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Highlights

- Subsequent family members with MS are diagnosed faster than non-familial cases
- Family history of Multiple sclerosis is a “red flag” for considering a genetic disorder
- Benefits / disadvantages of reducing delay of diagnosis in familial MS are discussed.
Familial multiple sclerosis patients have a shorter delay in diagnosis than sporadic cases

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\section*{Abstract}

\textbf{Background:} The diagnosis of multiple sclerosis (MS) is still complicated despite improvement in diagnostic guidelines. This means that time from first symptom to diagnosis in some cases is prolonged. Many aspects of MS aetiology are unknown, but the involvement of a genetic component is well established. This is also highlighted by the occurrence of familial MS cases, which represent 10-20\% of all MS cases. We hypothesize that subsequent family members in a MS family, have a shorter time from onset of disease to diagnosis compared to sporadic MS cases. To investigate this, we have conducted a register study comparing time from onset to diagnosis in familial and sporadic MS cases.

\textbf{Methods:} This is a nationwide register study based on information from the Danish Multiple Sclerosis Registry and the Danish Civil Registration System. We included familial (first-degree relatives) and sporadic MS cases and calculated time lag between onset and diagnosis of MS for sporadic MS cases and for 1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} family members within the MS families. Median test and Cox regression were the statistical methods used to compare the familial and sporadic groups.

\textbf{Results:} We found that 2\textsuperscript{nd} and 3\textsuperscript{rd} affected family member had a significant shorter time from first symptom to diagnosis compared to sporadic MS cases (2\textsuperscript{nd} family member: Hazard Ratio (HR): 1.12, CI: 1.03-1.21, \textit{p}=0.007 adjusted: HR: 0.95 \textit{p}= 0.22, CI 0.89-1-03 and 3\textsuperscript{rd} family member HR: 1.64 CI: 1.22-2.20, \textit{p}=0.001 adjusted model: HR: 1.70, \textit{p}-value: 0.000, CI: 1.32-2.18). The same difference was not seen between 1\textsuperscript{st} family members and sporadic cases (HR: 1.05, CI: 0.98-1.13, \textit{p}=0.15, adjusted: 0.98, \textit{p}-value: 0.53, CI: 0.91-1.05). Estimated marginal mean delay in the four
groups were 4.60 years (95% CI: 4.11-5.01) in 1st family members, 4.23 years (3.71-4.75) in 2nd family members, 2.11 years (0.95-3.26) in 3rd family members and 4.99 years (4.99-4.99) in sporadic MS cases.

**Conclusion:** The 2nd and 3rd family members in MS families tend to get diagnosed faster than sporadic cases. This has implications in the diagnostic process of familial MS cases.

Keyword: Multiple sclerosis, familial multiple sclerosis, delay in diagnosis, disease onset

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Introduction:

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system affecting young adults\(^1\). The aetiology is still unknown, but environment and genes are both expected to be important\(^1\). Several small scale MS twin studies have been conducted\(^3\), and the highest concordance rate reported is 24% in monozygotic twins and 3% in dizygotic twins\(^4\). Twin studies thus provide evidence that genes are involved in MS aetiology\(^3\), which is also supported by the fact that familial MS, meaning families with two or more MS cases, account for 12.6% of the total MS population\(^5\). Genetic sequencing in MS patients/families has disclosed several genes and loci to be associated with MS, but each of them only account for a small part of the aetiology. This means that many questions are still unanswered\(^6, 7\).

