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Occurrence, Survival and Prognostic Factors of Multiple Sclerosis in Finland

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ACADEMIC DISSERTATION

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List of original publications

This study consists of the following publications referred to in the text by their Roman numerals (I–IV).

I Sumelahti M-L, Tienari PJ, Wikström J, Palo J, Hakama M (2001): Increasing prevalence of multiple sclerosis in Finland. Acta Neurol Scand 103:153–158.

II Sumelahti M-L, Tienari PJ, Wikström J, Palo J, Hakama M (2000): Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979–1993. Neuroepidemiology 19:67–75.

III Sumelahti M-L, Tienari PJ, Wikström J, Palo J, Hakama M: MS in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses. Submitted for publication.

IV Sumelahti M-L, Tienari PJ, Wikström J, Salminen TM, Hakama M (2002): Survival of multiple sclerosis in Finland between 1964 and 1993. In press: Multiple Sclerosis.

1 Introduction

Multiple sclerosis (MS) is a chronic neurological disease, the first symptoms generally appearing at the age of 20–30 years. Female preponderance from 53 to 71% has been reported in most epidemiological studies (McDonald and Silberberg 1986, Phadke 1990). MS is pathologically characterized by multifocal damage of myelin and axonal loss in the central nervous system, resulting in various neurological symptoms and signs. Clinically silent, active lesions are observed in magnetic imaging (MRI), (Willoughby et al. 1989). The clinical disease course is variable, in most cases characterized by relapses and remissions after onset followed by progression at variable frequency, although a progressive form, without superimposed clinical relapses, is observed in about 20% of cases (Weinshenker and Ebers 1987).

The etiology of MS is unknown. Observations in epidemiological studies on uneven geographical distribution, high-risk regions in the areas inhabited by those of North-European descent, familial occurrence, twin studies, migration studies, clusters and epidemics have contributed to the prevailing conception that genetic predisposition as well as exposure to environmental agents are required for the development of MS (Kurtzke et al. 1979, Compston et al. 1998).

Although MS is a rare disease at population level, it is the most common cause of chronic neurological disability among young adults. As a chronic disease starting at early adulthood, MS causes a variable amount of disability and retirement (Rodriguez et al. 1994), impairing the quality of life. Also, a considerable excess mortality compared to age matched general population has been shown in MS (Percy et al. 1971, Wynn et al. 1990). In 1993 out of approximately 5,000 MS patients in a population of 5.1 million in Finland, 2,167 patients were on pension, representing 0.6‰ of the population of working age in the age-groups 16–64 years. In 1999 the number of patients on pension was 2,655 (1.2% of all pensions), 1,700 patients used the rehabilitation services provided by the Social Insurance Institution of Finland (SII) and 2,899 MS-patients received special refunds for medical costs (SII T1:35 1999).

The epidemiology of MS in Finland has been updated in successive studies since the 1960´s (Rinne et al. 1966, Wikström and Palo 1975 and 1976, Kinnunen et al. 1983). Based on these earlier observations, the districts in this study represented the high-risk populations in the western districts of Seinäjoki and Vaasa and average-risk population in southern Uusimaa. The purpose of this study was to estimate the prevalence and incidence in these districts. Based on the large population based MS cohort collected before the advent of disease modifying treatments, a study on the natural course of the disease was possible. This included the causes of death in MS population, the survival and the patient and disease related prognostic risk factors in MS.

2 Review of the literature

2.1 Occurrence of multiple sclerosis

Uneven geographical distribution and temporal variation are the characteristic features in MS epidemiology (Davenport 1922, Kurtzke 1977, Compston 1994). The concept of MS frequency zones was proposed in the 1970´s by Kurtzke (1977): the high risk areas, where prevalence exceeds 30 cases in 100,000 population ($30/10^5$) are in northern Europe, the British Isles and America, southern Australia and New Zealand. The largely uncharted regions, Asia and South America, belong to the low risk areas, where prevalence remains below 5 cases in 100,000 population ($5/10^5$). The medium risk areas ($5–30/10^5$) are located in southern Europe, the southern United States and north Australia. Although the worldwide prevalence has mainly increased since the 1970´s (Lauer 1994) the geographical differences have persisted. The extent of improved case recognition and survival as causes for the increasing occurrence is equivocal (Noseworthy et al. 2000).

In northern Europe the prevalence rates have shown similarity across the Fennoscandian high-risk areas (Kurtzke 1968). Incidence in these regions varies from approximately 3 to $5/10^5$ and prevalence from about 60 to 80 per 100,000 persons (Larsen et al. 1984a, Koch-Henriksen and Hyllested 1988, Svenningson et al. 1990, Grønning et al. 1991, Midgard et al. 1991, Edland et al. 1993).

In Finland, serial studies on MS prevalence have shown a steady increase since 1964. Results in different studies are presented in Table 1.

Table 1. Prevalences of multiple sclerosis in Finland and in southern and western counties in 1964, 1972 and 1978.

Area	Author	Year	N	Prevalence*
Finland	Rinne et al. 1968	1964	919	20
	Wikström and Palo 1975	1972	1866	40
Uusimaa	Rinne et al. 1968	1964	155	18
	Wikström and Palo 1975	1972	426	39
	Kinnunen et al. 1983	1978	599	54
Vaasa region**	Wikström and Palo 1975	1972	310	48
	Kinnunen et al. 1983	1978	388	92

*crude prevalence per 100,000
**includes the hospital districts of Vaasa, Seinäjoki and Kokkola

The regional gradient between the western and southern areas was largely due to incidence gradient, as the incidence during the period 1964–1978 in Vaasa region was $3.3/10^5$ as compared to $2.2/10^5$ person-years in Uusimaa. (Kinnunen et al. 1983).

The geographically varying MS occurrence at the level of smaller hospital districts was already detected in 1964: the crude prevalence in the two districts of Vaasa region, $30/10^5$ in Vaasa hospital district and $39/10^5$ in Seinäjoki district, were almost twice as high compared to $18/10^5$ in Uusimaa, and the prevalence of Seinäjoki was the highest reported in Finland (Rinne et al. 1968).

2.2 Etiological considerations

The theory of polygenic ethnic susceptibility is based on observed uneven geographical distribution, while the locally fluctuating trends in the high-risk areas may indicate environmental effects (Koch-Henriksen 1995).

The highest prevalence rates in MS have been observed among populations of North European descent (Davenport 1922, Kurtzke 1980). The theory of polygenic ethnic susceptibility in these populations is supported by HLA-observations, DR2w15,DQw6, Dw2 associations with MS, which is found most often among the white population of European origin (Kinnunen et al. 1984, Olerup and Hillert 1991). Genetic susceptibility in MS is suggested to be polygenic, which is also supported by the findings in familial studies. The estimated familial occurrence in white MS populations is about 15% (varying between 4 to 20%). In twin studies the concordance of monozygotics is around 30%, and among dizygotics 2–5%, supporting the effect of genetic factors (Kinnunen et al. 1988, Compston 1994), further supported by the observation in a Canadian study (Ebers et al. 1995).

The migration studies suggest that the risk of acquiring MS may be altered by change in environment (Dean 1967, Alter et al. 1978, Kurtzke 1980, Elian et al. 1990). There are reports on rare epidemics involving a small number of patients in geographically isolated regions (Kurtzke and Hyllestedt 1979, Kurtzke and Hyllestedt 1982). Interpretations of these results have included the influence of environmental factors as well as critical views on improved diagnostics and chance in small populations. The demographic features typical in MS, for example gender distribution and age at onset, the effect of migration, clusters, epidemics (Kurtzke and Hyllestedt 1982), and sociocultural factors have led to a search for wide range of etiological factors including nutritional, hormonal and viral or bacterial causes involved in triggering the disease (Lauer 1991).

The geographical variation in MS, as in type 1 diabetes (Tuomilehto et al. 1999, Karvonen et al. 2000), seems to reflect the global distribution of the major ethnic groups, pointing at genetic predisposition. It is unlikely, however, that changes in genetics alone explain the variation and increasing occurrence in MS, type I diabetes, or asthma and allergic symptoms (Magnus and Jaakkola 1997, The International Study of Asthma and Allergies in Childhood Steering Commitee 1998), as any genetic changes in populations are slow.

2.3 Diagnosis

The diagnosis of multiple sclerosis is fundamentally clinical, and requires that a patient at the appropriate age has been shown to have two distinct episodes of neurological disturbances implicating distinct sites in the white matter of the central nervous system. Other possible causes need to be actively sought and excluded (Compston et al. 1998).

Clinical MS is characterized by the presence of symptomatic central nervous system (CNS) lesions and by progressive neurological impairment. Paraclinical evidence includes abnormalities typical for MS found in the cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) and evoked potential (EP) studies, positive results however being nonspecific for MS (Poser et al. 1983).

Typical lesions in white matter in MRI are identified in 70–95% (Ormerod et al. 1987), of patients with clinically definite MS and in approximately 50% of patients with suspected MS (Paty et al. 1988). There is a minor group of about 2% fulfilling the clinical MS diagnostic criteria who do not have MRI abnormalities (Youl et al. 1991). MRI lesion cannot, however, be regarded as pathognomonic of MS since white matter lesions present in MRI can be found in common conditions such as arterial hypertension, multi-infarct dementia, vasculitis, diabetes mellitus and cardiac disease (Paty et al. 1988). Lesions are often encountered in asymptomatic individuals over age 50 even in the absence of the above mentioned diseases (Fazekas et al. 1988). The characteristics and distribution of spinal cord lesions in MS have been well documented, as is their absence in healthy controls, even among older adults (Thorpe et al. 1993). The frequency, distribution and main characteristics of spine MS plaques detected with MRI have recently been examined, as well as the description of differential diagnosis with other spinal cord disease (Bastianello et al. 2000).

Radiological criteria for diagnostic purposes in MS were first assessed by Paty et al. (1988) and Fazekas et al. (1988). The new diagnostic criteria for MS (McDonald et al. 2001) include radiological criteria (Barkhof et al. 1997, Tintoré et al. 2000). These criteria provide an acceptable degree of sensitivity while providing greater specificity,

including the criteria of brain abnormality and dissemination of lesions over time, than the criteria proposed by Fazekas et al. (1988) and Paty et al. (1988).

Evoked potential (EP) examinations (visual, auditory, and somatosensory) show abnormal results in about three quarters of patients with clinically definite disease (Sanders et al. 1984, Hume and Waxman 1988). In this category they are abnormal in approximately half of patients who have no abnormal signs related to the pathway they are tested (McDonald 1989). Abnormal evoked potentials tend to be less common in the less definite cases, but nevertheless useful in diagnosis. Abnormal visual evoked potential (VEP) typical in MS shows a delayed potential with well-preserved wave-form (Halliday 1993) is the most useful test in showing a silent lesion by EPs because of its sensitivity and the stability of the abnormalities.

The CSF of patients with MS typically show normal glucose, a normal to mildly elevated total protein, and oligoclonal banding (OCB) in up to 95% of patients with definite MS (McLean et al. 1990). Regular cerebrospinal fluid findings in MS, pleocytosis and increasing IgG synthesis (Lauer 1984), are nonspecific signs of intrathecal immunological activity.

