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REVIEW ARTICLE

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Changes in multiple sclerosis epidemiology in Finland over five decades

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Finland is a high-risk region for multiple sclerosis (MS) with several epidemiological studies on the subject published since 1964, but these have not been comprehensively scrutinized. The objective of this study was to review previous studies of Finnish MS epidemiology, introduce new data on MS prevalence in western parts of Finland and do further analyses on data from previous studies. We performed a systematic search on articles regarding MS epidemiology in Finland in PubMed database, and all relevant articles were included in this review. MS prevalences in the western hospital districts of Vaasa, South Ostrobothnia and Pirkanmaa were calculated in 1980-2007 by using previously unpublished data obtained from a retrospective search from hospital administrative registries. To enhance comparability of the epidemiological figures, we calculated age-standardized prevalence of MS from the new data from western hospital districts and previous data from North Ostrobothnia, Southwest Finland and North Karelia. Marked regional differences in MS epidemiology were confirmed with concentration of the disease in the western and southwestern parts of the country. The highest regional age-standardized MS prevalence of 288/100 000 was reported in South Ostrobothnia in 2007. A clear and stable increase in MS prevalence was observed through the decades, but the only marked increase in incidence happened in 1990s. Methodological differences hampered direct comparisons of different studies, highlighting the importance of common principles of reporting and standardizing the epidemiological figures. More comprehensive studies on MS epidemiology are still warranted to yield important information concerning the aetiology of the disease.

KEYWORDS
epidemiology, Finland, incidence, multiple sclerosis, prevalence

1 | INTRODUCTION

Multiple sclerosis (MS) is the most common chronic neurological disorder causing disability among young adults, estimated to affect 2.2 million people worldwide[1] and incurring high costs.[2] An almost universal increase in the prevalence of MS has been reported during recent decades. This is estimated to be due to improved and earlier diagnostics and prolonged survival of patients but also an actual

increase in MS incidence.[3,4] Interestingly, incidence has been found to have increased especially in women, and female-to-male (F/M) ratio in MS incidence has thus increased.[5-7] Migration from rural areas and urbanization have been linked to increasing incidence in women.[8]

Both incidence and prevalence of MS have been observed to increase with latitude north or south of the equator, but this latitude gradient has been questioned recently in the northern hemisphere.[9-12] High rates of MS in the Nordic countries do, however, suggest association of latitude with the occurrence of MS. Finland belongs to the global high-risk regions of MS. First epidemiological studies of MS in Finland were published over five decades ago, and several regional reports have been published since then. However, reliable nationwide epidemiological MS research has not been conducted in the era of modern diagnostic methods. In this article, we present new data on MS prevalence from 1980 to 2007 in western parts of Finland, conduct further analyses on data from North Ostrobothnia and review previous studies in order to describe relevant time trends and evolution of MS epidemiology in Finland.

2 | METHODS

Relevant articles in the PubMed Medline database (last search: 2 January 2020) were identified using the following keywords: "multiple sclerosis prevalence in Finland" or "multiple sclerosis incidence in Finland." Our search was limited to English-language studies published in peer-reviewed journals. The search revealed 147 hits of which 132 were excluded and 15 were considered relevant for the presentation of evolution of MS epidemiology in Finland. Additional publications were identified from references of the articles. Altogether, 17 articles concerning Finnish MS epidemiology were included in the review.

MS prevalence in the hospital districts of Pirkanmaa, South Ostrobothnia and Vaasa was calculated in 1980, 1990, 2000 and 2007 by using previously unpublished data obtained from a retrospective search from hospital administrative registries as described before.[13] Cases were reassessed by neurologists, and only definite diagnoses included. Population data were obtained from Statistics Finland.[14] To enable more reliable comparability of the epidemiological figures, we calculated age-standardized prevalence rates of MS from the new data from western hospital districts in 1980-2007 and old data from North Ostrobothnia, Southwest Finland and North Karelia obtained for previous studies.[6,15,16] The MS incidence in North Ostrobothnia was analysed using Poisson regression, adjusted because of overdispersion.

Finland is located between the latitudes 60° and 70° in Northern Europe. It is divided into 21 hospital districts (Figure S1). During the study period, the population of Finland increased from 4.54 million people in 1964 to 5.53 million people in the end of 2019. The population is rapidly ageing, and in 2018, the median age of the Finnish population was 43 years while in 1960 it was only 28 years. The population density in Finland is unevenly distributed (from 2 to 178 inhabitants per square kilometre), and the population is concentrated in the southern and western parts of the country with 42% of the population in 2016 living on a 20-kilometre deep coastal region running from North Ostrobothnia to Kymenlaakso and every third person in the country living within 100 kilometres from the capital, Helsinki. The mean population density is low at 18 inhabitants per square kilometre. While in 1950s most people in Finland lived in rural areas, in 2018 already 86% of population lived in urban regions which cover only about 5% of the country´s total area. In 2018, degree of urbanization was highest in southern Uusimaa (96%) and lowest in Åland and eastern Finland (63%-72%).