MS is a heterogeneous disorder and patients present with a wide range of different symptoms, neurological signs and paraclinical findings\(^8\). Diagnostic criteria have been suggested by Poser\(^9\), and MacDonald\(^10, 11, 12\), but since no simple test can establish the diagnosis the diagnostic process in MS can be rather challenging. The National Institute for Health and Clinical Excellence (NICE) has provided clinical guidelines for management of MS\(^13\), but it may be difficult to fulfil them within the recommended time period\(^14\). Due to the complexity in the diagnostic process, MS patients can experience a long time-period from first symptom to diagnosis. Only few studies have addressed this issue, and if they do the aim is often to evaluate the diagnostic services\(^15\). It is overall believed that early treatment in MS is an advantage, thus delayed diagnosis is assumed to have an impact on severity and progression of the disease\(^16, 17\). The 2017 revision of the McDonald criteria have also highlighted the need for MRI and CSF early in the process, contributing to a faster diagnosis\(^12\).

In the diagnostic criteria for MS it is included that the condition cannot be explained by another disorder\(^18\). This criteria it complex to fulfill\(^19\), since there is many differential diagnosis to MS\(^18, 20\). There are “red flags”, indicating that differential diagnosis to MS are to be considered\(^21, 22\), but even then around 5-10% of MS cases are found to be misdiagnosed\(^23\). Inherited disorders do also contribute to the misdiagnoses. Based on numerous case reports of simplex MS families\(^24-26\) and studies on sporadic and familial MS populations\(^27\) there are several examples of MS cases found to have a genetic disorder mimicking MS.

The hypothesis of this study is that the subsequent family members, in a MS family, have a shorter time from disease onset to diagnosis compared to sporadic MS cases. To investigate this, we have
conducted a registry study comparing time from disease onset to MS diagnosis in 1st, 2nd and 3rd MS family members and sporadic MS cases.

**Material and Methods:**

This study is a nationwide register study based on the Danish Multiple Sclerosis Registry and the Danish Civil Registration System.

*The Danish Multiple Sclerosis Registry*\(^{28,29}\) is established in 1956 and keeps information on all Danes with MS, who were alive in 1949 and all cases diagnosed since. All patients listed in the registry fulfil the diagnostic criteria of Allison/Millar\(^9\), Poser\(^9\) and/or McDonald\(^12\). The registry receives information on MS patients from the Departments of Neurology at Danish hospitals, from private Danish neurologist and from the Danish National Patient registry. The MS registry is updated regularly and is found to be >90% complete\(^{28}\). From the registry we have used variables on MS diagnosis, year of diagnosis and disease onset and classification of the MS diagnosis.

*The Danish Civil Registrations System*\(^{31}\) is a nationwide registration of all Danish inhabitants. The registry was established in 1968 (Greenland 1972). All citizens born after or alive in 1968 are assigned with a personal identification number. This unique identification number makes it possible to link different registries. The registry also holds a long list of personal information on all Danes, including gender, year of birth, residence and familial relations. Information on familial relations is based on parent/child relations and is kept for nearly all individuals born since 1960\(^{31}\). This information makes it possible to define 1st degree familial relation. Since the main purpose of the registry is administration, the familial relations are based on a guardian relationship and not necessarily a biological relation; hence biological and adoptive relationships can’t be differentiated. The main variables from the registry used in the study are familial information, gender, place and year of birth.

Using the personal identification numbers as linkage, we have defined a unique cohort of MS patients including the following variables: MS diagnosis, validity of MS diagnosis, year of MS diagnosis, year of first symptom, year of birth, place of birth, gender and information on first-degree relatives. From these variables, we have further defined the following:
Family information: Based on information on MS diagnosis and first-degree relations, we have defined familial MS as MS cases having one or more first-degree relatives with MS. Since there is a risk of including adoptive cases, we have excluded MS families if the child in a parent/child relation or one sibling in a sibling/sibling relation is born outside Scandinavia. Sporadic cases are defined, as MS cases not having first-degree relatives with MS.

Delay: The variable is the differences in years between year of first symptom and year of diagnosis, both provided by the MS registry. The variable is an integer, since we only have full years and not exact dates. The variable on year of onset is retrospectively asssed by the neurologist based on the clinical records.

