UiT The Arctic University of Norway

Faculty of Health Science
Department of Clinical Medicine

Multiple sclerosis in Northern Norway, epidemiology and comorbidity

Espen Benjaminsen

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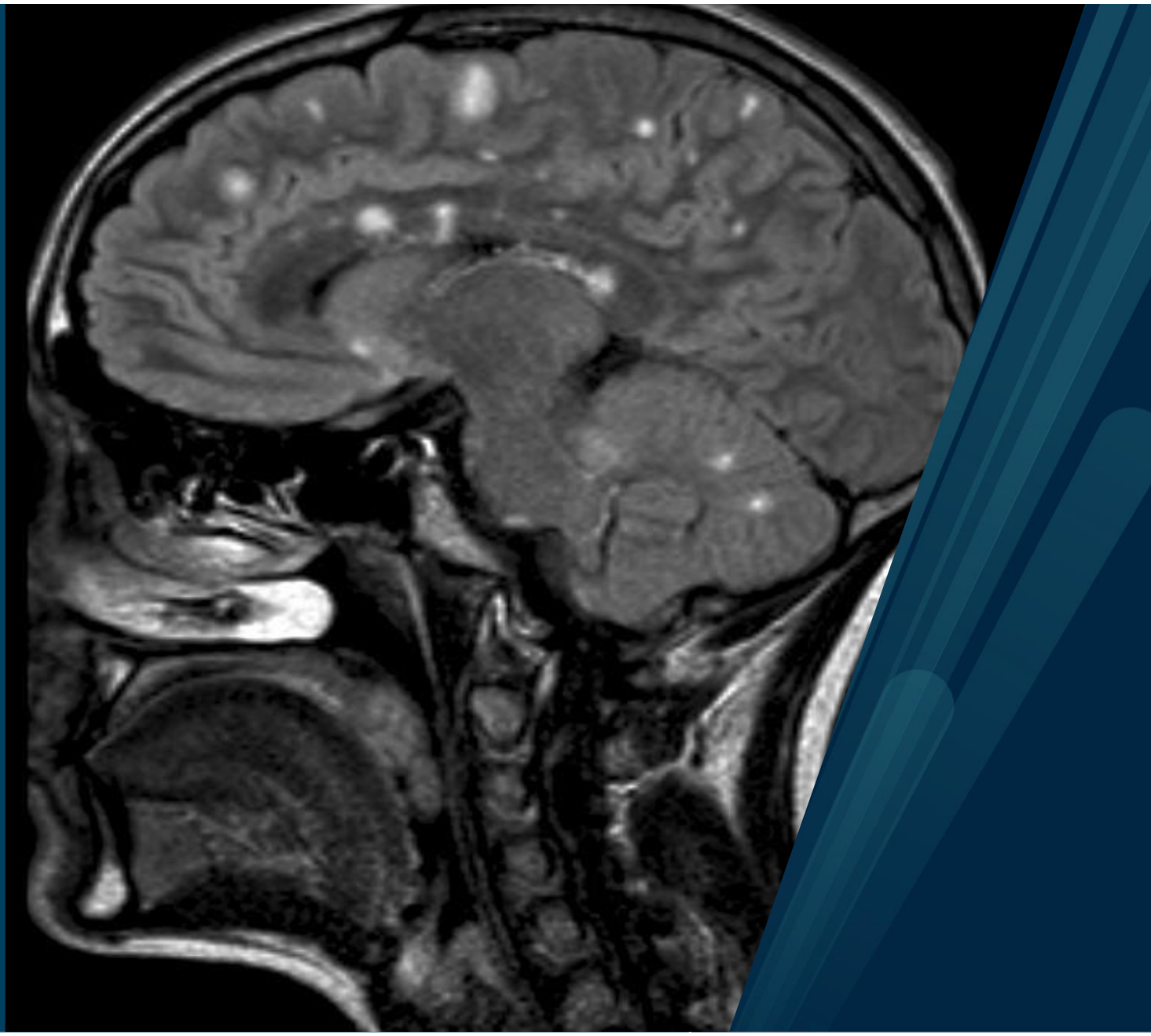

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Espen Benjaminsen

Bodø, January 2022

Preface

This work started as my colleague and later supervisor Karl Bjørnar Alstadhaug initiated the investigation of the epidemiology of MS in Nordland County. This was a project I later had the opportunity to take part in.

In my clinical practice, I came across several MS patients with epilepsy. Ignorant of the literature that already existed on the topic, I decided to investigate the comorbidity of epilepsy in the MS population. As I gave a talk on this subject, Kjell-Morten Myhr in the audience suggested that I could expand my research activity and take a closer look on comorbidity in MS in general. He later became my second supervisor.

This eventually grew in to a project of such scope, that I could have the ambition to write a thesis.

Espen Benjaminsen
Bodø, January 2022

Writing is thinking
- Toril Moi

Acknowledgements

First, I want to express a sincere gratitude to my main supervisor Karl Bjørnar Alstadhaug for his encouragement and guidance. Without his initiative, this work would not have been commenced.

I am also grateful to my co-supervisor Kjell-Morten Myhr for his advice and support.

I want to thank all my colleagues at the Department of Neurology at Nordland Hospital Trust in Bodø, who have supported me in my research project.

Last, I send warm thoughts to my mother and to my children Miriam and Edvard. I am grateful to have you in my life.

Table of Contents

Norwegian summary (sammendrag)

Bakgrunn: Multippel sklerose (MS) er en alvorlig kronisk inflammatorisk sykdom i sentralnervesystemet, som i hovedsak rammer unge voksne. Prevalensen varierer mellom ulike deler av verden, men hovedregelen er at den øker med økende breddegrad. Komorbide tilstander ved MS har vært forholdsvis lite studert, men dette har fått økende interesse i løpet av de siste årene.

Mål: Å beskrive forekomsten av MS i Nordland, og undersøke i hvilken grad tallene for registrerte tilfeller av MS i Norsk Pasient Register (NPR) samsvarer med det reelle antall MS pasienter i fylket. Undersøke forekomsten av komorbide tilstander i MS populasjonen.

Metode: Tverrsnitts- og longitudinelle studier gjort ved bruk av Nordlandssykehusets elektroniske journalsystem kombinert med data fra NPR.

Resultater: Den gjennomsnittlige årlige insidensen per 100 000 var 0.7 i perioden 1970-1974 og 10.1 i perioden 2005-2009. Prevalensen var 270.5 per 100 000 den 1. januar 2017.

Sensitiviteten for at en person med MS skal være korrekt registrert i NPR var 0.97, og den positive prediktive verdien for at en person registrert i NPR faktisk har MS, var 0.92. Cohens kappa var 0.94.

Prevalensen av aktiv epilepsi var 3.2 % blant MS pasientene bosatt i fylket 1. januar 2010. Av MS-pasientene som var korrekt registrert i NPR 1. januar 2017, hadde 2.8 % epilepsi, 1.3 % hadde inflammatorisk tarmsykdom og 1.7 % hadde non-melanom hudkreft.

Konklusjon: Forekomsten av MS har vært økende i hele perioden fra 1970 til 2017, og prevalensen i Nordland er nå like høy som i områder sør i Norge.

Antall MS-pasienter i Nordland registrert i NPR samsvarer godt med det reelle antallet MS-pasienter i fylket.

Prevalensen av epilepsi, inflammatorisk tarmsykdom og non-melanom hudkreft er økt sammenlignet med hva man finner i den generelle norske befolkningen.

English summary

Background: Multiple sclerosis (MS) is a severe chronic inflammatory disease in the central nervous system, mainly affecting young adults. The prevalence varies between different parts of the world, but the general rule is that it increases with increasing latitude. Studies on comorbid conditions in MS are limited, but this topic have gained increasing interest.

Aims: To describe the occurrence of MS in Nordland County, and explore the extent to which the number of registered cases of MS in the Norwegian Patient Registry (NPR) corresponds to the actual number of MS patients in the county. To study the occurrence of comorbid conditions in the same MS population.

Methods: Cross-sectional and longitudinal studies with the use of the electronic medical record system at the Nordland Hospital Trust in Bodø combined with data from the NPR.

Results: The average yearly incidence per 100 000 was 0.7 during the period 1970 – 1974 and 10.1 in the period 2005 – 2009. The prevalence was 270.5 per 100 000 as of January 1, 2017.

For an individual with MS to be correctly registered in the NPR, the sensitivity was 0.97, and for an individual in the NPR to have MS the positive predictive value was 0.92. The Cohen's kappa was 0.94.

The prevalence of active epilepsy was 3.2 % in those with MS living in the county as of January 1, 2010. In the MS patients correctly registered in the NPR as of January 1, 2017, epilepsy was found in 2.8 %, inflammatory bowel disease in 1.3 % and non-melanoma skin cancer in 1.7 %.

Conclusion: The occurrence of MS has been increased during the whole period from 1970 to 2017, and the prevalence in Nordland is now as high as in southern regions of Norway.

The number of MS patients in Nordland registered in the NPR corresponds well with the actual number of MS patients in the county.

The prevalence of epilepsy, inflammatory bowel disease and non-melanoma skin cancer is increased compared to what is found in the general Norwegian population.

List of papers

Paper 1

Benjaminsen E, Olavsen J, Karlberg M, Alstadhaug KB.

Multiple sclerosis in the far north - incidence and prevalence in Nordland County, Norway, 1970-2010.

BMC Neurology. 2014; 14(1): 226

Paper 2

Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB.

Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry.

Brain and Behavior. 2019; 9(11): e01422

Paper 3

Benjaminsen E, Myhr KM, Alstadhaug KB.

The prevalence and characteristics of epilepsy in patients with multiple sclerosis in Nordland county, Norway.

Seizure – European Journal of Epilepsy. 2017; 52: 131-135

Paper 4

Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB.

Comorbidity in multiple sclerosis patients from Nordland County, Norway - validated data from the Norwegian Patient Registry.

Multiple Sclerosis and Related Disorders. 2021; 48: 102691

Abbreviations

ALS	amyotrophic lateral sclerosis
CNS	central nervous system
EDSS	expanded disability status scale
EEG	electroencephalogram
FN	false negative
FP	false positive
HUNT	Helseundersøkelsen i Nord-Trøndelag
IBD	inflammatory bowel disease
ICD	international classification of disease
MRI	magnetic resonance imaging
MS	multiple sclerosis
NPR	the Norwegian Patient Registry
PPMS	primary progressive multiple sclerosis
RA	rheumatoid arthritis
RRMS	relapsing remitting multiple sclerosis
SLE	systemic lupus erythematosus
SPMS	secondary progressive multiple sclerosis
STEMI	ST-elevation myocardial infarction
TN	true negative
TP	true positive
UNN	University Hospital of North Norway
VEP	visual evoked potential

1 Background

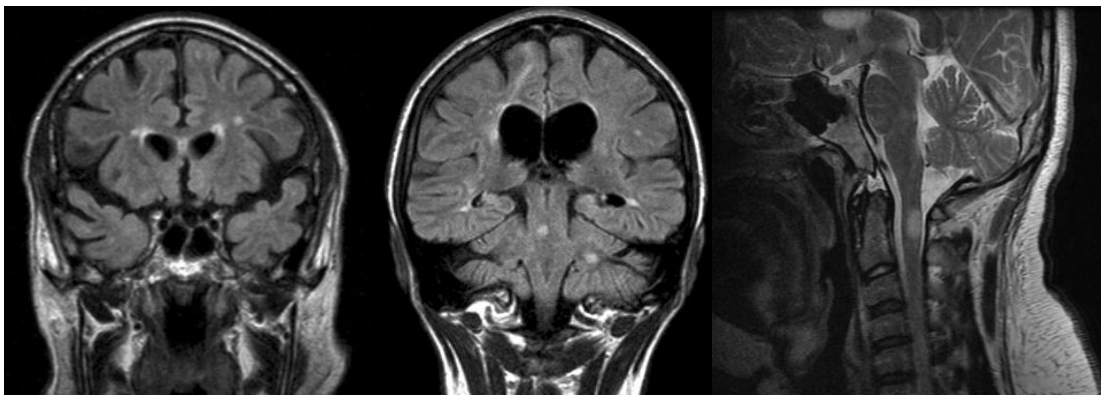
1.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease in the central nervous system (CNS). It was first recognized as a distinct nosological entity in the second half of the 1800's by Charcot, who named the disease "sclérose en plaque" [Zalc 2018]. Next to traumatic injury, it is considered as the most common neurological cause of disability in young adults. The clinical course is diverse, but without medical treatment about 50 % of the affected will need walking aid within 15 years [Weinshenker 1989].

Histopathologically, the disease is characterized by multifocal inflammatory demyelinating lesions, associated with axonal loss and astrocytic gliosis [Thompson 2018].

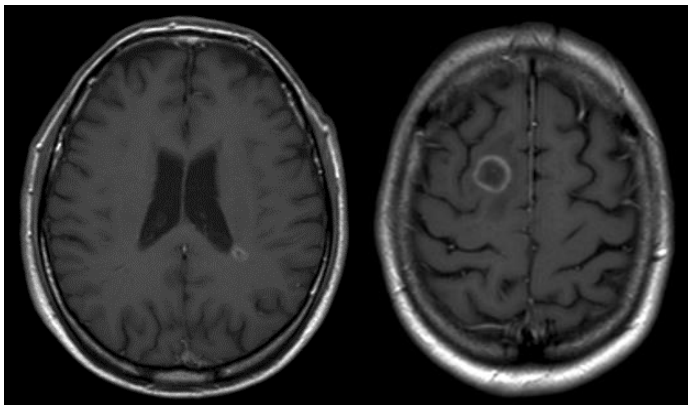
The lesions can be visualized on magnetic resonance imaging (MRI) scans, as hyperintense areas on T2 weighted images. Lesions can occur anywhere in the white and gray matter of the brain, but are typically located in the cortical, juxtacortical, subcortical and periventricular areas. Lesions are also found in the brain stem, cerebellum and the spinal cord (Figure 1-A).

Figure 1-A. T2 high signal lesions demonstrated on MRI FLAIR and T2 sequences.



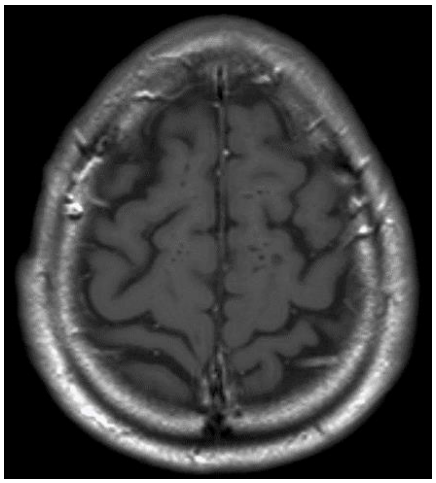
Gadolinium-enhancing lesions (Figure 1-B) are an indication of leakage in the blood brain barrier, usually seen in newer lesions with active inflammation.

Figure 1-B. T1 weighted axial MRI scan with gadolinium-enhancing lesions.



Hypointense lesions on T1 weighted images, often named “black holes”, indicate extensive axonal loss and gliosis (Figure 1-C).

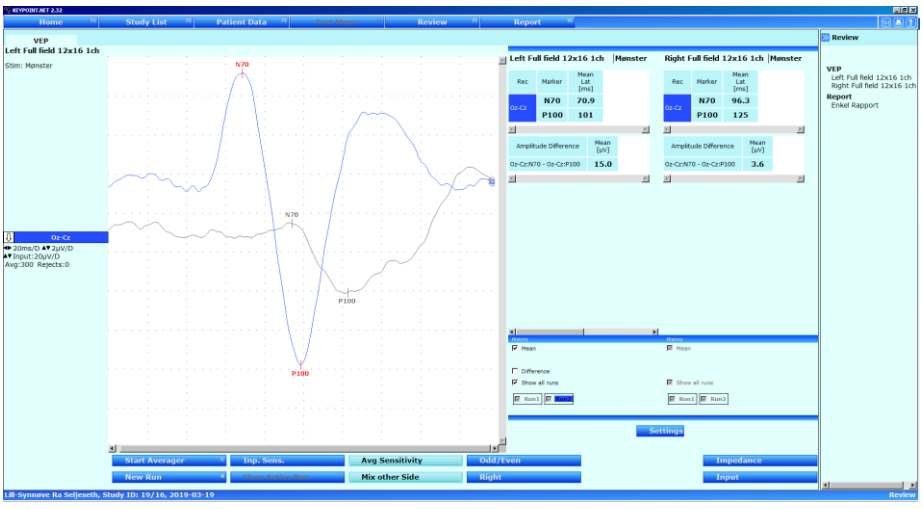
Figure 1-C T1 weighted axial MRI scan with black holes.



Symptoms and clinical findings vary depending on the location of the CNS lesions. A common manifestation of MS is optic neuritis, and this is the first sign of the disease in approximately 20 % of the cases [Weinshenker 1989, Sørensen 1999]. Clinically, this is characterized by afferent pupillary deficit, periocular pain and visual loss with reduced visual acuity, aberrant color vision and scotoma. Visual evoked potential (VEP) shows delayed cortical response, indicating demyelination of the optic nerve (Figure 2).

Figure 2-A. Normal visual evoked potential.

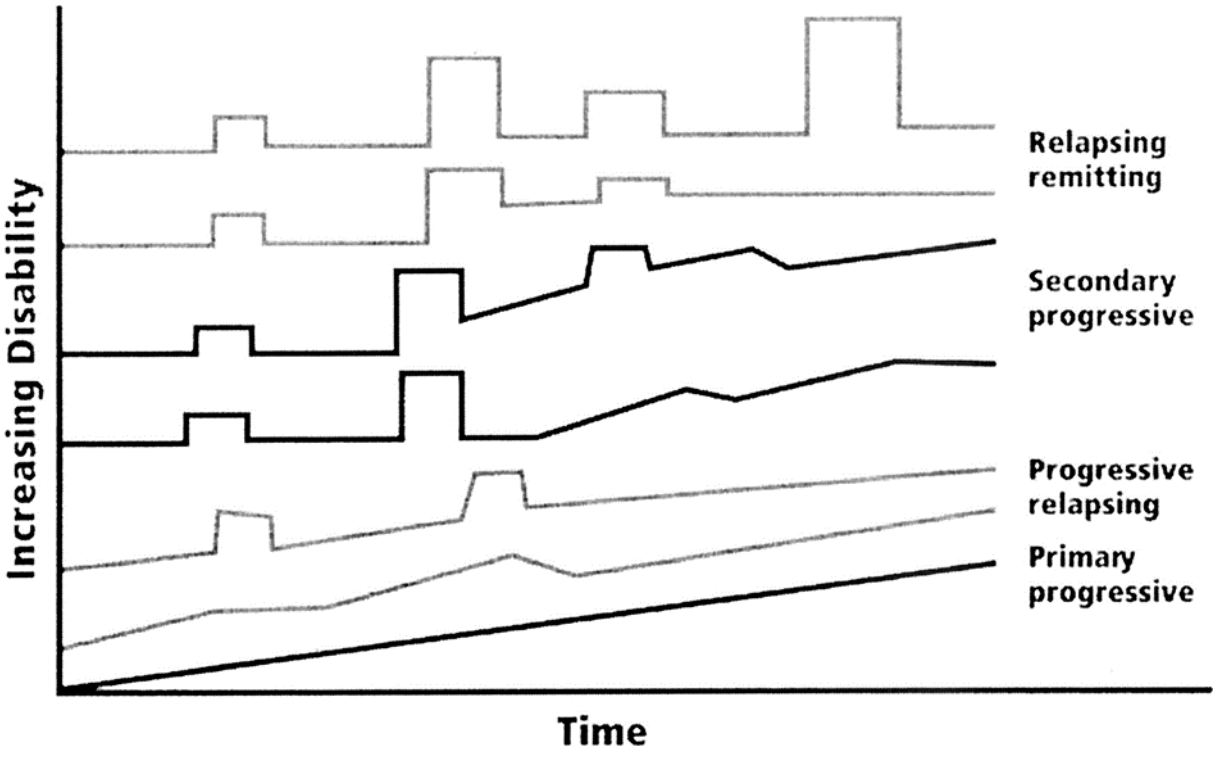
Figure 2-B. Pathological visual evoked potential, showing delayed cortical response of the right eye.



In typical cases, the disease presents with sub-acute episodes of neurological worsening, called exacerbations, attacks or relapses, followed by remission with or without full recovery. Given time and without therapy, the disease often converts to a progressive form with a steadier deterioration. Untreated, 50 % will transform to a progressive form within 10 years [Weinshenker 1989, Kremenchutzky 2006]. The course can also be progressive from the start. This is reported in up to 20 % of the cases [Sumelahti 2003], but the proportion seems to be decreasing [Westerlind 2016].

In 1996, the designation of the clinical course of MS was defined [Lublin 1996]. MS was divided into relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) (Figure 3). They also considered a progressive relapsing (PRMS) form, but recommended that this term should be omitted.

Figure 3. Illustration of the clinical forms of MS. From Rizvi 2004.



In 2013, the definition of the clinical course of MS was revised [Lublin 2014]. The basic features of the descriptions were maintained, but in addition it should now be emphasized whether the disease is “active” or “progressive”.

The treatment of MS aims to minimize the disease activity by suppression or modulation of inflammation. Methylprednisolone is recommended to promote faster remission from attacks. Disease modifying therapies became available during the 1990’s. Interferon β-1a [Jacobs 1996, PRISMS 1998], interferon β-1b [IFNB Multiple Sclerosis Study Group 1995] and glatiaramer acetate [Johnson 1998] all reduced the relative risk of the annual attack rate with about 30 % compared to placebo. Mitoxantrone was also demonstrated to be effective [Millefiorini 1997], but was reserved for particularly severe cases.

The identification of α4-integrin as critical in lymphocyte homing paved the way for a breakthrough in MS-therapy with the development of natalizumab, which was approved by the Food and Drug Administration for the treatment of RRMS in 2004 [Steinman 2012]. Later the treatment options in MS have become numerous and include (in alphabetical order) alemtuzumab, cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, ocrelizumab, ofatumumab, ozanimod, ponesimod, rituximab, siponimod and teriflunomide. This progress has made it possible to individualize the treatment aiming to reduce the attack rate and slowing the disability progression, combined with a minimum of side effects. However, this has also made it a challenge to offer the best suited therapy for each individual with MS.

1.2 Diagnostic criteria

There are no tests or markers that alone can give a diagnosis of MS in an individual patient, and the diagnosis is based on a set of criteria. In his pioneer work, Charcot insisted on the variability and versatility of symptoms, but he also pointed to the "classic triad" of nystagmus, dysarthria and ataxia [Zalc 2018]. It should, however, be noted that this is not a common clinical picture.

The main principle for the diagnosis is that the disease evolves with "multiplicity in time and space". Technological innovations have changed the diagnostic workup. Electrophoresis of the cerebrospinal fluid detects evidence for inflammation in the central nervous system. Evoked potentials, foremost VEP, may demonstrate multiplicity in space, and MRI can demonstrate multiplicity both in space and time.

The diagnostic criteria applied have changed throughout time, and I will describe some important attempts to define them. The overview is not exhaustive, but is chosen based on impact and relevance. The mentioned sets of criteria are used in at least one study of the epidemiology of MS in Norway.

With the criteria described by Allison in the 1950s, MS was divided in three categories [Allison 1954, Allison 1960]. Individuals with *early probable MS* have few or no objective findings, but some signs have previously been observed, and the history contains more than one attack. Individuals with *probable MS* are physically handicapped and have objective findings which can only be explained by MS, and the history contains notes on remission. *Possible MS* lacks the evidence of multiple lesions, and has a rather progressive course.

In his article on benign MS from 1961, McAlpine mentioned that the lack of standard diagnostic criteria made it difficult to compare the results of different studies [McAlpine 1961]. His definition differentiated between definite, probable and possible MS. A diagnosis of *definite MS* can be set if there is a history of an episode with symptoms known to occur in multiple sclerosis followed by one or more relapses, with the presence of signs of multiple lesions in the central nervous system.

In 1965, Schumacher suggested six diagnostic criteria that were essential to classify a condition as *clinically definite MS* [Schumacher 1965]. According to these criteria, there should be:

a) Objective abnormalities on neurological examination attributable to dysfunction of the central nervous system.

b) Evidence of involvement of at least two separate parts of the central nervous system, either by history or by neurological examination.

c) Objective evidence for the predominantly neurological abnormalities to be related to involvement of the white matter.

d) Two or more episodes lasting at least 24 hours at least one month apart. Alternatively, there could be a slow or step-wise progression of signs and symptoms, over a period of at least six months.

e) Onset of the disease between the age of 10 and 50 years.

f) No better explanation for the condition.

The purpose of these criteria was to standardize studies on MS, and was not intendent for the use in a clinical setting.

The Poser criteria were introduced in 1983 [Poser 1983]. The diagnosis of MS could be made by exploring clinical symptoms and signs, combined with para-clinical findings. If there were two attacks and two separate clinical findings, there were multiplicities in both time and

space, and the criteria were fulfilled. If there was only one clinical finding, a pathological evoked potential could demonstrate additional pathology in the optic nerve or in the medulla or brain stem. MS was classified as *clinical definite, laboratory supported definite, clinical probable* and *laboratory supported probable*. Para-clinical examination included evoked potentials and inflammatory markers in the cerebrospinal fluid. The criteria were:

Clinically definite MS

• two attacks and clinical evidence of two separate lesions.
• two attacks and clinical evidence of one and para-clinical evidence of another separate lesion.

Laboratory supported definite MS

• two attacks and either clinical or para-clinical evidence of one lesion, and typical CSF abnormalities.
• one attack and clinical evidence of two lesion, and typical CSF abnormalities.
• clinical evidence of one lesion and para-clinical evidence of another lesion, and typical CSF abnormalities.

Clinically probable MS

• two attacks and clinical evidence of one lesion.
• one attack and clinical evidence of two separate lesions.
• one attack, clinical evidence of one lesion and para-clinical evidence of another lesion.

Laboratory supported probable MS

• two attacks and typical CSF abnormalities.