The diagnostic categories of varying certainty in MS, historically arising from the clinico-pathological definition established by Charcot in the 1860´s (Compston et al. 1998), are frequently revised. The first widely accepted diagnostic criteria were based on history and physical examination developed by Allison and Millar (1954). One of the best known criteria, devised for clinical trials with more restrictive definition, was published by Schumacher (Schumacher et al. 1965) (Appendix 1). The criteria can be considered safe and have been used in several epidemiological studies.

Diagnostic criteria were revised to include both clinical and paraclinical examinations in 1983 in the Poser criteria (Poser et al. 1983), criteria applied to clinical practice and used for inclusion in various studies and protocols (Appendix 2). In 2001 new criteria were recommended by the International Panel on the Diagnosis of MS (McDonald et al. 2001). In 2001 the new criteria integrated magnetic resonance imaging (MRI) into the diagnostic scheme and included a scheme for the diagnosis of primary progressive disease (Thompson et al. 2000). According to the new criteria, an individual is usually classified either as having MS or as not having MS. A patient with the appropriate clinical presentation who has not yet been assessed, or whose evaluation meets some but not all of the necessaray criteria, is considered to have ´possible MS´. Subcategories that define the types of studies used in the diagnostic workup (´clinically definite, ´laboratory supported´, etc.) are thus unnecessary according to the new recommendations.

2.4 Clinical course of multiple sclerosis

The course of multiple sclerosis is characterized by a great variation between individuals. The course ranges from slow to rapid deterioration and early death (McAlpine 1961, Detels et al. 1982, Thompson et al. 1986). MS patients with the benign form of the disease are characterized by less inflammation in MRI (Kidd et al. 1994) and benign cases are characterized by remaining fully functional in all neurological systems even 15 years after disease onset (McAlpine 1964, Thompson et al. 1986), representing about 27–40% of the patients (Ramsaransing et al. 2001). Filippi, according to the results of brain and spinal cord MRI study (Filippi et al. 1996), suggests that that patients with a benign form of MS have two different patterns of disease evolution, one characterized by very low clinical and MRI activities, and the other in which the lack of disabling symptomatology might be related to factors like site, size and nature of lesions. Patients with benign MS and high MRI lesion load may therefore have a risk of secondary progression even several years after onset (Filippi et al. 1996). In clinical practice, the Expanded Disability Status Score by Kurtzke (EDSS) (Kurtzke 1983) may be used as an indicator of prognosis (Hawkins and McDonnell 1999). However, Hawkins and McDonnell showed that the benign course is often temporary as the apparently benign course often becomes disabling.

The biological basis for the differences between those with benign MS (slight disability after 10 yrs) (Detels et al. 1982) and others with more disabling MS, and how the differences change over time are not fully understood. It is therefore difficult to be certain that agents that influence the course of MS over the short term, for example attack frequency or changes in disability scales, will have a substantial long-term effect (Weinshenker et al. 1996). Favourable course in MS is associated in several studies with female sex, early onset, and presentation with optic neuritis and sensory symptoms (Hawkins and McDonnell 1999). One of the most recent observations emphasizes the effect of age (Trojano et al. 2002) showing, however, that current age has a greater effect on disease severity than age at disease onset, and furthermore, older patients showing a faster rate of disease progression.

Recent studies have evinced the possibility that different pathways may predominate in different clinical forms of MS (Lucchinetti et al. 2000), but the factors which contribute to different patterns of disease evolution in MS are not exactly known (Filippi et al. 1994, Detels et al. 1982). Relapses indicating an inflammatory event in the CNS (McAlpine 1973) are variably remittent during the course of MS, however, the relation between the relapse and progression is confusing (Weinshenker et al. 1989, Runmarker and Andersen 1993, Confavreux et al. 2000). The situation may be complicated by the fact that relapses in many cases occur several years, or decades

(Rodriguez et al. 1993) before the diagnosis is confirmed. The disease progression is influenced by axonal degeneration (Smith and McDonald 1999), but the relation between inflammation and degeneration is unclear (McDonald 2000).

The symptoms of MS can be categorized into primary, secondary and tertiary (Smith et al. 1986). The primary symptoms during the course of the disease most commonly arise from lesions in the spinal cord with sensory or motor symptoms, the optic nerves and the brainstem with vertigo and diplopia. In progressive MS a spastic paraparesis with ataxia and sphincter incontinence typically develops. Mental symptoms with cognitive dysfunction, emotional lability, euphoria and even dementia occur. The secondary symptoms include urinary tract infections, fibrous contracture and pressure sores. Tertiary symptoms include the various psychosocial and professional restrictions caused by MS.

The initial clinical symptoms in multiple sclerosis are highly varied. Several isolated or combined symptoms, for example vertigo and sensory symptoms, are found in many conditions of variable anatomical site, whereas isolated optic neuritis or transverse myelitis may be regarded as harbingering signs for central demyelination in MS according to several studies. The probability of developing MS after uncomplicated optic neuritis has shown a high conversion rate from 10% to 85% (Weinshenker 1995), 64% within 40 years in a study by Rodriguez et al. (1993), and a significantly increased risk for women (Kinnunen 1983, Rizzo and Lessell 1988). The less often observed, but prominent onset signs in transverse myelopathy have shown 80% conversion rate to definite MS in 15 patients with acute partial transverse myelopathy at mean follow-up of 3 years (Ford et al. 1992).

In history, several patterns of clinical course have been described, and the terminology has been much discussed (McAlpine and Compston 1952, Lublin and Reingold 1996, Kremenchutzky et al. 1999). Today, as in the late 1800´s, the subtyping of the MS course is based on clinical and temporal characteristics, causing particular challenges in disease typing, in addition to terminological questions.

A primary progressive course (primary progressive MS, PPMS) from onset is reported in 8–37% of cases (Minderhoud et al. 1988, Thompson et al. 1997). Higher mean age at onset of 35–39 years and motor symptoms at onset are typical (Paty and Ebers 1998). Relapses are reported in 28% of cases, even three decades from onset, which may cause misclassification (Minderhoud et al. 1988, Kremenchutzky et al. 1999).

The majority, approximately 70–80% of MS patients, show an initial relapsing-remitting course (RRMS) (Weinshenker et al. 1989). The average first inter attack interval of 3 years (1–25 years) (Weinshenker et al. 1989) and relapses, of varying length (Rice and Ebers 1998), and complete or partial remission are characteristics in

RRMS. Attack rate is variable, approximately 1 in 1–2 years, the frequency showing a decline over time (Weinshenker et al. 1991). The development of a secondary progressive phase (secondary progressive MS, SPMS) is highly variable between individuals. The conversion to secondary progressive disease has been shown to increase steadily: 10% of those followed up from onset converted within 5 years, but 40% patients followed up from 6–15 years from onset had developed progressive MS. At 11–15 years from onset, 57% of primary RRMS cases had converted to SPMS (Weinshenker et al. 1989). In one study, the conversion took place approximately 9 years after onset (Minderhoud et al. 1988).

According to recent results the development of progressive course seems to be the most important predictor of long-term disability (Cottrell et al. 1999). Confavreux et al. (1980) first observed a comparable year of progression both for secondary and primary progressive cases, and subsequently an almost identical course. An even lower survival in SPMS was reported by Minderhoud (Minderhoud et al. 1988) in a similar study setting. The varying terminology to categorize the intermediate progressive forms, such as secondary progressive (SP), relapsing-progressive (RP), progressive relapsing (PR) forms has been based e.g. on the differences in disease outcome. The classification of progressive or intermediate courses has recently been evaluated, results providing justification for retaining only SPMS and PPMS subgroups, accepting temporary improvements in the primary progressive group (Kremenchutzky et al. 1999).

2.5 Mortality and comorbidity

Several long-term survival studies report an excess mortality in MS: in a Canadian study the duration of life was shortened 6–7 years (Sadovnick et al. 1992), while in a Danish study life expectancy was 11–13 years less compared to average population (Brønnum-Hansen et al. 1994). Deaths due to multiple sclerosis vary between 62 and 74% of all causes of death in MS patients (Allen et al. 1978, Phadke and Downie 1987).

The mortality study based on the largest MS register in Denmark has shown an increased risk of death from infectious pulmonary diseases, cardiac or vascular diseases, suicide and accidents after standardization with age (Koch-Henriksen et al. 1998). Incomplete case ascertainment of cancers in disabled MS patients was suspected to result in low cancer risk. The following hospital discharge diagnoses in one study were significantly more common among MS patients: urinary tract infection, pneumonia, septicaemia and cellulitis. Compared to age and sex matched

groups, underreporting in comorbidity with other age-related conditions, such as myocardial infarction, heart failure, hypertension, angina pectoris, cerebrovascular disease, diabetes mellitus and chronic obstructive pulmonary disease, has been shown among MS patients in age groups older than 65 years. (Fleming and Blake 1994). No significant increase has been found in cancer morbidity among MS patients (Palo et al. 1977, Wynn et al. 1990, Møller et al. 1991, Koch-Henriksen et al. 1998). Previous studies examining an association with other autoimmune diseases (Kinnunen et al. 1990a, Henderson et al. 2000, Kimura et al. 2000) have suggested the existence of a generalized autoimmune tendency in patients with multiple sclerosis. Another study claims risk of autoimmune disease rather among first degree relatives than among MS patients (Broadley et al. 2000), and hypothesizes that common genetic susceptibility factors for autoimmunity co-exist with additional disease specific genetic or environmental factors, which determine clinical phenotype in the individual.

However, in general, incomplete case ascertainment and decreased accuracy of clinically confirmed causes of death (Hakulinen and Teppo 1977) in addition to globally declining necropsy rates (Khong 1996) hamper the feasibility of etiological conclusions in morbidity and mortality studies.

2.6 Survival and prognostic factors

The results for 25-year survival from MS onset vary between 60 and 76% (Miller et al. 1992, Wynn et al. 1990). Poor survival has been reported during the first fifteen years of follow-up 1970–84 by Midgard (Midgard et al. 1995) but survival in MS seems to improve in longer follow-ups (Riise et al. 1988, Brønnum-Hansen et al. 1994). Results from a 25-year survival study in Olmstead County, Minnesota showed no increase in survival for patients diagnosed with MS in more recent decades. The estimated survival (76%) was 15–20% less than in an age- and sex-matched population. (Wynn et al. 1990.)

There is consistency in favourable outcome of relapsing-remitting course compared to primary progressive course (Riise et al. 1988, Midgard et al. 1995, Cottrell et al. 1999). There is controversy regarding the risk by gender, age at onset and type of initial symptoms (Weinshenker and Ebers 1987, Confavreux et al. 2000). Unfavourable disease evolution has been associated with late age at onset, male gender, progressive course, and pyramidal and cerebellar symptoms at the first episode (Ramsaransing et al. 2001). Pregnancy was shown to protect from disease progression in the long term (Runmarker and Andersen 1995, Zaffaroni and Ghezzi 2000).

