error occurs. As the number of tests increases, the probability that one of them would be falsely positive increases, but that is only because many tests are being conducted (Rothman, 2014). In paper II we considered performing multiple corrections, such as a Bonferroni, but we are aware that these corrections are done at the expense of increasing type II errors that are non-significant results in the presence of real associations. Thus, we chose not to adjust for multiple corrections, but we are aware of the risk of false-positives (type I errors) in these explorative hypothesis generating studies.

In the planning of statistical analysis, we considered the probability for confounders and colliders, as described in previous section. As we also used a prognostic strategy, we were not interested in studying potential confounders. We did, however, among other considerations about the data and before conducting the first analysis, check our SES-variables in adolescence for multicollinearity, the phenomenon in which two or more variables are strongly correlated to another. This was done using a Spearman correlation coefficient ≥ 0.7 as limit for multicollinearity (Rothman, 2014). We also performed a collinearity check for the educational variables against the centrality of residency in adolescence. The resulting correlation coefficients are -0.095, -0.173 and -0.013 for the respective maternal-, paternal- and the pwMS' own level of education versus the centrality of residency at age 16, which is acceptable.

In the prognostic strategy, we were only interested in possible socioeconomic factors associated with progression or access to DMTs in MS patients. All possible socioeconomic factors included in this study were preplanned based on literature and availability. In paper II we performed a regression analysis in three steps: First, a univariate regression analysis, using only one variable at the time; and

second, a multivariate regression analysis, combining the variables that were shown to be significant in the univariate analysis, while excluding (other) variables with collinearity. At this point we were finally building a final model by eliminating non-significant variables in the multivariable analysis until all reached significance. In paper III, after the univariable analysis, all important factors from an expert opinion were included in a multivariable binary logistic regression analysis to investigate the strongest factors/predictors of access to DMTs when taken together.

7.5 Sample size

The probability of rejecting the null hypothesis, if really untrue, will increase with higher number of observations and heighten the precision. The number needed to be included in a study is also an assessment of how many subjects will remain in the study. As this is a retrospective study, with a fixed number of cases, we have not calculated a sample size in advance.

Paper I is a descriptive study, estimating prevalence by including all persons with MS in Telemark, (450 at prevalence date 01.01.2019). Power calculations were thus not relevant.

For paper II we included 1598 persons with MS to evaluate socio-economic factors' influence on disease progression. This is fewer than in similar studies, such as Hardings' study from MS databases in Canada and the United Kingdom (n=3113) (Harding et al., 2019b) or Calocer's study from France (n=3641) (Calocer et al., 2020). However, it is, large enough to record highly significant differences in most endpoints of interest. We had to merge the two highest levels of maternal education, as the number with the highest educational achievements (more than 17 years of education) was too low for an analysis of the level of education against different subclasses of socioeconomic variables, such as the centrality of residence. With a higher number, we might have been able to investigate if the correlation of the progression of the disease and the number of years of higher maternal education follow a linear trend throughout the whole scale.

For paper III we included the 1314 persons from the BOT-MS registry with RRMS. This is higher than Calocer's study of the same question (n=733), namely whether socioeconomic status influences access to DMT in MS (Calocer et al., 2018). The number of available cases was fixed, and we did not perform a priori sample calculations.

8. ETHICAL CONSIDERATIONS

The projects included in this thesis were approved in advance by the Regional Committee for Research Ethics (REK 2015/670). The Oslo University Hospital Data Protection Office (PVO) has approved the journal review and the patient - and treatment registry at Oslo University Hospital (OUS). In addition, the study was approved by the local hospitals of Vestre Viken and Telemark, based on the approval at OUS. The combining of the registry data with data from Statistics Norway was also approved by REK, PVO and Statistics Norway.

All persons with MS identified as eligible for the study who were still alive and resident within Buskerud, Oslo or Telemark received a request to participate in the study, sent by postal mail. The participant had to sign a consent form, which was returned by postal mail in pre-stamped envelopes.

No invasive or study specific tests were performed as a part of the study. Together with the request for participation, the study population received two questionnaires for a mapping of socioeconomic data and fatigue. The questionnaires were returned in the same pre-stamped envelope as the consent form. The questionnaire and the clinical data were linked by a study-specific, non-identifiable code.

The author of this thesis is one of two physicians responsible for the follow-up and treatment of all persons with MS in Telemark. There is a possibility that the participants felt obliged to participate in the study to receive the best treatment, and in the consent form we have specified that there will be no consequences for the treatment and follow-up routines if they decided not to participate.

The patients were included in the development of the questionnaire regarding socioeconomic variables (validation project, as described in section 6.3.1). We also provided information about the project and results along the way through meetings with the different local MS organisations, and the project has also been discussed with the four MS patients on the user panel of the MS research group, OUS.

9. DISCUSSION

The overall aim of this project was to evaluate the impact of socioeconomic factors on different aspects of multiple sclerosis (MS). The first paper was, however, meant to be a description of the incidence and prevalence of MS in Telemark. As we found a higher prevalence of MS in the rural parts of the county, this led to a hypothesis that the differences in prevalence can partly be explained by the differences in socioeconomic background. In the further work on the project, we found that a high maternal level of education for people with MS (pwMS) at age 16 was significantly associated with less pronounced disease progression measured by the multiple sclerosis severity score (MSSS). A high maternal level of education was also associated with younger age and a lower expanded disability status scale (EDSS) at disease onset, as well as a shorter time from onset to diagnosis. Paternal level of education had no significant association with these variables. Finally, we found that socioeconomic factors had a partial impact on access to disease modifying treatment (DMT). People with the highest levels of education, and those who are married, were more likely to be ever treated with a DMT. However, when analysing access to high efficacy DMT as a first drug, as strategy focused on in the updated national treatment strategies, we did not find that deprived pwMS had less access. On the contrary, we found that level of education, household income and marital status were inversely related to high efficacy DMT as a first drug. Moreover, we found that those pwMS treated with a high efficacy DMT as a first drug had a higher EDSS at diagnosis compared to those treated with a moderate efficacy DMT as a first drug. Finally, we found that none of the above listed socioeconomic differences persisted when analysing the subgroup diagnosed within the last six years (2012-2017). We concluded that the pwMS in this Norwegian cohort are treated equally with DMT in terms of different measures of socioeconomic position.

Prevalence and incidence of MS in the county of Telemark.

The list of prevalence studies from different counties in Norway had for a long time been missing data from Telemark, and previous national studies had indicated that there was reason to expect a high prevalence in this area of Norway (Berg-Hansen et al., 2014).

In the calculation of the prevalence and incidence of MS, a complete data set is crucial. In previous sections, we have argued that the cohort from Telemark is complete and that the prevalence estimates are valid. The completeness of data gave us the opportunity to calculate prevalence and incidence at several time points, from 1999 until 2019. The prevalence has been estimated for January 1st in 1999, 2009 and 2019, and the incidence is presented at five-year intervals between 1999 and 2018.

The prevalence estimate for MS in Telemark in January 2019 was 260/10^5, which is among the highest ever reported, both nationally and globally. Another convincing result is the marked increase in prevalence over the last twenty years, from 106/10^5 in January 1999 and 178/10^5 in January 2009 up until the more recent estimate in 2019. This is consistent with the major trend of all prevalence investigations in MS over recent decennials (Grytten et al., 2015, Walton et al., 2020). A change in prevalence is most often explained by a function of changes in incidence and/or changes in survival time.

The average life expectancy in the general population has increased (Scalfari et al., 2013, Kontis et al., 2017), and the median survival of pwMS in a Norwegian study was 41 years after disease onset, more than twice as long as reported in the first study on the topic from 1969 (Lunde et al., 2017). The excess mortality among pwMS compared to the general population has been a focus of previous research (Smestad et al., 2009). However, longitudinal studies reveal increased life expectancies and a decline in the excess mortality rate over the recent decades (Koch-Henriksen et al., 2017, Grytten et al., 2016, Kingwell et al., 2012). The introduction of DMT has made a significant contribution to improving the prognosis of MS (Simonsen et al., 2020a), although Koch-Henriksen et al. concluded that the decline in excess mortality in MS in Denmark started decades before DMT became available (Koch-Henriksen et al., 2017). The publication discussed that the improved survival may be a result of the increasing female incidence in cohorts (Koch-Henriksen et al., 2017). On the other hand, Smestad et al. found that the excess mortality of pwMS was more pronounced among women than men (Smestad et al., 2009). Better treatment of comorbidities and rehabilitation in the MS population could be another explanation (Grytten, 2017).

In paper I we found that the age of the pwMS in our cohort had increased over the recent decades. This is consistent with global reports (G. B. D. Multiple Sclerosis Collaborators, 2019). However, there are differences in age distribution in different populations. To be able to compare prevalence and incidence results more precisely, both nationally and globally, age-adjusting of the data is of importance. We used adjustment according to the European standard population from 2013 (Pace, 2013), which changed the 1999 crude prevalence from 97.3/10^5 to 105.8/10^5, the 2009 crude prevalence from 176.1/10^5 to 177.7/10^5 and the 2019 crude prevalence from 259.6/10^5 to 260.5/10^5. However, the first two prevalence estimates in our study were dated to before the updated version of the European standard population (Pace, 2013). We therefore also calculated the prevalence with an adjustment according to the 1976 European standard population. For 2009, the result from using the old standard population was lower (163.9/10^5) compared to the result from using the updated standard population (177.7/10^5). This gives us reason to believe that the Norwegian population was not in accordance with the previous European Standard population, and thus there is a possibility

that adjusted prevalence studies from Norway during the first decade of the millennium may be underestimated.

There was an increase in prevalence of MS for all age groups from 1999, via 2009, to the estimates in 2019. In particular, we observed an increase in prevalence in the population older than 60 years of age. The highest age-adjusted prevalence was observed for females aged 60-69 for the prevalence date in 2019. This sub-group has an MS prevalence of $683/10^5$. The increased median age of pwMS may be a consequence of increased survival, alternatively explained by the increase in median age at diagnosis. A previous publication from the BOT-cohort found that the proportion of older pwMS significantly increased when comparing those with disease onset before and after 2006. The proportion of the pwMS with a disease onset after 50 years of age was 6.2% before 2006, which increased to 12.9 % when the onset was registered in 2006 and later (Simonsen et al., 2020a). The Danish MS registry concluded that the increase in the proportion of women with MS was most prominent for people with an onset of disease at an older age (50 years or more) (Magyari and Sorensen, 2019). According to the previously used Schumacher criteria, a person could not be diagnosed with MS if they were 50 years or older (Schumacher et al., 1965). Consequently, we have reason to believe that older people were not accurately diagnosed in historical data (Siva, 2013), as many of them were diagnosed with undefined neurological symptoms, at least before the introduction of MRI (Kaisey et al., 2019).

The incidence of MS world-wide has been relatively stable, or slightly increased, over the past four to five decades. This stable incidence is primarily observed in Caucasian populations, although there are more often reports of increasing incidence rates in selected ethnic groups (G. B. D. Multiple Sclerosis Collaborators, 2019). We did find an increase in the incidence of MS in the county of Telemark over time. The yearly incidence rate was $8.2/10^5$ in the first five-year interval (1999-2003), increasing to 13.9/105 in the last five-year interval (2014-2018). In the two middle five-year intervals, the yearly incidence rates were approximately stable, $11.8/10^5$ (2004-2008) and $11.1/10^5$ (2009-2013).

The publications reporting increased incidence over time often point to the increasing female/male ratio as an explanation (Magyari and Sorensen, 2019). A study from the Danish Multiple Sclerosis Register reported that the incidence of MS in women has more than doubled over the last 60 years (Koch-Henriksen et al., 2017). We found an increase in incidence rates for both genders when comparing the first and last five-year intervals. For women, the increase was $11.0/10^5$ (1999-2003) to $17.6/10^5$ (2014-2018), while for males the corresponding increase was $5.4/10^5$ to $10.2/10^5$. The female proportion in the prevalence cohorts, however, slightly increased from 63.8% in 1999 to 67.5% in 2009.

Incidence rates will also change if there is a change in the diagnostic criteria of a disease. The diagnostic criteria of MS have been evaluated and re-evaluated several times during the years from 1999 until 2019. The current McDonald 2017 diagnostic criteria allows a diagnosis of MS in persons previously classified as having clinically isolated syndrome (Thompson et al., 2018a).

Changes in environmental factors may also explain the increase in incidence. For example, improved hygiene and an increase in childhood obesity are two potential risk factors with increasing occurrence in the general population (Alfredsson and Olsson, 2019). Smoking, a known risk factor for MS on an individual level, is however decreasing in the general population. According to Statistics Norway, the proportion who smoke regularly has decreased from 32% in 1999 to 12 % in 2018, although this is not fully reflected in the observed incidence and prevalence estimates of MS in our study.

The prevalence results in Telemark seemed to be the highest found in Norway, but in a paper Willumsen et al. published only weeks before paper I of this thesis, an all-time high prevalence of $335.8/10^5$ was reported as of January 1st 2018 in the County of Møre and Romsdal (Willumsen et al., 2020). This result is also in accordance with the earlier publications on the prevalence of MS in Norway, where mid-Norway, which includes Møre and Romsdal, has the highest crude prevalence estimates (Berg-Hansen et al., 2014).

Socioeconomic status and susceptibility of MS.

MS is more prevalent in the wealthier countries, and there has been a long-standing theory that MS is a disease of affluence (Moghaddam et al., 2021). Several studies have shown an increased risk of developing MS in countries or areas with higher socioeconomic status, but the results are conflicting (Goulden et al., 2015).

To investigate the susceptibility of MS, one should ideally perform a prospective study, but the studies that include socioeconomic factors' impact on the risk of MS are mostly case-control studies (Dobson et al., 2020, Pakdel et al., 2019, Abdollahpour et al., 2018, Goulden et al., 2016b, Magyari et al., 2014).

We performed a retrospective analysis, and for the calculations of prevalence, we did not have a control group. However, we soon became aware of a pattern concerning a high number of pwMS from the rural parts of Telemark. As a consequence, we evaluated the prevalence and incidence according to municipality, sub-grouped in urban and rural areas. For the latter, we used the governmental index of centrality, classifying municipalities according to the number of service

functions (including health care) and work places a resident can reach within 90 minutes by car (Høydahl, 2017). This has never been done in previous prevalence or incidence studies of MS in Norway.

Next, we compared the 2019 rural prevalence of MS with the 2019 urban prevalence of MS. We found a significantly higher age-adjusted prevalence in rural areas ($316.2/10^5$) compared to the age-adjusted prevalence in urban areas ($250.4/10^5$). The significant difference was only seen in the female gender. There were no significant differences in mean age for the study population in rural versus urban areas. It is, however, interesting to note that after adjustment to the European standard population, the crude prevalence in urban areas remained approximately unchanged, and in the rural areas, the adjusted prevalence was lower than the crude prevalence ($316/10^5$ vs $322/10^5$), which again reinforces the need for age-adjustment to be able to compare, as the age-distribution in rural areas may seem to be different from the urban age distribution.

Previous publications discussing differences in the rural and urban prevalence of MS have results contradicting to ours. For example, Daltrozzo et al. published a prevalence study from Bavaria, Germany in 2018. When investigating the regional distribution, they found that the urban areas were associated with a higher prevalence than partially urbanised and rural areas. The Bavarian study used a definition of rural and urban areas by measures of density of population. The authors explained the observed difference in accordance with better access to health care providers in urban areas, including access to neurologists and MRI-scanners (Daltrozzo et al., 2018). In another study, presented by Becks et al. in 2005, a lower prevalence of MS was found in more provincial areas of Canada. This study discussed whether the provincial differences are explained by environmental factors, among them socioeconomic status. The region of Quebec was claimed to be the province with the largest proportion of inhabitants with a low income, as well as the region with the lowest prevalence of MS (Beck et al., 2005). A study from Finland also observed differences in prevalence between regions, describing a pattern of higher prevalence in the bigger cities. This study also concluded that better access to health care in the bigger cities was a possible explanation (Pirttisalo et al., 2019). A pattern of higher prevalence in urban rather than rural areas was even described in studies dating further back, as (Beebe et al., 1967) and (Lowis, 1990) from the US. Even though the studies above discuss different environmental factors as risk factors for MS that particularly affect urban dwellers, most of them concluded that the differences are more likely due to the lower access to specialised health care services in rural areas (Roddam et al., 2019).

There has, however, been some evidence for the opposite conclusion. Marcoci et al., for example, have shown a higher prevalence in the rural areas of Moldova, when comparing with the prevalence

in the country as a whole. They state that both environmental and ethnic factors may play a role (Marcoci et al., 2016). Conradi et al. performed a case-control study in MS populations from Berlin, Germany, where they aimed to identify childhood environmental factors that could be associated with MS later in life. They hypothesised that growing up in rural areas would mean greater exposure to infections, due to more frequent contact with pets and less sanitary equipment. Their results, however, were contrary to what they expected: Growing up in rural areas was associated with an increased MS risk. The publication concluded that the rural–urban comparison must not be taken as a proxy for the hygiene hypothesis and argued that a search for other explanations is needed (Conradi et al., 2011).

Interestingly, the trend of higher incidence of MS in rural areas in Norway was already outlined in a paper by Swank in 1952. In his paper, dietary factors are highlighted as a possible explanation for the high incidence. He postulated that areas of Telemark, among others, were "farming and dairy areas" (…) and the food markets "relatively isolated by mountains and fjords" (Swank et al., 1952). Today, the isolation of the food markets is no longer an issue, and the selection of goods in stores in Norway is similar in all parts of the country. In fact, the surveys of living conditions in Norway, performed by Statistics Norway, show no significant differences in the intake of fish/seafood or milk products between urban and rural areas in Telemark. The fact that Telemark is geographically characterised by mountainous areas has, however, raised the question whether the finding of a high prevalence in this county, especially in the rural areas, can be evidence of the vitamin D/sunlight theory. Apart from one small exception, however, there is no reason to believe that there are differences in sunlight exposure between the different areas of Telemark. It is nevertheless interesting to note that one of the largest rural municipalities (Tinn) is surrounded by high mountains and its inhabitants are not exposed to sunlight for almost half of the year. The size of the population of Tinn is, however, too small to base any further arguments for this.

In a previous study from Norway, non-western immigrants had a lower crude and adjusted prevalence estimate compared to the total population (Berg-Hansen et al., 2015). The same pattern is also described in other countries (Evans et al., 2013, Pugliatti et al., 2002). Statistics Norway confirms that the proportion of the population with a non-Western background is 4.1 % in the rural areas and 6.4 % in the urban areas of Telemark, but this difference can only partly explain the higher rural prevalence of MS in our study. As previously argued, smoking is a known risk factor of MS (Hedström et al., 2009) and according to Statistics Norway, there are differences in the proportion of daily smokers between urban (11%) and rural (15%) areas. Statistics Norway also presents data showing that people with lower levels of education represent a higher proportion of smokers, and this reveals an important association between smoking and socioeconomic status.

It is worth noting that Statistics Norway reports an overall higher life-expectancy in rural municipalities compared to urban municipalities in Telemark. In 2020, the mean life-expectancy in Skien (an example of an "urban" area of Telemark) was 81.0 years for men and 83.2 years for women. In Vinje (an example of a "rural" area of Telemark) the respective ages were 83.0 years and 86.9 years. A shortcoming in our study is thus that we have not performed incidence calculations according to the centrality index (urban/rural areas). This is a consequence of a low absolute number of new pwMS per year related to municipality, even in five-year intervals.

Whether regional differences in prevalence can be partly explained by socioeconomic conditions has not previously been explored in MS research in Norway. In Norway, there is no tradition of using residence in itself as a measure of socioeconomic status. Even in small, well-defined geographical areas in Norway, there will be a wide spread of the traditional measures of socioeconomic status, such as household income. Residency can, however, be a proxy for other socioeconomic measures, particularly level of education, which is generally lower in the more rural areas of Norway. This is presented in section 6.1 showing differences between the counties of Buskerud, Oslo and Telemark. However, these geographical areas are too large to represent a defined region of interest. With the exception of the largest cities, we maintain that area deprivation indices are not a suitable method for grouping socioeconomic status in Norway. We, consequently, cannot conclude that there are socioeconomic differences that can fully explain the different prevalence between rural and urban areas of Telemark. We do, however, conclude that our results reinforce the hypothesis of a possible association between level of education and the risk of MS.

There has been some attention given to the susceptibility of MS associated with level of education in previous research. In a Danish cohort, individuals had a reduced rate of MS later in life if, at 15 years of age, their maternal level of education was greater than the secondary school level, compared with individuals whose highest maternal education was primary school (Nielsen et al., 2013). Another study from California, US, has shown independent effects of adverse childhood and adulthood SES on risk of MS, even after accounting for known heritable factors, other established environmental risk factors and family history of MS (Briggs et al., 2014). Furthermore, a multinational study from 2016 shows no consistent association between parental SES measures, such as level of education, and MS risk in Norway, Canada and Italy, with a protective effect of low SES only found in Canada (Goulden et al., 2016a).

The arguments for regional differences in prevalence rates between rural and urban areas often highlights better access to the health care system in the urban areas as an explanation. We, nevertheless, find it difficult to compare the access to health services between different areas in

Norway in real life. The distance to a hospital is one factor that may have an impact on the availability of diagnosis. The people from the most rural parts of Telemark have a more than three-hour drive to see a neurologist. That said, health care services, including treatment, are free of charge after a small deductible fee in Norway, and while there is only one department of neurology in Telemark, this secures equal access to a specialist for all inhabitants in the county, despite the large difference in distance to health care providers. These are factors that can conceivably influence the access to health care despite the greater distance to health services in the rural areas of Telemark.

Health literacy.

In the further discussion of socioeconomic factors' influence on different aspects of MS, we will refer to the concept of health literacy, as introduced in section 3.8.3. Health literacy is a construct that includes the capacities of people to meet the complex demands of health. Figure 19 shows different aspects of personal characteristics with an impact on health literacy.

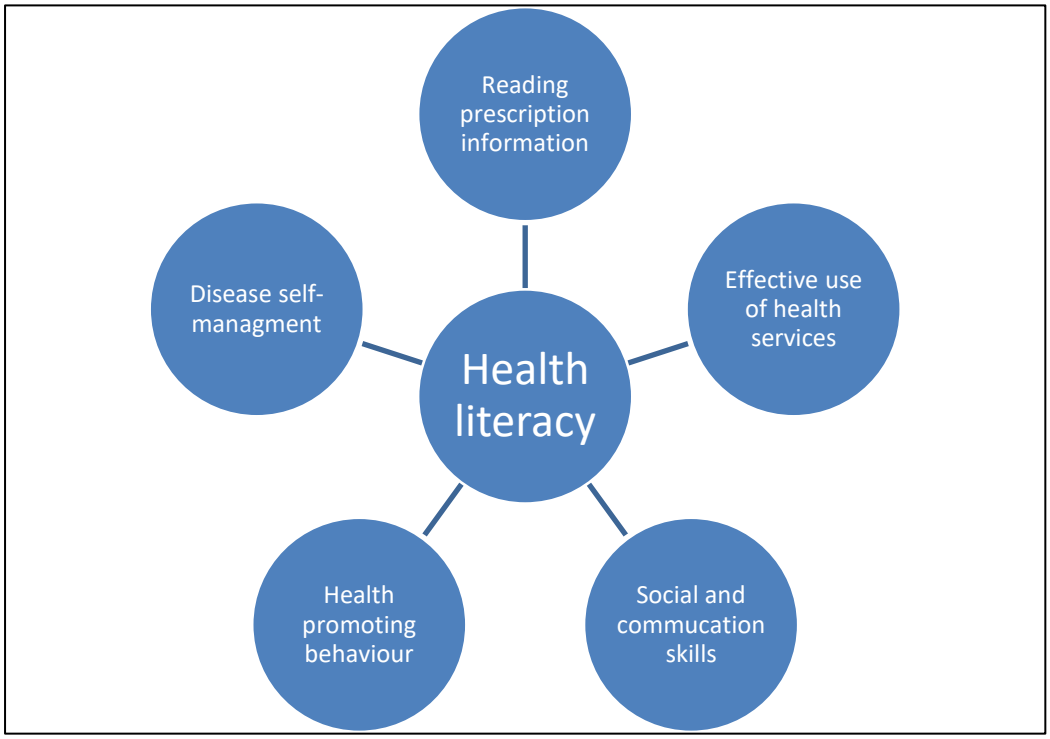


Figure 19: Different aspects of health literacy.

Governments around the world place great value on achieving high levels of health literacy in their populations, as this is associated, both directly and indirectly, with a range of health outcomes (Nutbeam and Lloyd, 2021). Health literacy is not a fixed asset but can be improved and is a governmental responsibility and focus (Sorensen et al., 2015). In an effort to understand the parental

influence on health outcome in later life, it is tempting to suggest that the individual's health literacy is taught by parents from the start of life. The ability to take care of one's own health concerns questions such as the following: What do you do when you feel unwell? Which symptoms should be given attention? With whom do you share your worries? What do you do if you are affected by a disease? Do you trust the health care system? Will you follow the advice given by your neurologist? Health-related behaviour is thus adopted from parents in childhood and will be reflected in the person's later life (Gunnarsdottir et al., 2017).