2.1 | Ethical standards

According to Finnish law, ethical committee approval was not required since the study was based on administrative register data and included no contact with patients.

3 | RESULTS

3.1 | 1964-1979

Already the first studies on the prevalence of MS, performed nationwide in the beginning of 1964, showed that the geographical distribution of patients was not even but rather concentrated to western and south-western parts of the country. Medical documentary data of all MS cases diagnosed in hospitals (hospitalized in 1955-1965) or drawing a national pension for MS were scrutinized. A nationwide MS prevalence of 20.1/100 000 inhabitants was reported, and prevalence was higher in districts of South Ostrobothnia, Vaasa, Turku and Åland (30.1-39.1/100 000; Figure 1). The prevalence was lowest in eastern districts of Finland (North Karelia, Kainuu and all three regions of Savonia; 11.0-13.7/100 000). There was no correlation between the distribution of MS cases and medical facilities. The observed mean prevalence was rather low which was explained by the stringency of the patient ascertainment because no diagnostic criteria could be used. Taking into account other epidemiological research data of that time, the actual nationwide prevalence was estimated to be 30-40/100 000. F/M ratio in MS patients was 1.2. Interestingly, clear regional differences were seen in this gender ratio already in the 1960s, since there were more female patients in the largest hospital districts of Helsinki, Turku and Tampere.[17,18]

Following the Second World War, Finland ceded to the Soviet Union the majority of the south-eastern province of Viipuri, amounting to 7% of the land area of Finland and home to 10% of its population, practically all of whom were evacuated to other parts of the country. When the evacuees were studied in 1971, MS prevalence was observed to be rather similar among people evacuated to different provinces and no accumulation of cases in people evacuated to high-risk areas was observed.[19] However, the non-evacuated patients born after 1944 were not included in the analysis, thus making

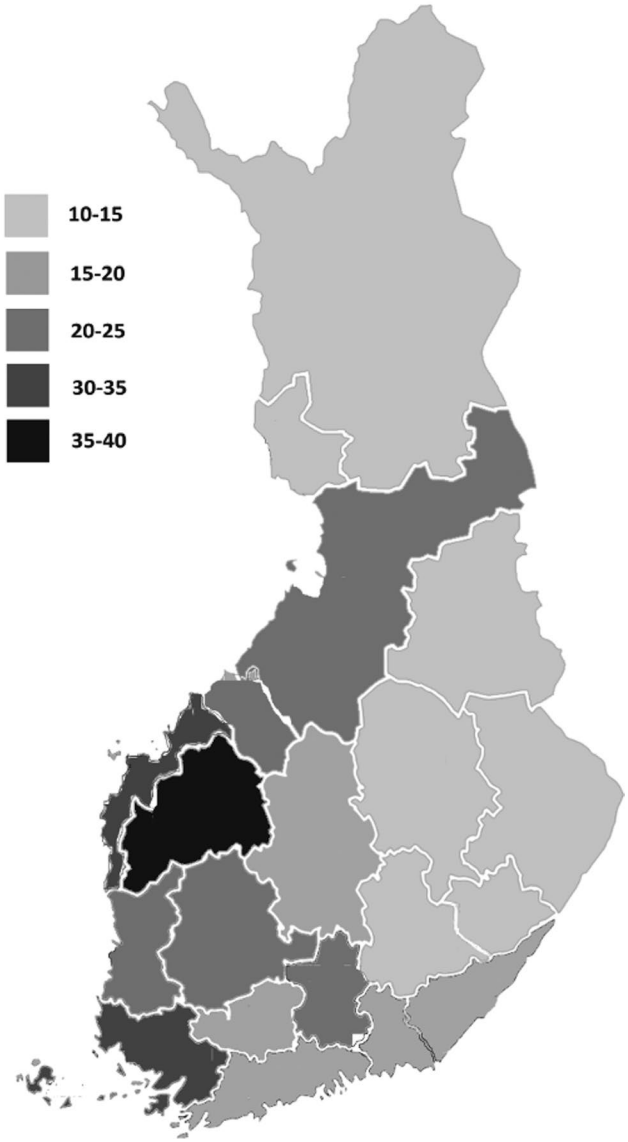

FIGURE 1 The prevalence of MS per 100 000 in the first nationwide study by Rinne et al in 1964

it impossible to infer any conclusions concerning any possible effects being born and of early childhood environmental exposure in the high-risk areas.