The possible difference in risk by gender has been debated in several short and long term studies, with different methodologies and endpoints of follow-up (Poser et al. 1989, Brønnum-Hansen et al. 1994). In a Danish study, which is prospective and so far the largest 40-year follow-up, 8,842 cases were followed up from a retrospectively assessed onset during the period 1948–93 to the endpoint of all causes of deaths. The survival for men was about 23% and for women 35%. However, the risk for women increased more than for men by age of onset (Brønnum-Hansen et al. 1994). In a North American study in 1992, Wallin et al. (2000) reported a 40-year survival rate of 32% for white women, 17% for white men and 23% for black men. This was a World War II veteran cohort of 2,500 MS cases followed up during the period 1956–96 from disease onset in 1956 to all deaths, the cohort being originally ascertained by Kurtzke (Kurtzke et al. 1979). Midgard´s (Midgard et al. 1995) incidence cohort of 251 cases followed up from MS onset to 1950–84 in western Norway (districts of Møre and Romsdal) showed a 75% probability of survival at 15 years for men and at 24 years for women when the end point was all deaths. In the case of MS deaths, no significant difference between the sexes was found, and the survival was 75% at 21 and 24 years.

3 Aims of the study

The first aim of the study was to estimate the prevalence of MS, to find out the geographical distribution of the disease in the hospital districts of Uusimaa, Seinäjoki and Vaasa in 1993. Temporal prevalence changes, indicating changes in incidence or survival were estimated by comparing the rates in 1983 and 1993 (article I).

The second aim was to estimate MS incidence during a 15-year period in 1979–93 in Finland in order to find clues for etiology. The total and gender specific trends as well as geographical distribution of incidence were studied (article II).

Thirdly, disease course specific trends in incidence of MS were compared between the districts for further etiological considerations. Disease course specific rates were also analyzed to understand the trends for total MS in each district (article III).

The fourth aim was to study the natural course of MS in cases diagnosed in Finland up to 1993, before the advent of new disease course modifying drugs. Survival from onset to both MS related and all causes of death in the whole cohort was estimated to assess the contribution of MS to the risk of death among MS patients. The prognostic value of patient and disease related factors was estimated (article IV).

4 Material and methods

4.1 Populations

The population of Finland was 5.1 million in 1993. The annual increase from 4.8 million in 1979 was 0.4%. The three health care districts in this study in southern and western Finland constituted approximately 1/3 of the total population of Finland in 1993. The southern, largely urban population of Uusimaa region, including the capital, Helsinki, is growing due to migration from other parts of Finland. The population in the age-groups 10–70 years during the period 1979–93 increased by 12% in Uusimaa and 5% in the western districts Vaasa and Seinäjoki. In 1979 of the patients living in the municipalities in the western region, 91% were also born there, 87% in 1993 being in Seinäjoki, illustrating the stability of these populations. The rural populations of the districts of Vaasa and Seinäjoki are stable in size, and socio-economically similar.

Neurological services have historically been better in Uusimaa, where the population was 1,277,932 on December 31, 1993. Diagnostic facilities are mainly provided by the Helsinki University Hospital, which is one of the five university hospitals in Finland, and the central hospital in Uusimaa. In addition, five local hospitals provide neurological services. At the end of 1993 three neurologists in the Central Hospital of Vaasa served a population of 179,079 and four neurologists in the Central Hospital of Seinäjoki served a population of 197,042.

4.2 Data collection and case ascertainment

The cases diagnosed before January 1, 1979 in the districts of Uusimaa, Vaasa and Seinäjoki, have been included in the present studies from the three former studies on prevalence (Rinne et al. 1966, Wikström 1975, Kinnunen et al. 1983) and incidence (Kinnunen 1984).

The first surveys of MS occurrence in Finland were carried out in the 1960´s, when regional differences were studied in the 21 hospital districts. (Rinne et al. 1966, 1968). The hospital records of all patients hospitalized for the first or subsequent times in the period 1955–65 with a diagnosis of multiple sclerosis at the neurological clinics, central hospitals, and central mental hospitals in Finland were scrutinized. The reliability of the diagnosis drawing a national pension for MS on January 1, 1964 was reassessed. The domicile of patients were checked from the census registration index. Total of 919 controlled MS cases in Finland were classified according to the diagnostic

criteria presented by Allison and Millar (1954), 155 (94 women and 61 men) cases in Uusimaa, 82 (47 women and 35 men) cases in Seinäjoki and 49 (29 women and 20 men) cases in Vaasa 1954).

The data were complemented by Wikström (1975) including cases alive in December 31, 1971. Cases were collected from the patient records of the central hospitals and departments of neurology, psychiatry and internal medicine, and from the National Pension Institute of Finland. Mortality data was used to track patients who had died of MS during the 9-year period before the prevalence date December 31, 1971. The diagnosis of MS was accepted only if it fullfilled the criteria established by the Schumacher Committee (Schumacher et al. 1965). A total of 1,866 controlled MS cases in Finland were classified, 426 cases in Uusimaa, 148 cases from Seinäjoki region and 74 cases from Vaasa region.

In 1978 new MS cases from January 1, 1972 to January 1, 1979 in the regions of Uusimaa and Vaasa (including the districts of Vaasa and Seinäjoki) were scrutinized (Kinnunen et al. 1983) from the registers of the National Board of Health and the Social Insurance institutions, departments of neurology, psychiatry, ophthalmology and pediatrics of the university and central hospitals and from the general hospitals and health centres, in addition to the cases diagnosed from 1964 in these regions (Rinne et al. 1968, Wikström 1975). Regional differences in Uusimaa and Vaasa were studied on the level of smaller (clergical) districts, similarly to the study by Wikström (1975). The data were based on clinically definite MS cases that fullfilled the criteria of the Schumacher Committee (Appendix 1). As exception, some patients with onset symptoms after the age of 50 were included. Kinnunen (1984) observed 337 new MS cases (at the onset of the disease) in Uusimaa and 211 cases in the Vaasa region from 1964 to 1978. In January 1, 1979, 599 MS cases in Uusimaa, 223 cases in the districts from Seinäjoki region and 115 cases in the districts from Vaasa region were included in the prevalence study.

For the purposes in this dissertation the regional differences were studied on the level of hospital districts, comparable to the study of 1964 (Rinne et al. 1966). Yearly patient visits from January 1, 1979, to December 31, 1993, at the University Hospital of Helsinki in Uusimaa and at the local and central hospitals in Uusimaa, Seinäjoki and Vaasa with diagnoses of MS, morbus demylinans or neuritis retrobulbaris, papillitis optica (340, 341, 3773 in ICD 8 and 9 versions) during the period 1979–93 where scrutinized by the author (MLS). The case collection started in 1993 and the final examination for disease courses ended in 1997. The data were checked and complemented with the 991 definite cases classified by the Schumacher criteria in the earlier prevalence study (Wikström 1975) and 558 cases in the incidence study (Kinnunen 1984). Data on place of birth, district of residence at diagnosis, year of first symptoms, nature of first symptoms, and year of diagnosis. The results of

cerebrospinal fluid examinations (CSF), evoked potentials studies (EP) and magnetic resonance imaging (MRI) were collected. The data was complemented by the place of residence on December 31, 1993 from the Population Registry of Finland by using the personal identification number for linkage. The dates and causes of death were complemented from the Statistics Finland by the personal identification number from 1967, and before that from the National Population Registry from 1962.

Patients were retrospectively evaluated to meet the Poser criteria (Appendix 2) and were divided into groups of relapsing-remitting MS (RRMS) and primary progressive MS (PPMS), following the accepted quidelines (McAlpine and Compston 1952, Lublin and Reingold 1996). RRMS group included the cases that later showed secondary progression. Cases were excluded due to inadequate information for diagnostic ascertainment or due to residence outside the districts.

Cases were classified according to Poser criteria with diagnoses of definite and probable MS in 1964–93. The cases included were divided into three cohorts. The largest was prevalence cohort including the cases living in the districts of Uusimaa, Vaasa and Seinäjoki on December 31, 1993. The incidence cohort included only cases with definite MS, diagnosed between January 1, 1979 and December 31, 1993 and living in the districts of Uusimaa, Vaasa and Seinäjoki at the time point of diagnosis. The survival cohort included the cases with definite MS diagnosed between January 1, 1964 and December 31, 1993 and living in the districts of Uusimaa, Vaasa and Seinäjoki at the timepoint of diagnosis.

4.3 Methods

Prevalence Prevalence calculations were based on the MS cases fulfilling the criteria for definite or probable MS by Poser (Poser at al. 1983). The age-adjusted and age-specific prevalence in 10-year age-groups per 100,000 population were calculated for each district with 95% confidence intervals (95% CI) on December 31, 1983 and 1993.

The calculations were based on the formula for prevalence (dos Santos Silva1999):

> Prevalence (P) = (number of existing cases in defined population at a point of time/number of people in the defined population at the same point of time) x 100,000

The standardized prevalence ratio (SPR), on December 31, 1993 was calculated by using the indirect method (Armitage and Berry 1994a, dos Santos Silva 1999). The rates for Uusimaa were chosen as the standard. To calculate the standardized prevalence, number of observed cases were divided by the expected number of cases. The expected number of MS cases was calculated by multiplying the number of person-years in each sex-age-group in Seinäjoki and Vaasa by the corresponding average MS

prevalence in the population of Uusimaa. Relative prevalence rates for Vaasa and Seinäjoki were thus obtained after adjusting for age and sex to the standard population. Confidence intervals of 95% were estimated assuming that the number of observed cases followed the Poisson distribution.

Incidence Incidence calculations were based on cases fulfilling the criteria for definite MS by Poser (Poser et al. 1983). The crude incidence per 100,000 person-years with 95% CI in the age-group between 10 and 70 years was calculated for each district, as were the age- and sex-specific incidences. To study the incidence trend and regional variation, the incidence was also calculated for 5-year calendar periods (1979–83, 1984–88, 1989–93) for genders and disease courses in each district.

The calculations were based on the formulas for incidence (dos Santos Silva 1999):

Incidence (I) per 100,000 person-years = (Number of new cases arising in a defined population in a specific period of time/ Total person-years at risk in that population during that period of time) x 100,000

and

Age-specific incidence per 100,000 person-years = (Number of new cases arising in certain age-group in a defined population and in a specific period of time/ Person-years at risk in that age group in the same population and during that period of time) x 100,000

The standardized incidence ratios (SIR) were calculated using the indirect method (Armitage and Berry 1994a, dos Santos Silva 1999). To calculate the SIR, number of observed cases were divided by the expected number of cases. For that purpose the standard rates were those of Uusimaa in each sex-age-group, and the rates of definite MS in Vaasa and Seinäjoki were adjusted to those in Uusimaa. The resulting standardized incidence rate (SIR) is the ratio of the observed cases in the population of Vaasa and Seinäjoki to that expected if the age-specific rates in Uusimaa had been observed in the other areas. Confidence intervals of 95% were estimated assuming that the number of observed cases followed the Poisson distribution.

Survival The survival rates in five-year intervals were estimated by the life table method (Armitage and Berry 1994b) for definite MS cases diagnosed from January 1, 1964 to December 31, 1993, which was the end of follow-up. Survival was estimated for the total cohort and for the three districts. The survival in the whole cohort was calculated from the clinical onset of MS (first symptoms) and from the definite diagnosis. Two endpoints were selected: death due to MS or MS-related causes, and death due to any cause. The survival in the districts was calculated from the diagnosis to all causes of death.