Socioeconomic status and progression of MS

The aim of paper II was to investigate if socioeconomic status (SES) in adolescence influences disease progression in later life. The reason for using SES in adolescence is the traditional perception that since MS usually occurs at a younger age, the disease can impair the cognitive performance for years prior to symptom onset. As a consequence, the pwMS' own level of education may be affected, and thus this may not be an accurate measure of their SES. Cortese et al. have shown that the men who later develop MS perform significantly lower than controls in the intelligent quotient tests at the conscription examination at age 18 -19 years (Cortese et al., 2016), although this study is on men only. A study from our BOT-cohort, which included both genders, has shown that there was no significant difference in days of absence or grades achieved in upper secondary school in the four years leading up to disease onset in MS cases compared to a control group (Simonsen et al., 2021b). This is, however, an investigation of school achievements, but not the highest achieved level of education in itself. In paper II we present the level of education in the background population of the three counties of BOT-MS compared with the level of education of the included pwMS, and we concluded that our MS population and the background population had a similar level of education, including when the known correlation between parental and individual level of education was taken into account (Weinberg et al., 2019). We, consequently, included both parental and individual levels of education in the further analysis of the impact on progression measured as MSSS. We are, however, aware of that the similar level of education between our pwMS population and the background population can be a result of selection bias, as people with a higher level of education are more likely to participate in studies (Reinikainen et al., 2018).

Previous studies dealing with SES and the progression of MS have used self-reported patient outcome measures (Boorgu et al., 2022, Gray-Roncal et al., 2021) or time to EDSS 4 and 6 (Calocer et al., 2020, Harding et al., 2019b, D'Hooghe M et al., 2016) as data. Others have used upper and lower extremity function, cognitive function (Abbatemarco et al., 2022) or optical coherence tomography (Vasileiou et al., 2021). All of these report an association between lower SES and higher degrees of disease progression measures. A strength in our study is the completeness of the data in the cohort

for disease courses, as we have registered as many EDSS as we could find and validate this from the electronic journal systems. Consequently, we could use a different presentation of clinical outcome measure as markers of disease progression. We calculated the change in EDSS from diagnosis to year five after diagnosis and divided the pwMS into four subgroups according to the change in EDSS, where an increase in EDSS by more than 2 points was labelled as marked progression, an increase by 1-2 points was labelled as moderate progression and a change +/- 0.5 points was labelled as stable disease. Finally, a reduction of EDSS by 1 point or more was considered as improvement. We also used time to EDSS 6 and, finally, we calculated the MSSS at a prevalence date in January 2018.

We found a significantly higher degree of disease progression in pwMS whose maternal level of education was limited to primary school, whereas pwMS whose mothers completed graduate level education more often displayed improvement in EDSS by year five. Paternal level of education showed a similar pattern, but did not reach statistical significance. The association of progression with pwMS' own level of education showed the same patterns as those for maternal level of education. Centrality of municipality was not significantly associated with progression, neither at age 16, nor at prevalence date. Moreover, we found that the persons with an improvement of EDSS at year five had a mean age of 35 years at diagnosis, whereas those with a marked progression of EDSS at year five had a mean age of 45 years at diagnosis. This corresponds with previous research (Langer-Gould et al., 2006).

Some of the previous studies on SES and progression of MS have used time to different milestones in the disease course. An EDSS of 6 is the state in which the pwMS is in need of a crutch or a cane to be able to walk more than 100 meters without resting (Kurtzke, 1983). Calocer et al. found that the median time to reach EDSS 6 was 1.5 years less for pwMS in the quintile 5 (most deprived) compared to those in quintile 1 of the distribution of the European deprivation index, an area level measure of SES (Calocer et al., 2020). We used individual measures in our study as we investigated time to EDSS 6 against socioeconomic factors in adolescence and found significant influence only from maternal level of education. The results are convincing: We found a time to EDSS 6 of 28 years (95 % confidence interval 22.7-33.3) if maternal level of education was limited to primary school, and 39 years (95 % confidence interval 35.4-42.6) if maternal level of education was secondary school ($p=<0.001$). The subgroup with graduate level maternal education (15/308) was too small to perform further an analysis on with regards time to EDSS 6.

When evaluating progression using the MSSS in 2018, we found significant associations with the same set of SES variables as those associated with progression measured by the EDSS. We used a linear regression analysis, first performing a univariate, and then a multivariate analysis, before

building the final regression model, in which the included factors explained 11 % of the variance in MSSS. The final model highlighted younger age at diagnosis, female sex, use of DMTs, the pwMS own level of education and the maternal level of education at age 16 as the significantly reducing coefficients for the prediction of MSSS. The influence of the maternal level of education on MSSS was at the same level as that for ever treated with DMT. The beta coefficient in the final model was of equal size (-0.49) for both having a mother with a graduate level of education and being ever treated with DMT. We have not found any other publications evaluating MSSS against socioeconomic variables.

The impact of parental level of education on their off-spring's health is seen in many other studies in different parts of medical research. In a systematic review presented in Lancet in 2021, lower parental education represents a significant increase in risk of child mortality, even after controlling for other markers of family socioeconomic status (Balaj et al., 2021). It is claimed that the link between education and child mortality is one of the strongest relationships established in public health (Gakidou et al., 2010). Most studies focus on the maternal level of education, but the lack of evidence for the association with paternal level of education may be due to a lower number of publications addressing this question (Balaj et al., 2021). Different pathways have been hypothesised, linking education to maternal and child health including socialisation, skill building, information provision and delays in childbearing (Mensch et al., 2019).

Why is parental education important for child outcome? Proposed causal pathways include the improved knowledge and greater economic resources that accompany education (Lundborg, 2012). This is understandable in the measures of health during childhood. Why parental education is important for health outcomes in later life is more possibly a question of their influence on the individuals' health literacy, as discussed in a section above. When it comes to MS in particular, it is conceivable that parents exert an influence on known risk factors for the disease, as well as risk factors for disease progression, such as ensuring healthy diet (vitamin D) and lifestyle (training), and by avoiding obesity.

For the progression of MS, in addition to the impact on health literacy, parental influence may be mediated by general support from close relatives. Wilski et al. showed that receiving adequate support from close relatives and having larger available socioeconomic resources are the strongest predictors of self-management in MS (Wilski et al., 2015).

Socioeconomic status and access to disease-modifying treatment

In paper III we have attempted to evaluate the access to disease-modifying treatment (DMT) in the BOT-cohort.

When analysing the access to treatment, it is important to keep in mind the history of the use of DMTs in MS. The first DMT for RRMS became available in Norway in 1997. The development of new DMTs for RRMS over the years has given us an increasing number of treatment alternatives, and there has been a rapid change in treatment algorithms. When the first DMT became available, the group of untreated pwRRMS (people with relapsing remitting MS) consisted of both newly diagnosed and people who had lived with a diagnosis of MS for many years. The latter group included a heterogeneous population of which some showed evidence of ongoing inflammatory activity and were, as such, also qualified for DMT. Consequently, there was a large variation in time from onset to commencing DMT. In the first years of the treatment era, the initiation of treatment was based on less evidence than today – and the choice of initial DMT was influenced by preferences and experience, personal knowledge and attitudes in both the clinicians as well as the pwMS (Giovannoni et al., 2016). Over the years, many countries have developed national treatment strategies, with a focus on securing equality in treatment. However, the national reimbursement guidelines vary between countries and place different restrictions on prescriptions. Consequently, the international comparison of access to treatment is challenging.

One of the aims of paper III was to examine if socioeconomic factors have an impact on the access to treatment for participants in the BOT cohort. The BOT-cohort includes data from pwMS diagnosed within the recent decennials, and both the number of available drugs and the treatment strategies have varied over these years. As a consequence, it was difficult to assess the impact of socioeconomic factors on the access to DMT for the entire time period. To adjust for this, we have performed some of the analysis on subgroups according to the year of diagnosis.

We found that the proportion of pwMS treated with DMT, as well as the proportion starting with a high efficacy DMT as a first treatment, have increased over the last two decades. Among pwMS diagnosed before 1997, less than 40 % have ever been treated with a DMT, whereas of those diagnosed between 2012 and 2017, more than 80 % are or have been treated with a DMT. We documented that the mean time to start DMT after diagnosis has decreased significantly over the years, from 111 months (SD 80.4) for those diagnosed before 1997 to 3 months (SD 5.6) for those diagnosed between 2012 and 2017. We found that the proportion treated with high efficacy DMT as a first drug has increased, but only after 2012. This is in accordance with an increasing amount of evidence supporting early high efficacy DMT to better outcome (Simonsen et al., 2021a, Harding et

al., 2019a, He et al., 2020). Even though the effect of starting high efficacy early has been known for some years, there is a large variation in the degree of compliance in clinical practice. In a study from the Swedish and Danish National MS registries, differences in treatment strategies for RRMS and the consequences for disability outcome are shown at national levels. The use of more efficacious DMT as an initial treatment, as the Swedish strategy entails, was associated with better outcome (Spelman et al., 2021). In the updated version of the national treatment strategy for MS in Norway, published in September 2022, it is emphasised that a high efficacy treatment should be used first, if there are no contraindications (Norwegian Directorate of Health, 2022).

Previous studies have argued that people from less-deprived areas have a less severe form of disease and shorter time from onset to diagnosis, which again makes them more suitable for a DMT (Owens et al., 2013). It has been suggested that persons with lower SES have more difficulties in communicating their needs, impeding shared decision making (van Ryn and Burke, 2000). However, most of these studies have used area-level measures of SES, with the risk of missing individual level variation within the same area (Reyes et al., 2020).

When evaluating the access to DMT in our cohort, we used level of education, an individual-level measure of SES, and found a tendency for more DMT among the highly educated in the historical cohort, both when measuring the level of education for pwMS and their parents. This could be explained by higher health literacy in this subgroup of pwMS with the highest levels of education. The choice of DMT should be discussed collaboratively by the pwMS and their treating clinician, where the risk, benefits and personal factors must be considered, resulting in shared decision making (Giovannoni et al., 2016, Scolding et al., 2015). For the ever-treated subgroup, we found a lower EDSS at diagnosis compared to participants who had never been treated. We attribute this pattern to cautious prescribing practices among neurologists in the early days of DMT.

When we investigated the most recently diagnosed MS population separately (from 2012 to 2017), the associations between access to treatment and SES disappeared. This is an interesting and gratifying result. It is possible that the focus on national treatment strategies secured a more equal treatment in the MS population. However, the group treated with DMT is still younger and has a shorter time from onset to diagnosis than the not-treated group.

A potential confounding factor for the choice of DMT in MS is comorbidity. PwMS with other autoimmune diseases or a history of cancer are subject to specific recommendations or even contraindications to DMTs. Consistent with previous reports (Chouhfeh et al., 2015), we did not find any influence of other autoimmune disease on any treatment strategies.

The further focus in paper III was to perform a comparison of the pwMS treated with a high efficacy DMT as a first drug with those treated with a moderate efficacy DMT as a first drug. Calocer et al. performed a study on the association of SES and the delay in accessing a second-line (=high efficacy) DMT in persons with RRMS in France. The main strategy in this population was the escalation treatment strategy, and, therefore, this addresses the time between starting a first-line DMT and a second-line DMT. The conclusion of the Calocer study was that a high SES may facilitate access to a second line DMT a few years after the first DMT exposure (Calocer et al., 2020). As we have evaluated access to high-efficacy treatment as the first drug, we cannot compare directly with the Calocer study, and we have not found any other studies addressing SES's impact on access to high-efficacy DMT as the first treatment.

As the first high-efficacy DMT was available in Norway as of late 2006, we used only the data from the pwMS diagnosed after 2006 for this part of the study. We did not find any signals indicating that high SES facilitates high efficacy treatment as first. We did, however, find an inverse impact on the level of education, where the pwMS with the lowest degree of educational achievements have a higher proportion of high efficacy treatment as a first drug. Moreover, there are fewer married pwMS in the high efficacy treatment as first group. Finally, median household income is significantly lower in the subgroup with high efficacy DMT as a first treatment. Nevertheless, the differences in median household income and marital status are not significant in pwMS diagnosed between 2012 and 2017. The EDSS was higher among the pwMS receiving high efficacy treatment as a first treatment. This is in line with previous findings (He et al., 2020). It is likely a sign of a more severe disease at diagnosis and, consequently, more active treatment from the start.

When analysing the impact of the disease course and SES on high efficacy treatment as of first DMT, we performed a regression analysis. We found a higher odds ratio (OR) for receiving high efficacy treatment as the first DMT for people with an EDSS at diagnosis of 3 or more compared to those with an EDSS of 0-1.5. This is also in line with previous results (He et al., 2020). The level of one's own or parental education did not significantly influence the OR of receiving a high efficacy treatment as a first drug. We did, however find some signs of the opposite effects of SES. The OR for high efficacy treatment as the first drug was lower with increasing quartiles of household income. This difference disappeared when analysing only the subgroup diagnosed in 2012-2017. We also found that persons with self-perceived excellent overall health status had a higher OR for high efficacy treatment as a first DMT compared to the group with self-reported fair or poor health. This may be seen as a tendency to treat persons with better general health more often and more effectively.

Finally, paper III showed that the time to initiation of high efficacy treatment was not influenced by the level of education. We did, however, find that the median time to high efficacy treatment for persons living in rural areas was 12 months (95 % CI 6.9-17.1), significantly lower compared to 40 months (95 % CI 30.1-49.9) for those living in the most central areas. Time to high efficacy treatment also increased with increasing household income. The other measures of SES did not reach significance on time to treatment. Once again, we must conclude that this is probably due to a more severe disease at diagnosis for the persons with lower SES.

The time to treatment can be measured as time from onset, or time from diagnosis. We have used the time from onset for our calculations. Both of these time-frames are, however, possible to decrease, and should be kept as short as possible for bettering the long term prognosis (Giovannoni et al., 2016, Simonsen et al., 2021a). The time from onset to start of treatment presupposes a special health service with a high efficacy diagnostic routine. The delay from symptom onset to diagnosis is steadily decreasing, as documented already in 2005, when Marrie et al. showed that the diagnostics were 10 times more rapid than in 1980 (Marrie et al., 2005). To keep the time from onset to diagnosis as low as possible, there is also a need for an awareness of MS among the general public and among the clinicians in primary care who refer persons under suspicion of MS to adequate health care (Giovannoni et al., 2016). This is reinforced by the results in paper II where we found a shorter time from onset to diagnosis in the group with higher educated mothers.

Another interesting observation in paper III is the differences in the self-perceived overall health status. This parameter was collected by the BOT-questionnaire. We found significant differences in the subgroup never treated and ever treated with a DMT. In the subgroup ever treated, 15.3 % scored their own health status as fair or poor, whereas the proportion was 20.8 % in the group never treated. On the other hand, in the treated subgroup, 14.8 % ranged their health-status as excellent, compared to 9.7 % in the never treated subgroup. These differences can, in part, be explained by the differences in mean age in the two groups, as the never treated subgroup is an average of 13 years older than the treated subgroup. An alternative explanation is the fact that the quality of life will decrease as the disease advances (Giovannoni et al., 2016).

Now what? Is evening out social differences a task for the health care system?

When considering the results of paper II and paper III together, we must admit it is disheartening to see that pwMS with lower levels of socioeconomic status are at higher risk of a rapid progression, regardless of the adequate access to high efficacy DMT.

Access to disease modifying treatment does not necessarily equal a proper use of treatment. In low-income persons discontinuing medications, 40 % reported a lack of symptom improvement as the reason. This implies an inadequate understanding of the purpose of these medications, whose goal is primarily to reduce the frequency of relapses and slow the progression of disability, not to ameliorate present symptoms (Shabas and Heffner, 2005). If the DMTs are taken incorrectly, a poorer effect may occur. A major part of the high-efficacy DMTs for use in Norway in this cohort are those given intravenously (natalizumab and alemtuzumab), where compliance, as a consequence, is most often secured by an appointment at the hospital. However, the prescription of oral DMT is dependent on good compliance by the individual pwMS at their homes. The ability of the individual pwMS to follow all advices to improve the prognosis, such as physical exercise, cognitive training, no smoking and an adequate intake of vitamin D, will depend on the individual's health literacy.

As health care providers, we must focus on reducing inequalities in health. As a society, we must focus on reducing the gap between the different parameters of SES that potentially influence the health status. Figure 20 shows different areas in society where an effort can be made to equalise differences in health.

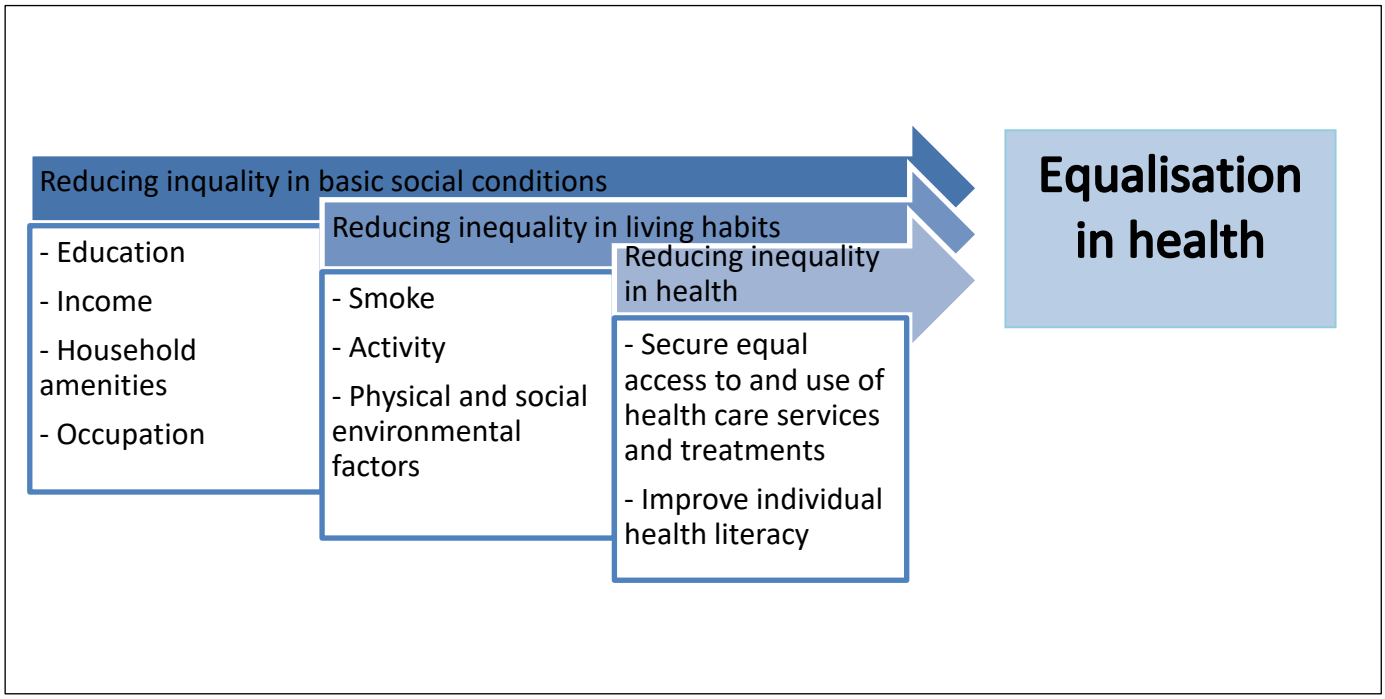


Figure 20: Different areas of focus to reduce inequality in health*. Figure based on figure 1 from "Folkehelserapporten 2014" – "Public health report" (Norwegian Institute of Public Health, 2014)*

In 2007, the Minister of Health, Sylvia Brustad, presented a national strategy to reduce health inequalities (Report No. 20 to the Storting (2006-2007), 2006-2007). The main aim of this strategy was to reduce the inequality by focusing on health behaviour, use of health services, integration and general public education. The strategy emphasised that the effort must be made on all administrative levels (Strand and Næss, 2007). However, it took five years from the presentation of the national strategy before the Act on Municipal Health Care Service (§§1-2) was revised. As of 2012, it specifically states that all administrative levels have a legal responsibility to improve public health, including reducing social inequalities in health (Bekken et al., 2017, Act on Public Health work, 2012).

A Norwegian study published in JAMA, examined the association between household income and life expectancy in Norway between 2005 and 2015. The trend showed an increasing gap in life expectancy by income level. Moreover, the gap between the lowest and highest income quartiles was increasing in both genders, from 2.5 years in 2005 to 6.2 years in 2015 for women and from 6.2 years to 8.,4 years, respectively, for men (Kinge et al., 2019).

We obviously have a ways to go. Suggested strategies for reducing inequalities in health in the US includes reducing income inequalities, strengthening social insurance programmes and increasing the access to health services (Adler et al., 2016). In the European Review of Social Determinants and the Health Divide, the following is stated: *"If a country has made little progress on social policies that would advance health equity, do something. If further along, do more. And if you are (Sweden or) Norway, do better"* (Marmot, 2017).

10. FUTURE PERSPECTIVES

Despite the growing recognition of the impact of social determinants on health, little progress has been made towards addressing these determinants in pwMS (Dobson et al., 2022).

This thesis shows that the prevalence of MS is even higher in the rural areas compared with the urban areas of Telemark. We found that socioeconomic status had an impact on the progression of the disease, and that more deprived pwMS are at risk for a more pronounced progression. This pattern contrasts with the result of no influence of SES on the access to disease-modifying treatments in contemporary pwMS.

There is good reason to expect that socioeconomically disadvantaged pwMS are at greater risk of disability than those less deprived with the disease. This is an example of social inequality in health. From a larger perspective, this is an opportunity for future work, as we can focus on SES as a modifiable risk factors on a populational level (Hillert, 2020). The challenge is, however, to find effective interventions targeting social determinants of health that have substantial effects on MS outcomes (Dobson et al., 2022).

The BOT group will continue to follow this geographically well-defined and complete population and include newly diagnosed pwMS. The cohort will be expanded by including the neighbouring county of Vestfold.

We will be able to repeat the estimation of the prevalence of MS by centrality indices in the expanded group. This will reveal important information and add another piece to the puzzle of socioeconomic status influence on the risk for development of the disease.

By using data from Statistics Norway, we can continue to search for associations between different measures of SES and the disease course. This work will identify individual parameters associated with increased risk for disease progression, as the term “personalised treatment” can be expanded to include different strategies for improving the individual’s health literacy.

11. CONCLUSION

The following conclusions may be drawn from this thesis:

- The Norwegian county of Telemark is a highly prevalent area for MS, the prevalence as of January 1st 2019 was 260.6/10^5.

- The prevalence of MS is even higher in the rural areas of Telemark; in 2019 the prevalence rates were 250.4/10^5 in urban and 316.2 /10^5 in rural areas

- High maternal level of education when pwMS' were aged 16 was significantly associated with less pronounced disease progression measured by MSSS, younger age and lower EDSS at disease onset, and shorter time from onset to diagnosis.

- Maternal level of education has an impact on disease progression in later life similar to that of disease modifying treatment.

- The pwMS treated with DMT was younger at onset, had shorter time from onset to diagnosis and lower EDSS at diagnosis.

- The subgroup treated with a high efficacy DMT as a first drug was younger and had 0.5 point higher EDSS score than those not treated with a high efficacy DMT as a first drug.

- Level of education, household income and marital status were inversely related to access to high efficacy DMT as first drug.

- We describe a change over time to the current pattern where the pwMS are treated equally with DMT in terms of different measures of socioeconomic position.

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ERRATA

Page	Line	Original text	Corrected to
15	7	including suggestion a hereditary pattern	including suggestion of a hereditary pattern
26	3	In addition to a through neurological examination	In addition to a thorough neurological examination
28	6	protein and glucoses	protein and glucose
28	25	advantage of thee IgG index	advantage of the IgG index
38	7	overlap of MS loci that of other autoimmune disease loci	overlap of MS loci with that of other autoimmune disease loci
47	47	The risk of disability progression increases with at higher age at onset influence the risk of disability increase with higher age at onset	The risk of disease progression increases with a higher age at onset
57	8	clinical support-tool	clinical support-tools
61	16	he tries to call for action to prevent further development	he called for action to prevent further development
68		influenced is by place of residency	influenced by place of residency
91	6	the Pearson chi-square tests of the Fisher exact test	the Pearson chi-square tests or the Fisher exact test
101	28	To be emphasised in the discussion will probably depend on several factors	To be emphasised in the discussion, this will probably depend on several factors
116	22	for pwMS in quintile 5 (less deprived	for pwMS in quintile 5 (most deprived)
123	8	public heath	public health

APPENDIX

- Expanded disability status scale (EDSS) full-text
- The BOT MS questionnaire
- Paper I, II and III

Rating neurological impairment in multiple sclerosis Score, EDSS.

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Functional systems (FS)

Pyramidal Functions

0. Normal.
1. Abnormal signs without disability.
2. Minimal disability.
3. Mild or moderate paraparesis or hemiparesis; severe monoparesis.
4. Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia
5. Paraplegia, hemiplegia, or marked quadriparesis.
6. Quadriplegia.

Cerebellar Functions

0. Normal.
1. Abnormal signs without disability.
2. Mild ataxia.
3. Moderate truncal or limb ataxia.
4. Severe ataxia, all limbs.
5. Unable to perform coordinated movements

Brain Stem Functions

0. Normal.
1. Signs only.
2. Moderate nystagmus or other mild disability.
3. Severe nystagmus, marked extra& weakness, or moderate disability of other cranial nerves.
4. Marked dysarthria or other marked disability.
5. Inability to swallow or speak.

Sensory Functions

0. Normal.
1. Vibration or figure-writing decrease only, in one or two limbs.
2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs.
3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs.
4. Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs.
5. Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head.
6. Sensation essentially lost below the head.

Bowel and Bladder Functions

0. Normal.
1. Mild urinary hesitancy, urgency, or retention.
2. Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence.
3. Frequent urinary incontinence.
4. In need of almost constant catheterization.
5. Loss of bladder function.
6. Loss of bowel and bladder function.

Visual (or Optic) Functions

0. Normal.
1. Scotoma with visual acuity (corrected) better than 20/30.
2. Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59.
3. Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99.
4. Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100 to
5. 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less.
6. Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less.
7. Grade 5 plus maximal visual acuity of better eye of 20/60 or less.

