The global prevalence of familial multiple sclerosis: an updated systematic review and meta-analysis

Naeim Ehtesham (✉ na.ehtesham@uswr.ac.ir)
University of Social Welfare and Rehabilitation Sciences

Maryam Zare Rafie
Zanjan University of Medical Sciences

Meysam Mosallaei
Isfahan University of Medical Sciences

Research Article

Keywords: Familial multiple sclerosis, pediatric-onset multiple sclerosis, systematic review, meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-250607/v1

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Abstract

Background: Considering that familial multiple sclerosis (FMS) can reveal the extent to which genetic and environmental factors each involve in the etiopathogenesis of the disease, we performed an updated meta-analysis of the worldwide prevalence of FMS by addition of recent publications.

Methods: A search in PubMed, Scopus, the ISI Web of Science, and Google Scholar up to 20 December 2020 was done. The inclusion criteria were based on the CoCoPop approach (condition, context, and population). The qualified studies entered the process of the meta-analysis by using comprehensive meta-analysis ver. 2 software.

Results: The pooled prevalence of MS in relatives of 16179 FMS cases was estimated to be 11.8% (95% CI: 10.7-13) based on a random-effects model. The pooled mean age of disease onset in adult probands was calculated to be 28.7 years (95% CI: 27.2± 30.2). In 13 studies that reported the data of FMS in pediatrics (n=6636) and adults (n=877), the FMS prevalence was 10.8% (95% CI: 8.1-14.2) and 15.5% (95% CI: 13.8-17.4), respectively. Considering the data of 9 studies, the prevalence of FMS in males (n=5243) and females (n=11503) patients was calculated to be 13.7% (95% CI: 10.1-18.2) and 15.4% (95% CI: 10.3-22.4), respectively. The odds ratio of male/female in FMS cases was not statistically significant (OR= 0.9; 95% CI: 0.6-1.2, \( P=0.55 \)). Subgroup analysis demonstrated a significant difference in the prevalence of FMS between the geographical areas (\( P=0.007 \)). The meta-regression model for FMS prevalence was significantly lower in terms of higher latitude (\( P<0.001 \)) and increased MS prevalence (\( P<0.001 \)). In contrast, meta-regression based on prevalence day was not statistically significant (\( P=0.29 \)).

Conclusions: The prevalence of FMS is more in the pediatric group than that of adults, is distinct between geographical areas, and diminishes with the increment of MS prevalence and latitude. Also, the symptoms initiate relatively at lower ages in FMS cases. By contrast with multifactorial diseases, our analysis unveiled that the prevalence of FMS was not more prevalent in men than women and the risk of MS development in relatives was not more when the affected proband was male.

Background

Multiple sclerosis (MS), chronic inflammatory demyelinating disorder of the central nervous system, is the most common cause of non-traumatic neurological disability in a range of age groups especially young adults and afflicts more than 2.5 million individuals in the world [1]. Both genetic variations, each of them with a small effect, and environmental factors partake synergistically in the development of MS. The identified risk factors for MS subsumes distance from the equator (latitude), vitamin D deficiency, lack of sunlight, infection by viruses like Epstein-Barr, smoking, and obesity [2]. The heterogeneous distribution of MS in populations is attributed to the interplay between different genetic background and environmental exposures [3].

Ample evidence has indicated that first-degree relatives of affected individuals have a 20 to 40 times higher chance to develop MS in comparison to the general population [4]. Monozygotic twins have a higher concordance rate (25-30%) than those dizygotic twins (3-5%), representing a high heritability [5]. The existence of MS in families (familial MS or FMS) mirrors sharing of similar genetics and environmental conditions. The earliest report of FMS date back to 1933 [6]. In the years since then, many studies have revealed the prevalence of MS in many populations. All of them considered FMS as the occurrence of the same disease in at least one any-degree relative of patients; however, two nationwide population-based register studies in Denmark did not consider the presence of MS in distant relatives comprising 2nd or 3rd-degree relatives as FMS cases [7, 8].

In considering that MS has a multifactorial nature, seeking the prevalence of familial form could unravel the extent to which genetic and environmental determinants each contribute to the pathogenicity of the disease. Therefore, in this
study, we aimed to perform an updated systematic review and meta-analysis about the worldwide prevalence of FMS by the addition of new studies. Furthermore, in contrast to the previous study [9], we conducted a separate meta-analysis on the prevalence of FMS in pediatric-onset MS (POMS) and adult-onset MS (AOMS) and in men and women, subgroup analysis based on geographical area, meta-regression based on latitude, prevalence date, and MS prevalence, and meta-analysis of sex ratio and mean age of onset among FMS cases.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] were recruited to perform the present systematic review focusing on the prevalence of FMS in the world. Each process of research was done independently by two investigators and any disagreement was resolved by group discussion.

