Epidemiology of multiple sclerosis in Iceland 2002–2007

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Thesis for the degree of Philosophiae Doctor

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Faraldsfræði heila- og mænusiggs á Íslandi 2002–2007

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Ágrip

Tilgangur og markmið: Heila- og mænusigg (*multiple sclerosis* skammstafað *MS*) er sjálfsofnæmissjúkdómur sem leggst á miðtaugakerfið. Áhættuþættir MS eru meðal annars D vítamin skortur og fyrri sýking af EBV veiru. Að vera fæddur að vori til hefur verið tengt hærri tíðni á MS miðað við þá sem fæddir eru að hausti/vetri. Tíðni MS sjúkdómsins er mismunandi eftir löndum og er nýgengi og algengi hans hærra á norðurhveli jarðar. Tíðni sjúkdómsins hefur einnig breyst með tímanum og hafa mörg lönd birt faraldsfræðilegar rannsóknir sem sýna aukningu á nýgengi og algengi sjúkdómsins á sl. 50 árum. Mikilvægt er því að hafa nýlegar upplýsingar um tíðni sjúkdómsins sérstaklega í ljósi nýrra og öflugra meðferða sem nú standa til boða. Markmið með rannsóknum okkar var að uppfæra þekkingu um nýgengi og algengi MS sjúkdómsins á Íslandi ásamt því að kanna dánartíðni af völdum sjúkdómsins sem ekki hefur áður verið gert á Íslandi. Einnig könnuðum við áhrif fæðingarmánaðar á áhættu á því að þróa með sér sjúkdóminn síðar á lífsleiðinni.

Þátttakendur og aðferðir: Allir sjúklingar sem greindust með MS skv. Poser greiningarskilmerkjum um *clinically definite MS* og *primary progressive MS* á árunum 2002–2007 á Íslandi (grein I og II) auk þess voru sjúklingar sem uppfylltu skilmerki Poser um *laboratory supported definite MS (LSD-MS), clinically probable MS (CP-MS)* og McDonald 2010 greiningarskilmerkin með í grein II um algengi MS. Sjúklingarnir voru fundnir út frá greininganúmerum í ICD10 (G35, G37,9), ICD9 (340,341) og ICD8 (340,341) frá Landspítala, öllum sjálfstætt starfandi taugalæknum, minni spítölum og endurhæfingar–stofnunum, röntgen deild LSH, Domus Medica og Deild lyfjamála á Landspítala (grein I, II og IV). Auk þess frá upplýsingum um örorkubætur vegna MS og hjálpartækja hjá Tryggingastofnun ríkisins og Sjúkratryggingum Íslands (grein II og IV). Nýgengi var reiknað fyrir árin 2002–2007 og algengi fyrir 31.desember 2007. Dánartíðni MS sjúklinga var borin saman við heildarþýði Íslands leiðrétt fyrir aldri og kyni með s.k. *life table* aðferð. Í grein III voru upplýsingar um MS sjúklinga fengnar frá sænsku MS sjúklingaskránni. Sænski hópurinn var fæddur á árunum 1940–1996 og íslenski hópurinn á árunum 1981–1996. Viðmiðunarhópar voru fengnir frá sænska manntalinu (*Swedish Total Population Registry*) og Hagstofu. Leiðrétt var fyrir fæðingarári og fæðingarstað.

Niðurstöður: Nýgengi MS á Íslandi 2002–2007 var 7,6 á hverja 100 000 íbúa. Sjúkdómurinn var 3 sinnum algengari hjá konum en körlum. Meðalaldur við greiningu var 36,3 ár (Grein I). Algengi MS fyrir 31.desember 2007 var 176 á hverja 100 000 íbúa (Grein II). Áhætta á MS síðar á lífsleiðinni reyndist ekki aukin eftir fæðingarmánuði (Grein III). Dánartíðni MS sjúklinga á Íslandi er tvöfalt hærri en hjá íslensku meðalþýði leiðrétt fyrir kyni og aldri (Standardized mortality ratio SMR: 2,0, 95%CI:1,3–3,0). Enginn munur var á dánartíðni fyrstu 10 árin eftir greiningu (SMR: 0,95, 95%CI:0,1–3,0). Enginn munur var á SMR karla og kvenna með MS. Dánarorsakir MS sjúklinga voru í 48% tilvika (29/61) tengdar MS sjúkdómnum (Grein IV).

Umræða: Nýgengi og algengi MS sjúkdómsins á Íslandi er hátt, líkt og birtar niðurstöður frá hinum Norðurlöndunum sýna. Dánartíðni MS sjúklinga er hærri en hjá íslensku meðalþýði og er það í samræmi við erlendar rannsóknir. Fæðingarmánuður er ekki áhættuþáttur fyrir MS síðar á lífsleiðinni. Truflandi þáttur (*confounding factor)* gæti hafa haft áhrif á niðurstöður fyrri rannsókna, en frekari rannsókna er þörf á því.

Lykilorð:

Heila- og mænusigg, faraldsfræði, nýgengi, algengi, dánartíðni.

Abstract

Purpose and aims: Multiple sclerosis (MS) is an autoimmune disease that leads to damage in the central nervous system. Although the cause of MS is still unknown, the generally accepted view is that environmental and life-style factors influence the risk of MS in genetically predisposed individuals. The frequency of MS varies between countries. Countries with a more distant position from the equator have the highest reported incidence and prevalence rates. This association may be partially explained by lower exposure to sunlight and low vitamin D levels, two of the established risk factors for MS. According to previous studies the incidence and prevalence of MS appear to have increased since the middle of the past century. Knowledge of changes in disease epidemiology is important to dimension the need for health care resources, especially in light of new and expensive treatment alternatives, but also to identify risk factors of disease. We aimed to assess the incidence (Study I), prevalence (Study II), and mortality (Study IV) of MS in Iceland. In addition, we wanted to assess the influence of birth month in Sweden and Iceland on the risk of being diagnosed with MS later in life (Study III). Such an association has been noted in previous studies and has been hypothesized to be linked with low vitamin D levels during the winter season in pregnant women.

Subjects and methods: Studies I, II and IV are population-based, nationwide studies on the epidemiology of MS in Iceland. Cases were identified by searching in multiple sources: administrative databases of both hospitals, private offices and difference government authorities such as the Directorate of Health, and the Social Insurance Administration. When applicable the search was based on diagnosis codes from: ICD10 (G35, G37.9), ICD9 (340, 341) and ICD8 (340, 341). Inclusion criteria for studies I and II were diagnosis of *clinically definite MS* or *primary progressive MS* according to the Poser diagnostic criteria. In addition, Study II included patients with *laboratory-supported definite MS (LSD-MS)* or *clinically probable MS (CP-MS)* according to Poser's criteria or those fulfilling the McDonald 2010 criteria. Study IV was based on these prevalence and incidence cohorts. Incidence was calculated for the years 2002–2007 (Study I) and prevalence for the 31st of December 2007 (Study II). Mortality was analyzed by calculating the standardized mortality ratio (SMR) with a life

table approach (Study IV). For study III data was extracted from the Swedish MS Registry on all MS patients born between 1940 and 1996. An Icelandic group was created for Study III using the same case ascertainment as described for studies II and IV including cases born between 1981 and 1996. Control groups were created based on data from the Swedish Total Population Registry and Statistics Iceland. The analysis was adjusted for birth year and birth place.

Results: We identified 136 patients diagnosed with MS in Iceland in 2002–2007. The incidence was 7.6 per 100 000. The female-to-male sex ratio was 3:1. Mean age at diagnosis was 36.3 years (Study I). There were 526 patients alive on the prevalence day, December 31st 2007. The prevalence was 176 per 100 000 (Study II). We found no connection between birth month and risk of developing MS later in life (Study III). The mortality in the prevalence group was higher than in the general population (SMR: 2.0; CI: 1.3 –3.0). For patients diagnosed between 2002 and 2007 there was no difference in mortality compared to the general population after the first 11 years following diagnosis (SMR: 0.95; CI: 0.1-3.0). Cause of death was related to MS in 48% (29/61) of cases (Study IV).

Conclusion: In line with recent similar surveys from other countries, we found an increase of incidence and prevalence of MS in Iceland. The current incidence and prevalence of MS in Iceland was of comparable magnitude as in studies from the other Nordic countries. The excess mortality in MS relative to the general population of Iceland is in accordance with results of previous work from other countries. Birth month does not seem to be a risk factor for developing MS later in life. This is in contrast to some previous studies where confounding factors might have influenced the results, although further research is needed for clarification.

Keywords:

Multiple sclerosis, epidemiology, incidence, prevalence, mortality, risk factors, Iceland

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List of abbreviations

CI	Confidence interval
CIS	Clinically isolated syndrome
CVD	Cardiovascular disease
COD	Cause of death
CNS	Central nervous system
CSF	Cerebrospinal fluid
CDMS	Clinically definite MS
CPMS	Clinically probable MS
CMR	Crude mortality rate
DMD	Disease modifying drugs
DIS	Dissemination in space
DIT	Dissemination in time
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
EMR	Excess mortality rate
HLA	Human leukocyte antigen
IM	Infectious mononucleosis
LSDMS	Laboratory-supported definite MS
LSPMS	Laboratory-supported probable MS
MHC	Major histocompatibility complex
MOB	Month of birth
MS	Multiple Sclerosis
NFL	Neurofilament light
OR	Odds ratio
OCB	Oligoclonal bands
PPMS	Primary progressive MS
PRMS	Progressive-relapsing MS

RRMS	Relapsing-remitting MS
PYO	Person-years of observation
SPMS	Secondary-progressive MS
SMR	Standardized mortality ratio
SMSreg	Swedish MS registry
UVR	Ultraviolet radiation
VEP	Visual evoked potential

List of figures

List of tables

List of original publications

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

Study I **Incidence of multiple sclerosis in Iceland, 2002-2007: a population-based study.** Eliasdottir OJ, Olafsson E, Kjartansson O (2011). *Mult Scler 17*(8):909–13

Study II **Prevalence of Multiple Sclerosis in Iceland.** Eliasdóttir Ó, Kjartansson Ó, Olafsson E (2018). *Neuroepidemiology 51*(1-2): 50–56

Study III **A nationwide survey of the influence of month of birth on the risk of developing multiple sclerosis in Sweden and Iceland.** Eliasdottir O, Hildeman A, Longfils M, Nerman O, Lycke J (2018). *J Neurol 265*(1): 108–114

Study IV **Mortality of Multiple Sclerosis in Iceland.** Eliasdóttir Ó, Kjartansson Ó, Olafsson E (2020). Manuscript.

All papers are reprinted with kind permission of the publishers. In addition, some unpublished data is presented. The papers and manuscript are not included in the online version of this thesis.

Declaration of contribution

The doctoral student, Ólöf Elíasdóttir designed and planned all of the studies together with her supervisors. She conducted all paperwork regarding ethical approval for all studies. She collected all data for studies I, II and IV. The doctoral student conducted the statistical analysis in studies I, II and IV. She interpreted the statistical analysis together with her coauthors for paper III. She wrote all the manuscripts together with her coauthors, prepared them for submission and responded to reviewers together with her supervisors. The doctoral student wrote the thesis with guidance from her supervisor and doctoral committee.

1 Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS). Although the etiology is unknown, MS is considered an autoimmune disease, with multiple genetic and environmental risk factors contributing to the development of the disease (Gourraud et al., 2012). Dysregulated innate and adaptive immune cells are involved in attacks on the CNS. Auto-reactive CD4+ T-cells are considered to play a central role in this inflammatory process, causing demyelination, neuronal- and axonal damage, oligodentrocyte loss, and astrogliosis (Duddy et al., 2007; Gandhi et al., 2010). Nerve cells with damaged myelin conduct nerve impulses more slowly, leading to symptoms of MS. The grey matter is also affected in MS, most probably due to secondary damage of the axons, which in turn leads to neurodegeneration which manifests as a slowly progressive phase of the disease. (Gandhi et al., 2010). MS is second only to accidents as a leading cause of disability among young adults (Koch-Henriksen & Sorensen, 2010).

Previously, infection was considered a potential cause of MS, but based on both pathological (Magliozzi et al., 2007) and epidemiological studies, MS is now considered to be an autoimmune disease. Early family studies (Gourraud et al., 2012) on MS showed an increased risk amongst first degree relatives. Later genetic studies have linked MS to different loci in the genome, almost all of which are closely linked to genes associated with the immune system. The strongest connection has been to genes coding for proteins used by antigen presenting cells in the immune system, known as the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) (Murray et al., 2014). Currently, more than 200 genes have been associated with an increased risk of MS (Andlauer et al., 2016). From epidemiological studies we have learned that genetic susceptibility alone is not sufficient for the disease to develop later in life. Numerous environmental factors have also been associated with an increased risk of MS (see 1.5) (Amato et al., 2017).

1.1 Short overview of epidemiology

Epidemiological studies of diseases, such as MS, lead to important knowledge. Although there is no universally accepted definition of what epidemiology encompasses, a commonly cited definition was put forth by Last in a publication from 2001 (Frerot et al., 2018), defining epidemiology as:

"*The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems*".

Key to most definitions of epidemiology is that the population under study needs to be well defined. Epidemiological studies with follow-up over longer periods of time can describe the prognosis of disease, and even describe how modification of risk factors in a population can affect the outcome. Comparing epidemiological studies from different areas can give valuable clues to the underlying causes of disease. Finding clusters or small epidemics may be of particular value (Warren, 2001). Although risk factors can be identified and may point to possible causes of a disease, proving a causal relationship with epidemiological studies can be difficult.

In epidemiology, two principal parameters are used to describe occurrence; incidence and prevalence. The incidence of a disease can be defined as the number of new cases rising from the population being studied during a specific time interval (Dos Santos Silva, 1999). It is usually reported as the number of cases per 100 000 individuals in the population or person-years at risk.

Prevalence is the proportion of existing cases in a population at a certain point in time (Dos Santos Silva, 1999). It reflects both the incidence and the duration of a disease. Prevalence can be reported as point prevalence, i.e., prevalence at certain point in time and period prevalence, i.e., prevalence presented over a specified time period.

When conducting, interpreting or comparing epidemiologic studies, it is important to reflect on several characteristics of the study, including:

1) How are the cases defined?
2) What are the characteristics of the population that the cases are drawn from?
3) Are all cases in that population included, e.g., from an entire country?
4) Distribution of demographic variables such as: age, gender, race and ethnicity (Warren, 2001).
5) Period of time under study, as the frequencies of diseases can change considerably with time (Dos Santos Silva, 1999).

1.2 Bias and confounding in epidemiological studies

Bias and confounding are of major concern in clinical research, potentially distorting the results. Bias is generally defined as, any systematic error that leads to incorrect estimates of the outcome being studied. There are two main types of bias. 1) Selection bias, where the selected cases do not represent the population being studied. This can happen, e.g., when relatively mild cases are not identified. 2) Information bias, where inaccurate information of disease status or exposure, of the study subjects, affects the results (for example observer bias and recall bias) (Dos Santos Silva, 1999).

Confounding is when an additional factor affects both the risk factor under investigation and the disease being studied, resulting in a distortion of their association (Dos Santos Silva, 1999). Confounding can result in the wrong conclusion being drawn from the study results, e.g., when investigating the effect of smoking on the risk of having a stroke. If the smokers are younger than non-smokers, age is a confounding factor because it is known that older individuals have an increased risk of suffering from a stroke (Skelly et al., 2012)(See 1.5.3.3).

1.3 Diagnostic criteria

The diagnostic criteria used for MS have changed over the years, due to a better understanding of the immunopathogenesis of the disease and advances of imaging techniques, allowing more accurate and earlier diagnosis.

1.3.1 Early diagnostic criteria

Early diagnostic criteria determined the certainty of the diagnosis based on clinical presentation and physical examination. Allison and Millar (1954) categorized patients into three groups: 1) possible; 2) early probable, and 3) latent probable. The Allison and Millar criteria were followed by the Schumacher criteria, published in 1965, by Schumacher et al (1965), mainly developed for the purpose of including patients in clinical trials and consisted only of definite cases. McAlpine (Warren, 2001) included probable and possible cases again. Both Rose et al. (1976) and McDonald & Halliday (1977) attempted to combine the Schumacher and McAlpine criteria while Bauer (1980) made the first attempt to incorporate laboratory results. All of these criteria have been used to some extent in older epidemiologic studies.

1.3.2 Poser criteria

Overall, the most widely used diagnostic criteria in the MS literature are the Poser criteria form 1983 (Poser et al., 1983). They take into account both clinical signs and symptoms as well as analysis of cerebrospinal fluid (CSF) and *visual evoked potential* (VEP). There are 4 categories inferring different degrees of certainty of the diagnosis (table 1). Primary progressive MS does not conform fully to the Poser 1983 criteria but was described as: 6 months progression of neurological symptoms with evidence of one lesion combined with signs of another clinical or paraclinical lesion (VEP) and oligoclonal bands (OCB) or increased IgG production in the CSF.

Table 1 Poser diagnostic criteria. Four main diagnostic groups of MS: Clinically definite (CD), Laboratory-supported definite (LSD), Clinically probable (CP), Laboratory-supported probable (LSP) and the combinations and number of different evidence types (Relapses, Clinical evidence, Paraclinical evidence and CSF analysis) needed to belong to the different diagnostic groups

Category	Relapses		Clinical Evidence[a]		Paraclinical evidence[b]	Positive CSF[c] analysis[d]
CD, Clinically **definite**						
CD-MS A1	2	and	2			
CD-MS A2	2	and	1	and	1	
LSD, Laboratory-supported **definite**						
LSD-MS B1	2	and	1	or	1	+
LSD-MS B2	1	and	2			+
LSD-MS B3	1	and	1	and	1	+
CP, Clinically **probable**						
CP-MS C1	2	and	1			
CP-MS C2	1	and	2			
CP-MS C3	1	and	1	and	1	
LSP, Laboratory-supported **probable**						
LSP-MS D1	2					+

[a]Clinical Evidence, signs of neurological dysfunction on neurological examination

[b]Paraclinical evidence, demonstration of the existence of lesions in the CNS by diagnostic tests, lesions that have caused symptoms in the past but without remaining signs

[c]CSF, Cerebrospinal fluid; [d]high OCB/high IgG index in the CSF

1.3.3 McDonalds Criteria from 2010

The McDonald criteria were introduced in 2001, but have been revised three times since: 2005, 2010 and 2017 (Thompson et al., 2018). The diagnosis of *relapsing-remitting MS* (RRMS) requires:

> "*at least 1 episode of symptoms from the central nervous system consistent with demyelination in absence of infection, lasting 24 hours with objective evidence of lesions disseminated in space (DIS) and time (DIT)"* (Polman et al., 2011)."

In practice DIS and DIT is often achieved with MRI (Tables 2 and 3). According to the McDonald 2010 criteria, PPMS can be diagnosed after 1 year of progression of neurological symptoms with 2 of 3 of the following: DIS in the brain, DIS in the spinal cord (≥2 T2 lesions in the cord) or positive CSF (OCB/elevated IgG index).

Table 2 McDonald 2010 criteria, dissemination in space (DIS)

DIS is fulfilled when there are 1 or more T2 lesion in at least 2 of the following 4 areas:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[a]

[a]Asymptomatic spinal cord lesion

Table 3 McDonald 2010 criteria for dissemination in time (DIT)

DIT can be determined by:
1 A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2 Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

1.3.4 Barkhof-Tintoré MRI criteria

The MRI criteria were included in the first two versions of the McDonald criteria year 2001 and 2005 (McDonald et al., 2001; Polman et al., 2005). They allow DIS by MRI (Table 4) (Barkhof et al., 1997; Tintore et al., 2000).

Table 4 Barkhof/Tintoré MRI diagnostic criteria for DIS[a]

Three of four features must be present:
1 At least 1 gadolinium-enhancing lesion Or at least 9 lesions[b] on T2-weighted images
2 At least 3 periventricular lesions
3 At least 1 juxtacortical lesion
4 At least 1 infratentorial lesion

[a]DIS, dissemination in space

[b]One spinal cord lesion can be substituted for one brain lesion

1.4 Incidence and prevalence of MS

1.4.1 Occurrence of MS worldwide

Previous studies have found a clear geographical variation in the incidence and prevalence of multiple sclerosis between both countries and continents (Koch-Henriksen & Sorensen, 2010). The disease is most common in Caucasians (Warren, 2001). The frequency of MS is highest in the northern part of Europe and the USA while the lowest incidence and prevalence is in Asia and Africa (Ahlgren et al., 2014; Dean, 1967; Koch-Henriksen & Sorensen, 2010).

1.4.1.1 Incidence of MS

Europe: There are numerous previous studies on the incidence of MS in Europe. Comparison of studies can be difficult due to differences in the diagnostic criteria used and time periods under study. The highest incidence is found in studies from the Nordic countries, ranging from 2.4–14.7 (see 1.4.1.3) (Ahlgren et al., 2014; Benjaminsen et al., 2014; Holmberg et al., 2013; Joensen, 2010; Simonsen et al., 2017). The incidence is high in the United Kingdom and Ireland as well, ranging from 6.5–9.7/100 000 (Hirst et al., 2009; Kearns et al., 2019; McDonnell & Hawkins, 1998). Generally, the incidence has been found to be lower in other parts of Europe although there is an appreciable range (de Sa et al., 2014): 8/100 000 in Germany (Fasbender & Kolmel, 2008), 4.2/100 000 in Poland (Brola et al., 2016), 6.3/100 000 in the Netherlands (Kramer et al., 2012), 4.3/100 000 in Italy (Iuliano & Napoletano, 2008) and 7.9/100 000 in San Marino (Caniglia-Tenaglia et al., 2018).

Most countries in the northern and western parts of Europe have fairly recent data on incidence available. For some countries, e.g., in southern and eastern parts of Europe, the only available estimates of incidence come from older studies using obsolete methods of case retrieval and diagnostic ascertainment (Dobec-Meić & Puljić, 2007). When reviewing newer studies from these regions similar incidence and prevalence rates of MS are reported as those from recent surveys from northern and western parts of Europe, e.g., the MS incidence rates reported from Lithuania and San Marino, were 6.5/100 000 and 7.9/100 000, respectively (Valadkeviciene et al., 2019) (Caniglia-Tenaglia et al., 2018). This emphasizes the need to consider study period and methodology, including case ascertainment, when comparing results of studies on incidence.

USA and Canada: According to a systematic review only one study has reported population-based incidence of MS in the United States (Evans et al., 2013). The study found an incidence of 7.5/100 000 in Olmstead county, Minnesota (Mayr et al., 2003). There are a number of regional studies on incidence from Canada with three of the more recent reporting an incidence in the range of 5.17–15.8 (Kingwell et al., 2015; Marrie et al., 2013; Marrie et al., 2010).

Asia: Although data is limited, a low incidence of MS has been reported from Asia. In a study from Northern Japan the incidence was 0.8/100 000 (Houzen et al., 2008) while a systematic review identified 2 studies from Japan and one from Taiwan reporting an incidence in the range of 0.1–0.79 (Eskandarieh et al., 2016).

Africa: Data from Africa is limited as well. In one study from 1967, Dean and associates (1967) reported an incidence of 0.4/100 000 amongst Caucasians in South Africa.

Latin America: Data on the incidence of MS in Latin America is limited but a review from 2017 identified studies from the West Indies, Panama and Argentina reporting an incidence from 0.3–1.8 (Cristiano & Rojas, 2017). A study from Puerto Rico reported an incidence between 6–7/100 000 (Chinea et al., 2017).

Further information on studies reporting on the incidence of MS including: inclusion criteria, number of cases, study period and size of the population studied is presented in Tables 5 (nationwide studies) and 6 (regional studies).

Table 5 Nationwide studies on the incidence of MS, from outside the Nordic countries

Country	First author	Publication year	Incidence[a] (95% CI)	Cases (n)	Population (N)	Time period	Inclusion criteria[b,c]
France	Fromont	2010	7.5 (7.3–7.5)	4 497	52 359 912	2003–2004	NA[d]
Irland	O'Connell	2017	6.0 (5.3–6.6)	292	4 581 269	2014–2015	McDonald 2010
Malta	Dean	2002	0.7 NA[d]	7	378 500	1979–1998	Poser: CD-MS, CP-MS
San Marino	Caniglia-Tenaglia	2018	7.7 (4.9–11.4)	24	31 269	2005–2014	Poser: CD-MS, CP-MS
Scotland	Kearns	2019	8.8 NA[d]	3 680	5 299 900	2010–2017	McDonald 2005

[a]Incidence, number of cases per 100 000 population per year. [b]CD-MS, Clinically definite MS; [c]CP-MS, Clinically probable MS; [d]NA, not available

Table 6 Non-nationwide studies on the incidence of MS, from outside the Nordic countries

Country	Region	First author	Publication year	Incidence[a] (95% CI)	Cases (n)	Population (n)	Time period	Inclusion criteria[b,c,d,e]
Australia	Newcastle	Ribbons	2017	6.7 (5.4–8.01)	100	148 535	2001–2011	Poser<2001 and McDonalds criteria >2001
Bosnia Herzegovina	Western	Klupka-Sarić	2007	1.6 (0–3.3)	NA[f]	300 746	1994–2003	McDonald
Canada	British Columbia	Kingwell	2015	7.8 (7.6–8.1)	4 222	53 442 828	1996–2008	NA[f]
Germany	Erfurt ,Thüringen	Fasbender	2008	8.0 (6.39–10.0)	81	201 267	1998–2002	Poser: CD-MS, CP-MS
Greece	Western	Papathanasopoulos	2008	10.7 NA[f]	92	619 642	2004	Poser: CD-MS and McDonald
Iran	Isfahan province	Etemadifar	2011	9.1 (8.3–10.0)	431	4 741 615	2009	Poser: CD-MS and McDonald
Italy	Salerno	Iuliano	2008	4.3 (3.2–5.6)	56	259 681	2001–2005	Poser and McDonald
Japan	Tokachi Province	Houzen	2008	0.8 (0.4–1.3)	14	360 992	2000–2004	Poser
Netherlands	NA[f]	Kramer	2012	6.3 (5.2–7.2)	146	648 656	1996–2008	Poser: CD-MS, CP-MS
Poland	Swietokrzyskie province	Brola	2016	4.2 (3.7–4.4)	267	1 263 176	2010–2014	McDonald
Spain	Northern Seville District	Izquierdo	2015	4.6 (4.1–5.1)	156	163 324	1991–2011	Poser: CD-MS, LSD-MS
United Kingdom	Leeds	Ford	2002	6.1 NA[f]	136	728 840	1996–1998	Poser
USA	Olmsted County, MN	Mayr	2000	7.3 (5.9–8.3)	132	1 756 607[g]	1985–2000	Poser: CD-MS, LSD-MS, CP-MS, LSP-MS
Wales	South East	Hirst	2009	9.7 (7.1–13.1)	582	424 633	2007	Poser and McDonald

[a]Incidence, number of cases per 100 000 population per year. [b]CD-MS, Clinically definite MS; [c]LSD-MS, Laboratory-definite MS; [d]CP-MS, Clinically probable MS; [e]LSP-MS, Laboratory-supported probable MS; [f]NA, not available; [g]PYO, person years of observation

1.4.1.2 Prevalence of MS

Inspired by the observed differences in occurrence of MS in different parts of the world, Kurtzke classified geographical areas into 3 frequency zones based on prevalence as: High (>30 per 100 000) Medium (5–30 per 100 000) and Low (<5 per 100 000) (Kurtzke, 1975). However, Kurtzke´s frequency zones are not in common use any longer due to the substantial rise in prevalence observed during the past decades that has rendered this classification less relevant. As of yet, no generally accepted, new or updated classification is available.

Europe: High prevalence rates have been reported from countries in Northern and Western Europe but with a wide dispersion, from 87.9/100 000 in Belgium to 248/100 000 in Scotland (van Ooteghem et al., 1994; Visser et al., 2012). Table 7, 8 and figure 7 show the prevalence in European countries with data from 1990 and onwards. In the Nordic countries (Table 10) the reported prevalence of MS has ranged from 105–280/100 000 (Ahlgren et al., 2011; Bentzen et al., 2010; Berg-Hansen et al., 2014; Pirttisalo et al., 2019; Sarasoja et al., 2004; Simonsen et al., 2017).