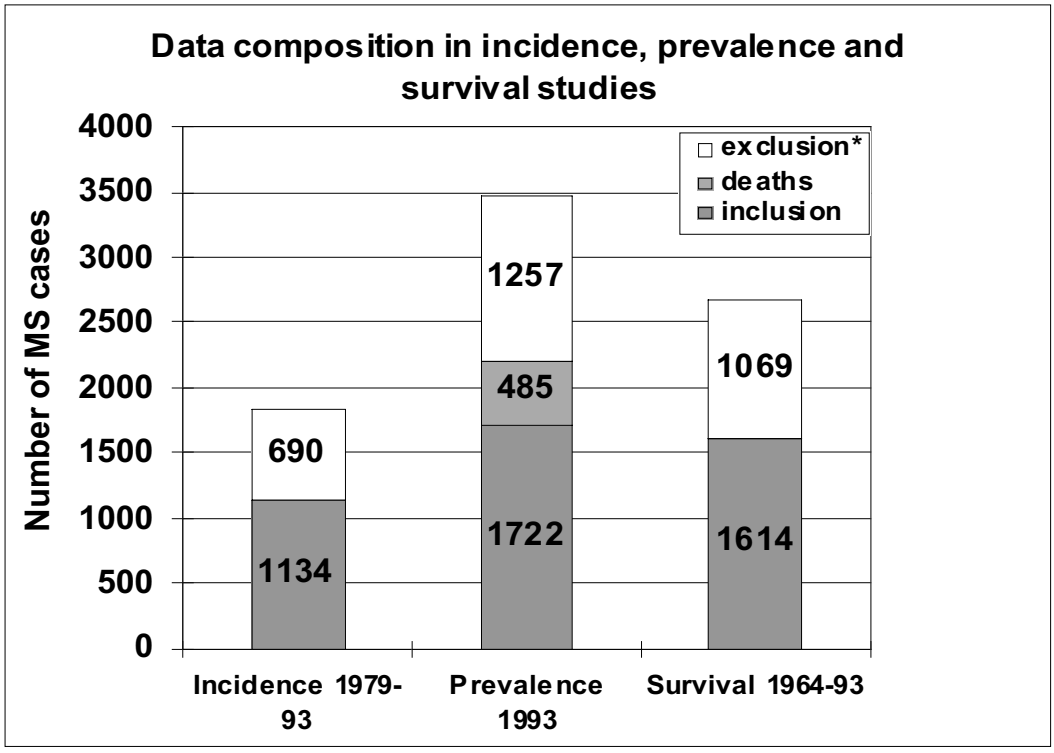
Cox´s proportional hazards model (Cox and Oakes 1984) was used to estimate the relative risk of death (RR) for definite MS by prognostic factors, using both crude and adjusted models. Confidence intervals (CI) were reported at 95% level, assuming that

cases followed the Poisson distribution. Prognostic factors were gender, disease course, age at onset, age at definite diagnosis, diagnostic latency, period of diagnosis, initial symptoms and district.

5 Results

5.1 Study cohorts

For the original sample, a pool of 3,685 cases was scrutinized by the author, and out of this pool a total of 2,683 patients (1,758 women and 925 men) were screened. The composition of data in the three series for incidence from January 1, 1979 to December 31, 1993, prevalence in December 31, 1993 and survival for cases diagnosed from January 1, 1964 to December 31, 1993 is presented in figure 1.



* exclusion:
-incidence series : 680 (340 cases with inadequate information for diagnosis and 340 cases including cases diagnosed outside the districts, diagnosed before 1979, suspected cases or cases outside the age limits of 10–70 years).
-prevalence series: 1963 (1,002 duplicates, 485 deaths, 476 cases living outside the districts in December 31, 1993, suspected cases or cases with inadequate information for diagnosis).
-survival series: 1,069 (680 exclusions in the incidence series 1979–93 and 389 exclusions among cases diagnosed before 1979, including cases diagnosed before 1964, and cases with inadequate information for diagnosis or cases outside the age-limits 10–70 years).

Figure 1. The composition of data in the three series for incidence cases diagnosed from January 1, 1979 to December 31, 1993, prevalence cases in December 31, 1993 and cases diagnosed from January 1, 1964 to December 31, 1993.

Prevalence cohort The prevalence cohort in December 1983 included 1,339 patients, fullfilling the criteria of Poser, the number of probable MS cases was 309 (23%). In December 1993, 1,722 patients were included, the number of probable MS cases was 192 (11%). The diagnosis was clinically based on 93% cases (93 in Uusimaa, 94 in Seinäjoki and 90% in Vaasa). For the definite MS cases, CSF was most often used among the paraclinical tests, in 76% of cases. Testing was performed in 79% in Uusimaa, 60% in Vaasa and 77% in Seinäjoki, being positive in 91–94% of cases. MRI was performed in 37% (83% positive) in Uusimaa, 10% in Seinäjoki (77% positive) and 10% in Vaasa (94% positive). Evoked potentials (VEP/ SEP/ BAEP) were studied in 70% in Uusimaa (89% positive), 42% in Seinäjoki (88% positive) and 45% in Vaasa (67% positive).

Incidence cohort The incidence cohort of cases diagnosed from January 1, 1979 to December 31, 1993 in the hospital districts of Uusimaa, Vaasa and Seinäjoki included 1,066 cases fulfilling the criteria for definite MS by Poser. Out of 1,814 screened subjects who visited hospitals in Uusimaa, Vaasa and Seinäjoki from 1979 to 1993, 340 cases were excluded on the basis of inadequate information for diagnosis, or living outside the districts, or diagnosed before 1979. Out of the 1,474 subjects 340 were excluded on the basis of suspected MS (optic neuritis or other solitary symptom), these constituted 20%, 25% and 25% of the subjects in Seinäjoki, Vaasa and Uusimaa, respectively. 68 (6%) cases with probable MS were excluded.

Of the paraclinical tests, CSF was used most often, in 92% (oligoclonal bands in 86%) of cases. Test was positive in 91% of cases in Uusimaa, 94% in Vaasa and 92% in Seinäjoki. MRI was performed in 50% of cases in Uusimaa (86% positive), 14% in Vaasa (88% positive) and 12% in Seinäjoki (92% positive). Evoked potentials (VEP/ SEP/ BAEP) were studied in 63% of cases in Uusimaa (88% positive), 12% in Seinäjoki (82% positive) and 12% in Vaasa (55% positive).

Survival cohort The survival cohort consisted of 1,614 patients diagnosed for definite MS by Poser criteria from January 1, 1964 to December 31, 1993: 1,109 patients in the hospital district of Uusimaa, 369 in Seinäjoki and 136 in Vaasa. Out of these cases 488 definite cases according to the criteria of Poser were diagnosed from 1964 to 1978 in the hospital districts of Vaasa, Seinäjoki and Uusimaa. F/M ratios were 2.1 in Uusimaa, 1.4 in Seinäjoki and 2.2 in Vaasa. The diagnosis was clinical in 93% of cases. Probable MS cases (155 cases, 9%) were excluded. During the period 1964–93 number of recorded deaths was 219. Demographic features for cases diagnosed during a 30-year follow-up 1964–93 in Uusimaa, Seinäjoki and Vaasa are presented in Appendix 3.

5.2 Prevalence

On December 31, 1993, 1,530 definite MS patients were alive and recorded in the study districts (Table 2). The age-adjusted prevalence per 100,000 was 93 in Uusimaa (n = 1,052), 188 (n = 322) in Seinäjoki and 107 (n = 156) in Vaasa. Total, gender and disease course specific rates with 95 % CI´s are presented in Table 2.

The inclusion of probable cases in 1993, 162 in Uusimaa, 24 in Seinäjoki and 6 in Vaasa, increased the total number of cases to 1,722, but increased the prevalence significantly only in Uusimaa (15%) to 108.8 (95% CI 102–114), due to an increase among women, while in Seinäjoki and Vaasa the prevalence remained fairly stable, 202.0 and 111.0/10^5. Age-specific prevalences for men peaked at 50–59 years and for women at 40–49 years in Uusimaa and Seinäjoki and 50–59 years in Vaasa.

The standardized prevalence ratios (SPR) for definite MS in December 31, 1993 showed a significant difference in trend in Seinäjoki (annual increase 2.2, 95% CI 1.9–2.4) compared to Vaasa (1.2, 95% CI 1.0–1.4) and Uusimaa (1.0). The increased risk for men was not significant compared to that of women. The risk for PPMS in Seinäjoki was four-fold, and risk for RRMS three-fold as compared to Uusimaa and Vaasa.

Table 2. Age-adjusted prevalence per 100,000 (with 95% confidence intervals) by gender and disease course on December 31, 1993 in Seinäjoki, Vaasa and Uusimaa.

District	Number			Prevalence		
	Total	PPMS	RRMS	Total	PPMS	RRMS
Seinäjoki						
Total	322	88	234	187 (167–208)	51 (40–62)	136 (119–153)
Men	118	40	78	140 (115–165)	47 (33–62)	93 (72–113)
Women	204	48	156	233 (201–264)	55 (39–70)	178 (150–206)
Vaasa						
Total	156	22	134	107 (90–124)	15 (9–21)	92 (76–108)
Men	47	5	42	66 (47–85)	7 (1–13)	59 (41–77)
Women	109	17	92	146 (118–173)	23 (12–34)	123 (98–148)
Uusimaa						
Total	1052	204	848	93 (88–99)	18 (16–21)	75 (70–80)
Men	320	74	246	60 (54–67)	14 (11–17)	46 (41–52)
Women	732	130	602	123 (114–132)	22 (18–26)	101 (93–109)

During the 10 years from 1983 to 1993 the prevalence of definite cases increased significantly in Uusimaa (26%) and Seinäjoki (45%), and decreased (8%) in Vaasa. In December 31, 1983, 1,030 definite MS cases were alive and recorded in the study districts. The age-adjusted prevalence per 100,000 (10^5) was 69.0 (n = 688) in Uusimaa, 116.0 (n = 196) in Seinäjoki and 102.0 (n = 146) in Vaasa. Inclusion of 246 probable cases in Uusimaa, 30 cases in Seinäjoki and 33 cases in Vaasa increased the total number of cases to 1,339. The age-adjusted prevalence per 100,000 increased to 87.0 in Uusimaa, 117.0 in Seinäjoki and 108.0 in Vaasa.

5.3 Incidence

From January 1, 1979 to December 31, 1993, 1,066 definite cases fulfilled the diagnostic criteria: 736 in Uusimaa, 240 in Seinäjoki and 90 in Vaasa. The incidence in the total population during the period 1979–93 per 100,000 person-years was 4.7 (95% CI 4.3–5.0) in Uusimaa, 9.3 (95% CI 8.1–10.4) in Seinäjoki and 4.2 (95% CI 3.–5.1) in Vaasa.

The incidence in the age groups 10–69 years was 5.1 (95% CI 4.8–5.5) in Uusimaa, 11.6 (95% CI 10.2–13.1) in Seinäjoki and 5.2 (95% CI 4.1–6.3) in Vaasa. Total, gender and disease course specific rates with 95 % CI are shown in Table 3. F/M ratios were 2.1 in Uusimaa and Vaasa and 1.5 in Seinäjoki. Age specific incidences peak at 30–39 years in Uusimaa and at 40–49 years in Vaasa. Distribution of incident cases in the total cohort was 3% in the age group 10–19 years and 13% in age groups over 50 years.