Search strategy

We accomplished a comprehensive search in PubMed, Scopus, the ISI Web of Science, and Google Scholar up to 20 December 2020. Boolean operators (AND & OR) were utilized to search by a combination of these keywords: "multiple sclerosis", "familial", "epidemiology", "prevalence", "incidence", "recurrence" and "frequency". No language or date restriction was applied to the literature search. We manually checked the reference lists of obtained articles to not miss any additional documents.

Eligibility criteria

For defining the criteria for inclusion and exclusion of studies, we employed the CoCoPop approach (condition, context, and population) which is used for systematic reviews of prevalence studies [11]. According to this approach, the original studies with available full-text that investigated the prevalence of MS in full biological relatives of patients with definite MS (not probable, possible, or suspected), and conducted in a specific region, time, and target population was enrolled. The reason behind the criteria for definite MS is that some neurological disorders mimicking MS. The studies in the same region but with different time periods and sample frames were also included. Studies with duplicate data were excluded.

Data extraction

By using a pre-prepared sheet, these data were collected from the eligible studies: first author’s last name, publication year, prevalence day or period, setting and case ascertainment, the place that research was done, diagnostic criteria of probands, the method for the ascertainment of MS in relatives, the number of FMS cases and total patients, mean age of disease onset in probands, the prevalence of MS, POMS in FMS cases, geographical area, and sex ratio of probands. For providing insight into the difference between the prevalence of FMS in adults and pediatrics, we considered the studies that reported FMS prevalence in AOMS and POMS separately as two different data set.

Quality assessment

For assessing the methodological quality of included studies, Joanna Briggs Institute's critical appraisal tool was exploited which comprises 9 questions [12]. If the answer to a question was "Yes", 1 score was considered. Points 0-5, 6-7, and 8-9 were regarded as low, moderate, and high quality, respectively. The minimum score for enrolment of the studies was 5.

Statistical analysis
For choosing between random-effects and fixed-effects models, heterogeneity of studies was evaluated by Cochran’s Q and $I^2$ tests. For verification of the stability of data, a sensitivity analysis was performed. In addition to a meta-analysis of the prevalence of FMS in all studies, a separate analysis was implemented on studies that reported, separately, the prevalence of FMS in AOMS and POMS cases and males and females. By using the number of FMS and total MS in male and female groups, we calculated the odds ratio (OR) and 95% CI of prevalence to estimate the effect of gender. To find the underlying cause of heterogeneity, subgroup analysis was performed based on geographical area and meta-regression was carried out in terms of latitude, MS prevalence, and prevalence day. We assessed the publication bias by using Begg and Egger's tests. Comprehensive meta-analysis ver. 2 software was utilized for analysis and statistical significance was set at $p$-value<0.05.

Results

Literature Search and Characteristics

Collectively, database and manual search lead to the finding of 746 records. After removal of duplicates, initial screening was performed based on titles and abstracts which left 119 articles for assessment of the full-text. Of these, 73 articles were excluded with these reasons (Additional file 1): six were duplicates, 3 considered more than one specific region, 6 did not determine the prevalence day, 5 reported the data in a combination of Neuromyelitis Optica (NMO), acquired demyelinating syndromes (ADS) and MS cases, 2 was performed in two or more populations and time periods, one without available of the full-text, 25 with the inclusion of probable and/or possible cases, 24 low-quality studies and 1 with no determination of the target population. Finally, 49 studies from 46 articles with a sample size of 16179 FMS cases were included in our analysis (Figure 1) which their characteristics are represented in Table1. The eligible articles published from 1984-2020 and regardless of six studies, the rest of included studies had a cross-sectional design.

Meta-analysis of whole data

Because of high total heterogeneity ($Q= 1662.2$, $I^2 = 97.112\%$ and $P<0.001$), a random random-effects model was used. The polled prevalence of FMS was estimated to be 11.8% (95% CI: 10.7-13) of the total MS population (Figure 2). The highest and lowest prevalence was found in Saskatchewan of Canada (32.7%) [36] and Hungary (2.2%) [49], respectively. The sensitivity analysis indicated our robust pooled estimate (Figure 3).

Meta-analysis of mean age of onset in AOMS and prevalence of FMS in AOMS and POMS

The pooled mean age of disease onset in AOMS probands of 15 studies (n=6114) that reported this variable was 28.7 years (95% CI: 27.2± 30.2) (Figure 4). In this regard, the lowest and highest age of disease onset was recorded in Shiraz city of Iran (24.3 years) New York of USA (36.2 years), respectively. In 13 studies that reported the data of AOMS (n=6636) and POMS (n=877), the FMS prevalence was 10.8% (95% CI: 8.1-14.2) and 15.5% (95% CI: 13.8-17.4), respectively (Figure 5). The difference between these two groups was statistically significant ($P= 0.019$).