The use of MRI to demonstrate MS lesions was incorporated in the criteria from 2001, the McDonald criteria [McDonald 2001]. If there are two or more attacks and clinical evidence of

two or more lesions, the diagnosis could still be set solely on clinical basis. However, if there is only one attack or evidence of only one lesion, the diagnosis can be made with the use of MRI, sometimes in combination with abnormal VEP and the presence of oligoclonal bands in the CSF.

If there are two or more attacks, the criteria of dissemination in time is fulfilled. If there is evidence of only one lesion, the dissemination in space is fulfilled if there are multiple MS lesions demonstrated by MRI. If there, on the other hand, is evidence of at least two lesions but only one attack, repeated MRI scans can demonstrate dissemination in time. With only one attack and one clinical lesion, or if there are insidious neurological progression, both dissemination in space and dissemination in time can be demonstrated by the use of MRI.

To demonstrate the *dissemination in space*, the MRI findings must fulfill the criteria suggested by Barkhof [Barkhof 1997] and Tintoré [Tintoré 2000]. At least three of the following should be present:

• more than nine T2 hyperintense lesions or more than one gadolinum-enhancing lesion
• more than three periventricular lesions
• more than one juxtacortical lesions
• more than one infratentorial lesion

Dissemination in time could be demonstration with MRI if there were:

• more than one gadolinum-enhancing lesion three months after the event or
• more than one new T2 lesion three months after the prior scan

The McDonald criteria were revised in 2005 [Polman 2005], in 2010 [Polman 2011] and in 2017 [Thompson 2018]. In the 2005 criteria, dissemination in space is defined as in 2001, but to fulfill dissemination in time, it is sufficient to have one gadolinium-enhancing lesion on a

MRI scan 30 days after the initial symptom. Hence, with the revised criteria it was possible to fulfill the diagnosis within shorter time.

With the revision in 2010, fewer T2 lesions on the MRI are required to fulfill the dissemination in space. There should be *two or more* lesions in two of four areas typical for MS; juxtacortical, infratentorial, periventricular or spinal cord. The dissemination in time can be fulfilled if there is a new T2 or enhancing lesion on a follow up scan, regardless of time passed. Dissemination in time can also be demonstrated if there is a gadolinium-enhancing lesion and a non-enhancing lesion on the same MRI scan. The enhancing lesion should be non-symptomatic. The enhancing lesion and the non-enhancing lesions are of different age, and the required multiplicity in time is fulfilled.

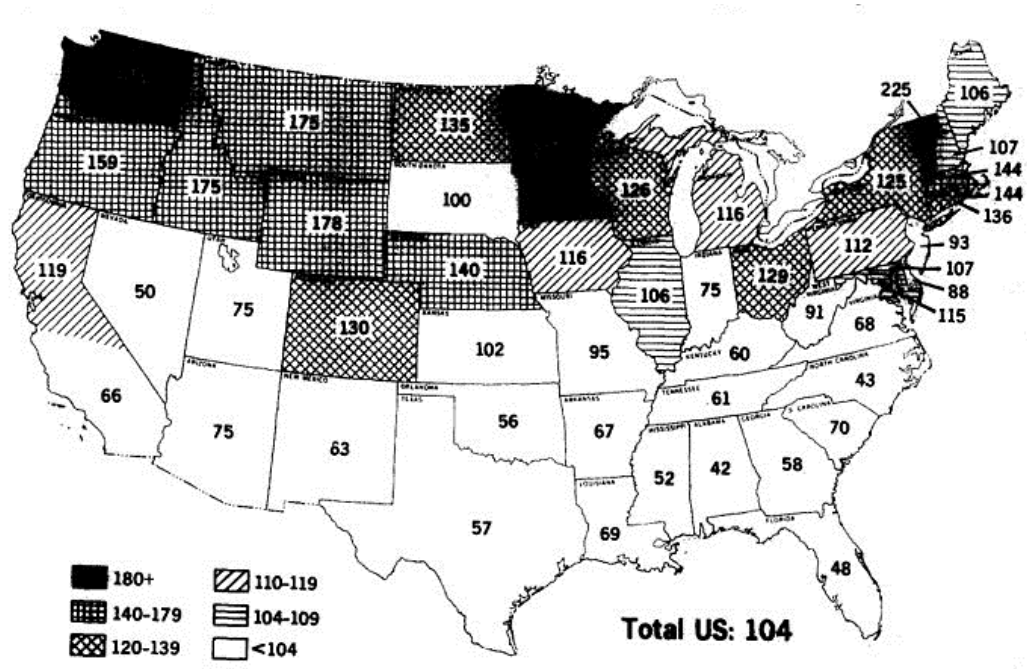
The McDonald criteria were again revised in 2017 [Thompson 2018]. It is now sufficient with *one or more* lesion in *at least two* of four of the typical areas, and if there are clinical evidence of two or more lesions, the dissemination in time is fulfilled if there are oligoclonal bands in the CSF, even if there has been only one attack.

1.3 Worldwide distribution of MS and the latitude gradient

It is estimated that around 2.2 million people were living with MS worldwide in 2016, which corresponds to a prevalence of about 30 per 100 000 [GBD 2016 Multiple Sclerosis Collaborators]. The prevalence is increasing, but it is not clear to what extent this can be attributed to increased survival, increased incidence, or improvements in diagnosis and reporting [Browne 2014].

MS is unevenly distributed worldwide. The prevalence varies between countries, but can also vary within national borders. Studies in US veterans based on where they lived at the time of diagnosis, suggest that latitude is a risk factor [Norman 1983]. In 1983, Kurtzke presented a map that showed the distribution of MS in case-control ratios for US white male veterans (Figure 4) [Kurtzke 1983]. The ratios are generally higher in the northern than in the southern states.

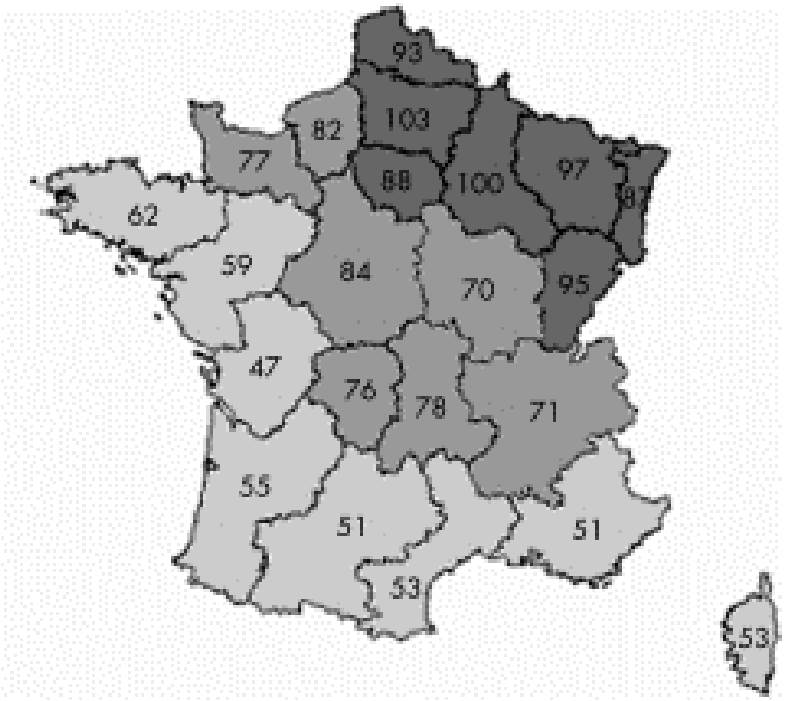
Figure 4. The distribution of MS as case-control ratios. From Kurtzke 1983.



A south to north gradient of the prevalence of MS in USA has actually been acknowledged for a century [Davenport 1922, quoted in Norman 1983].

In Europe, a study on French farmers showed an overall age standardized prevalence of 65.0 per 100 000 as of January 1, 2003. The prevalence varied between the administrative regions, and was 103.2 per 100 000 in Picardie, but only 46.8 in Poitou-Charentes [Vukusic 2007]. There was a trend to higher prevalence in the north-east and to lower prevalence in south-west (Figure 5).

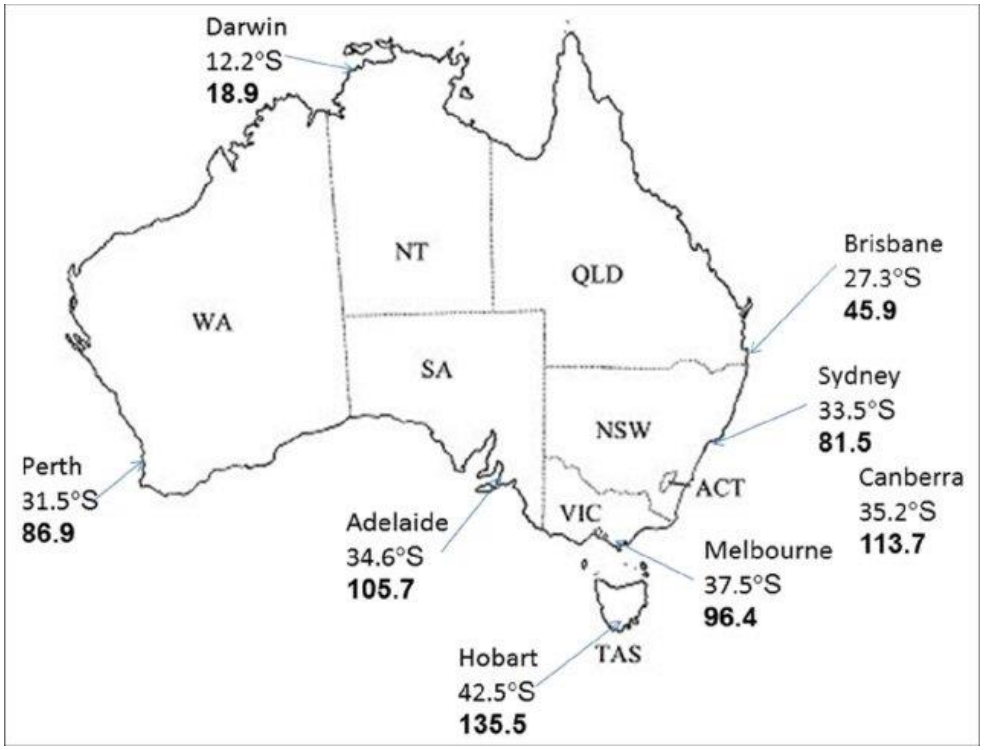
Figure 5. Estimates of the regional age standardized prevalence of multiple sclerosis among French farmers as of January 1, 2003 per 100 000 inhabitants. From Vukusic 2007.



In Australia, van der Mei found a prevalence of MS of 11.8 per 100 000 in tropical Queensland. The prevalence increased to 21.0 per 100 000 in the subtropical Queensland,

36.6 per 100 000 in New South Wales, and 75.6 per 100 000 in Tasmania [van der Mei 2001]. The differences in prevalence, with relatively low numbers in the north and relatively high numbers in south, are also shown in a later study [Palmer 2013] (Figure 6).

Figure 6. The distribution of MS in Australia. From Palmer 2013.



Combined, these studies give the expression that the prevalence increases when we move to the north in the northern hemisphere and when we move to the south in the southern hemisphere. Indeed, meta-analyses indicate that there is a significant correlation between the prevalence of MS and the latitude, where the prevalence increases with increasing latitude [Simpson 2011, Simpson 2019].

There are, however, exceptions that argues against this latitude gradient hypothesis. One of these exceptions has been observed in Norway (see section 1.5).

1.4 Risk factors for MS

The cause of MS is not known, but is probably multifactorialha and a combination of genetic and environmental risk factors [Ellis 2014, Yadav 2015, Ascherio 2016]. As described in section 1.3, the risk of MS increases with increasing latitude. This could be due to differences in genetic vulnerability in different ethnic groups, but could also be due to environmental risk factors.

Heritability and genetic factors

First-degree relatives to those with MS have increased risk of developing the disease, compared to the general population. Data from 815 MS index cases showed that first-degree relatives have 30-50 % increased risk of MS compared to the general population [Sadovnick 1988]. A Danish study found an increased risk among first-degree relatives, with a relative risk of 7.1, but found no increased risk in the spouses of the index persons [Nielsen 2005]. The risk in persons adopted in to a family with a first-degree relative with MS is not greater than in the general population [Ebers 1995]. A Canadian study found that the concordance was 30.8 % in monozygote twins and 4.7 % in dizygote twins [Sadovnick 1993]. This finding is supported by a register study from Denmark, where the concordance was 24 % in monozygote twins and 3 % in dizygote twins [Hansen 2005].

This strongly indicates a hereditary component in MS. It has been known for almost 50 years that a locus on the human leucocyte antigen (HLA) on chromosome 6p21 is associated with MS [Jersild 1972], and the association is strongest for the gene HLA-DR15 [Schmidt 2007].

However, more than 200 gene variants that can contribute to the susceptibility of the disease have been identified [Waubant 2019].

The risk for MS is about two times higher in women than in men [Orton 2006, Koch-Henriksen 2010, Ramagopalan 2010, Koch-Henriksen 2018].

Environmental risk factors

Low levels of vitamin D is a risk factor for MS. In a study of U.S. military personnel, samples of blood had been drawn from 257 individuals that later developed MS. Among whites, the level of vitamin D was significantly lower in this group than in the matched control group [Munger 2006]. A study from northern Sweden compared blood samples of 192 MS patients retrieved before the onset of MS with matched controls. High levels of vitamin D were associated with reduced risk of MS [Salzer 2012].

The most important source of vitamin D is the production of the vitamin in the skin after exposure to sun radiation [Prietl 2013], and low exposure for sun radiation is a risk factor for MS [Kampman 2007, Bjørnevik 2014, Tremlett 2018, Magalhaes 2019]. In the higher latitudes, the sunlight is sparse during wintertime, and this have been suggested as an explanation of the observed latitude gradient in the MS epidemiology.

Obesity and high body mass index in the young age are associated with MS [Langer-Gould 2013, Wesnes 2015], especially in females [Munger 2013]. This observation might be linked to the vitamin D hypothesis, as obese have increased risk of vitamin D deficiency [Pereira-Santos 2015].

Past infection with Epstein Barr virus is linked to MS [Lucas 2011]. Infection with the virus is often asymptomatic in early age, but tends to give mononucleosis in adolescence or adulthood. Mononucleosis is associated with a two to threefold increase in the risk of MS [Ascherio 2010]. In a study of U.S. military personnel, 5 % were Epstein Barr virus negative at the first blood sample. Of those, ten individuals later developed MS, and all of them had converted to Epstein Barr virus positive prior to the diagnosis of MS [Levin 2010]. It has also been shown that the risk of MS increases with increasing Epstein Barr virus antigen titers [Munger 2011]. Furthermore, the risk for MS is almost non-existing for individuals who are Epstein Barr virus antibody negative [Ascherio 2000].

An association with smoking and MS was suggested in 1965 [Antonovsky 1965]. In a Norwegian study, the risk of MS was significant higher in smokers than in never-smokers, with a rate ratio of 1.8 [Riise 2003]. In a register-based Swedish study, smokers had significantly increased risk of developing MS compared to never-smokers, with an odds ratio of 1.5 [Hedström 2013]. The risk also seems to be increased among those exposed to passive smoking [Oturai 2021].

1.5 Studies of epidemiology of MS in Norway up to 2010

In the following, I present an overview of studies of prevalence and incidence of MS in Norway published prior to my work. Studies published after 2010 are presented in section 5.4. The prevalence and incidence numbers are given per 100 000.

The first epidemiological study of MS in Norway found an annual incidence of 2.7 in the period 1935 -1948 [Swank 1952]. The incidence was lowest in the northern parts of the country, with 1.8 in Nordland County, 1.1 in Troms and 0.4 in Finnmark. The incidence was relatively high in the southeastern part of Norway, and in general the incidence was higher in inland areas than in coastal areas. This was observed in Nordland as well, and "a very small area inland from the coastal town of Bodø in the province of Nordland also demonstrated a high incidence of this disease" [Swank 1952]. Since then, there have been many contributions to map the epidemiology of MS in all parts of Norway. Based on data on death rates and disability, Westlund published nationwide studies in 1970 and 1982. Again, relatively low occurrences of MS in coastal regions and in the northern parts of Norway were found [Westlund 1970, Westlund 1982].

Independent of these national studies, other studies have been reported from several counties. These studies have applied different diagnostic criteria. They also vary in inclusion criteria, since some studies recorded the time of diagnosis and others employed the time of onset.

Southeastern Norway

In *Vestfold County* the prevalence was 80.2 as of December 31, 1959, including 13 % with possible MS [Oftedal 1965]. The prevalence of definite and probable MS was 61.6 as of

January 1, 1963 and 86.4 as of January 1, 1983. The annual incidence was 3.90 in the period 1953-1957, 3.44 in 1958-1962, 1.92 in 1963-1967, 2.17 in 1968-1972, 3.51 in 1973-1977 and 2.14 in 1978-1982 [Edland 1996].

In *Oslo* the prevalence was 120.4 as of January 1, 1995. The annual incidence was 3.6 in the period 1972 – 1976, 4.4 in 1877 – 1981, 4.9 in 1982-1986, 7.2 in 1987-1991 and 8.7 in 1992-1996 [Celius 2001]. The prevalence had increased to 148 as of December 31, 2005 [Smestad 2008].

In *Oppland County* the prevalence was 174.1 as of January 1, 2002. The annual incidence rate was 6.5 in the period 1989-1993, 7.4 in 1994-1998, and 3.8 in 1999-2001 [Risberg 2010].

In *Vest-Agder County*, the prevalence was 180 as of January 1, 2007. The crude annual incidence was 7.2 in the period 1996-2000 and 7.5 in 2001-2006 [Vatne 2010].

Western Norway

In *Hordaland County* a study found that the prevalence of definite and probable MS was 20.1 as of January 1, 1963 and 59.8 as of January 1, 1983. The crude annual incidence increased from 1.10 in the period 1953 – 1957 to 3.15 in the period 1973 – 1977, and 1.69 in the period 1978 - 1982 [Larsen 1984].

A later study of the incidence reported a slightly higher rate [Grønning 1991]. The average annual incidence was 1.75 in the period 1953-1957, 2.17 in the period 1958-1962, 2.75 in the period 1963-1967, 3.85 in the period 1968-1972 and 4.13 in the period 1973-1977. The incidence was in this study found to be 4.70 in the period 1978 – 1982, and 3.2 in the period 1983-1987.

In later investigations, however, the incidence was 6.7 in the period 1978 – 1982. The incidence was 6.0 in the period 1993 – 1997, and 3.0 in the period 1998-2002. The prevalence was 150.8 as of January 1, 2003 [Grytten 2006].

Mid Norway

In *Møre and Romsdal County*, the prevalence of probable and early probable MS was 25.7 as of January 1, 1961. If the cases with possible MS were included, the prevalence was 37.8. The incidence rate was 1.9 [Presthus 1966].

The prevalence had increased to 75.4 as of January 1, 1985. The average annual incidence increased from 1.68 in the period 1950 – 1954 to 3.42 in the period 1975 – 1979 and 2.04 in 1980 – 1984 [Midgard 1991]. A later study found an incidence of definitive and probable MS of 5.59 in the period 1975 – 1979, 5.68 in 1980 – 1984 and 4.01 in 1985 – 1991 [Midgard 1996 A].

A study from *Nord-Trøndelag* showed a prevalence of 163.6 as of January 1, 2000. The annual incidence was 3.4 in the period 1974 -1978, 5.1 in 1979 – 1983, 7.4 in 1984-1988, 4.7 in 1989-1993, 5.3 in 1994-1998 and 0.8 in 1999 [Dahl 2004].

Northern Norway

In *Troms and Finnmark*, the northernmost part of Norway, the prevalence was 20.6 in 1973. The incidence was 1.0 in the period 1953-1957 and 2.0 in the period 1968-1972 [de Graaf 1974]. In the period 1974 – 1982, the annual incidence rate was 1.9, and the prevalence was 31.5 in 1983 [Grønning 1985]. A later study found that the average annual incidence was 2.6

in the period 1974-1978 and 3.0 in the period 1979-1983, and increased to 3.5 in the period 1984-1988 and 4.3 in the period 1989-1992. The prevalence was 73.0 as of January 1, 1993 [Grønlie 2000].

In *Nordland*, the prevalence was 105.6 as of December 31, 1999. The incidence was 0.7 in the period 1970-1974, 4.5 in 1980-1984 and 5.4 in 1995-1999 [Alstadhaug 2005].

Thus, the prevalence increased over time in all Norwegian counties that have been studied. In general, it is also an increase in the incidence. However, in those studies applying the time of the first symptom as inclusion point (Vestfold, Hordaland, Møre and Romsdal, Nord-Trøndelag), the incidence tends to decrease towards the end of the study periods. This is expected, because when a person gets the diagnosis of MS, he/she will often be recorded in a previous time period because the first symptom probably occurred years prior to the diagnosis. When a study is repeated in the same area, the incidence is found to be higher in these periods than was previously reported. In Hordaland, however, the incidence has been quite stable in 30 years, with an incidence of 5.3 in the period 1973-1978 and 6.0 in the period 1993-1997.

One should also notice that the studies combined indicate that both the prevalence and the incidence is lower in the northern parts of Norway than in the more southern areas. Based on epidemiological studies, the prevalence was estimated to be 100 per 100 000 in Northern Norway and 150 per 100 000 in the rest of the country [Torkildsen 2007]. This inverted north to south gradient in Norway is in contrast with international studies, where the prevalence of MS increases with the increasing latitude.

There have been attempts to explain this paradoxical low prevalence in the highest latitudes. One explanation could be that the suspected high consumption of seafood in the northern coastal areas provides sufficient vitamin D to compensate for the lack of solar radiation [Kampman 2007, Kampman 2008]. Another possible explanation is related to ethnicity and genetics. The Sami is considered the indigenous people of northern Norway. There is a low prevalence of MS in the Norwegian Sami population [Grønlie 2000, Harbo 2007]. This could be due to less vulnerability due to a low frequency of the disease-associated DRB1*15-DQB1*06 haplotype in the Sami population [Harbo 2007]. The relatively high proportion of Sami in the northern population could thus partly account for the low prevalence of MS in this region.

1.6 Comorbidity in multiple sclerosis

In recent years the comorbid conditions in MS have gained interest [Magyari 2020].

Knowledge of comorbidity is important to optimize personalized therapies [Torkildsen 2016, Dobson 2019]. Without effective therapy, most individuals with MS will develop severe disability, but when treatment is started early, the prognosis improves [Cerqueira 2018, Iaffaldano 2021]. Early diagnosis and treatment are therefore important, but comorbidity may delay the diagnosis of MS [Marrie 2009, Thormann 2017] and increase the probability of delayed initiation of disease modifying therapy [Zhang 2016]. Furthermore, comorbid conditions in the MS population increase the risk of hospitalization [Marrie 2015 A], reduces the quality of life [Berrigan 2016], and tend to reduce life span [Marrie 2015 B, Thormann 2017].

Prior to this thesis, there have been a few Norwegian studies that have investigated comorbidity in MS. Two studies have addressed the epidemiology of epilepsy in MS [Engelsen 1997, Lund 2014]. There have been studies on neuropsychiatric symptoms [Figved 2005, Dahl 2009], and of bladder, bowel and sexual problems [Bakke 1996, Nortvedt 2007], Midgard has investigated inflammatory diseases [Midgard 1996 B] and cancer [Midgard 1996 C]. A recent Norwegian study on cancer included 6883 MS patients born between 1930 and 1979 [Grytten 2020]. The population described by Midgard in 1996 and partly the Nordland County population were included in this study. It is, however, not a complete overlap with the cohort we present in paper 4.

Comorbid conditions are prevalent in various degrees in the MS population and for many conditions the studies show contradictory results.

1.6.1 Cancer

The Norwegian study by Grytten found an increased overall risk of cancer in the MS population compared to the control group [Grytten 2020]. This supports a prior study based on data from the US Department of Defense database, where the rate of cancer was higher in the MS group than in the non-MS control group [Capkun 2015]. These findings are in contrast to a report from British Colombia, where a study comparing 6820 MS patients to a matched control group, indicated a lower risk of overall cancer in the MS population [Kingwell 2012]. Neither did a Danish register-based study of 10752 MS patients diagnosed between 1995 and 2015, demonstrate any increase in the incidence of overall cancer in the MS group compared to the general population [Nørgaard 2019].

Lung cancer

The Norwegian study from 2020 found a significantly increased risk of cancer in respiratory organs in the MS group, with a HR of 1.66 [Grytten 2020]. Neither the study from British Colombia [Kingwell 2012] nor the study from Denmark [Nørgaard 2019] could confirm these differences in occurrence of lung cancer between the MS population and the reference groups.

Colorectal cancer

The study from British Colombia found a decreased risk of colorectal cancer in the MS group [Kingwell 2012], while other studies have found no difference in the occurrence between the MS population and the reference groups [Nørgaard 2019, Grytten 2020].

Cancer in the urinary tract

The Norwegian study from 2020 found a significantly increased risk of cancer in the urinary organs in the MS group, with a HR of 1.51 [Grytten 2020]. The study from British Colombia found an increased risk of bladder cancer in the MS group, but this was not statistically significant [Kingwell 2012]. The Danish register study from 2019 did not find any difference between the MS group and reference group [Nørgaard 2019].

Breast cancer

A study based on the National Health Insurance System of Taiwan, including 1292 MS patients, found an increased risk of breast cancer in the MS population compared to a control group [Sun 2014]. This is supported by a study from the US Department of Defense database that shows an increased rate of breast cancer in the MS group [Capkun 2015]. A Swedish study of 19330 women with MS diagnosed between 1968 and 2012 found a 13 % increased risk of breast cancer in postmenopausal women [Hajiebrahimi 2016]. Other studies find no difference in the occurrence of breast cancer in the MS population compared to the reference groups [Kingwell 2012, Nørgaard 2019, Grytten 2020].

Skin cancer

An English study of 5004 MS patients found a low incidence of skin cancer in the MS population compared to a control cohort of individuals with other diseases [Goldacre 2004].