MS prevalence rates are generally lower in other parts of Europe although they are widely distributed (Baumhackl et al., 2002; Beer & Kesselring, 1994; Brola et al., 2016; De Sa et al., 2006; Izquierdo et al., 2015) with generally the lowest rates in Southern- and Southeast Europe (Becus & Popoviciu, 1994; Dean et al., 2002; Gross et al., 1993; Klupka-Saric & Galic, 2010; Marcoci et al., 2016; Milanov et al., 1997; Pekmezovic et al., 2001; Peterlin et al., 2006). However, some of the more recent studies from regions outside of Northern and Western Europe have shown higher rates, 90/100 000 in

Hungary (Zsiros et al., 2014) and 167/100 000 in San Marino (Caniglia-Tenaglia et al., 2018). Again, it must be emphasized that the study period has considerable impact on the reported incidence and prevalence of MS.

North America: Data on prevalence in the USA is limited but a recent study based on administrative health claim datasets estimated the national prevalence in 2010 to be 309.2 per 100 000 (Wallin et al., 2019). Results are available from some previous regional studies reporting prevalence rates. The lowest prevalence has been reported to be 39 per 100 000 in Lubbock, Texas and surrounding counties (Evans et al., 2013). The highest prevalence is reported from Olmsted county, Minnesota, by Mayr and associates (2003), 177/100 000.

Canada: Recent regional estimates of prevalence from Canada include Nova Scotia (266.9/100 000), British Columbia (179.9/100 000) and Ontario (265/100 000), for the most recent time periods studied (Kingwell et al., 2015; Marrie et al., 2013; Marrie et al., 2010).

Latin America: Few studies have been published in English on the prevalence of MS in Latin America but according to a systematic review the prevalence is between 0.83–38.2/100 000 (Cristiano & Rojas, 2017).

Australia and New Zealand: An MS prevalence of 124.2/100 000 has been found in Newcastle, Australia (Ribbons et al., 2017) and in New Zealand it was 72.4/100 000 (Taylor et al., 2010).

Asia: The prevalence in Asia is generally low, for example 13.1/100 000 in Japan (Houzen et al., 2008) and 73.3/100 000 in Iran (Etemadifar & Maghzi, 2011).

Africa: Although data from Africa is limited, Bhigjee (2007) and associates reported a prevalence of 0.22/100 000 in blacks in the province of KwaZulu-Natal in South Africa.

Many of the potential explanations for differences between incidence rates between countries, also apply to differences in prevalence rates. There is a difference in prevalence between continents, thought to be mainly due to differences in ethnic origin (Koch-Henriksen & Sorensen, 2010). In this regard, studies on subpopulations of different ethnic origins living in the same area have been studied, e.g. Japanese Americans have a much lower risk of MS than white Americans living in the same area in California (Detels et al., 1977). Further, the Sámi people living in the northern part of the Scandinavian peninsula have a lower risk for MS than other populations living in the area (Gronlie et al., 2000). A difference in genetic predisposition has

been suggested although more limited access and utilization to health care could play a role as well.

Further information on: inclusion criteria, number of cases, prevalence dates and population size is found in Table 7 (nationwide studies) and 8 (regional studies).

Table 7 Nationwide studies on the prevalence of MS, from outside the Nordic countries

Country	First author	Publication year	Prevalence[a]	(95% CI)	Cases (n)	Population (N)	Prevalence date	Inclusion criteria[b,c]
Austria	Baumhackl	2002	98,5	NA[d]	7 982	8 078 400	1999	Poser: CD-MS
France	Fromont	2010	94,7	(94.3–95.1)	49 417	52 359 912	31.07.2004	NA[d]
Malta	Dean G	2002	16,7	NA[d]	63	378 500	01.01.1999	Poser: CD-MS, CP-MS
Moldova	Marcoci C	2016	20,9	(14.7–27.1)	747	3 559 541	31.12.2012	McDonald
New Zealand	Taylor	2010	72,4	NA[d]	2 917	4 027 950	07.03.2006	McDonald
San Marino	Caniglia-Tenaglia	2018	204,3	(158.4–259.5)	67	32 789	31.12.2014	Poser: CD-MS, CP-MS
South Korea	Kim	2010	3,6	(3.2–4.0)	1 681	47 041 434	31.12.2005	McDonald

[a]Prevalence, number of cases per 100 000 population. [b]CD-MS, Clinically definite MS; [c]CP-MS, Clinically probable MS; [d]NA, not available

Table 8 Non-nationwide studies on the prevalence of MS, from outside the Nordic countries

Country	Region	First author	Publication year	Prevalence[a]	(95% CI)	Cases (n)	Population	Prevalence date	Inclusion criteria[b,c,d,e]
Australia	Newcastle	Ribbons	2017	124,2	(106.3–142.5)	182	148 535	09.08.2011	Poser and McDonald
Borsnia Herzegovina	Western	Klupka-Sarić	2007	27	(20-34)	81	300 746	31.12.2003	McDonald
Canada	British Columbia	Kingwell	2015	179,9	(176.0–183.8)	8 546	4 384 310	01.07.2008	NA[f]
Germany	Erfurt ,Thüringen	Fasbender	2008	128	NA[f]	256	201 267	31.01.2006	Poser: CD-MS, CP-MS
Greece	Western	Papathanasopoulos	2008	119,6	NA[f]	780	652 108	31.12.2006	Poser: CD-MS and McDonald
Hungary	Csongrád County	Zsiros	2014	89,8	NA[f]	379	421 827	01.01.2013	Poser: CD-MS, McDonald and CIS
Iran	Isfahan province	Etemadifar	2011	73,3	(70.9–75.8)	3 522	4 804 458	31.12.2009	Poser: CD-MS and McDonald
Italy	Salerno	Iuliano	2008	71,6	(62.03–82.30)	186	259 681	31.12.2005	Poser and McDonald
Japan	Tokachi Province	Houzen	2008	13,1	(9.6–17.4)	47	358 439	31.03.2006	Poser: CD-MS, LSD-MS
Northern Ireland	Northeast region	Gray	2008	230	(207.0–255.4)	469	160 446	31.12.2004	Poser: CD-MS, LSD-MS, CP-MS, LSP-MS and McDonald
Poland	Swietokrzyskie Voivodeship	Brola	2016	115,7	(111.2–121.4)	1 462	1 263 176	31.12.2014	McDonald
Portugal	Lisbon	De Sá	2006	46,3	(29.5–63.2)	29	62 621	01.11.1998	Poser: CD-MS
Scotland	Aberdeen, Orkney and Shetland	Visser	2012	248	(229–269)	590	248 102	24.09.2004	Poser: CD-MS, LSD-MS, CP-MS, LSP-MS and McDonald
Slovenia	Gorski kotar-Kocevje region	Peterlin	2006	151,9	(123.2–187.4)	87	57 258	01.06.1999	Poser: CD-MS, LSD-MS
South Africa	KwaZulu Natal	Bhigjee	2007	0,22	(0.12–0.40)	12	5 316 060	31.12.2005	McDonald
Spain	Catalonia	Otero-Romero	2008	79,9	(66.3–95.6)	120	150 139	31.12.2008	McDonald
Switzerland	Canton of Berne	Beer	1994	110	NA[f]	1 016	920 000	01.01.1986	Poser: CD-MS, CP-MS
United Kingdom	Leeds	Ford	2002	108,7	(101.2–116.5)	792	728 840	31.10.1999	Poser
USA	Olmsted county	Mayr	2000	177	NA[f]	218	123 386	01.12.2000	Poser
Wales	South East	Hirst	2009	146	(135–158)	620	424 633	01.09.2005	Poser and McDonald
Yugoslavia	Belgrade	Pekmezovic	2001	41,5	(38.5–44.7)	823	1 602 226	31.12.1996	Poser: CD-MS, LSD-MS

[a]Prevalence, number of cases per 100 000 population. [b]CD-MS, Clinically definite MS; [c]LSD-MS, Laboratory-supported definite MS; [d]CP-MS, Clinically probable MS; [e]LSP-MS, Laboratory-supported probable MS; [f]NA, not available

1.4.1.3 Epidemiological studies on MS in the Nordic countries

1.4.1.4 Denmark

The Danish MS Registry was established in 1956 and was the first MS registry in the world. The first cases from 1956 were documented retrospectively but since then registration has been prospective. An informed consent from the patient is not required for data registration. The completeness in 1988 was estimated to be 91% which might have decreased somewhat with time (Koch-Henriksen et al., 2001).

Incidence. A study published in 2018 reported an increase in incidence from 5.4 in 1950 to 9.43 per 100 000 in 2009, based on 19 536 cases. During this long study period the following diagnostic criteria have been used at different points of time: Allison and Millar (onset <1994), Poser (onset 1994-2005) and MacDonald (onset >2005) (Koch-Henriksen et al., 2018).

Prevalence. The point prevalence was 173.3 per 100 000 in 2005 in a study including 9 377 patients with *clinically definite MS* CD-MS and *clinically probable MS* CP-MS (Bentzen et al., 2010).

1.4.1.5 Finland

Finland has a newly established MS registry starting documentation in the year 2014. By 2018, 15 out of 21 of Finland's public hospitals were connected to the registry. The coverage was estimated to be 80% in 2018. Informed consent of the patient is not required for data registration (Laakso et al., 2019).

Incidence. In a study based on three different regions in Finland the incidence of MS was 8.2–14.7 per 100 000 between 2001–10, based on 659 cases (Holmberg et al., 2013). Another regional study reported an incidence (2012–16) of 11.7 per 100 000 based on 211 cases in Southwest Finland (population 430 064) (Pirttisalo et al., 2019).

Prevalence. A point prevalence of 105 per 100 000 for 277 cases was reported for the year 2000 (Sarasoja et al., 2004). A more recent study showed a point prevalence from Southwest Finland of 280 per 100 000 for 1 184 cases (Pirttisalo et al., 2019).

1.4.1.6 Norway

Norway has had a nationwide MS registry since 2001. In 2015 there were approximately 6 000 patients registered (Myhr et al., 2015). According to a study from 2012 there were 10 121 prevalent cases of MS in Norway (Berg-Hansen et al., 2014). Based on these numbers the completeness of the Norwegian MS registry should be close to 60%.

Incidence. Studies from Norway have reported an incidence of MS in the range of 8.5–11.8 per 100 000. Grytten et al (2015) studied incidence in Norway during a similar time period as we did for Iceland (Study I). Grytten et al (2015) found the incidence in Hordaland county (2003–2007) to be 8.5 per 100 000 for 1 402 cases in a population of 441 660.

Prevalence. Although a number of studies have reported the regional prevalence of MS in Norway the only nationwide study to date is by Berg-Hansen et al. (2014). There, the estimated prevalence in 2012 was reported to be 203 per 100 000 for 10 121 patients in a population of 4 985 870. Further information on epidemiological studies of MS in Norway is provided in table 9 and 10.

Table 9 Publications on MS incidence in the Nordic countries

Country/ region	First author	Year of publication	Incidence[a] (CI 95%)	Cases (n)	Population (n)	Time period	Inclusion criteria[b,c,d]
Denmark	Koch-Henriksen	2018	9.4 (5.60–9.69)	19 536	5 700 000	2000–2009	McDonald
Faroe Islands	Joensen	2010	2.4 (2.1–3.3)	6	48 014	2003–2007	Poser and MacDonald
Finland	Holmberg	2013				2001–2010	Poser CD-MS and LSD-MS
Pirkanmaa			8.2 (7.3–9.1)	298	485 911		
Seinäjoki			14.7 (12.7–16.7)	218	198 469		
Vaasa			11.7 (9.8–13.6)	143	166 250		
Finland	Pirttisalo	2019				2012–2016	Poser CD-MS
North Karlia			7.8 (6.4–11.2)	49	151 707		
Southwest Finland			11.7 (10.5–13.8)	211	430 064		
Norway							
Nordland	Benjaminsen	2014	10.1 (8.36-12.98)	119	235 779	2005–2009	Poser and MacDonald
Buskerud	Simonsen	2017	11.8 (10.6–13.1)	582	272 228	2003–2013	McDonald
Hordaland	Grytten	2015	8.5 (7.3–9.7)	1 402	441 660	2003–2007	Poser CD-MS CP-MS <2003, McDonalds >2003
Sweden	Ahlgren	2014	10.2 NA[e]	7 361	9 054 658	2001–2008	Poser and McDonald

Table 10 Publications on MS prevalence in the Nordic countries

Country/ region	Author	Year of publication	Prevalence[a] (95%CI)	Cases (n)	Population (n)	Prevalence date	Inclusion criteria[b,c,d]
Denmark	Bentzen	2010	173.3 (169.9–176.7)	9 377	5 410 000	01.01.2005	Poser CD-MS and CP-MS
Finland	Pirttisalo	2019					
North Karlia			168 (148-190)	253	151 707	31.12.2016	Poser CD-MS
Southwest Finland			280 (264–296)	1 184	430 064	31.12.2016	Poser CD-MS
Finland	Sarasoja	2004					
Central Finland			105 (93–118)	277	263 886	31.12.2000	Poser CD-MS and LSD-MS
Norway	Berg-Hansen	2014	203 (199–207)	10 121	4 985 870	01.01.2012	Poser and McDonald
Sweden	Ahlgren	2011	188.9 (186.1–191.7)	7 361	9 256 347	31.12.2008	Poser and McDonald

[a]Prevalence, number of cases per 100 000 population. [b]CD-MS, Clinically definite MS; [c]LSD-MS, Laboratory-supported definite MS; [d]CP-MS, Clinically probable MS

1.4.1.7 Sweden

The national Swedish MS registry was established in 1996. All healthcare units in Sweden caring for patients with MS contribute to the registry. The registry was estimated to include 80% of all MS patients in the country in 2015. Informed consent from the patient is required for data to be registered (Hillert & Stawiarz, 2015). Two nationwide studies have been conducted in Sweden both based on the Swedish MS registry.

Incidence. A study from 2014 reported an incidence (2001–07) of 10.2 per 100 000 for 7 361 patients (population of 9 256 347) (Ahlgren et al., 2014).

Prevalence. A nationwide study found a point prevalence (2008) of 189 per 100 000 based on 17 485 cases (Ahlgren et al., 2011).

1.4.1.8 Iceland

Currently, there is no nationwide MS database in Iceland.

Incidence. Sveinbjörnsdóttir et al. (2014) reported an increase in incidence from 2.6 for the years 1950–59 (41 cases) to 5.1 for the years 1990–1999 (136 cases). Inclusion criteria were a diagnosis of either Poser CD-MS or CP-MS.

Prevalence was 123/100 000 in 2000 according to the previously mentioned study by Sveinbjörnsdóttir et al. (2014), based on 345 patients.

There have been several previous studies on the incidence and prevalence of MS in Iceland. Table 11 gives and overview of their main characteristics and results (Benedikz et al., 1994; Benedikz et al., 2002; Gudmundsson, 1971; Gudmundsson et al., 1974; Gudmundsson & Gudmundsson, 1962; Sveinbjornsdottir et al., 2014).

Table 11 Previous publications on the epidemiology of MS in Iceland

		Incidence			Prevalence			
First author	**Year of publication**	**Incidence[a]**	**Cases (n)**	**Time period**	**Prevalence[b]**	**Cases (n)**	**Prevalence date**	**Inclusion criteria**
Guðmundsson	1962	3.1	44	1946–1955	38.4	51	31.12.1945	Schumacher
Guðmundsson	1971	5.3	44	1946–1955	45.8	66	31.12.1950	Schumacher
Guðmundsson	1974	3.4	34	1956–1965	52.3	101	31.12.1965	Schumacher
Benedikz	1994	3.5–4.5	252	1975–1990	100	323	31.12.1989	Poser
Benedikz	2002	5.3	319	1986–1990	58	NA[e]	31.12.1959	Poser
					119	NA[e]	31.12.1999	
Sveinbjörnsdóttir	2014	2.6	41	1950–1959	123	345	01.01.2000	Poser, CD-MS[c], CP-MS[d]
		5.1	136	1990–1999				

[a]Incidence, number of cases per 100 000 population per year; [b]Prevalence, number of cases per 100 000 population; [c]CD-MS, Clinically definite MS; [d]CP-MS, Clinically probable MS; [e]NA, not available

1.4.2 Changing incidence in Western countries over time?

A review article from 2010 by Koch-Henriksen and Sørensen (2010) found a correlation between time and incidence. Most of the studies that the analysis was based on included patients diagnosed 1950–2000. To the contrary, a systematic review by Alonso and Hernán (2008) found no association between study year and the incidence of MS after adjusting for latitude. More recently published studies continue to give conflicting results. Nevertheless, it seems when comparing incidence data from between 1950–1970 to more recent data that there has been an increase in the incidence of MS (Grytten et al., 2016; Koch-Henriksen et al., 2018; Ribbons et al., 2017). The study by Koch-Henriksen (2018) is a nationwide population-based study from Denmark that found that the incidence had increased from 5.91 in 1950–1959 to 12.33 in 2000–2009. Whether there has been a change in incidence in the past three decades in Western countries is less clear. Studies from this period cover a varying span of years. Some have found an increase in incidence (Koch-Henriksen et al., 2018; Simonsen et al., 2017) while others have found no difference (Ahlgren et al., 2014; Grytten et al., 2016; Kingwell et al., 2015; Marrie et al., 2013). A study from the UK even found a trend towards decreasing incidence between 1990 and 2010 (Mackenzie et al., 2014). Whether Western countries have reached a balance in incidence, reflecting a balance in the risk of acquiring MS as well as diagnostic activity amongst other factors, remains to be seen in future studies.

1.4.3 Latitudinal gradient

The so-called *latitudinal gradient* implies that the frequency of MS is lowest among populations living close to the Earth's equator, increasing with distance (higher latitude) from the equator. Such an association was noted as early as during the 1920s (Davenport,1922). The latitudinal gradient is also known as the *north-south gradient* when referring to the northern hemisphere. Over the years, the latitudinal gradient has been the topic of numerous studies. The existence of a latitudinal gradient for prevalence is fairly well established, with a recent meta-analysis showing an increase in prevalence of 3.64/100 000 for every degree of latitude, after adjusting for ascertainment methods and age (Simpson et al., 2019). The existence of a latitudinal gradient for incidence is more controversial. In fact, a meta-analysis by Koch-Henriksen and Sörensen (2010) found no effect of latitude on the incidence of MS in Western Europe or North America, even when older epidemiological data before 1980 was analyzed separately. The results of more recent studies continue to be inconsistent. In studies from both

Ireland (O'Connell et al., 2017) and Scotland a latitudinal gradient was observed for incidence while such an association was not found in recent studies from Denmark (Bihrmann et al., 2018) and Brithish Columbia Canada (Rotstein et al., 2018). An advantage of studying the latidudinal gradient within countries is that occurrence of others risk factors for MS would be expected to be more even than when including data from multiple countries. The disadvantage is that most countries span only a narrow latitudinal band, reducing the ability to detect any such effect. In any case, the theory of the latitudinal gradient has stimulated further research including the role of ultraviolet radiation (UVR), vitamin D and month of birth on the development of MS.

1.4.4 Gender

MS is more common among women than men. In recently published studies the sex ratio (female-to-male) of incidence has been in the range of 1.4–3.4 (Etemadifar & Maghzi, 2011; Fasbender & Kolmel, 2008; Kearns et al., 2019; Otero-Romero et al., 2013). Numerous studies have investigated temporal trends of the sex ratio. A few studies found no change in sex ratio with time, including an Icelandic study reporting a stable ratio of approximately 2.6:1 between 1950–2000 (Sveinbjornsdottir et al., 2014). Other studies reporting stable sex ratios are from Tasmania, Australia (Simpson et al., 2011), Trøndelag County, Norway (Dahl et al., 2004) and Møre and Romsdal (Midgard et al., 1996)), Sweden (Bostrom et al., 2013) and Olmsted County, Minnesota, USA (Mayr et al., 2003). Studies reporting a stable sex ratio and rise in incidence are from Italy (Granieri et al., 2007; Pugliatti et al., 2005). Nevertheless, most studies have found an increase in the sex ratio with time (Hirst et al., 2009; Koch-Henriksen & Sorensen, 2010; Orton et al., 2006; Westerlind, Bostrom, et al., 2014), often together with an increase in incidence (Hirst et al., 2009; Koch-Henriksen et al., 2018). In a Danish population based study, the incidence increased and the sex ratio increased from 1.3:1 for patients with onset in 1950–1959 to 2.0:1 for patients with onset in 2000-2009 (Koch-Henriksen et al., 2018). The increase remained unchanged when data were analyzed by birth year. The sex ratio was higher for younger age at onset, the F:M ratio was 2.3:1 for the age group 0–29 years and 1.7:1 for those with onset after 50 years of age. Orton et al. (2006) used a year of birth approach in their MS cohort to try to diminish the bias due to differences in time to diagnosis between genders. In Saskatoon, Canada the sex ratio had increased from 2.0–2.9 in the years 1970–2004 but the incidence remained stable (Hader & Yee, 2007). The increase for females, described predominantly in relapsing-remitting MS (RRMS), has

been linked to higher latitude (Celius & Smestad, 2009; Koch-Henriksen & Sorensen, 2010; Ramagopalan et al., 2010; Trojano et al., 2012).

1.4.5 Age

Analysis of age-specific incidence reveals that the incidence of MS peaks around 30–40 years of age and then gradually declines with advancing age. Onset of MS is rare after around 60 years of age (Koch-Henriksen et al., 2018). The mean age at clinical onset is around 35 years (Koch-Henriksen et al., 2018) and around 40 years for the diagnosis of MS being made (Kearns et al., 2019). The prevalence peaks in the 50–60 year age group (Mackenzie et al., 2014). High- and low-risk areas seem to have similar patterns of age distribution (Ahlgren et al., 2014; Heydarpour et al., 2015). No differences have been found in age distribution between urban and rural areas (Warren, 2001). A recent study from Denmark found that the highest relative increase of incidence over time was between 50–64 years, i.e., in the oldest age group studied (late-onset MS) (Koch-Henriksen et al., 2018).

1.4.6 Migration

The reported differences in MS distribution between geographical areas have prompted research into the effect of migration on the risk of MS. Studies on migration provide an opportunity to gain insights into the relative roles of genetic- versus environmental exposures. For example, individuals who migrate from a low-risk area to a high-risk area retain their genetic make-up for sure but are exposed to the potentially more risk-burdened environment of the new host country. In a systematic review from 1995 Gale & Martyn (1995) summarized the results of pioneering studies conducted in the preceding decades and concluded that individuals moving from low-risk areas, for example Asia and Africa, to high-risk areas, retained the low risk of their country of origin while individuals moving from high-risk areas to low-risk areas showed a decrease in disease rate. Methodological limitations of these early studies as well as changes in the occurrence of MS have warranted further studies on the topic, resulting in a number of publications in recent years. In contrast to the pioneering studies which focused more on migration from high-risk areas to low-risk areas, recent studies have focused more on migration from low-risk areas to high-risk areas.

Moving from low-risk to high-risk areas. Recent studies include three nationwide population-based studies, from Sweden (Ahlgren et al., 2012), Norway (Berg-Hansen et al., 2015) and Denmark (Munk Nielsen et al., 2019) as well as a regional study from Ottawa, Canada (Rotstein et al., 2019). All of

these are high-risk areas. First generation immigrants have generally been found to have a lower risk of MS compared to long-term residents. In the Danish study (Munk Nielsen et al., 2019), the relative risk of first-generation immigrants, compared to ethnic Danes, was associated with the risk ratio in their native country (RR): low-risk countries (0.21), intermediate-risk countries (0.43), and high-risk countries (0.75). These observations indirectly support the idea that first-generation immigrants retain the risk ratio of their native country to some extent, supporting the role of genetics. However, studies regarding the age at migration, indicate that the environment is of importance as well. It is commonly cited that individuals migrating before the age of 15 years have a risk ratio similar to that of the host population while those migrating after 15 years retain the risk ratio of their native country. Recent work from Canada and Denmark (Munk Nielsen et al., 2019; Rotstein et al., 2019) suggests that the risk of MS in first-generation immigrants in fact decreases gradually with age at immigration, even into adulthood. The Canadian study even found an increase in the risk of MS with increasing duration of stay, suggesting a dose-response relationship. A further support of the role of environment is based on the observation that in some groups of immigrants the risk of MS is higher in second generation-immigrants than in first-generation immigrants (Berg-Hansen et al., 2015; Munk Nielsen et al., 2019).

Limitations. The risk may have been underestimated in the country of origin because of differences in case ascertainment and access to health care. It is also important to remember that people who emigrate may not represent their native population since they are often younger than average and have better education (Gale & Martyn, 1995).

1.5 Risk factors

1.5.1 Multiple sclerosis and genetics

Different research methods have been utilized to assess the role of genetics in MS. Family studies are one type of methodology. Family studies have shown that approximately 3–5% of first degree relatives of MS patients also have MS (Sadovnick et al., 1996). Sibling risk is a useful parameter for describing aggregation in families. For full siblings the risk of MS has been found to be 3.5%, but 1.2% for half siblings (Sadovnick et al., 1996). The association is even stronger for monozygotic twins, with a concordance rate of 17–25% (Westerlind, Ramanujam, et al., 2014; Willer et al., 2003). Thus, the results of family studies support the idea that susceptibility to MS is at least in part genetic.

Comparison of ethnic groups also supports the role of genetics in the development of MS. For example, observational studies have found the Sami people, living in the northern part of the Scandinavian peninsula, have a lower incidence and prevalence of MS than other ethnic groups in the area (Harbo et al., 2007).

Currently, there is nothing to suggest that MS is caused by a single gene defect. Rather, MS is thought to be a multifactorial genetic disorder (Gourraud et al., 2012). Over 200 loci in the genome have been linked to a risk of MS (Andlauer et al., 2016). In Caucasians the strongest association has been found with the HLA class II compound on chromosome 6 (Gourraud et al., 2012). HLA DRB1*15:01 has the highest risk of MS, displaying an odds ratio (OR) of 3.08 (Sawcer et al., 2011). The best-described protective allele is the HLA A*02, with an OR of 0.67 (Link et al., 2012). The HLA compound plays an important role in the immune system's recognition of *self*- and *non-self-antigen*. A correlation has been found between early age at onset of MS and the presence of the HLA DRB1*15:01 allele (Gourraud et al., 2012). There is no association between HLA and gender, clinical course, disease severity, or month of birth (Gourraud et al., 2012). The HLADRB1*15:01 allele is present in approximately 15% of healthy individuals and in 35% of persons with MS (Link et al., 2012).

Thus, although it has been clearly established that susceptibility to MS is in part genetic it is generally believed that development of disease is most commonly the result of an interplay between genetic and environmental factors. Two Swedish epidemiology studies, EIMS (Epidemiological Investigation of Multiple Sclerosis) and GEMS (Genes and Environment in Multiple Sclerosis), have attempted to clarify the interaction of genetics and environmental risk factors by combining results of questionnaires and genetic studies. For example, when present in isolation, each of the following factors increases the risk of MS: high EBNA1 IgG antibodies (evidence of previous infection with Epstein-Barr virus, see section 1.5.3), presence of a HLA DRB1*15:01 allele or absence of the protective A*02 allele. When all factors are present simultaneously, the risk of MS increases synergistically leading to an OR of 16.0, compared to when none of these factors is present (Sundqvist et al., 2012). The same type of interaction has also been found between the same genetic factors and other environmental factors such as adolescent obesity (Hedstrom, Lima Bomfim, et al., 2014; Hedstrom et al., 2011) (see below, 1.5.4).

1.5.2 Multiple sclerosis and vitamin D

As mentioned previously a latitudinal gradient in MS occurrence has been postulated. A number of possible underlying explanations for this observation have been studied. Exposure to ultraviolet radiation (UVR) from sunlight decreases with more northern latitude and correlates with increased risk of MS (Bjornevik et al., 2014). The plausibility of this theory is based on the fact that UVR is required to metabolize vitamin D which has in turn been implicated in a number of processes in the immune system, the dysfunction of which might contribute to the pathogenesis of MS: Low vitamin D levels might reduce the tolerance of T cells to self-antigens (Smolders & Damoiseaux, 2011), influencing mechanisms responsible for protection and regeneration of myelin in the CNS (Wergeland et al., 2011), as well as reducing the ability of regulating over 80% of genes related to MS, including HLA DRB1*15:01 (Niino & Miyazaki, 2015). Studies have in fact found higher exposure to UVR to be an independent protective factor for MS later in life (Baarnhielm et al., 2012; Bjornevik et al., 2014; Lucas et al., 2011).