3.4. Meta-analysis of FMS prevalence in men and women and OR of male/female

With regard to data of 9 studies, the prevalence of FMS in males (n=5243) and females (n=11503) patients was calculated to be 13.7% (95% CI: 10.1-18.2) and 15.4% (95% CI: 10.3-22.4), respectively (Figure 6). The OR of male/female in FMS cases was not statistically significant (OR= 0.9; 95% CI: 0.6-1.2, P=0.55) (Figure 7).

3.5. Subgroup analysis and meta-regression
Subgroup analysis revealed a significant difference in the prevalence of FMS between the geographical areas (Test for subgroup differences: $Q = 12.070$, df($Q$) = 3, $P= 0.007$) (Figure 8).

The meta-regression model for FMS prevalence was significantly lower in terms of higher latitude (meta-regression coefficient: -0.025, 95% CI: -0.027 to -0.023, $P< 0.001$) (Figure 9 A). Similarly, a slight downward trend was observed in terms of increased MS prevalence (meta-regression coefficient: -0.0018, 95% CI: -0.0021 to -0.0016, $P< 0.001$) (Figure 9 B). While, meta-regression based on prevalence day was not statistically significant (meta-regression coefficient: -0.002, 95% CI: -0.005 to 0.001, $P=0.29$) (Figure 9C).

3.6. Publication bias

No publication bias was found in our analysis (Egger= 0.98, and Begg’s=0.25), as depicted in the funnel plot (Figure 10).

Discussion

Convergent lines of evidence have indicated that MS can run in families [57]. The number of affected family members in a given proband ranges from one (the most proportion) to even seven and eight [24, 36]. Although, no Mendelian pattern has seen in the pedigree of multigenerational families. In this regard, cohort studies could be well suited on the account of a longer time period for the accumulation of new cases in the family. Concerning the degree of relatedness, the occurrence of the same condition is more prevalent in first-degree relatives, particularly siblings of the affected individuals, which underscores the combined role of shared genetic and environmental factors in MS etiology [16, 24, 25, 29, 33, 34]. While, one study reported parent-child relationship as the prevalent kinship [28]. In this context, the probability of the transmission of disease from mother to child is more than father to child [13, 8, 58]. Amongst the siblings, sister-sister, sister-brother, and brother-brother relation are, respectively, more prevalent [29, 34]. Evidently, after first-degree relatives, third-degree relatives have more chance for the development of MS [13, 18, 34].

The pooled prevalence of FMS in our study (11.8%) (Figure 2) was lower than previous meta-analysis (12.6%) [9]. Hence, we performed a meta-regression analysis based on prevalence day to examine if the prevalence of the FMS is decreased over time. Our results showed a non-significant lowering trend (Figure 9C). Hence, it seems that the worldwide frequency of FMS is steady-state over time. Nonetheless, some studies in middle-east reported the increasing [13, 24] or decreasing [16] prevalence of FMS over time, highlighting the existence of substantial difference in terms of genetic and environmental factors between different populations even in a same geographical area. Moreover, the overwhelming majority of the studies have been performed in a cross-sectional setting; while, sufficient long follow-up period is needed to evaluate the development of the disease in new members of the relatives, primarily distant relatives that would not have been found in short-term periods.

POMS is defined as the manifestation of symptoms before/under the age of 16 or 18 [59]. According to our analysis, the frequency of FMS in POMS was higher than AOMS (Figure 5). However, only 3 to 10% of sporadic cases are reported to be POMS [60]. This informs us that increased genetic load may be a pivotal feature of POMS and family history of MS could be a crucial contributing factor for POMS predisposition. It is important to remember that one reason for the difference between the results of studies on the prevalence of POMS, either in FMS or sporadic MS, is the usage of different cut-off points for POMS, extending from 15 to 18 years old. By considering follow-up time bias, it seems that the prevalence of FMS is underestimated in the pediatric group due to not emergence of this disease in relatives especially siblings at the time of the study, at least in cross-sectional studies.

The mean age of onset in adult probands with FMS was estimated to be 28.7 (Figure 4), which indicates an earlier age of onset among FMS cases in comparison to sporadic cases [61, 7]. This highlights the point that the preclinical phase
of the disease would be shortened in cases with higher genetic load and consequently symptoms initiate at a lower age at onset.