In the beginning of 1972, MS prevalence was re-evaluated nationwide using the same source of data than before but Schumacher Committee criteria[20] were used to ratify the diagnosis. The MS prevalence matched the earlier extrapolated estimate being 39.6/100 000 for the whole country. The highest prevalence was again reported in the western and south-western counties, whereas lowest figures were from eastern and south-eastern counties. Study of single clerical districts revealed a narrow coastal zone in the western and south-western parts of the country with lower MS prevalence where residents were mostly Swedish-speaking.[21] The western high-risk county for MS was studied further in the level of single communes, villages and even houses. Clustering of the birthplaces of MS patients was observed in the small high-risk area of Jalasjärvi and along the rivers. The prevalence of MS according to birthplace in 1930 was 65.2/100 000 for those born in Vaasa or South Ostrobothnia, whereas the prevalence of MS in the same area was 60.7/100 000 and in Helsinki only 44.2/100 000. Furthermore, only 99 of the 229 MS patients living in Helsinki had been born there. The findings could not be explained by chance, and the author suggested that they implied the importance of environmental influences in early childhood rather than genetic factors.[22]

Because of the increasing prevalence figures and uneven geographical distribution of MS, its incidence was studied in the western high-risk province of Vaasa and South Ostrobothnia and the southern medium-risk province of Uusimaa from 1964 to 1978. The annual MS incidence was higher in Vaasa and South Ostrobothnia (3.3/100 000) than in Uusimaa (2.2/100 000) as expected. Surprisingly, F/M ratio in MS incidence increased from 1.2 to 2.0 in Uusimaa and from 1.0 to 2.2 in Vaasa and South Ostrobothnia during the study period (Table 1). No change in total MS incidence was observed during the study period (Figure 2; Table S1), pointing at increased incidence in women and decreased incidence in men.[23] In the beginning of 1979, MS prevalence was reassessed in the same provinces. The data were collected from hospitals, health centres, the National Board of Health and Social Insurance Institution. The prevalence was 52.9/100 000 in Uusimaa and 92.9/100 000 in Vaasa and South Ostrobothnia, representing a threefold increase since 1964. F/M ratio was reportedly 1.8 in Uusimaa and 1.4 in Vaasa and South Ostrobothnia. Taking stable MS incidence into account, researchers considered improved registration of patients as the most plausible explanation for the markedly increased prevalence figures, but true increase in MS prevalence could not be ruled out.[24]

3.2 | 1979-2000

Sumelahti et al reassessed the MS incidence in the western Vaasa and South Ostrobothnia districts and in the southern Uusimaa province during 1979-1993. The criteria of Poser[25] were used to ensure diagnoses, and only definite cases were included. It is of note that cerebrospinal fluid oligoclonal bands were studied in 86%-96% of cases, but MRI was performed only in 12%-50% of cases depending on its availability in the hospital district. Regional difference between areas persisted; MS incidence was 11.6/100 000 in South Ostrobothnia and 5.1-5.2/100 000 in Vaasa and Uusimaa. F/M ratio was 1.6 in South Ostrobothnia, 2.2 in Vaasa and 2.4 in Uusimaa. During the study period, MS incidence had increased in South Ostrobothnia, especially in men. In contrast, incidence had decreased in Vaasa and remained stable in Uusimaa.[26,27] During 1983-1993, MS prevalence increased from 116/100 000 to 188/100 000 in the district of South Ostrobothnia, from 102/100 000 to 107/100 000 in Vaasa and from 69/100 000 to 93/100 000 in Uusimaa (Figure 3; Table S2). A 1.7-fold increase in prevalence was observed in South Ostrobothnia in both genders, whereas increased prevalence in Uusimaa was largely due to increased rates in women. Highest prevalence figures (200-300/100 000) were reported in the southern and western parts of

TABLE 1 Female-to-male ratio in MS incidence in different hospital districts

	1964-1968	1974-1978	1979-1993	1979-1998	1981-1990	1991-2000	1992-2007	2001-2010	2004-2012	2012-2016
Southwest Finland										2.6
Vaasa			2.2		1.8	2.1		2.8		
South Ostrobothnia			1.6		1.8	1.9		2.3		
Vaasa + South Ostrobothnia	1.0	2.2								
Pirkanmaa					2.5	2.1		2.2		
Uusimaa	1.2	2.0	2.4							
Central Finland				2.2						
North Ostrobothnia							2.2			
North Savo									2.4	
North Karelia										1.0