Studies with various methodologies have indicated an association between low levels of vitamin D and an increased risk of MS. Retrospective dietary studies have found that consumption of food rich in vitamin D, such as cod liver oil and fatty fish decreases the risk of MS (Baarnhielm et al., 2014; Cortese et al., 2015). Munger et al. (2004) prospectively collected dietary information from 187 000 women in the Nurses' Health Study and found that women in the highest quartile of vitamin D intake (at least 641 international units (IU) a day) had an incidence of MS that was approximately 1/3 of that for women in the lowest quartile. In a nested case-control study from 2006, Munger et al. (2006) prospectively evaluated the risk of MS based on the level of 25-hydroxyvitamin D in blood at baseline. A reduced risk of MS was found, with an OR of 0.59, for every 50-nmol/L increase in 25-hydroxyvitamin D level. A meta-analysis of 11 studies found that blood levels of 25 hydroxyvitamin D were significantly lower for the 1007 MS patients compared to 829 controls (Duan et al., 2014).

Mendelian randomization is a method that uses genetic predisposition for the independent variable to investigate its effect on the dependent variable. This method can correct for possible reverse association bias and confounding. Some Mendelian randomization studies have found a causal relationship between low vitamin D levels and MS using three single nucleotide polymorphisms (SNPs) known to be associated with a high vitamin D level in serum. The authors found an OR of 0.85 for MS in those with this genetic make-up compared with those without (Rhead et al., 2016).

1.5.3 Infections

Various aspects of infection have been suggested to affect the risk of developing MS, including both occurrence of infection and lack of exposure to infection, the latter generally referred to as the *hygiene hypothesis*.

As early as during the 1960s, an exposure to a higher level of sanitation in childhood was suggested as a risk factor for developing MS later in life (Poskanzer et al., 1963). The idea was that MS was caused by an unknown pathogen and that acquiring the infection during childhood involved less risk of developing MS than primary infection later in life. Thus, less hygiene would promote exposure to infection in early childhood resulting in a lower risk of developing MS later in life. These ideas are inherent to the *hygiene hypothesis*, a term originating from a publication on hay fever by Strachan (1989), published in 1989. The hygiene hypothesis has gradually been extended to encompass autoimmune diseases in general. Nevertheless, it is currently unclear how relevant the hygiene hypothesis is for MS. Some observations have been in support such as a negative correlation between an infection with *Helicobacter pylori* and the risk of MS as well as an observed protective role of helminth infection. Results from studies of other factors such as the number of siblings and attendance to daycare have been inconsistent (Wendel-Haga & Celius, 2017).

Over the years, numerous pathogens have been suggested to play a role in the pathogenesis of MS as reviewed by Andersen (2017). Some of the suggested pathogens are no longer thought to be of relevance, such as slow virus disease. A series of pioneering experiments on slow virus disease were done in sheep in Iceland in the late 1950s.

A number of pathogens are still considered of potential importance but the data on the role of some of these is currently equivocal including for: human herpes virus 6, cytomegalovirus and herpes simplex virus (Waubant et al., 2019). However, it is clear that an infection with Epstein-Barr virus (Frerot et al.) will increase the risk of MS. In an umbrella review of systematic reviews and meta-analysis on the risk factors of MS, Belbasis and associates (2015) concluded that three risk factors had the strongest consistent evidence of association. One of these was smoking but the other two were related to EBV: a history of infectious mononucleosis and being seropositive for anti-EBNA IgG. Furthermore, the level of anti-EBNA1 has been found to be higher in MS patients than controls (Sundstrom et al., 2004). Virtually all patients with MS have evidence of previous EBV infection when two independent methods are used to assess seropositivity. On the other hand, the risk of

developing MS for individuals without serological evidence of EBV is very small (Pakpoor et al., 2013). In a nested case-control study by Levin et al. some individuals were at base line free of both MS and negative for EBNA1. Those who were later diagnosed with MS had all developed antibodies to EBNA1 (evidence of EBV infection) prior to the MS diagnosis while none of the patients that remained EBV negative developed MS (Levin et al., 2010).

1.5.4 Smoking

Smoking is a strong risk factor for MS. A systematic review and meta-analysis of risk factors for MS from 2016 found smoking to have an OR of 1.51 in MS patients (Belbasis et al., 2015). Even passive smoking increases the risk of MS (Hedstrom, Lima Bomfim, et al., 2014). Further, there is a dose-response relationship between smoking and the risk of MS (Poorolajal et al., 2017). The risk of MS will decrease steadily after cessation of smoking, eventually reaching baseline after 10 years (Hedstrom et al., 2013). The interaction between smoking and haplotypes has been studied. In a study by Hedstrom et al. (2011) the overall odds ratios for MS were: 1.6 for smoking, 3.5 if the HLA DRB1*15:01 allele was present and 1.7 in the absence of the protective HLA A*02 allele. A synergistic effect was observed when all factors were present simultaneously with an OR of 13.5. Disproportionate changes in smoking habits amongst men and women over the years have been suggested as an explanation for the observed temporal increases in the female-to-male ratio of MS (Amato et al., 2017).

Smoking has even been shown to aggravate the clinical course of MS and increase mortality (Manouchehrinia et al., 2013). A partial explanation might be that smoking has been associated with the induction of neutralizing antibodies against disease modifying drugs (DMD), such as natalizumab (Hedstrom, Alfredsson, et al., 2014) and interferon β (Hedstrom, Ryner, et al., 2014).

In contrast to smoking, oral tobacco has been shown to have a protective effect against MS with an OR of 0.3 (Hedstrom et al., 2009). A potential explanation is the anti-inflammatory effect of nicotine observed in animal models (Nizri et al., 2009).

1.5.5 Adolescence obesity

Obesity in adolescence has been associated with an increased risk of MS later in life. The highest ORs are seen for BMI>27 (Hedstrom, Lima Bomfim, et al., 2014; Wesnes et al., 2015). Mendelian randomization studies have also indicated obesity in adolescence as a risk factor for MS (Gianfrancesco

et al., 2014). An unfavorable synergistic interaction between adolescent obesity and DRB*15:01 positivity and HLA*A 02 negativity has been observed (Hedstrom, Lima Bomfim, et al., 2014; Hedstrom et al., 2015). In addition, obesity has been shown to have a negative effect on the prognosis of MS. Obese patients have a reduced response to interferon beta-1b (Kvistad et al., 2015), more numerous T1 lesion on MRI (Kappus et al., 2016) and higher EDSS (Expanded Disability Status Scale) scores (Tettey et al., 2016).

1.5.6 Month of birth and the risk of developing MS later in life

The first epidemiological studies on the effect of month of birth (MOB) on the risk of developing MS later in life, date back to the 1980s, found (Watad et al., 2016) that individuals that are born in the spring time (April and May) are overrepresented amongst MS patients. On the other hand, individuals born in the autumn (October and November) had a lower risk of developing MS later in life. Some subsequent studies, some of which are population-based, have been in agreement with this (Table 8).

1.5.6.1 UV exposure and vitamin D in pregnancy

The risk of developing MS based on season of birth year has been explained by UV radiation and vitamin D during the pregnancy, with lower levels in mothers giving birth to their offspring born in the spring time (Nielsen et al., 2017).

The offspring of women with low vitamin D levels during the first trimester of pregnancy showed a twofold increase in the risk of developing MS later in life (Munger et al., 2016). Studies from Australia report increased MS risk among the offspring of women who reported low sun exposure during the first trimester (Staples et al., 2010). This has been considered a possible explanation for the association between birth in spring and increased risk of MS later in life. A study of 25(OH) vitamin D levels in newborns found that lower levels of 25-hydroxyvitamin D increased the risk of MS (Nielsen et al., 2017). In contrast, an earlier study from Sweden found no association between 25-hydroxyvitamin D level at birth and the risk of MS (Ueda et al., 2014).

1.5.6.2 Month of birth and MS risk later in life

A number of studies have found an effect of birth month on the risk for MS later in life. A population based study from Scotland (n=1 309) showed that there were 17% more MS births in spring, and 13 % fewer in the autumn,

compared to the general population (Bayes et al., 2010). Findings of studies from the Nordic countries have found similar effects (Grytten et al., 2013; Saastamoinen et al., 2012; Salzer et al., 2010).

A study from Italy (n=810) showed more MS births in the spring compared to the general population (Sotgiu et al., 2006) and a study from Poland showed fewer MS births in September and December but no increase in the spring (Dobrakowski et al., 2017). Other studies have not found any effect of month or season of birth on the risk of developing MS (Barros et al., 2013).

A meta-analysis from 2013 found significantly fewer observed MS births in October and November than expected (Observed/Expected=0.95 p=0.04 and 0.92 p=0.01) and more MS births than expected in April (Observed/Expected=1.05, p=0.05) (Dobson et al., 2013). There was also a significant effect between observed/expected MS births in December and latitude, i.e., the effect of MOB was not present at lower latitudes. This has even been described in Norway (Grytten et al., 2013).

1.5.6.3 Possible confounding factors in MOB studies

In 2013 Fiddes et al. (2013) suggested that the alleged effect of MOB on MS risk later in life was due to a confounding effect . The study showed how the distribution of birth months varies in the general population with year and location. Most prior studies had compared MOB in MS patients to the average proportion of births in a particular month over the whole study period, sometime stretching over 10–20 years, irrespective of place of birth, thus assuming homogeneity in time and geography that according to the results of Fiddes at al studies is not true (Fiddes et al., 2013; Fiddes et al., 2014). A study from Norway adjusted the analysis for the potentially confounding effect of year of birth and place of birth, but still found a significant increase in MS risk for individuals born in April (Torkildsen et al., 2014). Table 12 shows MOB studies specifying whether correction has been made by birth year and birth place.

Table 12 Overview of studies on the effect of season or month of birth, on the risk of developing MS later in life, with adjustment for either birth year and/or birth place

Publication year	First author	Country	Birth year of cases	Cases (n)	Controls (n)	Main findings, effect on risk of developing MS: Birth in spring	Birth in autumn
Adjusted for birth year only							
2012	Grytten	Norway	1930–1979	6 649	2 899 260	Increased	Decrased
2012	Saastamoinen	Finland	1900–1988	8 739	7 014 435	Increased	Decreased
2015	Sidhom	Tunisia	1948-2008	1 912	11 615 912	Increased	No effect
2017	Dobrakowski	Poland	1962–1986	2 574	NA[a]	No effect	Decresed
2018	Koch-Henriksen	Denmark	1925–1994	19 536	5 700 000	No effect	No effect
2019	Walleczek	Austria	1940–2010	7 886	7 256 545	No effect	No effect
Adjusted for birth place only							
2010	Bayes	Scotland	1922–1992	1 309	6 198 352	Increased	Decreased
2010	Staples	Australia	1920–1950	1 524	2 468 779	NA[a]	Increased
2013	Barros	Portugal	1992–1943	421	1 150 362	No effect	No effect
2015	Akhtar	Kuwait	1950–2013	1 035	3 454 222	No effect	Increased
Adjusted for both birth year and birth place							
2013	Fragoso	South America[b]	NA[a]	1 207	1 207	No effect	No effect
2014	Torkildsen	Norway	1930–1979	6 649	2 899 260	No effect	No effect
2016	Cruz	UK	1938–1980	21 138	21 138	Increased	Decreased
2017	Elíasdóttir	Sweden	1940–1996	12 020	3 503 550	No effect	No effect

[a]NA, not available; [b]Argentina, Brazil, Chile and Peru

1.6 Mortality

Mortality is a robust and well-defined outcome parameter. *Mortality rate*, is a commonly used measure of mortality, and is defined as the number of deaths per unit of time, divided by the population at risk. Mortality rate is referred to as crude mortality rate (CMR) when all causes of death are included, as opposed to disease-specific mortality.

Different methods can be used to present and analyze mortality data, each with its own inherent strengths and weaknesses (Scalfari et al., 2013). One comprehendible way is to present the difference in time between death and various events such as birth, onset of disease or diagnosis. Another way is to present the difference in mean age at death between cases and a reference group, such as the general population, giving more weight to deaths in young people. Although easily comprehendible, these methods do not take into account the fact that the mortality of MS patients is dependent on the mortality in the general population, which can differ between countries as well as time periods. Therefore, other methods such as the standard

mortality ratio (SMR) are favored when feasible. The SMR is defined as the number of observed deaths divided by the expected deaths. Expected deaths is the theoretical number of deaths in the patient group, if they were subject to the same mortality as the general population, by age, gender or other factors of interest. An analogous method is the *excess mortality rate* (EMR), the difference between the expected and observed mortality. Amongst other methods that can be applied are Kaplan-Meier curves, although they only allow for analysis of categorical variables (Scalfari et al., 2013). Cox analysis allows for the analysis of multiple explanatory variables, but is limited by the proportional hazards assumption.

1.6.1 Mortality from MS

The mean age at death of MS patients was around 60 years in most of the studies included in a systematic review from 2013 (Scalfari et al., 2013) with the exception of a Canadian study with a mean age at death of 76.7 years (Kingwell et al., 2012). In Denmark, the mean time of survival from birth was 69.1 years (general population, 80.2 years) and 74.7 years in Norway (general population, 81.8 years) (Koch-Henriksen et al., 2017; Lunde et al., 2017). Reported mean survival from onset by location is (years): South Wales (38), British Colombia, Canada (47.5) and Italy, Sicily (20.6) (Hirst et al., 2008; Kingwell et al., 2012; Ragonese et al., 2010). In Denmark the median survival from onset was 35.0 years as compared to 49.1 in the general population, matched for age. Further, the Danish study found that the age at death had increased from 50.6 years in 1950–1959 to 65.4 in 2000–2009 (Koch-Henriksen et al., 2017).

1.6.2 Standardized mortality ratio (SMR)

A meta-analysis from 2016 (Manouchehrinia et al., 2016) found the pooled all-cause SMR in MS to be 2.56. The analysis included data from the UK, Spain, Canada, France, Italy, Denmark, Norway and Finland. An overview of recently published studies reporting SMR is provided in table 13. The previously mentioned meta-analysis did not find evidence of a change in SMR over the time period covered by the studies included (1949–2012). Nevertheless, some later studies have found a decrease in mortality of MS patients over time (Burkill et al., 2017; Koch-Henriksen et al., 2017; Lunde et al., 2017; Rotstein et al., 2018).

Table 13 Overview of population-based studies reporting SMR (standardized morality ratio)

Country	Region	First author	Publication year	Time period of diagnosis	End of follow-up	Patients (n)	Deaths (n)	SMR[a]				
								Over-all	Females	Males	RRMS[b]	PPMS[c]
Canada	British Columbia	Kingwell	2012	1980–2004	2007	6 917	1 025	2.89	3.01	2.68	2.9	2.9
Denmark	Nationwide	Koch-Henriksen	2017	1950–1999	2015	18 847	6 102	2.4	2.5	2.36		
Finland	Nationwide	Sumelahti	2010	1971–2006	2006	1 595	464	2.8	3.4	2.2		
France	Nationwide	Foulon	2017	2013	2013	78 805	1 080	2.56	2.55	2.58		
Hungary	Csongrád county	Sandi	2016	1993–2013	2013	740	121	2.52	2.57	2.46	2.3	4.1
Norway	Hordaland	Lunde	2017	1953–2012	2012	1 388	291	2.7	2.9	2.5	2.4	3.9
Norway	Oslo	Smestad	2009	1971–2005	2006	386	263	2.47	2.94	2.02		
Spain	Bizkaia, Basque Country	Zarranz	2014	1987–2011	2011	1 283	89	2.78	2.73	3.26		
Wales	South East	Hirst	2008	1985–2006	2006	379	221	2.79	3.14	2.26		

[a]SMR, Standardized mortality ratio; [b]RRMS, Relapsing-remitting MS; [c]PPMS, Primary progressive MS;

1.6.3 Changes in mortality over time

When interpreting and comparing studies on mortality from MS the study period needs to be noted as a decrease of mortality over time has been suggested although the evidence is not entirely unequivocal. A meta-analysis from 2016 found no temporal changes in SMR over time (Manouchehrinia et al., 2016). However, a nationwide population based study from Denmark found SMR to have decreased from 4.48 in 1950–1959 to 1.80 in 1990–1999. Further support for a decrease in mortality over time came from a nationwide population based study from Sweden (Burkill et al., 2017) and a population-based study from Ontario, Canada (Rotstein et al., 2018).

There are a number of potential explanations for a decrease in mortality with time, including possible changes in both case mix and the introduction of new treatments. A proportional increase in the identification of more benign cases might have occurred over time. For instance, more subtle symptoms, such as transient sensory symptoms, might not have led to a diagnosis of MS as commonly in the past. A higher proportion of more benign cases would presumably lead to a better outcome on a group level. In addition to indications of an improvement in mortality over time there are other indicators of improved outcome, for example a study using a multi-national MS database found that with time, the age of MS patients for reaching a certain EDSS score increased (Kister et al., 2012). The observed decrease in time from onset to diagnosis (Lunde et al., 2017), could be interpreted as indirect support for an increase in diagnostic activity. The decrease in time from onset to diagnosis can in itself cause information bias since there is a risk for a false impression of improved survival or outcome due to the fact that the disease is detected at an earlier stage (Dos Santos Silva, 1999).

Improvement in mortality over time might also be influenced by advances in available treatments. The long-term outcome of disease modifying

treatments will continue to be unraveled in the coming years but a pioneer study by Goodin et al. (2012) found a lower mortality in the group treated with interferon β compared to a placebo group after 21 years of follow-up. Further, a recent study from Denmark found that patients who started treatment within 2 years of onset reached an EDSS score of 6 later and had lower mortality compared to patients that received treatment more than 2 years after onset, although the difference in mortality was not statistically significant (Chalmer et al., 2018). Nevertheless, in a different study, the same group noted that SMR began to decrease years before a wider array of treatment options became available and a more aggressive approach towards treatment was adopted (Koch-Henriksen et al., 2017). Other treatments have improved as well, for example those for dysphagia and cough resulting from immobility. In any case, improved treatments have led to optimism and more emphasis on early diagnosis, to some degree fueling an increase in diagnostic activity.

1.6.4 Gender and mortality

Results of studies on the effect of gender on mortality have been contradictory. Some studies have found the SMR for women to be higher than for men, as for example the previously mentioned meta-analysis from 2016 and a recent study from Norway (Lunde et al., 2017; Manouchehrinia et al., 2016). In contrast, in a large study from Denmark, there was no statistically significant difference in SMR between men and women (Koch-Henriksen et al., 2017).

1.6.5 Clinical phenotype and mortality

There are four main clinical phenotypes of MS: *Relapsing-remitting MS* (RRMS), *secondary progressive MS* (SPMS), *Primary progressive MS* (PPMS) and *Progressive relapsing MS* (PRMS). About 90% of all patients with MS have the RRMS phenotype, characterized by recurrent episodes of neurological symptoms (exacerbations) that either go completely into remission or give rise to residual symptoms, with disability gradually accumulating with repeated exacerbations. Without treatment, up to 70–90% of patients with RRMS convert to so-called *secondary progressive MS* (SPMS), on average 20-30 years after diagnosis (Weinshenker et al., 1989). For 10–15% of MS patients the course is slowly progressive from onset and this clinical course is designated PPMS. Compared to patients with RRMS, those with PPMS have: fewer lesions on MRI that are usually not Gadolinium enhancing (Ingle et al., 2002), higher age at onset (43.6 compared to 36 years) (Westerlind et al., 2016), a faster progress of disability (Harding et al., 2015) and higher mortality (Kingwell et al., 2012). Additional differences are

that the proportion of women is higher for RRMS and the gender distribution is more even for PPMS (Tremlett et al., 2005; Westerlind et al., 2016).

Mortality has been found to be associated with phenotype. A study from Norway found a significantly longer life expectancy for patients with RRMS compared to PPMS (77.8 compared to 71.4 years, respectively) and a significantly lower SMR (2.4 in RRMS compared to 3.9 in PPMS) (Lunde et al., 2017). A study from Hungary also found a shorter duration of time from onset to death for patients with PPMS (14 years) compared to those with RRMS (35 years) (Sandi et al., 2016).

1.6.6 Mortality and: Presenting symptoms, EDSS and Treatment

The symptoms and clinical course of MS varies substantially. In line with the development of new and more effective DMDs for MS, diagnostic criteria have evolved becoming more objective and sensitive without losing specificity (Polman et al., 2011). Diagnostic criteria rely on MRI results and to some extent also on the detection of signs of inflammation in the cerebrospinal fluid (Thompson et al., 2018). The time from presenting symptoms to diagnosis has decreased (Benedikz et al., 2002; Dahl et al., 2004).

The effect of presenting symptoms on survival has been studied with conflicting results. A Norwegian study found that the presence of brainstem- and cerebellar symptoms at onset improved survival compared to patients with motor symptoms (Smestad et al., 2009) while other studies have found the presence of cerebellar symptoms to reduce survival (Phadke, 1987). In a study from Denmark, mortality was higher for patients with pyramidal, cerebellar or sphincter symptoms at onset compared to those with optic, sensory or brainstem symptoms (EMR 14.75 compared to 8.6, respectively) (Koch-Henriksen et al., 2017). Other studies have not found any association between presenting symptoms and survival (Leray et al., 2007).

Although a robust and well-defined outcome parameter, mortality is troublesome to use in clinical research. Compared to different measures of disability that are more commonly used, mortality necessitates longer follow-up periods and a higher number of patients (van Munster & Uitdehaag, 2017). Nevertheless, clinical studies that use mortality as an outcome parameter exist. In a long-term follow-up of a trial comparing treatment with interferon-β1b and placebo, Goodin et al. (2012) found a lower mortality in the treatment group compared to the placebo group after 21 years of follow-up (hazard ratio 0.5, p=0.017). In contrast, a study from Spain found no

difference in time from onset to death between patients treated with disease-modifying drugs and those receiving no treatment (Rodriguez-Antiguedad Zarranz et al., 2014)..

1.6.6.1 Expanded disability status scale EDSS

The Expanded Disability Status Scale (EDSS) is the most widely used instrument to assess disability in MS. The EDSS consist of an ordinal scale, with scores ranging from 0–10 (Kurtzke, 1983). A score of 0 on the EDSS scale illustrates no impairment while 10 corresponds to death. The scale is based on neurological examination. Categories are based on the evaluation of several different functional systems (FS): vision, brainstem, sensory, strength, cerebellum, cognition, and bowel/bladder. The scale is non-linear. Categories 0–3.5 center mostly on FS while categories 4–6 address walking distance. Categories 6.5 and above focus on the patient's independence of ambulation (need of assistance, cane or wheelchair). A commonly used definition of a clinically meaningful change is 1.0 for baseline scores between 1 and 5.5 but 0.5 for higher baseline scores (van Munster & Uitdehaag, 2017). Higher EDSS scores correlate with increased risk of mortality (Rodriguez-Antiguedad Zarranz et al., 2014)

1.6.7 Cause of death (COD)

While it seems fairly clear from the literature that mortality is higher amongst patients with MS compared to the general population, less is known about the reasons for the observed difference. Studies on the cause of death have however, advanced our knowledge. Information on the cause of death of MS patients is most commonly based on death certificates. According to the definition by Kurtzke (Kurtzke, 1983), a death due do to MS is:

> "an acute death due to brainstem involvement or to respiratory failure or death as a consequence to the chronic bedridden state with terminal pneumonia, sepsis, uremia, cardiorespiratory failure"

In light of this rather narrow definition of death due to MS, MS would be expected to rarely be the immediate cause of death. Rather, death would be expected to be secondary to complications of disability and immobility, with MS being the underlying cause. Most studies based on death certificates have found that 50% or more of deaths were attributed to MS as the underlying cause (Kingwell et al., 2019). For example, in a Norwegian study from 2017 (Lunde et al., 2017) the distribution of causes of death was as follows (%): MS (56.4), cardiovascular disease (14.8), cancer (14.1), respiratory causes and infection (3.8) and accidents and suicide (4.5).

In an attempt to acquire further knowledge about the circumstances leading to death, antecedent and immediate causes of death can be included in the analysis in addition to the underlying cause (multi-cause-of death mortality data). Unfortunately, errors in documentation of cause of death are common, potentially affecting mortality statistics (McGivern et al., 2017). Although informative in its own right, data on the distribution of causes of death in MS patients does not relate to the frequency of the particular cause of death in the general population. For that purpose, disease-specific SMRs are useful. A meta-analysis from 2016 found that, compared to the general population, MS patients had a significantly higher mortality for (SMR): cardiovascular disease (1.29), suicide (2.13) as well as for infection and respiratory disease (2.91). These results are in line with two recent population-based studies from Sweden and British Columbia, Canada, including both underlying causes as well as contributory causes of death (Burkill et al., 2017; Kingwell et al., 2019). Results of studies on the risk of death from cancer in MS patients compared to the general population have been conflicting. A meta-analysis from 2010 (Handel & Ramagopalan, 2010) found a decreased risk while a meta-analysis from 2016 (Manouchehrinia et al., 2016) found no difference. In more recent work from Norway, Lunde et al. found an increased risk (2017) while Kingwell et al. (2019) in a study from British Columbia, Canada, found no difference.

2 Aims of the study

In Iceland, circumstances are in many ways favorable for conducting nationwide population-based epidemiological studies. The population is relatively homogenous with well studied genetics (Gudbjartsson et al., 2015). The health care system is of a good standard and accessible to the whole population. A nationwide registry of MS patients has not been established but every resident is assigned a unique national identification number which greatly facilitates tracing of data, for example in different databases administered by hospitals, other health care facilities and other authorities.

This thesis is based on four studies on the epidemiology of MS that are in turn based on national-wide population-based data from Iceland. The overall aims are summarized as follows:

Study I Assess the incidence, and describe the clinical characteristics, of MS in Iceland, during a 5-year period (2002–2007).

Study II Determine the point prevalence of MS in Iceland on the 31st of December 2007.

Study III Evaluate the effect of season and month of birth on the risk of developing MS later in life, with particular emphasis on controlling for the potentially confounding effect of birth year and birth place. In addition to data from Iceland, this study included data on a Swedish cohort as well.

Study IV To compare the mortality of patients with MS to the mortality in the general population, as well as to determine causes of death.

3 Patients and methods

Iceland is an island in the North Atlantic Ocean, between latitudes 64 and 66°N. According to the Icelandic met office (2007) the mean annual temperature in the capital Reykjavík was 5.5°C. Approximately 62% of the Icelandic population live in the capital or nearby communities.

The Icelandic healthcare system is easily accessible to all residents and mostly governmentally funded. The only neurology department in Iceland is, located at the *National University Hospital of Iceland (Landspítali)* in Reykjavík. There are five radiology units equipped with MRI scanners. During the study period from 2002–2007 there were, on average, 17 neurologists practicing in the country, or approximately 52 neurologists per one million inhabitants.

3.1 Patients

3.1.1 Study I

The incidence cohort included patients diagnosed with MS in the years 2002–2007, meeting the Poser criteria for *clinically definite* (CD-MS) and *primary progressive MS* (PPMS) (Poser et al., 1983) for the primary analysis. The diagnosis of all incident cases was made by a neurologist, with a number of patients being evaluated by more than one neurologist. The time point of diagnosis was recorded as when the second observed attack occurred or when Posers criteria for PPMS (progression of neurological symptoms that increased over at least 6 months, evidence of one lesion combined with another clinical or paraclinical lesion and *Oligoclonal bands* (OCB) or IgG production in the *Cerebrospinal fluid* (CSF)) were fulfilled. (Poser et al., 1983). Individuals who only had a single clinical attack (*clinically isolated syndrome* (CIS)) were not included in the study. In addition to the primary analysis an incidence calculation was done for an *extended group* that included patients with CD-MS, *laboratory-supported definite MS* (LSD-MS), *clinically probable MS* (CP-MS) and patients fulfilling the 2010 McDonald criteria (Polman et al., 2011).

3.1.2 Study II

The prevalence cohort included MS patients, residing in Iceland according to Registers Iceland, alive on the prevalence day, 31st of December 2007.

The included cases were diagnosed in the years 1946–2007 (n=526). All met at least one of the following criteria: (1) the 2010 McDonald criteria for *dissemination in space* (DIS) and *time* (DIT) (2) the Poser criteria for CD-MS, (3) LSD-MS, or (4) CP-MS; or (5) McDonalds 2010 criteria for primary progressive MS (progression of neurological symptoms that increased over at least 1 year, and 2 of 3; DIS, DIT or OCB/IgG production in the CSF) (Polman et al., 2011; Poser et al., 1983). These patients constituted the incident cases of the study. The diagnosis was made by a neurologist in all cases. The time of diagnosis was defined as when a second attack of MS occurred, or when the patient was informed of the diagnosis.