In total we received information on 25,471 MS cases from the Danish MS Registry. We only included cases with definite MS and excluded possible adoptive cases. After applying these criteria 4,753 cases were excluded, including 3 possible adoptive MS families. Further, we only included cases diagnosed with MS after 1960. Information on familial relations from the Civil Registration System is nearly complete for parent/child relations for all children born after 1960. We wanted to ensure sufficient information on familial relations and to be able to include children born in 1960 and forward as well as their parents. Two thousand ninety-two cases were excluded due to this criterion. Finally, 231 MS cases were excluded, as no information on year of first symptom was registered. Of those 14 (7%) are familial and 217 (83%) are sporadic cases. The distribution of gender and age of onset is similar to the one seen in the total population of MS cases (data not shown). Information on year of MS diagnosis was available for all included cases in the final cohort.

We ended up with a total of 18,095 MS cases included in the cohort for the analysis (figure 1). In the cohort 1,122 cases have a first-degree relative with MS and are grouped as familial MS. The remaining 16,973 cases are grouped as sporadic MS. Within MS families, each family-member is numbered as 1st, 2nd or 3rd case. This numbering is based on the year of diagnosis. In 19 families two first-degree relatives were diagnosed the same year. Therefore, we have done the analysis by ordering the cases by either 1) year of birth (oldest first), 2) year of onset or by 3) excluding the families.
The Regional Health Research Committee for Southern Denmark (S-20150175) and the Danish Data Protection Agency (j.nr: 15/52395) have approved the study. This is in accordance with national rules and regulations on registry studies and does not require accept from the patients.

Statistics:
The non-parametric k-sample test for equality of medians is used to compare delay in diagnosis in familial (1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} family member) and sporadic MS cases. Medians are reported together with interquartile range (IQR).

Furthermore, we estimated a Kaplan-Meier curve on delay in diagnosis in the different categories. Moreover, we estimated Hazard ratios (HR) for delay with respect to MS group (1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} family member or sporadic MS) by Cox regression, to enable comparison with other studies with un-censored data. Further the results of a Wilcoxon ranksum test comparing the median delay among the different MS groups are reported. As a supplement we carried out a generalized linear model (GLM) with gamma distribution to estimate marginal means of delay in diagnosis.

Since we are analysing familial relations, we clustered families in the analysis. A proportion of cases have delay=0. To include these cases, we added 0.1 to all delay values. To investigate sensitivity to size of this added delay, we investigated adding 0.5 or 1 and did not observe any relevant changes in results.

Covariates included in the analysis are sex, age at diagnosis and year of birth. Proportional hazard assumption was tested by Schoenfeld residual test.

Results:
In table 1 descriptive statistics of the cohort are listed. We found no differences in gender distribution between familial and sporadic MS cases. We did see a difference in distribution of age and year of diagnosis between the groups (table 1). The median delay in diagnosis is reported by year of diagnoses (table 1). We find that the median has decreased since the first cases were diagnosed. It is a minor decrease from a median on 3 years in 1960-1980 to a median on 2 years in 2000-2016. In the same time-period the mean in delay has decreased from approximately 5 years in 1960 to 4 years in 2010.
Testing for equality of medians we found a significant difference in delay in diagnosis between sporadic MS, 1st, 2nd and 3rd family members (p=0.013). The test is based on medians in delay in the groups of 1st, 2nd, 3rd familial cases and sporadic cases, which were 2 years (IQR: 6-0), 2 years (IQR: 6-1), 1 year (IQR: 2-0) and 2 years (IQR: 7-1), respectively. The 19 families, who have the same year of diagnosis, are numbered by year of birth. If we instead number these families by year of onset (Pearson’s chi-square: 13.27, p=0.004, Fisher’s exact, p= 0.004) or excluded them (Pearson’s chi-square = 10.33, p = 0.016. Fischer exact, p=0.016), the result do not change significantly.