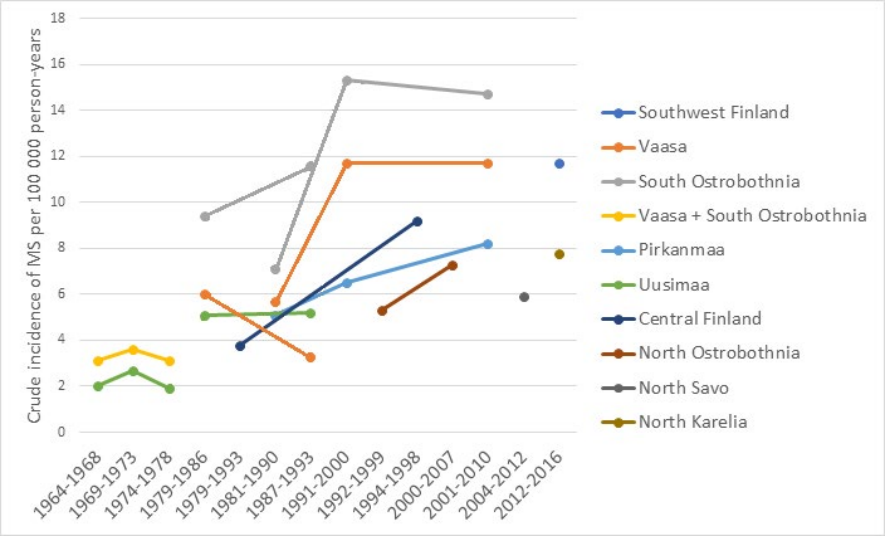

FIGURE 2 Crude incidence of MS per 100 000 person-years in different hospital districts. Results regarding same areas within a single study connected (same background population and methods)

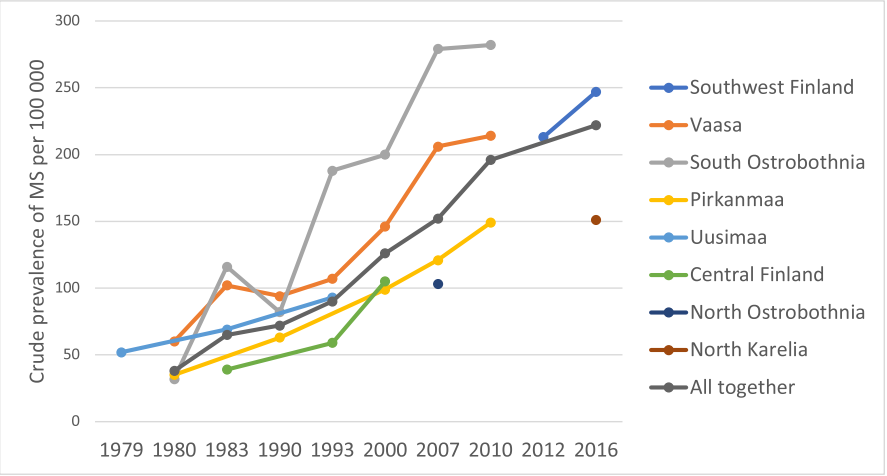

FIGURE 3 Crude prevalence of MS per 100 000 in different hospital districts

South Ostrobothnia where a high frequency of familial MS had been earlier documented.[21,22] Simultaneous increase in MS incidence and prevalence was found only among male population of South Ostrobothnia. Among other populations, the prevalence increased in presence of stable or decreasing incidence pointing at better survival of MS patients.[28]

In the district of Central Finland, MS incidence remained stable during the period from 1979 to 1993, being 3.8/100 000 in age

group 10-69 years. However, in 1994-1998 the incidence increased up to 9.2/100 000. Incidence showed increase in all age groups but focused on patients aged 40-59 years and was higher in women. The prevalence of MS was 59/100 000 in 1993 but increased up to 105/100 000 in 2000. The diagnostic use of MRI among MS patients increased from 10% to 97% during the same period, which was thought to largely explain the increase in epidemiological figures. Despite the development in diagnostics and first disease-modifying therapies (DMTs) entering the market in 1996, no change in diagnostic delay was observed.[29]

3.3 | 2000-2016

Since then, several regional epidemiological studies have been conducted extending to both sides of the millennium (Figure 4). In 1981-2010, MS incidence was investigated in the western hospital districts of Pirkanmaa, South Ostrobothnia and Vaasa. The highest reported incidence of 15.3/100 000 was observed in 1991-2000 in South Ostrobothnia, where the MS risk was reported to be nearly twofold (standardized incidence rate, SIR 1.9) during the study period compared to Vaasa (1.2) and Pirkanmaa (1.0). Incidence increased twofold in Vaasa and South Ostrobothnia from 1981-1990 to 1991-2000 and remained stable thereafter, whereas in Pirkanmaa a steady albeit milder increase was observed during the entire study period. F/M ratio increased from 1.8 to 2.3 in South Ostrobothnia and from 1.8 to 2.8 in Vaasa while the ratio remained stable between 2.1 and 2.5 in Pirkanmaa. High MS risk in South Ostrobothnia was interpreted to reflect both genetic and environmental effects.[30] Between 2000 and 2010, prevalence increased by 45% in the same western region consisting of Vaasa, South Ostrobothnia and Pirkanmaa. Age-standardized prevalence (ESP2013) in the whole western area was 192/100 000 in the end of the study period.[13] MS prevalence in the same western hospital districts of Vaasa, South Ostrobothnia and Pirkanmaa was calculated in 1980, 1990, 2000 and 2007 from new and previously unpublished data. Results in each area show increasing MS prevalence from 1980 to 2010 (Figure 3).