3.1.3 Study III

The study was based on nationwide population cohorts from Sweden and Iceland. All patients had CD-MS or CP-MS according to the Poser diagnostic criteria or MS according to the 2010 McDonalds criteria (Polman et al., 2011). In addition, patients with PPMS were included in the study.

3.1.3.1 The Swedish MS cohort

The cohort included MS patients born in Sweden between 1940–1996 (n=12 020). This period was chosen as information on place of birth is lacking for a significant number of patients born before 1940. Patients born after 1996 were not included because of the possibility that they might not have developed the disease at the time-point of data extraction.

3.1.3.2 The Icelandic MS cohort

The Icelandic cohort consisted of MS patients born in Iceland between 1981–1996 (n=108). A control group of people born in the same years was created based on data from *Statistics Iceland*. Patients born before 1981 were not included because information on the date of birth prior to 1981 was not available for the control group.

3.1.4 Study IV

Study IV was mainly based on the prevalence cohort from study II which is described in more detail in section 3.1.2. Mortality was also analyzed for the extended incidence group (n=222), diagnosed between 2002–2007, described in more detail in section 3.1.1. Follow-up was from the prevalence day for the prevalence cohort and from the date of diagnosis for the incidence cohort and lasted until 31st December 2018 or death, whichever occurred first.

3.2 Case ascertainment

3.2.1 The incidence cohort: Studies I and IV

MS cases were searched for and identified in a number of different type of sources including medical records and databases of: (1) The Department of Neurology at Landspítali- The National University Hospital of Iceland; (2) All privately practicing neurologists in Iceland; (3) Regional hospitals and (4) Rehabilitation centers. The following diagnosis codes for MS were used when applicable: ICD10 (G35,G37.9), ICD9 (340,341) and ICD8 (340,341). In addition, MS cases were searched for in results from: (5) VEP studies and (6) all MRI studies done in Iceland due to suspected demyelinating disease. Finally, (7) MS cases were searched for amongst all patients approved for DMDs by the special committee at Landspítali granting permission for such treatment. Many cases were found in more than one source. The results of diagnostic studies were reviewed to further support the diagnoses of the incident cases.

3.2.2 The Prevalence cohort: Studies II and IV

MS cases were identified the same way as noted above (1–7) but additionally information was gathered from the *Icelandic Social Insurance Administration* and *Icelandic Health Insurance*, identifying all residents in Iceland who received disability benefits due to MS between 1990–2007, and those applying for mobility aids between 1997–2007. We reviewed medical records to verify the diagnosis. The diagnoses searched for were: ICD10 (G35, G37.9), ICD9 (340,341) and ICD8 (340,341).

3.2.3 Study III

Sweden is situated in Northern Europe, between latitudes 55 and 69°N. The mean annual temperature is 6.4°C (*SMHI* 2011). In Sweden there are 16 neurology departments (with at least 4 neurologists employed) and 30 smaller units (with 1–3 neurologists employed) *(The Swedish Neurological Society* 2016). Sweden has approximately 34 neurologist per one million inhabitants (Remahl et al., 2012).

3.2.3.1 The Swedish registries

Information about the Swedish MS cohort was obtained from the *Swedish MS registry (SMSreg*) (see 1.4.1.7). Patients with MS according to the Poser (Poser et al., 1983) or McDonald criteria (Polman et al., 2005) have been prospectively registered since the year 1996 (www.neuroreg.se).

3.2.3.2 The Icelandic cohort

Please see 3.2.1 and 3.2.2. Case ascertainment for the Icelandic cohort in study III was the same as in studies I and II.

3.3 Population

Study I The population is well defined and was 296 835, on average, during the study period (Statistics Iceland, 2002).

Study II The population of Iceland was 315 459 on the prevalence day, December 31st, 2007 (2007). In 2007, 8.6% of the inhabitants had been born abroad or had both parents born abroad (Statistics Iceland 2007).

Study III The Swedish population increased from 6.4 to 8.8 million people during the course of the study period (1940–1996). The population density is higher in the southern part of the country. The mean age increased from 37.0 years in 1968 (the first year of registration of mean age) to 39.7 years. The birth rate per 1 000 decreased from 15.1 to 10.8 1 000 population, and the mortality decreased from 11.4 to 10.6 per 1 000 (*SCB* 2016).

The population of Iceland increased from 230 000 in 1981 to 270 000 in 1996. Between the years 1981 and 1996 the mean age increased from 31.6 to 33.9 years, the birth rate per 1 000 decreased from 19.0 to 16.2, and the mortality rate per 1 000 decreased from 7.2 to 7.0, respectively (Statistics Iceland 2007).

Study IV Information on the death rate of the Icelandic general population, by gender and age, was obtained from Statistics Iceland (2007).

3.4 Methods

Study I The study period was from the 1st of January 2002 until the 31st of December 2007.

Information collected from medical records included: gender, date of onset and diagnosis, clinical phenotype (RRMS or PPMS), presenting symptoms, MRI results at diagnosis, results of CSF analysis and VEP tests.

Incidence rate was determined by dividing the number of cases with the total person-years of observation during the 6-year study period. We used the midyear population for each year as provided by Statistics Iceland. We calculated age- and gender-specific incidence. Age-standardized incidence was calculated based on the year 2000 US standard population (US Cencus 2015).

Study II

We reviewed medical records of incident cases to: verify diagnosis, determine gender, confirm residency in Iceland on the prevalence day, date of onset and diagnosis. The patients were classified according to the Poser or McDonald criteria, based on symptoms and clinical findings present when the first or second attack occurred. For patients diagnosed based on only the McDonald criteria, we assigned a Poser category when possible. We reviewed the results of CSF analysis and MRI scans obtained at initial presentation. In selected cases, MRI images were reevaluated (Ó.K. and Ó.E.), to determine fulfillment of the McDonald 2010 radiological criteria. When MRI results were available, we determined the time from first assessment by a neurologist until the McDonald 2010 imaging criteria were fulfilled.

We calculated the MS prevalence of MS on the 31st of December 2007 (prevalence day) in the population of Iceland based on data provided by Statistics Iceland (2007). Age-adjusted prevalence was calculated based on the 2000 and 2010 US standard populations (US Cencus 2015).

Study III

Data for the Swedish patient cohort was exported from SMSreg on the 31st of January 2016 and included information on: social security number, date of birth, gender, date of MS onset, MS phenotype (RRMS, SPMS, PRMS, PPMS), and the date when patients reached an EDSS score of 6 (Kurtzke, 1983). Information on the place of birth for the MS patients came from the Swedish *Total Population Register (TPR)*.

Data analogous to that for the Swedish MS cohort was gathered for Icelandic MS patients from medical records, aside from information about secondary progression which was not available.

A Swedish control group was created (n=3 503 550) consisting of all people born in Sweden 1940–1996. Information about gender and county of birth was retrieved from the TPR.

An Icelandic control group was created (n=69 913) consisting of the Icelandic population born 1981–1996, divided according to gender, based on data from Statistics Iceland (2007)(http://www.statice.is).

Study IV

The following additional data, on patients in the incidence and prevalence cohorts, (see 3.2.1 and 3.2.2.) was collected from medical records: date of

onset, clinical phenotype and EDSS score. The physical examination had most commonly been performed close in time to the prevalence day but in some cases up to 6 months earlier.

Information on the date of death was collected from medical records. Information on cause of death was collected from death certificates from the *Causes of Death Register* held by the *Directorate of Health*. The register holds information about causes of death from the year 1971 (2019). Death certificate are to be completed according to guidelines of the *World Health Organization* (WHO) (2016). In part 1 of the death certificate the chain of events (diagnoses) leading to death are registered in a successive manner with the *immediate cause of death* registered furthest up (line 1a) and any *antecedent causes* in sequence below and finally the *underlying cause* furthest down. The WHO has defined the underlying cause of death as: "the disease or injury which initiated the train of morbid events leading directly to death". An example for a patient with MS could be: 1a, Pneumonia due to aspiration; 1b, dysphagia and 1c would be multiple sclerosis. In part 2 of the death certificate any conditions that contribute to death, but are not directly related to the chain of events, can be registered, as for example heart failure. Information on death rates in the Icelandic population was retrieved from Statistics Iceland (2019).

3.5 Statistics

3.5.1 Studies I and II

Descriptive statistics are presented as percentages, means or median values. The 95% confidence intervals (CIs) were calculated, for mean annual incidence and point prevalence assuming a Poisson distribution. Statistical analysis was performed using Microsoft Excel and SPSS.

3.5.2 Study III

Observed numbers of births in a certain month or season were compared to adjusted expected means. Expected means where created as suggested by Fiddes at al (2014) by applying simple Bernoulli distributions for each case with probabilities equal to the relative frequency of births in the MS case specific stratum (gender, birth year, and county), that is making contribution of each birth year similar in both the MS group and the control group.

The observed versus expected numbers of births were compared with a two-sided T-test. The analysis was performed for seasons but also by month of birth. Seasons were defined as follows: Spring, March to May; Summer,

June to August; Autumn, September to November; Winter, December to February. A sub-analysis was done for Southern and Northern Sweden. A northern and a southern region were defined by dividing Sweden through its geographical middle, i.e., 62°N. Thereafter, the observed and expected MS MOB in the two regions were calculated. The same calculations were made for subgroup analysis of gender, clinical phenotype (RRMS, SPMS, PPMS), and early onset age (≤ 30, years of age). Calculations were done using Matlab (Mathworks, Natick, MA).

3.5.3 Study IV

Chi-square test was used for comparison of categorical variables between groups and the independent sample t-test was used for comparison of continuous variables. The significance level was set to 0.05. Survival of the MS group was compared to the Icelandic population by means of the life table method with 95% confidence intervals. The life table was created with data from Statistic Iceland (2019), with corrections made for age, gender and calendar year of diagnosis for each patient. Standardized mortality ratio (SMR) was used to assess excess mortality of the MS group compared with the general Icelandic population (see 1.6). Statistical analysis was done in Excel and SPSS.

3.5.4 Ethical approval

The Icelandic studies were approved by the *Icelandic National Bioethics Committee* and *Data Protection Authority* (Reference numbers: 2007090624 and VSNb2007090018/03-15 (Study I), VSNb2012010020/03.11 (Studies II, III and IV)). Study III was also approved by the *Central Ethical Review Board* in Gothenburg, reference number: 084-14.

4 Results

4.1 Study I

4.1.1 Cases, diagnosis and clinical phenotype

We identified 136 individuals who met the primary inclusion criteria of CD-MS according to the Poser criteria (Poser et al., 1983). With the exception of one individual of Danish origin, all were native-born Icelanders. The diagnosis of MS was based on a historic relapse in 9 of the incident cases (6%) who had the following symptoms at onset: typical sensory-level symptoms (n=4), gait ataxia (n=3), sensory impairment in one arm and Lhermitte's sign (n=1) and hemidysesthesia (n=1). All 9 had their second and third relapses, verified by a neurologist, during the study period.

In addition to patient with CD-MS the extended study group also included patients diagnosed with MS 2002–2007 with Poser's laboratory-supported definite MS (LSD-MS), clinically probable MS (CP-MS) and patients fulfilling the 2010 McDonald criteria (Polman et al., 2011). A total of 222 patients fulfilled the requirements for the extended study group.

4.1.2 Incidence of MS in Iceland in the years 2002–2007

The average annual incidence for MS was 7.6 per 100 000 population (95% CI 6.4–9.0) and 8.2 per 100 000, after standardization to the US white population in year 2000. Age-adjusted incidence is presented in Table 14 and Figure 1. The incidence peaked between 35–39 years of age for women and 30–34 years for men. The average annual incidence for the extended study group (n=222) was 12.5 per 100 000.

Table 14 Age-specific incidence of MS in Iceland 2002–2007, by sex

	All, both sexes (n=136)			Women (n=102)			Men (n=34)		
Age in years	Incidence[a]	Cases (n)	Person-years	Incidence[a]	Cases (n)	Person-years	Incidence[a]	Cases (n)	Person-years
All	7.6	136	1 781 101	11.5	102	884 140	3.8	34	896 872
0–14	0.0	0	393 962	0.0	0	193 072	0.0	0	200 890
15–19	3.1	4	130 005	6.3	4	63 439	0.0	0	66 566
20–24	9.9	13	131 781	18.5	12	64 775	1.5	1	67 004
25–29	17.6	23	130 561	29.7	19	64 022	6.0	4	66 529
30–34	18.8	24	127 455	25.9	16	61 920	12.2	8	65 515
35–39	20.5	26	127 070	32.0	20	62 460	9.3	6	64 595
40–44	11.4	15	131 814	15.4	10	64 998	7.5	5	66 804
45–49	12.7	16	125 856	18.0	11	61 121	7.7	5	64 722
50–54	3.6	4	111 131	5.6	3	53 977	1.5	1	57 151
55–59	5.4	5	93 320	6.6	3	45 386	4.2	2	47 928
60–64	5.7	4	70 546	5.7	2	35 270	5.7	2	35 268
65–69	0.0	0	56 187	0.0	0	28 777	0.0	0	27 410
70–74	1.9	1	53 391	3.6	1	28 122	0.0	0	25 269
75–79	2.3	1	44 389	4.1	1	24 273	0.0	0	20 116
>80	0.0	0	53 633	0.0	0	32 528	0.0	0	21 105

[a]Incidence, number of cases per 100 000 population per year

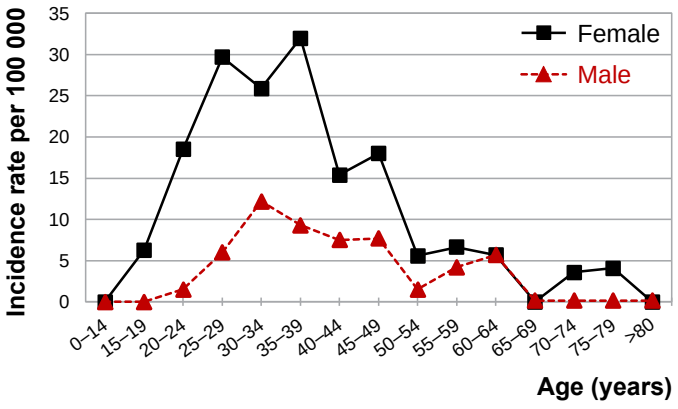

Figure 1 Age-specific incidence of MS in Iceland 2002 to 2007, by gender (n=136)

4.1.3 Sex ratio and clinical phenotype; the incidence cohort

There were 102 women (75%) and 34 men (25%) in the incidence cohort. The female-to-male sex ratio was 3:1 (table 15). The sex ratio was higher in patients with onset before 30 years of age compared to those with onset after 30 years of age (p=0.01). There were 126 cases (93%) of RRMS and 10 cases (7%) of PPMS. The sex ratio was 1:1 for PPMS compared to 3:1 for RRMS, although this difference was not statistically significant.

Table 15 Female-to-male sex ratio, by age of onset and clinical phenotype

	Incidence cohort		Prevalence cohort	
	F:M[a]	**p-value**	**F:M[a]**	**p-value**
Age at onset in years				
<30	6:1	0.01	3:1	0.06
≥30	2:1		2.5:1	
Clinical phenotype				
RR-MS[b]	3:1	0.06	3:1	0.005
PP-MS[c]	1:1		1:1	

[a]F:M, Female:male ratio; [b]RR-MS, Relapsing-remitting MS; [c]PP-MS, Primary progressive MS

4.1.4 Age at onset and diagnosis; the incidence cohort

The overall mean age at diagnosis was 36.3 years (median 35; range: 16–75), 35.7 years for women (median 34.5) and 38.3 years for men (median 40.0). The overall mean age at onset was 32.0 years, 30.7 for women and 35.8 for men.

4.1.5 Presenting symptoms; the incidence cohort

Table 16 demonstrates the presenting symptoms of patients in the incidence cohort (n=136). A number of patients had more than one symptom at presentation with a total of 188 symptoms observed. Sensory symptoms were the most commonly observed symptoms, present in 78 (57%) of the patients, followed by loss of vision and motor symptoms, both of which were present in 29 (21%) of patients. Motor symptoms were more common in men (n=12, 35%) than in women (n=16, 16%); (p=0.005). Sensory symptoms were observed in 15 men (44%) and 63 women (62%); (p=0.072). Table 17 shows the location of the presenting symptoms in the CNS.

Table 16 Presenting symptoms (present at onset) in the incidence cohort (n=188)

Presenting symptoms[a]	Patients (n=136) with each symptom	
	n	(%)
Memory impairment	5	(4)
Sensory symptoms	78	(57)
Loss of vision in one eye	29	(21)
Double vision	16	(12)
Motor symptoms	29	(21)
Other symptoms[b]	31	(23)

[a]49 patients had multiple symptoms present at onset;

[b]Unsteady gait, vertigo, urinary urgency or incontinence, headache, Lhermitte's sign, truncal ataxia, pain and dysarthria

Table 17 CNS[a] location of the presenting symptoms in the incidence cohort (n=195)

Location of symptoms in the CNS[a]	Patients (n=136) with each location of symptoms[b]	
	n	(%)
Spinal cord	63	(46)
Brainstem	56	(41)
Cerebral hemisphere	37	(27)
Optic nerve	29	(21)
Cerebellum	10	(7)

[a]CNS, central nervous system;

[b]39 patients had multiple locations of CNS affection at onset

No significant difference was found in brainstem and optic symptoms between men and women. Brainstem symptoms were observed in 14 men (41%) and 43 women (42%) and optic neuritis in 8 men (24%) and 20 women (20%).

4.1.6 Results of MRI and CSF analysis; the incidence cohort

MRI was done at the time of diagnosis for all but one of the cases, a 73-year-old woman with typical symptoms of MS and oligoclonal bands (OCB) in the CSF). One patient had a normal MRI scan at the time of diagnosis but later developed typical MS lesions. MRI of both the brain and spinal cord was done for 94 cases, while for 12 only an MRI of the cervical spine was available. There were 83 patients (61%) who fulfilled the Barkhof criteria (Barkhof et al., 1997). CSF analysis was performed in 106 (78%) cases, and 80 (75%) had *oligoclonal bands* (OCB). The Barkhof MRI criteria were fulfilled in 52 (65%) of the cases with OCB as compared to 15 of 26 (58%) without OCB (p=0.82).

OCB was detected in 33 of 36 (92%) patients <30 years of age at diagnosis, as compared to 48 of 69 (69%) of those older, although the difference was not statistically significant (p=0.062). There was no difference in the occurrence of OCB between men and women (68% compared to 57%; p=0.267).

4.2 Study II

4.2.1 Cases, diagnosis and clinical phenotype

We identified 526 residents in Iceland who had MS on December 31st, 2007, whereof 13 (2%) were of foreign origin. These cases fulfilled either the Poser criteria (94%) or the 2010 McDonald criteria (6%).

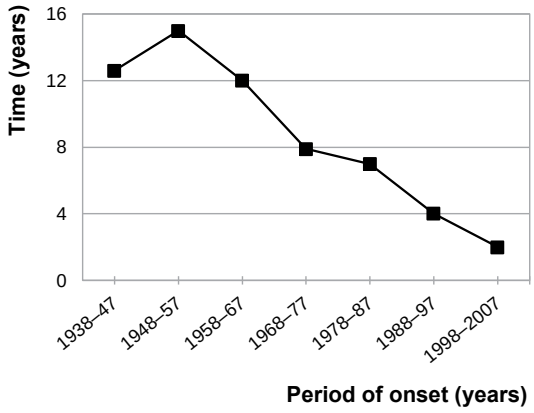

Figure 2 The mean time from onset of symptoms to diagnosis in patients with clinically definite MS (n=446)

Of the 526 patients, 75 (14%) had only experienced a single clinical episode by the prevalence day. Thirty of these patients met the McDonald criteria for MS (both DIT and DIS). The remaining 45 patients were included because they met the Poser criteria, either for LSD-MS (n=23) or CP-MS (n=22). All of these cases were examined with MRI at presentation and fulfilled DIS, but not DIT according to the McDonald 2010 criteria.

Patients who only met the criteria for LSP-MS were not included. Three patients were diagnosed with MS, but excluded from further analysis because information on clinical evaluation was not available. Patients with CIS and normal diagnostic work-up, including MRI, were excluded.

RRMS was the most common clinical phenotype, present in 93% (n=489) of patients, followed by PPMS, 6% (n=32). The clinical form could not be determined for 1% (n=5) of the patients.

Figure 2 shows the duration of time from the appearance of the first symptoms until the diagnosis of MS was made, for patients with CD-MS (n=446). The mean time elapsed from onset to diagnosis was 4.5 years (median 2.0 years; range 0–30 years).

4.2.2 Prevalence in Iceland on the 31st of December 2007

The crude point prevalence of MS was 167.1 per 100 000 population (95% CI 153–181) on the prevalence day, December 31st, 2007. With age adjustment to the 2000 and 2010 U.S. populations, the prevalence was 166.5 (95% CI 166.0–167.0) and 171.1 (95% CI 170.5–171.4) per 100 000, respectively. The prevalence of cases only fulfilling Poser criteria for CD-MS (n=447) was 139.5 per 100 000. The age-specific prevalence (Table 18) increased with advancing age until about 65 years, and declined thereafter.

4.2.3 Gender; the prevalence cohort

The prevalence cohort comprised 73% (n= 382) women and 27% (n=144) men (sex ratio 2.6:1). The gender-specific prevalence per 100 000 was 248 (95% CI 223–273) for women and 89 (95% CI 74–104) for men. The sex ratio was higher for patients with RRMS compared to PPMS (Table 15).

No significant changes were found in the sex ratio over time. The sex ratio was 2.1:1 in the years 1975–1985 (n=60), 2.5:1 1986–1996 (n=122), and 2.6: 1 for 1997–2007 (n=320). Earlier time periods were not included in the analysis due a low number of patients.

Table 18 Age-specific prevalence on the prevalence day, December 31st 2007, by sex

Age in years	All, both sexes (n=526)			Women (n=382)			Men (n=144)		
	Prevalence[a]	Cases (n)	Population (n)	Prevalence[a]	Cases (n)	Population	Prevalence[a]	Cases (n)	Population (n)
All	167	526	315 459	248	382	15 4563	89	144	160 896
0–14	2	1	65 979	3	1	3 2374	0	0	33 605
15–19	4	1	23 685	9	1	1 1524	0	0	12 161
20–24	49	11	22 604	82	9	1 1023	17	2	11 581
25–29	174	43	24 667	291	34	1 1690	69	9	12 977
30–34	253	58	22 890	382	41	1 0743	140	17	12 147
35–39	202	44	21 816	291	30	1 0311	122	14	11 505
40–44	383	88	22 954	583	65	1 1153	195	23	11 801
45–49	289	65	22 525	446	48	1 0768	145	17	11 757
50–54	354	73	20 620	526	52	9877	195	21	10 743
55–59	241	42	17 435	355	30	8456	145	13	8 979
60–64	375	52	13 875	457	31	6782	296	21	7 093
65–69	192	19	9 882	318	16	5029	62	3	4 853
70–74	92	8	8 671	132	6	4555	49	2	4 116
75–79	76	6	7 897	142	6	4235	0	0	3 662
80–84	201	11	5 483	283	9	3175	87	2	2 308
85–89	130	4	3 088	212	4	1889	0	0	1 199
>90	0	0	1 388	0	0	979	0	0	409

[a]Prevalence, number of cases per 100 000 population

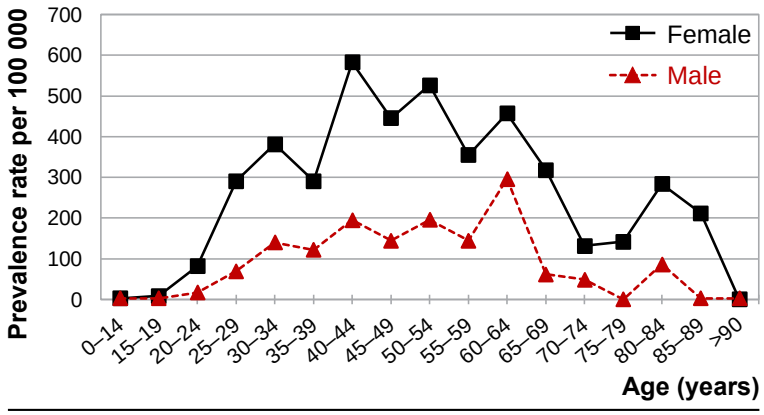

Figure 3 Age-specific prevalence of MS in Iceland on the 31st of December 2007 (n=526), by gender

4.2.4 Age at onset and diagnosis; the prevalence cohort

The mean age on the prevalence day was 47 years (range 13–89). The mean age at diagnosis was 36 years (range 13–77), 35 years for women and 36 years for men. The mean age at onset was 31 years (range 10–74), 31 for women and 33 for men. Figure 3 shows age-specific prevalence for men and women which follows a similar pattern as for age-specific incidence, except that the peak rates occur about two decades later, with the highest rates among people in their mid to late 40s.

4.2.5 MRI results; the prevalence cohort

Most of the patients (n= 460, 87%) had undergone at least one MRI scan by the time of the prevalence day. The 66 patients (13%) who had not been examined with MRI had a longer duration of time from diagnosis to the prevalence day (mean 22.8 years, range 2–53 years) compared to patients who had undergone an MRI scan (mean 9.1 years, range 0–61). 382 (83%) fulfilled the DIS criteria, the mean time from onset to fulfilling the DIS criteria was 6 years (range 0–44). 301 (65.3%) fulfilled the DIT criteria, the mean time from onset to fulfilling the DIT criteria was 7.1 years (range 0–36).

4.2.6 Mobility aids; the prevalence cohort

Information on the use of mobility aids (cane, walker, or wheelchair) was available for the 11 years preceding the prevalence day (1997–2007). During this period 320 patients were diagnosed with MS whereof 11% (35/320) began using a walking aid prior to the prevalence day. 6% (19/320) of patients with available data had begun using a mobility aid 5 years after diagnosis of MS.

4.3 Study III

4.3.1 The Swedish MS cohort

On the day of export (31st of January 2016) from the *Swedish MS registry* (SMSreg) there were 15 801 patients registered with a diagnosis of MS, whereof 13 398 were born in Sweden during the period of interest, 1940–1996. Of these, information on place of birth was available for 12 020 and they were included in the study. Table 19 shows the characteristics of the Swedish and Icelandic cohorts.

4.3.1.1 The risk of MS according to season and month of birth

We found no relationship between season of birth and the risk of developing MS later in life (Appendix, table A). Further, we found no difference between observed and expected numbers of MS patients when each MOB was analyzed separately, with (Figure 4) or without adjustments for birth year and county of birth.

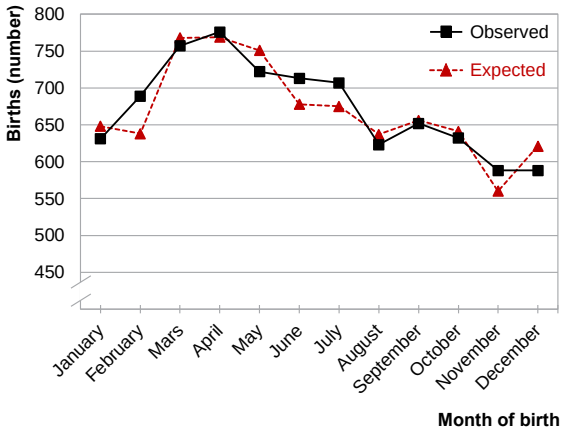

Figure 4 Number of births of MS cases per month. Observed number of births and expected number of births based on controls with adjustment for birth year and birth place

Table 19 Demographic- and clinical characteristics of the cohorts in study III

	Swedish cohort	Icelandic cohort
	n=12 020	n=108
Age at onset in years[a], mean (range)	32.9 (1–70)	22.5 (10–37)
Age at diagnosis in years[b], mean (range)	37.4 (6–73)	23.7 (13–39)
Age at data export in years[c], mean	51.0	30.0
Sex ratio, female-to-male	2.5:1	2.1:1
MS phenotype, n (%)		
RRMS[d]	7 087 (59)	106 (98)
PPMS[e]	932 (8)	1 (1)
PRMS[f]	154 (1)	
SPMS[g]	3 239 (27)	
Missing	608 (5)	1 (1)
Residence, n (%)		
Southern part of Sweden[h]	10 283 (86)	
Northern part of Sweden[h]	1 458 (12)	
Missing	279 (2)	

[a]Missing for 7.3% of cases; [b]Missing for 16.3% of cases; [c]Missing for 5.0% of cases

[d]RRMS, Relapsing-remitting MS; [e]PPMS, Primary-progressive MS; [f]PRMS, Progressive-relapsing MS; [g]SPMS, Secondary-progressive MS

[h]Divided at 62°N, the approximate central latitude of Sweden

After adjustment, there seemed to be 7% more MS births in February than expected (1 030 compared to 961.8, p=0.0208, Appendix, table B). However, when Bonferroni correction was applied this difference was not significant (p<0.0042 needed for statistical significance).