In the Cox regression (table 2), we found that the 2nd and the 3rd family member in familial cases are diagnosed significantly faster than sporadic cases. A significant difference in delay in diagnosis is not found between the 1st family-members diagnosed compared to sporadic cases. It is noticeable that there are a limited number of 3rd family members, meaning these results are to be taken with caution.

Again, the 19 families with 2 family members diagnosed the same year are numbered by year of birth (table 3). If we instead number these 19 families by year of onset (1st family member p=0.20, 2nd family member p=0.004, 3rd family-member: p=0.001) or exclude them (1st family member p=0.18, 2nd family member: p=0.014, 3rd family member: p=0.002) the overall results were practically unchanged.

The analysis is also done including covariates; age at diagnosis, year of diagnosis and gender. This has an impact on the final result, as the difference found between delay in diagnosis of MS among 2nd MS cases in families compared to that among sporadic MS cases no longer reached statistical significance in the fully adjusted mode (table 2)

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard ratio</th>
<th>Standard error</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic MS cases</td>
<td>1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial total</td>
<td>1.09</td>
<td>0.029</td>
<td>0.002</td>
<td>1.03-1.14</td>
</tr>
<tr>
<td>Sporadic cases</td>
<td>1*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: The table shows the calculated Hazard ratios for sporadic cases compared to 1st, 2nd and 3rd family relations. We find a significant difference in sporadic cases and 2nd and 3rd family members, which is not seen in relation to 1st family members. The results are influenced by including covariates; age at diagnosis, year of diagnosis and gender. Numbering in the families is based on years of diagnosis. In 19 families two family members are diagnosed the same year, these cases are numbered by year of birth (oldest numbered first).

CI: confidence interval.

* Reference

** Based on Wilcoxon ranksum test comparing the group of sporadic MS cases with 2nd familial MS cases we found a significant difference between the two groups (P=0.044)

Results of a generalized linear model (GLM) with gamma distribution are shown in table 3. Covariates have been included in the analysis.

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>P value</th>
<th>95% CI</th>
<th>Estimated marginal mean delay (years)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic cases, baseline</td>
<td>1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st family member</td>
<td>-0.079</td>
<td>0.054</td>
<td>0.142</td>
<td>0.55-1.14</td>
<td>4.60</td>
<td>4.11-5.01</td>
</tr>
<tr>
<td>2nd family member</td>
<td>-0.168</td>
<td>0.063</td>
<td>0.008</td>
<td>1.03-1.18</td>
<td>4.23</td>
<td>3.71-4.75</td>
</tr>
<tr>
<td>3rd family member</td>
<td>-0.860</td>
<td>0.278</td>
<td>0.002</td>
<td>-0.35-(-0.36)</td>
<td>2.11</td>
<td>0.95-3.26</td>
</tr>
</tbody>
</table>

Model adjusted for age at diagnosis, year of diagnosis and gender
Table 3: The table shows the results of the GLM analysis comparing sporadic cases to 1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} familial relations. We find a significant difference in sporadic cases and 2\textsuperscript{nd} and 3\textsuperscript{rd} family members, which is not seen in relation to 1\textsuperscript{st} family members. Including covariates influences the results. Numbering in the families is based on years of diagnosis. In 19 families two family members are diagnosed the same year, these cases are numbered by year of birth.

Times from disease onset to MS diagnoses in familial (1st, 2nd and 3rd family members) and sporadic cases are illustrated in the Kaplan-Meier curve (figure 2).

![Kaplan-Meier curve](image)

Figure 2: Kaplan-Meier curve showing delay in diagnosis in 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} familial cases and sporadic MS. Delay is time from disease onset to MS diagnosis.