Table 3. Incidence per 100,000 (with 95% confidence intervals) person years by gender and disease course in Seinäjoki, Vaasa and Uusimaa during the period 1979–93.

District	Number			Incidence		
	Total	PPMS	RRMS	Total	PPMS	RRMS
Seinäjoki						
Total	240	73	168	11.6 (10.1–13.1)	3.5 (2.7–4.3)	8.1 (6.9–9.3)
Men	93	33	60	9.1 (7.2–11.0)	3.7 (2.6–4.8)	5.9 (4.4–7.4)
Women	147	39	108	13.9 (11.7–16.1)	3.3 (2.1–4.5)	10.2 (8.3–12.1)
Vaasa						
Total	90	21	69	5.2 (4.1–6.3)	1.2 (0.7–1.7)	4.0 (3.1–4.9)
Men	28	7	21	3.4 (2.2–4.6)	0.8 (0.2–1.4)	2.5 (1.4–3.6)
Women	62	14	48	7.0 (5.3–8.7)	1.6 (0.8–2.4)	5.4 (3.9–6.9)
Uusimaa						
Total	736	145	591	5.1 (4.8–5.5)	1.0 (0.8–1.2)	4.1 (3.8–4.4)
Men	217	56	161	3.1 (2.7–3.5)	0.8 (0.6–1.0)	2.3 (1.9–2.7)
Women	519	89	430	7.0 (6.4–7.6)	1.2 (1.0–1.4)	5.8 (5.3–6.3)

The standardized incidence ratios (SIR) during the period 1979–1993 were 2.2 in Seinäjoki, 1.0 in Vaasa and Uusimaa, showing thus a 2.2-fold (95% CI 2.0–2.6), significantly increased risk for MS patients in Seinäjoki compared to Uusimaa and Vaasa (1.0). The risks for both PPMS and RRMS in Seinäjoki were significantly higher, four-fold for PPMS and three-fold for RRMS, as compared to Uusimaa and Vaasa, but no significant differences were observed between genders.

During the first five-year period from December 31, 1979 to December 31, 1983 the total incidence in age group 10–70 years in Uusimaa was 5.2 (95% CI 4.6–5.9) per 100.000 person-years, 8.0 (95% CI 5.7–10.3) in Vaasa and 9.8 (95% CI 7.4–12.1) in Seinäjoki. During the last period from December 31, 1984 to December 31, 1993 the stable trend in Uusimaa resulted in similar rate of $4.7/10^5$ (95% CI 4.1–5.3). Decrease was observed in Vaasa, incidence being $3.1/10^5$ (95% CI 1.7–4.5) in 1989–93. The high rates in Seinäjoki showed a further increase to $13.3/10^5$ (95% CI 10.6–16.0). (Figure 2.)

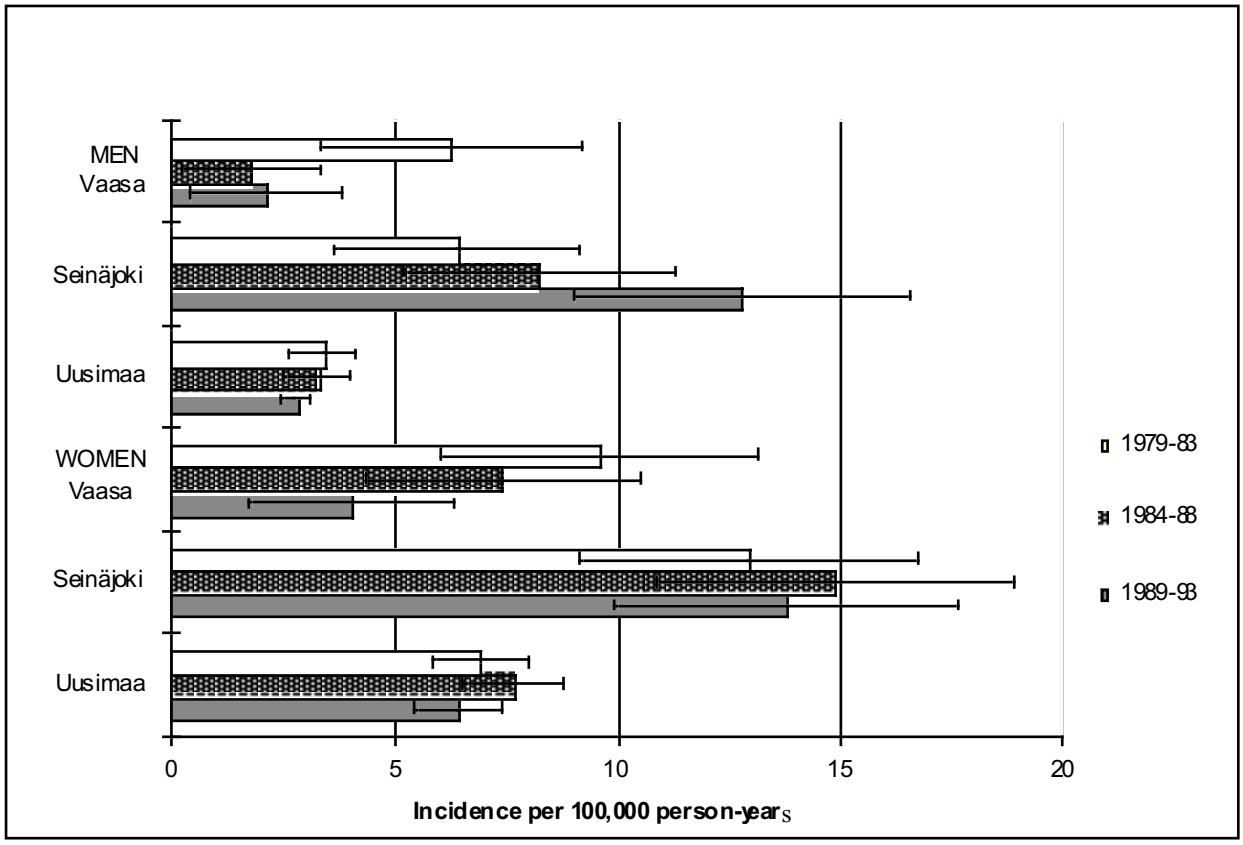


Figure 2. Incidence trends by gender in the period 1979–93 with 95 % confidence intervals in Vaasa, Seinäjoki and Uusimaa.

The SIRs showed a significant decrease in Vaasa from 1.5 (95% CI 1.1–2.0) for the period 1979–83 to 0.6 (95% CI 0.4–1.0) the period 1988–93, and an increase in Seinäjoki from 1.8 (95% CI 1.4–2.3) to 2.8 (95% CI 2.3–3.5), compared to rates in Uusimaa. The risk for men was significantly higher in Seinäjoki, 2.8 (95% CI 2.3–3.5), however, non-significant compared to women 2.1 (95 % CI 1.8–2.4), while no difference was observed in Vaasa and Uusimaa between the genders.

The sharp incidence changes in Seinäjoki were mainly due to increase among men, and in Vaasa a decrease in incidence was observed among both genders. In Uusimaa incidence remained fairly stable for both genders.

Overall, the disease course specific incidence trends paralleled the total incidence trends 1979–93 in all three districts (Figure 3). The stable trend in Uusimaa, decrease in Vaasa and increase in Seinäjoki were nonsignificant for RRMS, while in Vaasa the decrease in PPMS from $2.5/10^5$ (95% CI 1.2–3.8) to $0.3/10^5$ (95% CI 0.1–0.8) was significant. The gender-specific RRMS and PPMS trends were parallel during the period 1979–93 (not shown).

Male and PPMS incidences in Vaasa and Seinäjoki in the period 1979–83 were practically the same: incidence for men 6.3 (95% CI 3.3–9.2) in Vaasa and 6.4 (95% CI 3.7–9.2) in Seinäjoki and for PPMS 2.5 (95% CI 1.2–3.8) and 2.8 (95% CI 1.5–4.1) respectively. In the period 1989–93, however, the male incidence showed a 6-fold, and PPMS incidence a 15-fold difference between the districts. Thus, the resulting two-fold incidence gradient in 1993 between Vaasa (SIR 1.0) and Seinäjoki (SIR 2.2) is relatively larger among men and in patients with the PPMS disease course.

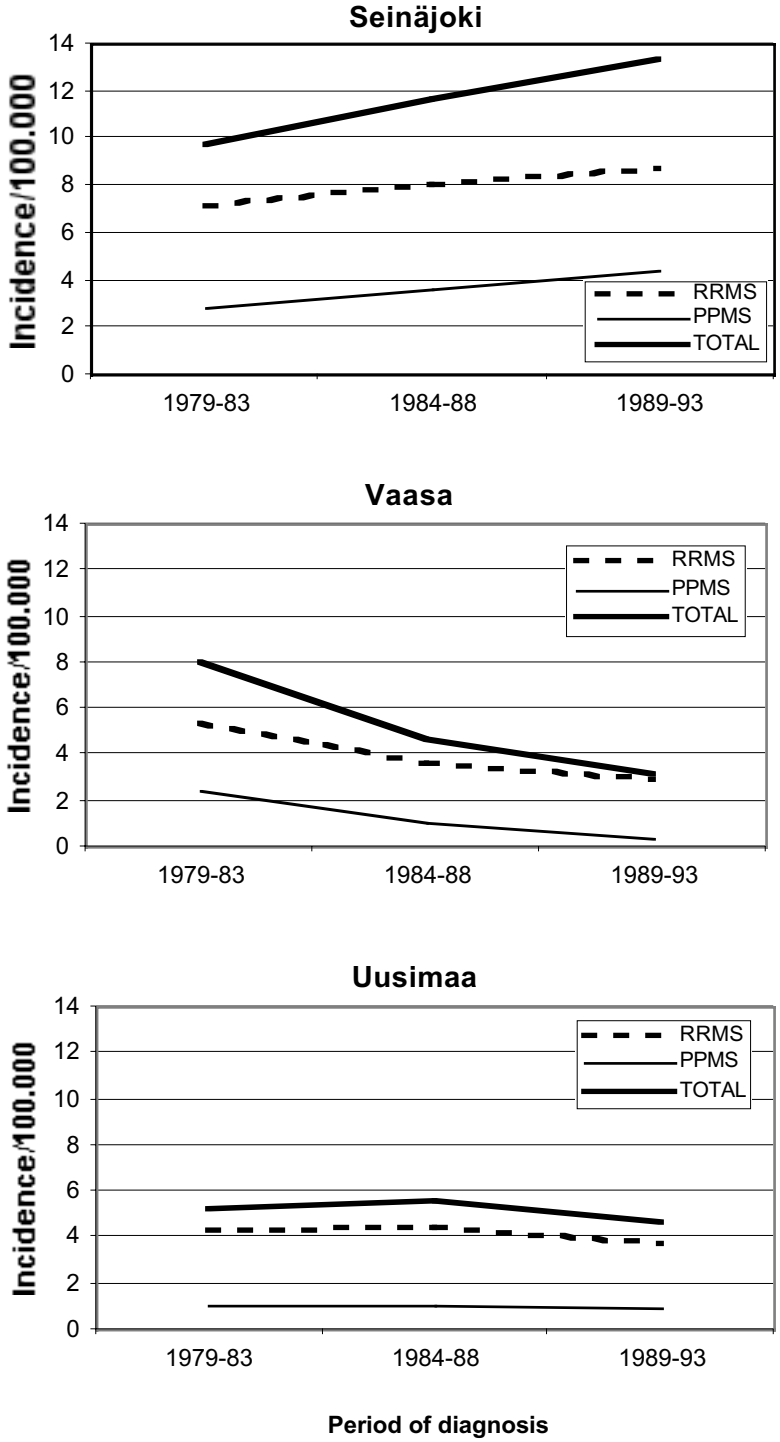


Figure 3. Incidence trends in MS 1979–1993 per 100,000 by total MS and relapsing-remitting (RRMS) and primary progressive (PPMS) disease courses in Seinäjoki, Vaasa and Uusimaa.