4.3.1.2 The effect of latitude on the association between MOB and risk of MS

When the effect of latitude was taken into account by analyzing the southern and northern regions separately, there were 10% more MS births in February than expected in the Southern region of Sweden (900 compared to 824.5, p=0.00574). Again, after Bonferroni correction for multiple comparisons, the effect was not statistically significant (Appendix, table B).

4.3.1.3 The risk of MS associated with month of birth and gender, phenotype and age of onset

No significant difference was found in observed births compared to expected births when analyzing the genders separately or when analyzing phenotypes separately. In spring there were fewer MS births than expected (1 372 compared to 1 442 p=0.0285) but a p value ≤0.0125 would have been needed for statistical significance after Bonferroni correction. No significant difference was found in the number of MS births per month in the subgroup with early age of onset (younger than 30 years of age) (Appendix, table B).

4.3.1.4 The risk of MS according to season and month of birth in the Icelandic cohort

Based on data from studies I and II we identified 108 patients born in Iceland from 1981 to 1996 (table 19). We found no relationship between season of birth or MOB to the risk of developing MS later in life (Appendix, table A and C).

4.4 Study IV

4.4.1 Follow-up

Mortality data was based on both the prevalence cohort (study III) and the incidence cohort (study II). In the prevalence group (n=526) all cases were followed from the prevalence day on the 31st of December 2007 until the 31st, of December 2018 or the date of death. There were a total of 5 483 *person-years of observation* (PYO) at risk and a mean length of follow-up of 10.4 years (range 1-11). Cases in the incidence group (n=222) were followed from

the date of diagnosis until December 31st, 2018 or death, whichever occurred first. There were a total of 2 877 PYO at risk and a mean length of follow-up of 13.0 years (range 4–17).

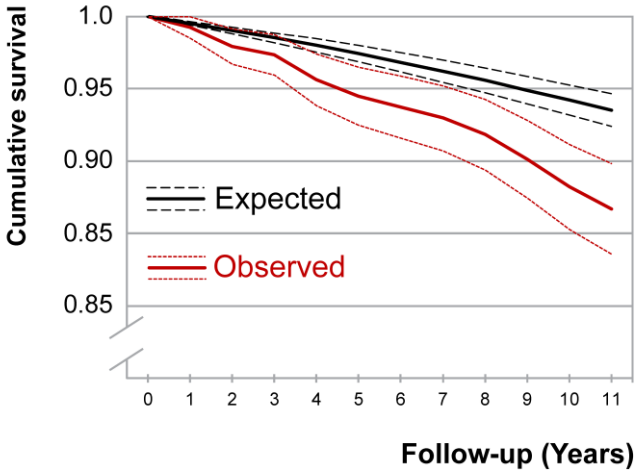

Figure 5 Survival of the prevalence cohort (n=526) from the 31st of December 2007 until the 31st of December 2018 or death. Analyzed with the life table method. Expected survival, based on the general population, with respect to age and gender and observed survival are displayed with 95% confidence intervals

4.4.2 Survival, age at death, CMR and SMR; prevalence cohort

In the prevalence group there were 70 deaths during the follow-up period. The over-all mean age at death was 69 years of age (range 35–97). Based on the life table method the observed survival after 11 years of follow-up was 86.7%. There was a steady decrease in the cumulative survival throughout the follow-up period (figure 5 and table 20). The expected survival after 11 years of follow-up was 93.5% resulting in an SMR of 2.0 (95%CI 1.3–3.0). The CMR for the study period was 12.8 per 1 000 PYO while the expected mortality was 6.5 per 1 000 PYO.

4.4.3 Survival age at death, CMR and SMR; incidence cohort

There were 7 deaths in the incidence cohort with a mean age of death at 63 years (range 36–90). The crude mortality rate was 2.4 per 1 000 PYO while the expected mortality rate was 2.3 per 1 000 PYO. The observed survival was 97.3% compared to 97.2% expected survival. Thus, the overal SMR for the study period was 0.95 (95% CI: 0.1–3.0).

Table 20 SMR **(**Standardized mortality ratio) for the prevalence group (n=526), by years of follow-up, from 31st of December 2007

Follow-up (years)	Observed survival (%)	Expected survival (%)	SMR (95% CI)
1	99.2	99.5	1.58 (0.02–4.08)
2	97.9	99.0	2.13 (0.71–4.44)
3	97.3	98.5	1.80 (0.0–3.59)
4	95.6	98.0	2.17 (1.05–3.98)
5	94.5	97.4	2.14 (1.11–3.74)
6	93.7	96.8	1.98 (1.1–3.37)
7	93.0	96.2	1.86 (1.05–3.09)
8	91.3	95.6	1.85 (1.46–2.98)
9	90.1	94.9	1.93 (1.19–3.02)
10	88.2	94.2	2.03 (1.29–3.09)
11	86.7	93.5	2.05 (1.34–3.06)

4.4.4 Risk factors for death, gender, age and clinical phenotype

4.4.4.1 Clinical phenotype

The SMR according to gender, age and clinical phenotype is presented in table 21. Of 489 patients with RRMS, 57 (12%) died during the follow-up compared to 12 of 32 patients in the PPMS group (38%) (p=0.0008). The mean age at death was 68 years in the RRMS group compared to 74 years in the PPMS group (p=0.16) (Table 21).

4.4.4.2 Gender

The SMR was higher for men, 2.6 (95%CI 1.4–4.8) than for women, 1.8 (95% CI 1.1–3.1), although the confidence intervals overlapped (Table 21).

4.4.4.3 Degree of disability

EDSS was available for 98% of all (n=513) cases, including all 70 patients that died. EDSS was analyzed in the following categories: 0–2.5, 3.0–5.5 and 6.0–9.0. The SMR increased with higher EDSS score category from 1.3 (95% CI 0.6–2.5) for EDSS 0–2.5 to 3.0 (95% CI 1.8–4.7) for EDSS 6.0–9.0 although the CIs overlapped.

The overall EDSS score (n=513) was 3.1 for all patients, compared with 5.9 for those who died (n=70); (p=0.0001) (Table 21).

Table 21 Standardized mortality ratio (SMR) of the prevalence cohort according to: clinical phenotype, EDSS[a] score, and gender. Analyzed with the life table method, follow-up from the 31st of December 2007 until the 31st of December 2018 or death

			Life table analysis		
	Deaths (n)	**Patients at-risk (n)**	**Observed survival (%)**	**Expected survival (%)**	**SMR[b] (95% CI)**
Clinical phenotype[c]					
RRMS[d]	57	489	88.1	94.2	2.1 (1.4–3.1)
PPMS[e]	12	32	65.7	83.8	2.1 (0.8–5.5)
EDSS[f]					
0–2.5	19	305	93.8	95.3	1.3 (0.6–2.5)
3–5.5	10	100	90.0	94.2	1.7 (0.5–4.6)
6–9.0	41	110	62.7	87.6	3.0 (1.8–4.7)
Gender					
Female	46	381	87.9	93.3	1.8 (1.1–3.1)
Male	24	145	83.5	93.8	2.6 (1.4–4.8)

[a]EDSS, Expanded Disability Status Scale; [b]SMR, standardized mortality ratio; [c]Clinical phenotype missing for 5 patients; [d]RRMS, Relapsing-remitting MS; [e]PPMS, Primary-progressive MS; [f]EDSS missing for 11 patients

4.4.4.4 Age at diagnosis

Table 22 shows survival from the prevalence day and SMR according to age at diagnosis.

Table 22 Survival of the prevalence cohort[a] after 11 years of follow-up, according to age at diagnosis (n=526). Analysis of SMR with life table method

				Life table analysis		
Age at diagnosis	Deaths (n)	Patients at-risk (n)	Time from prevalence day to death in years (mean)	Expected survival (%)	Observed survival (%)	SMR[b] (95% CI)
0–34	3	113	9.0	97.4	99.4	4.3 (-0.5–11.2)
35–54	18	270	6.7	93.3	97.8	3.0 (1.5–4.6)
≥55	49	143	6.4	66.4	80.8	1.8 (1.2–2.6)

[a]Follow-up lasted from the prevalence day, December 31st, 2007 until December 31st 2018 or date of death; [b]SMR, standardized mortality ratio

4.4.5 Cause of death

Death certificates were available for 61 (87%) of the deceased patients in the prevalence group. The number and proportion of patients that had the following diagnosis mentioned anywhere in the chain of events on the death certificates was: Multiple sclerosis 48% (n=29), infection 46% (n=28), cancer 18% (n=11) vascular disease 30% (n=18), respiratory disease 7% (n=4), drug abuse 7% (n=4) and accident 2% (n=1). Notably, no suicide was documented. Of those 29 who had MS noted anywhere in the chain of events, 19 patients also had an infection mentioned somewhere in the chain of events. In 23% (n=14) of patients, MS was not noted in the death certificate, neither in the chain of events nor as a contributory cause of death.

In the incidence group (n=222), 7 individuals died with the following primary causes of death (n): Multiple sclerosis (3), sepsis (1), drowning (1) and unknown (2).

5 Discussion

The main findings of this thesis were the updated nation-wide incidence and prevalence of MS in Iceland. The incidence was high (7.6/100 000) as well as the prevalence (167.1/100 000) and for the first time the mortality of Icelandic MS patients was reported. We confirm that MS has a major influence on mortality and it was twice as high as in the general population of Iceland (SMR 2.0). However, during the first 11 years after diagnosis of MS, patients did not have an increased risk of death compared to the general population. We did not find any association between birth month and the risk of developing MS later in life.

5.1 Incidence of MS

Circumstances in the Nordic countries resemble those found in Iceland most closely, including: latitude, genetics and a mainly publicly funded health care system accessible to the whole population. The incidence in the extended study groups was 12.5. This definition is similar to how cases have been defined in studies from the other Nordic countries. As anticipated, the incidence in the extended study group was similar to the reported range of 7.6–11.8 (Risberg et al., 2011; Simonsen et al., 2017) from the other Nordic countries.

A number of confounding factors might contribute to the wide span of incidence rates reported from countries around the world. One of them is the use of different diagnostic criteria (Warren, 2001). We chose to include definite cases in the primary analysis of the incidence cohort, to minimize the number of uncertain cases with higher likelihood of alternative diagnosis. The same selection of cases has been done in studies from Norway and Finland although the incidence turned out to be a bit higher than in our study, 8.7 and 11.4 per 100 000, respectively (Celius & Vandvik, 2001; Pirttisalo et al., 2019). Our incidence findings are thus more likely under- than overestimating the true incidence during the study period.

Case ascertainment methods can differ between studies. When using retrospective case ascertainment, the completeness of the results would be expected to increase by searching multiple sources. Examples of different sources could be institutional databases from: hospitals, outpatient clinics, general practices and long-term care facilities. If incidence estimates are

based on data from only one single institution there is a risk for bias depending on the type of institution. For instance, it has been shown that MS patients that attend MS clinics differ from those that visit general neurology departments: they are younger, have faster disability progression, less comorbidity and are more likely to have PPMS (Debouverie et al., 2009; McKay et al., 2016). Financial status can affect the access of patients to health care which in turn can lead to selection bias when identifying cases retrospectively, for example in institutional databases. The results of such searches further depend on the structure of the electronic medical record system and the accuracy of coding practice (for example with ICD-10).

Prospective case ascertainment such as from registries is not completely without problems either. Requirement for informed consent by the patient for registration can lead to bias. Another potential cause of bias may be differences in the proportion of health care units reporting to registries between countries or geographical areas within a country (Hillert & Stawiarz, 2015; Koch-Henriksen & Sorensen, 2010; Laakso et al., 2019).

Figure 6 presents incidence rates per 100 000, reported in Europe from 1990 and onward. The reported incidence rates cover a wide range: 0.7–19.5 (Dean et al., 2002; Salhofer-Polanyi et al., 2017).

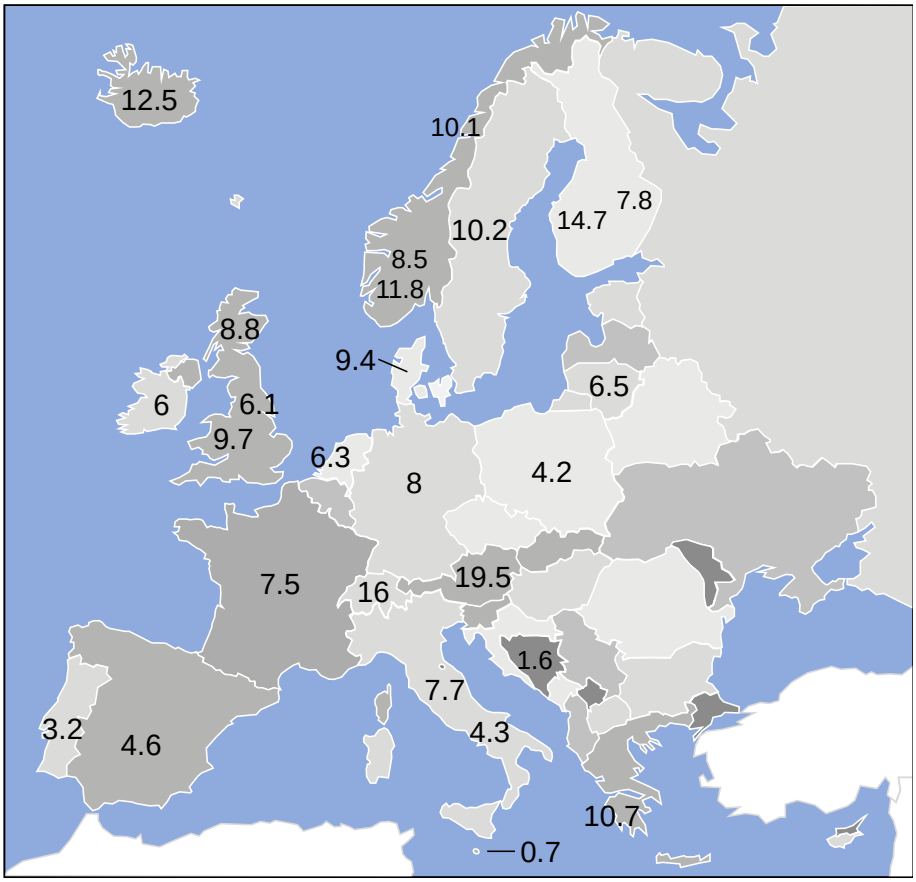

Figure 6 Incidence rates of MS per 100 000 population in Europe

5.1.1 Gender

The female-to-male sex ratio in our study was 3:1 which was higher than that reported in the study by Sveinbjörnsdóttir (2014). Their data was based on cases retrieved 1900–2000, where the sex ratio was approximately 2:5:1. Notably, they could not show any clear change in sex ratio over time, although covering a whole century.

Some studies have found the sex ratio to be stable over time (Bostrom et al., 2013; Mayr et al., 2003; Midgard et al., 1996) while other authors have reported an increase in the number of women compared to men over the years (Hirst et al., 2009; Koch-Henriksen & Sorensen, 2010; Orton et al., 2006). An increased incidence amongst women may largely be due to an increase in incidence in younger age groups, where RRMS is the most common phenotype, dominated by women (Gronning et al., 1991). In

contrast, a decrease in PPMS has been reported, although this change was evenly distributed between women and men and seemed independent of gender (Westerlind et al., 2016). Benign cases of MS are more common in women than in men (Hawkins & McDonnell, 1999). Thus, a lower threshold for diagnostic investigation, including MRI may partly explain this development. There are probably other still unknown factors also contributing to a change in gender ratio in RRMS (Koch-Henriksen & Sorensen, 2010).

5.1.2 Increase in incidence in Iceland

As presented in study I, the incidence of MS in Iceland was 7.6/100 000 in the years 2002–2007, when including patients with CD-MS and 12.5/100 000 when also including patients with: CD-MS, LSD-MS, CP-MS and fulfilling the McDonald 2010 criteria. Previous publications from Iceland have reported incidence for seven different study periods (table 11), four are from the years 1946–1965, with an incidence ranging from 2.6–5.3. The remaining three are reports of incidence ranging from 3.5–4.5 (1975–1990), 5.3 (1986–1990) and 5.1 (1990–1999).

Thus, the incidence of MS in Iceland during the second half of the 20th century was consistently reported between 2.6 and 5.3. Based on our results there seems to have been an increase in the incidence of MS in Iceland although there are methodological differences between the studies including the use of different diagnostic criteria. As previously mentioned, one possible explanation for an increase in incidence is an increase in diagnostic activity. There seems to have been a decrease of the interval between onset and diagnosis in our study lending indirect support to an increase in diagnostic activity over time. Another indirect indicator of increased diagnostic activity is the apparent increase in sensory symptoms at diagnosis. In the incidence cohort (Study I) the presenting symptoms were sensory in 57%, compared to 17% in an earlier Icelandic study based on data from 1946–1965 (Gudmundsson et al., 1974). This suggests suggesting that milder symptoms may be considered more often for a diagnostic workup than previously (Simonsen et al., 2017; Warren, 2001; Weinshenker et al., 1989). Furthermore, the use of the first DMDs began in Iceland after 1996 which could also have influenced the diagnostic activity.

Apart from changes in diagnostic criteria and activity, environmental and life-style factors might have affected the incidence of MS in Iceland. For example, the increase of adolescence obesity which has been observed in Iceland (Eiðsdottir et al., 2010) is a known risk factor for MS (Gianfrancesco et al., 2014) and lower consumption of fish, an important source of vitamin D,

which is another risk factor of MS (Munger et al., 2004). This change of diet was most pronounced in young adults and in particular women. (Þorgeirsdóttir et al., 2011; Steingrímsdóttir et al., 1991). On the other hand, data from Statistics Iceland reveal that smoking, a well-established risk factor of MS (Hedstrom et al., 2013), has decreased over the years in the age group 18–40 years. The decrease in smoking was most pronounced in women (Statistics Iceland, 2019) which might have influenced the incidence of MS in the opposite direction.

5.1.3 Age

The age-specific incidence and prevalence in our study was similar to previous studies (Ahlgren et al., 2012; Dahl et al., 2004; Etemadifar & Maghzi, 2011; Kearns et al., 2019; Koch-Henriksen et al., 2018; Pirttisalo et al., 2019). The risk of MS rised from adolescence, peaks around the age 30–35 years thereafter decreased to a low risk of developing MS after the age of 60 years. This pattern has been observed in countries with both high and low frequencies of MS (Warren, 2001).

5.1.4 Onset of symptoms

In our incidence cohort (n=136), sensory symptoms were the most common symptoms at onset (57%) followed by visual loss in one eye (21%) and double vision (21%). This distribution is similar to what others have reported (Ribbons et al., 2017; Scalfari et al., 2010) but as previously mentioned in contrast to an older Icelandic study from the period 1946–1965 where sensory symptoms were seen at onset in 17% of patients (Gudmundsson et al., 1974).

5.2 Prevalence of MS

The prevalence of MS has increased over time. A systematic analysis from 2019 estimated that the prevalence of MS had increased globally 10.4% since 1990 (Wallin. et al., 2019). When adding our prevalence of 167 from 2007 to data in Iceland there seems to have been a continuous increase in the prevalence of MS over time since the first study was published by Gudmundsson et al. in 1962 (1962). A number of factors can potentially explain changes in prevalence although the effects of incidence and mortality are dominant. Increasing incidence would be expected to lead to an increase in prevalence. Mortality has been reported as decreasing with time which (Koch-Henriksen et al., 2017) should predictably contribute to an increase in prevalence. Prevalence could also be influenced by changes in the age

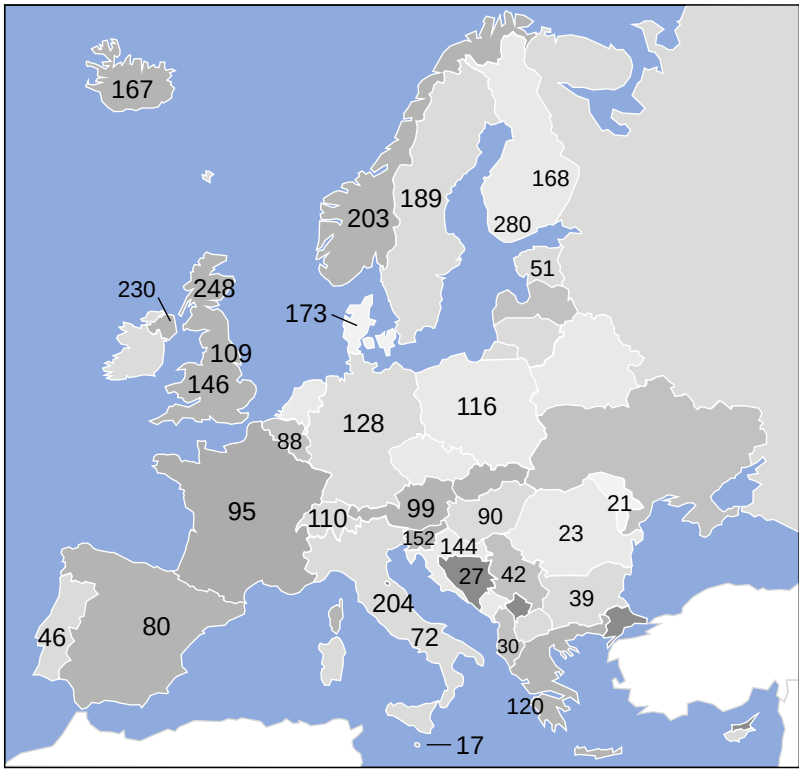

Figure 7 Prevalence rates of MS per 100 000 population in Europe

distribution of the general population. However, in Iceland the proportion of people in the age group 20–49 years, a group with a high risk for MS, decreased between 1985–2019 (Statistics Iceland, 2019). As different ethnic groups have been found to have different risks for MS (Langer-Gould et al., 2013), changes in the ethnic composition of a population would be expected to influence prevalence. At least until recently, the effect of ethnicity on the prevalence of MS in Iceland is probably limited. Historically, immigration to Iceland has been low. In 2007 only 8.6% of the inhabitants were of foreign origin (Statistics Iceland 2007).

Figure 7 gives an overview of the prevalence in Europe.

5.2.1 Gender

In the prevalence cohort the overall sex ratio was 2.6:1. The sex ratio was higher for RRMS (3:1) than for PPMS (1:1) which is in line with results of previous studies (Tremlett et al., 2005; Westerlind et al., 2016).

5.2.2 Disability

In the prevalence group, 6% of Icelandic patients used a mobility aid 5 years after their diagnosis of MS. In a study from Canada based on 2 837 patients, 28% needed a cane 15 years after diagnosis (Tremlett et al., 2006).

5.2.3 Month of birth and risk for MS later in life

In study III, we found no association between month of birth and the risk of developing MS later in life, either with or without correcting for the potentially confounding effect of year of birth and place of birth, as suggested by Fiddes et al. (2014). As we found no difference in the primary analysis we are unable to draw conclusions as to year and place of birth are likely to have affected the results previous studies.

Furthermore, we found that the MS incidence was higher than expected in February in the Southern region of Sweden. The p-value was 0.5% but became not significant after correction for months. This association was not in line with previous hypothesis, suggesting an increase in risk of MS risk with more northern latitude and less sun exposure.

After the publication of our study, two studies have failed to show a connection between month of birth and risk of MS. A study from Austria including over 7000 MS patients analyzing month of birth, correcting for birth year. The authors found no difference between observed MS births and expected births in the population (Walleczek et al., 2019). Another study from Denmark spanning over 60 years and including 19 536 patients with MS found no association between birth month and the risk of MS, compared to the general population (Koch-Henriksen et al., 2018). This might suggest that confounding factors have influenced results of earlier studies but there has been a study from Norway that found an increased frequency of MS among patients born in April after adjusting for confounding factors (Torkildsen et al., 2014). Further research is needed for clarification. Our results do not support the hypothesis that pregnancy during autumn and winter with low levels of sun exposure and low vitamin D levels influence the offspring´s risk of MS later in life.

5.3 Mortality from MS

5.3.1 SMR

We found a SMR of 2.05 for MS patients in the prevalence cohort. This is

similar to results from previous studies from other countries. Table 13 gives an overview of population-based mortality studies reporting SMR. Regional studies from Hungary (Sandi et al., 2016) and Wales (Hirst et al., 2006), also based on prevalence data, reported an SMR of 2.5 and 2.8, respectively. A meta-analysis from 2016 found the pooled all-cause SMR in MS patients to be 2.56 (Manouchehrinia et al., 2016).

However, no difference was seen in mortality between patients diagnosed with MS in Iceland 2002–2007 compared to the general population, 13 years after diagnosis on average. In a regional study from Norway the SMR was 0.8 for patients diagnosed in the most recently studied time period (1997–2012) (Lunde et al., 2017). In a recent nationwide population-based study from Denmark, the SMR was a bit higher than in our incidence cohort 1.8 for cases with onset 1990–1999 (Koch-Henriksen et al., 2017), again, the most recent time period studied. A longer follow-up of the incidence group could be necessary to reveal changes in SMR compared to the general population as studies have shown that increase in SMR does not emerge clearly until the second decade after diagnosis (Koch-Henriksen et al., 2017). A meta-analysis from 2016 found the pooled all-cause SMR in MS patients to be 2.56 (Manouchehrinia et al., 2016).

This is the first study from Iceland to present data on mortality of MS patients; it is therefore not possible to draw any conclusions about temporal changes. As mentioned in the introduction (see 1.6.2) the results of studies on temporal changes of MS mortality have been conflicting.

5.3.2 Gender and mortality

The previously mentioned meta-analysis from 2016 found the SMR to be higher for women with MS, 3.12 (95% CI 3.02–3.22), than for men 2.6 (95% CI 2.50-2.70) (Manouchehrinia et al., 2016). However, a recent study of a large patient population from Denmark found no difference in SMR between males and females (Koch-Henriksen et al., 2017) while a study from Norway found a significantly higher SMR in females (2.5) compared to males (2.9), p=0.0009 (Lunde et al., 2017). In our prevalence group the SMR was 1.8 (CI: 1.1–3.1) for women but 2.6 (CI:1.4–4.8) for men. Thus, there was a trend for a more favorable mortality in women than for men compared to the general population. Although these results are in contrast to some previous studies it should be noted that the confidence intervals were wide and the differences were not statistically significant. Our study was based on a prevalence cohort. Two previous studies, from South Wales and Hungary, also based on prevalence cohorts found no statistically significant difference in SMR between men and women (Hirst et al., 2008; Sandi et al., 2016).

5.3.3 Clinical phenotype and mortality

Some previous studies have found patients with PPMS to have a higher SMR than those with RRMS including studies from Norway, Hungary and France (Leray et al., 2015; Lunde et al., 2017; Sandi et al., 2016). In contrast, we found no difference in SMR between patients with RRMS and PPMS, both groups had an SMR of 2.1. This could be due to a small sample size although a large study form Canada including 6 917 patients, whereof 1 025 had died during 25 years of follow-up (Kingwell et al., 2012), did not find a difference in SMR between patients with RRMS and PPMS.

5.3.4 Cause of death (COD)

Comparison of causes of death between studies can be difficult. Differences in the age distribution of populations can affect the distribution of causes of death in both the general population and amongst patients with disease, such as MS. Coding practice can deviate as well, coding errors have been found to be common (McGivern et al., 2017). Comparing studies is further made difficult as different studies do not include the same types (immediate cause, antecedent cause, underlying cause or contributory) of diagnosis or combinations.

Our review of death certificates revealed that MS was registered somewhere in the chain of events leading to death for 48% of the 61 deaths with COD information. Most previous studies have found MS to be the cause of death in 50% or more of cases (Kingwell et al., 2019; Lunde et al., 2017; Scalfari et al., 2013; Sumelahti et al., 2010). In our study, 30% of patients had MS registered as a contributory cause, thus MS was mentioned somewhere on the death certificate for 77% of patients.