In 1992-2007, MS epidemiology was studied in North Ostrobothnia. MS incidence during the study period was 6.3/100 000, and prevalence in the end of 2007 was 103/100 000. F/M ratio in new diagnoses was 2.2. The incidence showed a tendency to increase over the study period, but the finding was not statistically confirmed.[6] We analysed further the previous data and the MS incidence increased by 4.2% annually (95% CI 1.6%-6.8%, P = .002) over the study period. We also calculated the mean incidence in North Ostrobothnia in two time periods: 1992-1999 and 2000-2007 (Figure 2). In North Savo, MS incidence was stable at 5.9/100 000 in 2004-2012.[31]

In the end of 2012, MS prevalence was reported to be 213/100 000 in the hospital district of Southwest Finland with a F/M ratio of 2.6.[15] Four years later, the MS prevalence in the same area had already increased to 275/100 000 in the population aged ≥10 years. In the same time, the prevalence of MS in eastern North Karelia was 167/100 000 in the same population. MS prevalence in the whole population was 247/100 000 in Southwest Finland and 151/100 000 in North Karelia. MS incidence during 2012-2016

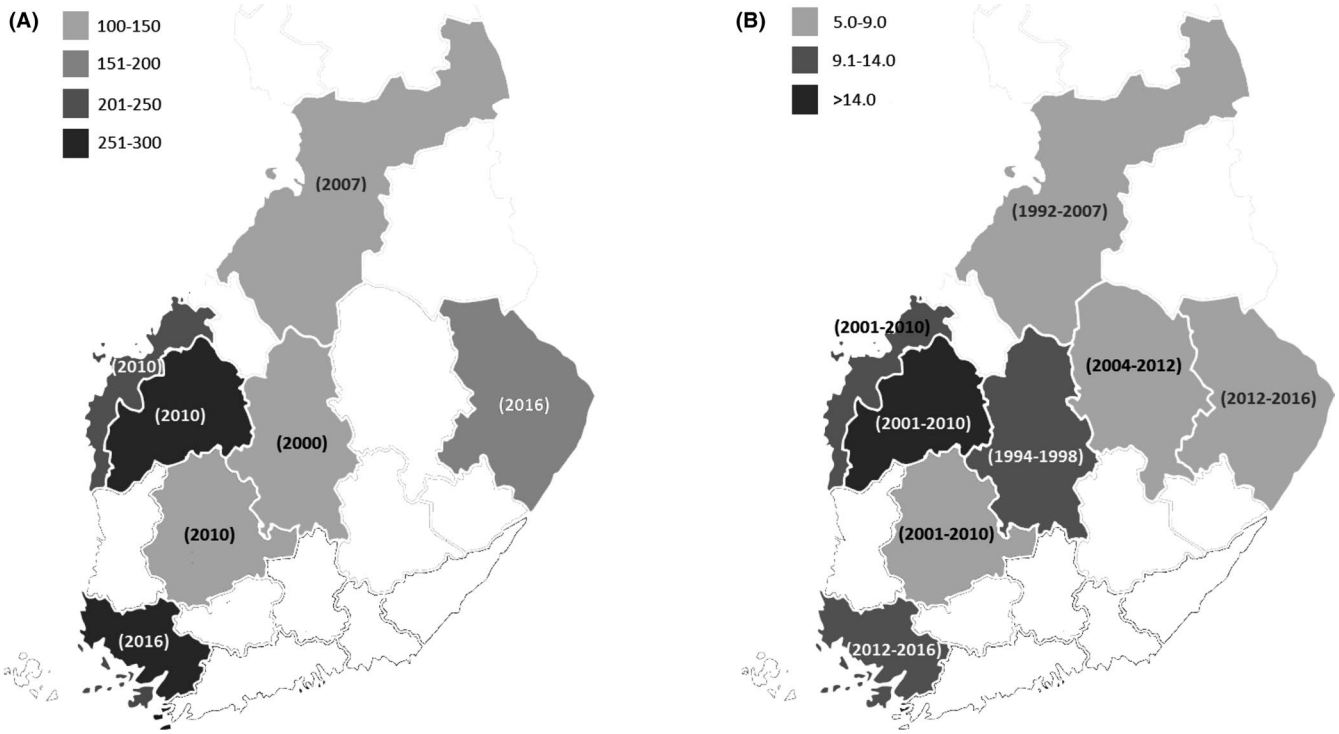

FIGURE 4 Latest prevalence (A) and incidence (B) figures of MS per 100 000 in different hospital districts of Finland (study period in parenthesis)

