Multiple Sclerosis and Related Disorders 45 (2020) 102352

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

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

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

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

ARTICLE INFO

Keywords:
Multiple sclerosis
Epidemiology
Prevalence
Incidence
Rural
Norway

ABSTRACT

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

1. Introduction

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

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

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

https://doi.org/10.1016/j.msard.2020.102352
Received 23 March 2020; Received in revised form 17 June 2020; Accepted 30 June 2020

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

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

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

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

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

2. Material and methods

2.1. Geographical setting

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

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

2.2. Data collection and study population

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

2.3. Prevalence and incidence

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

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

2.4. Statistical analysis

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

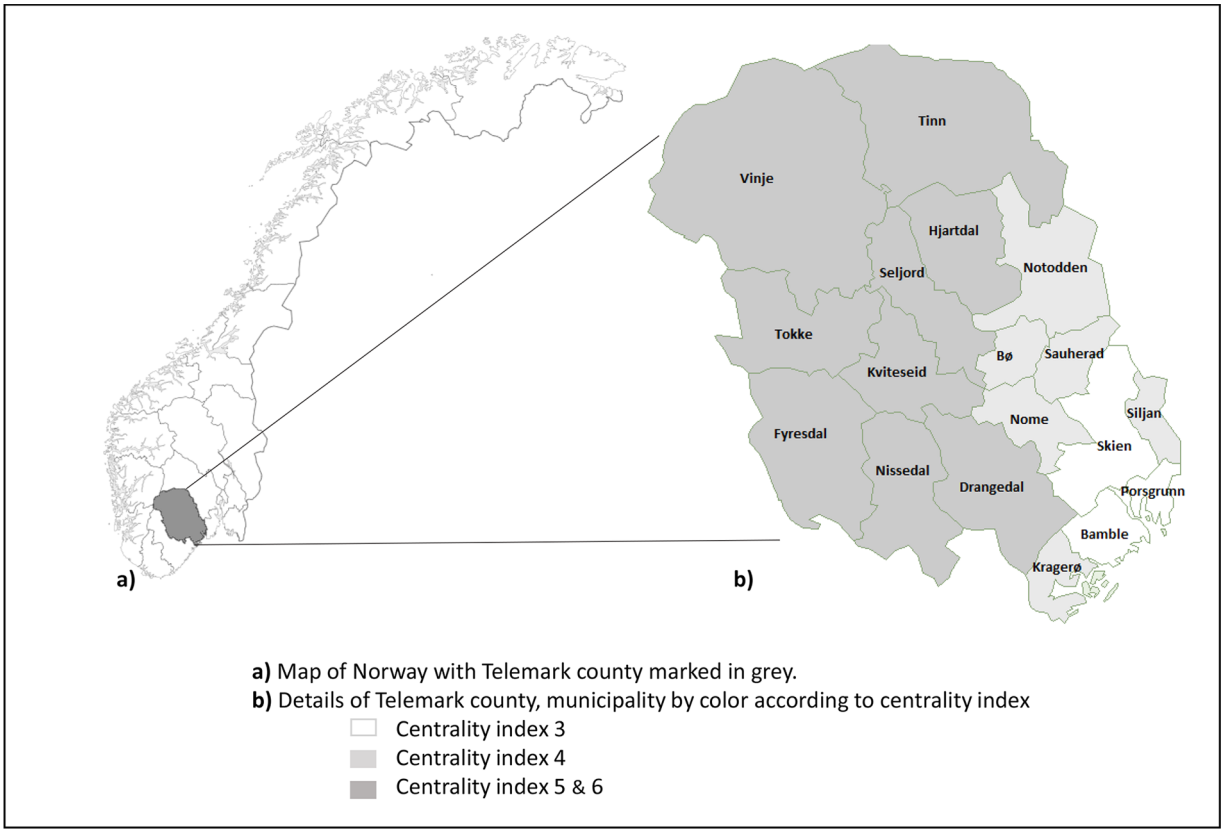

Fig. 1. a) Map of Norway with Telemark county marked in grey. b) Details of Telemark county, municipality by color according to centrality index