5.4 Causes of death

In the cohort of MS patients diagnosed between January 1, 1964 to December 31, 1993, 219 cases of death were recorded during the period 1964–93. The median year of death was 1988. In 1,54 cases (70%), death was classified as MS or MS-related and in 65 cases as due to other causes (30%). During the period 1964–93, 133 (61%) deaths occurred in Uusimaa, 63 (29%) in Seinäjoki and 23 (11%) in Vaasa. The distribution was similar in the case of MS related deaths: 63%, 26% and 11%, respectively.

Among the deaths due to causes other than MS there was an overrepresentation of malignant tumours (35%), and accidents (19%) compared to general mortality in 1988 (20% for tumours and 9% for accidents). The percentage of suicides (5%, only 3 cases all in men) was not substantially higher than in the general population (3%). Cardiovascular causes of death were fewer (26%) than expected.

5.5 Survival

When followed from clinical onset (first symptoms) to all causes of death, the 25-year survival rate was 78% and 40-year survival rate 53%. For MS-related deaths the corresponding figures were 84% and 64%. When followed from time of diagnosis, the 25-year survival rate was 62% for all causes of deaths, and 66% for MS-related deaths (Figure 4).

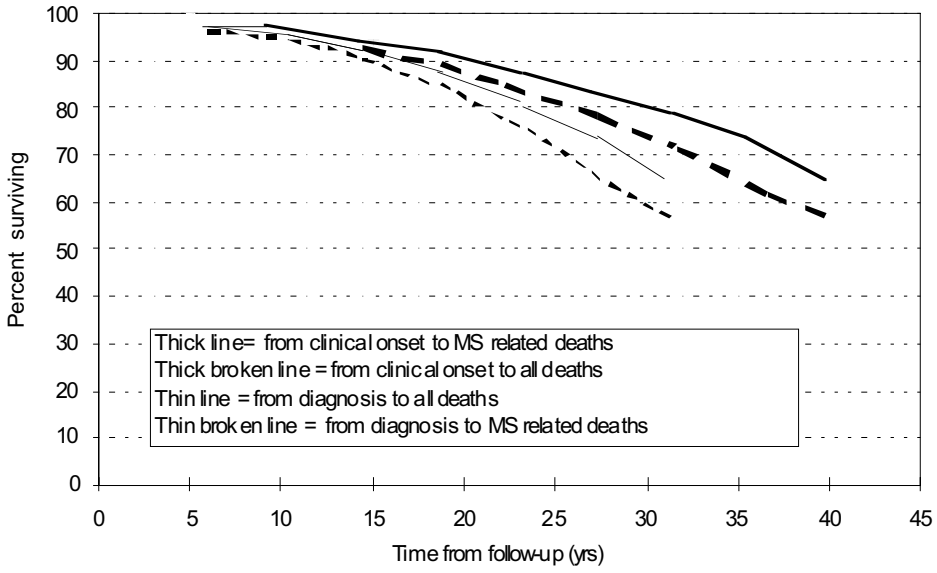


Figure 4. Survival curves for cases followed from onset and diagnosis of definite MS to MS related or all causes of death.

The effects of prognostic factors were calculated for several patient and disease related variables using Cox´s model in four subgroups: cases followed from clinical onset or definite diagnosis either to MS related, or all causes of death from 1964 up to 1993 (Appendix 4.). The risk of death from onset to MS related deaths was largely similar compared to all causes of death. The same was true among cases followed from diagnosis. Also, crude and adjusted risks of death during each of the four follow-up periods gave roughly the same results with few exceptions. The excess risk of death for men could be accounted for by other prognostic factors: in the case of all causes of death risk of death was slightly higher compared to women, but adjusted risks between genders were similar (1.1, 95% CI 0.8–1.6, MS-related deaths), indicating that the high risk of death among male patients is accounted for by the high mortality in men from causes other than MS as compared to women.

For cases followed up from onset, over 30 years age at onset showed a strong independent prognostic strength, as the risk of death was signficantly increased, also being high in case of MS related deaths (adjusted risk 1.4, 95% CI 1.0–1.9**).** For cases followed up from diagnosis, age over 35 years at diagnosis was a prognostic factor for marginal effect only. When only MS related deaths were considered, the adjusted relative risk was 1.2 (95% CI 0.9–1.6).

Primary progressive disease course (PPMS) showed the highest risk of death in any model: the risk for cases followed-up from onset to all deaths in the adjusted model was 2.9 (95% CI 2.0–4.1) and in the case of MS deaths 3.0 (95% CI 2.0–4.6). When followed from diagnosis to all deaths the risk in the adjusted model was 2.1 (95% CI 1.5–3.1) and in the case of MS related deaths 2.3 (95% CI 1.5–3.6). 12% of cases (n = 197) were not classified for disease course. The highest risk of death was observed among these patients. The ultimate effect of these unclassified cases on the risk of death was studied adding the cases separately to either group: inclusion of cases to the RRMS group still showed an increased crude risk ratio for PPMS of 1.5 (95% CI 1.1–2.2) and inclusion in PPMS groups resulted in a risk ratio of 2.6 (95% CI 1.8–3.6). In either case the risk of death for PPMS was higher than for RRMS. Hence, incomplete information on disease type could not account for the result of higher risk of death among PPMS than in RRMS patients.

For cases followed up from onset, favourable prognosis for initial sensory symptoms and optic neuritis were shown: adjusted risk of death was 0.4 (95% CI 0.2–0.9) in MS deaths, and 0.6 (95% CI 0.3–0.9) in all causes of death. Low rates were also observed for infratentorial symptoms including the brainstem, cerebellar and medullary symptoms. The risk was highest for cases with lacking information on onset symptoms.

For cases followed up from diagnosis, the period of diagnosis showed no changes in risk, except in the case of all causes of death in the adjusted model showing an increase during the last decennium 1984–1993. Period of diagnosis had a nonsignificant effect when followed up from onset.

To analyze the regional differences in the risk of death, survival in Uusimaa, Vaasa and Seinäjoki was estimated from the definite diagnosis to any cause of death by Cox´s model. A slightly increased crude risk of death in Seinäjoki (RR 1.4, 95% CI 1.03–1.9) compared to Uusimaa was accounted for the prognostic variables (gender, disease course, age at onset, 10-year period of diagnosis). The risk in Vaasa was in between Seinäjoki and Uusimaa (RR = 1.2, 95% CI 0.8–1.9).

6 Discussion

This population-based study includes MS patients with multiple sclerosis in three hospital districts in southern and western Finland. In the centralized health care system in Finland, multiple sclerosis is traditionally diagnosed by a neurologist in the local, central or university hospitals in almost 100% of cases according to the same principles, why the original data forms a truly population based cohort. All cases with even suspected multiple sclerosis up to December 31, 1993 were scrutinized in the hospital records. Cases were reclassified as MS patients and included if they had fulfilled the diagnostic criteria of Poser (Poser et al. 1983). This was the timepoint of diagnosis. Retrospective classification allowed incorporation of ancillary investigations and the separation to clinical and laboratory supported diagnoses (Poser 1994), which was necessary in estimating the effect of the regional differences in diagnostics during a long follow-up period. Definite cases were included for the incidence study to improve the regional comparison. Definite cases, as well as possible, probable and definite cases, were studied in the prevalence study, in order to achieve regional comparisons as well as to estimate the amount of suspected MS in the populations. Only definite cases were included in the survival study, to ensure the homogeneity of the material from three districts. Exclusion of probable cases in the incidence and survival studies may distort the results minutely, but nevertheless give results based on definite MS.

The primary aims of this study were to estimate recent MS occurence in Finland regionally by gender, age and disease course for temporal and geographical comparisons. Epidemiological studies in MS, based on different diagnostic criteria and methods applied in different regions and at different times (Weinshenker and Ebers 1987, Weinshenker et al. 1989), hamper both geographical and temporal comparisons and these aspects were considered in the study design of this thesis. In contrast to several other studies and earlier studies in Finland, diagnosis based approach was chosen here to avoid several problems faced in onset based studies (Compston 1997). These include problems in recognition and definition of historical and often arbitrary onset, which may result in false risk estimations (Hibberd 1994). Limitation for age at onset (Noseworthy et al. 1983) was also excluded by including cases older than 50 years at onset, results maintaining a reasonably reliable distribution of definite MS in population. To improve the validity and consistency of disease course classification (McAlpine and Compston 1952, Lublin and Reingold 1996), and to reduce potential interrater bias (Minderhoud et al. 1988, Kremenchutzky et al. 1999), the material was retrospectively classified by the same person (MLS). To avoid classification bias with time, patients were divided into primarily progressive group and into relapsing remitting group, including cases that later

turned into secondary progression. A restriction to clearly characterized subtypes at onset and separation of classification during the disease evolution, such as inclusion of different forms of progression, allows for practical assessments for medication and prognosis as well as retaining the description of largely individual phenotype during the course of MS.

In regional comparisons the random variation in time and different population structures, especially in MS with rare occurrence, are best controlled by confidence intervals and age-standardization (Ahlbom and Norell 1990). Indirect standardization is generally preferable to a direct method when age specific rates are based on small number of subjects, also chosen in this study. However, direct standardization is less open to bias than indirect, but in practice they tend to give broadly similar results (dos Santos Silva 1999). The population of Uusimaa was chosen as a reference population for epidemiological MS research in Finland from the 1970´s (Kinnunen et al. 1983) as also in this study.

In 1993 the prevalence of $100/10^5$ and incidence of $5.1/10^5$ person-years 1979–93 were observed in Uusimaa. These results allow for an estimation of the total number of MS patients in Finland, which may be approximated to be about 5,500 in 1993 and close to 6,000 in 2000. However, the most obvious observation is the increased and high prevalence in Seinäjoki and the now even rates in Uusimaa and Vaasa, shown in Table 4. The increasing number of cases and increasing prevalence in 1993 (article I) as compared to the rate in 1964 (Rinne et al. 1964) shows a six-fold increase in Uusimaa, while increase is four-fold in Vaasa and five-fold in Seinäjoki.

Table 4. Number of MS cases, crude and age-adjusted prevalences per 100,000 in the hospital districts of Uusimaa, Vaasa and Seinäjoki in 1964 and 1993.