TABLE 2 Age-standardized prevalence (European standard population 2013; except 1976 version in 1993) of MS per 100 000 in different hospital districts of Finland

	Southwest Finland	Vaasa	South Ostrobothnia	Pirkanmaa	Uusimaa	Central Finland	North Ostrobothnia	North Karelia
1980		66	36	34				
1990		103	90	61				
1993		93	163		78	58		
2000		154	206	94				
2007		214	288	123			106	
2010		226	276	149				
2012	215							
2016	251							150

was 11.7/100 000 in Southwest Finland and 7.8/100 000 in North Karelia in the age group 10-69 years. F/M ratio in incidence was 2.6 in Southwest Finland and 1.0 in North Karelia. Regional differences in epidemiological figures and gender distribution between eastern and south-western region were interpreted to be due to demographic, social and genetic circumstances.[16]

3.4 | Age-standardized prevalence

Standardization of epidemiological figures allows more reliable comparisons between different studies and populations. In most epidemiological MS studies conducted in Finland, internationally comparable standardized rates were not available which makes comparison of the studies more difficult. Age-standardized prevalence and incidence rates were reported in 1993[29] for four hospital districts, but the European standard population that was referred to was predated even the 1976 version. For the prevalence data obtained from Vaasa, South Ostrobothnia and Pirkanmaa in the end of 1980, 1990, 2000 and 2007, North Ostrobothnia in the end of 2007 and Southwest Finland in the end of 2012, we calculated the age-standardized rates using direct method and European standard population (ESP2013). Prevalence rates from our previous epidemiological study in Southwest Finland and North Karelia were also standardized for age using the same method and whole population as a reference. Age standardization raises the prevalence rates slightly more in the regions with migration loss but does not affect the general outlook. Highest age-standardized prevalences were observed in South Ostrobothnia (288/100 000) and Southwest Finland (251/100 000; Table 2).

4 | DISCUSSION

This review and analysis of new data confirmed that Finland is a high-risk area for MS, but with regional differences in epidemiology and no latitudinal gradient. The disease has consistently been found to be the most common in the western and south-western parts of the country, whereas lower rates have been observed in the east and the north. Moreover, there were some very specific and fine-grained regional differences. A clear trend of increasing MS prevalence was observed through the decades, but the only marked increase in incidence happened in the last decade of the 20th century.

These findings were very similar compared to those reported from Finland's nearest Nordic neighbours Sweden and Norway, although a latitudinal prevalence gradient has been reported in Sweden, and in Norway, MS incidence appears to have increased steadily from 1961 to 1995 before stabilizing.[3,32-36] Data from Iceland also show a steady increase in prevalence and an increase in incidence up to the year 2000.[37,38] Arguably the best data on MS epidemiology in the world, derived from a prospective registry, are available from another Nordic country, Denmark, where incidence has steadily increased from 1950-1959 to 2000-2009 accompanied by prevalence increasing steadily through decades.[5,39] It is unclear what causes these differences between neighbouring countries. The area is among those with the highest risk of MS in the world, and the disease does not appear to be markedly more common in any of these countries compared to the others.[40] Interestingly, the prevalence of MS in Finland's southern neighbour Estonia in 1989 was 55.3/100,000 among native Estonians, not very different from the figures reported for Finland at the time.[41]

Very high rates in all these neighbouring countries suggest that their geographical position may be associated with MS risk. Indeed, the importance of shared environmental factors is suggested by the fact that Finland is an outlier in Europe and an isolate, even possessing its "own" set of inherited diseases[42-45] with Swedes being genetically closer to Germans and the British than to Finns.[46] The most obvious culprit would be their location in the North, meaning a long winter with little sunshine. However, there is no latitude gradient of MS in Finland or Norway. Instead, in Finland the highest incidence and prevalence have consistently been reported in western and south-western parts of the country. This is in marked contrast to the epidemiology of many other brain disorders, such as Parkinson's disease, psychotic disorders and stroke, all of which are more common in eastern Finland.[47-49] This again suggests a role for heredity as there are considerable genetic differences reported between the populations of eastern and western Finland.[50] Indeed, eastern and western Finns have been shown to be genetically further apart from

each other than Germans are from Britons.[46] Interestingly, the HLA B35 haplotype, reported to be protective against MS, is more common in eastern compared to western Finland.[51,52]