3. Results

3.1. Demographics

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

3.2. Prevalence

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

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

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

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

3.3. Incidence

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

The yearly incidence rate increased, although not significantly, from

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

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

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

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

4. Discussion

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

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

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

Table 3
Changes in MS population in Telemark 1999-2019

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

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

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

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

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

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

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

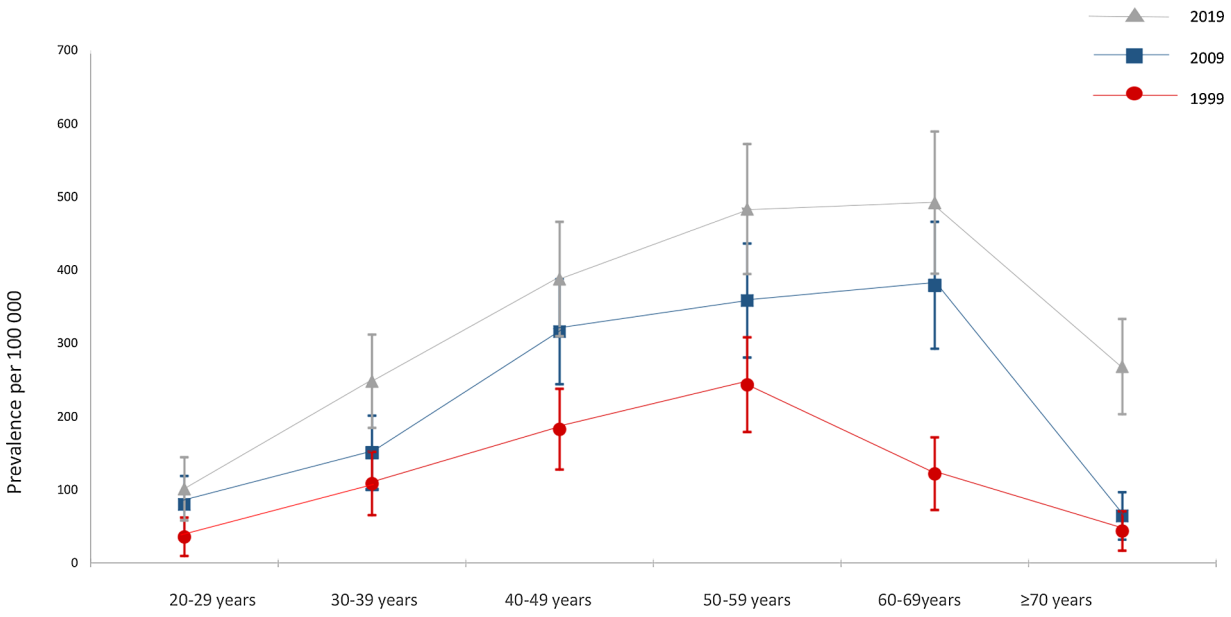

Fig. 2. Age-adjusted prevalence of MS in Telemark with 95% confidence interval, 1999 - 2009 2019.