Cerebral (or Mental) Functions

0. Normal.
1. Mood alteration only (Does not affect DSS score).
2. Mild decrease in mentation.
3. Moderate decrease in mentation.
4. Marked decrease in mentation (chronic brain syndrome – moderate).
5. Dementia or chronic brain syndrome-sever or incompetent.

Other Function

0. None.
1. Any other neurologic findings attributed to MS (specify)

Expanded Disability Status Scale EDSS)
0 = Normal neurologic exam (all grade 0 in Functional Systems [FS]; Cerebral grade 1 acceptable).

1.0 = No disability, minimal signs in one FS (ie, grade 1 excluding Cerebral grade 1).

1.5 = No disability minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).

2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 = Moderate disability in one FS (one FS grade 3, others 0 or l), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).

4.0 = Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or l), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters.

4.5 = Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.

5.0 = Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (eg, to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)

5.5 = Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0.)

6.0 = Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

6.5 = Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

7.0 = Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in w/c some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4 +; very rarely, pyramidal grade 5 alone.)

7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+)

8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4 + in several systems.)

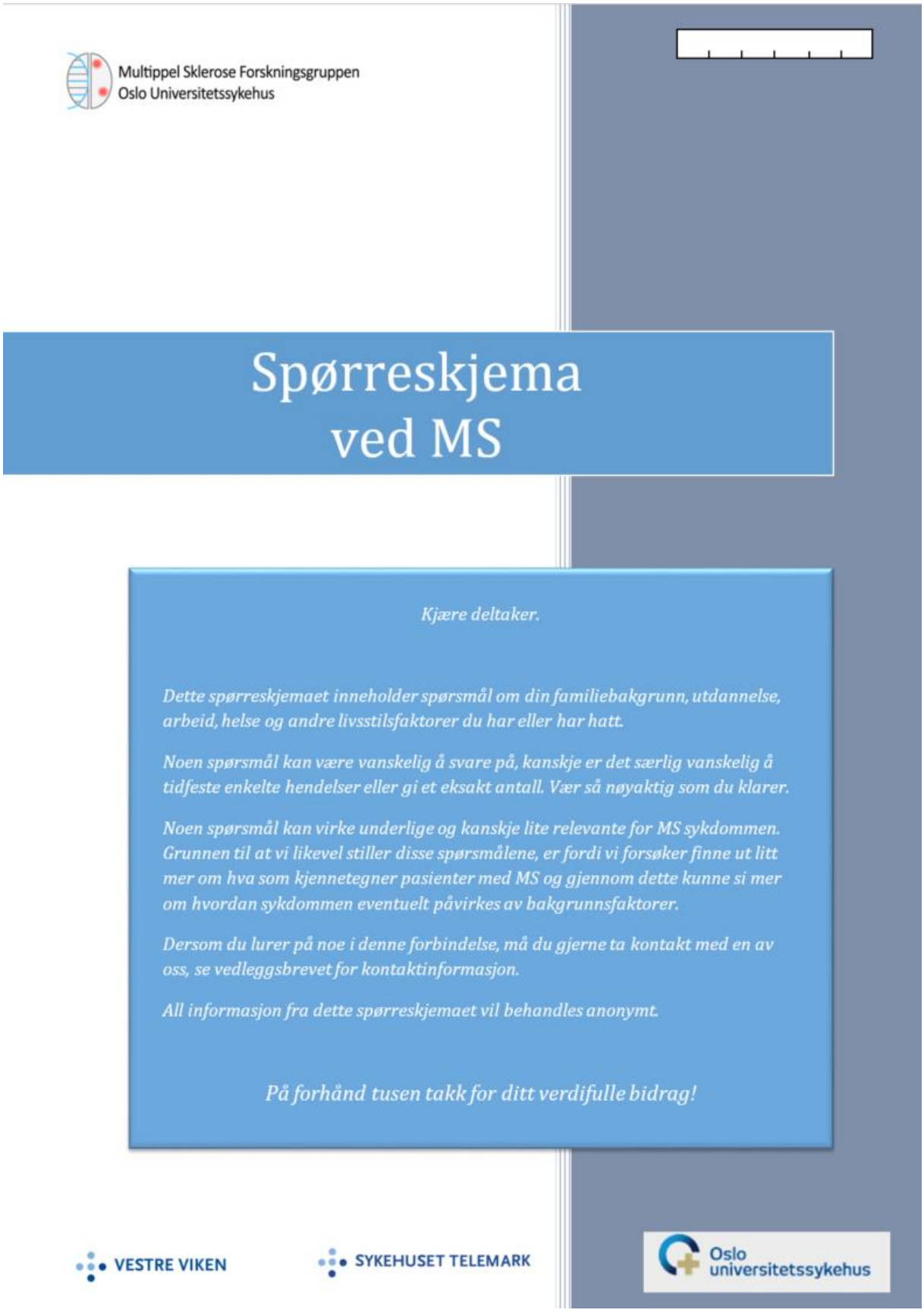
8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4 + in several systems.)

9.0 = Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4 +)

9.5 = Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4 +)

10. = Death due to MS

The BOT MS questionnaire:



Dato for utfylling: ☐☐☐☐☐☐

Personopplysninger

1. **Kjønn:**

   ☐ Kvinne

   ☐ Mann

2. **Fødselsmåned:** *(skriv 01 for januar, 02 for februar osv.)* ☐☐

3. **Fødselsår:** ☐☐☐☐

4. **Er du født i Norge?** ☐ Ja ☐ Nei

   - Hvis nei, i hvilket land? _____

5. **Hvis du ikke er født i Norge, hvilket år kom du til landet?**
   (Angi årstall) ☐☐☐☐

6. **Fødeland biologiske foreldre og besteforeldre**:

6.1 Er din **mor** født i Norge? ☐ Ja ☐ Nei

   - Hvis nei, i hvilket land? _____

6.2 Er din **far** født i Norge? ☐ Ja ☐ Nei

   - Hvis nei, i hvilket land? _____

6.3 Er din **mormor** født i Norge? ☐ Ja ☐ Nei

- Hvis nei, i hvilket land? _____

6.4 Er din **morfar** født i Norge? ☐ Ja ☐ Nei

- Hvis nei, i hvilket land? _____

6.5 Er din **farmor** født i Norge? ☐ Ja ☐ Nei

- Hvis nei, i hvilket land? _____

6.6 Er din **farfar** født i Norge? ☐ Ja ☐ Nei

- Hvis nei, i hvilket land? _____

7. Nummer i søskenflokken:
Her skal du angi din plass i søskenflokken, du kan telle inn eventuelle «halvsøsken» og «stesøsken» slik det kjennes riktig for deg.

«Jeg er nr. ☐☐ av totalt ☐☐ søsken.»

8. Sivilstatus
Angi din nåværende sivilstatus

Gift ☐ Ugift ☐ Enke/enkemann ☐
Samboer ☐ Separert/Skilt ☐ Annen sivilstand ☐

Ev spesifiser_____

9. Barn
Har du barn?

Ja ☐ Nei ☐

Hvis ja, hvor mange barn? ☐☐

Utdannelse og arbeid

10. Hvilken utdanning er den høyeste du har fullført?

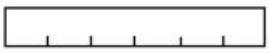
- ☐ Mindre enn grunnskole 7 år
- ☐ Grunnskole 7-10 år
- ☐ Videregående skole 10-13 år
- ☐ Høgskole/universitet 1-4 år
- ☐ Høgskole/universitet mer enn 4 år

11. Betrakter du deg hovedsakelig som yrkesaktiv?

☐ Ja ☐ Nei

12. Hvis *«nei»* i spørsmål 11; hva slag situasjon er du i?

- ☐ Arbeidsledig
- ☐ Skoleelev eller student
- ☐ Alders- eller uførepensjonist
- ☐ Arbeidsuør
- ☐ På arbeidsavklaringspenger
- ☐ Vernepliktig eller sivilarbeider
- ☐ Hjemmearbeidende
- ☐ Annet



13. Hva er ditt nåværende eller tidligere arbeid?
Besvares også om du er trygdet eller pensjonert, sett kryss:

- Leder ☐
- Akademisk yrke (eks. siv.ing, lege, spesialsykepleier, lektor, jurist) ☐
- Høyskoleyrke (eks. ingeniør, sykepleier, radiograf, tannpleier, lærer) ☐
- Kontoryrke ☐
- Salgs- , service- eller omsorgsyrke ☐
- Skogbruker, jordbruker ☐
- Håndverker ☐
- Prosess-, maskinoperatør, montør, transportarbeider ☐
- Renholder, hjelpearbeider (i jordbruk, industri, renovasjon osv.) ☐
- Militært yrke (menig, befal, offiser) og andre yrker ☐

Helse

14. Egenopplevd helse.
Hvordan vurderer du din egen helse sånn i alminnelighet?

- Svært god ☐
- God ☐
- Verken god eller dårlig ☐
- Dårlig ☐
- Svært dårlig ☐

15. Høyde og vekt.

Høyde i dag ☐☐☐ cm Vekt i dag ☐☐☐ kg

16. Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene?

Sett kryss i venstre kolonne om du har/har hatt:		*Angi alder for når sykdommen eventuelt oppsto*
☐	Leddgikt (rheumatoid artritt)	☐☐
☐	Psoriasis	☐☐
☐	Lavt stoffskifte (hypothyreose)	☐☐
☐	Høyt stoffskifte (hyperthyreose)	☐☐
☐	Inflammatorisk tarmsykdom (ulcerøs kolitt, Mb Crohn)	☐☐
☐	Lupus (SLE- systemisk lupus erytematosus)	☐☐
☐	Cøliaki	☐☐
☐	Bekhterevs sykdom	☐☐
☐	Sjøgrens sykdom	☐☐

17. Har du hatt kyssesyke (mononukleose)?

☐ Ja ☐ Nei ☐ Vet ikke

18. Om du svarer *«ja»* på spørsmål 17; hvor gammel var du da du hadde kyssesyke?
Oppgi alder ☐☐

19. Har du hatt en infeksjonssykdom som har krevd sykehusinnleggelse før du fylte 18 år?

☐ Ja ☐ Nei ☐ Vet ikke

20. Fulgte du vanlig vaksinasjonsprogram som barn?

☐ Ja ☐ Nei ☐ Delvis/avbrutt ☐ Vet ikke

Tobakk

21. Har du noen gang bodd sammen med en eller flere personer som daglig har røykt i hjemmet?

☐ Ja ☐ Nei

22. Om du svarer «ja» på spørsmål 21; angi tidsperioder da du har bodd sammen med personer som røyker:

Periode(r)bosatt med røyker	
Fra og med (årstall)	*Til og med (årstall)*
☐	☐
☐	☐
☐	☐

23. Røyker du selv?

Nei, jeg har aldri røykt ☐

Hvis du aldri har røykt, gå videre til spørsmål 24

Nei, jeg har sluttet å røyke ☐

Ja, sigaretter av og til (fest/ferie, ikke daglig) ☐

Ja, sigarer/sigarillos/pipe av og til (fest/ferie, ikke daglig) ☐

Ja, sigaretter daglig ☐

Ja, sigarer/sigarillos/pipe daglig ☐

27. Hvis du svarte ja på spørsmål 26:

Hvor gammel var du da du begynte med snus?	☐	*Alder (år gammel)*
Hvor mange esker/bokser snus bruker/brukte du i måneden?	☐	*Antall bokser/esker*

Alkoholvaner

28. Hvor ofte drikker du alkohol?

Aldri	☐
1 gang per måned eller sjeldnere	☐
2-4 ganger per måned	☐
2-3 ganger per uke	☐
4 ganger per uke eller mer	☐

I de to neste spørsmålene (nr. 29 og 30), brukes begrepet alkoholenhet. På bildet under, vises ulike eksempler på hva som regnes som en alkoholenhet.
En flaske pils/øl = et glass vin = et lite glass hetvin = en drink med brennevin.

Kilde: Audit C - Snakkomrus.no

29. Hvor mange alkoholenheter drikker du på en typisk «drikkedag»?

- 1-2 alkoholenheter ☐
- 3-4 alkoholenheter ☐
- 5-6 alkoholenheter ☐
- 7-9 alkoholenheter ☐
- 10 eller flere enheter ☐

30. Hvor ofte drikker du 6 alkoholenheter eller mer?

- Aldri ☐
- Sjelden ☐
- Noen ganger per mnd. ☐
- Noen ganger per uke ☐
- Nesten daglig ☐

Oppvekst

31. I hvilken kommune har du bodd mesteparten av barndommen?
(Angi den kommunen du anser som din «oppvekstkommune»)

Oslo ☐	Drammen ☐	Bamble ☐
Asker eller Bærum ☐	Lier ☐	Notodden ☐
Bodø ☐	Kongsberg ☐	Porsgrunn ☐
Kristiansand ☐	Øvre Eiker ☐	Skien ☐
Bergen ☐	Nedre Eiker ☐	Kragerø ☐
Trondheim ☐	Ringerike ☐	Annen ☐
Stavanger ☐	Røyken ☐	Hvis annen/utland: Hvilken kommune/land?
Tromsø ☐	Modum ☐	----------

32. Vokste du opp med kjæledyr eller husdyr?

Nei ☐	
Ja, katt ☐	Ja, hund ☐
Ja, hest ☐	Ja, annet levende dyr ☐

Sosioøkonomiske faktorer

33. Hvilken utdannelse er den høyeste gjennomførte for hver av dine foreldre

A. <u>Mors utdannelse:</u>

- Mindre enn grunnskole 7 år ☐
- Grunnskole 7-10 år ☐
- Videregående skole 10-13 år ☐
- Høgskole/universitet 1-4 år ☐
- Høgskole/universitet mer enn 4 år ☐

B. <u>Fars utdannelse:</u>

- Mindre enn grunnskole 7 år ☐
- Grunnskole 7-10 år ☐
- Videregående skole 10-13 år ☐
- Høgskole/universitet 1-4 år ☐
- Høgskole/universitet mer enn 4 år ☐

34. Hvor mange bøker var det i barndomshjemmet ditt, der du vokste opp?
Anta at det i en vanlig hyllerad er om lag 40 bøker.

- Ingen bøker ☐
- 1-10 bøker ☐
- 11-50 bøker ☐
- 51-100 bøker ☐
- 101-250 bøker ☐
- 251-500 bøker ☐
- Mer enn 500 bøker ☐

35. Hvor mange bøker er det i ditt nåværende hjem?
Anta at det i en vanlig hyllerad er om lag 40 bøker.

- Ingen bøker ☐
- 1-10 bøker ☐
- 11-50 bøker ☐
- 51-100 bøker ☐
- 101-250 bøker ☐
- 251-500 bøker ☐
- Mer enn 500 bøker ☐

36. Hvor mye har du benyttet ulike kulturtilbud siste 12 måneder?

Sett kryss i venstre kolonne dersom du har vært på et slikt kulturarrangement siste 12 mnd.:		*Angi antall besøk siste 12 mnd.*
☐	Kino	☐
☐	Konsert	☐
☐	Idrettsarrangement	☐
☐	Folkebibliotek	☐
☐	Teater/musikal/revy	☐
☐	Museum	☐
☐	Kunstutstilling	☐
☐	Tros-/livssynsmøte	☐
☐	Kulturfestival	☐
☐	Ballett/danseforestilling	☐
☐	Opera/operette	☐

37. «Mac Arthurs stige»

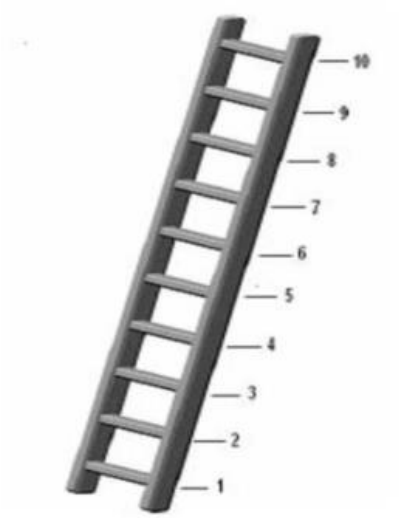
Se på denne stigen som et uttrykk for posisjoner i det norske samfunnet.

På toppen av stigen finner du dem som har det «best»; de med mest penger, høyest utdannelse og mest respekterte jobber.

I bunnen av stigen finner du dem som har det «dårligst»; de med minst penger, lavest utdannelse og minst respekterte jobber, eller ingen jobb.

Jo høyere opp du er på denne stigen, jo nærmere er du personene helt på toppen. Jo lengre ned du er på denne stigen, jo nærmere er du personene helt på bunnen.

Hvor vil du plassere deg selv på denne stigen?
Kryss av i kolonnen til høyre der tallene 1-10 er angitt.



☐ 10
☐ 9
☐ 8
☐ 7
☐ 6
☐ 5
☐ 4
☐ 3
☐ 2
☐ 1

Dersom du er mann, er du nå ferdig med spørsmålene.

Kvinnehelse

38. Hvor gammel var du da du fikk første gang menstruasjon?

Angi alder: ☐

39. Har du sluttet å menstruere (Har du kommet i «overgangsalderen»)?

☐ Ja ☐ Nei

40. Hvis ja på spørsmål 39 – hvor gammel var du da du kom i overgangsalderen?

Angi alder: ☐

41. Har du noen gang gjennomgått hormonell behandling for barnløshet?

☐ Ja ☐ Nei

42. Har du vært gravid?

☐ Ja ☐ Nei

43. Hvis ja på spørsmål 42 (hvis du har vært gravid):

Antall graviditeter (totalt) ☐

Antall levende fødsler ☐

Antall aborter ☐
(spontanaborter eller provoserte)

44. Hvis ja på spørsmål 42 – fyll ut for hvert levende fødte barn:

Barn nr.	Fødselsår	Antall mnd. amming	Barn nr.	Fødselsår	Antall mnd. amming
1	☐	☐	5	☐	☐
2	☐	☐	6	☐	☐
3	☐	☐	7	☐	☐
4	☐	☐	8	☐	☐

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Original article

Prevalence of multiple sclerosis in rural and urban districts in Telemark county, Norway

Heidi Øyen Flemmen[a,b,*], Cecilia Smith Simonsen[c,d], Pål Berg-Hansen[d,e], Stine Marit Moen[f], Hege Kersten[g,h], Kristian Heldal[i,j], Elisabeth Gulowsen Celius[d,e]

[a] Department of Neurology, Telemark Hospital Trust, P.b. 2900 Kjørbekk, 3710 SKIEN, Norway
[b] Institute of Health and Society, University of Oslo, P.b. 1072 Blindern, 0316 OSLO, Norway
[c] Department of Neurology, Vestre Viken Hospital Trust, P.b. 800, 3004 Drammen, Norway
[d] Institute of Clinical Medicine, University of Oslo, P.b. 1072 Blindern, 0316 OSLO Norway
[e] Department of Neurology, Oslo University Hospital, Ullevål, P.b. 4956 Nydalen, 0424 OSLO, Norway
[f] MS-Centre Hakadal, Blomsterbakken 33, 1487 HAKADAL, Norway
[g] Department of Research, Telemark Hospital Trust, Skien, Norway
[h] Department of Pharmaceutical Bioscience, University of Oslo, Boks 1072 Blindern, 0316 OSLO Norway.
[i] Clinic of Internal Medicine, Telemark Hospital Trust, P.b. 2900 Kjørbekk, 3710 SKIEN, Norway
[j] Department of Transplantation Medicine, Section of Nephrology, Oslo University Hospital, Rikshospitalet, P.b. 4950 Nydalen, 0424 OSLO, Norway

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ABSTRACT

Objective: To explore the trends in prevalence and incidence of multiple sclerosis (MS) in Telemark, Norway (latitude 58.7-60.3°N), over the past two decades, with focus on differences between rural and urban areas.
Methods: Data from all patients with a confirmed diagnosis of MS in Telemark since 1993 were prospectively recorded and collected in a retrospective chart review. Prevalence estimates on January 1st 1999, 2009 and 2019, and incidence rates at five-year intervals between 1999 and 2018 were calculated and all results were adjusted to the European Standard Population. The study population was divided into urban and rural residency using a Norwegian governmental index.
Results: We registered 579 patients with MS in Telemark between 1999 and 2019. The adjusted prevalence estimates for January 1st 1999, 2009 and 2019 were 105.8/10^5, 177.1/10^5 and 260.6/10^5, respectively. In 2019, the prevalence estimates were 250.4/10^5 in urban and 316.2 /10^5 in rural areas. Between 1999 and 2018, the yearly incidence increased from 8.4/10^5 to 14.4/10^5.
Conclusions: The prevalence of MS in Telemark is among the highest ever reported in Norway, consistent with an increasing incidence in the county over the past twenty years. The even higher prevalence in the rural areas is unlikely to be explained by possible risk factors like latitude, exposure to sunlight and diet. Further studies on differences between urban and rural areas are required to reveal possible new risk factors.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease with neurodegeneration. Onset is mainly in young adulthood with impact on function, employment, income and quality of life (Thompson et al., 2018). Globally, there are an estimated 2.2-2.3 million people living with MS, and Europe is a region with high prevalence, estimated at 127/100 000 (10^5) in 2016 (Collaborators GBDMS. 2019). The over-all prevalence in Norway was 203/10^5 in 2012, among the highest in the world (Berg-Hansen et al., 2014). Different regions of Norway have reported prevalences for separate counties, showing an increase over time, see table 1 (Midgard et al., 1991; Gronlie et al., 2000; Dahl et al., 2004; Risberg et al., 2011; Lund et al., 2014; Smestad et al., 2008; Vatne et al., 2011; Benjaminsen et al., 2014; Grytten et al., 2016; Simonsen et al., 2017).

The first nationwide study describing the incidence of MS in Norway was published by Swank et al in 1952 (Swank et al., 1952). They claim that parts of Telemark are high-incidence areas for MS, and postulate that there is an association with farming, dairying and low seafood consumption in inland areas. The incidence and prevalence of MS in Telemark have not been systematically investigated before, but a nationwide study from Norway in 2012, estimated the prevalence in

* Corresponding author.
E-mail address: fleh@sthf.no (H.Ø. Flemmen).

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Table 1
Reported prevalence in separate counties, Norway. In counties with more than one publication, the last study is included.

County	Prevalence year	Crude prevalence per 100 000 population (95 % confidence interval)
Møre and Romsdal (Midgard et al 1991)	1985	75.4 (not reported)
Finnmark (Grønlie et al)	1993	51.3 (not reported)
Troms (Grønlie et al)	1993	84.0 (not reported)
Nord-Trøndelag (Dahl et al 2004)	2000	163.6 (142.2-187.5)
Oppland (Risberg et al 2011)	2002	174.4 (not reported)
Vestfold (Lund et al 2014)	2003	166.8 (not reported)
Oslo (Smestad et al 2008)	2006	148 (138-158)
Vest-Agder (Vatne et al 2011)	2007	180 (161-202)
Nordland (Benjaminsen et al 2014)	2010	182.4 (165.6-200.5)
Hordaland (Grytten et al 2016)	2013	211.4 (198.3-224.2)
Buskerud (Simonsen et al 2016)	2014	213.8 (196.4-231.1)

Telemark to be 194/10^5 (Berg-Hansen et al., 2014; Berg-Hansen et al., 2015).

There has been some focus on the variations in prevalence between rural and urban areas worldwide. A recently published study from Bavaria, Germany, describes a higher incidence and prevalence in urban than in rural areas (Daltrozzo et al., 2018), a pattern that has also been described in previous studies (Lowis, 1990, Beebe et al., 1967). This pattern has been associated with lower access to specialist services in rural areas (Roddam et al., 2019). However, studies on environmental factors in early childhood have shown a significantly increased risk of developing MS among inhabitants in rural areas (Conradi et al., 2011), and a Moldavian study have shown higher prevalence in rural than urban areas (Marcoci et al., 2016). Differences between rural and urban areas in Norway concerning the risk of developing MS have not been studied since the Swank paper in 1952 (Swank et al., 1952).

The aim of this study was to explore the trends in prevalence and incidence of MS in Telemark over the past two decades, particularly focusing on differences between rural and urban areas.

2. Material and methods

2.1. Geographical setting

Telemark county is located in the southeastern part of Norway, at latitude 58.7-60.3°N, with a total area of 15 296 km^2 (Fig. 1a). The county extends from the coastline of Skagerrak to the Hardanger Plateau, approximately 1 200 meters above sea level. The main city is Skien, where the county's only neurological department is located. Telemark and Skien had a population of 173 318 and 54 645 respectively as of January 1st 2019. Telemark consists of 18 municipalities with a wide variation in population density, topography and culture, comprising both smaller cities and rural areas, and the distance to specialist health services varies greatly.

The Norwegian government has developed an index characterizing the different municipalities by how centrally they are located. The index comprises information on service functions and work places a resident can reach within 90 minutes. Added up, each municipality receives an index from 1 to 6, where 1 denotes the most central areas (Høydahl, 2017). In Telemark, the different municipalities have indices ranging from 3 to 6. For the comparison of different areas, we have considered an index of 3 as an urban area whereas indices 5 and 6 are grouped together as rural areas. Fig. 1b shows the different municipalities of Telemark, labelled by the centrality index.

2.2. Data collection and study population

This study is a part of the ongoing BOT-MS project, which is a database consisting of all patients registered with a confirmed MS diagnosis at the two regional hospitals in the counties Buskerud (Vestre Viken Hospital Trust in Drammen) and Telemark (Telemark Hospital Trust in Skien). The BOT database also includes the majority of the MS patients registered at Oslo University Hospital (OUS). The regional ethics committee of South East Norway and the Data Protection Officer at OUS have approved the project. All individuals registered in the electronic patient records with the ICD-10 code G35 (MS) between 1999 and 2019 and patients who fulfilled the diagnostic criteria for definite or probable MS (Polman et al., 2011; Thompson et al., 2018) were included. An additional search for the ICD-9 code 340 (MS) between 1993 and 1998 was performed and patients with a verified diagnosis of MS were included. We registered all patients by their unique personal identification number and noted the year of change in status (deceased, migrated to or from the county). The year of the first symptom suggestive of MS was defined as the year of onset. This information, as well as year of diagnosis and subtype of MS, were derived from the medical record review. We classified subtypes of MS as progressive-onset or relapse-onset, the latter including those initially registered with a clinically isolated syndrome (CIS) that was later verified as definite MS, as well as those with secondary progressive MS at the time of diagnosis.