Highest MS occurrence in Finland is consistently found in the western region of South Ostrobothnia, where clustering of MS cases has especially been detected in southern area of Jalasjärvi. As an exception, a narrow western and south-western coastal zone has been distinguished with lower MS risk compared to neighbouring region already in 1972. The population in the high MS-risk region of South Ostrobothnia has been shown to be quite heterogeneous, and researchers divided the area into three distinct regions with respect to its historical settlement. The known high-risk region of southern South Ostrobothnia (MS prevalence 219/100 000 in 1993) was populated beginning from the 13th century from south-western Finland. Distinctive settlement history, historical link with the other south-western high-risk foci and molecular genetic evidence were thought to suggest a founder effect behind western high-risk region of MS.[53] Considering the consistently high occurrence of MS also in Southwest Finland,[16,18] this appears plausible. Interestingly, earlier research has reported that the genetic and socio-economic background in the western districts is similar both in rural areas of partially Swedish-speaking Vaasa, Finnish-speaking Seinäjoki (in South Ostrobothnia), and in the more urbanized Pirkanmaa.[54,55] However, current data show that although the population in all these areas share a common major south-western haplotype, this can be further divided into more specific haplotypes that are different in Southwest Finland, Pirkanmaa and South Ostrobothnia.[50]

However, there are also clues for the role of environmental factors. Indeed, the northern part of South Ostrobothnia with a concurrent MS prevalence of 136/100 000 was inhabited later from the 16th century from eastern Finland.[53] Considering that this is a clearly higher figure than those for its immediate neighbours, namely Central Finland in the east (59/100 000, also inhabited from the east) and coastal Vaasa in the west (107/100 000, inhabited mostly by Swedes in the 13th century), it appears possible that local environmental factors may have increased the risk of MS in the east-derived population of northern South Ostrobothnia. A study investigating the prevalence of MS concurrently in the northern part of South Ostrobothnia and the eastern districts of Finland would therefore be of great interest.

The finding that the people evacuated from the Viipuri province to high MS-risk areas manifested no increase in their risk of the disease suggests that if there are environmental factors at play here, they would probably exert their effect early in life.[19] Recent results from Sweden, Norway and Denmark concerning MS in immigrants also suggest this.[56-58] Interestingly, the majority of patients in Helsinki in 1970s may have had the origins of their MS somewhere else in Finland before moving to the capital.[22] The water of the Kyrönjoki river and the regularly flooded swamps in the South Ostrobothnia and Vaasa area were suggested as factors of interest.

Indeed, an association between high MS-risk areas and the global distribution of mires, especially of raised bogs in the northern hemisphere, has been observed. Up to 30% of the total area in South Ostrobothnia and Vaasa consists of mires, and the two main rivers of South Ostrobothnia, along which the heaviest concentrates of MS cases are, originate from mires. In addition, severe acid sulphate soil types in terms of metal leaching have observed to coincide well with the MS clustering in South Ostrobothnia and especially along the Kyrönjoki river.[59] The concentration of total selenium, along with soluble potassium, calcium, magnesium and strontium, was lower in South Ostrobothnia and Vaasa compared to Uusimaa, whereas the concentrations of soluble iron, zinc, chromium and aluminium showed the opposite.[60] In the end, it is probable that gene-environment interactions are important to MS susceptibility also here,[61] and identifying them remains a challenging task.

MS incidence increased markedly in several regions in Finland in 1990s but has remained remarkably stable since then. The steep and abrupt increase in incidence is probably mainly explained by improved diagnostics of MS, especially the increased availability of MRI. Indeed, in Vaasa, South Ostrobothnia and Pirkanmaa the use of MRI in MS diagnostics increased from 36% of cases in 1981-1990 to 98% in 2001-2010,[30] and in Central Finland in 1979-1983, only 10% of MS patients had had a brain MRI but in 1994-1998 it had been performed on 97%.[29] Moreover, the first DMTs entered the market in Finland in 1996 increasing the importance of making and recording the diagnosis immensely. DMTs have developed significantly since then, and due to increased possibilities of treatment, early diagnosis has also become more important. Indeed, the median diagnostic delay in Vaasa, South Ostrobothnia and Pirkanmaa halved from 4.0 to 2.0 years during 1981-2010.[30] Interestingly, the increase in incidence has been much milder in the university districts of Pirkanmaa and North Ostrobothnia when compared to Vaasa and South Ostrobothnia. Furthermore, the increase has continued past the year 2000 in these university hospital districts. The reasons for these differences are not readily apparent.