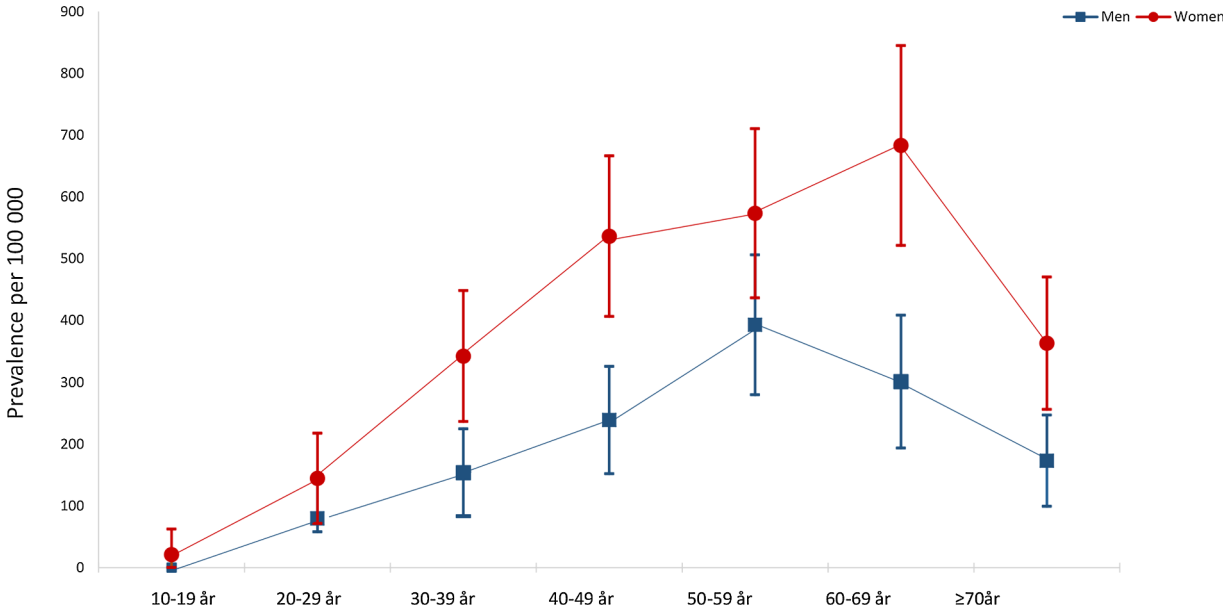

Fig. 3. Age-adjusted prevalence in Telemark at 01,01.2019, by gender, with 95 % confidence interval

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

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

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

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

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

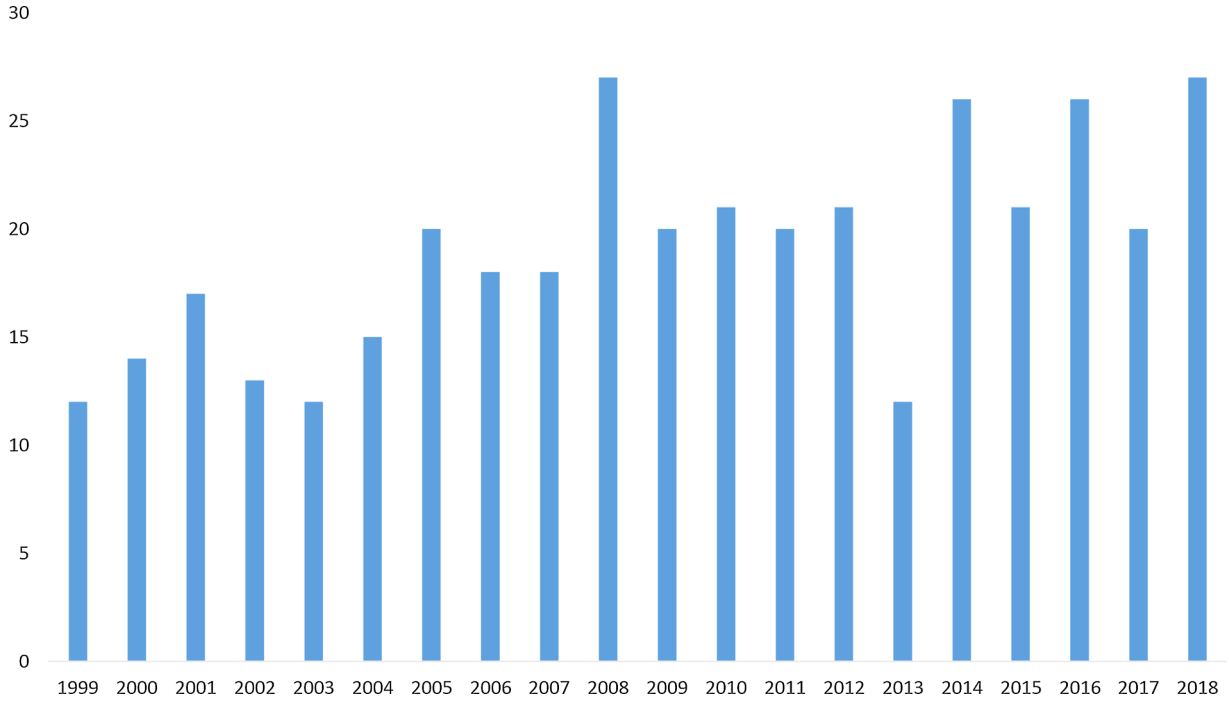

Fig. 4. Number of new cases diagnosed per year in Telemark, 1999-2018

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

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

Author contributions for paper

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

Data statement,

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

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

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

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

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

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

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

CRediT authorship contribution statement

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

Declaration of Competing Interest

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

Acknowledgments

We would like to thank all the patients that were included in this study as well as Dr. Frøydis Moan Dalene and Dr. Tore Jørgen Mørland, both of them neurologists at Telemark Hospital Trust.