However, data from the US Department of Defense database shows an increased rate of malignant melanoma in the MS group compared to the control group [Capkun 2015]. The Danish study from 2019 also found an increased incidence of malignant melanoma [Nørgaard 2019]. The study from British Colombia did not find any difference in the risk of malignant melanoma between the MS population and the control group, but the risk of non-melanoma skin cancer was increased [Kingwell 2012].

1.6.2 Non-cancer

Inflammatory Bowel Disease

A population-based study of 474 patients with inflammatory bowel disease from Olmsted County, Minnesota found the prevalence of MS to be higher than expected, with a standardized morbidity rate of 3.7 [Kimura 2000]. A British study using data from the General Practice Research Database identified 7988 patients with Crohn's disease and 12185 patients with ulcerative colitis. Demyelinating diseases were significantly more prevalent in this group with inflammatory bowel diseases, than in a matched control group [Gupta 2005]. A study based on data from the US Department of Defense database found an increased rate of ulcerative colitis, event rate ratio 2.0, and regional enteritis, event rate ratio 1.9, in the MS group compared to the non-MS control group [Capkun 2015]. A Danish study of 12 403 MS patients found increased risk of ulcerative colitis (RR 2.0). In first degree relatives, there was an increased risk of both ulcerative colitis (RR 1.3) and Crohn's disease (RR 1.4) [Nielsen 2008].

Thyroid Disease

A study found significant increase of Graves' disease in 491 MS patients in the Canadian province of Newfoundland and Labrador [Sloka 2005]. However, a larger study of 4192 MS patients in the Canadian province of Manitoba found no difference in the incidence and prevalence of thyroid diseases [Marrie 2012].

Diabetes

In 1090 people with MS in Sardinia the prevalence of type-1 diabetes was 2.6 %. This was a three-fold increase ($p = 0.001$) compared to their healthy siblings and a five-fold increase ($p < 0.0001$) compared to the general population [Marrosu 2002] A Danish population-based study found 11 cases of MS among 6078 individuals with type-1 diabetes, while only 3.38 cases were expected, a relative risk of 3.26 [Nielsen 2006].

Connective tissue diseases

Midgard found three individuals with rheumatoid arthritis among 155 MS patients, and zero in the control group [Midgard 1996 B]. These numbers are too small to conclude. In a Danish study of 12 403 MS patients, there was decreased risk of both rheumatoid arthritis (RR 0.5) and systemic lupus erythematosus (RR 0.5) [Nielsen 2008].

Myocardial infarction and ischemic stroke

A combined case-control and matched cohort register based study of 8947 Danish MS patients showed a significant increased probability of cardiovascular comorbidity (hazard ratio 1.08) and cerebrovascular comorbidity (hazard ratio 1.84) compared to controls, after the onset of MS. In the same MS population, the probability of cardiovascular and cerebrovascular diseases had been lower than in the control group prior to the onset of MS [Thormann 2016]. Data from the US Department of Defense database including 15 684 MS patients have shown an increased rate of myocardial infarction in the MS group, with an event rate ratio of 2.1 compared to the control group, and the study also reported that cerebrovascular disorders were more common in the MS group than in the control group, with an event rate ratio of ischemic stroke of 3.8 [Capkun 2015]. A Canadian register-based study

including 14 565 MS patients found increased risk of acute myocardial infarction in MS patients compared to matched controls, with a hazard ratio of 1.63 after age adjustment [Marrie 2019]. Another study found that individuals with MS had increased odds of hospitalization due to ischemic stroke compared to a matched control group, with an odds ratio of 1.66 [Allen 2008]. A study based on the National Health Insurance System of Taiwan including 1174 MS patient found an increased risk of stroke. The hazard ratio was 12.1 compared to the matched control group [Tseng 2015].

Psychosis

A study including 10367 MS patients based on data from the universal public health care insurance system in the Canadian province of Alberta, found a significant increase in the prevalence of psychotic disorders in the MS population in the period 1985 to 2003. The association was strongest in the youngest age group [Patten 2005]. A study of 898 MS patients based on data from the National Health Insurance System of Taiwan found psychosis in 7.5 %. This was significantly higher than in the control group, with an odds ratio of 4.0 [Kang 2010].

Epilepsy

High risk of epilepsy in the MS population has long been recognized, with a prevalence 3-6 times higher than in the general population [Poser 2003]. A Swedish register-based study found epilepsy in 3.5 % in the MS population [Burman 2017]. Two Norwegian studies address the prevalence of active epilepsy in the MS population. In a study from Hordaland, the prevalence was 3.2 % [Engelsen 1997], and in Vestfold County, it was 3.6 % [Lund 2014].

2 Aims of the thesis

The aims of this thesis were to:

- describe the prevalence and incidence of MS in Nordland County (paper 1).

- validate the diagnosis of MS recorded in the Norwegian Patient Registry (NPR) (paper 2).

- describe the prevalence of epilepsy in the MS population (paper 3).

- describe the comorbidity in the MS population with validated data from the NPR (paper 4).

3 Materials and methods

3.1 Design

This thesis is based on four retrospective studies, one longitudinal (paper 1), and the others cross sectional (paper 2-4).

3.2 Geographic area

Nordland County stretches about 500 km between the latitudes 64°56' N and 69°20' N, and is situated in the northern part of Norway. The Arctic Circle at 66°33' N is running through the county in between Mo i Rana and Bodø, the two largest cities.

Nordland has an area of 38 153 km², and includes the regions of Helgeland, Salten, Ofoten, Lofoten and Vesterålen.

The county had 243 179 inhabitants in 1970, and the population has been quite stable with 236 271 (117 734 females and 118 537 males) inhabitants at the beginning of 2010 and 242 866 (119 758 females and 123 108 males) as of January 1, 2017.

The public health service includes the Department of Neurology at the Nordland Hospital Trust in Bodø, where most MS patients in the county are followed. There are also neurological out-patient services at the hospitals in Mosjøen (Helgeland) and Stokmarknes (Vesterålen).

Neurological patients living in the north of the county (Ofoten) are often served by the University Hospital of North Norway (UNN) in Tromsø (Troms County). This became noticeable from 2007, when the hospital in Narvik, located at the upper border of Nordland,

was merged with UNN. Patients in the south of the county (Helgeland) are sometimes referred to the hospitals in Trøndelag, the neighbouring county south of Nordland.

Figure 7. Nordland County in the northern part of Norway. Modified from Store Norske Leksikon.

3.3 Data sources and case ascertainment

All individuals who got the diagnosis of MS while living in Nordland County, Norway, or lived in the county at the prevalence points were included in the study.

The data were collected from the medical records at participating hospitals, and from the Norwegian Patient Registry (NPR).

3.3.1 The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) is a nationwide health registry, and includes information about everyone who receives healthcare from the specialist health care service in Norway. The registry is run by the Norwegian Directorate of Health and was established in 1997. The information is personal identifiable from 2008.

Whenever a patient is treated at a hospital or a private practice specialist with public reimbursement, the International Statistical Classification of Diseases and Related Health Problems (ICD) codes that correspond to the given diagnoses, are reported to the NPR. Reporting to the registry is mandatory.

The main purpose of the NPR is to form a basis for administration, management and quality assurance of the specialist health service. The NPR shall also contribute to medical research, and upon application, data can be provided.

3.3.2 Case ascertainment

Paper 1

We performed an electronic search for the MS diagnosis according to ICD 8 (340.08), ICD 9 (340) and ICD 10 (G35) in the medical records at Nordland Hospital Trust in Bodø.

We also requested cases from the neurological outpatient services at the hospitals in Mosjøen and Stokmarknes in Nordland, from the neurological department in Namsos in Trøndelag, and from the University Hospital of North Norway in Troms. Duplicates were removed.

The medical records were scrutinized, and cases that did not fulfill the diagnostic criteria for MS were excluded. We recorded sex, year of birth, year of the first symptom, year of the diagnosis, and classified the course of the disease as relapsing remitting or primary progressive.

If an individual had moved from the county or passed away, the case was included in the incidence calculation but not in the prevalence numbers. If an individual had moved to the county, the case was included in the prevalence calculations.

Paper 2

Using the same methods as for paper 1, the dataset was updated by January 1. 2017. We searched the hospital records and requested relevant information from the hospitals in Mosjøen, Namsos and Tromsø.

On request, we received a data set from the NPR containing information on all individuals registered with G35 (the ICD-10 diagnosis of MS) reported from Nordland, or living in

Nordland and reported from elsewhere. Only individuals living in Nordland County at the prevalence point were included in the study. Duplicates were excluded.

All the cases in the dataset from NPR were scrutinized to ensure that they fulfilled the diagnostic criteria for MS.

We were then able to divide the cases in three categories:

- Individuals with MS not registered in the NPR.
- Individuals with MS correctly registered in the NPR.
- Individuals without MS incorrectly registered with a MS-diagnosis in the NPR.

Paper 3

We scrutinized the medical records manually for all individuals with MS living in Nordland County as of January 1, 2010 (included in paper 1), for history and signs of epilepsy. Individuals with epilepsy according to the definition by the International League Against Epilepsy, were included. If the individual used antiepileptic drugs or had experienced seizures within the last five year, the epilepsy was defined as “active”. We recorded the year of the diagnosis of epilepsy. With the combination of the seizure semiology and the electroencephalogram findings, we classified the epilepsy as focal or not. We noted the use of anti-epileptic drugs and the use of disease modifying therapy for MS. For all the individuals in the MS population with a relapsing-remitting course at onset, we decided whether the disease had converted to secondary progressive MS or not.

Paper 4

The dataset obtained from the NPR for paper 2, included the ICD-10 codes for all registered diagnoses, in addition to MS. For each individual with a confirmed diagnosis of MS registered in the NPR, we scrutinized the medical records to confirm or reject comorbid diagnosis. We recorded sex, year of birth, year of the MS diagnosis and year of the diagnosis of the comorbid conditions.

3.4 The selection of comorbid conditions for the study

The study of epilepsy presented in *paper 3* started prior to and independently of the study including the other comorbid conditions presented in *paper 4*, and this paper was published before we obtained the dataset from the NPR.

For all the individuals in Nordland registered with MS in the NPR as of January 1, 2017, we obtained all the other ICD-10 codes that were registered on these individuals for paper 4.

The data based on the NPR was used to once again find the prevalence of epilepsy in the MS population. The other comorbid conditions in paper 4 were selected based on findings in the literature, but we had to take into account the limitations incorporated in the method with the use of the NPR. Condition handled exclusively in the primary health care system, are not reported to the NPR.

We defined comorbidity as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [Feinstein 1970]. This mean that acute diseases, such as myocardial infarction and stroke, had to occur after the individual was diagnosed with MS. Chronic conditions, like inflammatory bowel disease and

rheumatoid arthritis, could have started prior to the MS diagnosis. As these conditions, as well as MS, will be present for the rest of the life, they have to coexist at some point. This definition is explicitly stated in paper 4, but the included epilepsy cases in paper 3 fulfilled these criteria as well.

3.5 Statistics

The incidence of a condition was defined as all new cases of the condition in a given population in a given time period.

The prevalence of a condition was defined as the number of individuals with the condition in a given population at a given time. The prevalence of MS is dependent on the new cases (the incidence), survival time and migration.

For continuous variables, like age and different time spans, we calculated the mean with standard deviation. To determine differences between groups, we used chi-squared test. The difference was regarded statistically significant if $p < 0.05$.

The 95 % confidence interval is given by the formula

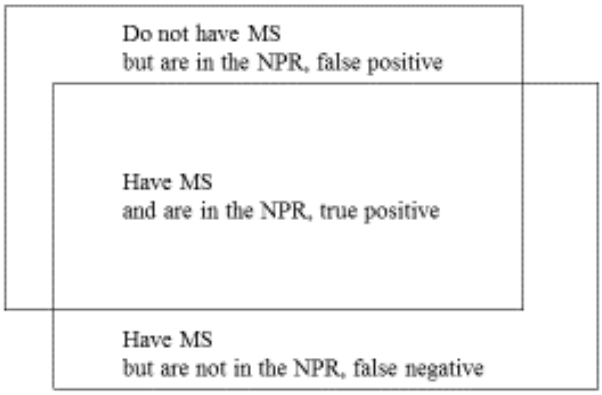
$$\hat{p} \pm 1.96 * \sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

where $\hat{p}$ is the standard error.

In paper 2, we defined the *true positive* (TP) cases as those who was registered with MS in the NPR and had a validated MS diagnosis. *False positive* (FP) cases were those who were registered in the NPR, but did not fulfill the criteria for MS. The *false negative* (FN) cases

were not registered in NPR, but fulfilled the criteria for MS (Figure 8). *True negative* (TN) did not have MS, and were correctly not registered in the NPR.

Figure 8.



With these numbers we calculated the sensitivity, positive predictive value and Cohens kappa. The *sensitivity* is the probability that an individual is registered in the NPR if the individual has MS. The *positive predictive value* is the probability that an individual has MS if the individual is registered in the NPR.

Figure 9.

		Do have MS		
		yes	no	sum
Registered in the NPR	yes	TP	FP	
	no	FN	TN	
	sum			total

The sensitivity is given by the formula TP / (TP+FN), and the positive predictive value is given by the formula TP / (TP+FP) (Figure 9).

Cohens kappa is usually used to give a measure of agreement between observers or tests. In our study, Cohen's kappa was calculated to measure the agreement between the occurrence of MS in the NPR and the real occurrence of MS.

The Cohens kappa is given by the formula

$$\kappa = \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

where P_o is the relative observed agreement among raters, and P_e is the hypothetical probability of chance agreement. The Kappa statistic varies from 0 to 1, where 0 is agreement equivalent to chance and 1 is perfect agreement.

The age standardization prevalence was calculated with the direct method based on the European standard population [Waterhouse 1976].

3.6 Ethical considerations

The studies did not cause any inconvenience to the participants. The main concern has been confidentiality and data security. Collected information is stored securely and de-identified. Link key and data are stored separately. There are extensive rules for access to data in the Norwegian Patient Registry to ensure anonymity and data security. It is not possible to identify any participants from the published studies.

The studies were approved by the Regional Committee for Medical and Health Research Ethics (REK Nord 2009/2592 and REK Nord 2016/1531).

4 Results – summery of the papers

4.1 Paper 1

Multiple sclerosis in the far north - incidence and prevalence in Nordland County, Norway, 1970-2010.

The crude prevalence of MS was 13.9 per 100 000 in 1980, and increased to 63.5 in 1990, and further to 115.0 in 2000 and to 182.4 per 100 000 in 2010. The age adjusted prevalence was 16.9 per 100 000 in 1980 and 174.4 in 2010. In the same period the mean age at prevalence point increased from 45.3 to 51.2 years.

The incidence increased in every 5-year period from 0.7 per 100 000 in the period 1970 – 1974 to 10.1 per 100 000 in the period 2005 – 2009. The mean age at the time of the diagnosis was stable at around 40 years, and the time from the first symptom to diagnosis was stable at around 5 years.

The female to male prevalence ratio was 3.3 in 1980, but was later stable at 2.2 in 1990, 2000 and 2010. The sex specific incidence demonstrated a woman to male ratio of 7.0 in the period 1970 – 1974, but then dropped to 2.1 in the period 1975 – 1979 and was stable until the end of the study period with 2.2 in the period 2005 – 2009.

Of those who acquired the diagnosis of MS in the period 1970 – 1979, 33.3 % had PPMS. This proportion dropped to 20. 6% in the period 1990 – 1994 and was 21.8 in the period 2005 – 2009. Of those with MS as of 1980, 38.2 % had PPMS. The proportion of PPMS decreased in every decade to 18.6 % as of 2010.

4.2 Paper 2

Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry

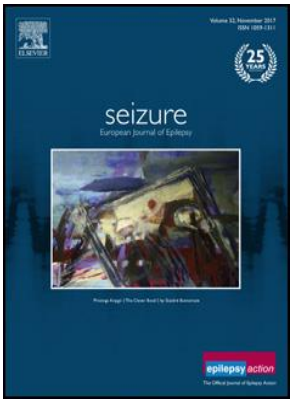
From the Norwegian Patient Registry (NPR) we obtained data for all individuals registered with the ICD-10 code G35 (MS) in Nordland County. We excluded individuals that had passed away, emigrated or of other reasons did not live in the county as of January 1, 2017. The dataset was validated by scrutinizing the medical records.

In the NPR, 696 individuals were registered with G35 MS. However, 59 (8.5 %), did not fulfill the diagnostic criteria. Twenty individuals were not registered with G35 MS in the NPR despite that their diagnosis was confirmed by scrutinizing the medical records. Thus, the real number of individuals with MS in the county was 657, corresponding to a prevalence of 270.5 per 100 000.

A total of 91.5 % of the individuals registered with MS in the NPR had a confirmed MS-diagnosis. Three percent of the individuals with MS were not registered in the NPR. The sensitivity was 0.97 for an individual with MS to be correctly registered in the NPR, and the positive predictive value was 0.92 for an individual registered in the NPR to have MS. The Cohen's kappa was 0.94.

4.3 Paper 3

The prevalence and characteristics of epilepsy in patients with multiple sclerosis in Nordland county, Norway.



Of 431 individuals with MS living in Nordland County as of January 1, 2010, 19 had a history of epilepsy. Of those, 14 individuals (3.2 %) had active epilepsy as defined as having a seizure within the last 5 years or using antiepileptic drugs.

The mean age at the diagnosis of MS was 41.2 (SD ± 13.7) years, and the mean age at the diagnosis of epilepsy was 46.3 (SD ± 17.3) years. Eleven patients (79 %) had their first epileptic seizure after the diagnoses of MS, but only one had seizure prior to any other symptoms of MS. For those without epilepsy, the mean age at the diagnosis of MS was 38.2 (SD ± 10.3) years.

Twelve of the 14 individuals, 86 %, had focal epilepsy registered at least at one occasion.

In the group with active epilepsy, four had PPMS and 10 had RRMS onset, of whom seven (70 %) had converted to SPMS. Three of the seven (43 %) had converted to SPMS before, and four (57 %) had converted after they got epilepsy. In the group consisting of 417 individuals without active epilepsy, 341 had RRMS at onset, of whom 119 (35 %) had converted to SPMS. Seventy-six had PPMS at onset. The conversion from RRMS to SPMS was significantly higher for those with active epilepsy than in those without epilepsy ($p = 0.02$).

Five (36 %) of the patients had received disease modifying therapy for MS, of whom three received therapy at the prevalence day. One individual received disease modifying therapy at the time of the first epileptic seizure.

Four individuals had experienced status epilepticus. At the prevalence point, ten individuals (72 %) received antiepileptic treatment as monotherapy, two (14 %) received two anti-epileptic drugs, and two (14 %) were untreated.

4.4 Paper 4

Comorbidity in multiple sclerosis patients from Nordland County, Norway - validated data from the Norwegian Patient Registry

Of those with a correct registered diagnosis of MS in the NPR, 97.5 % were registered with at least one additional diagnosis. The additional diagnoses were validated by the patients' medical hospital records.

In total, 6.4 % of the MS-patients were correctly registered with a cancer diagnosis. The location of the cancer was mouth and pharynx 0.2 %; the digestive organs 0.3 %; melanoma of the skin 0.5 %; non-melanoma skin cancer 1.7 %; the urinary organs 0.2 %; the lymphoid or hematopoietic tissue 0.2 % and 0.2 % had other or unspecified cancer (this was metastasis of unknown origin). In the female MS population, 3.3 % had breast cancer and 0.5 % had cancer in the genital organs. In the male population, 2.4 % had cancer in the genital organs. Of those with non-melanoma skin cancer, 64 % had basal cell carcinoma and 36 % had squamous cell carcinoma.

There were no registered cases of cancer in the respiratory organs, thyroidal or other endocrine glands, bones or soft tissues. Neither were there any registrations of cancer in the central nervous system, the eye or the autonomic nervous system, and there were no mesotheliomas.

Of the different types of cancer, breast cancer was significantly ($p = 0.015$) more prevalent in the female MS population than in the total Norwegian female population. However, when calculated only for the population of 20 years and older, the difference was no longer significant ($p = 0.16$). Non-melanoma skin cancer was found significantly more prevalent ($p < 0.001$) in the MS population than in the general Norwegian population. The difference remained significant ($p < 0.001$) even when only the population of 20 years and older was considered.

Thyroid disorder was found in 3.6 %, including hypothyroidism that was found in 3.1 %. Type-1 diabetes was found in 0.3% and type-2 diabetes in 3.9 %. Inflammatory bowel disease was found in 1.3 % and rheumatoid arthritis was found in 0.6 % of the MS population. None was registered with systemic lupus erythematosus. Inflammatory bowel disease was more prevalent than what is reported in studies of the general Norwegian population.

Myocardial infarction had occurred in 1.7 %, giving a mean annual incidence 250.4 per 100 000, and 0.6 % had suffered brain infarction, giving a mean annual incidence of 91.7 per 100 000. None had intracerebral hemorrhage, but 0.2 % (one individual) had a subarachnoid hemorrhage.

Psychosis was correctly registered in 0.6 % and epilepsy in 2.8 %. Epilepsy was more prevalent than what is reported in studies of the general Norwegian population.

5 Discussion

5.1 Case ascertainment and completeness

A complete data set is crucial in the study of prevalence and incidence of MS. Despite our efforts to ensure complete case registration, the possibility of missed cases could not be excluded. The collection of data from neighboring regions are particularly vulnerable.

From the dataset in paper 2, we realized that the data presented in paper 1 was incomplete. In paper 2 we were interested in the data for 2017. We used the same procedure as in paper 1, with a search in the medical records at Nordland Hospital Trust in Bodø, and requested the hospitals in Mosjøen, Stokmarknes, Namsos and Tromsø for the medical records of patients followed at these hospitals. Applying this new data set, we could calculate the prevalence as of January 1, 2010. The prevalence increased from 182 to 189 per 100 000. In addition, when we included the data from the NPR the prevalence increased even further to 202 per 100 000.

Increases in reported prevalence and incidence at a given time in repeated follow-up studies are observed in other regions. A study from Hordaland reported a prevalence of 150.8 per 100 000 as of January 1, 2003 [Grytten 2006]. When the authors made a follow-up study ten years later and looked back to 2003, they found that the prevalence at that point had increased to 191 per 100 000 [Grytten 2016]. In Møre and Romsdal, the incidence was found to be 2.04 per 100 000 in 1980 – 1984 [Midgard 1991], but was then found to be 5.68 in this period in a later study [Midgard 1996 A].

5.2 Is the increase in prevalence and incidence in multiple sclerosis real?

We find a steady increase of the prevalence throughout the study period.

One contribution to the increased prevalence could be increased survival. We have not analyzed this in peticular, but we notice that the mean age at prevalence point increased from 45.3 to 51.2 years from 1980 to 2010.

Another contribution is the observed increased incidence. An important question is whether the increase is real, or if it is just an artefact that could be explained by other factors.

To minimize the effect of random variation from one year to another, we calculated the incidence as average annual incidence for 5-year periods, and we calculated the 95 % confidence interval for the incidence and prevalence figures. With a continuous and statistically significant increase in prevalence and incidence through a 40 years period, the possibility that this is due to random variation is unlikely.

Three factors may influence the observed increased incidence: 1) The change of diagnostic criteria, 2) the use of MRI in the diagnostic workup and 3) the introduction and increased possibilities of medical treatment.

As described in section 1.2, the diagnostic criteria have changed over time, and it is possible that this could account for an increase in diagnosted cases. In the seventies, the diagnosis of MS could be based on the criteria suggested by Schumacker and McAlpine. However, colleagues working as neurologists at that time, have told that they did not consistently apply any particular criteria to set the diagnosis. This changed from 1983, when the Poser criteria were introduced. We observe a marked increase in numbers of new cases in 1983 and 1984

compared to the previous years. MRI has become an ever more important tool in the diagnostic work up of MS, and this was emphasised in the McDonald criteria that was established in 2001. Again, we observe an increase in the incidence of diagnosed cases. More patients will probably fulfill the diagnostic criteria when the McDonald criteria are applied instead of the Poser criteria. Monosymptomatic cases and clinically isolated syndromes will not necessarily fulfill the Poser criteria. If dissemination in time and space is demonstrated by MRI, the diagnosis can be given based on the McDonald criteria. This will tend to increase the incidence. On the other hand, MRI scans will rule out cases where other diagnoses are more likely. When both the Poser and the McDonald criteria are applied on the same population, studies have found only small differences in the prevalence [Fox 2004, Hirst 2009].

We tried to explore this challenge, and looked closer at the 163 individuals who got the diagnosis of RRMS during the period 2000 – 2009. The disease was mono-symptomatic at the time of diagnosis in 38 individuals (23 %). In these cases, the diagnosis was based on dissemination in time demonstrated by MRI. Although they did not fulfill the diagnostic criteria of Poser they had MS according to the McDonald criteria. However, by the time of the prevalence point, 21 of these 38 (55 %) had experienced a new clinical attack, and thereby fulfilled the criteria for clinically definite MS after Poser as well. If the remaining 17 individuals, who did not fulfil the Poser criteria for clinical MS were excluded, the prevalence rate as of January 1, 2010 would have dropped with 3.9 %, from 182.4 to 175.2 per 100 000. However, such comparison is not straightforward. Although MRI findings are not included in the Poser criteria, the use of MRI will most likely increase the diagnostic sensitivity for MS also by these criteria as well. If a patient with mild symptoms or mainly sensory symptoms have typical lesions on MRI scan, more emphasis is probably put into the patient interview to

reveal MS manifestations in the past that may lead to a MS-diagnosis also fulfilling the Poser criteria.

In Nordland, the first MRI scanner was put into use during the autumn 2000. Prior to this, MRI was available in other regions of Norway, from 1986 in Trondheim and from 1991 in Tromsø. As of January 1, 2010, there were five MRI scanners in Nordland County and in 2017 the number had increased to eight. Improved access to this important diagnostic tool could lead to more individuals being diagnosed.

Disease modifying therapies for MS became available in clinical practice from the second half of the 1990`s. The possibility of treatment has urged the necessity of early diagnosis of the condition, and could thereby have increased the diagnostic sensitivity.