5.3.5 Mortality studies on MS - methodological considerations

Interpretation and comparison of studies on mortality from MS can be difficult for several reason including differences in how death is identified and due to presumed changes in mortality over time.

Different methods have been used to identify patients for mortality studies, including identification through: nationwide MS registries, hospital-based registries, data from specialty clinics and mortality data registries (based on death certificates). (Koch-Henriksen et al., 2017; Landtblom et al., 2002; Leray et al., 2007; Llorca et al., 2005; Redelings et al., 2006; Sandi et al., 2016). The characteristics of patients attending specialized MS clinics deviate from MS patients in general (McKay et al., 2016) and they presumably have

different survival rates. Using death certificates to identify cases is a method particularly vulnerable to selection bias. Study IV found that for 20% (n = 14) of our previously identified and deceased MS patients, the diagnosis of MS was not mentioned at all in the death certificate. This is comparable to studies from Norway (Smestad et al., 2009), Wales (Hirst et al., 2008) and Leeds, England (Ford et al., 2002). These observations emphasize that identifying cases based on mortality data (death certificates) is susceptible to selection bias, potentially leading to underestimates of mortality. Thus, prospective mortality studies should be preferred whenever feasible.

5.4 Strengths and weaknesses

Methodological problems are commonly encountered in epidemiological research, potentially leading to different types of bias such as: selection bias, information bias and confounding. Studies on the epidemiology of MS, including those presented in this thesis, are no exception. One problem specific to studies on the epidemiology of MS is the variable clinical course of the disease.

The main strength of the studies presented in this thesis is that they are nationwide and population-based. Although selection bias is probably present to some degree regarding inclusion of patients, the risk should be minimal as the health care system in Iceland is accessible to all and unique personal national identification numbers greatly aid in identifying cases in comprehensible databases run by both health care institutions and other authorities. In addition, we have searched for cases in multiple parallel sources, which should help to minimize selection bias. The main strength of study III is the large size of the study population. In addition, cases were chosen by birth year in an attempt to reduce selection bias and the potential effect of confounding factors, largely omitted in previous studies, was controlled for in the analysis (birth year and birth place).

In the incidence and prevalence cohorts we chose to include patients by time of diagnosis rather than onset of disease. This is mainly because year of diagnosis can be established more accurately than onset in most cases, although onset may be closer in time to any possible exposure to causative factors.

A main weakness of studies I, II and IV is that information on some of the clinical variables was gathered retrospectively, for example: date of onset, date of diagnosis as well as clinical phenotype. Another weakness of studies I, II and IV is the small size of the MS cohort. For study IV longer follow-up of

the incidence group would be useful as most MS patients live with the disease for a considerable number of years after onset, 35 years on average in a recent Danish study, (Koch-Henriksen et al., 2017) with mortality not manifesting clearly until the second decade after diagnosis. Due to these drawbacks of the incidence cohort, data from the prevalence cohort was used for analysis of mortality as in some previous studies (Hirst et al., 2008; Sandi et al., 2016). Estimates of mortality based on prevalence data are subject to a certain selection bias. Only patients who were alive on the prevalence day were included. Many of the cases were diagnosed a considerable number of years prior to the prevalence day. Patients diagnosed during the same early time period who died prior to the prevalence day were not included in the prevalence cohorts.

The incidence and prevalence of MS has been found to vary with time. Studies I and II are based on data from 2007 and therefore do not reflect the current situation in Iceland. However, studies on temporal tends are an interesting subject for future research on the epidemiology of MS in Iceland. The population of Iceland and the cohort of MS patients are well defined, offering a unique opportunity to study interaction between environmental risk factors and genetic susceptibility in future studies.

The tradition for Health Care Quality Registries is very limited in Iceland compared to the other Nordic countries. Hopefully it will be possible to establish a nationwide MS registry in Iceland in the future, which would both enhance the quality of patient care as well as facilitate research on MS.

6 Conclusions

In this thesis four studies on the epidemiology of MS are presented. Three of them deal with the epidemiology of MS in Iceland, including the incidence, prevalence and mortality of MS. The fourth study is done in Sweden and looks at the question whether there is an excessive risk for the future development of MS, associated with a certain month of birth.

I and my coworkers find that both incidence and prevalence MS is relatively high in Iceland and comparable to other Nordic countries. We also find that the mortality associated with MS is increased above that expected in the general population. We found no association between month of birth and risk of MS later in life, but we were unable to conclude about the possible effect of the confounding effect of place and year of birth as our results were negative both before and after adjustment for these factors.

We like many others find that the incidence and prevalence is higher than reported in older studies. This increase is most likely due to a combination of more trained neurologist in the community, better and continuously improving imaging technology, used for diagnosing MS, and ever greater attention given to early and mild cases of MS, after the advent of effective disease modifying treatment. We believe this effect will continue over coming years and then our research will serve as a useful reference point. The increase could be driven by new revision of the diagnostic criteria. The currently most widely used diagnostic criteria for MS, the McDonald criteria, have been revised since the versions used in our studies allowing for even earlier diagnosis of MS (Thompson et al., 2018). Continuous improvement in the ability of MRI imaging in identifying demyelinating lesions, typical of MS, increasing the sensitivity and the specificity, e.g. by improving the ability of MRI to differentiate MS lesions from non-specific white matter lesions (Filippi et al., 2019). In the same way evolvement of equipment could make a change in diagnosis of MS, e.g., the 7 tesla MRI, now available in some countries.

Epidemiology done in a closed well-defined community with modern health care is a very powerful method to elucidate the nature of a disease like MS, both its frequency and also how it affects the individuals over time. We have helped shed some light on MS disease in Iceland, but much more work is needed and our work will become useful as a well-defined reference point for future studies.

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Original publications

Paper I

Research Paper

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Incidence of multiple sclerosis in Iceland, 2002–2007: a population-based study

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Abstract

Background: We conducted a study to determine the incidence of multiple sclerosis (MS) among the whole Icelandic population during a 6-year period (2002–2007).

Methods: We included all Icelandic residents diagnosed with MS during the study period. Cases were identified from records of the only neurology department in Iceland, plus the records of all practicing neurologists and all radiology departments. All patients had experienced at least two confirmed MS relapses (i.e. clinically definite MS) or had primary progressive MS as defined by the Poser criteria.

Results: We identified 136 individuals who met the inclusion criteria, including 102 (75%) women. The mean age at diagnosis was 36.3 years (women 35.7 years, men 38.3 years). Average annual incidence was 7.6 per 100,000 population. All but one patient (99%) had an MRI study done at diagnosis and 61% of these (83/135) fulfilled the Barkhof criteria for diagnosis of MS; one had a normal MRI. A visual evoked potential test was done in 68% (93/136) at the time of diagnosis and 44% (41/93) were abnormal. Spinal fluid was obtained from 78% (106/136), and 75% (80/106) had oligoclonal bands.

Conclusion: A total population study is the most reliable method of determining the spectrum of clinical symptoms and the results of investigations in MS patients at diagnosis.

Keywords

demyelination, epidemiology, incidence, magnetic resonance imaging, multiple sclerosis

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Introduction

The incidence of multiple sclerosis (MS) most accurately portrays the variability of disease severity[1] and study results at diagnosis. In recent years, MRI has assumed a greater role in the evaluation of patients with suspected MS. We are aware of only one recent population-based[2] incidence study of MS where 'the majority' had an MRI study done, but the exact proportion was not specified.

Two studies from Iceland have reported the incidence of MS to be 4.98–5.28 per 100,000 (1981–1990)[3] and 1.94 per 100,000 (1956–1965).[4] We determined the incidence of clinically definite MS and the results of the principal diagnostic studies used in the diagnosis of MS. The study included the entire population of Iceland over a 6-year period.

Materials and methods

Iceland is an island in the North Atlantic, between latitudes 64° and 66° north, and the mean all-year temperature in Reykjavík, the capital, is 4.6°C.[5] The population is well defined and was 296,835, on average, during the study period.[5] Approximately 62% of the population lives in the area of the capital.[5]

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The Icelandic healthcare system is modern and easily accessible to all residents. There is one neurology department in Iceland and three radiology departments with MRI equipment. During the study period there were, on average, 17 neurologists practicing in the country, or 6 per 100,000 population.

The 6-year study period was from 1 January 2002 through 31 December 2007 and, for the first time, made an effort to identify all residents of Iceland diagnosed with MS during the study period. We only included individuals who met the Poser criteria for clinically definite and primary progressive MS[6] and these are the index cases of this study. All the index cases were diagnosed by a neurologist and many were seen by more than one neurologist. The time of diagnosis was set at the second observed attack or when fulfilling Poser criteria for primary progressive MS. Individuals who only had a single clinical attack (clinically isolated syndrome) are not included in the study and are not further considered.

Affected individuals were identified from the records of: (1) the neurology department at the Landspitali University Hospital; (2) all practicing neurologists in Iceland; (3) smaller hospitals and rehabilitation centres; (4) the results of visual evoked potential (VEP) studies; (5) all MRI studies done in Iceland because of suspected demyelinating disease; and (6) all those approved for treatment of MS with interferon, glatiramer acetate or natalizumab, which need approval by a centralized agency. Many affected individuals were identified in two or more ways. We reviewed the records of the index cases to verify the diagnosis and determine gender and age at diagnosis, time of diagnosis and results of diagnostic studies. We determined the incidence rate for MS in Iceland by calculating the total person-years of observation during the 6-year study period (2002–2007). We determined the age- and gender-specific incidence. We used the mid-year population for each year as provided by Statistics Iceland.[5] We calculated the incidence, adjusted to the year 2000 US standard population. The study was approved by the Icelandic National Bioethics Committee and Data Protection Authority.

Results

We identified 136 individuals who met the inclusion criteria; these are the index cases of this study. All had clinically definite MS according to the Poser criteria. The majority (93%) (126/136) had relapsing–remitting MS and 7% (10/136) had primary progressive MS, according to the Poser criteria[6] (at least a 6-month progressive course with no remissions or exacerbations). None had secondary progressive MS at diagnosis. All were native-born Icelanders, except one individual who was of Danish origin.

The diagnosis of MS was based on a historic relapse in nine (6%) of our index cases. Their initial symptoms had occurred prior to the study period and included typical sensory-level symptoms (4 patients), gait ataxia (3), sensory impairment in one arm and Lhermitte's sign (1) and hemidysesthesia (1). All nine had second and third relapses, both verified by a neurologist, during the study period. Eight individuals had a single verified relapse during the study period and gave a history of prior poorly described transient symptoms, not verified as a relapse. They were considered by us to have clinically isolated syndrome and were not included in the study.

The average annual incidence for MS (Table 1) during the 6-year study period was 7.6 per 100,000 population (95% CI 6.4–9.0) and 8.2 per 100,000, when adjusted to the 2000 US white population. The incidence peaked between 30 and 34 years for men and 35 and 39 years for women. The two eldest index cases were diagnosed after 70 years of age (Figure 1). There were 102 women (75%) and 34 men (25%).

The overall mean age at diagnosis was 36.3 years (median 35; range 16–75), the mean age for women was 35.7 years (median 34.5) and the mean age for men was 38.3 years (median 40.0). The overall mean age at onset was 32.0 years (30.7 for women and 35.8 for men).

MRI was done in 99% (135/136) at the time of diagnosis and 61% (83/135) of these fulfilled the Barkhof criteria.[7] One index case had a normal MRI scan and one did not have an MRI study done (73-year-old woman with typical MS symptoms and oligoclonal bands in the CSF). Seventy percent (94/135) of the patients had MRI of both head and spinal cord, but 13% (12/94) only had MRI of the cervical spine.

Spinal fluid analysis was done in 78% (106/136). Oligoclonal bands were found in 75% (80/106) and 65% (52/80) fulfilled the Barkhof MRI criteria, compared with those without oligoclonal bands, of whom 63% (15/24) fulfilled the Barkhof criteria ($p = 0.82$).

VEPs were measured in 68% (92/136) and abnormally prolonged VEP, consistent with optic neuritis, were found in 43% (42/92). An MRI scan was done in all those with normal VEP ($N = 50$), and 66% (33/50) of them fulfilled the Barkhof criteria. All those with abnormally prolonged VEP ($N = 42$) had an MRI scan, and 60% (25/42) of them fulfilled the Barkhof criteria ($p = 0.52$).

Discussion

Our incidence of 7.6 per 100,000 is similar to several reports from northern Europe and North America.

Table 1. Age and sex-specific incidence of multiple sclerosis in Iceland, 2002–2007

	Men ($n = 34$)			Women ($n = 102$)			Total ($n = 136$)		
Age group	Person years of observation	*n*	Incidence*	Person years of observation	*n*	Incidence*	Person years of observation	*n*	Incidence*
0–14	200,890			193,072			393,962		
15–19	66,566			63,439	4	6.3	130,005	4	3.1
20–24	67,004	1	1.5	64,775	12	18.5	131,781	13	9.9
25–29	66,529	4	6.0	64,022	19	29.7	130,561	23	17.6
30–34	65,515	8	12.2	61,920	16	25.8	127,455	24	18.8
35–39	64,595	6	9.3	62,460	20	32.0	127,070	26	20.5
40–44	66,804	5	7.5	64,998	10	15.4	131,814	15	11.4
45–49	64,722	5	7.7	61,121	11	18.0	125,856	16	12.7
50–54	57,151	1	1.7	53,977	3	5.6	111,131	4	3.6
55–59	47,928	2	4.2	45,386	3	6.6	93,320	5	5.4
60–64	35,268	2	5.7	35,270	2	5.7	70,546	4	5.7
65–69	27,410			28,777		0.0	56,187		
70–74	25,269			28,122	1	3.6	53,391	1	1.9
75–79	20,116			24,273	1	4.1	44,389	1	2.3
80+	21,105			32,528			53,633		
	896,872	34	3.8	884,140	102	11.5	1,781,102	136	7.6

*per 100,000 person years of observation.

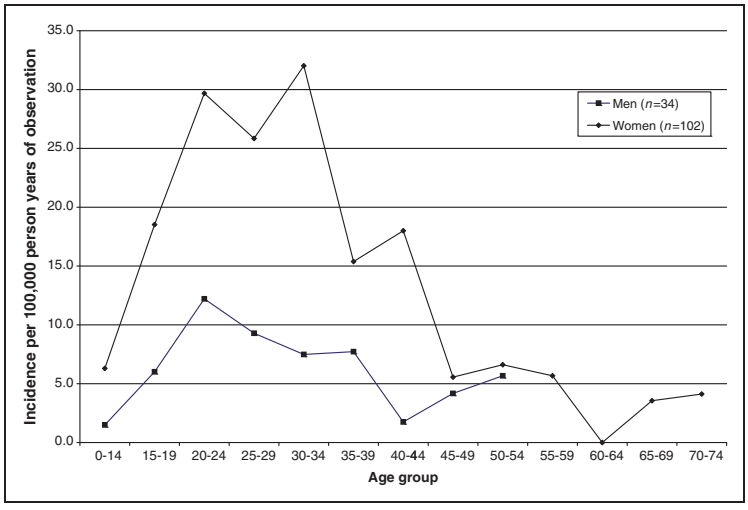

Figure 1. Age-specific incidence of multiple sclerosis in Iceland, 2002–2007.

A population-based study from Oslo, Norway found an incidence of 8.7 per 100,000 for clinically definite MS.[8] A population-based study from Finland[9] (1979–1993) reported the incidence of clinically definite MS in three separate and defined populations to be 9.4, 6.0 and 5.1 per 100,000, respectively. The investigators concluded that the difference between the three populations was caused by 'unknown environmental factors'. A population study from Scotland[10] in 1989–1992 found a higher incidence of 12.2 per 100,000

population. The study included both probable and definite MS and is consequently not directly comparable with our results.

A study from Olmsted County, MN, USA[11] for the period 1985–2000 reported an incidence of 7.3 per 100,000 population for probable and definite MS, when age and sex were adjusted to the 2000 US population. This compares with the higher incidence of 8.2 per 100,000 population for definite MS in the current study, when adjusted to the 2000 US population. A population study[2] from Saskatoon, Canada (1970–2004) reported an incidence for definite and probable MS of 8.1 per 100,000 population (7.8 per 100,000 when adjusted to the 2000 US population). The differences in incidence between the various studies may be explained by differing inclusion criteria.

The annual incidence in the present study (7.6 per 100,000 population) is considerably higher than the 5.3 per 100,000 population reported from Iceland[3] for the period 1986–1990. We do not know the explanation for this difference. The availability of MRI (first introduced in Iceland in 1991), the increased emphasis on early MS diagnosis, because of the availability of effective treatment, and the heightened awareness of MS among physicians and the public may all have led to earlier diagnosis of MS.

All the index cases were diagnosed by a neurologist and most were extensively studied. All but one (99%) had at least one MRI study done. Cerebrospinal fluid (CSF) was examined in 78% (106/136) and VEPs in 68% (93/136). The McDonald criteria[12] became available during the study period but were not used in this study. We included only those who also fulfilled the time-honoured Poser criteria for definite diagnosis. This was done to avoid the impact of the diagnostic uncertainty sometimes associated with a single clinical episode. Due to the difficulty in accurately timing the first symptoms of MS by the medical history, we used the date of the second confirmed attack as the reference point in calculating the incidence of MS.

Presumed MS symptoms may precede the diagnosis of MS by decades (up to 37 years in Olmsted County[11] and 61 years in Wales).[13] Patient identification in incidence series of MS is based on the diagnosis, but several authors have also determine the so-called onset adjusted incidence. We believe that determining onset of MS retrospectively is difficult for many reasons (e.g. recall bias) and can be hard to interpret (e.g. not population-based) and therefore we have not calculated this parameter.

We found that 75% of patients were women, compared with 70% in the Oslo study[1] and 71% in Olmsted County.[8] Older studies from Iceland found the proportion of women to be 58% (1956–1965)[4] and 69% (1986–1990).[3] This apparent increase in the proportion of women with MS in Iceland is comparable with several studies that have reported an increasing proportion of women[2] being diagnosed with MS.

The overall mean age at diagnosis in our study was 36.3 years. This is similar to the 38.3 years reported in Oslo, Norway[8] and 36.2 years in Olmsted County.[11] The highest age- and gender-specific incidence is among women aged 35–39 years of age or 32.0 per 100,000 years. Iceland has a modern healthcare system and one of the lowest infant mortality rates in the world.[5] There is a relatively easy access to neurologists and to MRI. We believe we identified the great majority, probably all, who fulfilled the inclusion criteria for diagnosis of clinically definite MS during the study period.

We find the incidence of MS in Iceland comparable with recent studies from Scandinavia and higher than previously reported from Iceland. Most studies from Europe and North America are not directly comparable because we included only clinically definite cases, as defined by the Poser criteria.

Our results are generally comparable with most population-based studies[8,11] from Western Europe and North America, even if these studies vary as to whether they include only clinically definite MS or also probable MS cases. There are only a few incidence studies available from the MRI era[2,8–11,14] and our study describes the MRI results. MRI was done for 99% of the individuals in this study, and 61% of them met the Barkhof criteria at the time of diagnosis; this proportion was comparable regardless of the presence of abnormal VEP or oligoclonal bands.

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Conflict of interest statement

The authors report no conflicts of interest.

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Paper II

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Prevalence of Multiple Sclerosis in Iceland

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Keywords
Multiple sclerosis · Epidemiology · Prevalence · Population-based · Mean age · Magnetic resonance imaging · Clinical phenotype

Abstract
Background: In this study, we examined multiple sclerosis (MS) point prevalence in the well-defined island population of Iceland. ***Methods:*** This study included all registered residents of Iceland with MS on the prevalence day, December 31, 2007. All included patients met at least one of the following criteria: McDonald criteria; Poser criteria for clinically definite MS, laboratory-supported definite MS, clinically probable MS; or criteria for primary progressive MS. The patients' medical records were reviewed, including all available MRI data acquired prior to the prevalence day. ***Results:*** We identified 526 patients, of whom 73% (382) were women. The crude point prevalence of MS was 167.1 per 100,000 population on the prevalence day. With age adjustment made to the 2000 U.S. population, the prevalence was 166.5 per 100,000 population. The mean patient age on the prevalence day was 47 years(range 13–89) for both men and women. The mean age at diagnosis was 36 years (range 13–77): 35 years for women and 36 years for men. ***Conclusion:*** MS prevalence was high in Iceland compared to the prevalence mentioned in reports from most of the world, and was similar to prevalence rates in other Nordic countries.

Introduction

Over recent decades, many studies have reported an increasing prevalence of multiple sclerosis (MS) in different parts of the world, including Sweden, Finland, Japan, and Iran [1–4], while other studies have found a more stable prevalence [5]. The reason for the apparent increase in some studies remains unknown, but it may be influenced by the presence of improved diagnostic imaging, and the increased focus on MS in association with the increasing availability of effective treatment [6].

Comparisons between various studies are difficult to make for many reasons. While most studies use the Poser

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criteria from 1983 [7], recent studies have used the McDonald criteria [8–10]. The studies using the Poser criteria all include clinically definite MS (CD-MS), and some also include clinically probable MS (CP-MS) and even clinically possible MS.

Notably, prevalence varies according to geographic location. Higher MS frequency is consistently found in the Nordic countries [1, 2, 11, 12], northern parts of Western Europe, and North America, while lower MS frequencies are reported in Asia, the Middle East, and Africa [2, 4, 13–15]. Prevalence data from before 2000 imply a rising MS prevalence in Iceland [16].

We examined the MS prevalence in a well-defined island population.

Methods

Background

Iceland is an island in the North Atlantic with a well-defined population of 315,459 on the prevalence day, December 31, 2007 (hagstofa.is). In 2007, 12% of the population had been born abroad. Iceland has a modern healthcare system that is accessible to all residents, and it has 1 neurology department and 3 radiology departments with MRI equipment.

Cases

This study included registered residents of Iceland who were alive on the prevalence day, according to the Icelandic national registry. All met at least one of the following criteria: (1) the 2010 McDonald criteria for dissemination in space (DIS) and time (DIT) on MRI imaging; (2) the Poser criteria for CD-MS, (3) laboratory-supported definite MS (LSD-MS), or (4) CP-MS; or criteria for primary progressive MS [7, 8]. These individuals were the index cases of the study. All index cases were diagnosed by a neurologist, and many were seen by several neurologists. The time of diagnosis was defined as the time of the second observed MS attack, or when the patient was informed of the diagnosis. Patients with primary progressive MS exhibited neurological symptoms that increased over at least 1 year.

Case Finding

To identify all Iceland residents with an MS diagnosis who were alive on the prevalence day, we searched records from (1) the neurology department at Landspitali University Hospital; (2) all practicing neurologists in Iceland; (3) smaller hospitals and rehabilitation centers; (4) the results of visual evoked potential studies, done at the Landspitali University Hospital neurology department; (5) and all patients treated with disease-modifying agents (interferon, glatiramer acetate, or natalizumab), all of which required approval from a centralized agency. We retrieved information from the Icelandic Social Security Agency, identifying all residents of Iceland who received disability benefits due to MS from 1990 to 2007, including those applying for a walking aid from 1997 to 2007. Most index cases were identified from multiple sources. We reviewed the index cases' medical records to verify the diagnosis, and determine gender, residence in Iceland on the prevalence day, times of onset and diagnosis, and age at diagnosis.

The index cases were classified according to the Poser or McDonald criteria, based on symptoms and clinical findings at the first and/or second attack, or the findings at the first presentation to a neurologist. For each individual diagnosed based on only the McDonald criteria, we attempted to assign a Poser category. We reviewed the CSF and MRI results obtained at the initial presentation, and in selected cases, we reviewed the actual studies (Ó.K. and Ó.E.), to assign the McDonald criteria. When MRI was available, we determined the time from presentation to a neurologist until the fulfillment of McDonald imaging criteria for MS.

Calculations

We calculated the MS prevalence on the prevalence day in the population of Iceland as provided by Statistics Iceland (hagstofa.is). The prevalence was adjusted to the 2000 and 2010 US standard population (census.gov). The 95% CIs were calculated, assuming a Poisson distribution for the prevalence cases. Statistical analyses were performed using Microsoft Excel. The study was approved by the Icelandic National Bioethics Committee and Data Protection Authority.

Results

We identified 526 residents of Iceland who had MS on December 31, 2007, of whom 2% (13) were of foreign origin. These index cases were diagnosed based on either the Poser criteria 94% (496/526) or 2010 McDonald criteria 6% (30/526) for MS. Those who met the McDonald criteria, predominantly also fulfilled the Poser criteria, with 70% (21/30) classified as LSD-MS, 13% (4/30) as CP-MS, but 17% (5/30) were not classifiable since oligoclonal bands were not determined. Among the 94% (496/526) meeting the Poser criteria, 90% (446/496) were classified as CD-MS, 5% (24/496) as LSD-MS, and 5% (26/496) as CP-MS [7, 8]. Patients who only met the Poser criteria for laboratory-supported probable MS were not included. Three patients (0.6%) were diagnosed with MS, but details of their symptoms, findings, and work-up were unavailable. We identified several individuals with clinically isolated syndrome [17] and a normal diagnostic work-up including MRI. These patients were not included in the study. Relapsing-remitting MS was diagnosed in 93% (489/526), primary progressive MS in 6% (32/526), and the clinical form was unknown in 1% (5/526) of patients.

Of the 526 patients, 75 (14%) had experienced only a single clinical event by the prevalence day. Thirty of these patients met the McDonald criteria for MS (both DIT and DIS), and their mean time from onset to prevalence day was 4.7 years (median 3.0; range 0–36). The other 45 did not meet the McDonald criteria but were included because they met the Poser criteria: LSD-MS in 4% (23/526), and CP-MS in 4% (22/526). All these 45 patients had un-

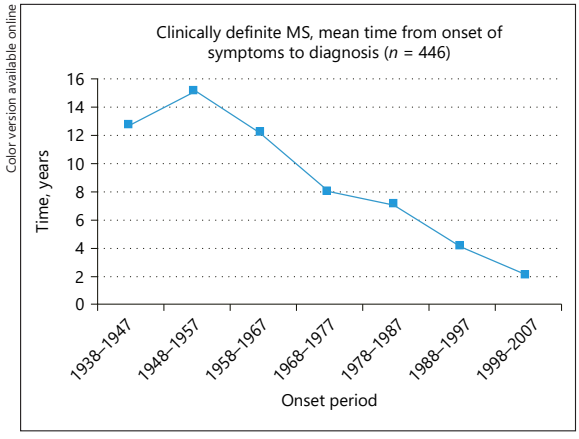

Fig. 1. Mean duration from onset to diagnosis among patients fulfilling the Poser diagnostic criteria for clinically definite multiple sclerosis (MS).

dergone MRI and fulfilled DIS, but not DIT criteria. They had a mean duration from onset to prevalence day of 6.6 years (median 4.0; range 0–31). The time from first symptoms to MS diagnosis for CD-MS cases (n = 446) was 4.5 years (median 2.0 years; range 0–30 years; Fig. 1).

Prevalence

The crude point prevalence of MS was 167.1 per 100,000 population (95% CI 153–181) on the prevalence day. With age adjustment to the 2000 and 2010 U.S. populations, the prevalence was 166.5 (95% CI 166.0–167.0) and 171.1 (95% CI 170.5–171.4) per 100,000 population respectively. The prevalence of cases only fulfilling definite Poser criteria at diagnosis (n = 447) was 139.5 per 100,000. The age-specific prevalence (Table 1) increased with advancing age until about 65 years, and declined thereafter.

Gender

The prevalence cohort comprised 73% (382/526) women and 27% (144/526) men (sex ratio 2.6:1). The gender-specific prevalence per 100,000 population was 248 (95% CI 223–273) among women and 89 (95% CI 74–104) among men. The gender ratio in the prevalence group according to the year of diagnosis was 2.1: 1 for 1975–1985 (n = 60), 2.5:1 for 1986–1996 (n = 122), and 2.6:1 for 1997–2007 (n = 320). The number of patients diagnosed earlier was too low to be informative.

Age

The mean age on the prevalence day was 47 years (range 13–89) for both men and women. The mean age at diagnosis was 36 years (range 13–77): 35 years for women and 36 years for men. The mean age at symptom onset was 31 years (range 10–74): 33 for men and 31 for women. Figure 2 shows the age-specific prevalence.