2.3. Prevalence and incidence

Prevalence was calculated based on population data for Telemark on January 1st 1999, 2009 and 2019. The prevalence was defined as the total number of MS patients residing in Telemark per 10^5 inhabitants in the county at each date. Prevalence according to the centrality index was calculated based on population data for each municipality.

The crude annual incidence was defined as the number of patients diagnosed with definite MS or CIS later converting to definite MS per year when residing in Telemark per 10^5 inhabitants. We calculated mean yearly incidence at five-year intervals between 1999 and 2019, using the average population at risk during the corresponding five-year interval. Population data stratified by age and sex was obtained from Statistics Norway. For the calculation of age standardized incidence and prevalence, we used the new European Standard Population as reference population (Pace M et al., 2013). For comparison with previous studies, we also standardized using the previous reference population (Pace M et al., 2013).

2.4. Statistical analysis

We used IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA) for the main statistical analysis, including two-sample independent t-test to compare characteristics at the first and last prevalence dates. 95 % confidence intervals (CI) for prevalence were calculated manually from the formula p ± 1,96 x SD, where SD is the standard deviation, given by the formula $\sqrt{p(1-p)/n}$, p being the crude prevalence and n the number of persons participating. We used the mid-P exact test (Rothman et al., 2008) to compare the prevalence in rural versus urban areas of Telemark, using OpenEpi.com.

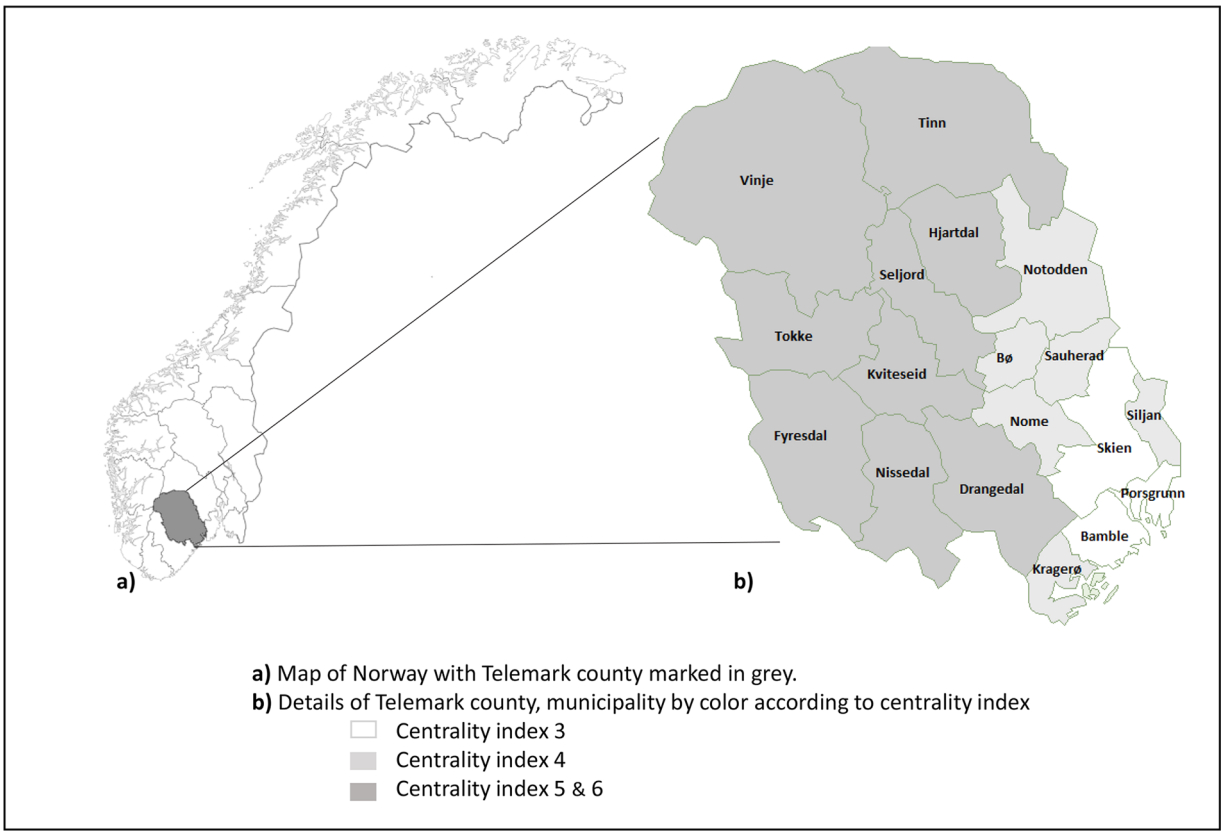

Fig. 1. a) Map of Norway with Telemark county marked in grey. b) Details of Telemark county, municipality by color according to centrality index

3. Results

3.1. Demographics

Table 2 shows the demographic characteristics of the population on the three prevalence dates. The percentage of females with MS increased from 1999 to 2009 and remained stable from 2009 to 2019. The mean age at onset increased over the two decades, from 32.5 years in 1999, to 36.0 years in 2019. The increase in age at onset was significant for the whole group, as well as for both sexes separately. Accordingly, the study cohort had a significantly higher age in 2019 (53.8 years) than in 1999 (50.5 years) ($p = 0.009$). There was an equivalent significant increase in mean age in the female cohort separately ($p = 0.009$), but not for males. The mean time from onset to diagnosis decreased between 1999 and 2019, from 6.0 to 5.0 years respectively, but the reduction was not significant. The proportion of patients with a relapsing disease at diagnosis increased from 84.7% in 1999 to 90.9% in 2019, with a corresponding trend for each sex separately.

3.2. Prevalence

A total of 625 patients were identified by the ICD-10 code G35, and 32 patients were identified by the ICD-9 code 340. Based on information from the electronic patient record, we excluded 74 patients as they did not fulfill the diagnostic criteria or were miscoded, and 9 patients as deceased prior to the first prevalence date of 01.01.1999. Through the BOT-collaboration, we included five patients diagnosed and treated in Buskerud, while residing in Telemark. Finally, 579 patients with MS, residing in Telemark at any time during the time-period 1999-2018 were included in the calculations. Table 3 shows the changes in the MS population in Telemark during the twenty-year period.

The crude prevalence on 01.01.1999 was $97.3/10^5$, on 01.01.2009, it was $176.1/10^5$, and on 01.01.2019, it was $259.6/10^5$. Table 2 shows the prevalence calculations for all three prevalence dates, including 95 % confidence intervals (CI) for the estimates. After adjusting to the European standard population, the prevalences were $105.8/10^5$, $177.7/10^5$, and $260.6/10^5$ respectively. We also calculated the prevalence with adjustment according to the 1976 European standard population, finding a lower prevalence for 1999 and 2009, but the exact same prevalence for 2019 (data not shown).

The age-adjusted prevalence increased for all age groups over the two decades as shown in Fig. 2. The highest age-adjusted prevalence observed was for females aged 60-69 years on prevalence date 01.01.2019, with a prevalence of $683/10^5$, as shown in Fig. 3.

Comparing the prevalence in the most rural (centrality indices 5 and 6) with the most urban areas (centrality index 3) of Telemark showed a significantly higher prevalence in rural areas. There was a significantly higher prevalence of MS among females in rural areas compared to females in urban areas, while no such difference was seen for males. The finding of a prevalence for females living in areas with centrality index 4 (suburban) of 354.6/105, indicating a gradual decrease towards more urban areas, reinforced this sex-specific pattern. There were no significant differences in mean age for the whole study population, nor for females residing in rural versus urban areas. Data for the last prevalence date are shown in Table 4.

3.3. Incidence

The crude number of persons in Telemark diagnosed with definite MS or CIS later converted to definite MS in the period 1999-2018 varies between 11 and 27 per year (Fig. 4), with an overall increasing trend. Table 5 shows the crude incidence rates at five-year intervals, and age-adjusted incidence rates using the 2013 European standard population as a reference. Table 6 shows the age-adjusted incidence per year at five-year intervals, per sex.

The yearly incidence rate increased, although not significantly, from

Table 2
MS population demographics at the prevalence dates 01.01.1999, 01.01.2009 and 01.01.2019

	Prevalence date 01.01.1999			Prevalence date 01.01.2009			Prevalence date 01.01.2019		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of cases (% of total)	58 (36.3)	102 (63.8)	160 (100)	96 (32.5)	199 (67.5)	295 (100)	150 (33.3)	300 (66.7)	450 (100)
Population at risk	80 964	83 559	164 523	82 849	84 699	167 548	86 739	86 579	173 318
Prevalence/10^5 (95% C.I.)	71.6 (53.2-90.1)	122.1 (98.4-145.7)	97.3 (52.2-112.3)	115.9 (92.7-139.0)	234.9 (202.3-267.6)	176.1 (156.0-196.1)	172.9 (145.3-200.6)	346.5 (307.4-385.7)	259.6** (235.7-283.6)
Age-adjusted prevalence/10^5 (95% C.I.)	80.0 (60.5-99.5)	133.7 (109.0-158.5)	105.8 (90.1-121.5)	118.2 (94.8-141.6)	239.8 (206.9-272.7)	177.7 (157.6-197.9)	175.1 (147.2-202.9)	345.8 (306.7-384.9)	260.6** (236.6-284.6)
Mean age at onset (95% C.I.)	32.3 (29.5-35.1)	32.6 (30.6-34.6)	32.5 (30.9-34.2)	35.8 (33.7-37.9)	34.0 (32.5-35.6)	34.6 (33.3-35.9)	37.7** (35.9-39.5)	35.1* (33.9-36.4)	36.0** (34.9-37.0)
Mean age at prevalence date (95% C.I.)	52.6 (49.2-55.9)	49.4 (47.2-51.6)	50.5 (48.7-52.4)	52.2 (49.7-54.7)	51.3 (49.4-53.1)	51.6 (50.1-53.0)	54.4n.s (52.3-56.4)	53.4** (51.8-55.0)	53.8** (52.5-55.0)
Mean time (years) from onset to diagnosis (95 % C.I.)	5.8 (3.7-7.9)	6.1 (4.8-7.5)	6.0 (4.9-7.2)	5.1 (3.9-6.2)	6.2 (5.1-7.2)	5.8 (5.0-6.6)	4.8n.s (3.8-5.8)	5.1n.s (4.3-5.9)	5.0n.s. (4.4-5.6)
Percentage with RMS at diagnosis	78.4	87.4	84.7	81.0	91.7	88.3	83.0	94.8	90.9

C.I. = confidence interval, RMS = relapse-onset MS.
The significance level is given at prevalence date 2019 when compared to 1999
n.s. = not significant,
* $p < 0.05$,
** $p < 0.01$

$8.2/10^5$ to $13.9/10^5$ from the first five-year interval to the last. Both sexes analyzed separately show the same trend, with an increase from $11.0/10^5$ to $17.6/10^5$ in females and from $5.4/10^5$ to $10.2/10^5$ in males. There is a dip in incidence from the second to third five-year intervals for the total group and for the females, which is due to low numbers and the large variation in new cases from one year to the next. When adjusted to the 2013 European standard population, the incidences were higher for all time-intervals for the female subgroup, whereas the adjustment only led to minor changes in the male subgroup and in the total population. We also calculated the adjustment according to the 1976 European standard (data not shown), which gave an even higher incidence for all time-intervals for females, but a lower incidence for males in the last time-interval. However, for the population as a whole, the differences between the two versions of European standards are minor.

4. Discussion

The prevalence of MS in Norway is among the highest worldwide, and studies from many Norwegian counties consistently report individually high rates. No systematic MS prevalence report from Telemark county has previously been published, and the present study confirms a prevalence of MS that has increased remarkably over the past 20 years, culminating in January 2019 with one of the highest MS prevalences ever published from Norway. Unlike previous studies, which have mainly pointed to a tendency towards increasing incidence of MS in urban versus rural areas, we report a clear trend towards higher prevalence of MS in the most rural areas, with a gradual decrease in more urban areas.

The prevalence estimate from Telemark was $105.8/10^5$ at the first time-point, which is lower than roughly simultaneous calculations from other parts of Norway. In January 1995 the prevalence estimate from Oslo was 120.4 $/10^5$, and even higher when only native Norwegians were considered ($136/10^5$) (Celius and Vandvik, 2001). Another county reported a prevalence in 2000 of 163.3 $/10^5$ (Dahl et al., 2004). For the second prevalence date in our study (2009), the simultaneous Norwegian reports (Vatne et al., 2011; Benjaminsen et al., 2014) corresponded with our finding of $177.8/10^5$ in Telemark in 2009. The most recent national study *estimated* the MS prevalence for Telemark at $194/10^5$ as of January 1st 2012 (Berg-Hansen et al., 2015), which also aligns with our result. The prevalence in the neighboring county of Buskerud was $213.8/10^5$ in 2014 (Simonsen et al., 2017), which is the latest reported prevalence from Norway until our finding of a prevalence in Telemark of $260/10^5$ in 2019. It is, however, difficult to compare different areas of Norway, with their differences in availability of neurological services and changes in diagnostic criteria (Høydahl; 2017, Polman et al., 2011), especially based on historical data. Despite the possibility for underestimation at the first time point (01.01.1999), the significant increase from the first five-year period (1999-2004) to the next, and throughout the whole study period, is clear.

Prevalence estimates can increase with repeated surveys from the same area for several reasons (Koch-Henriksen and Sorensen, 2011). The Telemark Hospital Trust has the only neurological department in the county, and there are no private neurologists treating MS in Telemark. A team consisting of MS neurologists and nurses organizes the MS care in Telemark, and the team keeps track of all the MS-patients with regular controls. The Telemark Hospital Trust implemented electronic patient records in 1993, thus making searches for diagnoses for historical data easy and precise. We used both ICD-9 and ICD-10 diagnosis of MS as search criteria in this study, and we believe there are few missed cases. Through the research collaboration with the neighboring county of Buskerud and the capital Oslo, we have only identified five patients who were followed up by other hospitals while residing in Telemark over a period of 20 years. Through clinical collaboration with MS neurologists from the other counties in our region, and an evaluation of data from the Norwegian prescription registry, we have not been

Table 3
Changes in MS population in Telemark 1999-2019

	Alive and resident in Telemark	Diagnosed and resident in Telemark	Immigrated to Telemark	Emigrated from Telemark	Deceased
Prevalence day 01.01.1999	**160**				
Changes in time period 1999-2008		*166*	*15*	*9*	*37*
Prevalence day 01.01.2009	**295**				
Changes in time period 2009-2018		*214*	*12*	*12*	*59*
Prevalence day 01.01.2019	**450**				

able to identify other MS patients from Telemark being followed up outside of the county. This confirms the impression of the completeness of our cohort.

The numbers of newly diagnosed MS patients per year is small, and a variation from one year to another is to be expected because of natural fluctuations, but the increase from 2017 to 2018 is most likely related to implementation of the latest revision of the McDonald diagnostic criteria (Thompson et al., 2018). However, the incidence rates for five-year periods in Telemark have shown a clear increase over the past twenty years.

The incidence and prevalence of MS are dependent on the population's age distribution, and adjustment of rates by a hypothetical standard population is common in more recent studies. We have adjusted all our findings to the European Standard Population to be able to compare our data with findings from other countries and regions. We would like to highlight the fact that there are two versions of the standard population: 1976 and 2013. The latter takes into account the growing age of the population (Pace M et al., 2013). In our data, this yielded different results for the first two prevalence calculations of 1999 and 2009, but no differences for the last prevalence date of 2019. There is reason to believe that the Norwegian population was not in accordance with the previous standard, and published adjusted Norwegian prevalence and incidence estimates from the first decade of the millennium using the old European standard may thus be underestimated.

In contrast to most previous studies, we have demonstrated an uneven geographical distribution in terms of rural aggregation of MS in Telemark. These differences are unlikely to be explained by an association of the prevalence of MS with latitude (Simpson et al., 2019), nor the observed reduced risk of MS when living in high ambient UV-B areas during childhood (Tremlett et al., 2018). In Telemark, there is a relatively small range of latitude (58.7-60.3°N) and the UV radiation is considered similar throughout the area, although it is interesting to note that one of the largest rural municipalities, Tinn (see Fig. 1), is surrounded by high mountains, and its inhabitants are not exposed to sunlight for half the year.

The composition of various ethnicities may influence the prevalence. In a previous study, non- western immigrants to Norway had lower crude and adjusted prevalence estimates compared to the total population (Berg-Hansen et al., 2015). Other countries have described the same pattern (Evans et al., 2013; Pugliatti et al., 2002). According to Statistics Norway, the proportion of the population with non-Western background is 6.4 % in the urban areas and 4.1 % in the rural areas of Telemark, and this can only in part explain the higher rural prevalence of MS.

Smoking is a known risk factor for MS on the individual level (Hedstrom et al., 2013). According to Statistics Norway, the proportion of Norwegians who smoke regularly has decreased from 32 % in 1999 to 12 % in 2018, but this is not reflected in the observed increase in incidence and prevalence estimates of MS. There are, however, well-documented differences in several lifestyle factors according to residency in Norway (2010, 2010), like findings of 15 % daily smokers in the most rural areas, versus 11 % daily smokers in urban areas (Statistics Norway, 2015). The level of individual education may influence the development of diseases. One Norwegian study showed an inverse relationship between higher education and MS risk (Riise et al., 2011). Statistics Norway confirms a higher education level among residents in urban versus rural areas of Norway. Dietary patterns have been discussed regarding differences in the prevalence of MS with, traditionally, a higher intake of fat in the inland farming areas, and higher consumption of fish in coastal areas (Kampman et al., 2008). This brings us back to the Swank theory from 1952 of dietary factors as an explanation for the high incidence in rural Telemark (Swank et al., 1952). Our

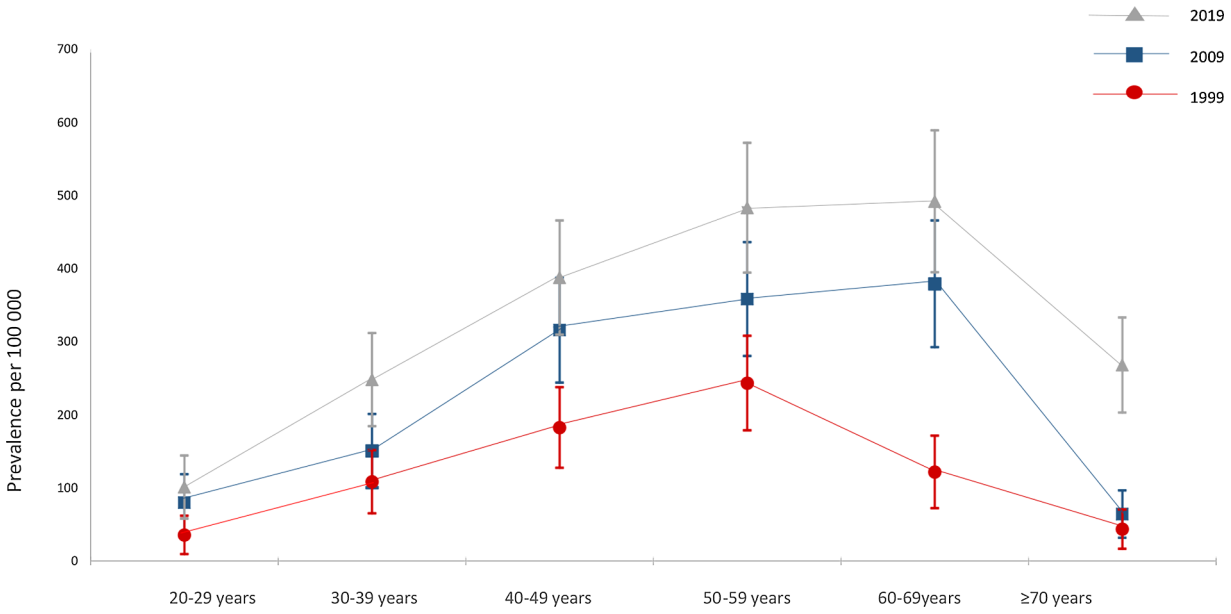

Fig. 2. Age-adjusted prevalence of MS in Telemark with 95% confidence interval, 1999 - 2009 2019.

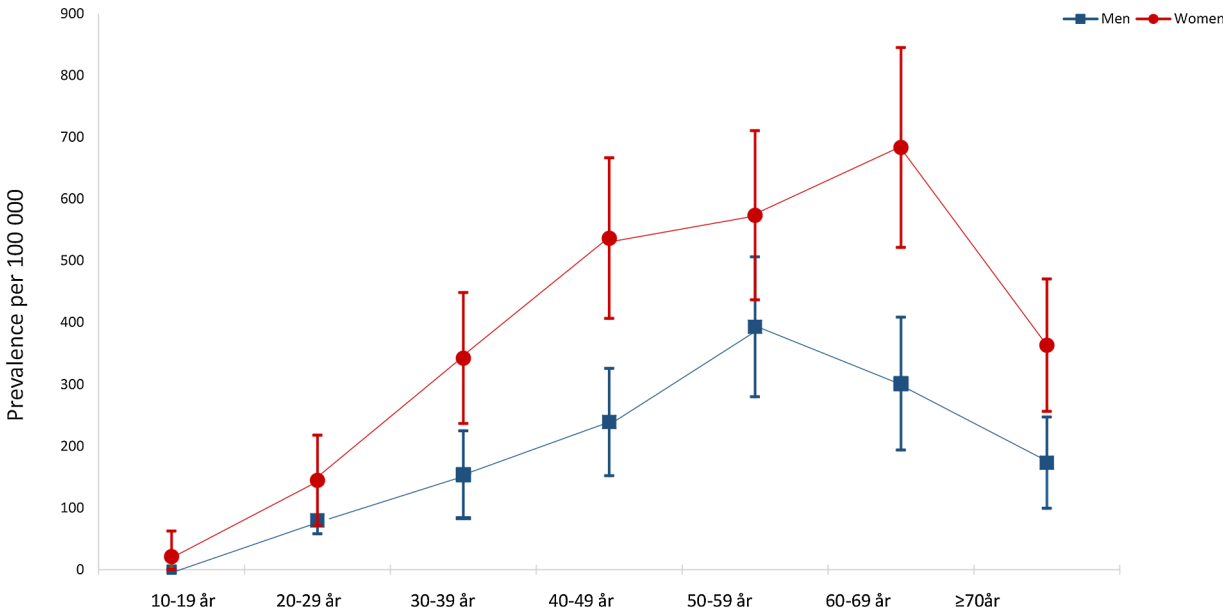

Fig. 3. Age-adjusted prevalence in Telemark at 01,01.2019, by gender, with 95 % confidence interval

experience, however, is that these differences are almost non-existent today. This statement is confirmed by the survey on living conditions performed by Statistics Norway, showing no significant difference in intake of fish/seafood, nor milk products between areas of residence. We would therefore argue that diet alone cannot explain the observed differences between rural and urban areas.

Due to a low sample size, we have not been able to report incidence related to urban and rural areas, which is a shortcoming in this study. Another limitation is the lack of a bigger city in the county (centrality indices 1 or 2). Our findings should be further investigated in a larger cohort, in order to be able to calculate incidence. The overall results should also be adjusted for lifestyle habits and other socioeconomic factors.