Funding

HØF has received research funding from Telemark Hospital Trust to perform this work.

References

Thompson, AJ, Baranzini, SE, Geurts, J, Hemmer, B, Ciccarelli, O, 2018. Multiple sclerosis. Lancet 391 (10130), 1622–1636.
Collaborators GBDMS., 2019. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18 (3), 269–285.
Berg-Hansen, P, Moen, SM, Harbo, HF, Celius, EG, 2014. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult. Scler. 20 (13), 1780–1782.
Midgard, R, Riise, T, Nyland, H, 1991. Epidemiologic trends in multiple sclerosis in more and Romsdal, Norway: a prevalence/incidence study in a stable population. Neurology. 41 (6), 887–892.
Gronlie, SA, Myrvoll, E, Hansen, G, Gronning, M, Mellgren, SI, 2000. Multiple sclerosis in North Norway, and first appearance in an indigenous population. J. Neurol. 247 (2), 129–133.
Dahl, OP, Aarseth, JH, Myhr, KM, Nyland, H, Midgard, R, 2004. Multiple sclerosis in Nord-Trondelag county, Norway: a prevalence and incidence study. Acta Neurol. Scand. 109 (6), 378–384.
Risberg, G, Aarseth, JH, Nyland, H, Lauer, K, Myhr, KM, Midgard, R, 2011. Prevalence and incidence of multiple sclerosis in Oppland county: a cross-sectional population-based study in a landlocked county of Eastern Norway. Acta Neurol. Scand. 124 (4), 250–257.
Lund, C, Nakken, KO, Edland, A, Celius, EG, 2014. Multiple sclerosis and seizures: incidence and prevalence over 40 years. Acta Neurol. Scand. 130 (6), 368–373.
Smestad, C, Sandvik, L, Holmoy, T, Harbo, HF, Celius, EG, 2008. Marked differences in prevalence of multiple sclerosis between ethnic groups in Oslo, Norway. J. Neurol. 255 (1), 49–55.
Vatne, A, Mygland, A, Ljostad, U, 2011. Multiple sclerosis in vest-Agder county. Acta Neurol. Scand. 123 (6), 396–399.
Benjaminsen, E, Olavsen, J, Karlberg, M, Alstadhaug, KB, 2014. Multiple sclerosis in the far north–incidence and prevalence in Nordland county, Norway, 1970-2010. BMC Neurol. 14, 226.
Grytten, N, Aarseth, JH, Lunde, HM, Myhr, KM, 2016. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland county, Western Norway. J. Neurol. Neurosurg. Psychiatry 87 (1), 100–105.
Simonsen, CS, Edland, A, Berg-Hansen, P, Celius, EG, 2017. High prevalence and increasing incidence of multiple sclerosis in the Norwegian county of Buskerud. Acta Neurol. Scand. 135 (4), 412–418.
Swank, RL, Lerstad, O, Strom, A, Backer, J, 1952. Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition. N Engl. J. Med. 246 (19), 722–728.
Berg-Hansen, P, Moen, SM, Harbo, HF, Celius, EG, 2015. Comments on the review article 'Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades' Acta Neurol Scand 132 (5), 364–367.
Daltrozzo, T, Hapfelmeier, A, Donnachie, E, Schneider, A, Hemmer, B, 2018. A systematic assessment of prevalence, incidence and regional distribution of multiple sclerosis in bavaria from 2006 to 2015. Front. Neurol. 9, 871.
Lowis, GW., 1990. The social epidemiology of multiple sclerosis. Sci. Total Environ. 90, 163–190.
Beebe, GW, Kurtzke, JF, Kurland, LT, Auth, TL, Nagler, B, 1967. Studies on the natural history of multiple sclerosis. 3. Epidemiologic analysis of the army experience in world war II. Neurology 17 (1), 1–17.
Roddam, H, Rog, D, Janssen, J, Wilson, N, Cross, L, Olajide, O, et al., 2019. Inequalities in access to health and social care among adults with multiple sclerosis: a scoping review of the literature. Mult. Scler. Relat. Disord. 28, 290–304.