In Nordland county, the risk of MS is twice as high in females as in males. This is in accordance with other studies, which in addition have found that the propoption of females increases during time [Orton 2006, Koch-Henriksen 2010, Ramagopalan 2010, Koch-Henriksen 2018]. The increased proportion of females is regarded an argument that the increase in the prevalence and incidence of MS is real, and not just an artefact due to changes in case ascertainment. One explanation for the increased incidence in women could be linked to female sex hormones. It is hypothesized that the use of hormonal contraception increases the risk of MS and other autoimmune diseases [Williams 2017]. On the other hand, there seems to be low disease activity of MS during the third trimester of pregnancy when the levels of estrogen are high [Maglione 2019]. Although debated, it is possible that pregnancy and childbirths reduce the risk for MS [Runmarker 1995, Magyari 2013]. In Norway, the total fertility rate has decreased from 2.50 in 1970 to 1.48 in 2020 [https://www.ssb.no/befolkning/artikler-og-publikasjoner/nok-en-gang-rekordlav-

fruktbarhet], and this could be a possible contribution to the increased incidence of MS. However, in Nordland County the female to male ratio of MS did not change during the study period.

Other factors may, however, support that the observed increase is real. Firstly, if the observed increase in incidence was only due to improved and faster diagnostic work up, we would expect that the time delay from the first symptom to the diagnosis should decline over time. Secondly, we would also expect a decline in the age at the time of the diagnosis. In the MS population in Nordland County this is not the case. The time delay from the first symptom to the diagnosis remained at about 5 years, and the mean age at the time of diagnosis was about 40 years during the whole period. Thirdly, if the increase in the incidence and the prevalence of MS was artificial and solely due to better and more rapid diagnostic workup, the same tendency could be expected for other neurological diseases. This is not the case for amyotrophic lateral sclerosis (ALS). We have studied the epidemiology of ALS in Nordland County over a period of 15 years, from 2000 to 2015, and the prevalence and the incidence were both stable [Benjaminsen 2018]. However, for ALS the diagnostic criteria and the use of MRI did not change during the study period.

Changes in environmental risk factors may influence the incidence of MS. Smoking is such a risk factor for MS. Changes in smoking habits, however, can probably not explain the increased incidence of MS. On the contrary, in northern Norway the proportion of smokers in the general population has decreased from 1974 [Njølstad 2016].

Overweight in the youth is a risk factor for MS. In Norwegian studies, the proportion of obesity has increased in teen agers from 1966-69 to 1995-97 [Bjørnelv 2007] and in adults

from 1984-86 to 2006-08 [Krokstad 2013 A]. This could be a partly explanation for the observed increase in the incidence of MS.

5.3 Latitude gradient

Our study showed that the incidence and prevalence of MS in Nordland were in line with the findings from several southern Norwegian counties, and that the south to north gradient seems to no longer exist. Indeed, a study based on register data covering the whole country, showed that the prevalence was much the same in northern Norway and southern regions as of 2012 [Berg-Hansen 2014]. The overall prevalence was 203 per 100 000, but was higher in the Mid Norway.

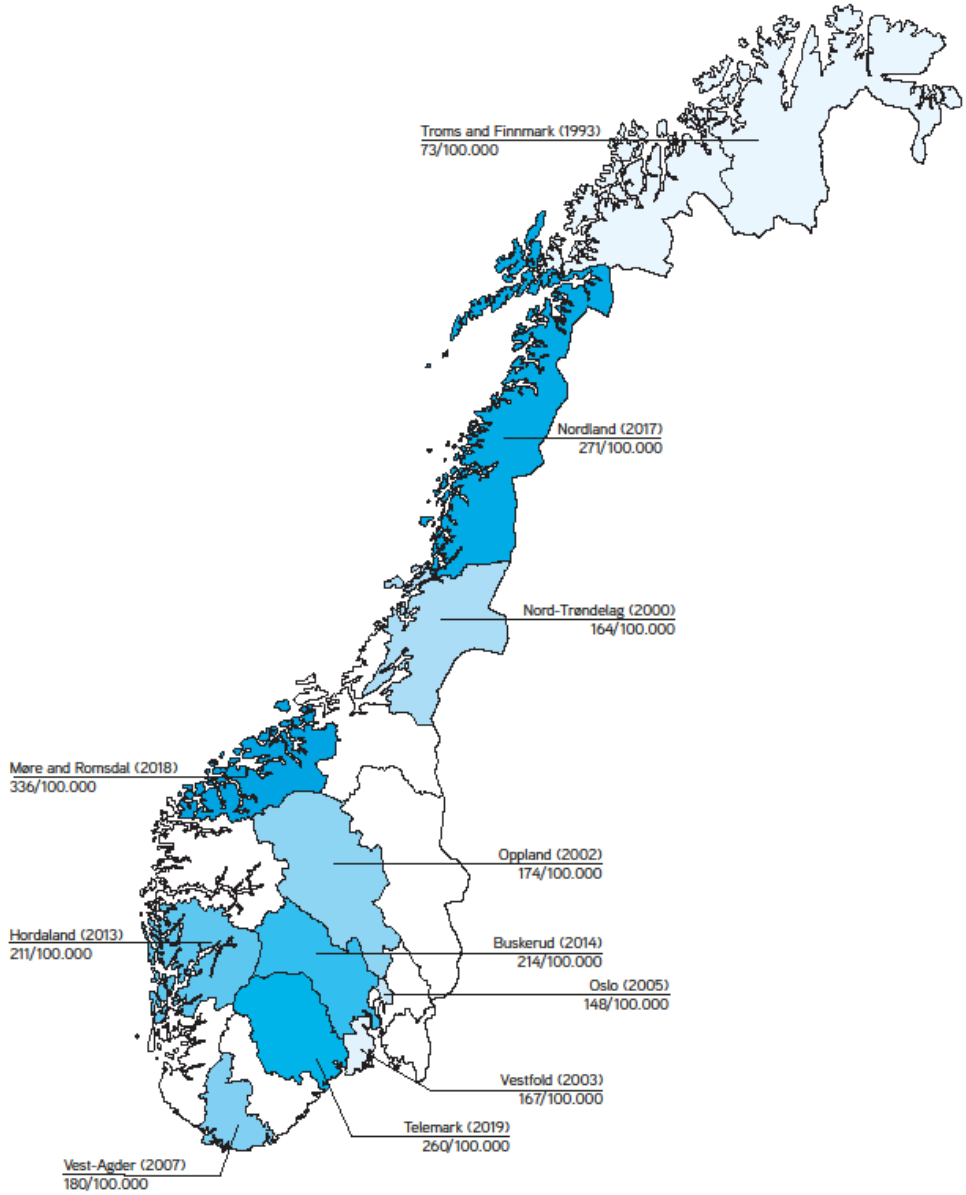
5.4 Studies from 2010 and thereafter – ever-increasing prevalence

As mentioned in section 1.5, there has been an increasing frequency of MS in all the studied regions in Norway up to 2010. Both the prevalence and the incidence have continued to increase in later studies. The prevalence and incidence numbers are given per 100 000.

In Hordaland in *Western Norway*, the prevalence was 211.4 as of January 1, 2013 [Grytten 2016]. In *Southeastern Norway* the prevalence in Vestfold was 166.8 as of January 1, 2003 [Lund 2014]. In Buskerud county, the prevalence was 213.8 as of January 1, 2014. The mean annual incidence was 11.8 during the period 2003 to 2013 [Simonsen 2017]. In Telemark the crude prevalence was 259.6 as of January 1, 2019, and had increased from 97.3 as of January 1, 1999 and 176.1 as of January 1, 2009. The mean annual incidence was 8.2 during the

period from 1999 to 2003 and 13.9 during the period from 2014 to 2018 [Flemmen 2020]. The high prevalence in *Mid Norway* was confirmed with a crude prevalence of 335.8 as of January1, 2018. The mean annual incidence was 14.4 during the period from 2015 to 2017 [Willumsen 2020]. An overview of the prevalence in the investigated counties by year is shown in Figure 9.

Figure 9. The prevalence of MS in Norwegian by year and county.



Internationally, the incidence of MS has increased in most of the areas where this have been studied [Koch-Henriksen 2021].

5.5 Validation of the NPR

Data from the NPR are used as a source in many epidemiological studies. It is also used for the administration and planning of the specialist health care services. It is therefore important that the data in the NPR are reliable.

This is the first Norwegian study that validates the MS-diagnosis in the NPR. The size of the MS cohort in Nordland is suitable for this purpose, since the population is not so large that the task is overwhelming, but still large enough to give reliable results.

Of those registered with MS in the NPR, 8.5 % did not fulfill the criteria for the diagnosis. In about 1/3 of these cases, the individual had been examined for MS, but the diagnosis was ruled out, 1/3 of the cases had no relation to MS, and the registration was probably due to typos, but in the remaining 1/3 of the cases the symptoms or findings were still suspicious of a diagnosis of MS.

The NPR has been evaluated for correctness for some other diseases, and the results are quite similar to our results. A study on intracranial hemorrhage in Trøndelag found that 8.8 % registered with the diagnosis in the NPR actually did not have this condition [Øie 2018]. In a study on ALS, data from the NPR was validated for the counties Akershus and Hordaland. Of those with at least one registration of ALS, 11 % had an incorrect diagnosis [Nakken 2018]. Analyses for the correctness and completeness of the registration of stroke in the NPR found a

sensitivity of 96.8 % and a specificity of 99.6 %, with a positive predictive value of 79.7 % [Varmdal 2016].

We found that about 3 % of the individuals with MS was not registered in the NPR. All, but one, had mild symptoms at the latest consultation prior to 2008. The relatively small number not registered will be even lower in the future, because all new diagnosed cases are now mandatory reported to the NPR.

In our study, the sensitivity was 0.97, the positive predictive value was 0.92 and the Cohens Kappa was 0.94. Thus, there was a good correlation between the numbers in the NPR and the true prevalence of MS in the county.

5.6 Comorbidity in multiple sclerosis patients in Nordland

Diseases may co-occur in many ways. One possibility is that they co-exist simply by chance and independently of each other. There could, however, be a true etiological association between the co-existent diseases. According to Valderas and colleagues, four models for a relation can be identified. One model is the *direct causation*. This means that one disease is directly responsible for another. This also includes complications of treatment for a disease. In a second model, there could be *associated risk factors*. This means that the risk factor for one disease is associated with a risk factor for another disease. A third model is called *heterogeneity*. This means that risk factors for one disease are risk factors also for another disease. The last model is called *independence*, and occurs when two diseases both correspond to a third disease [Valderas 2009]. Studies of comorbidity could hopefully give clues to understanding the etiology of MS.

5.6.1 Cancer

In the MS population of Nordland, the prevalence of cancer was 6.4 %. This is slightly higher than in the total Norwegian population, but the difference was not statistically significant, p = 0.13.

All cases of cancer in Norway are mandatorily reported to the Norwegian Cancer Registry. The epidemiology of cancer is easily available in the annual publication "Cancer in Norway". In the report, the prevalence data are given as absolute numbers, but with the use of the data from Statistics Norway on the population in Norway, the prevalence in percent can be calculated. As of January 1, 2017, there were 5 258 317 inhabitants in Norway, 2 609 187 women and 2 649 130 men.

The data are not given by sex, but this is relevant for some types of cancer. It is straightforward to calculate the prevalence for testis cancer, prostate cancer or ovarian cancer with the given information. However, although breast cancer mainly affects women, men can also be affected. We therefore obtained the number of breast cancer by sex from the Norwegian Cancer Registry (Finn Brynestad, personal correspondence).

Based on this information we made a table showing the prevalence of the different cancers, compared to our findings in the MS population (Table 1).

By correspondence, we also acquired information on the number of cases in the population 20 years and older for breast cancer and non-melanoma skin cancer, as this was found to be relevant.

In other studies, the data on the risk of overall cancer in MS patients are conflicting. Some find increased risk of cancer [Grytten 2020, Capkun 2015], and others do not [Kingwell 2012, Nørgaard 2019].

Table 1. Cancer in the Nordland MS cohort and in the Norwegian population.

		Cancer in the Nordland County MS-population			Cancer in the Norwegian Population	
ICD 10	**Site**	**n**	**Prevalence %**	**Age standardized prevalence %**	**n†**	**%††**
C00-96	**All sites**	**41**	**6.44**	**3.23**	**262 884**	**5.00**
C00-14	**Mouth, pharynx**	**1**	**0.16**	**0.15**	**4 992**	**0.09**
C00	Lip		0		1 389	0.03
C01–02	Tongue		0		1 001	0.02
C03–06	Mouth, other		0		774	0.01
C07–08	Salivary glands	1	0.16	0.15	630	0.01
C09–14	Pharynx		0		1 272	0.02
C15-26	**Digestive organs**	**2**	**0.31**	**0.21**	**39 117**	**0.74**
C15	Esophagus		0		647	0.01
C16	Stomach	1	0.16	0.06	1 987	0.04
C17	Small intestine		0		1 153	0.02
C18	Colon	1	0.16	0.08	21 532	0.41
C19-20	Rectum, rectosigmoid		0		11 789	0.22
C21	Anus		0		762	0.01
C22	Liver		0		529	0.01
C23-24	Gallbladder, bile ducts		0	0.07	469	0.01
C25	Pancreas		0		1 021	0.02
C26	Other digestive organs		0		191	0.00
C30-34, C38	**Respiratory organs**	**0**	**0**		**8 979**	**0.17**
C30–31	Nose, sinuses		0		351	0.01
C32	Larynx, epiglottis		0		1 108	0.02
C33-34	Lung, trachea		0		7507	0.14
C38	Heart, mediastinum and pleura		0		66	0.00
C40-41	**Bone**		0		**807**	**0.02**
C43	**Melanoma of the skin**	**3**	**0.47**	**0.26**	**24 594**	**0.47**
C44	**Skin, non-melanoma**	**11**	**1.73**	**0.83**	**15 425**	**0.29**
C45	**Mesothelioma**	**0**	0		**126**	**0.00**
C47	**Autonomic nervous system**	**0**	0		**245**	**0.00**
C48-49	**Soft tissues**	**0**	0		**1 599**	**0.03**
C50	**Breast***	**14**	**3.29**	**1.50**	**45 492**	**1.74**
C51-58	**Female genital organs***	**2**	**0.47**	**0.28**	**22 991**	**0.88**
C51–52, C57.7–9	Other female genital		0		960	0.04
C53	Cervix uteri		0		7 173	0.27
C54	Corpus uteri	1	0.23	0.11	10 347	0.40
C55	Uterus, other	1	0.23	0.17	50	0.00
C56, C57.0–4	Ovary etc.		0		4 657	0.18
C58	Placenta		0		154	0.01
C60-63	**Male genital organs****	**5**	**2.37**	**1.17**	**54 914**	**2.07**
C61	Prostate	3	1.42	0.58	47 088	1.78
C62	Testis	2	0.95	0.59	7 483	0.28
C60, C63	Other male genital		0		552	0.02
C64-68	**Urinary organs**	**1**	**0.16**	**0.09**	**20 531**	**0.39**
C64	Kidney (excl. renal pelvis)	1	0,16	0.09	6 816	0.13
C65-68	Urinary tract		0		13 877	0.26
C69	**Eye**	**0**	0		**1 086**	**0.02**
C70-72	**Central nervous system**	**0**	0		**13 165**	**0.25**
C73	**Thyroid gland**	**0**	0		**5 718**	**0.11**
C37, C74-75	**Other endocrine glands**	**0**	0		**3 900**	**0.07**
C39, C76, C80	**Other or unspecified**	**1**	**0.16**	**0.09**	**598**	**0.01**
C81-96	**Lymphoid/hematopoietic tissue**	**1**	**0.16**	**0.07**	**23 378**	**0.44**
C81	Hodgkin lymphoma		0		2 799	0.05
C82–86, C96	Non-Hodgkin lymphoma		0		9 672	0.18
C88	Immunoproliferative disease	1	0.16	0.07	597	0.01
C90	Multiple myeloma		0		2 045	0.04
C91–95	Leukemia		0		8 461	0.16

†based on numbers from Cancer Registry of Norway, †† based on numbers from Cancer Registry of Norway and Statistics Norway, *based on the female population, **based on the male population.

Lung cancer

We did not find increased risk of lung cancer in the MS population. As discussed in section 1.4, smoking is a risk factor for MS, and smoking in the MS population could be the reason why the Norwegian study from 2020 found an increased risk of cancer in respiratory organs in the MS group [Grytten 2020]. However, neither the study from British Colombia nor the Danish study found any differences in the occurrence of lung cancer between the MS population and the reference groups [Kingwell 2012, Nørgaard 2019].

Urinary tract

We did not find increased risk of cancer in the urinary tract in the MS population. Smoking is a risk factor both for MS and for bladder cancer, and the Norwegian study from 2020 found an increased risk of cancer in urinary organs in the MS group [Grytten 2020]. In the study from British Colombia there were reported a trend towards an increased risk of bladder cancer in the MS group, but this was not statistically significant [Kingwell 2012]. On the other hand, in the Danish register study there was not any difference between the MS group and the reference group [Nørgaard 2019].

Breast cancer

In the female MS population in Nordland County, we find a significantly increased risk of breast cancer when compared to the total Norwegian female population, $p = 0.015$. The groups are, however, not matched by age. The mean age in the Norwegian population is about 40 years, and the mean age in our MS cohort is slightly above 50 years. We therefore compared the female MS population aged 20 and above to the Norwegian female population

aged 20 and above. Only one MS patient, without breast cancer, had to be removed from this analysis. The annual report from the Cancer Registry of Norway does not include prevalence figures by age and sex, but we obtained this information from the registry via personal communication. In the Norwegian population, 232 males had breast cancer and nine individuals in the female population younger than 20 years had breast cancer. These small adjustments did not interfere with the calculations. The total number of females dropped from 2 609 187 to 1 995 180, and this changed the statistical analysis. There was still a trend for increased risk of breast cancer in our MS population, but the difference was no longer significant.

Although some studies do not find any difference in the occurrence of breast cancer in a MS population compared to a reference group [Kingwell 2012, Nørgaard 2019, Grytten 2019], others do [Sun 2014, Capkun 2015, Hajiebrahimi 2016]. We know that females have twice the risk of MS compared to men. If the increased risk of breast cancer in MS is real, it is tempting to think that hormones may play a role. The use of hormonal contraception increases the risk of breast cancer [Mørch 2017], and it is hypothesized that the use of hormonal contraception increases the risk of MS as well [Williams 2017]. High levels of estrogen and other sex hormones could thus be a possible common risk factor for breast cancer and MS.

Skin cancer

We found that the prevalence of non-melanoma skin cancer was six times higher in the MS population than in the normal population ($p < 0.001$). From communication with the Cancer Registry, we learned that 96 individuals aged under 20 years had non-melanoma skin cancer in Norway. Even when only the population aged 20 years and older was taken under

consideration, the prevalence of non-melanoma skin cancer was still 4.5 times higher in the MS cohort ($p < 0.001$).

Low incidence of skin cancer in the MS population has been described [Goldacre 2004]. In an Australian ecological study on regional variation in MS prevalence, there was an inverse association between the prevalence of MS and the prevalence of melanoma [van der Mei 2001]. These findings may seem logical in relation to the hypothesis that a low amount of sun radiation is a risk factor for MS. Sun exposure, although it might protect against MS, is a risk factor for malignant melanoma and other skin cancers. If we assume low sun exposure in the MS population, it could thus be expected that the prevalence of malignant melanoma is low. However, other studies have shown an increased rate of malignant melanoma in MS [Capkun 2015, Nørgaard 2019]. A study from British Colombia [Kingwell 2012] did not find any difference in the risk of malignant melanoma between the MS population and the control group. Notably, they found the risk of non-melanoma skin cancer was increased, in line with our results.

Colorectal cancer

We did not find any increase in the prevalence of colorectal cancer, nor did two Nordic studies [Nørgaard 2019, Grytten 2020]. The study from British Colombia even found a decreased risk of colorectal cancer in the MS group [Kingwell 2012]. This may be surprising, because cancer in the intestines is associated with inflammatory bowel disease [Keller 2019], and the prevalence of inflammatory bowel disease is quite convincingly increased in the MS population [Kimura 2000, Gupta 2005, Nielsen 2008, Capkun 2015], as also found in our study.

5.6.2 Immunological diseases

In our study, we investigated the occurrence of inflammatory bowel diseases, thyroid disorders, rheumatoid arthritis, systemic lupus erythematosus and diabetes.

In general, there are indications of increased risk of coexistence and clustering of immunologically mediated diseases, both at an individual level and in families [Sloka 2002, Somers 2006, Somers 2009]. This could be the case in MS, and some findings support that individuals with MS have increased risk of other immunological diseases [Midgard 1996 B, Henderson 2000, Laroni 2006, Barcellos 2006]. The results are, however, conflicting. A Canadian study did not find increased risk of autoimmune diseases in the MS population compared to controls [Ramagopalan 2007]. A Danish study found that, although MS patient had increased risk of some diseases, the overall risk of autoimmune diseases was not increased (RR 0.9) [Nielsen 2008].

Vitamin D deficit is a common risk factor that may contribute to the coexistence [Murdaca 2019]. Another possible link is the Epstein Barr virus. This virus is a risk factor for MS [Ascherio 2000, Ascherio 2010, Levin 2010, Munger 2011, Lucas 2011], and is also linked to other autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease and type-1 diabetes [Harley 2018].

Inflammatory bowel disease

In the MS population in Nordland County, the prevalence of inflammatory bowel disease is 1.3 %, and this is increased compared to what is found in the general Norwegian population. It has been claimed that the prevalence of Crohn's disease is 262 per 100 000 and of ulcerative colitis 505 per 100 000 in Southeast Norway [Ng 2018]. However, the prevalence

in Norway are probably lower. Høivik reported on the Norwegian Gastroenterology Forum in 2016, that the prevalence of Crohn's disease was 185 per 100 000 and the prevalence of ulcerative colitis was 250 per 100 000 in 2014 (Information from "Indremedisineren 10.08.2016", Inflammatorisk tarmsykdom – diagnostikk og behandling, by LCT Buer and BA Moum; *in Norwegian only).*

Our finding is in accordance with international studies [Kimura 2000, Gupta 2005, Nielsen 2008, Capkun 2015]. Many MS patients have bowel related problems [Bakke 1996, Alvino 2021]. Although this often is due to dysfunction in the nervous system [Preziosi 2013], perhaps more MS patients should be examined for inflammatory bowel diseases.

Thyroid disorders

We found that 3.6 % of the MS population had thyroid disorder and 3.1 % had hypothyroidism at the prevalence point, and this is not increased compared to the general population described in Trøndelag. The Trøndelag Health Study (the HUNT Study) is a large population-based health study in the northern part of Trøndelag County, inviting every citizen in North Trøndelag aged 20 years and older to participate [Krokstad 2013 B]. In HUNT 2 (1995-1997) and HUNT 3 (2006-2008), the information included thyroid function measurements. The prevalence of hypothyroidism was 9.2 % among women and 3.1 % among men in the period 2006-2008 [Asvold 2013].

We included these conditions in the study, even though we suspect that they are underestimated in the NPR. One reason for the inclusion is that alemtuzumab, a drug used in the treatment of MS, is known to increase the risk of thyroiditis and hypothyroidism [Pariani 2018, Scappaticcio 2020]. Two (10 %) of the cases of hypothyroidism were probably

associated to previous alemtuzumab therapy. Studies from the era prior to this medication are conflicting [Sloka 2005, Marrie 2012].

Connective tissue diseases

We found rheumatoid arthritis (RA) in 0.6 % in the MS population, and none with systemic lupus erythematosus (SLE).

One study has investigated the epidemiology of RA in the general population in Troms County. The prevalence was 0.47 % in the population older than 20 years in 1994, 0.63 % for females and 0.30 % for males [Riise 2000]. The mean annual incidence of SLE was 3.0 per 100 000 in Oslo in the period from 1999 to 2008, and the prevalence was 51.8 per 100 000 as of January 1, 2008 [Lerang 2012].

Hence, the prevalence of rheumatoid arthritis in the MS population do not differ from what is found in the general Norwegian population. Our study population is too small to conclude regarding the prevalence of SLE.

Diabetes

We found a prevalence of 0.3 % of type-1 diabetes and 3.9 % of type-2 diabetes.

In a Norwegian nationwide register-based study, the prevalence of type-2 diabetes was 6.1 % in the age group 30-89 years in 2014 [Ruiz 2018]. An epidemiological study on diabetes in Salten (Bodø and surrounding municipalities) has recently been published. The overall prevalence of diabetes was 3.8 % in 2014, with type-1 diabetes 0.45 % and type-2 diabetes

3.4 %. In the age group 20 years and older the prevalence of type-1 diabetes was 0.49% and of type-2 diabetes was 4.4 % [Slåtsve 2020].

The data on type-2 diabetes in our study is probably an underestimate, because we assume that this condition in many cases are handled by the primary health care service, and hence often not reported to the NPR

Studies have shown increased prevalence of type-1 diabetes in the MS population [Tettey 2015], but we could not confirm this in our study.

5.6.3 Myocardial infarction and ischemic stroke

We found that 1.7 % of the MS population had suffered myocardial infarction, and the mean annual incidence was 250.4 per 100 000. All reported cases of myocardial infarction in the NPR were correct.

There are high quality data on vascular diseases in Northern Norway, due to the Tromsø study. This population-based study was conducted for the first time in 1974. Since then, additional six surveys have been conducted with "Tromsø 7" in 2015-16, and this is the longest-running epidemiological study in Norway [Njølstad 2016]. The age- and sex-adjusted incidence of hospitalized myocardial infarction was 80 per 100 000 person-years for ST-elevation myocardial infarction (STEMI) and 144 per 100 000 person-years for non-STEMI in the population older than 25 years in 2010, which corresponds to a total annual incidence of 224 per 100 000 in this age group [Mannsverk 2016].

Hence, the incidence of myocardial infarction was not increased in the MS population compared to the general population. Thus, we could not confirm the findings in other studies

that have found an increased rate of myocardial infarction [Capkun 2015, Thormann 2016, Marrie 2019] in the MS group.

We found that 0.6 % of the MS population had suffered ischemic stroke, and the mean annual incidence was 91.7 per 100 000. In the normal population older than 30 years, the incidence was found to be 367 ischemic strokes per 116 703 person-years, 314.5 per 100 000, in the period 2006 – 2010, [Vangen-Lønne 2015].