The proportion of patients with progressive MS at diagnosis has varied between studies, most likely mainly due to different definitions and classifications (Pugliatti et al., 2006). There are also differences in the proportions of patients with a primary progressive disease course in Norwegian studies, with 22.3% in Oslo in 1995 (Celius and Vandvik, 2001), 16.8 % in Trøndelag in 2000 (Dahl et al., 2004), 14.9 % in Oppland in 2002 (Risberg et al., 2011), 11 % in Vest Agder in 2011 (Vatne et al., 2011), 8.2% in Hordaland in 2013 (Grytten et al., 2016), and 16.8 % in Buskerud in 2014 (Simonsen et al., 2017). These national

Table 4
2019 Prevalence of MS in urban (Centrality index 3), suburban (Centrality index 4) and rural (Centrality indices 5 and 6) areas, Telemark, by sex and total. See map in Fig. 1 for index areas. C.I. = confidence interval

	Prevalence date 01.01.2019		
	Male	Female	Total
Centrality index 3 (Urban areas)			
Number of cases (% of total)	97 (37.3%)	163 (62.7%)	260 (100%)
Mean age MS patient at prevalence date (95%C.I.)	53.2 (50.6-55.8)	53.9 (51.76-56.1)	53.6 (51.9-55.3)
Population at risk	52 197	52 761	104 958
Prevalence/100 000 (95% C.I.)	185.8 (148.9-222.8)	308.9 (261.6-356.3)	247.7 (217.6-277.8)
Age-adjusted prevalence/100 000 (95% C.I.)	189.8 (152.5-227.2)	308.3 (261.0-355.6)	250.4 (220.2-280.7)
Centrality index 4 (Suburban areas)			
Number of cases (% of total)	33 (30.6%)	75 (69.4%)	108 (100%)
Mean age MS pat at prev. date (95 % C.I.)	59.4 (55.2-63.6)	52.6 (49.3-55.9)	54.7 (52.0-57.4)
Population at risk	21 667	21 211	42 878
Prevalence/100 000(95% C.I.)	152.3 (100.4-204.2)	353.6 (273.7-433.5)	251.9 (204.4-299.3)
Age-adjusted prevalence/100 000 (95% C.I.)	155.3 (102.9-207.7)	354.6 (274.6-434.6)	252.3 (204.8-299.8)
Centrality indices 5&6 (Rural areas)			
Number of cases (% of total)	20 (23.5%)	62 (72.9%)	82 (100%)
Mean age MS pat at prev. date (95 % C.I.)	51.8 (46.7-56.9)	53.4 (50.2-56.6)	53.0 (50.3-55.7)
Population at risk	12 875	12 607	25 482
Prevalence/100 000(95% C.I.)	155.3 (87.3-223.4)	491.8 (369.7-613.9)	321.8 (252.3-391.3)
Age-adjusted prevalence/100 000 (95% C.I)	146.0 (80.0-211.9)	493.5 (371.2-615.8)	316.2 (247.3-385.1)
p-value for comparison prevalence in rural (indices 5&6) vs urban (index 3)	n.s. (0.237)	0.001	0.021

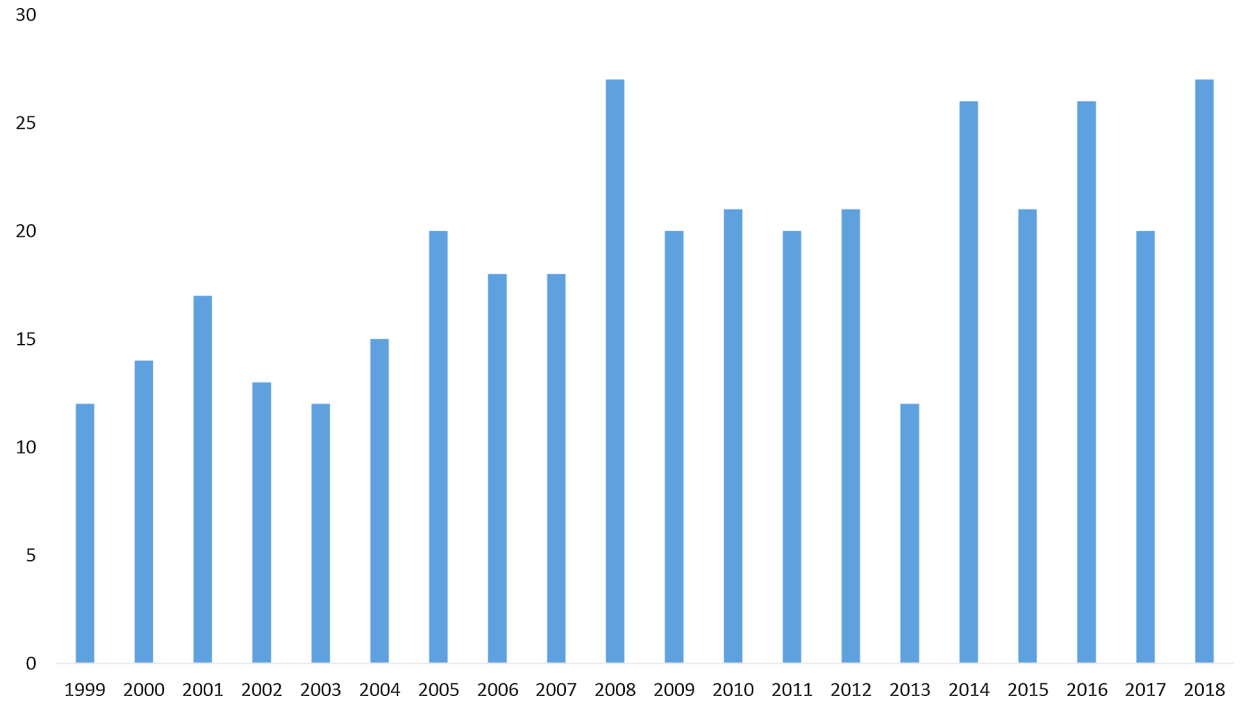

Fig. 4. Number of new cases diagnosed per year in Telemark, 1999-2018

reports show a time-trend of a decreasing proportion of primary progressive disease, and correspond to our findings in Telemark of 15.3 % primary progressive disease in 1999 and 9.1 % in 2019. This development is predictable, and is most likely due to several factors, including an increased focus on anamnestic reports of earlier episodes of relapsing symptoms. This secures the relapsing diagnosis, which is a prerequisite for disease modifying treatments. The mean age of onset and the mean age of the prevalent population increases over two decades in Telemark. These findings are in accordance with some Norwegian studies (Vatne et al., 2011; Simonsen et al., 2017) and slightly lower than others (Benjaminsen et al., 2014). The increase in age may be attributed to the previous reluctance in diagnosing MS in the elderly (Koch-Henriksen et al., 2018), as well as a change in diagnostic criteria. The increase in female to male ratio is seen in previous studies (Koch-Henriksen et al., 2018; Celius and Smestad, 2009; Orton et al., 2006). A flattening of the increase during the last ten-year period, as we found, may indicate that this is largely due to historically undiagnosed cases among females.

In conclusion, this study from Telemark shows one of the highest reported prevalences of MS in Norway, consistent with an increasing incidence in the county during the last twenty years. We also found an even higher prevalence of MS in the rural areas of the county, which partly confirms the findings of Swank from 1952 that claimed parts of Telemark were particularly high incidence areas. The results need to be further investigated in order to ascertain factors, other than latitude and sunlight, explaining the geographical differences in the prevalence of MS. An understanding of the distribution of MS is important to allow for better planning of health services, which may in turn bring us closer to an understanding of the disease susceptibility, and even development of further strategies for prevention of the disease.

Author contributions for paper

Prevalence of multiple sclerosis in rural and urban districts in Telemark County, Norway

Data statement,

Prevalence of multiple sclerosis in rural and urban districts in Telemark County, Norway

Table 5
Incidence of MS in Telemark in five-year intervals, 1999-2018. C.I. = confidence interval

Time period	Average population	Male New cases	Mean incidence per year (95%C.I.)	Age-adjusted incidence (95% C.I.)	Female New cases	Mean incidence per year (95% C.I.)	Age-adjusted incidence (95% C.I.)	Total New cases	Mean incidence per year (95% C.I.)	Age-adjusted incidence (95% C.I.)
1999-2003	165 344	22	5.4 (0.4-10.5)	5.4 (0.4-10.5)	46	11.0 (3.9-18.1)	11.4 (4.2-18.7)	68	8.2 (3.9-12.6)	8.4 (4.0-12.8)
2004-2008	166 291	33	8.0 (1.9-14.2)	8.0 (1.8-14.1)	65	15.4 (7.0-23.8)	15.9 (8.4-21.2)	98	11.8 (6.6-17.0)	11.8 (6.6-17.1)
2009-2013	169 178	35	8.3 (2.2-14.5)	8.3 (2.2-14.5)	59	13.8 (5.9-21.7)	14.3 (6.3-22.3)	94	11.1 (6.1-16.1)	11.3 (6.2-16.3)
2014-2018	172 523	44	10.2 (3.5-17.0)	10.6 (3.7-17.5)	76	17.6 (8.8-26.4)	18.5 (9.4-27.6)	120	13.9 (8.3-19.5)	14.4 (8.7-20.0)

Table 6
Age-adjusted incidence of MS in Telemark in five-year intervals, 1999-2018. By age-group, by sex and total.

Time period	Age group	MALE Average population per year	New cases per 5 y	Age-adjusted incidence	FEMALE Average population per year	New cases per 5 y	Age-adjusted incidence	TOTAL Average population per year	New cases per 5 y	Age-adjusted incidence
1999-2003	All		22	5.4		46	11.4	165 344	68	8.4
	15-19 years	5 160	0	0	4 889	1	4.3	10 048	1	2.2
	20-29 years	10 706	1	2.0	10 189	4	7.9	20 894	5	4.0
	30-39 years	11 698	9	16.4	11 281	15	26.5	22 979	24	21.5
	40-49 years	11 692	7	12.3	11 467	15	25.5	23 158	22	19.0
	50-59 years	10 841	3	5.5	10 588	9	15.9	21 429	12	11.6
	60-69 years	6 559	2	4.3	7 071	2	4.1	13 631	4	4.2
	≥70 years	8 772	0	0	13 156	0	0	21 927	0	0
2004-2008	All	81 994	33	8.0	84 297	65	15.9	166 291	98	11.8
	15-19 years	5 620	1	4.4	5 345	3	12.9	10 965	4	8.7
	20-29 years	9 673	4	8.1	9 128	12	23.7	18 801	16	16.0
	30-39 years	11 473	8	14.5	11 187	16	28.1	22 660	24	21.4
	40-49 years	11 708	11	19.2	11 537	15	25.4	23 244	26	22.3
	50-59 years	11 653	7	12.6	11 407	14	24.6	23 060	21	18.7
	60-69 years	8 024	1	2.1	8 328	5	10.3	16 352	6	6.3
	≥70 years	8 367	1	1.7	12 462	0	0	20 828	1	0.9
2009-2013	All	83 892	35	8.3	85 286	59	14.3	169 178	94	11.3
	15-19 years	5 872	0	0	5 517	2	8.5	11 389	2	4.3
	20-29 years	10 138	3	6.0	9 522	10	19.5	19 660	13	12.8
	30-39 years	10 413	8	14.1	10 146	13	22.6	20 559	21	18.4
	40-49 years	12 337	9	15.3	12 015	18	30.2	24 351	27	22.8
	50-59 years	11 640	11	19.4	11 467	14	24.3	23 107	25	21.9
	60-69 years	10 084	4	8.3	10 198	2	4.1	20 282	6	6.2
	≥70 years	8 428	0	0	12 124	0	0	20 551	0	0
2014-2018	All	86 164	44	10.6	86 359	76	18.5	172 523	120	14.4
	15-19 years	5 650	0	0	5 360	2	8.4	11 010	2	4.2
	20-29 years	11 048	7	13.5	10 056	20	38.6	21 104	27	26.1
	30-39 years	9 767	10	17.2	9 496	16	27.4	19 263	26	22.3
	40-49 years	12 452	11	18.2	12 130	19	31.4	24 581	30	24.8
	50-59 years	11 822	7	12.0	11 612	15	25.7	23 434	22	18.9
	60-69 years	10 913	4	8.1	10 977	3	6.0	21 890	7	7.1
	≥70 years	9 795	5	8.3	12 830	1	1.7	22 625	6	5.0

Due to the sensitive nature of the variables registered and the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

A limited version of the data can be released upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Heidi Øyen Flemmen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Cecilia Smith Simonsen:** Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing - review & editing. **Pål Berg-Hansen:** Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - review & editing, Supervision. **Stine Marit Moen:** Conceptualization, Methodology, Validation, Writing - review & editing. **Hege Kersten:** Writing - review & editing, Supervision, Funding acquisition. **Kristian Heldal:** Conceptualization, Writing - review & editing, Supervision. **Elisabeth Gulowsen Celius:** Conceptualization, Methodology, Software, Validation, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Original article

Maternal education has significant influence on progression in multiple sclerosis

Heidi Øyen Flemmen [a,b,*], Cecilia Smith Simonsen [c,d,e], Line Broch [c,d,e], Cathrine Brunborg [f], Pål Berg-Hansen [e], Stine Marit Moen [g], Hege Kersten [h,i], Elisabeth Gulowsen Celius [d,e]

[a] Department of Neurology, Telemark Hospital Trust, Skien, Norway
[b] Institute of Health and Society, University of Oslo, Norway
[c] Department of Neurology, Vestre Viken Hospital Trust, Drammen, Norway
[d] Institute of Clinical Medicine, University of Oslo, Norway
[e] Department of Neurology, Oslo University Hospital, Norway
[f] Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway
[g] MS-Centre Hakadal, Norway
[h] Department of Research, Telemark Hospital Trust, Skien, Norway
[i] Department of Pharmaceutical Bioscience, School of Pharmacy, University of Oslo, Norway

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ABSTRACT

Objective: The identification of potential risk factors for disease severity is of great importance in the treatment of multiple sclerosis. The influence of socioeconomic status on progression in multiple sclerosis (MS) is sparsely investigated. Our aim was to investigate how socioeconomic status in adolescence influences disease progression in later life.

Methods: A total of 1598 patients with multiple sclerosis from a well-defined population in Norway were included. Detailed information on disease progression, measured by expanded disability status scale (EDSS) and multiple sclerosis severity score (MSSS), were combined with data on socioeconomic factors. We used residency and parental level of education at patients' age 16 and exposure to second-hand smoking as a measure of socioeconomic status in adolescence, adjusting for the same variables as well as use of disease modifying treatments at prevalence date 01.01.18.

Results: High maternal level of education at patients' age 16 was significantly associated with less pronounced disease progression measured by MSSS (β-coefficient -0.58, p = 0.015), younger age and lower EDSS at disease onset, and shorter time from onset to diagnosis. No significant associations were found for paternal education level and MSSS. The use of any disease modifying treatment before prevalence date was significantly associated with disease progression (β-coefficient -0.49, p=0.004), while residence, current and second-hand smoking were not.

Conclusion: This study on a population-based, real-world cohort shows that the parental level of education has a significant impact on a timely diagnosis of MS. In addition to disease modifying treatment, maternal level of education also had an impact on disease progression in later life.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease with secondary neurodegeneration that causes significant disability in young people over time (Collaborators GBDMS 2019). The national prevalence in Norway was 203/100 000 in 2012, which is among the highest in the world (Berg-Hansen et al., 2014), and recent data suggest a marked increase (Flemmen et al., 2020). There is increasing evidence for an association between socioeconomic status (SES), defined as the standing of a person measured by a combination of economic and social factors in relation to others, and the risk for MS (FB et al., 2015). There is substantial evidence that individuals with low SES have poorer health conditions in general, compared to those with higher SES (Mackenbach et al., 2018). This is also seen in welfare states traditionally marked by

* Corresponding author at: Department of Neurology, Telemark Hospital Trust, 3710 Skien, Norway.
E-mail address: fleh@sthf.no (H.Ø. Flemmen).

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commitment to social equality, such as the Nordic countries (Lahelma et al., 2001).

MS occurs with greater frequency in high-income nations (Buchter et al., 2012). Some studies have concluded that there is a tendency for higher susceptibility to MS in households of greater affluence (Montgomery et al., 2004; Kurtzke and Page, 1997). The evidence in a multinational review is however inconsistent, and some studies find no social gradient, or even the opposite (Goulden et al., 2015). Some studies have examined the association between childhood SES and the risk of MS. In a Danish cohort, researchers found reduced rates of MS later in life if the maternal level of education was greater than secondary school when the offspring was aged 15 (Nielsen et al., 2013). A multinational study from 2016 did not find a consistent association between parental SES and MS risk in Norway, Canada and Italy (Goulden et al., 2016).

The association of SES with disease progression has been examined to a much smaller extent. Recent studies from Canada, UK and France show that there is an association between socioeconomic deprivation and a higher risk of disability progression, measured by time from onset to expanded disability status scale (EDSS) 4 and 6 (Harding et al., 2019; Calocer et al., 2020). A Flemish study showed that self-reported high levels of education prevented disability progression (D'Hooghe et al., 2016). Other studies have suggested variations within countries, with some evidence that place of residence, age, sex and ethnicity may influence disease progression in MS patients (Roddam et al., 2019).

When addressing socioeconomic factors and health, it is important to keep in mind that health-related behavior, such as smoking, is influenced by SES (Allen et al., 2017). Those who achieve a higher level of educational attainment are more likely to engage in healthy behaviors (van Oort et al., 2004). Smoking is an established risk factor for MS, and there is evidence of a causal relationship between smoking and subsequent development and progression of MS. Results on the effect of second-hand smoking are, however, mixed, and none of these are adjusted for SES (Degelman and Herman, 2017).

The aim of this study was to investigate how SES in adolescence influences disease progression later in life. Since the onset of MS usually occurs at a young age, and the disease can impair the patient's cognitive performance for years before the onset of symptoms (Cortese et al., 2016), the patient's own level of education may not be an accurate measure of SES. We have chosen the parental level of education as a more appropriate measure for the influence of education. To our knowledge, this has not been studied before.

2. Material and methods

2.1. Population

This study is part of an ongoing study on all MS patients in the counties Buskerud and Telemark, as well as the majority of patients in Oslo (BOT-MS, n=3965) (Simonsen et al., 2020). These counties comprise a population of 1.17 million people in South-Eastern Norway. The regional ethics committee of South-East Norway (REK 2015/670) has approved the project. All patients provided written, informed consent.

2.2. Methods

All patients with a definite diagnosis of MS according to the prevailing diagnostic criteria (Thompson et al., 2018) were registered, as described by Simonsen et al. (2020) Data were recorded prospectively, but retrospectively retrieved. Data collection for this study was terminated 01.01.2018, defined as prevalence date. For each patient, we collected time of onset and diagnosis, disease subtype at diagnosis, any disease modifying treatments (DMT) and disability as measured EDSS (Kurtzke, 1983). The EDSS assessments were collected at as many time points as possible by three Neurostatus certified neurologists (D'Souza et al., 2017). The multiple sclerosis severity score (MSSS) adds the element of disease duration to the EDSS, and is designed to provide a measure of disease severity (Roxburgh et al., 2005). We calculated the MSSS for each individual using the duration of MS from time of onset and the EDSS score nearest to prevalence date. We classified subtypes of MS as primary progressive (PP), secondary progressive (SP) or relapsing-remitting (RR), the latter included those initially registered with a clinically isolated syndrome (CIS), later verified as definite MS. In some sub analyses, we divided the population by diagnosis before and after 2006, the year the first high efficacy DMT, natalizumab, was introduced (Polman et al., 2006). We have further sub-grouped DMTs into moderate efficacy DMTs, including interferons, glatiramer acetate, teriflunomide and dimethyl-fumarate, and high efficacy DMTs, including natalizumab, fingolimod, alemtuzumab, rituximab and cladribine.

We have used three different measures for disease progression:

- **Change in EDSS the first five years after diagnosis**. For patients with more than five years since diagnosis, we have calculated change in EDSS in this period, using EDSS at the time of diagnosis and five years after diagnosis. If no EDSS score was available at year five (patient not seen by neurologist, presumably due to stable disease), the EDSS at the sixth (213/768) or seventh (81/768) year after diagnosis was used. An increase in EDSS by more than 2 points was labeled as *marked progression*, an increase by 1-2 points as *moderate progression*, a change by +/- 0.5 points as *stable disease* and, finally, a reduction in EDSS by 1 point or more as *improvement*.
- **Time to EDSS 6** was calculated in all patients who reached EDSS 6 by prevalence date.
- **The MSSS at prevalence date.** The MSSS is limited to 30 years after onset (Roxburgh et al., 2005). 251 patients were registered with onset of MS more than 30 years ago. For the individuals with 30-35 years since onset, we have registered the MSSS for year 30, but we have excluded the 147 patients with more than 35 years since onset. For patients with an unknown year of onset, we have not calculated an MSSS.

Statistics Norway has provided additional information, from annually performed censuses, on parental level of education and the municipality of residency at the patients' age 16, as well as the patients' own level of education and municipality at prevalence date. The level of education is divided into groups according to the total number of years in the Norwegian education system (0-9 years as primary, 10-12 years as secondary and 13 years or more as graduate level of education). We have also used the level of parental education combined, according to definitions given by Statistics Norway, labeled by the highest level of education both parents have achieved. The municipalities are recoded into six groups by the Centrality index. This index is developed by the Norwegian Government and measures how centrally the municipalities are located in terms of service functions and work places reachable for a resident within 90 minutes. Index 1 and 2 denotes the most central areas, index 5 and 6 the most rural areas (Høydahl, 2017). Statistic Norway has also provided data on level of education, smoking status and centrality indices for the general population in the three counties.

To add indicators of environmental factors and socioeconomic status, the patients provided information through a validated questionnaire (Unpublished, presented as e-poster at ECTRIMS 2019, P765 Socioeconomic factors as predictors for MS susceptibility and disease progression – validation of a new Norwegian questionnaire). In this study, we have only used information regarding smoking habits from this questionnaire.

2.3. Statistical analysis

We used IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Data are presented as means ± standard deviation (SD), median with interquartile range (IQR), or

numbers and percentages depending on distribution. Cross tabulations were computed in order to investigate the relationship between different indicators of socioeconomic status and disease progression, given by change in EDSS the first five years after diagnosis. The chi-square test was used to detect associations between categorical variables. For the variables with significant associations, we performed a posthoc analysis, using stable disease as comparator for the two categories of progression of EDSS. We used independent sample t-test for normally distributed data to assess differences in continuous variables between groups. One-way ANOVA was used to compare means of age, time from onset to diagnosis and MSSS across subgroups. Kruskal-Wallis test was used to compare differences in EDSS across subgroups, as EDSS was skewed. To estimate time to EDSS 6 by socioeconomic variables during adolescence, we used the Kaplan-Meier method. Follow-up time was calculated as patient-years from time of onset until the date of EDSS 6, date of emigration or death, or prevalence date 01.01.2018, whichever occurred first. Univariable and multivariable linear regression models were used to analyze the impact of socioeconomic variables on progression by MSSS. Factors that are strongly associated are not included in multivariable analysis in order to avoid multicollinearity, using a Spearman correlation coefficient ≥ 0.7 as limit for multicollinearity. The final regression model was made by eliminating non-significant variables until all significant. The results from the regression analyses are presented as β coefficients, standard error of β (SE), p-values and explained variance (R^2). Heteroscedasticity and normality of residuals were examined and found to be satisfactory. All p-values were two-sided with a significance level of 5 %. We used the two-proportion z-test to compare the proportions of education, smoke and residence between background population and study population, using OpenEpi.com.

3. Results

All 2512 MS patients from the BOT registry who were still alive were invited to participate in the study. We received 1598 written consents and 1573 of these have completed the questionnaire.

Table 1 shows demographic data for the MS population at prevalence date 01.01.2018. The female patients (71%) are younger at both diagnosis and at prevalence date. The proportion of females remain stable for all variables, with three exceptions: Progressive subtype at diagnosis, the subgroup that reached EDSS 6 within prevalence date, and of persons with secondary school level of education in 2018. In these subgroups, the female proportion is lower (respectively 51 %, 64 % and 66 %, data not shown).

The study population was compared to the background population in the three counties of Buskerud, Oslo and Telemark using data from Statistics Norway 2018 (Fig. 1). The proportion living in centrality indices 1 - 4 is significantly lower in our MS population compared to the background population. There were more smokers among the MS patients than the in the background population, but the level of education is similar in the MS population and in the background population. Fig. 2 shows how the combined parental level of education is associated with a person's level of education, both for the MS population and for the general population in the three counties of Norway. The tendency to achieve higher levels of education when parents are educated more than 13 years is significantly more pronounced for MS patients compared to the general population.

3.1. Progression measured as change in EDSS five years after diagnosis

Table 2 shows the associations of socioeconomic factors during adolescence and change in EDSS the first five years after diagnosis. We found a significantly higher degree of disease progression in patients whose maternal level of education was limited to primary school. Patients whose mothers completed a graduate level of education, on the other hand, more often displayed improvement in EDSS by year five. The post hoc analysis showed that the association is significant when

Table 1
Demographics.