McDonald MRI Criteria 2010 [8]

Of the 526 patients, 460 (87%) had undergone at least one MRI by the prevalence day. The brain was studied in all instances and the spinal cord in the great majority. DIS criteria were fulfilled for 382 (83%) of these 460 patients, and the mean time from first visiting a neurologist to fulfilling DIS criteria was 6 years (median 2 years; range 0–44). DIT criteria were fulfilled by 301 (65.3%) of these 460 patients, and the mean time from onset to fulfilling DIT criteria was 7.1 years (median 4; range 0–36). The 66 patients (13%) who had not undergone MRI were diagnosed an average of 22.8 years before the prevalence day (median 20.5; range 2–53 years), compared to an average of 9.1 years (median 6.0; range 0–61) among those who had undergone MRI.

MRI Studies at Diagnosis

Among the 430 patients with Poser CD-MS, 67% (289/430) had undergone MRI within 6 months following MS diagnosis. The mean duration from diagnosis to prevalence day was 6.0 years (median 5.0; range 0–32), compared to 25.6 years among those who had not undergone MRI at diagnosis (range 4–61, median 24). Among those who underwent MRI at diagnosis, 26% (110/430) met the criteria for both DIS and DIT, including 17% (75/430) in the initial MRI study. Normal MRI results at diagnosis were seen in 3% (9/348). During the 10 years after the prevalence day, 56% (5/9) of these patients met some MRI criteria for MS: 3 fulfilled both DIT and DIS, 1 fulfilled DIT only, and 1 fulfilled DIS only.

Disability

Among all patients diagnosed with MS during the 11 years prior to the prevalence day (1997–2007), 11% (35/320) started using a walking aid (cane, walker, or wheel chair): 1% (3/320) by the first year, 3% (9/320) by the second year and 6%(18/320) by the fifth year after diagnosis.

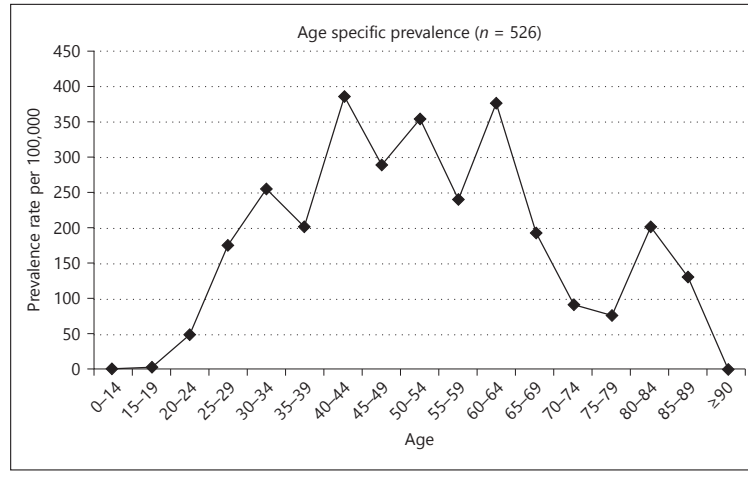

Fig. 2. Age-specific point prevalence of multiple sclerosis (MS) on December 31, 2007.

Table 1. Age-specific prevalence on December 31, 2007

Age at prevalence day	Male			Female			Both sexes		
	population	cases	prevalence rate per 100,000	population	cases	prevalence rate per 100,000	population	cases	prevalence rate per 100,000
0–14	33,605	0	0	32,374	1	3	65,979	1	2
15–19	12,161	0	0	11,524	1	9	23,685	1	4
20–24	11,581	2	17	11,023	9	82	22,604	11	49
25–29	12,977	9	69	11,690	34	291	24,667	43	174
30–34	12,147	17	140	10,743	41	382	22,890	58	253
35–39	11,505	14	122	10,311	30	291	21,816	44	202
40–44	11,801	23	195	11,153	65	583	22,954	88	383
45–49	11,757	17	145	10,768	48	446	22,525	65	289
50–54	10,743	21	195	9,877	52	526	20,620	73	354
55–59	8,979	13	145	8,456	29	355	17,435	42	241
60–64	7,093	21	296	6,782	31	457	13,875	52	375
65–69	4,853	3	62	5,029	16	318	9,882	19	192
70–74	4,116	2	49	4,555	6	132	8,671	8	92
75–79	3,662	0	0	4,235	6	142	7,897	6	76
80–84	2,308	2	87	3,175	9	283	5,483	11	201
85–89	1,199	0	0	1,889	4	212	3,088	4	130
>90	409	0	0	979	0	0	1,388	0	0
Total	160,896	144	89	154,563	382	248	315,459	526	167

Discussion

We found the nationwide point prevalence of MS in Iceland on December 31, 2007 to be 167 per 100,000 population for all cases, and 140 per 100,000 for CD-MS. Several population-based MS prevalence studies [2, 5, 9–12, 18–20] have been published in the last 2 decades (Table 2), with prevalence varying between studies. The differences may be partly due to the use of different inclusion criteria, and differences in healthcare among different countries. Some studies use Poser criteria only [3, 5, 12, 16, 19, 21], while others use only McDonald criteria [9], complicating comparisons between studies.

Table 2. Overview of data from population-based prevalence studies

Country (area)	Author	Publication year	Date of prevalence	Point prevalence*	Included patients, *n*	Population	Inclusion criteria
United Kingdom (South East Wales)	Hirst et al. [19]	2009	01.09.2005	146	620	424,633	Poser and McDonald
Sweden	Ahlgren et al. [2]	2011	31.12.2008	188.9	17,485	9,256,347	Poser and McDonald
Finland	Sarasoja et al. [21]	2004		105	277	263,886	CD-MS and LSD-MS Poser
Scotland	Visser et al. [10]	2012	24.09.2004	238	590	248,102	CD-MS, LSD-MS, CP-MS LSP-MS Poser and McDonald
Denmark	Bentzen et al. [12]	2005	31.12.2004	173	9,377	5,410,000	CD-MS and CP-MS Poser
Norway	Berg-Hansen et al. [11]	2014	01.01.2012	203	10,121	4,985,870	Poser and McDonald
Olmsted County	Mayr et al. [5]	2000	01.12.2000	177	218	123,386	Poser
Canada Saskatoon	Hader et al. [20]	2005	01.01.2005	293	587	196,815	CD-MS and CP-MS Poser
Catalonia	Otero-Romero et al. [9]	2008	31.12.2008	80	120	150,139	McDonald
Italy	Iuliano et al. [18]	2008	31.12.2005	71.6	186	259,681	Poser and McDonald

* Per 100,000.
CD-MS, clinically definite; MSLSD-MS, laboratory-supported definite MS; CP-MS, clinically probable MS.

We believe that we identified all residents of Iceland meeting the Poser criteria on the prevalence day, where those with laboratory-supported probable MS, we lacked adequate information for diagnosis (e.g., optic neuritis and Babinski response). However, LSP-MS presumably represented few cases, comprising only 0.3% in a population-based study from Wales [19]. We assigned a Poser category to the 6% of patients diagnosed based on only McDonald criteria, and determined that our total patient group fulfilled the Poser criteria as follows: 85% CD-MS, 9% LSD-MS, and 5% CP-MS.

In a 2000 population study from Finland [21], the MS point prevalence was 105 per 100,000 population (277 individuals; 53% women; population 263,886). The inclusion criteria were CD-MS (78%) and LS-DMS (22%). Our present results showed a higher comparable prevalence of individuals with CD-MS and LSD-MS (149 per 100,000). A 2005 population study from Wales [19] reported an MS prevalence of 146 per 100,000 (620 cases; 71% women; population 424,633), with inclusion criteria of CD-MS (83%), LSD-MS (5%), CP-MS (10%), LSP-MS (0.3%), and unclassified (1.3%). The CD-MS prevalence was 129 per 100,000, similar to our prevalence of 140 per 100,000.

A 2005 nationwide MS study from Denmark [12] reported a point prevalence of 173 per 100,000 (9,377 cases; 67% women; population 5,410,000). Their study was based on a registry covering over 90% of the MS population, including CD-MS and CP-MS without specifying the proportion of each. A year 2000 population study from Minnesota, USA [5] reported a point prevalence of 177 per 100,000 (218 cases; 69% women; population 123,386), with MS diagnosis based on the Poser criteria, without providing the proportions of the subcategories.

A 2008 nationwide population study from Sweden [2] found a point prevalence of 189 per 100,000 (17,485 cases; 70% women; population 9,256,347), with patients identified from a nationwide MS registry. Inclusion criteria were "definite" and "probable" MS based on the McDonald or Poser criteria (87%), "possible" MS according to McDonald criteria (7%), and "unclassified" MS (6%). This is a higher than our presently reported prevalence, even excluding the "possible MS" cases. A 2012 study of the entire population of Norway reported a point prevalence of 203 per 100,000 [11] (10,121 cases; 69% women; population 4,985,870)–higher than the prevalence in Iceland. The included patients fulfill either the Poser or McDonald criteria, with no further description. Both the Swedish and the Norwegian studies are comparable to our study and there is no obvious explanation for the difference in prevalence.

A 2009 population study from Scotland [10] reported a point prevalence of 238 per 100,000 (590 individuals; 70% women; population of 248,102). The study included all patients fulfilling Poser criteria for CD-MS

(91%), LSD-MS, CP-MS, or LSP-MS or McDonald criteria (85%), without further breakdown by subgroup. A 2005 population study from Saskatoon, Canada [20] reported a point prevalence of 293 per 100,000 (587 cases; 72% women; population of 196,815). They included Poser definite and probable cases without providing the relative proportions of patients. A 2008 study from Catalonia [9] reported a point prevalence of 80 per 100,000 (120 cases; 59% women; population of 150,139)–lower than in our study. They included patients fulfilling the McDonald criteria. A 2000 study from Iceland [16] reported a point prevalence of 123 per 100,000, and included cases with Poser possible and probable MS.

The female-to-male ratio was 2.6:1 in our study, 2.2:1 in Norway [11], 2.4:1 in Sweden [2], 2.4:1 in Wales [19], 2.4:1 in Scotland (23), and 2.6:1 in Canada [20]. Our results are comparable to findings in Nordic countries, Scotland, Wales, Olmsted county, and Saskatoon.

In Scotland, the female-to-male ratio was significantly higher among younger patients [22]. In Denmark, this ratio increased from 1.31 in 1950 to 2.02 in 2005 [12]. We did not find that the female-to-male ratio changed over time among those diagnosed during the last 3 decades before the prevalence day.

In our study, the mean duration from onset to MS diagnosis was 4.3 years. Other population-based prevalence studies report mostly similar results: Catania, Italy, 5 years [19]; Wales, 5 years [19]; and Scotland, 6 years [22]. The shortest period has been reported in Catalonia (1.5 years) [3]. In our study, the time from symptom onset to MS diagnosis progressively shortened with each decade (Fig. 1), likely due to improved access to neurologists and advances in diagnostic studies. Similar findings are reported in a study from Catalonia [9], while a study from Scotland [22] does not show a change from 1985 to 2005.

In our study, the mean age at diagnosis was 36 years, which was identical to a recent incidence study from Iceland [23], and similar to prevalence studies from Scotland (39 years) [22] and Wales (37 years) [19]. Among the cases in our study, 7% had primary progressive MS, compared with 10% in Scotland [22], 8% in Wales [19], 18% in Finland [21], and 4% in Italy [18].

EDSS score was not regularly available for most patients. We attempted to determine when an individual started using a walking aid [24], since this is an important surrogate for impaired gait. We found that 6% of patients required a walking aid (EDSS 6.0) within 5 years following MS diagnosis. In a case series from Austria, approximately 10% of 793 patients with MS had reached an EDSS of 6 after 10 years of observation [25].

Conclusion

The prevalence of MS in Iceland was high compared with that reported from most of the world, and similar to the prevalence rates in other Nordic countries. This supports previous observations of high MS prevalence in Nordic countries. Prevalence studies provide valuable information about the disease burden in society, and it is important to identify all eligible patients. In this study, we conducted an extensive search for all Iceland residents fulfilling the inclusion criteria. We reviewed each patient's medical information in detail, and believe that we identified the great majority–probably all–who met the inclusion criteria on the prevalence day. To our knowledge, this is the first population-based prevalence study of MS that includes MRI results.

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Disclosure Statement

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Paper III

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ORIGINAL COMMUNICATION

A nationwide survey of the influence of month of birth on the risk of developing multiple sclerosis in Sweden and Iceland

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Abstract
Previous studies have shown that the risk of multiple sclerosis (MS) is associated with season of birth with a higher proportion of MS patients being born in spring. However, this relationship has recently been questioned and may be due to confounding factors. Our aim was to assess the influence from season or month of birth on the risk of developing MS in Sweden and Iceland. Information about month of birth, gender, and phenotype of MS for patients born 1940–1996 was retrieved from the Swedish MS registry (SMSR), and their place of birth was retrieved from the Swedish Total Population Registry (TPR). The corresponding information was retrieved from medical journals of Icelandic MS patients born 1981–1996. The control groups consisted of every person born in Sweden 1940–1996, their gender and county of birth (TPR), and in Iceland all persons born between 1981 and 1996 and their gender (Statistics Iceland). We calculated the expected number of MS patients born during each season and in every month and compared it with the observed number. Adjustments were made for gender, birth year, and county of birth. We included 12,020 Swedish and 108 Icelandic MS patients in the analyses. There was no significant difference between expected and observed MS births related to season or month of birth in Sweden or Iceland. This was even the results before adjustments were made for birth year and birth place. No significant differences were found in subgroup analyses including data of latitude of birth, gender, clinical phenotype, and MS onset of 30 years or less. Our results do not support the previously reported association between season or month of birth and MS risk. Analysis of birth place and birth year as possible confounding factors showed no major influence of them on the seasonal MS risk in Sweden and Iceland.

Keywords Multiple sclerosis · Month of birth · Risk factors · Epidemiology · Sweden · Iceland

Introduction

There is accumulating evidence that implies low sun exposure and low levels of vitamin D as risk factors for multiple sclerosis (MS) [13, 15, 17]. This association may explain the increasing incidence and prevalence of MS observed with the distance from the equator [3, 20]. In fact, a gradient of increased MS prevalence with north latitude has also been reported in Sweden [1]. Moreover, low ultraviolet radiation of pregnant women during winter has been a reasonable explanation for the increased risk of MS observed in persons born during spring and the reduced risk in those born during winter [26]. The changed risk of MS related to month of birth (MOB) has also been reported in the Scandinavian countries [10, 16, 21] including Sweden [22]. However, this relationship has recently been questioned, and confounding factors rather than biology were suggested to generate the association between MOB and MS risk [7, 8]. The highly variable birth rate, which is influenced by birth year and regional (birth county) variations, may be responsible for the previous findings [7, 8]. Although a recent study of Norway did take these confounding factors into account for, they claimed an increased MS risk in persons born in April [25]. In light of this, we conducted a study of association between season or MOB and the risk for developing MS in Sweden

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and Iceland. Our aim was to compare our results with those previously published on MOB and MS risk from other populations and to clarify the effect from birth year and birth place as confounding factors.

Materials and methods

The study was based on two nationwide population cohorts of Sweden and Iceland. All patients had clinically definite or clinically probable MS according to Poser diagnostic criteria or MS according to the revised McDonalds criteria [18, 19].

Area and population

Sweden lies between latitudes 55° and 69° north in Northern Europe. There are 290 municipalities in Sweden. The population density is considerably higher in the southern part of the country. During the study period from 1940 to 1996, the Swedish population increased from 6.4 to 8.8 million people, the mean age increased from 37.0 years in 1968 (the first year of registration of mean age) to 39.7 years, the birth rate per 1000 decreased from 15.1 to 10.8, and the mortality per 1000 decreased from 11.4 to 10.6. (http://www.scb.se).

Iceland lies between latitudes 64° and 66°N. The population of Iceland increased between 1981 and 1996 from 0.23 to 0.27 million people, the mean age increased from 31.6 to 33.9 years, the birth rate per 1000 decreased from 19.0 to 16.2, and the mortality rate per 1000 decreased from 7.2 to 7.0. In 1996, approximately 70% of the population lived in Reykjavik, the capitol of Iceland which lies at 64°N (http://www.statice.is).

The Swedish registries

The Swedish MS registry (SMSR), started in 1996, became web based 2004, and 2008 included 14,500 of Sweden's estimated 17,500 prevalence patients, giving coverage of 80% [1, 11]. The registry serves as a national quality health care registry for Swedish MS patients. Patients with MS according to the Poser [19] or the McDonald criteria [18] have been prospectively or retrospectively registered (http://www.neuroreg.se).

The Swedish Total Population Registry (TPR), founded in 1947, registers residence over time for all residents in Sweden with some retrospectivity (http://www.scb.se). Before 1961, there was a chance that individuals were not included in the registry if they lived unmarried together with another person and without children; however, thereafter, the registry is complete [14].

The Swedish MS cohort

MS patients included in the study were born in Sweden between 1940 and 1996. This period was chosen to decrease the effect of decease bias for patients born before 1940 and the possibility that patients born after 1996 might not yet have developed the disease. Deceased patients were included. At 31 January 2016, the day of data export, the following data were retrieved from the SMSR for every patient: personal identity number, month, season and year of birth, gender, date of MS onset, age at MS onset, age at data export, MS phenotype (relapsing–remitting (RRMS), secondary progressive (SPMS), progressive relapsing MS (PRMS), and primary progressive MS (PPMS), date when patients reach Expanded Disability Status Score (EDSS) 6 [12]. The following data were retrieved from the TPR: place of birth.

The Swedish control cohort

We created a control group ($n = 3{,}503{,}550$) of every person born in Sweden 1940–1996, their gender and county of birth according to TPR.

The Icelandic MS cohort

The Icelandic MS patients were born in Iceland 1981–1996. There are no data available for persons born prior to 1981 in Iceland. Identical data as for the Swedish MS cohort were retrieved for Icelandic MS patients.

The patients were retrieved from different sources to make the cohort as complete as possible. The diagnosis searched for was: ICD10 (G35, G37.9), ICD9 (340, 341), and ICD8 (340, 341).

1. The neurology department at the Landspitali University Hospital; the only university hospital in Iceland which handles referrals for the whole country. Information was retrieved for both inpatients and outpatients.
2. All private practicing neurologists in Iceland.
3. Smaller hospitals and rehabilitation centers.
4. All patients approved for treatment of MS with disease modifying therapies, i.e., treatments in need of approval by a centralized agency.
5. Information from the Icelandic Social Security Agency to identify all who received disability benefits in Iceland.

The Icelandic control cohort

We created a control group ($n = 65{,}114$) from the Icelandic population born 1981–1996, divided according to gender (http://www.statice.is).

Statistical methods

All tests were based on the observed numbers of births in a certain season or month. These observations were compared to adjusted expected means. These adjusted means where derived from a simple Bernoulli distribution for each case with probabilities equal to the relative frequency of births in the MS case specific stratum (gender, birth year, and county). A central limit argument implies that we can use normal approximation for the null hypothesis reference distributions. By assuming independence between all Bernoulli distributions, we receive marginally larger variance than we would have got by taking multiple case correlations inside the strata into account.

Primarily, we look for over-representations, but we also acknowledge under-representations, if they would show up, using two-sided tests. The statistical approach was originally to test for seasonal effects [(March, April, May), (June, July, August), (September, October, November), and (December, January, February)]. When we did not find any signs of effects, there we started an exploratory phase of testing analyzing gender divided data, months instead of season, specific MS subgroups including early and late onset groups, and geographical north–south separation. Certainly, multiple correction problems arise in this second step. However, the purpose of this step was partly to enable comparisons with findings in the Norwegian study [25] and confirm the negative findings in the first step. For more arguments behind this approach, cf. the discussion section below.

A normal test was used with the null hypothesis that there is no difference in the probability of getting MS for male or female depending on the birth date. This null hypothesis was tested against an alternative hypothesis that there is an increased risk getting the disease in a certain period. We used the Bernoulli estimation model to calculate the expected number of MS patients being born in every month and compared it with the observed number with a two-sided T test ($p = 0.05$). The calculations were done with and without adjustments for gender, year of birth, and county of birth as suggested by Fiddes et al. [7]. This test was also applied when the cohort was divided according to birth in Southern or Northern Sweden. We divided Sweden into two regions, a northern and a southern region, divided at the geographical middle of Sweden, i.e., 62″N. Thereafter, we calculated the observed vs expected MS MOB in the two regions. Similar tests were used for subgroup analysis related to gender, MS phenotype (RRMS, SPMS, PPMS), and early onset age ($\leq$ 30 years of age). The statistical testing procedure is described in Supplement 1.

The calculation was done using Matlab (Mathworks, Natick, MA, USA).

The study was approved by the regional ethical review board of Gothenburg, Sweden and Icelandic National Bioethics Committee and Data Protection Authority.

Results

The Swedish MS cohort

We included 12,020 MS patients born in Sweden 1940–1996. The export from the MS registry was made 31st of January 2016. At that date, the SMSR included 15,801 patients, 14,157 of them were born in Sweden, 13,398 of them were born 1940–1996, and 12,020 of them had information of place of birth. The mean age of this final cohort was 51 years (median 51 years). The mean age at MS onset ($n = 11,137$) was 32.9 years (range 1–70 years). The mean age at MS diagnosis ($n = 10,065$) was 37.4 years (range 6–73 years). The female:male ratio was 2.5:1. MS phenotype was available for 11,412 patients: RRMS ($n = 7087$, 62.0%), PPMS ($n = 932$, 8.2%), PRMS ($n = 154$, 1.3%), and SPMS ($n = 3239$, 28.4%). There were 87.6% ($n = 10,283$) living in the Southern region of Sweden and 12.4% ($n = 1458$) in the Northern region of Sweden.

The risk of MS according to season and month of birth

We found no relationship between season of birth and the risk of developing MS later in life (Supplement 2). Neither did we find any difference between observed and expected number of MS patients when each MOB was analyzed separately (Fig. 1) with or without adjustments for birth year and county of birth. With adjustments, there seemed to be 7% more MS births in February than expected (1030 vs 961.8 $p = 0.0208$, Supplement 3). However, when Bonferroni correction is done, this difference is far from significant. To reject the null hypothesis for 5% level, we would need a p value of less than 0.0042 for statistical significance (0.0084 in case of one sided tests).

The risk of MS associated with month of birth and latitude

When latitude was tested, there were 10% more MS births in February than expected in the Southern region of Sweden (900 vs 824.5, $p = 0.00574$). After Bonferroni correction for multiple comparisons, the effect was not statistically significant (Supplements 4 and 5).

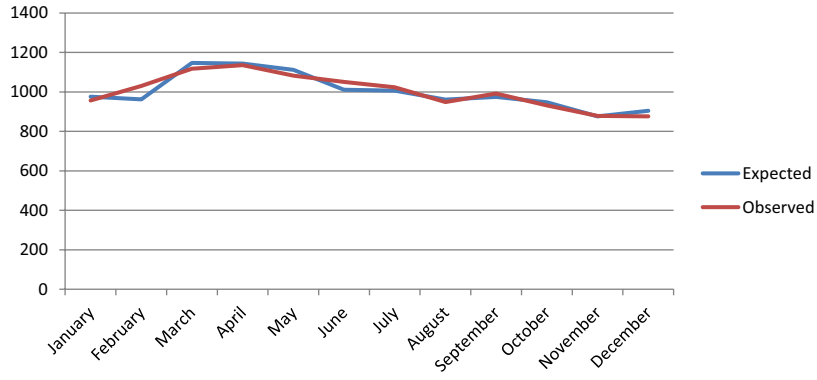

Fig. 1 Seasonality of MS births in Sweden, with adjustments for gender, year of birth, and county of birth

The risk of MS associated with month of birth and gender

No significant difference was found in observed vs expected births when gender was taken into account. There was a trend towards more MS births in February both in men (303 vs 276.9 $p = 0.099$) and females (727 vs 685.0 $p = 0.0912$).

The risk of MS associated with month of birth and phenotype

No effect of MOB was seen on the risk of MS when the cohort was divided according to MS phenotype.

The risk of MS associated with month of birth and early age of MS onset (≤ 30 years of age)

In spring, there were fewer MS births than expected (1372 vs 1442.0 $p = 0.0285$), but a p value of 0.0125 or lower would have been needed to reach statistical significance after correction for multiple tests (Supplement 6). Nor did we find any significant differences in the number of MS births related to month.

The Icelandic MS cohort

At the 01st of January 2016, we included 108 patients born in Iceland from 1981 to 1996. The mean age of the cohort was 30.1 years (range 20–35 years), the mean age at MS onset was 22.5 years (range 10–37 years), and the mean age at MS diagnosis was 23.7 years (range 13–39 years). The female:male ratio was 2.1:1.

The risk of MS according to season and month of birth

We found no relationship between season of birth and the risk of developing MS later in life (Supplement 7). Neither did we find any difference between expected and observed number of Icelandic MS patients when each MOB was analyzed separately (Supplement 8). In our original analysis, there seemed to be fewer MS births in the autumn (17.0 vs 26.9, $p = 0.028$). After correction for multiple tests, this effect disappeared.

Discussion

Our study showed no influence from season of birth or MOB on the risk of developing MS later in life in Sweden or Iceland with or without adjustments for possible confounding factors [7]. Even in the subgroup analysis, no observations remained as statistically significant after correction for multiple hypothesis testing, which confirms the negative result in the seasonal analysis. The only month that showed higher MS births was February, where we observed 7% more MS cases than expected. This corresponds to a p value of 2.08% before any multiple corrections. This significance disappeared after correction for multiple testing. Although low vitamin D levels during fetal development might be a risk factor for developing MS later in life [6], our results did not support that this risk is associated with season of birth or MOB.

In a recent study from Norway, including a cohort of 6649 MS patients born 1930–1979 [25], they found a 10% increase in MS births in April, a 15% increase in December, and, in contrast with our study, a 13% decrease in February before any cofounding factors adjustments. However, after correction for birth year, the increase in December disappeared, and after correction for birth county, the decrease in February became non-significant. However, a 10% increase in birth of the Norwegian MS patients remained in April, and this increase was also significant when comparing the incidence of MS in siblings, mothers, and fathers. Although the authors concluded that there was an increased risk in April births in the MS population,

the significance disappeared after correction for multiple testing. We showed only marginally smaller observed MS cases in April.

We also found that the MS incidence was higher than expected in February in the Southern region of Sweden. The p value is 0.5% but not significant after correction for months. Moreover, this association was not in line with the previous hypothesis, suggesting an increased MS risk with northern latitude, less sun exposure and low D vitamin levels.

In contrast with our results, a previous study from Sweden showed more cases of MS than expected in June (11%) and fewer than expected in December and January (8 and 10%), respectively [22]. Although their MS patients ($n = 9461$) were also retrieved from the SMSR registry, their study population and controls differed from ours in several aspects. Their patients had a median birth year of 1957 and included all patients registered in the SMSR until 2008. Our study cohort was younger with a median birth year of 1965, and included only patients born between 1940 and 1996 to decrease the effect of decease bias for patients born before 1940 and the possibility that patients born after 1996 might not yet have developed MS. However, even with our study design, we might have missed patients born after 1940 who due to severe MS died before 1996 when the SMSR was established. This limitation in year of birth influenced the size of the control cohort, and neither did we include controls from municipalities that did not have a case of MS. Another factor that should be noted is the change of MOB of patients with MS over recent years. In contrast with the previous investigation [22], we found no increased MS risk related to birth in June in patients registered after 2008.

Table 1 Owerview over studies of birth month and MS risk

Country	Author	Publication year	Birth years of MS group	Included patients (n)	Controls	Main findings	Adjustment for birth year/ birthplace
Canada, Great Britain, Denmark, Sweden [26]	Willer et al.	2005	1926–1970 (Canada)	17,874, 11,502, 6276, 6393 (total 42,045)	13,675,451 (Canada)	9.1% more in May, 8.5% fewer in November	No/no
Sweden [21]	Salzer J et al.	2010	1900–2007	9361	12,116,853	11% more in June, 8 and 10% fewer in December and January	No/no
Italy [23]	Sotgiu et al.	2006	nd[a]	810	247,612	More births in spring months	No/no
Scotland [5]	Bayes et al.	2010	1922–1992	1309	6,198,352	17% more in spring, 13% fewer in autumn	No/yes
Australia [24]	Staples et al.	2010	1920–1950	1524	2,468,779	1.34 risk for those born in November–December compared May–June[b]	No/yes
Kuwait [2]	Akhtar et al.	2015	1950–2013	1035	3,454,222	13% more in December	No/yes
Portugal [4]	Barros et al.	2013	1992–1943	421	1,150,362	No seasonal difference	No/yes
Norway [25]	Torkildsen et al.	2014	1930–1979	6649	2,899,260	No seasonal difference	Yes/yes
Finland [21]	Saastamoinen et al.	2012	1900–1988	8739	7,014,435	9.4% more in April, 11.1% fewer in November	Yes/no
South America [9]	Fragoso et al.	2013	nd[a]	1207	1207	No seasonal difference	Yes/yes

[a]Not defined

[b]Incidence rate ratio for two-month period with May–June as the reference period (1.0)

Moreover, no correction for year of birth or county of birth was made when analyzing the MS risk in that study. They used 2 × 2 Chi-squared test for calculating MOB and MS risk. Applying that test to our data for a direct comparison did not influence our results.