Several studies have found an increased rate of cerebrovascular disease [Allen 2008, Capkun 2015, Tseng 2015, Thormann 2016] in the MS group. We could not confirm these findings in our study. However, three times as many patients was reported with ischemic stroke in the NPR than we could confirm after validation. It is possible that similar conditions may affect other registry-based studies, and lead to artificially high numbers for stroke.

Smoking is found to be a risk factor for MS. Smoking is also a risk factor for vascular diseases such as myocardial infarction and ischemic stroke, and could represent a common risk factor for both these diseases and MS. To address this, future studies should adjust for smoking. Risk factors like hypertension and hyperlipidemia should also be taken into consideration. Vascular diseases that occur in the MS population are of particular interest, because they are shown to be associated with an increased progression of the neurological symptoms [Marrie 2010].

5.6.4 Psychosis

Our finding of a prevalence of psychosis of 0.6 % in the MS population is not different compared to the normal Norwegian population. A study based on interviews carried out in

Oslo in the period 1994-1997 found a lifetime prevalence of non-affective psychosis of 0.4% in the population age 18-65 years [Kringlen 2001].

Studies have indicated increased comorbidity of psychiatric disorders, foremost depression, anxiety and cognitive decline, in the MS population [Dahl 2009, Patten 2017, Whitehouse 2019]. Depression and anxiety are observed in various chronic diseases [Clarke 2009]. It could be due to pain or discomfort and be a psychological reaction to the chronic condition. Structural changes in the brain are most likely the cause of cognitive decline and dementia. We did not investigate these aspects of mental health, because we assume that these conditions would often not be reported to the NPR.

Cases of psychosis, on the other hand, will more likely be transferred to the specialist health care, and hence reported. The pathophysiology and etiology of psychosis are not well understood. One hypothesis is aberrant connections and interactions in the brain [Friston 2016, van Dellen 2020]. It is possible that inflammation and MS lesions could interact with the normal neuropsychological functions of the brain and cause psychosis. Increased prevalence of psychotic disorders in the MS population was found in the province of Alberta in Canada [Patten 2005] and in Taiwan [Kang 2010]. However, we could not confirm this in our study.

5.6.5 Epilepsy

For *paper 3*, the medical records of the 431 individuals with MS in Nordland presented in *paper 1*, were scrutinized for evidence of epilepsy. In total 34 cases were considered, but 15 were excluded as other conditions were more likely. Of the remaining 19 with a history of epilepsy, 14 had active epilepsy, 3.2 % of the MS population.

An epileptic seizure was defined as a transient occurrence of signs and symptoms due to abnormal activity in the brain [Fisher 2005], and epilepsy was defined as a condition with recurrent epileptic seizures. We used the designation “active epilepsy” if the person had seizure within the last five years *or* used antiepileptic drugs at the prevalence point [Thurman 2011]. We then used the same definition that was applied in the study of the epidemiology of epilepsy in Buskerud [Syvertsen 2015].

In *paper 4*, we reported compatible findings. Of the 637 individuals correctly registered with MS in the NPR in Nordland County as of January 1, 2017, 18 individuals (2.8 %) were correctly registered with epilepsy.

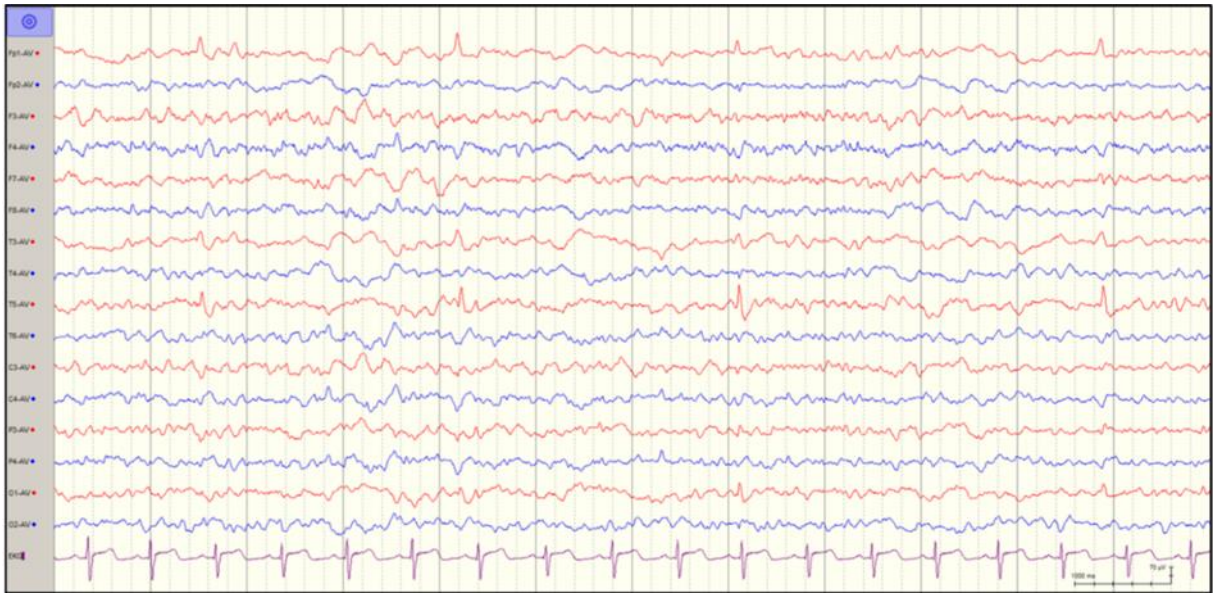
This was compared to studies of the prevalence of epilepsy in the general population. From 1995 to 1997, a study of the epidemiology of epilepsy was carried out in Vågå municipality, Oppland County. Active epilepsy was defined as fulfilment of the criteria for epilepsy and ‘at least one seizure in the last five years’, and was found in 0.67 % of the participants. Cases under treatment was 1.17 % [Brodtkorb 2008]. Another study, also in Oppland County, fond a prevalence of active epilepsy of 0.82 % at the end of 2001. Active epilepsy was defined as ‘more than one epileptic seizure during the last five years or the use of antiepileptic drugs’ [Svendsen 2007]. In a study from Buskerud, with the definition of active epilepsy as ‘current treatment with antiepileptic medication or at least one seizure within the last five years’, found the prevalence to be 0.65 % at the beginning of 2014 [Syvertsen 2015].

Thus, we found the prevalence of active epilepsy to be more than four times higher in the MS population than in the normal population. Our findings are quite similar to the findings in two other Norwegian studies [Engelsen 1997, Lund 2014].

In *paper 3*, we found that all patients with epilepsy, except one (93 %), had other symptoms of MS before they had their first epileptic seizures. This indicates that epilepsy may be caused by the MS.

It is well known that focal brain pathology may give rise to seizures and epilepsy. After an ischemic stroke, 2-4 % will develop epilepsy [Camilo 2004]. Among patients with brain tumors, epilepsy will occur in 10 % [van Breemen 2007]. The majority, 86 %, of the MS patients with active epilepsy reported in *paper 3* had focal epilepsy based on seizure semiology or EEG findings (Figure 12). Thus, it is reasonable that focal MS lesions can cause seizures.

Figure 10. EEG from an individual with MS, showing focal epileptic activity in the left temporal region.



Focal epilepsy is a disorder of the cerebral cortex, and the MS lesions responsible could be located juxtacortically in the white matter, or even more likely in the cortical gray matter. A study of 13 individuals with MS and epilepsy and 26 matched MS patients without epilepsy, found increased number of cortical or juxtacortical involvement evaluated by MRI in the group with seizure [Martínez-Lapiscina 2013]. An Italian study found pure intracortical

lesions in 90 % of patients with MS and epilepsy, and in less than half of the matched MS patients without epilepsy (p = 0.001) [Calabrese 2008].

In our cohort, the first indication of epilepsy occurred from zero to 30 years after the diagnosis of MS. At the prevalence date there was a large span in severity of MS, with EDSS ranging from 0 to 9.5. Epilepsy seems thus independent of the disability level, and can evolve at any time during the disease course. This view has some support in the literature. In a study of 13 MS patients with epilepsy, the EDSS ranged from 1.0 to 8.0, and the seizures started 1 to 23 years after onset of the MS [Striano 2003]. On the other hand, we found a significantly increased risk of having SPMS in the group of patients with epilepsy. If we include the patients with PPMS, almost 80 % of the individuals with epilepsy had progressive MS. A small study from Mexico also found that the progressive MS forms were significantly more common among patients with comorbid epilepsy [Martínez-Juárez 2009]. A Swedish register-based study found significant increased risk of epilepsy in the group that had progressed to SPMS, by an HR of 3.3 [Burman 2017]. It is therefore possible that patients with a progressive form of MS are more likely to develop epilepsy.

Another explanation for the increased risk of having SPMS in the group with epilepsy could be that epilepsy is a marker for more aggressive MS. Patients with MS and epilepsy are found to progress faster than the patients without epilepsy. They reach score 6 at the Kurtzke Disability Status Scale in a shorter time interval [Catenoix 2011] and seem to have a more rapid cognitive decline [Calabrese 2012] compared to MS patients without epilepsy. MS-patients with epilepsy also have a higher progression rate of cortical pathology [Calabrese 2012]. On the other hand, older studies did not find any correlations between epilepsy [Kinnunen 1986], frequency of seizures [Ghezzi 1990] and the severity of MS.

6 Conclusion

We have found a continuous increase in both the prevalence and the incidence of MS in Nordland County since the 1970's. The prevalence was 270.5 per 100 000 as of January 1, 2017.

Our findings indicate that the prevalence and incidence of MS is not lower in Nordland County than in more southern Norwegian regions – and thus reject a previous hypothesis that there is an inverse latitude gradient of MS in Norway, with a low occurrence in the north.

There is an overall good agreement between the number of MS patients registered in the NPR and the actual number of individuals with MS in Nordland County, but still almost 10 % registered with MS in the NPR does not fulfill the diagnostic criteria of the disease.

We found a more than four-fold increase of epilepsy in the MS population compared to the reported prevalence in Norway, by two different approaches, both by examining the medical records of all known MS patients in Nordland County as of 2010, and with the use of data from the NPR as of 2017.

There is an increased prevalence of inflammatory bowel disease in MS compared to the general population in Norway. The prevalence of non-melanoma skin cancer is significantly increased in our MS population when compared to the prevalence in the general Norwegian population.

7 Future perspectives

The study of geographical distribution and time trends in the incidence and prevalence of MS could potentially give clues to understand risk factors and the cause of the disease. The knowledge of the burden of the disease, both prevalence and comorbidity, is important for economic priorities and health care planning. Knowledge of comorbidity is essential for personalized therapy for MS.

We continue the inquiry of the epidemiology of MS in Nordland, and we are already working on a 50-years follow up study, where we include information from 1970 up to 2020. It would also be of interest to contribute to the study of the epidemiology of MS even further north, in Troms and Finnmark. This area has not been updated on the occurrence of MS by county since 1993.

Furthermore, we will expand the investigations on the comorbidity in MS by including data from the Norwegian Prescription Database, which hopefully will give important data of coexisting conditions like diabetes, hypertension and hypothyroidism that are often treated by the general practitioner, and thus underreported in the NPR.

The surprising association between MS and non-melanoma skin cancer is of particular interest in a region where the sun exposure in general is low, and it should be further and more deeply investigated.

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Paper 1

Multiple sclerosis in the far north - incidence and prevalence in Nordland County, Norway, 1970-2010.

Benjaminsen E, Olavsen J, Karlberg M, Alstadhaug KB.

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RESEARCH ARTICLE Open Access

Multiple sclerosis in the far north - incidence and prevalence in Nordland County, Norway, 1970–2010

Espen Benjaminsen[1*], Johnny Olavsen[2], Merethe Karlberg[1] and Karl B Alstadhaug[1,3]

Abstract

Background: The risk of multiple sclerosis (MS) increases with increasing latitude. Taking into consideration that Norway has a large latitude range, a south-to-north gradient would be expected. However, previous studies have reported an uneven distribution of the disease in Norway, with a relatively low prevalence in the most northern parts of the country.
We describe the incidence and prevalence of MS in a county in the north of Norway over a period of 40 years.

Methods: All patients with MS living in Nordland County in the period 1970–2010 were identified by reviewing hospital charts. The patients were included if they met the criteria of definitive or probable MS according to Poser [Ann Neurol 13:227-231, 1983] or MS according to McDonalds [Ann Neurol 50:121-127, 2001]. Point prevalence at the beginning of the decades was calculated. The average annual incidence was calculated for 5-year periods.

Results: The total crude prevalence on January 1, 2010 was 182.4 per 100 000. The annual incidence continuously increased from 0.7 per 100 000 in 1970 – 1974 to 10.1 per 100,000 in 2005 – 2009. The time delay from the first symptom to diagnosis was stable from 1975 to 2010. The proportion of primary progressive MS in the prevalence numbers was 38.2% in 1980, and decreases continuously, to 18.6% in 2010. The female to male prevalence ratio has been stable since 1990 at 2.2 to 1.

Conclusion: The prevalence and the incidence of MS have steadily increased over a 40 year period. Nordland County is a high-risk area for MS.

Keywords: Multiple sclerosis, Norway, Epidemiology, Prevalence, Incidence

Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease in the central nervous system with unknown aetiology. A latitude dependent gradient in the occurrence has been shown in many countries and regions. The risk of MS is increasing from south to north in Europe, North America and Japan [1-4] on the northern hemisphere, and from north so south in Australia and New Zealand [5,6] on the southern hemisphere. In general, the risk increases with increasing distance from the equator [7]. Norway has a long and narrow landscape, with the mainland stretching from 57° N to 71° N, and a similar north–south gradient of the MS prevalence would thus be expected. However, previous studies have shown an uneven distribution in Norway, with a relatively low prevalence in the most northern parts of the country (Figure 1) [8-15]. This variation has been attributed to specific genetic and environmental factors. There is accumulating evidence that hypovitaminosis D is an important risk factor for MS [16], and it has been suggested that low sun exposure, and thereby reduced production of cutaneous vitamin D, in the high latitudes could be one cause of the observed increase in these areas. The paradoxically low occurrence of MS in the north of Norway could then be explained by high dietary intake of vitamin D through fish consumption [17,18]. The genetics of the indigenous population of the far north could also be an explanation for the reversed gradient observed. The

* Correspondence: espen.benjaminsen@nlsh.no
[1]Department of Neurology, Nordland Hospital Trust, Post box 1480, 8092 Bodø, Norway
Full list of author information is available at the end of the article

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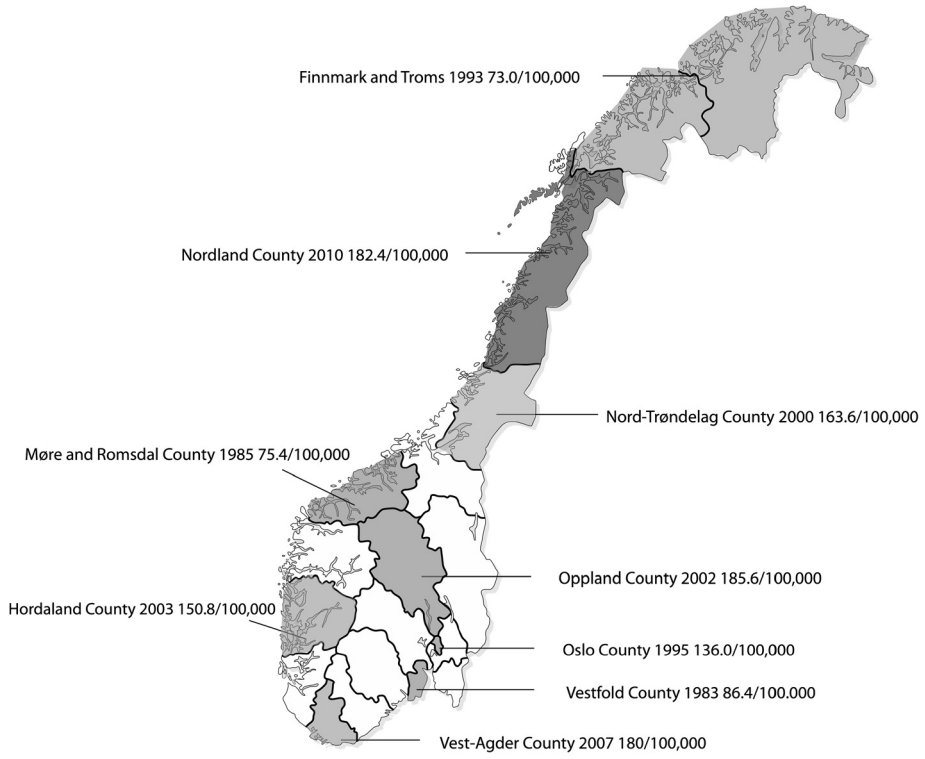

Figure 1 Prevalence of MS in Norwegian counties.

Sami people of northern Scandinavia seem to be partly protected against MS. The first known appearance among them is registered as late as the 1990s [10]. MS is associated with the human leukocyte antigen DRB1*15-DQB1*06, and the Sami have a low frequency of this haplotype [19].

To contribute to a more precise knowledge of the distribution of MS, we assess the prevalence and incidence of multiple sclerosis in Nordland County in the period 1970 to 2010. Interim data published in Norwegian in 2005, showed a prevalence of 105.6 per 100 000 at December 31, 1999 [20]. All data from this survey was reexamined. We describe trends in the occurrence over four decades in an area with a stable and relatively homogeneous population.

Methods

This is a retrospective cross-sectional epidemiological study.

Geographical area

Nordland is in the northern part of Norway, situated between latitude 64°56' N and 69°20' N. The Arctic Circle at 66°33' N is running through the county in between Mo i Rana and Bodø, the two largest cities. The county, covering a total area of 38456 km^2, includes the regions of Helgeland, Salten, Ofoten, and the islands of Lofoten and Vesterålen. The population at risk at January 1, 2010 was 236 271 (118537 men, 117734 women). The population was 243 179 in 1970, indicating an average yearly reduction in the population of 0.07% in the period.

The only neurological department is at the Nordland Hospital in Bodø, serving both outpatients and hospitalised patients. The department was founded in 1973, but a neurologist was at place a year earlier, and MS patients are registered from 1970. There are neurological outpatient services at the hospitals in Mosjøen (Helgeland) and Stokmarknes (Vesterålen).

Case ascertainment

All patient with the diagnoses of MS treated at the hospital in Bodø were identified by searching for the diagnosis according to ICD 8 (340.08), ICD 9 (340) and ICD 10 (G35) in the hospital's medical files. In addition to the files of Nordland Hospital in Bodø, we searched the files from the hospitals in Mosjøen and Stokmarknes. We also requested for files and cases from the neurological department in Namsos in the neighbor county to the south, and from the two nearest university hospitals, the University Hospital of North Norway in Tromsø in the neighbor county to the north and St. Olavs Hospital in Trondheim to the south. The records were examined and the diagnoses were confirmed by a neurologist. Patients were included if they satisfied the criteria for clinically definite MS, laboratory supported definite MS, clinically probably

MS or laboratory supported MS after the criteria described by Poser in 1983 [21] or MS after the criteria of McDonald from 2001 [22]. Cases that were misclassified or did not fulfill these criteria were excluded. Some patients had been treated at more than one hospital. By combining the files from different hospitals, additional information was obtained, and the diagnoses could be reconfirmed. We classified the cases as primary progressive MS (PPMS) or relapsing remitting MS (RRMS) course at onset. The stipulation of the year of the first symptom was based partly on older records of findings and symptoms in the files, and partly on the written information of the patients' later recollection of former symptoms.

Statistics

We have used the time of diagnosis as starting point for the epidemiological calculations. The point prevalence rate was defined as the proportion of the population in Nordland County with definitive or probable MS according to Poser or MS according to McDonalds at a specified time point. We calculated the point prevalence per 100 000 inhabitants for January 1, in 1980, 1990, 2000 and in 2010. The incidence rate was defined as the proportion of the population in Nordland County who got definitive or probable MS according to Poser or MS according to McDonalds during a specified time period. The average annual incidence was calculated for 5-year periods. Both prevalence and incidence were calculated for females and males separately, and we calculated the female to male (f/m) sex ratio.

We calculated the mean and median time delay from first symptom to diagnosis for each 5-year period. Data of population by age and gender were obtained from Statistics Norway [23]. Data considering the Sami population was obtained from the website of Sametinget, the Sami Parliament [24]. A Poisson distribution of the disease was assumed, and the 95% confidence interval (CI) for both the prevalence and the incidence was calculated. The age adjusted prevalence and incidence were calculated by the use of data from a standard European population [25]. A chi squared test was used to give a statistical description of the change of the proportion of PPMS in the prevalence rate over time. Statistical analyses were performed by the use of StatXact version 10 for Windows (Cytel Software, Cambridge, MA) and Microsoft Office Exel for Windows 7.

Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Nord).

Results

We identified a total of 533 persons with definitive or probable MS. Ten persons had got the diagnoses before 1970, while 26 had received the diagnosis elsewhere and moved to the county. Twenty-two subjects diagnosed with MS had left the county, five had moved both to and from the county. Eighty patients had died during the period. The number of new cases diagnosed in the county is shown in Figure 2. In 7 cases the time of the first symptom could not be determined, 4 of these patients had got the diagnosis before 1970, 1 had got the diagnosis in the period 1975–79, 1 in the period 1985–89 and 1 in the period 90–94.

The number of persons with MS in the county in the present study differs slightly from the data previous published for the period 1970–2000 (20). Three cases were reclassified not to be MS. Seven persons received the diagnosis per letter after they had performed MRI at other hospitals, and were not registered in our files until they were treated in our department years later. Nineteen patients had been treated at the hospital in Mosjøen, a hospital that had not been included in the previous study. In the present study a total of 36 patients were identified exclusively outside our hospital.

On January 1, 2000 there were 158 persons diagnosed with MS that had not been examined with MRI. In all of the patients diagnosed during the period 2000–2009 an MRI had been performed.

Prevalence

At January 1, 2010, 431 persons had definitive or probable MS. The crude prevalence was 182.4 per 100 000. The age adjusted prevalence was slightly lower, 174.4 per 100 000. The crude prevalence among women was 249.7 per 100 000 and among men 115.6 per 100 000. Table 1 shows the crude prevalence and prevalence by gender at the beginning of the decades. The prevalence increased significantly from 1970 to 2010, $p < 0.001$.

Figure 3 shows the age specific prevalence rates according to gender. The mean age of the MS patients increased continuously, and was 51.2 years in 2010. The female to male (f/m) prevalence ratio was 3.3 in 1980, but was then stable at 2.2 from 1990 to 2010 (Table 2).

The proportion of PPMS in the prevalence numbers was 38.2% in 1980, and decreases continuously, to 18.6% in 2010 (Table 3). This is a statistical significant decline, $p = 0.002$.

Incidence

In the period 1970–2009 there were 497 persons who received the diagnosis while living in the county. The incidence was continuously increasing in the whole period, and the yearly average incidence was 10.1 per 100 000 in 2005–2009. This was a significant increase from the period 2000–2004, $p = 0.031$. The increase was also significant from 1985–1989 to 1995–1999, $p = 0.031$. The

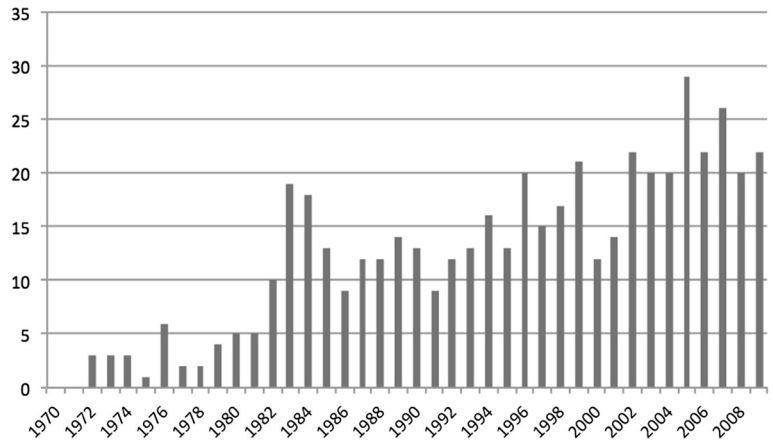

Figure 2 Number of new cases diagnosed per year 1970 – 2009.

average annual incidences calculated in 5-year periods are shown in Table 4.

The mean age at the time of the diagnosis was stable during the whole period, and the time from first symptom to diagnosis was stable from 1975 to 2010 both in terms of mean and median (Table 5).

The f/m ratio was 2.1 in the period 1975–1979 and 2.2 in the period 2005–2009 (Table 6).

In the incidence numbers the proportion of PPMS decreased from 33.3% in 1970–1974 to 20.6% in 1990–1994. The proportion of PPMS was 21.8% of the new cases in the period 2005–2009, and had been quite stable from 1990 (Table 7).

Discussion

The prevalence of MS has increased steadily in Nordland County during the last four decades. One contribution to this increase is the accumulation of cases. A total of 497 new patients were diagnosed, while only 80 died. The accumulation is reflected in the mean age, which increased from 45 to 51 years from 1980 to 2010. However, the main reason for the increase of prevalence is an increase of the incidence. The incidence was 0.7 per 100 000 in 1970–1974, and remained less than 5 per 100 000 until 1985. It reached 7 per 100 000 during 1995–1999, and was over 10 per 100 000 in the last period 2005–2010 (Table 4).

The Poser criteria were introduced in 1983, and we find a marked increase in new cases in 1983 and 1984 compared with previous years. In 2001 the diagnostic criteria of McDonald were established, again followed by an increase of diagnosed cases in our county. The new criteria probably made it easier to conclude in the diagnostic work-up. Also, following the introduction of new criteria more focus could have been put on the disease, and thereby increasing the diagnostic sensitivity. Because of the long time span of our study, we have included cases fulfilling the criteria either according to Poser or according to McDonald, or both. Other Norwegian studies were only Poser criteria are applied report increasing incidence [11,13]. Studies that compare the figures when Poser and McDonalds criteria are applied on the same population have found only small differences in the prevalence [26,27].