Total No.		1598
	Males (%)	469 (29.3)
	Females (%)	1129 (70.7)
Characteristics at 16 years of age	Centrality of municipality, n=1034	
	Centrality indices 1 and 2, %	40.7
	Centrality indices 3 and 4, %	45.2
	Centrality indices 5 and 6, %	14.2
	Paternal level of education, n=1374	
	Primary ≤ 9 years, %	30.7
	Secondary 10-12 years, %	46.1
	Graduate ≥ 13 years, %	23.1
	Maternal level of education, n=1404	
	Primary ≤ 9 years, %	35.3
	Secondary 10-12 years, %	48.7
	Graduate ≥ 13 years, %	16.0
	Exposed to second-hand smoke, n=1556, %	73.3
Characteristics at diagnosis	Mean age, years (SD), n=1535	39.5 (11.3)
	Mean age male, years (SD)	41.0 (10.9)
	Mean age female, years (SD)	38.9 (11.4)
	Mean time from onset to diagnosis, years (SD)	5.4 (7.0)
	Subtype MS, n=1528	
	RRMS, %	80.8
	PPMS, %	9.3
	SPMS, %	4.8
	Unknown, %	5.1
	Median EDSS (IQR)	2.5 (2.0-3.0)
Characteristics disease course	Mean change EDSS first five years after diagnosis (SD)	0.4 (1.5)
Characteristics at prevalence date 01.01.2018	Age, mean (SD), n=1598	52.5 (13.5)
	Mean age male, years (SD)	)53.9 (13.1)
	Mean age female, years (SD))	51.9 (13.6)
	Mean MSSS (SD)	3.34 (2.55)
	Reached EDSS 6, n=1362, %	24.8
	Treatment, n=1598	
	No treatment, %	40.1
	Moderate efficacy DMT, %	31.5
	High efficacy DMT, %	8.2
	Hospital responsible for follow-up, n=1298	
	University Hospital, %	25.8
	General Hospital, %	74.2
	Centrality of municipality, n=1595	
	Centrality indices 1 and 2, %	59.1
	Centrality indices 3 and 4, %	34.7
	Centrality indices 5 and 6, %	6.2
	Patient's level of education (n=1584)	
	Primary ≤ 9 years, %	17.5
	Secondary 10-12 years, %	38.5
	Graduate ≥ 13 years, %	44.0
	Current smokers, n=1563, %	27.1

n = numbers, SD = standard deviation, IQR = interquartile range, RRMS = relapsing remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, EDSS = Expanded Disability Status Scale, MSSS = Multiple Sclerosis Severity Score, DMT=disease modifying treatment

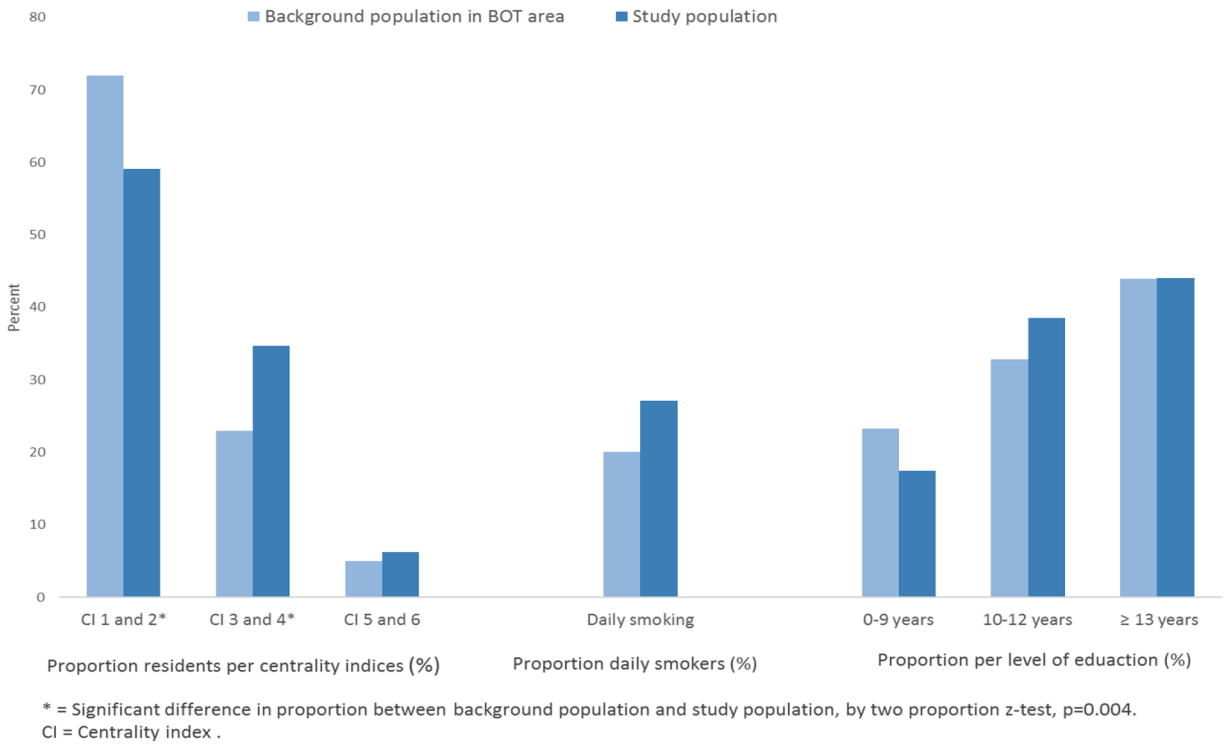

Fig. 1. Demographics 2018. Background population n= 925 483 (population 16 years and older in Buskerud, Oslo and Telemark, data from Statistics Norway) compared to study population n = 1598.

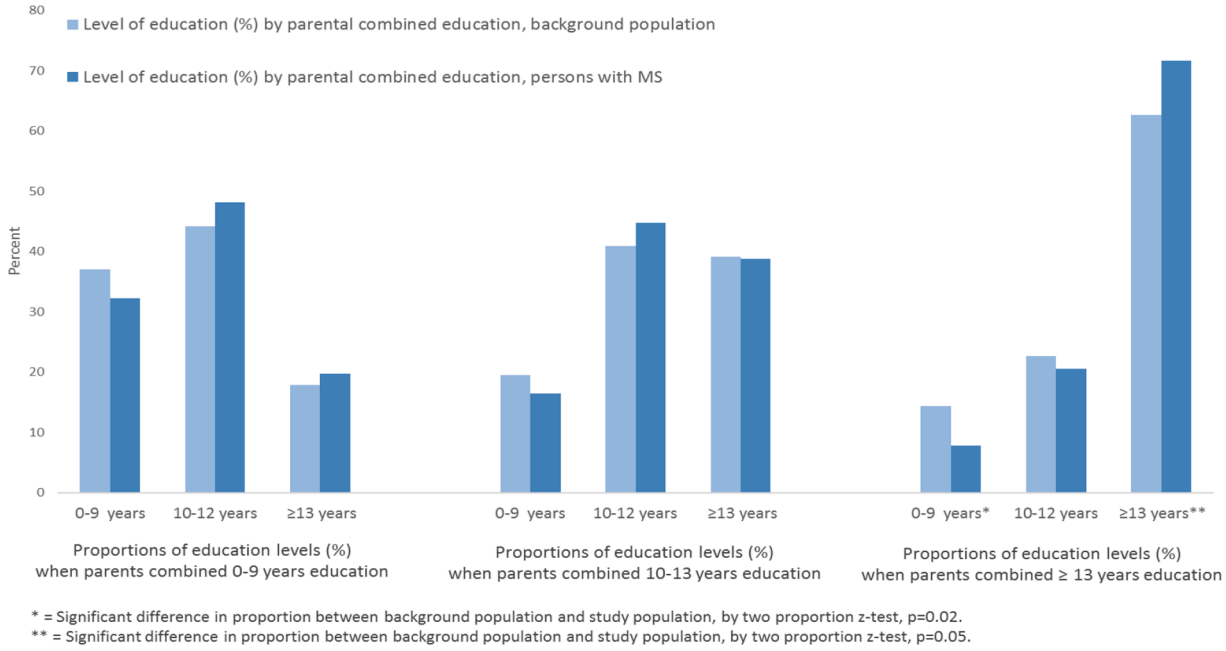

Fig. 2. Level of education by parents' combined level of education, 2018. Background population n= 925 483 (population 16 years and older in Buskerud, Oslo and Telemark, data from Statistics Norway) compared to study population n = 1598.

comparing stable disease to marked progression after five years of diagnosis. The association between the EDSS and the father's level of education shows a similar pattern, but does not reach significance. Patients who were diagnosed before year 2006 have a significantly more pronounced progression when compared with those diagnosed in 2006 and after. The post hoc analysis for this variable showed significant associations when comparing the category stable disease to both moderate and to marked progression. Neither living in a bigger city or in a rural area at age 16, nor exposure to second-hand smoking in the household reached significance with disease progression the first five years after diagnosis.

In Table 3, we present the grouped EDSS progression in the first five years against socioeconomic variables at prevalence date. The patient's own level of education and whether they were ever treated with DMTs are significantly associated with disease progression in the first five years after diagnosis.

Table 2
Association of socioeconomic factors in adolescence and time of diagnosis and change in EDSS year 0-5.

	Improvement (reduction of EDSS ≥1 point)	Stable disease (EDSS ±0.5 points)	Moderate progression (increase in EDSS 1-2 points	Marked progression (increase in EDSS ≥2 points)	Total
Total No. (%)	146 (22.1)	285 (43.1)	148 (22.4)	83 (12.5)	662 (100)
Sex					
Females (%)	103 (70.5)	210 (73.7)	103 (69.6)	51 (61.4)	467 (70.5)
Males (%)	43 (29.5)	75 (26.3)	56 (30.4)	32 (38.6)	195 (29.5)
p-value					*.193 (n. s.)*
Mean age at diagnosis, years (SD)	35.1 (10.2)	41.1 (11.6)	43.5 (10.6)	44.5 (11.0)	40.7 (11.4)
p-value					*<.001*
Paternal level of education at 16 years of age					
Primary ≤ 9 years (%)	43 (30.5)	78 (30.8)	51 (38.1)	30 (44.1)	202 (33.9)
Secondary 10-12 years (%)	62 (44.0)	118 (46.6)	62 (46.3)	31 (45.6)	273 (45.8)
Graduate ≥ 13 years (%)	36 (25.5)	57 (22.5)	21 (15.7)	7 (10.3)	121 (20.3)
p-value					*.077 (n. s.)*
Maternal level of education at 16 years of age					
Primary ≤ 9 years (%)	42 (30.0)	100 (38.8)	56 (41.8)	41 (58.6)	239 (39.7)
Secondary 10-12 years (%)	77 (55.0)	123 (47.7)	64 (47.8)	24 (34.3)	288 (47.8)
Graduate ≥ 13 years (%)	21 (15.0)	35 (13.6)	14 (10.4)	5 (7.1)	75 (12.5)
p-value				*	*.009*
Centrality of municipality at 16 years of age					
Centrality indices 1 and 2 (%)	57 (44.9)	71 (35.1)	30 (33.7)	18 (52.9)	176 (38.9)
Centrality indices 3 and 4 (%)	51 (40.2)	95 (47.0)	47 (52.8)	12 (35.3)	205 (45.4)
Centrality indices 5 and 6 (%)	19 (15.0)	36 (17.8)	12 (13.5)	4 (11.8)	71 (15.7)
p-value					*.224 (n. s.)*
Exposed to second-hand smoke					
Yes (%)	103 (72.0)	205 (74.3)	104 (73.2)	59 (75.6)	471 (73.7)
No (%)	40 (28.0)	71 (25.7)	38 (26.8)	19 (24.4)	168 (26.3)
p-value					*.936 (n. s.)*
Diagnosis before or after 2006					
Diagnosis ≤ 2006 (%)	53 (36.3)	114 (40.0)	76 (51.4)	55 (66.3)	298 (45.0)
Diagnosis > 2006 (%)	93 (63.7)	171 (60.0)	72 (48.6)	28 (33.7)	364 (55.0)
p-value			*	*	*<.001*

n= numbers, SD = standard deviation, n.s. =not significant
* = significant association at level < 0.05 in posthoc analysis when compared to category "stable disease"

3.2. Progression measured as time to EDSS 6

In total, 24 % (308/1304) had reached EDSS 6 by prevalence date, with a median time to EDSS 6 of 37.0 years (95 % confidence interval (CI) 32.8-42.2). We investigated time to EDSS 6 against socioeconomic factors in adolescence. Maternal level of education was significant associated with time to EDSS 6 (p <0.001) (Fig. 3). Only 15 of the 308 who reached EDSS 6 had mothers with a graduate level of education, and the significant results reflect the difference between maternal primary school and secondary school, with a median time to EDSS 6 of 28.0 years (95 % CI 22.7-33.3) and 39.0 years (95 % CI 35.4-42.6) respectively.

The time to EDSS 6 analysis for paternal level of education showed the same pattern as for maternal level of education, but did not reach significance (data not shown). Residency at age 16 and exposure to second-hand smoking were not significantly associated with time to EDSS 6.

3.3. Progression measured by MSSS in 2018

The mean MSSS was 3.39 (range 0.03-9.98, SD 2.56).The results of the linear regression analysis of the association between MSSS and SES at age 16 and at prevalence date, are shown in Table 4. In the univariable linear regression analysis, disease progression is significantly influenced by sex, age at diagnosis, the maternal level of education, disease subtype at diagnosis, second-hand smoking and treatment with DMTs. For the multivariable analysis, we included the variables identified as significant in univariable analysis, as well as all variables

Table 3
Association of socioeconomic factors, treatment and change in EDSS year 0-5 after diagnosis.

	Improvement (reduction of EDSS ≥1 point)	Stable disease (EDSS ±0.5 points)	Moderate progression (increase in EDSS 1-2 points	Marked progression (increase in EDSS ≥2 points)	Total
Mean age 2018, years (SD)	46.5 (11.0)	52.6 (12.2)	55.8 (10.2)	59.7 (10.9)	52.8 (12.1)
p-value					*<.001*
Patient's level of education					
Primary ≤ 9 years (%)	27 (18.5)	38 (13.5)	35 (23.8)	15(18.3)	115 (17.5)
Secondary 10-12 years (%)	51 (34.9)	124 (44.0)	62 (42.2)	33 (53.7)	281 (42.8)
Graduate ≥ 13 years (%)	68 (46.6)	120 (42.6)	50 (34.0)	23 (28.0)	261 (39.7)
p-value			*		*.010*
Centrality of municipality					
Centrality indices 1 and 2 (%)	86 (58.9)	133 (46.7)	68 (45.9)	43 (51.8)	330 (49.8)
Centrality indices 3 and 4 (%)	54 (37.0)	120 (42.1)	69 (46.6)	34 (41.0)	277 (41.8)
Centrality indices 5 and 6 (%)	6 (4.1)	32 (11.2)	11 (7.4)	6 (7.2)	55 (8.3)
p-value					*.076 (n. s.)*
Hospital responsible for follow-up					
University Hospital (%)	26 (20.8)	55 (22.2)	25 (18.4)	13 (18.6)	119 (20.6)
General Hospital (%)	98 (78.4)	193 (77.8)	110 (80.9)	571 (81.4)	458 (79.1)
p-value					*.761 (n. s.)*
Current smoking					
Yes (%)	26 (18.3)	80 (26.6)	44 (30.6)	22 (27.5)	172 (26.6)
No (%)	116 (81.7)	200 (71.4)	100 (69.4)	58 (72.5)	474 (73.4)
p-value					*.081 (n. s.)*
Ever treated with DMT					
Yes (%)	122 (83.6)	194 (68.1)	89 (60.1)	38 (45.8)	443 (66.9)
No (%)	24 (16.4)	91 (31.9)	59 (39.9)	45 (54.2)	219 (33.1)
p-value				*	*<.001*
Mean MSSS score (SD)	2.03 (2.05)	2.73 (2.10)	4.43 (2.44)	6.97 (1.99)	3.45 (2.65)
p-value					*<.001*

EDSS = Expanded Disability Status Scale, SD = standard deviation, n.s. = not significant, DMT = Disease Modifying Treatment, MSSS = Multiple Sclerosis Severity Score
* = significant association at level < 0.05 in posthoc analysis when compared to category "stable disease"

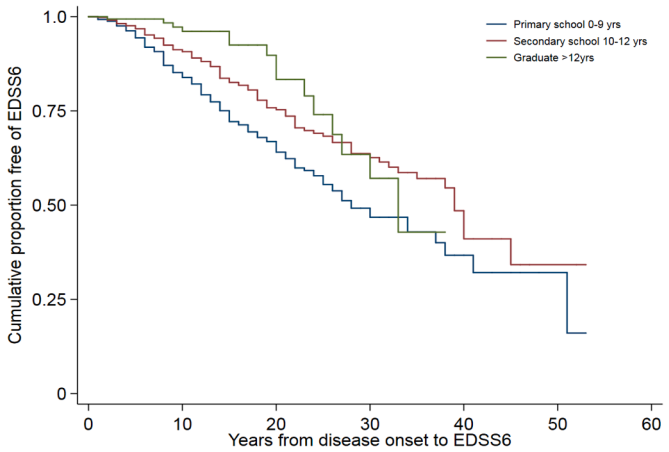

Fig. 3. Kaplan-Meier of time from onset to EDSS 6 against maternal level of education at patient's age 16.

describing conditions from adolescence. Subtype at diagnosis and treatment with DMTs are strongly associated, and to avoid multicollinearity, we only included treatment with DMT ("yes" or "no"). The final model highlights younger age at diagnosis, female sex, DMTs and the patients' level of education as the significantly reducing coefficient for the prediction of MSSS. From adolescence, the only variable significantly included in the final model, is maternal level of education at age 16, but in return, this variable influences MSSS at the same level as DMT. These factors explained 11 % of the variance in MSSS ($R^2 = 0.11$).

We have stratified the study population by the maternal level of education and the results of demographic data are shown in Table 5. The proportion of females is not significantly different in the three groups. Supplementary tables 5b and 5c show the results of demographic data for paternal level of education and residency at age 16.

4. Discussion

This study on the impact of socioeconomic status on disease progression in MS is the first to focus on SES in adolescence. We have used

Table 4
Socio-economic factors associated with MSSS using linear regression analyses.

	Univariable analyses β coefficient (SE)	p-value	Multivariable Model β coefficient (SE)	p-value	Final Model β coefficient (SE)	p-value
Sex						
Female	Ref.					
Male	-0.75 (0.15)	<0.001	-0.73 (0.17)	<0.001	-0.61 (0.16)	<0.001
Maternal level of education *						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.81 (0.16)	<0.001	-0.53 (0.18)	0.004	-0.49 (0.16)	0.003
Graduate ≥ 13 years	-1.25 (0.22)	<0.001	-0.57 (0.27)	0.04	-0.58 (0.24)	0.015
Paternal level of education*						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.26 (0.17)	0.13	0.15 (0.19)	0.43		
Graduate ≥ 13 years	-0.80 (0.21)	<0.001	0.11 (0.25)	0.66		
Centrality of municipality*						
Centrality indices 1 and 2	Ref.					
Centrality indices 3 and 4	-0.12(0.17)	0.50	-0.06 (0.16)	0.70		
Centrality indices 5 and 6	-0.16 (0.24)	0.50	-0.12 (0.24)	0.61		
Second-hand smoking						
No	Ref.					
Yes	0.48 (0.16)	0.003	-0.34 (0.17)	0.84		
Age at diagnosis, years	0.06 (0.01)	<0.001	0.04 (0.01)	<0.001	0.040 (0.01)	<0.001
Age in 2018, years	0.06 (0.01)	<0.001	Not included			
Subtype MS at diagnosis			Not included			
RRMS	Ref.					
PPMS	2.50 (0.23)	<0.001				
SPMS	2.73 (0.36)	<0.001				
Hospital responsible for follow-up			Not included			
University Hospital	Ref.					
General Hospital	0.12 (0.18)	0.50				
Disease modifying treatment			Not included			
None	Ref.					
Moderate efficacy DMT	-1.24 (0.17)	<0.001				
High efficacy DMT	-0.40 (0.26)	0.12				
Both moderate and high efficacy DMT	-0.81 (0.19)	<0.001				
DMT, dichotomized						
No	Ref.					
Yes	-0.97 (0.15)	<0.001	-0.52 (0.19)	0.007	-0.49 (0.17)	0.004
Patients own level of education(2018)						
Primary ≤ 9 years	Ref.					
Secondary 10-12 years	-0.49 (0.20)	0.02	-1.00 (0.22)	<0.001	-0.60 (0.21)	0.004
Graduate ≥ 13 years	-1.21 (0.20)	<0.001	-1.31 (0.22)	<0.001	-0.96 (0.21)	<0.001
Current smoking (2018)			Not included			
No	Ref.					
Yes	0.26 (0.16)	0.10				

* = variables at persons age 16.
MSSS = Multiple Sclerosis Severity Score, Ref. = reference value, SE= Standard error of β, RRMS = relapsing remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, DMT=disease modifying treatment

parental levels of education and residency at age 16, and exposure to second-hand smoking as measures of SES in adolescence. Of these factors, the maternal level of education has a significant impact on the patient's disease progression after diagnosis of MS. Maternal level of education beyond secondary school is associated with less pronounced disease progression measured by EDSS and MSSS. The impact of the maternal level of education is similar to the impact of DMTs. The paternal level of education shows the same pattern, but does not reach statistically significance. The place of residency (urban vs rural) at age 16 does not contribute to any of the measures of progression. Factors contributing to increased risk of disease progression are male sex, older age at diagnosis, progressive subtype of MS at diagnosis, exposure to second-hand smoking and primary school as the patient's highest level of educational attainment.

The impact of socioeconomic status in adolescence on disease progression in MS is in accordance with observations in other conditions (Wolfe, 2015; Ben-Shlomo and Kuh, 2002). The overall explanation for the finding of impact of parental level of education is likely complex in MS. People with a chronic illness need the cognitive resources to absorb information and follow recommendations for treatment and lifestyle. Receiving adequate support from close relatives, and having larger available socioeconomic resources are the strongest predictors of self-management in MS (Wilski et al., 2015).

Health-related behaviors are adapted from parents in childhood, and will be reflected in the person's later life (Gunnarsdottir et al., 2017). There is considerable evidence that a variety of symptoms and conditions precede a diagnosis of MS (Disanto et al., 2018; Wijnands et al., 2017), but these studies do not control for socioeconomic status. There is a clear correlation between education and several life-style factors. In this study, we chose the parental level of education as a central variable for the analyses, to compensate for the fact that a diagnosis of MS may influence the person's own educational attainment (Cortese et al., 2016). We did, however, find that our MS population has a similar level of education as the background population, also when the known correlation between parental and individual level of education is taken into account (Weinberg et al., 2019). This might also be seen as a potential selection bias, as our study only included patients who provided written consent. People with a higher level of education are more likely to participate in studies (Reinikainen et al., 2018).

Smoking is a lifestyle factor, as well as a risk factor of MS, which also has a significant impact on outcomes and overall prognosis in MS (Rosso and Chitnis, 2020). However, current smoking was not a significant risk factor for a more pronounced disease progression in our study. A limitation of our study is that we used smoking status in 2018. Hence, many

Table 5
Demographics by subgroups of maternal educational level.

	Maternal education level at age 16			
	Primary school (0-9 years)	Secondary school (10-12 years)	Graduate (>12 years)	p-value
Numbers all	496	684	224	
Numbers female (%)	349 (70.4)	482 (70.5)	162 (72.3)	n.s.
Age onset, mean (SD)	35.7 (10.5)	33.8 (10.1)	31.0 (9.4)	<.001
Time onset-diagnosis in years, mean (SD)	5.7 (6.6)	5.4 (7.3)	3.8 (5.6)	0.004
Age diagnosis, mean (SD)	41.1 (10.9)	39.0 (10.9)	34.7 (9.6)	<0.001
EDSS diagnosis, median (IQR)	2.5 (2.0-3.5)	2.0 (2.0-3.0)	2.0 (1.5-3.0)	<0.001
Proportion RRMS at diagnosis (%)	372 (76.5)	547 (83.8)	200 (94.8)	<0.001
Proportion treated with DMT (%)	286 (57.7)	434 (63.5)	166 (74.1)	<0.001
MSSS 2018, mean (SD)	3.89 (2.66)	3.10 (2.50)	2.63 (2.1)	<0.001
Proportion smoking 2018 (%)	172(35.6)	164 (24.3)	49 (22.8)	<0.001
Centrality of residency at 16 years age (%)				
Centrality indices 1 and 2	113 (35.6)	202 (39.9)	100 (50.3)	
Centrality indices 3 and 4	160 (50.5)	219 (43.3)	84 (42.2)	
Centrality indices 5 and 6	44 (13.9)	85 (16.8)	15 (7.5)	0.001

SD = Standard deviation, IQR=interquartile range, n.s.= not significant, EDSS = Expanded Disability Status Scale, RRMS = Relapsing remitting multiple sclerosis, DMT = Disease Modifying Treatment, MSSS = Multiple Sclerosis Severity Score

of the patients who self-report as non-smokers in 2018 might have been former smokers, and there are data arguing for a dose-response effect of smoking on MS (Wingerchuk, 2012). In Norway, as in most countries, the proportion of daily smokers has decreased in recent years (WHO global report on trends in prevalence of tobacco use 2000-2025 2019). The classification of former smokers in the group of current non-smokers may explain why we did not find the same impact of smoking on disease progression as previous studies (Degelman and Herman, 2017; Chan et al., 2002). The impact of second-hand smoking in adolescence on progression in our data supports the explanation of smoking as an important risk factor. We could also consider including ethnicity and lifestyle factors such as body mass index, nutrition, including level of vitamin D and level of physical in the multivariate analyses. However, these are all known risk factors for developing MS (Wesnes et al., 2015; Abdollahpour et al., 2020; Wesnes et al., 2018; Dobson et al., 2020) and one might argue that these factors are too strongly correlated with SES to be included as independent risk factors in the analysis, and that the level of both patient's and parental education is the most relevant measure.

The impact of the parental level of education cannot be explained by lifestyle factors alone. When dividing the population into groups by the parental educational level, we found that the age at onset, age at diagnosis and time from onset to diagnosis are significantly lower for the patients whose parents had a graduate level of education. Older age at disease onset is associated with poorer prognosis (Guillemin et al., 2017). The significant differences in these important characteristics of MS are shown both for maternal and paternal levels of education. In the subgroup with highly educated parents, the proportion of RRMS is higher and the median EDSS is lower at diagnosis, which we consider an expression of the same phenomenon. In a socioeconomic setting, the explanation may be that parents with a high level of education both pay more attention to symptoms and teach their children more relevant health-related behavior. In addition, they may also encourage early contact with the health care system for diagnostic clarification upon symptom onset, and provide valuable information when differentiating relapsing and primary progressive MS. Thus, the finding of a better disease outcome in patients whose parents had a higher level of education may possibly be reflected in increased awareness and earlier diagnosis of MS. Earlier diagnosis most often leads to earlier treatment initiation, and disease modifying treatment has had an impact on delaying disease progression (Simonsen et al., 2020). In accordance with previous studies (Brown et al., 2019), we found a significantly less pronounced progression for the DMT-treated population. There is evidence that access to the most effective treatment is facilitated by SES (Calocer et al., 2018), but this needs to be further investigated.

It is interesting that when addressing the impact on the different measures of progression, we only found significant impact with the maternal level of education. Numerous studies have, however, shown strong correlations between maternal education and various childhood outcomes, such as health and mortality. Different models have tried to explain this pattern, one of which includes the tendency for highly educated mothers to be older when giving birth and in general having fewer children, with potentially giving more attention to each (Lundborg P and Rooth, 2012). We have not adjusted our data for maternal age and numbers of siblings in our patients and therefore cannot comment further on this hypothesis.

A study from Telemark, one of the counties in our population, documented a higher prevalence of MS in rural versus urban areas in the period from 1999 to 2019 (Flemmen et al., 2020). The level of education is generally higher in urban areas (centrality indices 1 and 2) of Norway, and this may affect the results. However, we did not find any differences in progression in terms of place of residence, neither at 16 years of age, nor at prevalence date. The Norwegian health service aims to provide equal treatment for all patients. All MS patients attend a neurological department and the cost of DMT's are covered by the health care system. The BOT registry comprises patients who live centrally in the capital and are treated at a University hospital, as well as patients who live a 3-4 hours' drive from a neurologist at a general hospital. A potential weakness in our study is that the number of MS patients living in the most central areas (centrality indices 1 and 2) is relatively smaller than in the background population. However, we found no differences in progression depending on hospital responsible for follow-up.