Area	Study	Year	N	Crude	Age-adjusted
Uusimaa District	Rinne et al. 1968	1964	155	18	
Uusimaa District	This study I	1993	1214	93	108
Vaasa District	Rinne et al. 1968	1964	49	30	
Vaasa District	This study I	1993	162	107	111
Seinäjoki District	Rinne et al. 1968	1964	82	39	
Seinäjoki District	This study I	1993	346	187	202

The regional gradient in this stydy was marked. The high occurrence rates in Seinäjoki contrasted with the rates in southern Uusimaa and in neighbouring Vaasa, and the prevalence of $200/10^5$ and incidence of $12/10^5$ person-years in Seinäjoki are already now among the highest ever reported and showing a still increasing trend. The difference was consistent by demographic features, age at diagnosis and distribution of disease courses, as well as differences in the incidence trends. A special feature in Seinäjoki was the increased incidence risk for men 1979–93 and a low sex ratio (F/M = 1.6) in incidence study compared to two other areas (2.2 in Vaasa and 2.4 in Uusimaa) and to the ratio generally reported (2.0) (Compston et al. 1998). Furthermore, the prevalence at the level of local districts pinpointed a cluster in southern parts of the Seinäjoki district, met by the lower prevalence rates in bordering coastal area and unknown prevalence rates in other neighbouring districts. The exact border for the high risk MS focus thus remains unclear.

The recent prevalence and incidence in Finland indicate that world wide Finland belongs to the high risk areas of MS (Kurtzke 1977, Lauer 1994) together with other Fennoscandinavian countries, British Isles, Canada and some parts of US (Gross et al. 1993, Compston 1997). In Finland occurrence has also shown an increase which is approximately four-fold in 30 years (Rinne et al. 1966, Wikström and Palo 1975, Kinnunen 1983). Typical features in MS populations, such as disease course distribution (Weinshenker and Ebers 1987), were shown to prevail in Finnish MS populations as well, including female preponderance and rarity of cases in younger and older age groups (Noseworthy et al. 1983, Sindern et al. 1992, Ruggieri et al. 1999). Epidemiological features typical in high risk regions, such as temporally changing trends (Svenningson et al. 1990, Midgard et al. 1991) were shown also here in western districts.

The generally increasing MS prevalence in Finland from the 1960´s has undoubtedly been at least partly affected by improved awareness of MS and prolonged survival in the population (Noseworthy et al. 2000). A critical examination of the interrelation of incidence, survival and prevalence was possible in this study: the result of increased prevalence in Uusimaa was mainly explained by the better survival in Uusimaa than in the other districts, while in Seinäjoki the increasing prevalence was largely due to increased incidence, especially among men and across a wide age-group from 20 up to 70 years, and the stable prevalence in Vaasa, peaking in older age-groups of 50–59 years, in the presence of stable survival, is best explained by the decreasing incidence. In the case of a rare disease with variable diagnostic latencies, chance may distort the results in the short run. Considering these results up to fifteen years and several other observations on fluctuating MS incidence, the wide disparities between geographically close regions in MS as well as in type I diabetes (Larsen et al. 1984b,

Edland et al. 1993, Onkamo et al. 1999, Rosati 2001), and recent changes in MS incidence and prevalence in Finland are difficult to explain by changes in case ascertainment, disease awareness or improved general survival.

Incidence changes in homogenous populations may thus indicate true etiological changes and point at environmental factors in MS (Larsen et al. 1984a, b, Hammond et al. 1988, Edland et al. 1993). Changing ways of life, economy and sanitary improvements (Rosati et al. 1978, Rosati 2001) and unlikely to explain the recently occurring differences in typical northern high risk populations. In Finland the environmental changes in the past decades include decline in agriculture and increasing emigration from rural areas. The possible sociocultural differences associated with the Swedish-speaking population in Vaasa district (22%) is probably too small to explain the gradient observed here, and anyway the prevalence among Swedish-speaking population has not previously shown any differences (Panelius 1969). The environmental etiology of MS in Finland has been studied for a direct infection to measles (Panelius 1969), to some animal (muscular dystrophy in cattle) and corn diseases (Palo et al. 1973, Wikström 1975), occupational exposures to chemicals (Juntunen et al. 1989), and several viruses (Kinnunen et al. 1990b). Genetic epidemiology has focused on pedigree analyses (Wikström et al. 1984, Tienari et al. 1992a, b, Tienari et al. 1993) and familial occurrence, which in Seinäjoki has been increasing locally from 11% in 1979 to 29% in 1984 (Wikström et al. 1984). Based on this cluster extending over several families and pedigrees, the studies from the 1990´s have focused increasingly on molecular genetics and at least four putative susceptibility genes have been localised in families originating in Seinäjoki (Tienari et al. 1992a, b, Tienari et al. 1993, Kuokkanen et al. 1997).

Given that genetic changes in populations are slow, the recent changes in incidence in different parts of Finland are more consistent with environmental causes. The parallel incidences to different total trends in each district also indicate environmental modification, which is suspected to be similar for the relapsing remitting and primary progressive disease courses: Although the natural courses for RRMS and PPMS differ (Confavreux et al. 1980, Thompson et al. 1997), and there is increasing support for differences in neuroimaging, neuropathological and laboratory features (Olerup et al. 1989, Thompson et al. 1990, Pugliatti et al. 1994, Revesz et al. 1994), the clinico-pathological differences were not reflected in the incidence trends in this study (Larsen et al. 1985b). However, the increased age-adjusted risk for PPMS among both genders in Seinäjoki as compared to Uusimaa remains puzzling.

The etiological model for MS and autoimmune diseases postulates that an environmental agent triggers the disease in a genetically susceptible individual. (Ebers 1994, The International Study of Asthma and Allergies in Childhood Steering

Committee 1998, Magnus and Jaakkola 1997, Karvonen et al. 2000). This conjecture should also hold in case of MS in Finland. The complexity of the etiological models is accepted (Detels 1982, Atkinson and Eisenbarth 2001) and rather than exposure to one particular agent, environmental encounters could serve to promote (Hyppönen et al. 1999) and attenuate (Wasmuth et al. 2000) disease during different stages of development, which is in accordance with the results in this study and should be considered in future analytical studies.

The second wider aim of this dissertation was to study survival and related factors in a Finnish MS population. Causes of death, survival as well as prognostic factors in a Finnish MS population were studied here for the first time. The cohort of 1,614 patients is among the largest cohorts. The prospective follow-up period extended thirty years from 1964 and thus ended before the advent of new disease course modifying treatments in Finland (Goodin 2000), addressing the natural course in MS. Natural course in relation to prognostic factors were here studied for definite MS cases, which may distort the overall survival towards a poorer prognosis, but nevertheless, defines the survival among the definitely diagnosed cases.

The result for 40-year survival rates of 64% and 53% here were largely similar to other studies (Wynn et al. 1990, Runmarker and Andersen 1993). The survival was fairly stable over the period 1964–93 in the whole cohort and the regional differences could be accounted for by prognostic factors. These results suggest that established care involves no major regional differences affecting the outcome among MS patients in Finland. The causes of death in Finnish MS population were mainly MS related in 70% of cases, similar to other studies from 47 to 77% with varying follow-up periods (Malmgren et al. 1983, Larsen et al. 1985a, Phadke 1987, Sadovnick et al. 1991, Midgard et al. 1995, Koch-Henriksen et al. 1998). The 30% of cases representing any cause of death resulted in a 10% increase in mortality at 40 years from onset as compared to MS related deaths. These patients are believed to represent the cases shown to have a poor prognosis in the multivariate analysis, e.g. males, cases with lacking information on disease course or those with a primary progressive course**.**

The generally declining necropsy rates (Khong 1996) and controlling for the changes and accuracy of the mainly clinically evaluated causes of death may also be problematic in this study (Hakulinen and Teppo 1977). However, the mortality distribution presented here is similar to that of the rare necropsy proven case-control studies among 120 cases (Allen et al. 1978). A high proportion of malignant tumours, accidents and suicide and a low proportion of cardiovascular causes compared to general mortality in 1988 were here observed among Finnish MS cases in contrast to an earlier study in Finland (Palo et al. 1977). Selection bias may distort the crude results as geographical mortality differences have been observed: in south-western Finland a lower

risk was observed for cardiovascular deaths compared to eastern Finland (Näyhä 1989), and for e.g. breast cancer, the risk is high in south-western Finland (Teppo et al. 1994). The standardized mortality ratios (SMR) in the Danish study (Koch-Henriksen et al. 1998) showed that MS patients have an increased risk of dying of vascular diseases, suicide, and accidents, but a reduced risk of cancer. Low risk for cancer has been observed also in other studies (Møller et al. 1991, Sadovnick et al. 1991, Midgard et al. 1996), explained by under diagnosis of cancer in MS (Allen et al. 1978, Koch-Henriksen et al. 1998). In this study, in addition to selection bias, methodological differences may contaminate comparison with others. Thus, before any final conclusions, there is especially a need for a standardization for age.

The three fold increased risk of death for primary progressive as compared to relapsing remitting cases was larger than the effect any prognostic variable in this study, including gender, age at onset and initial symptoms. This study indicates the independent effects of disease course and sensory symptoms, while the interdependence of these predictive markers was associated in some other materials (Confavreux et al. 1980, Riise et al. 1988, Riise et al. 1992, Midgard et al. 1995, Myhr et al. 2001). The uninamously favourable outcome is associated with optic neuritis and sensory symptoms at onset (Phadke 1990, Weinshenker et al. 1991, Runmarker and Andersen 1993), observed also here. Unfavourable prognosis for cerebellar and motor symptoms (Phadke 1990, Riise et al. 1992, Runmarker and Andersen 1993) was not observed in this study, which may be explained by inclusion of paraparesis, bladder and bowel, brainstem and cerebellar symptoms with diverging prognoses (Phadke 1990, Weinshenker et al. 1991, Riise et al. 1992, Brønnum-Hansen et al. 1994), in the category of ´infratentorial´ symptoms at onset.

Young age at onset (< 30 years) is commonly considered a favourable prognostic factor in MS (Confavreux et al. 1980, Weinshenker et al. 1991), with few contradictory results (Liquori et al. 2000). However, the problems in determining the often arbitrary onset symptoms may weaken the prognostic reliability of onset symptoms (Poser et al. 1982) and for the same reason, onset age. Confavreux et al. (1980) has shown that disability status also depends on patients age at onset, so that those with a late onset show a shorter duration of years to progression stage in MS, compared to slower progression rate among those with early onset age. From the perspective of quality of life, Confavreux´s results on age at onset, progression rate and disease duration may hold good that the ´early benign form´ of the disease is not necessarily better than a ´late malign form´. Furthermore, the length of diagnostic delay in this study was shown to be a meaningful factor: The risk of death to those followed up from diagnosis was increased for those over 35 years of age at diagnosis, which suggests that delay among younger patients with a lower risk of death is longer.

The discrepancies for gender specific survival in different studies are largely explained by methodological differences (Riise et al. 1988 and 1992, Midgard et al. 1995, Wallin et al. 2000) The survival of men is generally poorer than survival of women, shown also here in the case of the endpoint being all causes of death. In the case of MS specific deaths, the risk of death was similar in both genders.