The F/M ratio in MS prevalence in Finland was barely over 1.0 in 1964, although regional differences were obvious.[18] In Denmark, the ratio had been 1.31 already in 1950.[39] In Finland, the ratio increased markedly already in the first epidemiological study regarding incidence of MS in Finland 1964-1978. Interestingly, this was observed to result from an increased incidence in women and a concurrent decrease in men's incidence. Indeed, overall incidence remained stable over that study period. Therefore, the change cannot be entirely explained by the facilitation of women´s access to medical services. After this, F/M ratio in new MS diagnoses has remained mainly over two but regional differences can still be observed, and a slight increase in the ratio has been observed in Vaasa and South Ostrobothnia still in the 2000s. Clearest exception from this quite established ratio was observed in North Karelia, where F/M ratio in MS incidence during 2012-2016 was only 1.0. Low ratio was thought to be at least partly explained by differences in population structures between different regions, since the population of North Karelia is declining and young women tend to migrate to southern Finland more often than men. The global increase in the ratio suggests the influence of one or several environmental factors that are still unknown.

However, some are known and changed over decades. Smoking increases the risk of MS[62] but has decreased in Finland during the past decades generally. Interestingly, smoking decreased markedly among men and increased slightly among women in Finland concurrently with the increase in F/M ratio in MS incidence in 1964-1978.[63] Low vitamin D levels are also known to affect MS risk.[64] The largest study directly supporting vitamin D deficiency as a risk factor for MS has been conducted in Finland. It showed a twofold MS risk in vitamin D deficient women diagnosed between 1983 and 2009.[65] Recommendations on vitamin D supplementation and widespread vitamin D fortification of milk products since 2003 have resulted in increased vitamin D intake in Finland. Dietary survey data have shown that, unlike before, Finnish adults met the vitamin D recommendations in 2012, except older women.[66] Increased vitamin D levels may have reduced the risk of developing MS, when considering mainly stabilized MS incidence rate after 1990s. Changes in environmental risk factors have been suggested to have contributed to the missing latitudinal gradient for MS incidence on the northern hemisphere.[67]

The prevalence of MS shows stable increase over the study period, and especially high prevalence has been reported recently in western and south-western parts of the country. The highest age-standardized prevalence in Finland was documented at 288/100 000 in South Ostrobothnia for 2007. Taking into account the rather stable incidence figures, the most important factors behind this increase are probably evolved patient care, earlier diagnosis and better survival of patients. Interestingly, excess mortality of patients with MS in Denmark has long decreased and this trend started well before the advent of DMTs, indicating the importance of other factors such as better living conditions and welfare.[68] In the first nationwide epidemiological studies in 1960s, MS prevalence was highest in age group of 40-49 years. Due to increased life expectancy of MS patients, the age-specific prevalence curve has shifted to the right during the last decades. However, the prevalence has still been highest in the same age group of 40-49 years in the recent studies conducted in 2000s.

Methodological differences make direct comparisons of different studies difficult. The diagnostic criteria have evolved over the study decades, from early clinically based criteria to current MRI-based McDonald criteria.[69] The first MRI scanner in Finland was acquired to Turku University hospital in 1987, and MRI has become steadily more important and central for diagnostic criteria of MS over time and enabled an early diagnosis. Inter-study comparisons are further hampered by the lack of standardization and use of different standard populations over time. Crude prevalence and incidence rates are calculated using partly different populations as a reference depending on the study protocol. For example, children and elderly are excluded from some incidence calculations to varying degrees. Indeed, even figures from studies conducted in the same area may not be directly comparable owing to differences between chosen background populations and methods of standardization in separate studies. Clearly, there indeed is a pressing need for common understanding of the reporting principles for studies on MS epidemiology worldwide.[40]

In conclusion, like other Nordic countries, Finland is a high-risk region for MS. There is no latitude gradient of MS in Finland but marked regional differences in incidence and prevalence that suggest that the traditional classification of MS-risk areas according to their distance from the equator is not detailed enough. The increase in MS prevalence is similar to that elsewhere. However, for unclear reasons the incidence trend pattern observed in Finland, Norway and Sweden differs from that observed in Denmark. Apparently, both more detailed and ever more comprehensive studies on MS epidemiology are still warranted and can be expected to yield important information concerning the aetiology of the disease.

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CONFLICT OF INTEREST

A-LP has received congress fee covering by Biogen and Sanofi Genzyme. MS-H has received congress fee covering and lecture and consultation fees by Biogen, Cellgene, Merck, Novartis, Roche, Sanofi and Teva. M-LS has received congress fee covering and lecture and consultation fees by Merck, Novartis, Roche, Sanofi and Teva. AM has received congress fee covering by Novartis. JS has received honoraria, travel grants and congress fee covering by Orion Corporation, Merck, Pfizer, Abbvie and Sanofi Genzyme and holds shares (Orion Corporation). OK and KH declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

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SUPPORTING INFORMATION

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

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