We have used a real-world, population-based cohort with patients diagnosed across a wide time span, living in a geographically well-defined area, but still with large variations in socioeconomic factors. This improves the validity of our results. All data used as measures for socioeconomic status are validated data from Statistics Norway, with the exception of information on smoking status, which was collected through questionnaires. This reduces the potential recall-bias. A recurring question in the search for factors that affect the course of diseases is if the measures obtained at one time reflect the same underlying processes as those obtained at other stages of life. Our population covers a wide time-span, diagnosed from 1943 to 2018. Even though the socioeconomic data are collected from a reliable source (Statistics Norway), the changes over time may affect the analyses, like proportion of smokers and the general level of education (Gakidou E et al., 2010).

Another potential bias is the possibility of misclassification in the registered EDSS. The EDSS at diagnosis may be influenced by an ongoing relapse, and thus possibly underestimating the change in EDSS the first five years. However, we found a similar significance of maternal level of education on time to EDSS 6, where the EDSS at diagnosis is irrelevant. We would argue that this misclassification is likely independent of socioeconomic status and will not have an impact on the results.

In conclusion, when investigating the impact of socioeconomic factors in adolescence on disease progression, we found the maternal level of education at patient's age 16 to be the most important impact factor.

We have demonstrated that the MS patients whose mothers have a higher level of education have a less pronounced disease progression with an impact similar to the impact of DMTs. This can partly be explained by earlier diagnosis and earlier initiation of DMTs. It is important to identify the association between socioeconomic status and disease progression, and the influence of SES on access to relevant treatment needs closer investigation.

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Author statement

Author contributions for paper: Maternal education has significant influence on progression in multiple sclerosis CRediT author statement:

Heidi Øyen Flemmen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization

Cecilia Smith Simonsen: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Writing – Review and editing

Line Broch: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Writing – Review and editing

Cathrine Brunborg: Methodology, Formal analysis, Writing – Review and editing

Pål Berg-Hansen: Conceptualization, Methodology, Software, Validation, Writing – Review and editing, Supervision

Stine Marit Moen: Conceptualization, Methodology, Validation, Writing – Review and editing

Hege Kersten: Writing – Review and editing, Supervision, Funding acquisition

Elisabeth Gulowsen Celius: Conceptualization, Methodology, Software, Validation, Writing – Review and editing, Supervision, Project Administration

Data statement

Maternal education has significant influence on progression in multiple sclerosis

Due to the sensitive nature of the variables registered and the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

A limited version of the data can be released upon reasonable request to the corresponding author.

Declaration of Competing Interest

Dr. Flemmen reports grants and personal fees from Biogen and Novartis, personal fees from Sanofi and Merck, grants from Odd Fellow research fund and grants from Ingrid and Fritz Nielsen's legacy during the conduct of the study.

Dr. Simonsen reports grants and personal fees from Sanofi Genzyme, grants from Novartis, personal fees from Merck, personal fees from Biogen, grants from Odd Fellow research fund and from Ingrid and Fritz Nielsen's legacy during the conduct of the study.

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Dr. Brunborg has nothing to disclose.

Dr. Berg-Hansen reports personal fees from Biogen, Novartis, Merck, UCB and Sanofi during the conduct of the study.

Dr. Moen has nothing to disclose.

Dr. Kersten has nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103052.

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Original article

The influence of socioeconomic factors on access to disease modifying treatment in a Norwegian multiple sclerosis cohort

Heidi Øyen Flemmen [a,b,*], Cecilia Smith Simonsen [c,b], Line Broch [c,b], Cathrine Brunborg [d], Pål Berg-Hansen [e], Stine Marit Moen [f], Hege Kersten [g,h], Elisabeth Gulowsen Celius [e,b]

[a] Department of Neurology, Telemark Hospital Trust, Skien 3710, Norway
[b] Institute of Clinical Medicine, University of Oslo, Norway
[c] Department of Neurology, Vestre Viken Hospital Trust, Drammen, Norway
[d] Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway
[e] Department of Neurology, Oslo University Hospital, Norway
[f] MS Center Hakadal, Norway
[g] Department of Research, Telemark Hospital Trust, Skien, Norway
[h] Department of Pharmaceutical Bioscience, School of Pharmacy, University of Oslo, Norway

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ABSTRACT

Objective: Several studies report an impact of socioeconomic factors on access to disease modifying treatment (DMT) in multiple sclerosis (MS), with a trend of less access to more deprived persons. We investigated the impact of socioeconomic status (SES) on access to treatment in a well-defined Norwegian MS cohort.
Methods: This is a study of a population-based Norwegian MS cohort. We collected detailed information on disease development, progression, and DMT administered. Socioeconomic data was obtained from Statistics Norway and a questionnaire.
Results: We included 1314 persons with relapsing remitting MS at the prevalence date 01/01/2018. The population ever treated with DMTs is younger at onset, has shorter time from onset to diagnosis and lower expanded disability status score (EDSS) at diagnosis. The persons with MS (pwMS) with the highest levels of education, and those who are married are more likely to be ever treated with DMT. In the subgroup treated with a high efficacy DMT as a first drug, the pwMS are younger at prevalence date (39.9 years (SD 12.1)) compared with those who are not treated with a high efficacy DMT as first drug (43.8 years (SD 10.3)). The subgroup treated with a high efficacy DMT as a first drug has a 0.5 point higher EDSS at diagnosis compared to those not treated with a high efficacy DMT as a first drug. The level of education, household income and marital status are inversely related to access to high efficacy DMT as a first drug. None of the above differences persist when analyzing the subgroup diagnosed within the last six years (2012-2017).
Conclusions: Since 2012, the pwMS in this Norwegian cohort are treated equally with DMT in terms of different measures of socioeconomic position.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease that may cause considerable disability in young people over time (Collaborators, 2019). The prevalence in Norway is among the highest in the world, estimated at 203/100 000 in 2013 (Berg-Hansen et al., 2014). Socioeconomic status (SES) is a composite description of an individual's relative position in society, mostly measured by level of education, income and occupation. There is substantial evidence that individuals with lower SES have poorer health compared to those with higher SES (Mackenbach et al., 2018, Amezcua et al., 2021). This relationship is also reported in welfare states traditionally marked by commitment to social equality, such as the Nordic countries (Lahelma et al., 2001). There is increasing focus on the relationship between SES and the risk of MS (Briggs et al., 2015), and observational studies show an association between socioeconomic deprivation and a more accelerated disease

Abbreviations: DMT, Disease modifying treatment; SES, Socioeconomic status; pwMS, Persons with MS.

* Corresponding author at: Department of Neurology, Telemark Hospital Trust, Skien 3710, Norway.
E-mail address: fleh@sthf.no (H.Ø. Flemmen).

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progression (Harding et al., 2019, Calocer et al., 2020, Flemmen et al., 2021).

A large number of disease modifying treatments (DMTs) for MS have become available during the last 25 years, alongside a focus on the importance of early effective treatment to improve prognosis (Giovannoni et al., 2016, Simonsen et al., 2021). The choice of a suitable DMT for each person with MS (pwMS) is more complex (Montalban et al., 2018, Rae-Grant et al., 2018), with accumulating evidence of inequalities in access to treatment (Browne et al., 2014). An American survey confirms that a substantial fraction of pwMS face financial and health plan-related barriers to obtain expensive DMTs (Iezzoni et al., 2008), and the rising cost of drugs adversely affect access to treatment (Wang et al., 2016). Even in high-income countries, where the cost of all treatments is fully reimbursed, access to therapies varies widely (Giovannoni et al., 2016). Older age and deprived SES are associated with a lower range of available DMT (Roddam et al., 2019). The access to a high efficacy DMT is higher for pwMS with lower deprivation indices (Calocer et al., 2018, Gomez-Figueroa et al., 2021). One possible explanation for this pattern is that less deprived persons were more able to influence decisions towards more efficacious treatments (Owens et al., 2013). However, there is also evidence for the opposite. A recent study from the United Kingdom did not find that SES was associated with the prescribing patterns of DMT in pwMS, and explained this in part by the "treat to NEDA strategy" (Reyes et al., 2020).

There are few population-based studies investigating access to DMTs. Previous studies have mainly recruited members of MS societies and are prone to selection bias and less likely to include those from lower socioeconomic and minority groups (Roddam et al., 2019). The aim of this descriptive study was to investigate if socioeconomic factors have an impact on access to DMTs in MS, with a special focus on access to high efficacy DMTs, in a population-based cohort in the South-East of Norway. The primary endpoints were the impact of socioeconomic factors on overall DMT use and the use of high efficacy drug as the first DMT.

2. Material and methods

2.1. Study design

This is a population-based cohort study of pwMS from the two counties of Buskerud and Telemark, as well as a large part of the MS population in Oslo (Simonsen et al., 2020). These hospitals serve a population of 1.17 million people.

2.2. Standard protocol approvals, registrations and patients consents

All participants provided written, informed consent. The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Regional Ethics Committee (REK 2015/670) and the Data Protection Officer at Oslo University Hospital (OUS).

2.3. Methods

This study is based upon the BOT-MS registry (Buskerud, Oslo, Telemark), a database comprising the complete population of pwMS in the two counties Buskerud and Telemark, as well as the majority of the pwMS in the Norwegian capital of Oslo. We registered all persons with a definite diagnosis of MS according to the prevailing diagnostic criteria. Detailed information on the database and data collection has previously been published (Simonsen et al., 2020). Data were recorded prospectively, but retrospectively retrieved by three neurologists specialized in MS. Data collection for this study was terminated 01/01/2018, defined as prevalence date. We collected time of onset and diagnosis, use of DMT, and time from onset and from diagnosis to initiation of DMT. DMTs were divided into moderate efficacy DMTs (interferons, glatiramer acetate, teriflunomide and dimethyl-fumarate) and high efficacy DMTs (natalizumab, fingolimod, alemtuzumab, rituximab and cladribine). For the pwMS treated with DMT, we registered whether or not a high efficacy DMT was started as the first medication. We further collected disability measured by expanded disability status scale (EDSS) (Kurtzke, 1983) at as many time points as possible. The EDSS at diagnosis was divided into three subgroups by score; 0-1.5, 2-2.5 and $\geq$3. The details on disease onset and progression and use of DMT are collected from the individual electronic patients' journals (EPJ) in each hospital. For this study, we excluded all participants with primary progressive MS as there were no DMT available for this group in Norway as of January 2018. We have further divided the population by diagnosis before 2007 and 2007–2017, because the first high efficacy DMT, natalizumab, was introduced in November 2006 (Polman et al., 2006). The population diagnosed within the last six-year period (2012–2017) was used for evaluating the most recent treatment patterns. This time-interval was chosen because the first per oral high efficacy DMT, fingolimod, was introduced in 2011 and with that supplement, the choice between moderate and high efficacy treatment as first DMT is considered relevant.

We have used different measures of socioeconomic status as possible predictors for influence on access to DMT. Statistics Norway provided additional information on country of birth, marital status, level of education, municipality and household income based on annually performed censuses. The level of education was divided into groups according to the total number of years in the education system (0–9 years as primary, 10–13 years as secondary, 14–17 years as graduate and $\geq$18 years as long graduate). In addition to the pwMS' own level of education at prevalence date, we have used the level of combined parental education at the pwMS 16 years of age based on the highest level of education one of the parents have achieved, measured in years and divided into groups as done on individual level. The municipality at both age 16 and prevalence date were recoded into six groups by the Centrality index. This index is developed by the Norwegian Government and measures how centrally the municipalities are located in terms of service functions and work places reachable for a resident. Indices 1 and 2 denote the most central area, while index 5 and 6 denotes the most rural areas (Høydahl, 2017). Birth country is sub-grouped into Norway, Western (Europe without Norway, US, Canada, New Zealand and Australia) and Non-Western (Africa, Asia, South America) countries. The marital status is presented as married, widowed, divorced or other, the latter including both single living persons and persons in a cohabitation. The household income is the after-tax income per consumption unit, corrected for differences in household size. The correction is performed by Statistics Norway using the European Union (EU)-equivalence scale. This scale assigns a value of 1 to the household head, of 0.5 to each additional adult member and of 0.3 to each child under the age of 17. We have converted the report of income from Norwegian kroner to the EU currency (Euro), using the exchange rate on 12/29/17 (9.851, according to DNB market).

The pwMS provided information through a validated questionnaire (ECTRIMS Online Library. Flemmen H. 09/12/19; 279125; P765). The questionnaire contained information on smoking habits, other autoimmune diseases, self-perceived SES using the 10-steps MacArthur Scale (Adler et al., 2000) and self-perceived health. The self-perceived SES was sub-grouped into three steps; low (steps 1–3), medium (steps 4–7) and high (steps 8–10). Self-perceived health status was assessed using the single-item question characterising the overall physical health in five possible responses (excellent, very good, good, fair and poor). In the results, we have grouped the categories fair and poor together.

2.4. Statistical analysis

We used IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Data are presented as means $\pm$ standard deviation (SD), median with interquartile range (IQR), or frequencies, depending on distribution. Cross tabulations were

computed in order to investigate the relationship between different variables and treated or not, and treated high efficacy DMT as first or not. The Pearson chi-square test or Fisher exact test were used to detect associations between categorical variables, as appropriate. We used independent sample t-test for the normally distributed, continuous variables, and Mann-Whitney U test for very skewed continuous and ordinal variables. Multivariable binary logistic regression models were used to analyze the impact of socioeconomic variables on access to high efficacy DMT as a first treatment. Factors to include in the multivariable model were chosen based on prior knowledge from the literature and by expert opinion. We present the complete multivariable model to show which socioeconomic variables were strongest associated with access to DMT. We have analyzed all factors together without subsequent elimination of variables driven by our data and the results are presented as odds ratio (OR) with 95 % confidence interval (CI) and *p*-values. The analyses were done within subgroups of year for diagnosis. All p-values were two-sided with a significance level of 5 %. To estimate time from onset to high efficacy DMT by socioeconomic variables, we used the Kaplan-Meier method.

Possible multicollinearity between socioeconomic measures was assessed using Spearman correlation coefficient with ≥ 0.7 as cut-off; none of the included variables are strongly associated. Linear trends were tested using Mantel-Haenszel test for linear trend, or by linear regression with categories of time-period for diagnosis treated as an ordinal score.

3. Results

The registry comprises 3951 pwMS, 2512 pwMS were alive and invited to participate in the study. We received 1598 written consents to participate (response rate 64 %), of which 1573 completed the questionnaire. We excluded 274 pwMS with a primary progressive or unknown phenotype at diagnosis, leaving 1314 pwMS for the final analysis. The cohort was further stratified by ever treated with DMT (n = 902) or never treated with DMT (n = 412), and by year of diagnosis; diagnosed ≤2006 (n = 592), diagnosed 2007-2017 (n = 715), and diagnosed 2012–2017 (n = 396). The year of diagnosis is unknown in seven pwMS. Fig. 1 shows a flowchart of the population and sub-groups.

The mean time from diagnosis to start of DMT has changed from 111 months (SD 80.4) for those diagnosed before 1997 to 3 months (SD 5.6)

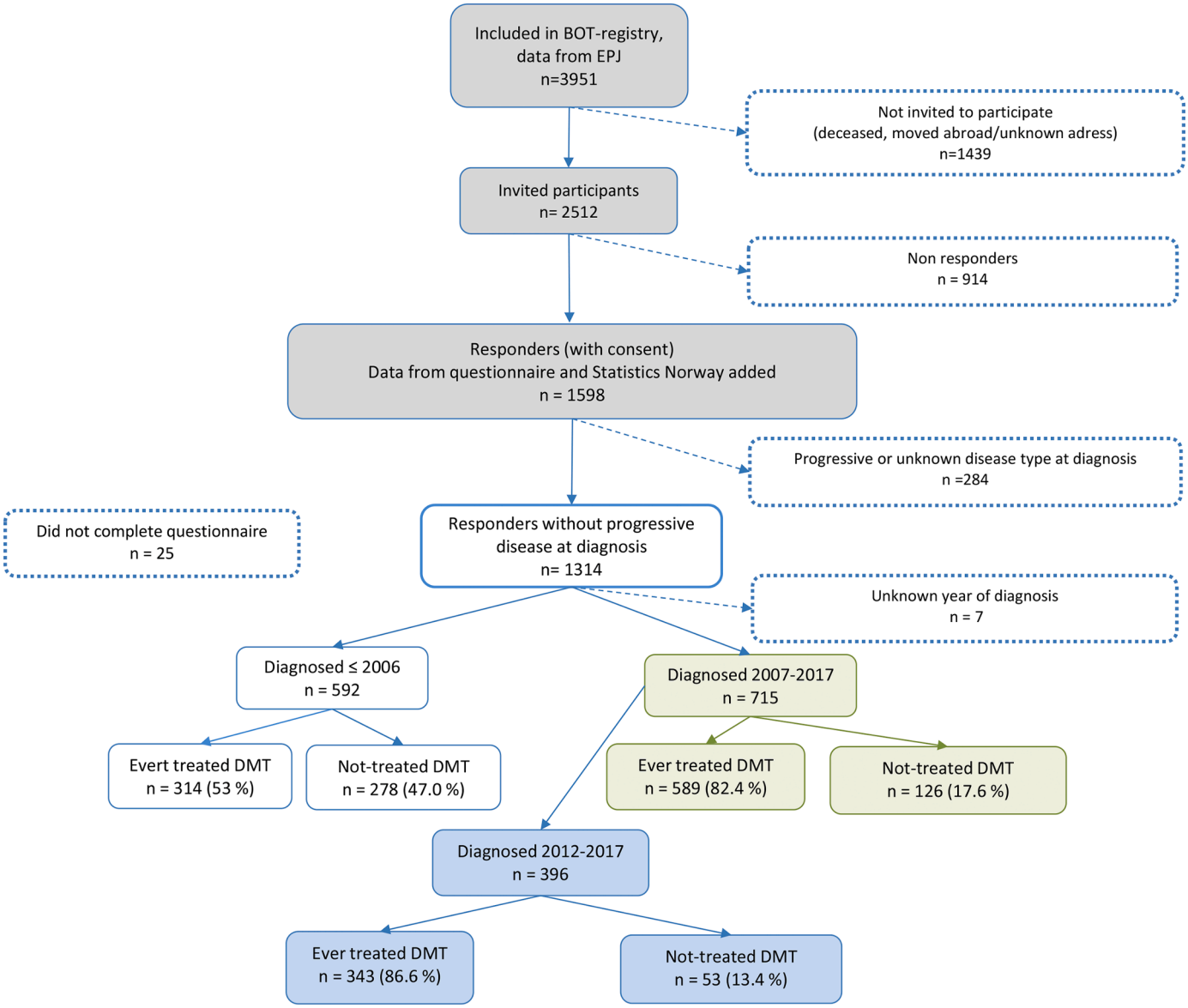

Fig. 1. Flowchart of study population and different sub-groups.
BOT = Buskerud Oslo Telemark (counties of Norway), EPJ = Electronic Patient Journal, n= numbers, DMT = Disease-modifying treatments

for those diagnosed 2012-2017, as shown in Fig. 2.

Table 1 shows the demographic data for the population at prevalence date by characteristics of disease, socioeconomic status at 16 years of age and current self-perceived health-status. The ever treated subgroup is younger at onset, at diagnosis and at present, has shorter time from onset to diagnosis and is characterized by a lower EDSS at diagnosis and at present compared with those never treated with a DMT. The treated subgroup is better educated and has better educated parents. The treated subgroup scored significantly higher on self-perceived health, while the never-treated group reported more additional autoimmune diseases. Never-treated pwMS were more frequently «widowed» or «divorced". We did not find any significant difference in centrality of municipality, self-reported SES, median household income, smoking status or country of origin. The median household income after the EU standard is 39 711 Euros for the general population in Norway, and 38 479 Euros for the general population in Buskerud, Oslo and Telemark at prevalence date. There are no significant differences in any of the socioeconomic parameters between never-treated and ever treated pwMS in the subgroup diagnosed 2012-2017. The most recent treated subgroup remains significantly younger at diagnosis and at present, have shorter time from onset to diagnosis and lower EDSS at diagnosis and present. These additional data are listed in the supplementary Table 1. We have performed the same analysis on the subgroup diagnosed 2007-2017 with the similar results (data not shown). The distribution at different levels of education has also remained stable, both for pwMS and their parents, when comparing the different subgroups (data not shown).

A comparison of pwMS treated with a high efficacy DMT as a first drug and those not, is shown in Table 2. The high efficacy treated group was younger at prevalence date, but not at onset or diagnosis, and the EDSS was 0.5 points higher. There is an inverse impact of the level of education, where the pwMS with the lowest degree of educational achievements have a higher proportion of high efficacy treatment as a first drug. Similarly, there are fewer married pwMS in the high efficacy treatment group. Finally, the median household income is significantly lower in the subgroup with high efficacy DMT as a first treatment. However, the differences in median household income and marital status are not significant in pwMS diagnosed 2012-2017.

Table 3 shows the impact of disease course and SES on high efficacy treatment as the first DMT with all factors taken together in a multivariable logistic regression analysis. In the multivariable logistic regression model, persons with self-perceived excellent overall health-status compared to the group with self-reported fair or poor health was identified as the strongest SES associated with high efficacy treatment (OR 4.99, 95% CI 1.66-15.01). The persons with self-perceived excellent overall health-status have an OR of 4.99 (95% CI 1.66–15.01) for high efficacy treatment compared to the group with self-

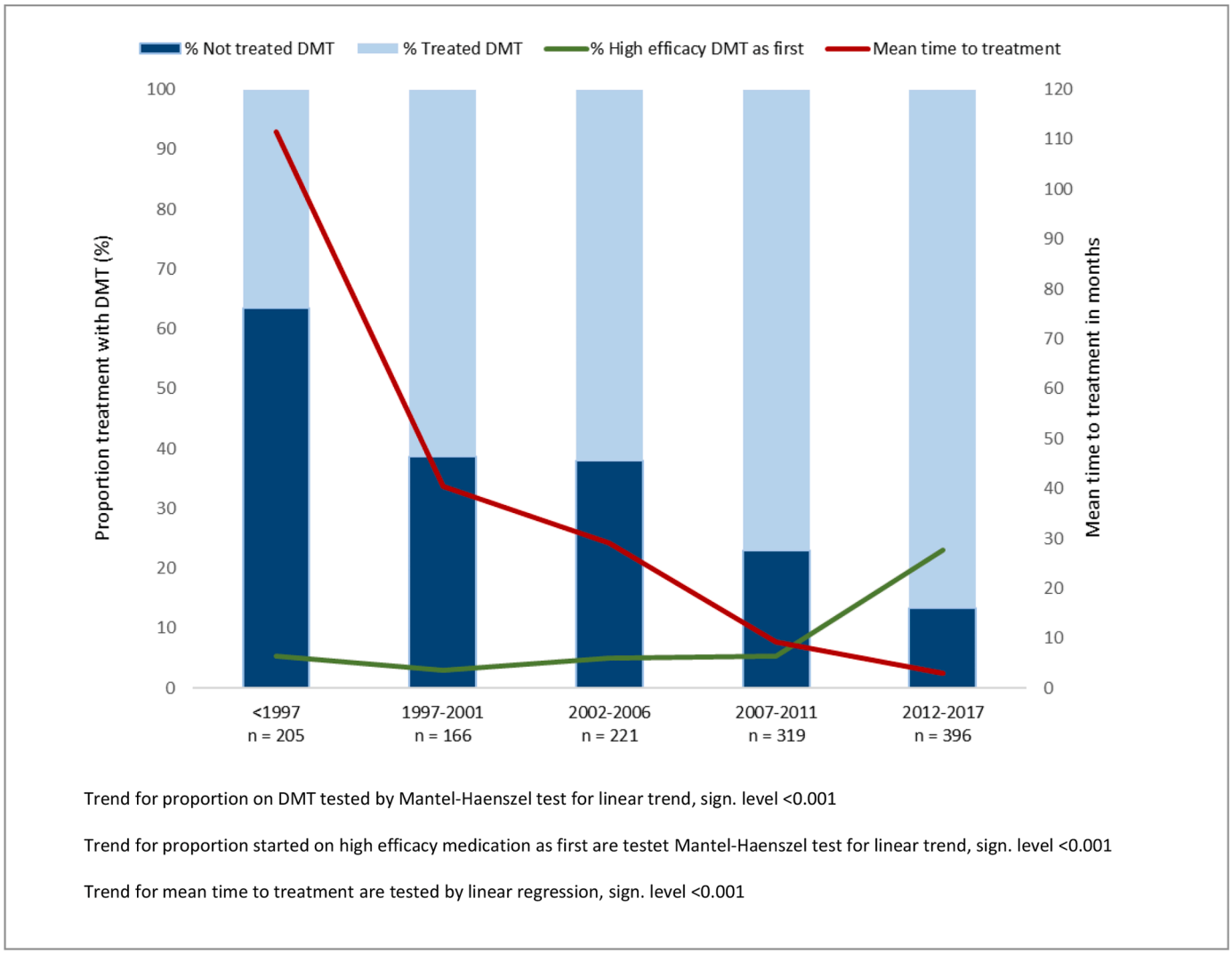

Fig. 2. Proportion of pwMS with and without disease-modifying treatment, proportion high efficacy treatment as first and mean time to treatment by time-period for diagnosis.
DMT= disease modifying treatment

Table 1
Characteristics of the study population and their association with use of DMT.