A common problem in cohort studies is loss-from-follow-up. Due to established registries in Finland, no losses occurred in this study. However, information on clinical evolution was inadequate in a total of 12% of cases diagnosed before 1979. The risk of death was increased among these cases, but did not account for the larger risk of death from PPMS than from RRMS. Considering the increased risk of death among these cases, and the generally increased risk of suicides and accidental deaths in MS (Koch-Henriksen et al. 1998), the information on comorbidity and psychosocial factors such as socio-economic status will be useful in future survival studies on all causes of death. The results advocate regular patient follow-ups in providing preventive actions by careful medical check-ups and counselling for patients and families.

The recent occurence of MS as well as the survival and related factors in Finland indicate that this study base by and large represents typical high risk MS populations. The exceptional clustering of cases in western Seinäjoki with a specific clinical MS profile has become even more pronounced. The causes for the recent changes in Finland point to environmental effects. Results on natural course here point to individual outcome among MS patients, which however, is accounted for by several prognostic factors, but is ultimately largely unpredictable. In contrast to earlier results in natural history studies, or due to inconsistent results for prognostic variables, this study supports the result of equal survival between men and women with MS, survival being independently affected by age and symptoms at onset, and the type of disease course. The early recognition of the disease course has also shown here to be the main value in determining long term outcome in MS (Kremenchutzky et al. 1999).

7 Summary

The main purposes of this study was to estimate the current occurrence and survival in MS in Finland. Patients were collected from three large hospital districts in southern and western Finland, representing industrialized and rural regions covering a population of almost 30% of the total population of Finland in 1993. This is a truly population-based study, and cases were classified into diagnostic categories mainly to improve the regional and temporal comparability. Comparisons of MS populations are commonly hampered by the problems in the reliability of the timepoint of onset and initial symptoms, as well as disease course classification. To improve validity, the cases were retrospectively classified by the same person, and disease course was divided into only relapsing-remitting and primary progressive groups. The diagnosis based approach chosen improved the reliability and comparability of incidence and prevalence.

In successive studies since the 1960´s Finland has been shown to belong to a high risk areas for MS together with areas in Northern Europe and America. Furthermore, uneven geographical distribution and temporally changing trends are the hallmarks in MS epidemiology in the high risk regions, shown also in this study. The rates in Seinäjoki were among the highest reported ever, prevalence being $200/10^5$ in 1993, mainly due to increasing incidence, which was about 12 in 100,000 population per year in the period 1979–93. The stable prevalence of $100/10^5$ in neighbouring Vaasa was observed in the presence of declining annual incidence of $5/10^5$ person-years in the period 1979–93. In Uusimaa both prevalence of $100/10^5$ and annual incidence of 5 remained stable. Hence, the age-adjusted incidence rates in Seinäjoki were more than two-fold compared to rates in Uusimaa and Vaasa in the period 1988–93. In addition to significantly differing incidence trends, the regional differences were characterized by a four-fold increased risk for progressive MS in Seinäjoki as compared to Uusimaa, and a significantly increased incidence among men.

Given the large differences in incidence trends by geographical area and time, and the slow changes in genetic code, this study points at local, and recently emerging environmental etiological factors. The similar disease course specific trends in each district furthermore point to similar causes for both disease types. The gender difference in Seinäjoki incidence trends remains unknown.

This study addressed the natural course of MS in Finland over thirty years, as the follow-up ended before the advent of the new immunomodulatory drugs in 1993. The overall MS-specific survival rates from disease onset of 64% over 40 years were in accordance with several other studies. The large proportion of deaths caused by accidents and malignancies in Finnish MS population was observed, but before any etiological conclusions can be drawn, more detailed analyses including age

standardization will be required. The stable overall survival by time and area indicates established care of MS patients up to 1993. The survival rates here give a crude estimate at population level, while individual prognosis in MS is difficult. However, the independent risk factors for favourable prognosis in this study were low onset age and sensory symptoms at onset, including optic neuritis, while primary progressive course indicated an unfavourable prognosis. The prognosis for men and women was similar for MS specific survival, supported by results in similar studies.

The distribution of cases in this material has shown female preponderance and locally disparate risk by gender and disease course. The uneven and temporal trends in incidence in Finland call for an analytical epidemiological study covering several environmental and social factors. The general increase in MS prevalence due mainly to increasing incidence and stable survival in the period 1964–93 indicates an increased need for health care and rehabilitation resources for MS patients in Finland. Increased mortality through accidents and cancer, as well as increased risk of death among primary progressive cases call for careful medical check-ups as well as counselling among the chronically ill.

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Appendix

Appendix 1.

Schumacher´s criteria (Schumacher et al. 1965) of clinically definite MS:

1. Neurological examination reveals objective abnormalities in CNS function.
2. Examination or history indicates involvement on two or more parts of CNS.
3. CNS disease predominantly reflects white matter involvement.
4. Involvement of CNS follows one or two patterns:

a) two or more episodes, each lasting at least 24 hours and a month a part.

b) slow or stepwise progression of signs and symptoms over at least 6 months.

5. Patients 10-50 years old at onset.

Signs and symptoms cannot better be explained by other disease process.

Appendix 2. The diagnostic criteria for multiple sclerosis by the Poser committee in 1983 (Poser et al. 1983).

Diagnostic classification		Attacks	Clinical Lesions	Paraclinical Lesions	Cerebrospinal Fluid
Clinically definite MS	1.	Two	Two separate	NR	NR
	2.	Two	One	Another separate	NR
Laboratory-supported definite MS	1.	Two	One	NR	OCB or increased IgG
	2.	Two	NR	One	OCB or increased IgG
	3.	One	Two separate	NR	OCB or increased IgG
	4.	One	One	One	OCB or increased IgG
Clicinally probable MS	1.	Two	One	NR	NR
	2.	One	Two separate	NR	NR
	3.	One	One	One	NR
Laboratory-supported probable MS	1.	Two	NR	NR	OCB or increased IgG

IgG= immunoglobulin G
NR= not required for diagnosis
OCB = oligoclonal bands

Appendix 3. Illustration on the clinical and demographic features in the survival cohort (Article IV).

Clinical and demographic features in the survival cohort diagnosed 1964–1993.

Variable	n	%
Men	548	34
Women	1066	66
All cases	1614	100
*CDMS 1,2	1469	91
LSDMS 1,2,3	145	9
Age at onset (mean 31.5 years)		
< 30	728	46
≥ 30	854	54
Age at diagnosis (mean 35.8 years)		
< 35	775	48
≥ 35	839	52
Diagnostic latency** (mean 4.2 years)		
≤ 5	1139	72
> 5	443	28
Period of diagnosis		
1964–73	339	21
1974–83	581	36
1984–93	694	43
Disease course		
RRMS	1081	67
PPMS	339	21
Not classified***	194	12
Initial symptom		
Corticospinal	429	26
Infratentorial	350	22
Sensory	527	33
Not classified***	308	19

*CDMS = clinically definite MS, LSDMS = laboratory supported definite MS
**latency from onset stymptoms to definite diagnosis
***cases with inadequate documentation or lacking information

Appendix 4.

Univariate (crude) and multivariate (adjusted) relative risks for MS cases followed from onset symptoms

	All causes of death				MS-related deaths			
	Crude	95 % CI	**Adjusted**	95 % CI	**Crude**	95 % CI	**Adjusted**	95 % CI
Age at onset:								
< 30 yrs	**1.0**		**1.0**		**1.0**		**1.0**	
>= 30 yrs	**1.9**	1.4-2.5	**1.7**	1.3-2.3	**1.5**	1.1-2.1	**1.4**	1.0-1.9
Gender:								
Women	**1.0**		**1.0**		**1.0**		**1.0**	
Men	**1.7**	1.3-2.2	**1.3**	1.0-1.8	**1.4**	1.0-2.0	**1.1**	0.8-1.6
Disease course:								
RRMS	**1.0**		**1.0**		**1.0**		**1.0**	
PPMS	**3.4**	2.4-4.8	**2.9**	2.0-4.1	**3.5**	2.3-5.3	**3.0**	2.0-4.6
Unknown	**3.7**	2.7-5.1	**1.9**	1.3-2.7	**3.7**	2.5-5.5	**1.8**	1.1-2.7
First symptom:								
motor	**1.0**		**1.0**		**1.0**		**1.0**	
infratentorial	**0.8**	0.5-1.3	**0.9**	0.6-1.4	**1.0**	0.6-1.8	**1.1**	0.7-1.9
sensory	**0.4**	0.3-0.7	**0.6**	0.3-0.9	**0.3**	0.2-0.6	**0.4**	0.2-0.9
unknown	**2.6**	1.9-3.7	**2.6**	1.8-3.8	**2.8**	1.9-4.2	**3.1**	1.8-5.0
Period of dg:								
1964-73	**1.0**		**1.0**		**1.0**		**1.0**	
1974-83	**0.7**	0.5-0.9	**0.9**	0.7-1.3	**0.7**	0.5-1.0	**0.9**	0.461.4
1984-93	**0.4**	0.2-0.6	**0.8**	0.5-1.4	**0.4**	0.2-0.7	**0.8**	0.4-1.6

Univariate (crude) and multivariate (adjusted) relative risks for MS cases followed from the definite diagnosis

	All causes of death				MS-related deaths			
	Crude	95 % CI	**Adjusted**	95 % CI	**Crude**	95 % CI	**Adjusted**	95 % CI
Age at dg:								
< 35 yrs	**1.0**		**1.0**		**1.0**		**1.0**	
>= 35 yrs	**1.5**	1.2-2.0	**1.5**	1.1-1.9	**1.2**	0.9-1.7	**1.2**	0.9-1.6
Gender:								
Women	**1.0**		**1.0**		**1.0**		**1.0**	
Men	**1.6**	1.2-2.0	**1.4**	1.0-1.8	**1.3**	1.0-1.8	**1.1**	0.8-1.6
Disease course:								
RRMS	**1.0**		**1.0**		**1.0**		**1.0**	
PPMS	**2.2**	1.6-3.1	**2.1**	1.5-3.1	**2.3**	1.5-3.5	**2.3**	1.5-3.6
Unknown	**2.7**	2.0-3.7	**1.7**	1.2-2.4	**2.9**	2.1-4.3	**1.6**	1.1-2.6
First symptom:								
motor	**1.0**		**1.0**		**1.0**		**1.0**	
infratentorial	**0.8**	0.5-1.3	**0.9**	0.6-1.4	**1.1**	0.6-1.8	**1.1**	0.7-1.9
sensory	**0.5**	0.3-0.8	**0.6**	0.4-1.0	**0.4**	0.2-0.8	**0.5**	0.3-1.0
unknown	**2.3**	1.7-3.3	**2.4**	1.7-3.6	**2.7**	1.8-4.0	**2.9**	1.9-4.6
Period of dg:								
1964-73	**1.0**		**1.0**		**1.0**		**1.0**	
1974-83	**0.8**	0.6-1.2	**1.1**	0.8-1.5	**0.8**	0.6-1.2	**1.0**	0.7-1.6
1984-93	**1.1**	0.6-2.0	**1.8**	1.0-3.2	**1.1**	0.6-2.2	**1.8**	0.9-3.6

Original publications