Magnetic resonance imaging (MRI) has become an important tool in the diagnostic work up of MS. The role of MRI in the study of MS-epidemiology and changes over time is an interesting but difficult issue. The first MRI scanner in Nordland was set up in autumn 2000. Prior to this, MRI was available in neighbouring regions, from 1986 in Trondheim and from 1991 in Tromsø. At prevalence day January 1, 2010 there were 5 MRI scanners in the county. Monosymptomatic cases and clinical isolated syndromes will not necessarily fulfill the criteria after Poser. If dissemination in time and space is demonstrated with MRI changes the diagnosis can be given with the McDonalds criteria. On January 1, 2000 there

Table 1 Prevalence of MS in Nordland County at the beginning of 4 decades

		Total			
Year	Population at risk	Cases	Prevalence (95% CI)	Age adjusted prevalence	Mean age (SD)
1980	243 808	34	13.9 (9.7-19.5)	16.9	45.3 (10.7)
1990	239 532	152	63.5 (53.8-74.4)	70.5	45.4 (12.0)
2000	239 109	275	115.0 (101.8-129.4)	117.9	48.1 (11.6)
2010	236 271	431	182.4 (165.6-200.5)	174.4	51.2 (12.2)

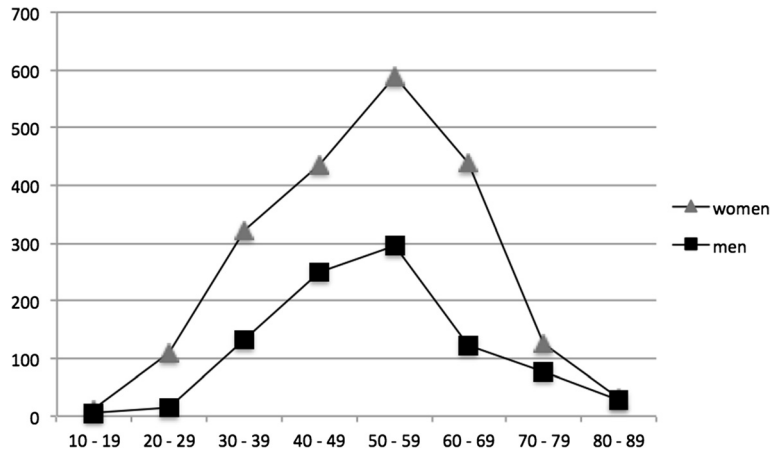

Figure 3 Age-specific prevalence rates by gender on January 1, 2010.

were 158 persons diagnosed with MS that had not performed MRI. All of the 207 patients diagnosed in the period 2000–2009 had performed a MRI scan. Of the 163 with RRMS, 38 were monosymptomatic at the time of diagnosis. The diagnosis was based on dissemination in time demonstrated on MRI. However, 21 of these 38 had a new clinical attack before 2010, thereby fulfilling the criteria for clinically definite MS after Poser as well. If those 17 not fulfilling the criteria for clinical MS after Poser were excluded, the prevalence rate at January 1, 2010 would drop from 182.4 to 175.2. This is a reduction of 3.9%. Although MRI findings are not included in the Poser criteria, the use of MRI will most likely increase the diagnostic sensitivity. Our experience is that if there are pathological findings on an MRI scan, more emphasis is put in the patient interview to reveal MS manifestations in the past. A patient with light symptoms or mainly sensory symptoms could be more easily diagnosed with this technique. On the other hand, MRI scans will rule out cases where other diagnoses are more likely.

Another potential contributor to increased diagnostics is the immunomodulatory treatment for MS that was available in clinical practice from the second half of the 90's. It may have urged the necessity of diagnosing the condition, and increased the diagnostic sensitivity.

In the present study we report a steady age at time of diagnosis (Table 5). The mean age at onset, that is the time of diagnosis, was about 40 years during the whole period. We also report a steady time delay from the first symptom to the diagnosis. The mean time delay was 5.0 years in 2005–2009. This may intuitively seem a bit high, but is in accordance with other Norwegian studies. The results from a study in Oslo [11], also applying "time of diagnosis" as onset, are almost identical to ours. In 1972–1985 a mean age at onset of 38.7 year, and a mean time from the first symptom to the diagnosis of 5.9 year were found. This changed only slightly until 1985–1999, where the mean age at onset was 38.1, and the mean time from the first symptom to diagnosis was 5.2 year [11]. Other studies, which use first symptom as time of inclusion, report a marked decrease in time delay [12,13]. If we had used the "time of the first symptom" as starting point for the calculation, the mean time delay would have been 1.1 year and the median time delay 1 year in the period 2005–09. This is however an artificial time decline. When the "time of first symptom" is used, everyone included from the latest year would, by definition, have a time delay less than one year. We think that if increased incidence was only due to improved and faster diagnostic work up, the time delay from the first symptom to the diagnosis would be expected to decline.

Our findings show that the female to male (f/m) sex ratio has been stable over time. Based on the prevalence numbers it was 2.2 in 2010 which is unchanged from 1990 (Table 2). The f/m sex ratio based on incidence

Table 2 Gender specific prevalences

	Women		Men		F/M sex ratio
Year	Cases	Prevalence	Cases	Prevalence	
1980	26	21.6	8	6.5	3.3
1990	104	87.3	48	39.9	2.2
2000	189	158.1	86	71.9	2.2
2010	294	249.7	137	115.6	2.2

Table 3 Distribution of the prevalence of PPMS and RRMS course at onset

Year	PPMS, % (n)	RRMS, % (n)	Unknown, % (n)
1980	38.2 (13)	52.9 (18)	8.8 (3)
1990	27.0 (41)	65.1 (99)	7.9 (12)
2000	21.5 (59)	76.0 (209)	3.3 (9)
2010	18.6 (80)	80.0 (345)	1.4 (6)

Table 4 Yearly average incidence of MS in 5-year periods

		Total		
Years	**Average population**	**Cases**	**Incidence (95% CI)**	**Age-adjusted incidence**
1970-1974	241867	9	0.7 (0.34-1.41)	0.9
1975-1979	242886	15	1.2 (0.69-2.04)	1.5
1980-1984	244614	57	4.7 (3.53-6.04)	5.3
1985-1989	241266	60	5.0 (3.80-6.40)	5.4
1990-1994	239953	63	5.3 (4.04-6.72)	5.4
1995-1999	240131	86	7.2 (5.73-8.85)	7.3
2000-2004	237783	88	7.4 (5.94-9.12)	7.6
2005-2009	235779	119	10.1 (8.36-12.98)	10.7

numbers was 2.1 in 1975–1979 and 2.2 in 2005–2009 (Table 6). Data from other high prevalence areas have also shown sex ratio stability over time [6,28], but across the world there has been an increase in the ratio [29]. For instance, a Canadian study of 27074 patients showed that the f/m ratio by year of birth increased over a period of at least 50 years [30]. In a Danish prevalence study including 9377 patients the f/m ratio increased from 1.31 in 1950 to 2.02 in 2005 [31]. A Swedish study including 8834 patients from the national MS patient registry did not find evidence for an increased f/m ratio by year of birth among MS patients born between 1931 and 1985 [32]. However, when the study was expanded to 19510 patients by including information from additional registers an increased sex ratio was identified. The f/m ratio was 1.70 among patients born 1931–1935, and increased to 2.67 among those borne 1981–1985 [33]. More than twice as many women than men have MS in Nordland, but as said this has been unchanged over the last decades. The data from our region is quite complete when it comes to registered patients in the given period, but we cannot exclude that the material is too small to demonstrate a trend.

We calculated the distribution of RRMS and PPMS both in the prevalence and the incidence numbers (Tables 3 and 7). We find a PPMS course of disease at onset in 18.6% of the prevalence at January 1, 2010. This is higher than other Norwegian studies performed after 2000, which find the proportion of PPMS ranging from 9.3 to 16.8% [12,13]. In a study from Finland, the proportion of PPMS was 22% in the period 1979–1993 [34]. We find that the proportion of PPMS has steadily decreased in the prevalence numbers from 1980 to 2010. However, the proportion of PPMS in the incidence numbers have been quite stable at approximately 20% from 1990–1994.

Findings from previous studies indicate a relatively low occurrence of MS in Troms and Finnmark, the two most northern counties of Norway, with a prevalence of 73.0 per 100 000 in 1993 [10]. The Sami is considered the traditionally indigenous inhabitants in northern Norway, Sweden, Finland and northwest Russia. It is a low prevalence of MS in the Sami population [19]. The majority lives in Finnmark, but there is no exact statistical data on the Norwegian Sami population. It is estimated that about 40 000 Sami are living in the country, of those are about 30 000 living north of the Arctic Circle. A clue about the distribution of the Sami population is the figures of the members in the Sami electoral register, in which membership is voluntary. At June 30, 2009 there were 13 890 persons registered in the Sami electoral register. In Nordland 1190 persons were registered. In Troms, with 156 494 inhabitants at 01.01.2010, 2807 persons were registered,

Table 5 Age at diagnosis and time from first symptom to diagnosis

	Age at onset, year		**Time from first symptom to diagnosis, years**			
Years	**Mean (SD)**	**Range**	**Mean (SD)**	**Median**	**Interquartil range**	**Range**
1970-1974	42.2 (8.7)	30-52	7.7 (5.9)	7	11	1-16
1975-1979	38.6 (10.5)	22-61	4.3 (5.3)	2,5	4.75	0-19
1980-1984	38.9 (11.8)	21-70	6.0 (7.9)	3	6	0-43
1985-1989	38.3 (11.1)	14-64	4.2 (5.9)	2	4.5	0-20
1990-1994	36.9 (10.4)	18-66	5.2 (6.5)	2	7	0-25
1995-1999	39.3 (10.0)	18-69	4.9 (5.6)	2,5	6	0-28
2000-2004	40.4 (11.4)	12-75	5.0 (6.1)	2	6	0-29
2005-2009	40.4 (11.0)	14-71	5.0 (6.1)	3	5.5	0-32

Table 6 Gender specific incidence

	Women		Men		F/M sex ratio
Years	Cases	Incidence	Cases	Incidence	
1970-1974	8	1.4	1	0.2	7.0
1975-1979	10	1.7	5	0.8	2.1
1980-1984	34	5.6	23	3.7	1.5
1985-1989	41	6.8	19	3.1	2.2
1990-1994	38	6.4	25	4.2	1.5
1995-1999	59	9.8	27	4.5	2.2
2000-2004	57	9.6	31	5.2	1.8
2005-2009	82	13.9	37	6.2	2.2

while in Finnmark, with 72 856 inhabitants, as many as 7432 persons were registered in the electoral register. The high proportion of Sami could thus, at least to some extent, count for the low prevalence of MS in Troms and Finnmark compared to Nordland.

When prevalence and incidence rates are compared from different regions, it must be noticed that the surveys are from different times. The incidence and prevalence are in general increasing, and older studies will show lover occurrence than newer. The prevalence data from Troms and Finnmark are from 1993. The prevalence reported is lower than the prevalence in Nordland in 2000, but higher than the prevalence in Nordland in 1990. Nevertheless, from the same period (1995) the prevalence is much higher in Oslo to the south in the country. The present study is one of the two newest epidemiological studies in Norway, the other is from Vest-Agder to the very south. The prevalence in Nordland in 2010 is quite equal to that in Vest-Agder in 2007. It therefore seems to be a tendency towards a more homogeneous distribution of the disease in Norway. There are indications of dispersion of MS in Sweden. This change of distribution over time indicates that genetic background is not the only explanation of the origin of the disease [35].

There are certain strengths in our study that need to be pointed out. Our study has a long time span in a region with a relatively homogenous and stable population. Norway has a well-developed public healthcare, and it is likely that a person with symptoms of MS nowadays will have a prompt medical examination. In Nordland County, all patients with MS are treated by a neurologist employed by a public hospital. This suggests that the number of cases of MS from a hospital based survey, is very close to the real number in the population. In the present study, all medical files were re-evaluated by a neurologist to confirm the diagnosis. There are, however, some limitations. In the days when the diagnosis was made without the help of MRI, the diagnosis was more uncertain. Patients with mimicking symptoms could wrongly be diagnosed with MS, giving higher estimate of the occurrence. On the other hand, it is likely that the threshold to seek medical help has decreased in parallel to an increasing supply of health service, implying that benign MS and other light symptoms earlier could have been easily ignored both by the patient and the doctor giving a lower estimate of the prevalence.

Table 7 Distribution of the incidence of PPMS and RRMS course at onset

Years	PPMS, % (n)	RRMS, % (n)	Unknown, % (n)
1970-1974	33.3 (3)	55.6 (5)	11.1 (1)
1975-1979	33.3 (5)	66.7 (10)	0 (0)
1980-1984	28.8 (13)	70.2 (40)	7.0 (4)
1985-1989	26.7 (16)	66.7 (40)	6.7 (4)
1990-1994	20.6 (13)	77.8 (49)	1.6 (1)
1995-1999	17.4 (15)	82.6 (71)	0 (0)
2000-2004	19.3 (17)	79.5 (70)	1.1 (1)
2005-2009	21.8 (26)	78.2 (93)	0 (0)

Conclusion

The occurrence of MS in Nordland County has been continuously increasing both in terms of prevalence and incidence over a period of 40 years. On January 1, 2010 the prevalence was 182.4 per 100 000. In the period 2005–2009 the average yearly incidence was 10.1 per 100 000. Nordland County is a high risk area for MS. Previous findings indicating a paradoxically low prevalence in the north of Norway could not be confirmed. Although the prevalence and incidence are higher among women then among men, we did not find an increased female to male ratio over time.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EB: Conception and design, acquisition of data, analysis and interpretation of data and statistics. JO: Conception and design, acquisition of data, revising the intellectual content. MK: Acquisition of data, revising the intellectual content. KA: Conception and design, analysis and interpretation of data, revising the intellectual content. All authors approved the completed manuscript.

Author details

[1]Department of Neurology, Nordland Hospital Trust, Post box 1480, 8092 Bodø, Norway. [2]Nordland Hospital Trust, Vesterålen, Norway. [3]Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway.

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Paper 2

Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry.

Benjaminsen E, Myhr KM, Grytten N, Alstadhaug KB.

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ORIGINAL RESEARCH

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Validation of the multiple sclerosis diagnosis in the Norwegian Patient Registry

Espen Benjaminsen[1,2] | Kjell-Morten Myhr[3,4] | Nina Grytten[5] | Karl Bjørnar Alstadhaug[1,2]

[1]Department of Neurology, Nordland Hospital Trust, Bodø, Norway

[2]Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway

[3]Department of Clinical Medicine, University of Bergen, Bergen, Norway

[4]Department of Neurology, Haukeland University Hospital, Bergen, Norway

[5]Department of Neurology, Norwegian Multiple Sclerosis Competence Centre, Haukeland University Hospital, Bergen, Norway

Correspondence
Espen Benjaminsen, Department of Neurology, Nordland Hospital, Pb. 1480, 8092 Bodø, Norway.
Email: espen.benjaminsen@nlsh.no

Abstract

Background: Health registries may yield important data for epidemiological studies. However, in order to be a valuable source for information, the registered data have to be correct.

Objectives: The aim of the study was to validate data from the Norwegian Patient Registry (NPR) regarding multiple sclerosis (MS).

Materials and Methods: We obtained data on individuals residing in Nordland County and registered with a MS diagnosis in the NPR or in local hospital records. The NPR data included a unique 11-digit personal identity number that made it possible to identify the individuals medical records. For each individual registered with MS in the NPR, the hospital record was scrutinized in order to confirm or rule out the diagnosis.

Results: In Nordland County, 657 individuals had MS 1 January 2017. Of these, 637 were recorded with a correct diagnosis of MS in the NPR, while 59 were recorded incorrectly. Incorrect registration was due to a diagnosis that did not fulfill the diagnostic criteria, later investigation had ruled out MS or it was an error in the diagnostic code registration process. Twenty individuals were not registered with MS in the NPR. These were patients who received their diagnosis before data in the NPR were person identifiable (before 2008), and who later had no MS-registered contact with public specialist healthcare services. The sensitivity is 0.97, and the positive predictive value is 0.92.

Conclusion: Data from the NPR gave a good estimate of the occurrence of MS, but nearly one in 10 registered diagnoses was not correct.

KEYWORDS

epidemiology, health registries, multiple sclerosis, validation

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1 | INTRODUCTION

Knowledge of the epidemiology of diseases can give clues to understanding the etiology and risk factors of diseases. It is also important in healthcare planning.

Health registries can be a valuable source of data for epidemiological studies. There are 18 mandatory national health registries in Norway (Norwegian Institute of Public Health, 2016). These are priceless for health-related research and innovation, and have provided answers to important medical questions (Håberg et al., 2013). However, the utility of the registries depends on the quality and reliability of the collected data.

One of these registries is the Norwegian Patient Registry (NPR). NPR is a nationwide Norwegian health registry run by The Norwegian Directorate of Health. The registry was established in 1997, and the information is person identifiable from 2008. Whenever a patient is treated at a hospital or a private practice specialists with public reimbursement, the given diagnoses with the corresponding International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes are mandatorily reported to the NPR. By application, researchers may get access to data from the registry.

Furthermore, all Norwegian citizens have a unique 11-digit personal identity number, an identity designation retained the whole life. This number is included in every hospital record and is linked to a unique number in the NPR.

With access to detailed hospital records, we aimed to validate data in the NPR regarding MS in Nordland County.

2 | METHODS

2.1 | Study population

According to Statistics Norway (Statistics Norway), the population in Nordland County was 242,866 (123,108 men, 119,758 women) January 1, 2017.

Nordland County is in the northern part of Norway and includes the regions of Helgeland, Salten, Ofoten, and the islands of Lofoten and Vesterålen. The public health services for diagnosing and treating MS include the Department of Neurology at the Nordland Hospital in Bodø, and the neurological outpatient services at the hospitals in Mosjøen (Helgeland) and Stokmarknes (Vesterålen). Neurological patients living in the very north of the county (Ofoten) are mostly served by the hospital in Tromsø (Troms County), and patients in the south of the county may be referred to the hospitals in the neighboring county to the south.

2.2 | Diagnostic criteria

The diagnosis of MS was based on the criteria of Poser (Poser et al, 1983) or McDonald (McDonald et al., 2001; Polman et al., 2011). Individuals were included in the present study if they fulfilled at least one of these criteria.

2.3 | Case ascertainment

From a previous study, we have detailed knowledge of individuals with MS in Nordland County from 1970 to 2010 (Benjaminsen, Olavsen, Karlberg, & Alstadhaug, 2014). In the present study, we expanded the scope to include data on all patients as of 1 January 2017. In addition to the numbers from the hospital in Bodø, we requested data from the neurological outpatient clinics in Stokmarknes and Mosjøen, Nordland County, and from the hospitals in the neighboring counties, Tromsø to the north, and Namsos and Trondheim to the south.

From the NPR, we received extracted data for all individuals with a diagnosis of G35 (ICD 10) from Nordland County and for all patients with G35 who had had address in Nordland recorded in the period from January 1, 2008, to January 1, 2017.

We validated the MS diagnosis by scrutinizing the hospital records, of which two of the authors (EB, KBA) had full access.

2.4 | Statistics

The true number of individuals with MS was determined by counting and ascertain all subjects identified in the hospital records who fulfilled the criteria for MS in Nordland County per January 1, 2017. A true positive (TP) was an individual with an MS diagnosis registered in NPR with a validated MS diagnosis based on the hospital records. A false positive (FP) was registered in the NPR, but did not fulfill the criteria for MS. A false negative (FN) was not registered in the NPR, but still fulfilled the criteria for MS. A true negative (TN) was without MS and not registered with MS in the NPR (Table 1). We calculated the sensitivity (TP/(TP + FN)), specificity (TN/(TN + FP)), the positive predictive value (TP/(TP + FP)) and the negative predictive value (TN/(TN + FN)). Cohen's kappa, where the value 0 is agreement equivalent to chance and 1 is a perfect agreement, was calculated to compare the data from the NPR with the true number of individuals with MS. Statistical analyses were performed by the use of Microsoft Excel for Windows 7 and IBM SPSS Statistics version 25.

TABLE 1 Cross-table indicating the true-positive, false-positive, false-negative and true-negative values of individuals with or without multiple sclerosis (MS) registered or not registered in the Norwegian Patient Registry (NPR)

	Confirmed MS according to hospital records		
	Yes	No	SUM
Registered MS in the NPR			
Yes	True positive	False positive	Total registered in NPR
No	False negative	True negative	Total not registered in NPR
SUM	Total with MS	Total without MS	Total population

2.5 | Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (Rek Nord 2016/1531).

3 | RESULTS

From the NPR we received information of 841 individuals who were registered with a MS diagnosis. We excluded 67 who had passed away, 69 who had emigrated, and nine who never had an address in the county (tourists, asylum seekers and guest patients). Thus, according to the NPR, there were 696 individuals with MS in Nordland County per January 1, 2017.

From hospital record searches, we identified 810 individuals with MS, of whom 608 were living in Nordland County per 1 January 2017. Only 49 of the additional individuals registered with MS in the NPR were TP, and the real number of individuals with MS per January 1, 2017, was thus 657, giving a prevalence of 270.5 per 100,000. Twenty of the individuals with MS identified in medical files were not included in the NPR, and 19 of those were mildly affected by the disease at the latest consultation prior to 2008. In 23 of the 59 individuals registered in the NPR who did not fulfill the diagnostic criteria for MS (Figure 1), later diagnostic work-up had ruled out MS. In 17 individuals, symptoms or findings were still suspect for MS, but in 19 there was no association to MS. The number of TN was 242,150 (Table 2).

Thus, of those registered with MS in the NPR, 8.5% did not have the disease, and 3.0% of those who have MS were not registered. The sensitivity was 0.97, and the positive predictive value was 0.92. The Cohen's kappa was 0.94.

4 | DISCUSSION

In Nordland County, 91.5% of those registered with MS in the NPR have a confirmed diagnosis of the disease.

Previous analyses of NPR data for correctness and completeness in stroke in Norway have shown a sensitivity of 96.8% and a specificity of 99.6%, with a positive predictive value of 79.7% (Varmdal et al., 2016). Another study, focusing on intracranial hemorrhage (ICH) in Trøndelag, 8.8% registered with ICH in the NPR showed to be false positive (Øie et al., 2018). In a study of amyotrophic lateral sclerosis (ALS), data from the NPR was validated for Akershus—Hordaland County, showing that 11% of individuals with at least one ALS-related entry in the NPR had an incorrect diagnosis (Nakken, Lindstrøm, Tysnes, & Holmøy, 2018). These results are in accordance with our findings. Because of the magnitude of the true-negative value, which is close to the total population in the county, the specificity and the negative predictive value is approximately one. The true-negative value also highly influences the Cohen's Kappa value, giving a near-perfect fit.

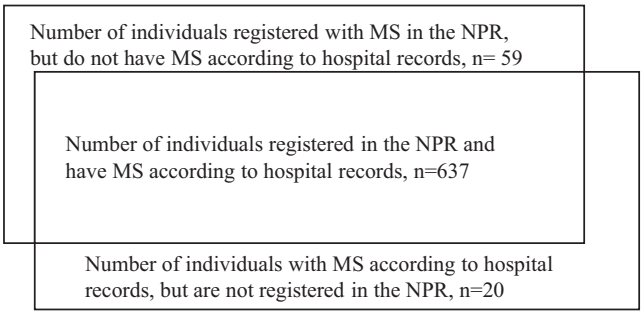

FIGURE 1 Number of individuals with or without multiple sclerosis (MS) registered or not registered in the Norwegian Patient Registry (NPR)

We found that 3.0% of those who actually have MS are not registered in the NPR. These were individuals that received the diagnosis before 2008 and who had not the diagnosis of MS registered at a hospital since, probably due to a benign course of the disease. This proportion will decrease during time, mainly because all new cases in the NPR are now person identifiable, and to a lesser degree due to the increasing probability that those who were diagnosed with benign disease prior to 2008 eventually will have their diagnosis registered.

Data from the NPR have previously been used in a nationwide prevalence study of MS in Norway, finding a national prevalence of 203 per 100,000 in 2010 (Berg-Hansen, Moen, Harbo, & Celius, 2014). In that study, unless they used MS specific treatment according to the Norwegian Prescription Database, only individuals with at least two entries of MS in the NPR were included. This was done with the intention to minimize the suspected overestimation of the occurrence.

If we, in the present study, only include those who are registered with MS in the NPR more than once, the overrepresentation of MS in the NPR is reduced from 8.5% to 3.3%. On the other hand, the proportion of those with MS that are not included increases to 6.4%.

4.1 | Study strengths and limitations

The strength of our study is that the data from the NPR is personally identifiable and that we were able to validate the diagnosis at an individual level. We have a complete overview of the MS population in our county and full access to the hospital records. The limitation with regards to generalizability is that we have validated the NPR

TABLE 2 Cross-table of individuals with or without multiple sclerosis (MS) registered or not registered in the Norwegian Patient Registry (NPR)

	Confirmed MS according to hospital records		
	Yes	No	SUM
Registered MS in the NPR			
Yes	637	59	696
No	20	242,150	242,170
SUM	657	242,209	242,866

with regards to MS in only one county, including <5% of the total Norwegian population.

5 | CONCLUSION

Data from the NPR give a good estimate of the real prevalence of MS in Nordland County, but nearly one in 10 with a registered diagnosis does not fulfill the diagnostic criteria. Data from the NPR should be combined with data from other sources if more accurate numbers are needed.

CONFLICT OF INTEREST

The authors have nothing to disclaim related to the topic.

DISCLAIMER

Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended or should be inferred.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Espen Benjaminsen https://orcid.org/0000-0002-7450-9534

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Paper 3

The prevalence and characteristics of epilepsy in patients with multiple sclerosis in Nordland county, Norway.

Benjaminsen E, Myhr KM, Alstadhaug KB.