Discussion:
The hypothesis of this study was confirmed since we found that time from disease onset to MS diagnosis is significantly shorter in the 2\textsuperscript{nd} and 3\textsuperscript{rd} family-members diagnosed in familial cases compared to sporadic MS cases, which was not found between the 1\textsuperscript{st} family members diagnosed and sporadic cases. Including covariates in the Cox regression influence the final results. Since we are analysing families the 2\textsuperscript{nd} and 3\textsuperscript{rd} family members are diagnosed after the first case, meaning that a difference in year of diagnosis is expected. However, the improvements in diagnostic procedures over time are also assumed to influence on delay in diagnosis. This could explain why including year of diagnosis as covariate influence the final results. Also familial MS cases are diagnosed at an earlier age compared to sporadic cases (table 1), meaning that including age at diagnosis as a covariate is assumed to influence on the results.

Overall, we find that a faster diagnosis in the 2\textsuperscript{nd} and 3\textsuperscript{rd} MS family member. In the fully adjusted model results are only significant for the 3\textsuperscript{rd} MS case diagnosed. We find that the difference seen is likely to be due to the family history of the disorder.

We have not found that former studies have addressed the same issue. The studies that do exist are mostly focusing on the clinical practice, and time from first visit at a neurological department to diagnosis\textsuperscript{14}. One study reports a mean delay in diagnosis of 34 weeks in their department. The aim of that study differs greatly from ours, since they are evaluating whether the diagnostic process was in accordance with the NICE guidelines\textsuperscript{15}. This analysis is based on a limited number of cases from none-nationwide data and they do not differentiate between familial and sporadic cases, meaning that it is not feasible to draw comparisons.

Over the last decades, the diagnostic process for MS has evolved, which allows for earlier initiation of treatment and guidance\textsuperscript{20,32}, but the numerous differential diagnoses\textsuperscript{18,21} to MS remains a challenge and cases misdiagnosed as MS have been reported\textsuperscript{33}. To compensate for this, several symptoms/signs are reported as “red flags” for when to consider differential diagnoses\textsuperscript{21}. Based on the fact that MS families occasionally are found to have an inherited neurological disorder mimicking MS\textsuperscript{24,27,34} and the present findings in this study of familial MS cases being diagnosed faster than sporadic cases, we suggest that “family history” might be a “red flag” for considering genetic differential diagnosis. The above factors all add to our knowledge on the question of benefits from a fast diagnosis compared to consequences of a misdiagnosis\textsuperscript{35}
We have analysed a nationwide population of MS patients diagnosed within the last 5 decades. This makes our cohort unique, but there are limitations. The variable on time of onset is based on retrospective information from medical records and might therefore be uncertain. Also the variables used to calculate time from first symptom to diagnosis are integers and not based on months, which add uncertainties to the calculations. Secondly, having a positive family history of MS might make the patient more aware of symptoms mimicking MS earlier on and thus possibly seek medical advice. Since we find that the differences seen between 1\textsuperscript{st} and 3\textsuperscript{rd} family members are larger than the one seen between 1\textsuperscript{st} and 2\textsuperscript{nd} family members, we do believe that family history of the disorder influence on delay in diagnosis.

Third, familial information is based on first-degree relations from the Civil Patient Registration System, but these relations are based on a guardian relationship, not allowing for differentiation between biological and adoptive children. The annual adoption rate in Denmark is low (1-2%) and around half of these cases are adoptions from foreign countries \footnote{36}. As earlier described we have tried to minimize this by eliminating possible adoptive families. Due to the overall low number of adoption cases in Denmark, we believe that the risk of having included adoptive families and their effect on the results is limited, and are not expected to influence on the results.

Fourth, information on first-degree relatives is more than 90% complete for individuals born after 1960. If only cases born after 1960 were included, the parents of this generation would be excluded. To ensure that we have high completeness on familial information and include parents to cases born after 1960, we have included all cases diagnosed with MS after 1960. This does not fully solve the issue and there are limitations to familial information on cases born before 1960. Overall, this is expected to account for at very limited number of cases.