We searched PubMed and Scopus for studies investigating the possible influence from season of birth or MOB on the risk of developing MS (Table 1). Except for the Norwegian study [25], other studies have not adjusted the results for birth year and birth place. They have made adjustments for either birth place [2, 4, 5, 24], or birth year [21], or none of these confounding factors [26]. However, without adjustments, similar result as we found was found in a South African study [9] and in a study from Portugal with 1207 MS patients and 1207 match controls, after adjusting the material for latitude of birth and gender [4]. However, birth year was not taken into account in this analysis. In all other studies, an association has been showed between increased MS risk and birth during spring and/or a decreased MS risk in persons born during autumn or winter [5, 21–24, 26] or the opposite in a study from the Southern hemisphere [2].

The main strength of our study is that data was retrieved from national registries with high patient recovery. The Swedish MS registry had high coverage, estimated about 80% of all cases according to the National Patient Registry (NPR) at the National Board of Health and Welfare (http://www.socialstyrelsen.se) [11]. In a previous study, we found that the rate of older MS patients might be lower in the SMSR than in the NPR, while early MS cases are almost completely included, but there might be regional variation in the inclusion rate [1]. However, these differences should not have influenced the result of our study. The Icelandic data were population based and probably included all MS patients in Iceland. Although we did not remove MS cases from the general Icelandic population, this should have minimal effect on the results due to the small number.

In conclusion, our results did not support the previously reported association between season or MOB and MS risk. Our results were unaffected by adjustments for possible confounding factors, and therefore, it remains unclear if those are responsible for the previously reported relationship between birth during spring and an increased MS risk [7]. Thus, our results do not support the hypothesis that pregnancy during autumn and winter with low levels of sun exposure and low vitamin D levels influence the risk of MS.

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Compliance with ethical standards

Conflicts of interest JL has received travel support and/or lecture honoraria from Biogen, Novartis, Teva, and Genzyme/SanofiAventis; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis, and Genzyme/SanofiAventis; serves on the editorial board of the Acta Neurologica Scandinavica; and has received unconditional research grants from Biogen, Novartis, and Teva. OE has received unconditional research grants from Biogen and Novartis.

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Paper IV

Mortality of Multiple Sclerosis in Iceland

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Abstract

Introduction Patients with MS have been found to have an unfavorable risk of mortality compared to the general population. Although there are several studies reporting on the incidence and prevalence of MS in Iceland there are no studies on mortality to date. We aimed to assess the mortality of patients with MS in Iceland in a nationwide population-based study.

Material and methods Analysis of mortality was based primarily on all individuals living with a diagnosis of MS in Iceland on December 31st, 2007 (n=526). For the years 2002–2007 information was available on all patients diagnosed in Iceland with MS (n=222), comprising a subgroup (incidence cohort) within the primary study group. Follow-up began on the prevalence day and lasted until death or December 31st 2018, whichever occurred first. For subanalysis of the incidence cohort, follow-up began on the day of diagnosis. Information on date of death was obtained from *Registers Iceland* and cause of death from the *Causes of Death Register* held by the *Directorate of Health*. We calculated the expected mortality, based on gender and age, using data from *Statistics Iceland*. The mortality associated with MS was assessed with the *standardized mortality ratio* (SMR).

Results The mean follow-up was 10.4 years (range 1–11). The cumulative SMR was 2.05 (95% CI 1.3–3.0). In the incidence cohort the SMR was 0.95 (95% CI 0.1–3.0) after a mean follow-up of 13 years (range 4–17).

Discussion We found a two-fold increase in mortality amongst Icelandic MS patients compared to the general population. This is similar to what previous studies from other countries have shown.

Introduction

Multiple sclerosis (MS) is the most common cause of non-traumatic neurological disability amongst young adults in Western countries[1]. Disability typically accumulates through recurrent episodes of autoimmune-mediated inflammation in the central nervous system (CNS)[2]. While outcome is most commonly evaluated in MS research by assessing the number of relapses or level of disability[3], information on mortality gives insights into long-term consequences of the disease. Mortality is a clearly defined parameter with the advantage of being relatively easily accessible in many countries through death certificate registries, therefore useful for global comparisons[4]. Patients with MS are not only burdened by disability as the *standardized mortality ratio* (SMR), used to analyze mortality of disease relative to the general population, was found to be increased (2.56) in a recent meta-analysis[5]. However, the increase in SMR varies between geographical regions and different time periods[6,7]. Thus, region-specific and up-to-date information on mortality is essential.

Although there are a couple of previous publications on both the incidence and prevalence of MS in Iceland[8-13] data on mortality has not been reported. We have previously published on the incidence and prevalence of MS in Iceland[14,15], based on cohorts identified through extensive searches in multiple sources. Some studies on the mortality of MS patients have identified patients based on mortality data but the risk of selection bias is substantial as MS is not mentioned on the death certificate of MS patients in up to 27% of cases[16]. Analysis of all causes of death (COD) mentioned on death certificates can give further insights into the circumstances that led to death.

We aimed to assess the mortality of MS in Iceland, analyze risk factors and determine COD.

Material and methods

We have done a retrospective analysis of mortality, based on prospectively gathered death registry death data, in two groups of MS patients in Iceland, those living with a diagnosis of MS on the 31st of December 2007 (prevalence group) and those diagnosed with MS in the years 2002–2007 (incidence group). The analysis was primarily based on the prevalence group but for the years 2002–2007 information was available on all patients diagnosed in Iceland with MS (n=222), comprising an incidence cohort, a subgroup within the primary study group.

Inclusion criteria

The inclusion criteria were the same for both the prevalence and incidence groups with fulfilment of at least one of the following: 1) 2010 McDonalds criteria, 2) Poser criteria for *Clinically Definite MS (CD-MS),* 3) Poser criteria for *Laboratory-Supported Definite MS*

(LSD-MS), 4) Poser criteria for *Clinically Probable MS (CP-MS)* or 5) *Primary Progressive MS (PPMS)* [16,17].

Identification of cases

Cases were identified in the same way for both the prevalence and incidence groups, though searches in multiple sources, including medical records and databases of: The Department of Neurology at *Landspítali-The National University Hospital of Iceland*, all privately practicing neurologists in Iceland as well as all regional hospitals and rehabilitation centers caring for MS patients. The following diagnosis codes for MS were primarily searched for: ICD10 (G35, G37.9), ICD9 (340,341) and ICD8 (340,341). In addition, MS cases were identified in the results of: *Visual evoked potential* (VEP) studies and all *Magnetic resonance imaging* (MRI) studies done in Iceland due to suspected demyelinating disease. The results of diagnostic studies were reviewed to confirm diagnosis of MS. Patients were also identified based on information from the *Icelandic Social Insurance Administration* on all residents receiving disability benefits for to MS from 1990 through 2007 and those applying for a walking aids from 1997 through 2007 with a diagnosis of MS. Finally, MS cases were searched for amongst all patients approved for *disease modifying drugs* DMDs by a special committee at *Landspítali-The National University Hospital of Iceland* reviewing applications for such treatment.

Clinical data

Clinical data including information on: gender, age of onset and diagnosis, clinical phenotype and disability status according to the *Expanded Disability Status Scale* (EDSS) was obtained from medical records. The EDSS was based on the visit to a neurologist that was closest in time to the prevalence day, usually within six months.

Characteristics of the prevalence group

We identified 526 patients for the prevalence group diagnosed between 1946 and 2007. In the prevalence group 73% (n=382) were women. The mean age on the prevalence day was 47 years and the mean age at diagnosis of 36 years. The prevalence cohort has been described in more detail in a previous publication[14].

Characteristics of the incidence group

There were 222 patients in the incidence group. Their mean age at diagnosis was 37 years and 74% (n=164) were women. The incidence group has been described in more detail in a previous publication[15].

Cause of death

Information on the cause of death was obtained from the *Causes of Death Register* held by the *Directorate of Health* based on death certificates completed according to recommendations from the *World Health Organization* (WHO). Part 1 of the death certificate includes the chain of events (diagnosis) leading to death with the *immediate cause of death* (e.g. pneumonia)

registered furthest up, followed beneath by any antecedent conditions (e.g. dysphagia) and finally, furthest down, the *underlying* medical condition (e.g. MS) is registered. Conditions contributing to death, but not directly related to the chain of events, can be registered as *contributory cause* of death (e.g., diabetes mellitus).

Survival

Follow-up began for the prevalence group on the 31st of December 2007 and for the incidence group on the date of diagnosis (2002–2007). Both groups were followed-up until the 31st of December 2018 or death, whichever occurred first. Information on date of death was obtained from *Registers Iceland*. The mortality of MS patients was compared to the general population with the *standardized mortality radio* (SMR). The SMR is defined as the number of observed deaths divided by the expected number of deaths, the theoretical number of deaths if the patient group were subject to the same mortality as the general population, by age, gender and calendar year. Information mortality in the general population was obtained from *Statistics Iceland* (statice.is).

Statistical analysis

The characteristics of groups were summarized with descriptive statistics. Independent sample t-test was used for continuous variables. Observed and expected survival was determined with the life table method. Expected survival was calculated based on sex, age and calendar year. The significance level was set at 5%. Analysis was done in Excel and SPSS.

Ethical issues

The study was approved by the Icelandic National Bioethics Committee and Data Protection Authority, reference numbers 2007090624 and VSNb2012010020/03.11, respectively.

Results

Length of follow-up

There were 526 patients in the prevalence group and 222 in the incidence group. In the prevalence group there were 5 483 person-years of observation (PYO) and a mean follow-up of 10.4 years (range 1–11 years). In the incidence group there were 2 877 PYO and a mean of 13.0 years of follow-up (range 4–17).

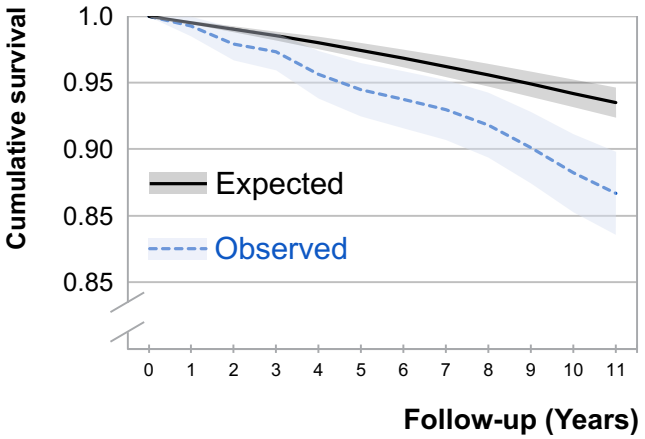

Figure 1 Survival of the prevalence cohort (n=526) from the 31st of December 2007 until the 31st of December 2018 or death. Analyzed with the life table method. Expected survival, based on the general population, with respect to age and gender and observed survival are displayed with 95% confidence intervals

Survival in the prevalence group

There were 70 deaths (13%) in the prevalence group. Mean age at death was 69 years (range 35–97). The crude mortality rate was 12.8 per 1 000 PYO while the expected mortality rate was 6.5 per 1 000 PYO. The observed cumulative survival at the end of the follow-up time was 86.7% compared with 93.5% expected. This corresponds to an SMR of 2.0 (95% CI 1.3–3.0). Life table analysis shows that the observed survival decreased steadily with time (Figure 1 and table 1). The SMR for the prevalence group, excluding the incidence cases (n=304), was 2.2 (95%CI 1.5 –3.4).

Table 1 SMR (Standardized mortality ratio) for the prevalence group (n=526). By years of follow-up, from 31st of December 2007

Follow-up (years)	Observed survival (%)	Expected survival (%)	SMR (95% CI)
1	99.2	99.5	1.58 (0.02–4.08)
2	97.9	99.0	2.13 (0.71–4.44)
3	97.3	98.5	1.80 (0.0–3.59)
4	95.6	98.0	2.17 (1.05–3.98)
5	94.5	97.4	2.14 (1.11–3.74)
6	93.7	96.8	1.98 (1.1–3.37)
7	93.0	96.2	1.86 (1.05–3.09)
8	91.3	95.6	1.85 (1.46–2.98)
9	90.1	94.9	1.93 (1.19–3.02)
10	88.2	94.2	2.03 (1.29–3.09)
11	86.7	93.5	2.05 (1.34–3.06)

Survival in the incidence group

There were 7 deaths in the incidence group. The mean age at death was 63 years (range 36–90). The mean duration from onset of MS until death was 14.7 (7–37) years and the mean time from diagnosis until death was 9.1 years (range 4–14). The crude mortality rate was 2.4 per 1 000 PYO with an expected mortality rate of 2.3 per 1 000 PYO. The observed cumulative survival in the end of the follow-up period was 97.3% compared to an expected survival of 97.2%. This corresponds to an SMR of 0.95 (95% CI 0.1–3.0).

Table 2 Standardized mortality ratio (SMR) of the prevalence cohort by predictive factors. Gender, Age at diagnosis, Clinical phenotype and EDSS[a] score. Analyzed with the life table method, follow-up from the 31st of December 2007 until the 31st of December 2018 or death

			Life table analysis		
	Deaths (n)	Patients at-risk (n)	Observed survival (%)	Expected survival (%)	SMR[b] (95% CI)
Gender					
Female	46	381	87.9	93.3	1.8 (1.1–3.1)
Male	24	145	83.5	93.8	2.6 (1.4–4.8)
Age at diagnosis					
0–34	3	113	97.4	99.4	4.3 (-0.5–11.2)
35–54	18	270	93.3	97.8	3.0 (1.5–4.6)
≥55	49	143	66.4	80.8	1.8 (1.2–2.6)
Clinical phenotype[c]					
RRMS[d]	57	489	88.1	94.2	2.1 (1.4–3.1)
PPMS[e]	12	32	65.7	83.8	2.1 (0.8–5.5)
EDSS[f]					
0–2.5	19	305	93.8	95.3	1.3 (0.6–2.5)
3–5.5	10	100	90.0	94.2	1.7 (0.5–4.6)
6–9.0	41	110	62.7	87.6	3.0 (1.8–4.7)

[a]EDSS, Expanded Disability Status Scale; [b]SMR, Standardized mortality ratio; [c]Clinical phenotype missing for 5 patients; [d]RRMS, Relapsing-remitting MS; [e]PPMS, Primary-progressive MS; [f]EDSS missing for 11 patients

Potential predictive factors for death

The results of analysis of potential predictive factors of death for the prevalence group, based on cumulative survival, are presented in table 2: Gender, Age at diagnosis, Clinical phenotype and EDSS score. The following groups had significantly higher mortality compared to the general population: females, males, age 35 years or older at diagnosis, RRMS and EDSS 6–9.0. Notably, men had a higher (2.6) SMR than women (1.8) although the difference was not statistically significant. The mean age at death was 68 years for patients with RRMS compared to 74 years of age for those with PPMS, (p=0.16) while both groups had an SMR of 2.1. EDSS was available for 98% of the cases (n=513), including all 70 deceased patients. EDSS was analyzed in the following categories: 0–2.5, 3.0–5.5 and 6.0–9.0. The survival decreased and SMR increased with higher EDSS category although this difference was not statistically significant either.

Cause of death

In the prevalence group a total of 70 of 526 patients died. Death certificates were available for 61 (87%) patients. These patients had at total of 95 diagnoses mentioned anywhere in the chain of events on the death certificate (immediate-, antecedent- and underlying causes of

death). The following proportion of patients had these diagnoses mentioned at least once in the chain of events: MS 48% (n=29), infection 46% (n=28), cancer 18% (n=11) vascular disease 30% (n=18), respiratory disease 7% (n=4), drug abuse 7% (n=4) and accident 2% (n=1). Notably, no suicide occurred. 19 of 29 patients with MS mentioned anywhere in the chain of events also had infection mentioned in the chain of events. In 23% (n=14) of patients, MS was not mentioned at all on the death certificate.

Seven individuals died in the incidence group. A death certificate was not available for 2 of these individuals. For the remaining five the underlying causes of death were as follows: multiple sclerosis (n=3), sepsis (n=1), drowning (n=1).

Discussion

We have done a nationwide population-based mortality study of multiple sclerosis in Iceland, the first study of MS associated mortality from Iceland. We studied both a prevalence cohort and an incidence cohort. In the prevalence cohort, with a follow-up for 11 years, the mortality was increased twofold (SMR=2.0; 95% CI 1.3–3.0) when compared with the expected mortality based on data on the Icelandic population adjusted for gender, age and calendar year.

Most previous studies have found patients with MS to have a higher mortality than expected compared to the general population. A meta-analysis from 2016 by Manouchehrinia and associates found the pooled all-cause SMR to be 2.80 (95% CI 2.74–2.87). The literature on the subject has continued to expand in recent years[6,7,17]. Table 3 provides an overview of population-based studies on SMR, which is consistently reported to be between 2 and 3[6,7,16-22]. However, there is a certain variation in the SMR between studies, most probably reflecting differences in factors such as geographical location, selection of cases, follow-up time and study period. Our SMR of 2.0 is in the lower range of previously reported values but the wide CIs preclude any speculation as to the causes of a possible difference. It should be noted that the SMR of 2.0 is based on prevalence data while some other studies are based on incidence data. Regional studies from Hungary[19] and Wales[16], also based on prevalence data, reported SMRs of 2.5 and 2.8, respectively.

As the current study presents the first data on mortality of MS patients in Iceland we are unable to draw conclusions regarding temporal changes. Data from other countries is somewhat equivocal as the previously mentioned meta-analysis found no temporal change in SMR while two recent studies from Denmark and Norway suggest that a favorable change has occurred. The Danish study[6] which is nationwide and population-based (18.847 patients, 6.102 deaths) found that patients with onset between 1950–1959 had an SMR of 4.5 (95% CI 4.06–4.92) compared to 1.8 (95% CI 1.62–1.99) for patients with onset between 1999 and 1999. The Norwegian study from Hordaland[7] (1 388 patients, 291 deaths) found a progressive

improvement in mortality with period of diagnosis (SMR; 95% CI):1953–1974 (3.0; 2.5–3.6); 1975–1996 (3.1; 2.6–3.5); 1997–2012 (0.8; 0.5–1.4). Future mortality studies will reveal whether patients with MS in Iceland are benefited with such a favorable development in mortality rate.

After a mean follow-up of 13 years from diagnosis the mortality in the incidence cohort was no different from the expected mortality, SMR 0.95 (95% CI 0.1–3.0). The period of follow-up was relatively short, some previous studies have also found no difference in SMR during the first years following diagnosis. In a study from Norway (386 individuals; 263 deaths) the SMR for the first 10 year was 0.54[20]. In a study from Finland (1 595 individuals; 464 deaths) the SMR was not higher in the MS population compared to the general population during the first 2 years of follow-up but was between 2–3 thereafter[21]. Likewise, in a study form France (27 603 individuals; 1 569 deaths) the SMR was 1.5 after 30 years of follow-up, but no difference was observed during the first 20 years of follow-up[23].

Table 3 Overview of population-based studies reporting SMR (standardized morality ratio)

Country	Region	First author	Publication year	Time period of diagnosis	End of follow-up	Patients (n)	Deaths (n)	SMR[a]				
								Over-all	Females	Males	RRMS[b]	PPMS[c]
Canada	British Columbia	Kingwell	2012	1980–2004	2007	6 917	1 025	2.89	3.01	2.68	2.9	2.9
Denmark	Nationwide	Koch-Henriksen	2017	1950–1999	2015	18 847	6 102	2.4	2.5	2.36		
Finland	Nationwide	Sumelahti	2010	1971–2006	2006	1 595	464	2.8	3.4	2.2		
France	Nationwide	Foulon	2017	2013	2013	78 805	1 080	2.56	2.55	2.58		
Hungary	Csongrád county	Sandi	2016	1993–2013	2013	740	121	2.52	2.57	2.46	2.3	4.1
Norway	Hordaland	Lunde	2017	1953–2012	2012	1 388	291	2.7	2.9	2.5	2.4	3.9
Norway	Oslo	Smestad	2009	1971–2005	2006	386	263	2.47	2.94	2.02		
Spain	Bizkaia, Basque Country	Zarranz	2014	1987–2011	2011	1 283	89	2.78	2.73	3.26		
Wales	South East	Hirst	2008	1985–2006	2006	379	221	2.79	3.14	2.26		

[a]SMR, Standardized mortality ratio; [b]RRMS, Relapsing-remitting MS; [c]PPMS, Primary progressive MS;

We found the mean age at death (n=70) to be 69 years (range 35–97) in the prevalence cohort. A study from Spain (1 283 individuals; 89 deaths) found the mean age at death to be similar for men and women (56.2 compared to 56.9 years) [22]. A study from Wales (379 patients; 221 deaths) found the mean age at death to be 65 years (65.3 for women and 65.2 for men)[16].

Men had a higher SMR (2.6) in our study than women (1.8). Although the wide confidence intervals preclude any firm conclusions to be drawn, this observation is noteworthy as previous studies have generally found the SMR of women to be either higher or similar as for men (Table 3). For example, a previously mentioned large longitudinal study from Denmark found no significant difference in SMR between men and women [6], as well as the also previously mentioned prevalence based study from Hungary [19]. A study from Norway showed a significantly higher SMR in females compared to men (2.9 vs 2.5)[7] and similar findings have been reported from Canada and Finland[18,21].

In the current study patients with RRMS and PPMS had the same SMR value of 2.1. In contrast, a study from Norway [7] found a lower SMR for patients with RRMS (2.4) compared to those with PPMS (3.9). The absolute difference in SMR between patients with RRMS and PPMS was smaller in a French study from 2015, 1.4 compared to 1.7, respectively[23]. Although the lack of difference in our study could be dictated by the relatively small sample size a large study from Canada (6 917 patients; 1 025 deaths) with 25 years of follow-up[18], also found no difference in SMR between patients with RRMS 2.87 (95% CI 2.68–3.08) and PPMS 2.89 (95% CI 2.54–3.28).

The SMR was higher, 3.0, for patients with EDSS between 6–9.0 around the time of the prevalence date compared to 1.3 for those with an EDSS of 0–2.5, although the confidence intervals overlapped. An association between higher EDSS scores and higher SMRs is plausible and is supported by two previous studies. In a study based on 1 879 French patients those with an EDSS between 1 and 3 had a SMR of 0.3 (95% CI 0.1–0.7) while those with an EDSS between 8 and 9 had an SMR of 11.0 (95% CI 8.3–14.3)[24]. Similarly, in a study based on 2 604 patients from Wales those with an EDSS of 8–8.5 and 9–9.5 had SMRs of 22.17 (95% CI 18.20–26.75) and 60.74 (95% CI 47.62–76.41), respectively[25]. The difference in magnitude of the SMRs between higher levels of EDSS in our study compared to these two studies is partly explained by the fact that the EDSS in the later was assessed in the last few years before death as opposed to close to the beginning of follow-up in our study.

In our material 48% of the deceased patients had MS listed somewhere in the chain of events on the death certificate. This varies between studies although most previous studies have found MS to be the cause of death in around 50% or more of cases [7,21,26,27]. Nevertheless, direct comparison of studies is difficult as coding practice presumably varies and coding errors have been found to be common [28]. Comparison is further made difficult as definition of MS related death varies and there are differences in which diagnosis on the death certificate are included in the analysis (immediate-, antecedent-, underlying- or contributory cause).

As 18 patients (30%) had MS registered as a contributory cause there were 14 patients (23%) that did not have the diagnosis *multiple sclerosis* mentioned on the death certificate. This is similar to some previous studies from other countries (rate): Norway (22%)[20], Wales (27%)[16] and Leeds (23%)[29]. These findings emphasize that identification of patients for mortality studies based on deaths certificates is a method prone to selection bias risking to underestimate the mortality rate and that studies based on predefined cohorts should be preferred.

Strengths and weaknesses

This study presents the first analysis of mortality of MS patients in Iceland. Another main strength of the current study is that it uses nationwide population-based data. Selection bias is a major issue in epidemiological studies, risking both exclusion of benign cases and patients with high comorbidity [30]. We identified cases through extensive searches in multiple sources

as described in the methods section. We therefore believe that we have been able to identify the great majority of all patients diagnosed with MS in Iceland during the study period and that the risk of selection bias should be minimal.

The main weakness is the small size of the study population. The larger size of the prevalence cohort made it more feasible for analysis than the incidence cohort. At the same time, analyzing mortality based on prevalence data can lead to certain bias as only those patients diagnosed in the preceding decades and alive on the prevalence day are included, excluding patients diagnosed during the same period that died earlier. The length of the follow-up was relatively short for both cohorts, extending the following could add important information as studies have shown that increase emerges more clearly in the second decade after diagnosis[6].

Conclusion

We conclude that, based on a prevalence cohort with 11 years of follow-up, the mortality of MS patients in Iceland is two times higher than expected with reference to the general population after adjustment for gender, age and calencer year. These results are comparable to previous studies, in particular studies from neighboring countries in Europe. For recently diagnosed cases in the incidence cohort, mortality did not deviate from that in the general population after a minimum of 11 years from diagnosis.

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Appendix

Table A Observed and expected MS births by season, in Sweden (n=12 019) and Iceland (n=108)

	Sweden (n=12 019)[b]			Swedish patients <30 years at debut (n=5 107)[b]			Iceland (n=108)[c]		
Season[a]	**Observed**	**Expected**	**p-value**	**Observed**	**Expected**	**p-value**	**Observed**	**Expected**	**p-value**
Spring	3 334	3 403	0.156	1 372	1 445	0.022	33	29	0.332
Summer	3 022	2 982	0.396	1 302	1 272	0.331	33	28	0.312
Autumn	2 802	2 804	0.970	1 223	1 184	0.193	17	27	0.028
Winter	2 861	2 830	0.497	1 210	1 211	0.888	25	24	0.853

[a]Spring: March, April, May; Summer: June, July, August; Autumn: September, October, November; Winter: December, January, February
[b]Adjusted for gender, year of birth and county of birth; [c]Adjusted for gender and year of birth

Table B Observed and expected MS births in Sweden (n=12 020), by month. Adjusted for gender, year of birth and county of birth.

	Sweden (n=12 020)			Southern Sweden[a] (n=10 283)			Northern Sweden[a] (n=1 458)		
Month	**Observed**	**Expected**	**p-value**	**Observed**	**Expected**	**p-value**	**Observed**	**Expected**	**p-value**
January	956	976	0.496	794	832	0.170	134	121	0.218
February	1030	962	0.021	900	825	0.006	102	113	0.260
Mars	1117	1147	0.356	961	983	0.457	125	136	0.310
April	1135	1143	0.804	958	978	0.510	150	139	0.301
May	1082	1112	0.343	935	954	0.507	125	134	0.419
June	1050	1011	0.194	896	865	0.263	136	124	0.248
July	1023	1006	0.568	878	858	0.471	121	126	0.675
August	949	961	0.677	805	823	0.501	126	118	0.439
September	992	975	0.557	844	831	0.639	117	120	0.809
October	932	948	0.578	799	812	0.640	116	114	0.869
November	878	876	0.944	751	751	0.995	110	105	0.595
December	876	904	0.332	762	772	0.699	96	109	0.193

[a]Divided at 62°N, the approximate central latitude of Sweden

Table C Observed and expected MS births in Iceland (n=108), by month. Adjusted for gender and year of birth.

Month	Observed	Expected	p-value
January	9	8.8	0.937
February	7	8.1	0.689
Mars	14	9.4	0.121
April	8	9.4	0.622
May	11	9.3	0.557
June	12	9.2	0.336
July	7	9.5	0.395
August	14	9.4	0.114
September	5	9.4	0.133
October	6	8.9	0.306
November	6	8.2	0.427
December	9	8.4	0.818