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The prevalence and characteristics of epilepsy in patients with multiple sclerosis in Nordland county, Norway

Espen Benjaminsen[a,*], Kjell-Morten Myhr[b,c], Karl B. Alstadhaug[a,d]

[a] Department of Neurology, Nordland Hospital Trust, Bodø, Norway
[b] Department of Clinical Medicine, University of Bergen, Norway
[c] Department of Neurology Haukeland Hospital, Bergen, Norway
[d] Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway

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ABSTRACT

Purpose: The prevalence of epilepsy among patients with multiple sclerosis (MS) has been found higher than in the general population. Although cortical pathology may be involved, the causal link between MS and epileptic seizures is still unclear. We aimed to identify and describe the patients with active epilepsy in a previously described population based MS-cohort.
Methods: Medical records of all patients with MS in Nordland County on January 1, 2010, were scrutinizing for evidence of comorbid seizures and epilepsy.
Results: Among 431 patients with MS, we identified 19 (4.4%) with a history of seizures or epilepsy. Fourteen (3.2%) of these had active epilepsy defined as use of antiepileptic drugs or seizures within the last 5 years. One patient got epilepsy before other signs of MS. In patients with relapsing-remitting MS (RRMS) at onset and active epilepsy (n = 10), 70% had converted to secondary progressive (SPMS) at prevalence date, compared to only 35% of those without active epilepsy (p = 0.02). 43% had converted to SPMS before they got epilepsy. Attack semiology or electroencephalogram recordings indicated a focal onset of seizures in 12 of 14 (86%) with active epilepsy.
Conclusion: The frequency of active epilepsy among MS patients in Nordland was 3.2%, approximately 4.5 times higher than in the general Norwegian population. RRMS patients with active epilepsy had more likely converted to SPMS than patients without active epilepsy. With a high frequency of focal epilepsy, the study supports that focal MS brain pathology is the cause of the comorbid epilepsy.
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1. Introduction

Multiple sclerosis is a chronic inflammatory disease of the central nervous system, characterized by focal white matter lesions, but both deep and cortical grey matter is also involved [1–3].

A review of 29 previously published clinical series found the mean prevalence of epilepsy among MS patient to be 2.3%, 3–6 times that in the general adult population [4]. In the general Norwegian population the prevalence of epilepsy is about 0.7% [5–7]. Epilepsy has previously been reported in 3.2 to 3.6% of the Norwegian MS patients [8,9]. The cause of the increased occurrence of epilepsy among patients with MS is unknown [4], but it is reasonable to assume an epileptogenic role of cortical lesions [10].

The aim of the study was to identify and describe the patients with epilepsy in a well-defined MS-population [11] of northern Norway at prevalence date January 1, 2010.

2. Methods

This was a retrospective cross-sectional epidemiological study based on patient records of all known MS patients living in Nordland County, Northern Norway at prevalence point.

Nordland County is situated between latitude 64°56′ N and 69°20′ N, and is covering a total area of 38456 km^2. The population was 236 271 (118537 men, 117734 women) at January 1, 2010.

There is only one neurological department in the county, at the Nordland Hospital in Bodø, serving the majority of the population, but there are also two neurological outpatient services at the hospitals in Mosjøen (Helgeland) and Stokmarknes (Vesterålen). We had full access to the MS-patients medical files. The medical records were consecutively written as electronic files from 1992, and older documents are scanned and added to the electronic files.

* Corresponding author at: Department of Neurology, Nordland Hospital Bodø, Post box 1480, 8092 Bodø, Norway.
E-mail address: espen.benjaminsen@nlsh.no (E. Benjaminsen).

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In a previous population study [11] we identified 431 persons (294 women and 137 men) with MS according to the diagnostic criteria of Poser or McDonalds [12,13] living in Nordland County at January 1, 2010, giving a prevalence of 182 per 100 000 inhabitants. At that time point, we classified the initial disease course to be RRMS for 345 (80.0%) of the patients, 80 (18.6%) had primary progressive MS (PPMS), and six (1.4%) with unknown disease course. In the present study, we were able to classify these six patients as having RRMS at onset. In the present study we also ascertained the transformation from RRMS at onset to secondary progressive MS (SPMS).

The medical files were scrutinized to identify seizures and epilepsy. The diagnosis of epilepsy was set in accordance with the 1989 criteria of the International League Against Epilepsy [14]. Active epilepsy was defined as use of antiepileptic drugs at prevalence point or seizures within the last 5 years [15]. Seizures were classified according to the criteria of the International League Against Epilepsy from 1981 [16]. We classified the epilepsy as focal or not, based on the described seizure semiology and electroencephalogram (EEG) findings. In addition, age, sex and treatment for MS and epilepsy were recorded.

Statistical analyses were performed by the use of Microsoft Office Excel for Windows 7. Normally distributed continuous variables were presented as means with standard deviations (SD). Independent-sample T-test was used to compare age and disease duration. Categorical variables were presented as numbers with percentages, and compared by using chi square test. All tests were two-sided. Statistical significance was set at $p < 0.05$. To estimate confidence interval for the sample proportion of patients with EP, Wilson's method was applied [17].

2.1. Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Nord).

3. Results

The cohort consisted of 431 patients, 351 (81.4%) with RRMS and 80 (18.6%) with PPMS at onset. At prevalence day of January 1 2010, 226 (64.4%) of those with an initial RRMS course still had a RRMS disease course, 122 (34.8%) had converted from RRMS to a secondary progressive MS (SPMS), and three had an unclassified disease course.

We identified 19 patients (age 53.3 ± 14.6 years), 14 women (age 53.3 ± 16.2 years) and 5 men (age 53.2 ± 11.0 years), with a history of epilepsy, accounting for 4.4% (95% CI 2.8–6.8) of the cohort. Three patients (two women and one man) with childhood epilepsy, and two patients (one woman and one man) who were diagnosed with epilepsy as adults, had not had any seizures during the last five years. Hence, 14 (3.2%, 95% CI 1.9–5.4), 11 women and three men, were classified to have an active epilepsy. Table 1 shows demographics and clinical characteristics of these patients.

Simple partial seizure was noted in four patients, and in one of these there was also evidence of complex partial seizures. In total, we classified three patients with complex partial seizures. In addition, one patient was reported to have slurred speech prior to a generalized seizure, and another reported feeling "strange" prior to generalized convulsions. Generalized seizures were reported in 11 patients, of which 10 had convulsive and one had nonconvulsive seizures. In two patients, eye deviation was noted during a generalized seizure. One of these patients also had a post-ictal transient hemiparesis (Todd's paresis) ipsilateral to the eye deviation.

All patients with MS and epilepsy had at least one electroencephalogram (EEG), and in total 69 EEG-recordings were registered. There were epileptiform discharges in 17 (Fig. 1), focal slow activity without epileptiform discharges in 20, diffuse slow activity without epileptiform discharges in 14, and 18 recordings were normal.

With the reported seizure semiology and the EEG findings combined, focal epilepsy was registered on at least one occasion in 12 of the 14 patients (86%) with active epilepsy.

Status epilepticus was reported in five (36%) of the patients. Four had generalized clonic seizures. Gaze deviation was noted in two of these. One patient had a simple partial status epilepticus with prolonged convulsions in the right part of her body. There were no fatal cases of status epilepticus.

One patient experienced a seizure before other symptoms of MS. Another patient was registered with a seizure as the onset symptom, and a third patient experienced her first seizure the same year as the first symptom of MS, but 10 years prior to the MS diagnosis. The remaining 11 patients got their first epileptic seizure after other symptoms of MS.

Table 1
Multiple sclerosis patients with active epilepsy in Nordland County, Northern Norway.

Sex	*Age (yrs)	Age (yrs) at 1. symptom of MS	Age (yrs) at diagnosis of MS	Disease course	*EDSS	Age (yrs) at diagnosis of EP	SPS	CPS	Generalized seizure	Status	Focal EEG	Focal EP	*Antiepileptic medication
f	47	19	21	RRMS → SPMS	9.5	23	-	-	+	-	-	-	CBZ
m	58	22	31	RRMS	3.0	54	-	-	+ (focal start)	+	+	+	CBZ
f	30	23	23	RRMS	0	29	-	+	+ (focal start)	-	+	+	LTG
f	39	23	37	RRMS → SPMS	4.0	30	-	-	+	-	+	+	VPA, LTG
m	53	24	28	RRMS → SPMS	9.0	43	+	+	+	+	-	+	CBZ
f	77	25	41	RRMS → SPMS	6.5	71	-	-	+ (eye deviation, Todd's paresis)	+	-	+	CBZ
f	41	27	27	RRMS → SPMS	5.5	27	+	-	+	-	-	+	-**
f	54	35	45	PPMS	6.5	35	+	-	-	+ (focal)	+	+	OXC, PGB
m	66	36	57	RRMS → SPMS	3.0	53	-	+	-	-	+	+	CBZ
f	70	39	44	RRMS → SPMS	8.5	65	-	-	+ (eye deviation)	+	+	+	PHT
f	55	48	50	PPMS	7.0	53	-	-	+	-	+	+	OXC
f	83	46	62	PPMS	7.5	77	-	-	+(non-convulsive)	-	+	+	-
f	63	51	57	PPMS	4.0	34	+	-	-	-	+	+	CBZ
f	55	54	54	RRMS	4.0	54	-	-	+	-	-	-	LTG

*At prevalence point January 1, 2010. **No treatment due to patient's choice.
CPS = complex partial seizure; EEG = electroencephalogram; EP = epilepsy; PPMS = primary progressive multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis; SPS = simple partial seizure; SPMS = secondary progressive multiple sclerosis.
CBZ = Carbamazepine; LTG = Lamotrigine; OXC = Oxcarbazepine; PHT = Phenytoin; PGB = Pregabalin; VPA = Valproate.

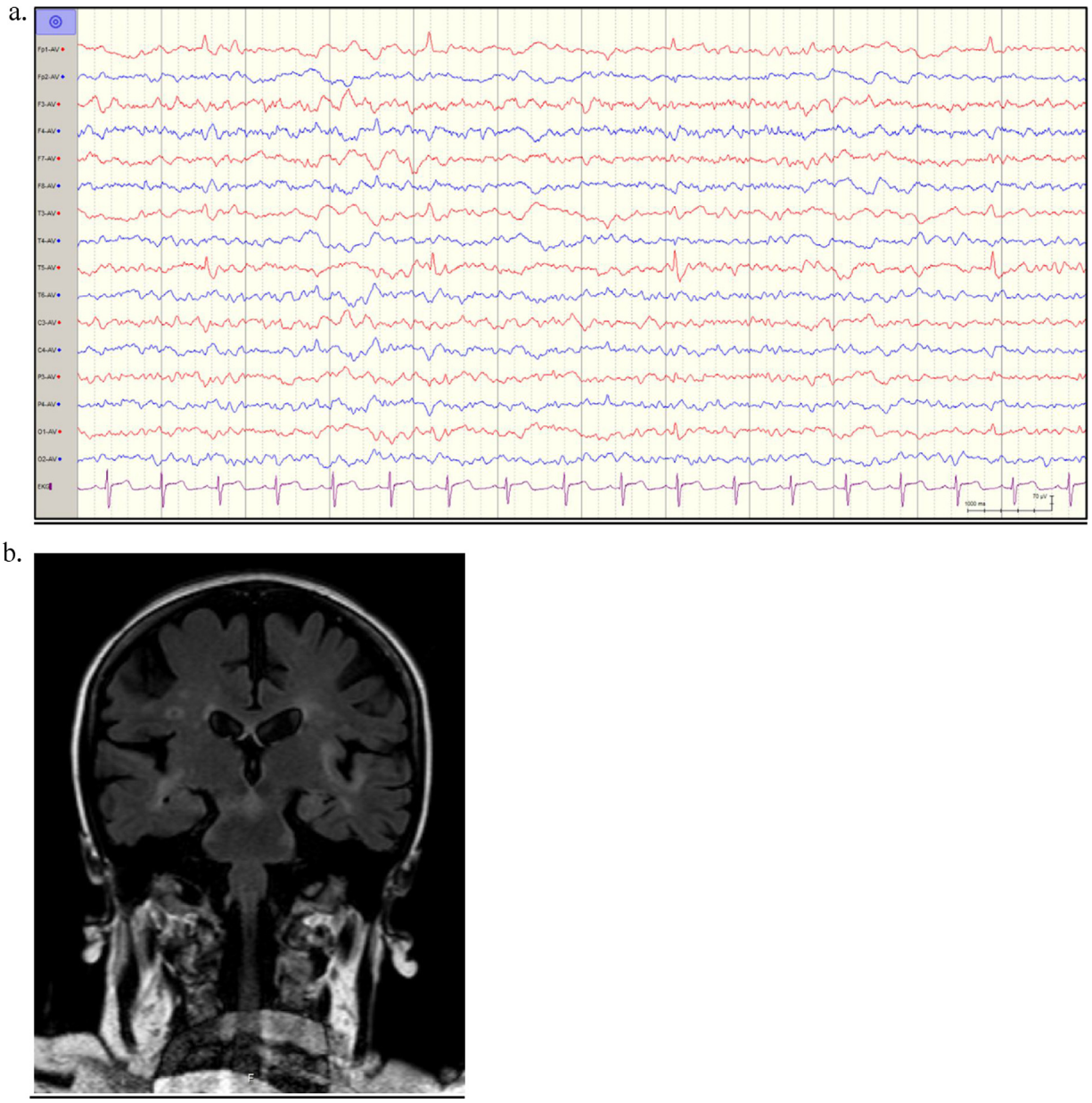

Fig. 1. EEG recording and MRI sequence of patient with multiple sclerosis and epilepsy.
A highly disabled 53 year-old woman, diagnosed with primary progressive multiple sclerosis three years earlier, was brought to the hospital due to three generalized seizures and prolonged confusion. Viral encephalitis was suspected, but investigations, including CSF-analyses, were negative. She recovered and was treated with oxcarbazepine.
a. EEG recording on the day of admission showing spike discharges on the left in the fronto-temporal region.
b. The coronal slice of a FLAIR MRI obtained the same day as the EEG showing multifocal areas of high signal intensity in the white matter, but there is also increased signal in the left insular cortex which is not typical for MS.

The mean age at prevalence day was 56.5 (±14.7) years, 55.8 (±16.4) years for women and 59.0 (±6.6) years for men. The mean age at the diagnosis of MS was 41.2 (±13.7) years, 41.9 (±13.8) years for women and 38.7 (±15.9) years for men. The mean age at the diagnosis of epilepsy was 46.3 (±17.3) years, 45.3 (±19.4) years for women and 50.0 (±6.1) years for men. The mean duration of MS from diagnosis to prevalence point, as well as the mean age at prevalence point and at diagnosis for the different forms of MS with and without epilepsy, is shown in Table 2. The differences between the groups with and without epilepsy are not statistically significant.

Four of the 14 patients with active epilepsy had PPMS and the remaining 10 had RRMS at onset, of whom seven had converted to SPMS. The conversion from RRMS to SPMS was significantly higher for those with active epilepsy than in those without epilepsy ($p = 0.02$). Three of the seven (43%) had converted to SPMS before, and four of seven (57%) after they got epilepsy.

Five (36%) of the patients with active epilepsy had been, or were exposed to immune modulating drugs for MS. Only one had used it (interferon beta-1b) at the time of the first epileptic seizure. Two other had used interferon beta-1b later, one had used interferon beta-1a and one had used glatiramer acetate. Three patients had immunmodulating therapy at prevalence point.

Table 1 shows the antiepileptic medication in use at prevalence point. Ten patients (71%) received monotherapy, two (14%) received two anti-epileptic drugs, and two (14%) were untreated.

Table 2
Age of patients with multiple sclerosis and comorbid epilepsy in Nordland County, Northern Norway.

	epilepsy	n	Mean age (yrs) at prevalence (±SD)	Mean age (yrs) at diagnosis of MS (±SD)	Mean disease duration (yrs) from diagnosis (±SD)
Total MS (n = 431)	+	14	56.5 (±14.7)	41.2 (±13.7)	15.3 (±11.3)
	-	417	51.1 (±12.1)	38.2 (±10.3)	12.8 (±9.0)
PPMS at onset (n = 80)	+	4	63.8 (±13.5)	53.5 (±7.5)	10.3 (±7.4)
	-	76	57.6(±10.6)	44.9 (±9.7)	12.7 (±10.1)
RRMS at onset (n = 351)	+	10	53.6 (±14.8)	36.3 (±12.6)	17.3 (±12.2)
	-	341	49.6 (±11.9)	36.7 (±9.9)	12.9 (±8.8)
Still RRMS at prevalence point (n = 226)	+	3	47.7 (±15.4)	36.0 (±16.1)	11.7 (±13.6)
	-	223	45.7 (±11.3)	35.6 (±9.6)	10.0 (±7.8)
Converted to SPMS at prevalence point (n = 122)	+	7	56.1(±14.9)	36.4 (±12.2)	19.7 (±11.8)
	-	115	56.9 (±9.5)	38.9 (±10.1)	18.1 (±8.2)

Three of the patients with RRMS at onset have unknown course.
SD = standard deviation, PPMS = primary progressive multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

4. Discussion

On January 1 2010, 3.2% of MS patients in Nordland County had active epilepsy. That is approximately 4.5 times higher than reported in the general Norwegian population. Our finding is in accordance with two previous Norwegian studies of similar sizes [8,9]. The findings are also comparable to international reports [18].

A prevalence study of 1717 subjects with active epilepsy in a general Norwegian population, reported that 65% had focal onset seizures [7]. Our results showing that 86% of the patients with MS had focal epilepsy, confirm a previous Norwegian study where all MS patients had a focal epilepsy [8]. The finding indicates that focal brain pathology in MS is the main cause of the comorbid EP. White matter lesions, with or without inflammation and edema, may irritate the cortex resulting in seizures. A study from France reported subcortical involvement in all of their 17 patients with MS and epilepsy [19]. Furthermore, it is an increasing concern that MS is not only a white matter disease, but that is also affects the gray matter in the cerebral cortex [1–3]. Increased number of both juxtacortical and cortical lesions in MS patients with comorbid epilepsy has been reported [20]. In MS-patients with epilepsy the cerebral cortex has shown signs of more extensive inflammation when compared to the cortex of MS patients without epilepsy matched for sex, age, disease duration and EDSS [21]. In this study by Calabrese et al, intracortical lesions were found in 90% of patients with RRMS and epilepsy, but only in 48% RRMS without epilepsy. Furthermore, the mean number of intracortical lesions was 6.8 ± 8.3 in RRMS patients with epilepsy, and 1.5 ± 2.4 in the control group.

Although epilepsy can be the first symptom of MS [22], in the present study only one of 14 patients with active epilepsy got a seizure before other symptoms of MS. This may support the idea that the risk of epilepsy in MS increases with disease duration and number of lesions.

However, excluding the sole patient who got epilepsy before MS, we find that the delay from MS to epilepsy ranges from 0 to 30 years. At prevalence date there was a large span in severity of MS, with EDSS ranging from 0 to 9.5. These findings are in accordance with previous reports. Among 21 MS patients with epileptic seizures, there seemed to be no clear correlation between the severity of MS and epilepsy [23]. In another study of 40 MS patients with comorbid epilepsy, no relationship was found between the frequency of seizures and the severity of MS [24]. In yet another study of 13 MS patients with epilepsy, EDSS ranged from 1.0 to 8.0, and the seizures started 0-23 years after onset of MS [25]. It therefore seems that EP is independent on the disability level, and can evolve at any time during the course of MS. It is possible that epilepsy in the early stage of MS is caused mainly by inflammation, and that epilepsy in the later stage is caused more by neurodegeneration. According to Spatt, most MS patients with comorbid seizures could be placed in one of two groups. They could either have symptomatic seizures associated with MS onset or relapse, usually without recurrent seizures, or they could have chronic epilepsy associated with progressive cognitive involvement and increasing disability [26].

It has been reported that MS patients with epilepsy are younger than those without epilepsy [27,28]. In our study, the mean age of patients with epilepsy was not significantly different from the mean age in the cohort of patients without epilepsy, neither at prevalence point nor at time of diagnosis of MS (Table 2).

It has also been reported that MS-patients with epilepsy have a higher progression rate of cortical pathology than MS controls, and also have a more rapid cognitive decline [29]. Furthermore, the time to reach a certain invalidity (score 6 at Kurtzke Disability Status Scale) has also been reported to be shorter in MS patients with epilepsy than in MS patients without epilepsy [27]. In our population, 7 of 10 (70%) of the patients with RRMS at onset had converted to SPMS. This was significantly higher ($p = 0.02$) than in the RRMS group without active epilepsy, where only 35% had converted to SPMS. The finding may imply that the patients with active epilepsy have a more aggressive form of MS. Most untreated RRMS patients will eventually convert to SPMS with time, around 80% within 20 years [30]. Disease duration may therefore be a confounder. In the present study the mean disease duration was about 4.5 years longer for the group of RRMS with active epilepsy than in those without epilepsy. However, a longer mean disease duration in the group with epilepsy is expected, as they, by definition, must have developed both MS and epilepsy, and the first seizures may occur many years after the diagnosis of MS. On the other hand, it is also possible that patients with SPMS are more likely to develop epilepsy. Our figures do not allow for a conclusion on this matter, as 3 of 7 had converted to SPMS before they got epilepsy and 4 of 7 after. If we add the four PPMS patients with active epilepsy, a total of 11 of 14 (78.6%) of the patients had progressive MS. This is similar to another small study that reported the progressive form of MS in 6 of 8 (75%) of the patients with epilepsy [31].

It has been hypothesized that interferon beta could have proconvulsive properties due to metabolic interference with antiepileptic drugs or due to a direct neurotoxic effect [32]. This view is not supported by our study, where the majority of the patients (64%) had never used immune modulating medication, and where only one used interferon beta at the time of the first

epileptic seizure. Secondary progressive MS was noted in 43% of patients prior to their diagnosis of epilepsy, and that may explain why so few patients with epilepsy was not on MS-therapy.

Status epilepticus was reported in 36% of the patients. Because of the risk of new seizures and status epilepticus, the importance of early use of antiepileptic drugs in MS patients with epilepsy has been emphasized [8]. Others report that the majority of MS patients with epilepsy responded well to antiepileptic therapy [25,31]. In the present study, 10 of 14 patients had monotherapy for epilepsy and two had no antiepileptic treatment. This indicates well-managed epilepsy with good seizure control.

A strength of our study is that the MS population is well defined, and that we have access to longitudinal clinical information from electronic patient records. Patients with MS consult a neurologist on a regular basis, and any event that raises the suspicion of epilepsy would most likely be further examined. In general, patients with a seizure will be referred for diagnostic work-up. The prevalence of epilepsy among MS patients reported in the present study will therefore probably be close to the real prevalence in the MS population. The diagnostic accuracy of epilepsy may however be cause for concern, especially among MS patients where there could be many different paroxysmal symptoms. The differential diagnosis include muscle cramps, dystonia and other involuntary movements in addition to syncope, hypoglycemia, and seizures not fulfilling the criteria for epilepsy. The medical records were scrutinized with this in mind, and if we were in doubt the case was not included in this study.

5. Conclusion

The prevalence of active epilepsy among MS patients is 4–5 times higher than in the general population. The fact that only one of the patient in the present study had epileptic seizure before any other signs of MS indicates that epilepsy may be a consequence of MS. Furthermore, the high frequency of focal epilepsy found, supports the idea that localized MS-pathology is the cause of the comorbid epilepsy. Patients with active epilepsy had more often converted to SPMS than MS patients without epilepsy. The association between the prevalence of epilepsy and progressive forms of MS should be further explored. It may indicate that epilepsy is a marker of a more aggressive form of MS, but it could also imply that progressive forms of MS are more likely to generate epilepsy.

Conflicts of interest

None.

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Paper 4

Comorbidity in multiple sclerosis patients from Nordland County, Norway - validated data from the Norwegian Patient Registry.

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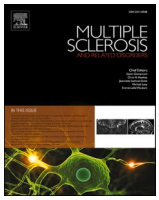

Original article

Comorbidity in multiple sclerosis patients from Nordland County, Norway – validated data from the Norwegian Patient Registry

Espen Benjaminsen [1,2,*], Kjell-Morten Myhr [3,4], Nina Grytten [4,5], Karl Bjørnar Alstadhaug [1,2]

[1] Department of Neurology, Nordland Hospital Trust, Bodø, Norway
[2] Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway
[3] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[4] Neuro-SysMed, Department of Neurology Haukeland University Hospital, Bergen, Norway
[5] Norwegian Multiple Sclerosis Competence Centre, Department of Neurology Haukeland University Hospital, Bergen, Norway

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ABSTRACT

Background: : Knowledge of comorbid disorders is important to optimize therapy for multiple sclerosis (MS), but data are limited. The aim of this study was to assess comorbidity in persons with MS living in Nordland County on January 1, 2017.

Methods: : Data were retrieved from the Norwegian Patient Registry (2008-2017) and validated through review of electronic hospital charts (1970-2017). Comorbidity was defined as any distinct disorder, classified in the *International Classification of Diseases* (ICD-10), that had existed or occurred after the diagnosis of MS was established.

Results: : Data from 637 subjects were reviewed, and 97.5% were registered with at least one comorbid condition. Malignant melanoma was found in 0.5%, and non-melanoma skin cancers in 1.9%. In female subjects, breast cancer was found in 3.3%. Hypothyroidism was confirmed in 3.1%, type-1 diabetes in 0.3%, type-2 diabetes in 3.9%, psychosis in 0.6%, epilepsy in 2.8%, myocardial infarction in 1.7%, subarachnoid hemorrhage in 0.2%, cerebral infarction in 0.6%, pulmonary embolism in 0.9%, inflammatory bowel disease in 1.3%, and rheumatoid arthritis in 0.6%.

Conclusion: : Compared to reports from other Norwegian epidemiological studies, a higher proportion of inflammatory bowel disease and epilepsy was found. This is in accordance with findings from other studies. The prevalence of non-melanoma skin cancers was significantly higher than in the general Norwegian population as they were reported by The Cancer Registry of Norway.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting mainly young adults [1]. Without tailored therapy, most patients will eventually develop severe disability. Early diagnosis and treatment is thus important in order to protect the CNS and to maintain function [2]. In patients with MS, comorbidity often increases the diagnostic delay [3] and delays the initiation of disease-modifying therapy [4]. A complete knowledge of comorbidity is important to optimize risk stratification of individual patients for personalized therapies [5,6].