Conradi, S, Malzahn, U, Schroter, F, Paul, F, Quill, S, Spruth, E, et al., 2011. Environmental factors in early childhood are associated with multiple sclerosis: a case-control study. BMC Neurol. 11, 123.
Marcoci, C, Lisnic, V, Gavriliuc, M, Odainic, O, Sangheli, M, Belenciuc, A, et al., 2016. Prevalence of multiple sclerosis in the republic of moldova. Neuroepidemiology 46 (3), 166–172.
Høydahl, E., 2017. Ny sentralitetsindeks for kommunene (New centrality index for municipality). Statistisk Sentralbyrå (Stat. Norway).
Polman, CH, Reingold, SC, Banwell, B, Clanet, M, Cohen, JA, Filippi, M, et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.
Thompson, AJ, Banwell, BL, Barkhof, F, Carroll, WM, Coetzee, T, Comi, G, et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.
Pace M, LG, Glickman, M, Zupanic, T, 2013. Revision of the European standard population: report of Eurostat's task force. Luxemb. Publ. Off. Eur. Union.
Rothman, KJ, Greenland, S, Lash, TL, Buehler, JW, Cahill, J, Glymour, MM, et al., 2008. Modern Epidemiology, 3rd ed. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia X, 758 s. p.
Celius, EG, Vandvik, B., 2001. Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. Eur. J. Neurol. 8 (5), 463–469.
Koch-Henriksen, N, Sorensen, PS., 2011. Why does the north-south gradient of incidence of multiple sclerosis seem to have disappeared on the northern hemisphere? J. Neurol. Sci. 311 (1-2), 58–63.
Simpson Jr., S, Wang, W, Otahal, P, Blizzard, L, van der Mei, IAF, Taylor, BV, 2019. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J. Neurol. Neurosurg. Psychiatry 90 (11), 1193–1200.
Tremlett, H, Zhu, F, Ascherio, A, Munger, KL, 2018. Sun exposure over the life course and associations with multiple sclerosis. Neurology 90 (14), e1191–e11e9.
Berg-Hansen, P, Moen, SM, Sandvik, L, Harbo, HF, Bakken, IJ, Stoltenberg, C, et al., 2015. Prevalence of multiple sclerosis among immigrants in Norway. Mult. Scler. 21 (6), 695–702.
Evans, C, Beland, SG, Kulaga, S, Wolfson, C, Kingwell, E, Marriott, J, et al., 2013. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology. 40 (3), 195–210.
Pugliatti, M, Sotgiu, S, Rosati, G, 2002. The worldwide prevalence of multiple sclerosis. Clin. Neurol. Neurosurg. 104 (3), 182–191.
Hedstrom, AK, Hillert, J, Olsson, T, Alfredsson, L, 2013. Smoking and multiple sclerosis susceptibility. Eur. J. Epidemiol. 28 (11), 867–874.
2010 F.Helsetilstanden i Norge/The status of public health in Norway. 2010.
Riise, T, Kirkeleit, J, Aarseth, JH, Farbu, E, Midgard, R, Mygland, A, et al., 2011. Risk of MS is not associated with exposure to crude oil, but increases with low level of education. Mult. Scler. 17 (7), 780–787.
Kampman, MT, Brustad, M., Vitamin, D, 2008. a candidate for the environmental effect in multiple sclerosis - observations from Norway. Neuroepidemiology 30 (3), 140–146.
Pugliatti, M, Rosati, G, Carton, H, Riise, T, Drulovic, J, Vecsei, L, et al., 2006. The epidemiology of multiple sclerosis in Europe. Eur. J. Neurol. 13 (7), 700–722.
Koch-Henriksen, N, Thygesen, LC, Stenager, E, Laursen, B, Magyari, M, 2018. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. Neurology 90 (22), e1954–e1e63.
Celius, EG, Smestad, C., 2009. Change in sex ratio, disease course and age at diagnosis in Oslo MS patients through seven decades. Acta Neurol. Scand. Suppl. (189), 27–29.
Orton, SM, Herrera, BM, Yee, IM, Valdar, W, Ramagopalan, SV, Sadovnick, AD, et al., 2006. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 5 (11), 932–936.