	ALL (n=1314)	Not treated with DMT (n=411)	Treated with DMT (n=903)	p-value
Sex (n=1314)				
Female, %	72.9	74.7	72.1	
Male, %	27.1	25.3	27.9	0.325
Proportion of females in fertile age18-40, %	*24.7*	*9.4*	*32.0*	*<.001*
Characteristics of disease (n = 1314)				
Mean age onset, years (SD)	33.5 (9.9)	34.5 (10.5)	33.1 (9.6)	**0.020***
Mean time onset to diagnosis, years (SD)	5.0 (6.9)	8.0 (8.5)	3.7 (5.5)	**<.001***
Mean age diagnosis, years (SD)	38.4 (10.8)	42.3 (11.5)	36.7 (9.8)	**<.001***
Mean age 2018, years (SD)	50.9 (13.1)	60.0 (11.8)	46.7 (11.4)	**<.001***
Median EDSS at diagnosis (IQR)	2.0 (1.5-3.0)	2.5 (2.0-3.5)	2.0 (1.5-3.0)	**<.001****
Median EDSS at prevalence date (IQR)	2.5 (1.5-4.0)	3.5 (2.0-6.0)	2.0 (1.5-3.5)	**<.001****
Characteristics of socioeconomic status in adolescence (16 years of age)				
Level of education parents combined (n=1197)				
Primary ≤ 9 years, %	19.5	25.8	17.0	
Secondary 10-13 years, %	51.8	53.3	51.2	
Graduate 14-17 years, %	18.0	15.1	19.1	
Graduate ≥ 18 years, %	10.7	5.8	12.7	**<.001**
Centrality of municipality (n = 922)				
Centrality indices 1 and 2, %	39.8	46.8	38.2	
Centrality indices 3 and 4, %	46.0	38.2	47.8	
Centrality indices 5 and 6, %	14.2	15.0	14.0	0.061
Characteristics of socioeconomic status at prevalence date 2018				
Level of education, pwMS (n = 1304)				
Primary ≤ 9 years, %	17.6	14.2	19.2	
Secondary 10-13 years, %	38.3	47.5	34.0	
Graduate 14-17 years, %	31.2	28.9	32.3	
Graduate ≥ 18 years, %	12.9	9.3	14.5	**<.001**
Centrality of municipality (n = 1312)				
Centrality indices 1 and 2, %	57.2	60.2	55.8	
Centrality indices 3 and 4, %	36.2	32.0	38.1	
Centrality indices 5 and 6, %	6.6	7.8	6.1	0.074
Self-reported SES median (IQR) (n = 1265)				
High (steps 8-10), %	22.1	22.1	22.1	
Medium (steps 4-7), %	67.5	70.0	66.4	
Low (steps 1-3), %	10.4	7.9	11.5	0.145
Median income household, Euros (IQR) (n = 1311)	39 063 (30 8062 - 50 638)	37 702 (31 313 - 48 332)	39 775 (30 612 - 51 379)	0.310**
Marital status (n = 1310)				
Married, %	49.9	51.0	49.4	
Widowed, %	2.7	6.3	1.0	
Divorced, %	16.6	21.7	14.2	
Other, %	30.8	21.0	35.5	**<.001**
Birth country (n = 1314)				
Norway, %	92.3	93.4	91.8	
Western country, %	5.9	5.1	6.2	
Non-western country, %	1.8	1.5	2.0	0.578
Smoking (n = 1285)				
Yes, %	27.9	29.2	27.3	
No, stopped, %	40.2	43.1	38.9	
Never, %	31.9	27.7	33.8	0.088
Comorbidity				
Additional autoimmune diseases (n = 1314)				
Yes, %	18.6	21.9	17.2	
No, %	81.4	78.1	82.8	**0.041**
Self-perceived overall health-status (n = 1291)				
Fair or poor, %	17.0	20.8	15.3	
Good, %	31.2	31.7	31.0	
Very good, %	38.6	37.9	38.9	
Excellent, %	13.2	9.7	14.8	**0.015**

n= numbers, SD = standard deviation, QR interquartile range, DMT = disease modifying treatment, pwMS = person with MS, EDSS = expanded disability status score, SES = socioeconomic status.
Significance tests by Pearson Chi-Square, except: * significance test by independent sample t-test, ** significance test by non-parametric, Mann Whitney independent samples

reported fair or poor health. The level of own or parental education does not significantly influence the OR of receiving a high efficacy treatment as a first drug. There is, however, a significantly lower OR for high efficacy treatment as the first drug with increasing quartiles of median household income. Finally, the group with EDSS 3 or higher at diagnosis has a significantly higher OR for high efficacy treatment as the first drug compared to those with EDSS 0-1.5. There was no significant difference between pwMS living in rural and urban areas. There is a similar pattern in the subgroup diagnosed 2012-2017 except for a lack of significant difference in the impact of household income.

The time to initiation of high efficacy treatment for the subgroup diagnosed 2007-2017, was 36 months (95 % CI 29.1–42.9). The median time to high efficacy treatment for persons living in rural areas was 12 months, (95 % CI 6.9–17.1) compared to 40 months (95 % CI 30.1–49.9) for those living in the most central areas. Time to high efficacy treatment increases with increasing household income, see Fig. 3. The other measures of SES do not reach significance on time to treatment. For the subgroup diagnosed 2012-2017, the overall median time to high efficacy treatment was 23 months (95 % 15.4-30.6), again with shorter median time for persons living in rural areas and with lower household income (data not shown).

4. Discussion

Our main finding is that contemporary pwMS are treated broadly equally with DMT in terms of socioeconomic position in this Norwegian cohort. Our findings consequently do not support previous reports of less DMT prescribing to the most socially deprived pwMS. We, admittedly, found a tendency for more DMTs among the highly educated in the historical cohort, both when measuring the level of education of pwMS themselves and their parents. However, these differences disappeared when investigating only the most recently diagnosed. In fact, the recent MS population with the lowest level of education was associated with a larger proportion of high efficacy DMT as the first treatment. We also

Table 2
Association high efficacy drug versus not high efficacy drug as first treatment, diagnosed after 2006 and after 2011.

	Diagnosed 2007-2017				Diagnosed 2012-2017			
		High effective treatment as first				High effective treatment as first		
	All treated (n = 588)	No(n = 496)	Yes(n = 92)	p-value	All treated(n= 343)	No(n = 264)	Yes(n = 79)	p-value
Sex								
Females, %	70.9	71.6	67.4		71.1	71.6	69.6	
Males, %	29.1	28.4	32.6	0.417	28.9	28.4	30.4	0.735
Proportion of females in fertile age 18-40, %	43.9	41.7	56.5	**0.031**	50.4	47.1	61.8	0.055
Characteristics of disease								
Mean age onset, years (SD)	34.9 (10.0)	34.5 (9.5)	34.0 (11.1)	0.676*	34.8 (10.0)	35.1 (9.5)	33.2 (11.2)	0.176*
Mean time onset to diagnosis, years (SD)	4.2 (6.7)	3.3 (5.5)	2.4 (4.6)	0.104*	4.1 (6.9)	3.5 (6.2)	2.4 (4.6)	0.092*
Mean age diagnosis, years (SD)	39.1 (11.3)	37.7 (10.1)	36.4 (11.4)	0.296*	38.9 (11.3)	38.5 (10.2)	35.6 (11.4)	**0.046***
Mean age 2018, years (SD)	44.9 (11.8)	43.8 (10.3)	39.9 (12.1)	**0.004***	42.3 (11.4)	42.0 (10.1)	38.3 (11.7)	**0.012***
Median EDSS at diagnosis (IQR)	2 .0 (1.5-3.0)	2.0 (1.5-3.0)	2.5 (2.0-3.5)	**<0.001****	2.0 (1.5-3.0)	2.0 (1.5-2.5)	2.5 (2.0-3.5)	**0.002****
Characteristics of socioeconomic status in adolescence (16 years of age)								
Level of education parents combined								
Primary ≤ 9 years, %	17.1	16.9	18.8		14.9	13.8	18.7	
Secondary 10-13 years, %	51.2	51.3	50.5		49.1	49.4	48.0	
Graduate 14-17 years, %	19.1	18.9	20.8		20.8	20.2	22.7	
Graduate ≥ 18 years, %	12.6	13.0	9.9	0.786	15.2	16.6	10.7	0.486
Centrality of municipality								
Centrality indices 1 and 2, %	37.0	36.5	39.5		36.8	35.2	42.3	
Centrality indices 3 and 4, %	49.0	49.1	48.1		50.2	51.3	46.5	
Centrality indices 5 and 6, %	14.1	14.4	12.3	0.823	13.0	13.6	11.3	0.545
Characteristics of socioeconomic status at prevalence date 2018								
Level of education, pwMS								
Primary ≤ 9 years, %	20.1	17.9	31.9		22.7	19.6	32.9	
Secondary 10-13 years, %	30.8	32.2	23.1		31.6	34.6	21.5	
Graduate 14-17 years, %	32.5	33.0	29.7		30.7	30.8	30.4	
Graduate ≥ 18 years, %	16.7	16.9	15.4	**0.020**	15.0	15.0	15.2	**0.046**
Centrality of municipality								
Centrality indices 1 and 2, %	57.1	58.4	50.0		57.0	58.2	53.2	
Centrality indices 3 and 4, %	37.5	36.4	43.5		37.4	36.5	40.5	
Centrality indices 5 and 6, %	5.5	5.3	6.5	0.327	5.6	5.3	6.3	0.683***
Self-reported SES								
High (steps 8-10), %	21.1	21.3	20.0		18.1	17.3	20.8	
Medium (steps 4-7), %	66.1	66.9	62.2		69.4	70.8	64.9	
Low (steps 1-3), %	12.7	11.8	17.8	0.295	12.5	11.9	14.3	0.621
Median income household in Euros (IQR)	38 708 (30 286-50 423)	39 727 (31 372-51 101)	33 168 (24 359-45 468)	**<0.001****	37 461 (28 681-47 378)	38 023 (29 615- 47 571)	36 074 (25 006-46 231)	0.153**
Marital status								
Married, %	45.2	47.2	34.8		38.6	40.7	31.6	
Widowed, %	0.9	1.0	0		0.6	0.8	0.0	
Divorced, %	11.4	11.9	8.7		10.8	11.8	7.6	
Other, %	42.5	39.9	56.5	**0.033*****	50.0	46.8	60.8	0.182***
Birth country								
Norway, %	90.6	90.7	90.2		91.0	90.9	91.1	
Western country, %	7.1	7.1	7.6		7.3	7.6	6.3	
Non-western country, %	2.2	2.2	2.2	0.948***	1.7	1.5	2.5	0.746***
Smoking								
Yes (%)	36.5	36.9	34.8		31.1	30.1	34.2	
No, stopped (%)	36.0	37.1	30.4		34.3	35.5	30.4	
Never (%)	27.5	26.1	34.8	0.206	34.6	34.4	35.4	0.668
Comorbidity								
Additional autoimmune disease								
Yes, %	16.8	17.1	15.2		21.0	22.0	17.7	
No, %	83.2	82.9	84.8	0.651	79.0	78.0	82.3	0.416
Self-perceived overall health-status								
Fair or poor, %	13.4	14.4	8.7	0.142	15.0	16.9	8.9	
Good, %	31.0	29.8	37.0		31.3	30.0	35.4	
Very good, %	38.4	39.5	32.6		38.3	40.0	32.9	
Excellent, %	17.1	16.3	21.7		15.3	13.1	22.8	0.052

n= numbers, SD = standard deviation, QR interquartile range, pwMS = person with MS, EDSS = expanded disability status score, SES = socioeconomic status. Significance tests by Pearson Chi-Square, except: * significance test by independent sample t-test, ** significance test by non-parametric, Mann Whitney independent samples, *** significant test by Fischer exact

Table 3
Complete multivariable logistic regression model for association between socioeconomic position and receiving high efficacy disease modifying treatment for MS as first drug.

	Diagnosed 2007-2017			Diagnosed 2012-2017		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Male	1.0 (ref.)			1.0 (ref.)		
Female	0.77	0.45-1.31	0.333	0.95	0.50-1.79	0.874
Age of onset, per year	0.99	0.97-1.02	0.428	0.97	0.94-1.00	0.055
EDSS at diagnosis						
0-1.5	1.0 (ref.)			1.0 (ref.)		
2-2.5	0.93	0.47-1.85	0.840	0.87	0.41-1.87	0.726
3 or more	**2.45**	**1.27-4.77**	**0.008**	**2.61**	**1.24-5.50**	**0.012**
Parental level of education at pwMS age 16						
Primary ≤ 9 years	1.0 (ref.)			1.0 (ref.)		
Secondary 10-13 years	1.07	0.53-2.15	0.856	0.74	0.33-1.67	0.466
Graduate 14-17 years	0.94	0.40-2.20	0.882	0.78	0.29-2.07	0.613
Graduate ≥ 18 years	0.63	0.21-1.83	0.392	0.43	0.13-1.41	0.165
Level of education in 2018, pwMS						
Primary ≤ 9 years	1.0 (ref.)			1.0 (ref.)		
Secondary 10-13 years	**0.37**	**0.19-0.75**	**0.005**	**0.34**	**0.15-0.77**	**0.009**
Graduate 14-17 years	0.63	0.31-1.28	0.200	0.56	0.24-1.31	0.181
Graduate ≥ 18 years	0.71	0.29-1.76	0.462	0.97	0.18-1.46	0.209
Centrality of municipality in 2018						
Centrality indices 1 and 2	1.0 (ref)			1.0 (ref.)		
Centrality indices 3 and 4	1.23	0.71-2.15	0.462	1.14	0.58-2.22	0.708
Centrality indices 5 and 6	1.28	0.45-3.64	0.644	1.55	0.46-5.16	0.478
Quartile income household in Euros						
Q1	1.0 (ref)			1.0 (ref.)		
Q2	**0.36**	**0.18-0.72**	**0.004**	0.50	0.22-1.12	0.092
Q3	**0.38**	**0.19-0.75**	**0.006**	0.46	0.20-1.05	0.065
Q4	**0.45**	**0.22-0.93**	**0.030**	1.02	0.43-2.37	0.964
Self-perceived overall health-status						
Fair or poor	1.0 (ref)			1.0 (ref.)		
Good	**3.13**	**1.17-8.40**	**0.023**	**4.22**	**1.37-13.06**	**0.012**
Very good	2.33	0.84-6.44	0.104	3.08	0.96-9.88	0.059
Excellent	**4.99**	**1.66-15.01**	**0.004**	**8.21**	**2.29-29.45**	**0.001**

EDSS = expanded disability status score, pwMS = person with MS.
OR = odds ratio, CI = confidence interval, ref = reference variable.
Q1 = quartile 1 (0-30 862 Euros) Q2 = quartile 2 (30 863 – 39 063 Euros), Q3 = quartile 3 (29 064 – 50 638 Euros) Q4 = quartile 4 (≥ 50 639 Euros) of household income. **Significant associations in bold**.

found an association between lower household income and high efficacy treatment. This reversed association of income did not persist when the analysis was limited to those diagnosed with MS within the last six-year period.

There is convincing evidence that the use of DMT in general (Brown et al., 2019), early use of high efficacy DMT (He et al., 2020, Harding et al., 2019) and time to treatment initiation (Simonsen et al., 2021, Chalmer et al., 2018) have considerable influence on the disease course and disability progression in MS. Focus on equal access of DMT for all pwMS, regardless of socioeconomic background, is therefore of great importance. There are numerous international and national treatment strategies and algorithms to support the choice of DMT. A newly published study from our neighboring countries Denmark and Sweden was the first to show that differences in national treatment recommendations have a marked association with disability outcome (Spelman et al., 2021). In Norway, there are no individual insurances affecting the choice of treatment, but we have national guidelines setting the standards for which DMT is preferred for the different patient categories. The guidelines have changed in recent years from a preferred escalation strategy to focus on early high efficacy treatment to reach no evidence of disease activity (Holmoy et al., 2021). The increasing number of available DMTs for relapsing-remitting MS allows for personalized treatment strategies (Giovannoni et al., 2016). Individual health professionals' interpretation and perception, in addition to organizational cultures, may influence the DMT prescribing decisions (Cameron et al., 2019). Our study was conducted in three centers, most likely mitigating the influence of local prescribing cultures.

Area-level measures of SES are a commonly used measure of deprivation, with a potential risk of missing individual level variation within the same area (Reyes et al., 2020). We have used both area-level and individual-level indicators of SES in our study, securing a more accurate measure of variations in deprivation. The individual level-indicators "household income" and "level of education" were the most significant predictors for being treated with a high efficacy DMT. We did not find differences in access to treatment according to the centrality of municipality, which is an area-level SES indicator. Nevertheless, the time to initiation of high efficacy treatment is considerably lower for pwMS in the most rural areas. We have previously shown that persons from this cohort who live in more rural areas have a more aggressive disease course, which we believe is due to confounding factors, in particular level of education (Flemmen et al., 2021).

Previous studies have argued that people from less-deprived areas have less severe disease and shorter time from onset to diagnosis, which makes them more suitable for treatment (Owens et al., 2013). A more general argument has been that persons with lower SES have more difficulties in communicating their needs, impeding shared decision making (van Ryn and Burke, 2000). Health literacy describes the capacities of people to meet the complex demands of health, and has a well described social gradient. The level of education is particularly important in measures of health literacy (Sorensen et al., 2015). Health literacy in adolescence is strongly associated with parental level of education (Fretian et al., 2020), and the strongest predictor of self-management of the disease for pwMS, is adequate support from close relatives (Wilski et al., 2015). When exploring the proportion ever treated in our cohort, we found a larger proportion with DMTs in the pwMS with parents of higher levels of education. This may be explained by high health literacy. However, when including only pwMS diagnosed after 2006 and access to high efficacy treatment as first choice of DMT, we did not find any impact of SES measures from adolescence. As for the group ever treated, we found that these participants had lower EDSS at diagnosis than participants who had never been treated. We attribute this pattern to cautious prescribing practices among neurologist in the early days of DMT. However, when investigating access to high efficacy treatment as a first DMT, the EDSS is higher among the pwMS receiving high efficacy treatment. This is in line with previous findings (He et al., 2020). It is likely a sign of more severe disease at diagnosis and,

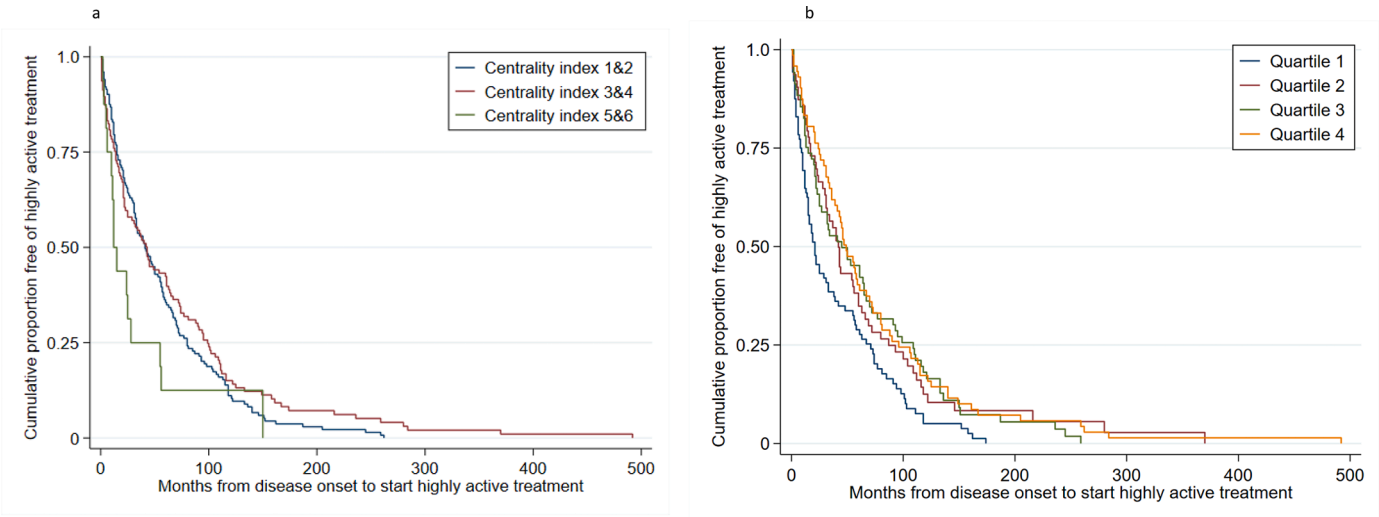

Fig. 3. Time to high efficacy treatment, a) By centrality of municipality, b) by household income. Kaplan Meyer plot.

consequently, more active treatment from the beginning. We believe this represents a change in the treatment pattern among neurologist with an increasing focus on personalized treatment.

We have previously shown that time to diagnosis is influenced by socioeconomic variables within this cohort (Flemmen et al., 2021). However, the present study shows that time from onset to high efficacy treatment is not associated with SES. In fact, time to high efficacy treatment was shorter for pwMS living in rural areas and for pwMS from lower income households. This may be explained by the fact that the pwMS within these groups have signs of more aggressive disease, in terms of higher EDSS at diagnosis (Flemmen et al., 2021), justifying the use of more efficacious DMTs. This is supported by an OR of 2.45 (95% CI 1.27-4.77) for high efficacy DMT as the first choice for pwMS with EDSS $\geq$ 3 at diagnosis compared to pwMS with EDSS $\leq$ 1.5

Smoking is a life-style factor associated with numerous diseases. Smoking did not contribute to the proportion of treatment. Ethnicity and pregnancy plans may represent other potential confounding factors. We did not find any impact of country of birth on the analysis of ever treatment. The total number of non-Norwegian participants is too small to perform any further detailed analysis regarding ethnicity. We did find a higher frequency of treatment in females of fertile age than in females above fertile age, probably due to the fact that this group represents a major part of the MS population. Pregnancy plans are likely not a significant contributor to the overall level of treatment.

The major strength of this study is the geographically defined complete population and the use of valid census data. A limitation of the study is the use of income at prevalence date, which represents a time span from time of diagnosis and, potentially, start of treatment. A clinically stable disease is associated with a reduced risk of losing income from salaries (Chalmer et al., 2020), with a possible influence on the proportion of high efficacy treatment as well as time to treatment. We have tried to minimize this non-differential misclassification by using the household income, not the salary for the pwMS alone. There is a possible misclassification in our study regarding the marital status, as Statistics Norway does not distinguish single living persons from unregistered cohabitant couples, categorizing both of them as "other" marital status. We do, however, recognize a tendency of treating the divorced pwMS more often with high efficacy DMT. This may, in part, be explained by the recognition of a more aggressive disease course among divorced persons, which may be associated with the general influence of marital status on healthy behavior (Hughes and Waite, 2002). In a previous study, we have published data (in supplementary Table 1) of demographic characteristics of participants versus non-participants in our cohort. The participants were slightly younger and had shorter disease duration at prevalence date compared to the non-participants (Broch et al., 2021). We believe this is not in conflict with the generalizability of our results, as of the younger pwMS is the most relevant to treatment with DMT.

The decision to start DMT and the choice of drug, is for most clinicians influenced by relapse rate, MRI findings and EDSS, as well as individual factors in the pwMS, like contraindication and comorbidity. The impact of MRI and relapse rate on the decision have change considerably over the years, and we have chosen not to include those factors in the analysis. This is a limitation to our study.

Another limitation that should be noted, is that a large number of statistical tests were performed, which increases the likelihood of one or more false positives. Nevertheless, we have chosen not to adjust for multiple comparisons as correcting for type I errors cannot be done without inflating type II errors (Rothman, 2014).

A potential confounding factor for choice of DMT in MS is comorbidity. PwMS with other autoimmune diseases or e.g. a history of cancer are subject to specific recommendations or even contraindications to DMTs. Consistent with previous reports (Chouhfeh et al., 2015), we did not find any influence of other autoimmune disease for any treatment strategies. We did not have available data for other comorbidities in this study, but we have included the pwMS' own perception of overall health. We found that persons with self-perceived excellent overall health status had higher OR for high efficacy treatment as a first DMT compared to the group with self-reported fair or poor health. This may be seen as a tendency to treat persons with better general health more often and more effectively. We have thus not been able to confirm the study from the US reporting persons with excellent overall health to be the least likely to have ever taken DMTs (Iezzoni et al., 2008). A weakness of this measure is that this self-report was collected in 2018 and is not an accurate measure of general health at the time of treatment initiation. The score may as well be seen as a consequence of treatment. This reinforces the impression that the choice of DMT is of great importance to the individual pwMS, and there is a need for extensive focus on levelling out differences that may be solely due to SES.

5. Conclusion

In this study on the impact of socioeconomic factors on the choice of DMT in MS in this Norwegian cohort, we describe a change over time to a current pattern where the pwMS are treated broadly equally with DMT regardless of socioeconomic position.

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Data statement

The influence of socioeconomic factors on access to disease modifying treatment in a Norwegian multiple sclerosis cohort Due to the sensitive nature of the variables registered and the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared. A limited version of the data can be released upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Heidi Øyen Flemmen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Cecilia Smith Simonsen:** Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Line Broch:** Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Cathrine Brunborg:** Methodology, Formal analysis, Writing – review & editing. **Pål Berg-Hansen:** Conceptualization, Methodology, Software, Validation, Writing – review & editing, Supervision. **Stine Marit Moen:** Conceptualization, Methodology, Validation, Writing – review & editing. **Hege Kersten:** Writing – review & editing, Supervision, Funding acquisition. **Elisabeth Gulowsen Celius:** Conceptualization, Methodology, Software, Validation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

Dr. Flemmen reports grants and personal fees from Biogen and Novartis, personal fees from Sanofi and Merck, grants from Odd Fellow research fund and grants from Ingrid and Fritz Nielsen's legacy during the conduct of the study.

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Dr. Brunborg has nothing to disclose.

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Dr. Moen has nothing to disclose.

Dr. Kersten has nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103759.

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