One way to assess co-occurring disorders in persons with MS, is to use data from medical registers. The Norwegian Patient Registry (NPR) is a nationwide health register run by the Norwegian Directorate of Health. It was established in 1997, and the information is individually identifiable from 2008 onwards. Whenever a patient is treated in a hospital or by a private practice specialist with public reimbursement, the given diagnoses, along with the corresponding International Classification of Disease version 10 (ICD-10) codes are mandatorily reported to the NPR. By application, researchers may gain access to these data. All Norwegian citizens are given a unique eleven-digit personal identity number that is retained throughout life. This number is included in every hospital record, and it is linked to another unique number in the NPR.

The aim of this study was to assess comorbidities in a cross-sectional, population-based cohort of all individuals with MS living in Nordland

* Corresponding author: Department of Neurology, Nordland Hospital, P.O. Box 1480, 8092 Bodø, Norway
E-mail address: espen.benjaminsen@nlsh.no (E. Benjaminsen).

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County, Norway on January 1, 2017.

Region

Nordland County covers an area of 38.456 km^2 in the northern region of Norway (Fig. 1). The population was 242 866 (119 758 females and 123 108 males) as of January 1, 2017. The mean age of inhabitants was 41.7 years.

The population in Norway was 5 258 317 (2 609 187 females and 2 649 130 males), and the mean age was 39.9 years. In total, 3 995 587 inhabitants were 20 years or older [7].

In Nordland, only public specialist health care in neurology exists, and this includes the Department of Neurology at Nordland Hospital in Bodø and the neurological outpatient services from the hospitals in Mosjøen and Stokmarknes.

Methods

On the prevalence date of January 1, 2017, 657 persons had confirmed MS in Nordland County according to the criteria of Poser [8] or McDonald [9,10]. However, only 637 had the MS diagnosis correctly registered in the NPR [11], and these are the subjects included in this study.

We retrieved, from the NPR, all additional ICD-10 codes that had been registered in the individually-identifiable records implemented from 2008 onwards. For each individual in this cohort, medical records were scrutinized and the comorbid condition was excluded if it could not be confirmed.

Comorbidity was defined as any distinct condition or disorder that had existed or occurred after a diagnosis of MS was established [12]. Cancers and chronic diseases were included regardless of whether they occurred before or after the diagnosis of MS. Acute disorders, however, such as myocardial infarction and stroke, were only included if they had occurred after the diagnosis of MS.

Statistics

The prevalence of different comorbid diseases in the MS population was calculated by dividing the number of individuals with a disease by the total number of MS patients. The age-standardized prevalence was determined by using data from a standard European population [13]. For the acutely occurring vascular comorbidities, the mean annual incidence was calculated by dividing the number of new cases by person-years. Demographics of the population were obtained from

Fig. 1. Nordland County, Norway

Statistics Norway [7]. Cancer frequencies in Norway as of December 31, 2016, were obtained from the Cancer Registry of Norway [14]. The prevalence of cancer in the Nordland County MS population was compared with the calculated prevalence in the Norwegian population using chi-square tables. The significance level was set to $p < 0.05$. The figures of the non-cancer conditions were compared with reports from other Norwegian epidemiologic studies.

Statistical analyses were performed by using Microsoft Excel for Windows 7 and IBM SPSS Statistics version 25.

Results

On January 1, 2017, 637 individuals in Nordland County were correctly registered with MS in the NPR [11]; 426 females, mean age 52.5 (±13.5) years; and 211 males, mean age 52.1 (±14.2) years. Three hundred and fifty-nine individuals were diagnosed with MS before 2008 and 278 after. The total person-years living with MS in Nordland during the period from 2008 to 2017 was 4 392.

One or more comorbid conditions were registered in the NPR for 621 (97.5%) of the patients. The distribution of comorbidities within the ICD-10 categories is shown in Table 1.

Malignant comorbidities

Cancer was registered in the NPR for 45 MS patients. Of those, 41 were registered correctly according to hospital records (Table 2). The mean age at the prevalence point was 62.2 (±10.0) years. The prevalence of overall cancer was 6.4%.

Malignant melanoma (C43) was correctly registered in three of the MS patients. The mean age at prevalence point was 50.7 (±5.3) years. The prevalence of malignant melanoma was 0.5%.

Non-melanoma skin cancer (C44) was correctly registered in 11 patients. The mean age at prevalence point was 63.1 (±10.2) years, ranging from 40 to 73 years. The age at MS diagnosis was 44.3 (±12.1) years and the age at cancer diagnosis was 57.7 (±10.3) years. Nine individuals were diagnosed with MS before they developed non-melanoma skin cancer. Of these individuals, four had used disease-modifying therapy (Table 3). The prevalence of non-melanoma skin cancer was 1.7%. This is significantly higher than in the Norwegian population, according to The Cancer Registry of Norway, among with the prevalence is 0.29%, $p < 0.001$. In the population aged 20 years and above, the prevalence is 0.38%, and the difference remained significant, $p < 0.001$.

Breast cancer (C50) was correctly registered in the NPR for 14 females. The mean age at prevalence point was 61.1 (±13.7) years. The prevalence of breast cancer was 3.3% in females with MS. This was significantly higher than in the Norwegian female population, among with the prevalence is 1.74%, $p = 0.015$. However, when compared with the prevalence of the Norwegian female population aged 20 years and above, where the prevalence is 2.28%, the difference was non-significant, $p = 0.16$.

One MS patient was registered with *colon cancer* (C18), and none were registered with cancer of the *lungs* (C33-34) or of the *urinary tract* (C65-68).

Table 1
Individuals with diagnosis according to ICD10 as registered in the NPR.

Chapter	Code range	Description	Patients
1	A00-A99	Certain infectious and parasitic diseases	74
	B00-B99		65
2	C00-C96	Cancer	45
		Carcinoma in situ	6
	D00-D09	Other neoplasia	103
	D10-D49		
3	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	32
4	E00-E89	Endocrine, nutritional and metabolic diseases	134
5	F01-F99	Mental, Behavioral, and Neurodevelopmental disorders	137
6	G00-G99*	Diseases of the nervous system	214
7	H00-H59	Diseases of the eye and adnexa	288
8	H60-H95	Diseases of the ear and mastoid process	88
9	I00-I99	Diseases of the circulatory system	171
10	J00-J99	Diseases of the respiratory system	139
11	K00-K95	Diseases of the digestive system	224
12	L00-L99	Diseases of the skin and subcutaneous tissue	148
13	M00-M99	Diseases of the musculoskeletal system and connective tissue	263
14	N00-N99	Diseases of the genitourinary system	368

* Except G35 and G37. ICD10 = International Classification of Diseases version 10, NPR = The Norwegian Patient Registry

Non-cancer comorbidities

An overview of the non-cancer comorbid disorders is given in Table 4.

Thyroid disorder was registered in the NPR for 26 MS patients. One was registered with "Post-procedural endocrine and metabolic disorders, not elsewhere classified" (E89), but in the hospital record no indication of thyroid disorder was found. Twenty were registered with "Other hypothyroidism" (E03), and the diagnosis was confirmed in 19, of which four had elevated anti-thyroid peroxidase (TPO) and one had elevated anti- thyroglobulin. Four were registered with "Other nontoxic goiter" (E04), but only three had confirmed goiter. One of these had elevated TPO, and in total six individuals had elevated antibody levels. One was registered with "Thyrotoxicosis" (E05), but actually suffered from hypothyroidism. Hence, 20 (3.1%) MS patients —16 (3.8%) females and 4 (1.9%) males— had hypothyroidism, four with increased TPO and one with increased anti-thyroglobulin. Twelve were diagnosed with hypothyroidism after the MS diagnosis, two in the wake of alemtuzumab treatment. The prevalence of thyroid disorder was 3.6%.

Diabetes mellitus (DM) was registered in the NPR for 29 MS patients. Twenty-six were registered with type-2 DM (E11), but the diagnosis was incorrect for two patients. Of the three patients registered with type-1 DM (E10), one had insulin treated type-2 DM. The prevalence of type-1 DM was 0.3%, and that of type-2 DM was 3.9%

Psychosis was registered in the NPR for four MS patients, one in each of the following diagnostic groups: "unspecified organic or symptomatic mental disorder" (F09), schizophrenia (F20), "acute and transient psychotic disorders" (F23) and schizoaffective disorders (F25). We confirmed that the diagnosis was correct in all four cases, comprehending three females and one male. Two had MS at the time of the first registered psychotic episode. The mean age at the prevalence point was 46.3 (±15.1) years. The mean age at the time of the MS diagnosis was 38.8 (±17.8) years and the mean age at the time of the psychosis diagnosis was 36.3 (±21.4) years. The prevalence of psychosis was 0.6%.

Epilepsy (G40) was registered in the NPR for 20 MS patients, but the diagnosis was incorrect for two of them. The mean age at the prevalence point was 24.4 (±13.8) years. The mean age at the time of the MS diagnosis was 38.9 (±11.5) years, and the mean age at the time of the epilepsy diagnosis was 41.1 (±16.1) years. The prevalence of epilepsy was 2.8%.

Acute myocardial infarction (I21) was registered in the NPR for 11 MS patients, four females and seven males. All were registered correctly, and all had MS at the time of the myocardial infarction. The mean

Table 2
Cancer in the Nordland MS cohort and in the general Norwegian population.

		Cancer in the Nordland County MS-population			Cancer in the Norwegian Population	
ICD 10	**Site**	**n**	**Prevalence %**	**Age standardized prevalence %**	**n†**	**%††**
C00-96	**All sites**	**41**	**6.44**	**3.23**	**262 884**	**5.00**
C00-14	**Mouth, pharynx**	**1**	**0.16**	**0.15**	**4 992**	**0.09**
C00	Lip		0		1 389	0.03
C01–02	Tongue		0		1 001	0.02
C03–06	Mouth, other		0		774	0.01
C07–08	Salivary glands	1	0.16	0.15	630	0.01
C09–14	Pharynx		0		1 272	0.02
C15-26	**Digestive organs**	**2**	**0.31**	**0.21**	**39 117**	**0.74**
C15	Esophagus		0		647	0.01
C16	Stomach	1	0.16	0.06	1 987	0.04
C17	Small intestine		0		1 153	0.02
C18	Colon	1	0.16	0.08	21 532	0.41
C19-20	Rectum, rectosigmoid		0		11 789	0.22
C21	Anus		0		762	0.01
C22	Liver		0		529	0.01
C23-24	Gallbladder, bile ducts		0	0.07	469	0.01
C25	Pancreas		0		1 021	0.02
C26	Other digestive organs		0		191	0.00
C30-34, C38	**Respiratory organs**	**0**	**0**		**8 979**	**0.17**
C30–31	Nose, sinuses		0		351	0.01
C32	Larynx, epiglottis		0		1 108	0.02
C33-34	Lung, trachea		0		7507	0.14
C38	Heart, mediastinum and pleura		0		66	0.00
C40-41	**Bone**		0		**807**	**0.02**
C43	**Melanoma of the skin**	**3**	**0.47**	**0.26**	**24 594**	**0.47**
C44	**Skin, non-melanoma**	**11**	**1.73**	**0.83**	**15 425**	**0.29**
C45	**Mesothelioma**		0		**126**	**0.00**
C47	**Autonomic nervous system**		0		**245**	**0.00**
C48-49	**Soft tissues**	**0**	0		**1 599**	**0.03**
C50	**Breast***	**14**	**3.29**	**1.50**	**45 492**	**1.74**
C51-58	**Female genital organs***	**2**	**0.47**	**0.28**	**22 991**	**0.88**
C51–52, C57.7–9	Other female genital		0		960	0.04
C53	Cervix uteri		0		7 173	0.27
C54	Corpus uteri	1	0.23	0.11	10 347	0.40
C55	Uterus, other	1	0.23	0.17	50	0.00
C56, C57.0–4	Ovary etc.		0		4 657	0.18
C58	Placenta		0		154	0.01
C60-63	**Male genital organs****	**5**	**2.37**	**1.17**	**54 914**	**2.07**
C61	Prostate	3	1.42	0.58	47 088	1.78
C62	Testis	2	0.95	0.59	7 483	0.28
C60, C63	Other male genital		0		552	0.02
C64-68	**Urinary organs**	**1**	**0.16**	**0.09**	**20 531**	**0.39**
C64	Kidney (excl. renal pelvis)	1	0,16	0.09	6 816	0.13
C65-68	Urinary tract		0		13 877	0.26
C69	**Eye**		0		**1 086**	**0.02**
C70-72	**Central nervous system**		0		**13 165**	**0.25**
C73	**Thyroid gland**		0		**5 718**	**0.11**
C37, C74-75	**Other endocrine glands**		0		**3 900**	**0.07**
C39, C76, C80	**Other or unspecified**	**1**	**0.16**	**0.09**	**598**	**0.01**
C81-96	**Lymphoid/hematopoietic tissue**	**1**	**0.16**	**0.07**	**23 378**	**0.44**
C81	Hodgkin lymphoma		0		2 799	0.05
C82–86, C96	Non-Hodgkin lymphoma		0		9 672	0.18
C88	Immunoproliferative disease	1	0.16	0.07	597	0.01
C90	Multiple myeloma		0		2 045	0.04
C91–95	Leukaemia		0		8 461	0.16

†based on numbers from Cancer Registry of Norway, †† based on numbers from Cancer Registry of Norway and Statistics Norway, *based on the female population, **based on the male population.

annual incidence was 250.4 per 100 000. The mean age at prevalence point was 65.8 (±9.9) years. The mean age at the time of the infarction was 61.4 (±9.0) years, and the mean duration for MS was then 16.1 (±10.0) years. The prevalence of myocardial infarction was 1.7%.

Pulmonary embolism (I26) was registered in the NPR for six MS patients, comprehending five females and one male. The diagnosis was confirmed in everyone, and all had an MS diagnosis at the time of embolism. The mean annual incidence was 136.6 per 100 000. The mean age at the event was 51.0 (±8.7) years, and the mean duration for MS was then 13.3 (±8.7) years. The prevalence of pulmonary embolism was 0.9%.

Subarachnoid hemorrhage (I60) was correctly registered in the NPR for one MS patient. The prevalence of subarachnoid hemorrhage was 0.2%. *Intracerebral hemorrhage* (I61) was not registered in the NPR for any MS patients.

Cerebral infarction (I63) was registered in the NPR for 12 MS patients. One, however, had suffered the stroke prior to 2008. Of the remaining, only four had a correct diagnosis, giving a mean annual incidence of 91.7 per 100 000. The mean age at prevalence point was 63.0 (±12.0) years. The mean age at the time of stroke was 58.8 (±13.1) years, and the mean duration for MS was then 16.5 (±10.3) years. The prevalence of cerebral infarction was 0.6%.

Inflammatory bowel disease (IBD) was registered in the NPR for ten MS patients. One, however, had a gastric ulcer and another had a colon polyp. Hence, eight MS patients had IBD, four with Crohn's disease (K50) and four with ulcerative colitis (K51). Six (75%) individuals were

Table 3
Non-melanoma skin cancer (ICD-10 C44).

Subject	Sex	Age at prevalence	Age MS	Age C44	Type of MS	Type of skin cancer	MS treatment prior to skin cancer	Occupation	Ever-smoker
1	f	40	39	36	rr	*basal cell carcinoma*	none	teacher	yes
2	m	57	47	56	rr	*squamous cell carcinoma*	glatiramer acetate	office worker	yes
3	f	57	33	53	rr	*squamous cell carcinoma*	interferon beta-1b, natalizumab, fingolimod	secretary	yes
4	m	59	34	50	rr	*squamous cell carcinoma*	interferon beta-1a, glatiramer acetate	factory worker	yes
5	f	59	48	52	rr	*basal cell carcinoma*	interferon beta-1a, glatiramer acetate	secretary	no
6	f	62	29	57	rr	*basal cell carcinoma*	none	nurse	yes
7	f	70	39	61	?	*basal cell carcinoma*	none	shop-keeper	yes
8	m	72	70	68	pp	*basal cell carcinoma*	none	plumber/clerk	yes
9	m	72	53	60	rr	*basal cell carcinoma*	none	fisherman/ farmer	yes
10	m	73	39	72	rr	*squamous cell carcinoma*	none	auto mechanic	yes
11	m	73	57	70	rr	*basal cell carcinoma*	none	artist	yes

Table 4
Non-cancer comorbid conditions in the Nordland County MS cohort.

	ICD10	n	Prevalence %	Age standardized prevalence %	Mean age (years) at prevalence (±SD)
Hypothyroidism	E03	20	3.1	2.0	59.1 (±16.6)
Diabetes mellitus I	E10	2	0.3	0.2	47.0 (±7.1)
Diabetes mellitus II	E11	25	3.9	2.2	62.5 (±12.1)
Psychosis	F09, F20, F23, F25	4	0.6	0.5	46.3 (±15.1)
Epilepsy	G40	18	2.8	1.8	54.4 (±13.8)
Myocardial infarction	I21	11	1.7	0.8	65.8 (±9.9)
Pulmonary embolism	I26	6	0.9	0.5	56.0 (±8.2)
Stroke intracerebral hemorrhage	I61	0	0	0	-
Stroke subarachnoid hemorrhage	I62	1	0.2	0.1	74
Stroke infarction	I63	4	0.6	0.3	63.0 (±12.0)
Inflammatory bowel disease	K50, K51	8	1.3	0.8	52.9 (±13.4)
Rheumatoid arthritis	M05, M06	4	0.6	0.3	61.3 (±11.5)

diagnosed with IBD before they were diagnosed with MS. The mean age at prevalence point was 52.9 (±13.4) years. The mean age at the diagnosis of MS was 41.9 (±10.2) yearsand the mean age at the diagnosis of IBD was 37.3 (±15.7) years. The prevalence of IBD was 1.3%.

Rheumatoid arthritis (RA) was registered in the NPR for nine MS patients, but the diagnosis was incorrect for four. Two patients had seropositive RA (M05) and two had seronegative RA (M06). None were registered with juvenile arthritis (M08). All were diagnosed with MS before they were diagnosed with RA. The mean age at prevalence point was 61.3 (±11.5) years. The mean age at the diagnosis of MS was 36.5 (±18.6) years, and the mean age at the diagnosis of RA was 54.3 (±16.6) years. The prevalence of RA was 0.6%.

SLE was registered in the NPR for one patient, but the diagnosis was incorrect.

Discussion

In the present study 97.5% of persons with MS were registered with comorbid conditions in the NPR. Comorbidity is thus prevalent in a cross-sectional MS- population.

Due to the large number of different comorbidities registered, a discretionary selection of conditions was validated. This was based on findings in the screening process, information from existing literature, and the likelihood of the disorder being treated and registered in hospitals or by a specialist.

The mean age of our MS cohort was 52.5 years, which is higher than that of the general Norwegian population: 39.9 years. This limits the possibility to compare our results directly with data from the general population. To account for this, we therefore compared some of our figures with data from the adult population, being those of 20 years of age and above. This was found relevant for non-melanoma skin cancer and breast cancer. The incidence of these types of cancer is rare in individuals younger than 20 years [14, page 32-35].

Low exposure to sun during childhood seems to be a risk factor for MS in our area [15]. Nordland County is located at a high latitude with limited sun exposure during the year. Studies have associated melanoma and non-melanoma skin cancers rates with latitude, sun exposure, and vitamin D [16]. Based on this, a low occurrence of melanoma and non-melanoma skin cancer in the MS cohort could be expected. Indeed, a British study found low incidence of skin cancer in the MS group [17]. In a more recent Canadian study, however, the risk of non-melanoma skin cancer was significantly increased in patients with relapsing-onset MS [18]. Data regarding malignant melanoma are contradictive, and increased incidence of malignant melanoma has also been reported [19]. We found a prevalence of malignant melanoma of 0.5% of the MS population, which is equal to the prevalence in the general Norwegian population. [14]. The prevalence of non-melanoma skin cancer, however, was significantly higher than what is found in the general population.

Some studies indicate increased incidence of breast cancer in the MS population [20]. We found a higher prevalence when compared with the prevalence in the total Norwegian population [14]. However, when using data from the population aged 20 years and older, the difference was no longer significant, and the increased incidence found is probably explained by the age of the MS -cohort.

Smoking is considered a risk factor for MS [21], and it is a major cause of lung- and urinary bladder cancers. We have recently reported an increased risk of cancers in the respiratory organs from a large MS-cohort [22], but this was not confirmed in this particular cohort from Nordland County. The same study also reported an increased risk of cancers in the urinary tract organs [22], but that was not confirmed in this cohort either. The longitudinal (life-long, for several patients) study

design, compared to this cross-sectional cohort study, may explain this difference. Unfortunately, we did not have reliable data on smoking from our MS population.

In the present study, the prevalence of IBD was 1.3%; this was 1.6 times higher than that reported in the general Norwegian population, among which the prevalence was 262 per 100 000 for Crohn's disease and 505 per 100 000 for ulcerative colitis [23]. Our result was, however, in accordance with other international studies. An increased risk of IBD in MS patients, as well as an increased risk of MS in IBD patients has previously been shown [24].

We found hypothyroidism in 3.7% of the females and 1.8% of the males in the MS population. This is lower than findings from a previous Norwegian study in a general population [25]. Increased risk of thyroid disease among MS patients has been reported [26], but contradicted by others [27]. We also found a low prevalence of DM compared to a recent Norwegian study, in which the prevalence of type-2 diabetes mellitus was 6.1% [28]. Both hypothyroidism and type-2 diabetes are most often diagnosed and treated by general practitioners, and thus they are not necessarily registered in the NPR; this may probably give an underestimated prevalence figures in our cohort.

We found rheumatoid arthritis in 0.6% of the MS population, a finding comparable to figures reported from the neighboring county, where the prevalence was 0.47% in 1994 [29].

We confirmed that epilepsy is frequent in the MS population, with prevalence four times higher than in the general Norwegian population, among which it is 0.7% [30]. The increased prevalence of epilepsy is in accordance with other studies [31].

A Norwegian study from 2001 found a lifetime prevalence of non-affective psychosis of 0.4% in the general population [32]. We found the prevalence of individuals who have experienced psychosis to be slightly higher (0.6%), but the numbers effected are too small to make a reliable statistic interpretation. Others have found an increased prevalence of psychosis in the MS population [33].

A recent study reported an increased risk of acute myocardial infarction in MS patients [34]. In the Nordland MS population, the mean annual incidence of myocardial infarction was 250.4 per 100 000. In a study from Northern Norway of the general population older than 25 years, the age- and sex- adjusted incidence of myocardial infarction in 2010 was 224 per 100 000 [35]. Studies have also found increased incidence of stroke among MS patients [36]. In the present study, 1.7% of the MS -population had suffered stroke in the period, with a mean annual incidence of 91.7 per 100 000. In comparison, a study from Northern Norway of individuals in the normal population older than 30 years found 367 strokes per 116 703 person-years in the period from 2006 to 2010, giving an annual incidence of 314.5 per 100 000 [37].

We found that only four out of 11 individuals registered with cerebral infarction (I63) in the NPR had actually suffered from stroke. For the others, the symptoms and findings were considered manifestations of their MS. In a clinical setting, it is sometimes difficult to distinguish stroke from the exacerbation of MS. Regarding classification and epidemiology, such difficulties may cause diagnostic misinterpretation in both directions.

Our data was validated and compared with reliable national data from the Cancer Registry of Norway and relevant epidemiological studies. However, we did not have a matched validated control group, and only diagnoses registered in the NPR were included. Important conditions, such as depression and anxiety, as well as risk factors like hypertension and hyperlipidemia, are presumed to be handled mostly in primary care and have thus been omitted, since these are not registered in the NPR. Furthermore, we cannot exclude the possibilitythat other conditions are under-reported to the NPR, and in that respect our figures may represent the lower limit of the real occurrence of comorbidities in MS.

Conclusion

The present study confirms an increased prevalence of inflammatory bowel disease and epilepsy in MS, but also suggests that the prevalence of non-melanoma skin cancer is increased. The association between non-melanoma skin cancer and MS should be further investigated.

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics (REK Nord 2016/1531) and was conducted in accordance with ethical principles for medical research.

Disclaimer

Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended or should be inferred.

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

CRediT authorship contribution statement

Espen Benjaminsen: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Kjell-Morten Myhr:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Nina Grytten:** Methodology, Writing - review & editing, Supervision. **Karl Bjørnar Alstadhaug:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interests

The authors have nothing to disclaim related to the topic.

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Appendix

Information letter to the individuals with MS included in paper 2 and paper 4.

INFORMASJON OM INNHENTING AV OPPLYSNINGER FRA NORSK PASIENTREGISTER OG PASIENTJOURNALER VED NORDLANDSSYKEHUSET, HELGELANDSSYKEHUSET, UNIVERSITETSSYKEHUSET I NORDNORGE, SYKEHUSET I NAMSOS OG ST OLAVS HOSPITAL I TRONDHEIM.

NLSH BODØ, DD.MM.YY

TIL DIN INFORMASJON

Pasienter med multippel sklerose (MS) har ofte andre sykdommer i tillegg, som kan komplisere sykdommen og behandlingen. Vi driver nå et prosjekt for å belyse slike problemstillinger.

I forbindelse med forskingsprosjektet «Forekomst av multippel sklerose og komorbide sykdommer i Nordland» er det innhentet informasjon om deg vedrørende diagnosekoder.

Regional komite for medisinsk og helsefaglig forskning har godkjent denne innhentingen uten forespørsel om samtykke (REK Nord 2016/1531). Det foreligger imidlertid informasjonsplikt i henhold til Personopplysningslovens § 20:
En behandlingsansvarlig som samler inn personopplysninger fra andre enn den registrerte selv, skal av eget tiltak informere den registrerte om hvilke opplysninger som samles inn og gi informasjon som nevnt i § 19 første ledd så snart opplysningene er innhentet. Dersom formålet med innsamling av opplysningene er å gi dem videre til andre, kan den behandlingsansvarlige vente med å varsle den registrerte til utleveringen skjer.

Med vennlig hilsen

Espen Benjaminsen
Overlege,
behandlingsansvarlig (sign)

Karl B. Alstadhaug
Overlege, PhD,
prosjektleder

Kontakt: Espen Benjaminsen, Nevrologisk avdeling, Nordlandssykehuset i Bodø
Telefon: 75534000 (sentralbord)
E-post: espen.benjaminsen@nlsh.no