**Conclusion:**

When the 2\textsuperscript{nd} of 3\textsuperscript{rd} family member in a MS familial present with symptoms compatible with MS, this should of course lead to clinical investigating to confirm any MS diagnosis, but we find that clinicians should also keep in mind, the possibility of that family having an inherited disorder mimicking MS. If family history led to considering genetic differential diagnoses, the diagnostic process might slow down, but it would be a more certain diagnosis and the risk of making a misdiagnosis is reduced.
Disclosure

The authors declare no conflicts of interest.

Acknowledgement and funding

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*Figure 1.* Flowchart showing selection criteria
<table>
<thead>
<tr>
<th></th>
<th>Familial MS*</th>
<th>Sporadic MS</th>
<th>Test for difference**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1,122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st family member</td>
<td>627</td>
<td>219(34%)</td>
<td></td>
</tr>
<tr>
<td>2nd family member</td>
<td>477</td>
<td>159(33%)</td>
<td></td>
</tr>
<tr>
<td>3rd family member</td>
<td>18</td>
<td>6 (33%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>219(34%)</td>
<td>159(33%)</td>
<td>5,959(35%) P=0.55***</td>
</tr>
<tr>
<td>Female</td>
<td>738 (66%)</td>
<td>318 (67%)</td>
<td>11,014 (65%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>144 (13%)</td>
<td>75 (12%)</td>
<td>1,573 (9%) P=0.000**</td>
</tr>
<tr>
<td>25-34</td>
<td>329 (29%)</td>
<td>189 (30%)</td>
<td>4,371 (26%)</td>
</tr>
<tr>
<td>35-44</td>
<td>309 (28%)</td>
<td>172 (27%)</td>
<td>4,810 (28%)</td>
</tr>
<tr>
<td>≥45</td>
<td>340 (30%)</td>
<td>191 (30%)</td>
<td>6,219 (37%)</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>266 (24%)</td>
<td>152 (24%)</td>
<td>3,121 (18%) P=0.000**</td>
</tr>
<tr>
<td>25-34</td>
<td>386 (34%)</td>
<td>211 (34%)</td>
<td>5,758 (34%)</td>
</tr>
<tr>
<td>35-44</td>
<td>278 (25%)</td>
<td>154 (24%)</td>
<td>4,532 (27%)</td>
</tr>
<tr>
<td>≥45</td>
<td>192 (17%)</td>
<td>110 (18%)</td>
<td>3,562 (21%)</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1950</td>
<td>274 (24%)</td>
<td>232 (32%)</td>
<td>6,261 (37%) P=0.000**</td>
</tr>
<tr>
<td>1950-1969</td>
<td>526 (47%)</td>
<td>274 (44%)</td>
<td>6,762 (40%)</td>
</tr>
<tr>
<td>≥1970</td>
<td>322 (29%)</td>
<td>121 (19%)</td>
<td>3,950 (24%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median in delay (years) by year of diagnosis***</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of diagnosis</td>
<td>IQR</td>
</tr>
<tr>
<td>1960-1969</td>
<td>3</td>
</tr>
<tr>
<td>1979</td>
<td>2.5</td>
</tr>
<tr>
<td>1980-1989</td>
<td>2</td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
</tr>
<tr>
<td>2000-2016</td>
<td>2</td>
</tr>
<tr>
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<td>IQR: 7-1</td>
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</tbody>
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**Test for difference**
Table 1 shows demographic data on the cohort, N=18,095. Cases are divided in familial and sporadic cases. The familial group is further divided into 1st, 2nd and 3rd family member* based on year of MS diagnosis. In 19 families two cases are diagnosed the same year, they are ordered based on year of birth.

** Test for difference is done for the total familial group compared to the sporadic group. Pearson’s chi-square test is used for numeric data and t-test for categorical data.

***The median in delay has decreased over time. The delay in diagnosis was longer in 1960 than today. In the same time-period the mean in delay has changed from approximately 5 years in 1960 to 4 years in 2010.

IQR: interquartile range