Considering the concept of the “carter effect” [62], we set out to investigate the notion that in male MS patients, the prevalence of FMS is more than in females patients, as well as transmission to other members of the family, is higher when the affected individual is male. However, the prevalence of FMS in male and female cases and OR of male/female of FMS cases did not confirm this theory (Figure 6 and 7). This represents that a greater than average background of susceptibility factors in an affected male which is the less frequently affected sex does not increase the occurrence of the MS in relatives. On the contrary, a higher prevalence of FMS and positive family in males than that in females was seen in the Iranian population [63]. However, we acknowledge that low sample size for scrutinizing the effect of sex might cause underpowered interpretation.

Subgroup analysis unveiled that the distribution of FMS is different between geographical areas (Figure 8). This emphasizes the distinct underlying etiology of FMS which emanates from susceptibilities of distinct racial and ethnic groups. Also, this finding could justify the high heterogeneity between studies, at least in part. Relevantly, other meta-analysis indicated different FMS prevalence in Iran (8.9%) [63] and the Middle East North Africa region (17.8%) [64].

It is expected that with the increasing prevalence of sporadic MS, the frequency of FMS rises, as well. Quite interestingly, our meta-regression analysis revealed a weak decreasing trend of FMS in terms of increasing MS prevalence (Figure 9 A). In the same vein, mete-regression in terms of latitude disclosed that the prevalence of FMS is decreased in conjunction with an increment of latitude (Figure 9 B); although, traditionally, MS has been more prevalent in regions at higher latitudes with decreased sunlight exposure, irrespective of some exceptions [65]. Thereby, we hypothesized that with the increasing frequency of MS in a region, the public awareness and familiarity of the people, especially genetic counselors, with the disease grows, too. Therefore, the rate of marriages in which one or both sides have one or more affected members reduces. This, in turn, lowers the load of genetic and environmental risk factors in families. On the other hand, the rate of consanguineous marriage as a predictor of positive family history of MS [16], is most probably diminished in regions with a high outbreak of this disease.

In this review, we would not address the difference between the clinical course of FMS and SMS cases. However, it must allude that there is a discrepancy between the results of the studies. Most of them uncovered that FMS is not a different clinical entity and closely resembles sporadic MS [16, 28, 33, 53]. Although, it appears that disease burden and progression in first-degree relatives with the most heavily genetic load is distinct from more distant relatives [15]. In this aspect, a systematic review with pertinent keywords is justified to obtain a more concrete conclusion.

In comparison to the previous systematic review [9], the strength of our study was recruiting of a quality assessment tool for inclusion of studies, no limitation of language for searching of articles, uncovering the prevalence of FMS in different geographical areas, in POMS and AOMS cases, and men and women, unveiling the relationship between the prevalence of FMS and prevalence day, MS prevalence and latitude, determining the mean age of the disease onset in adult probands and the effect of gender. Notwithstanding, there are some issues in the included studies which mostly derived from the retrospective design. For instance, recall bias could occur when the presence of affected relatives is assessed by employing questionnaires and medical records which hinges on patients self-reporting. This might result in the under-diagnosis of distant relatives. On the other hand, the diversity in case ascertainment methodology namely population (registry or community)-based or clinical (hospital)-based may cause the sampling bias.

Conclusion
In summary, the findings of this study demonstrated that the prevalence of FMS is more in POMS cases than that of AOMS, is different between geographical areas, and reduces with the growing MS prevalence and latitude. Likewise, the symptoms embark relatively at lower ages in FMS probands of AOMS. Unexpectedly, the prevalence of FMS was not more prevalent in men than women and the risk of MS development in relatives was not more when the affected proband was male. For preventing biases, we suggest that future studies be performed as longitudinal prospective to provide time for the development of new cases in relatives. Also, the reported affected members of the family must be reexamined by neurologists.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analysed during this study are included in this published article [and its supplementary information files]

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Not applicable

**Authors’ contributions**

NE performed writing, supervision, conceptualization, and review. MZR accomplished data curation, formal analysis, and editing. MM conducted data curation and formal analysis. All authors have read and reviewed critically and approved the final manuscript.

**Acknowledgements**

Not applicable

**Abbreviations**

| Familial multiple sclerosis | FMS |
|---------------------------|-----|
| Pediatric-onset MS        | POMS|
| Adult-onset MS            | AOMS|
| Preferred Reporting Items for Systematic Reviews and Meta-Analyses | PRISMA |
| Condition, context, and population | CoCoPop |
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Tables

Table 1 The characteristics of included studies
| First author, Published Year | Prevalence day or period | Setting/case ascertainment | Place | Diagnostic criteria of probands | Tool for ascertainment of MS in relatives | Number of probands | Sample size | Mean age of MS onset in probands | FMS Prevalence % | MS Prevalence (Per 100,000) | Latitude | POMS in probands (below 18 or 16) | Geographical area | Sex ratio of probands (F/M) | Quality score |
|--------------------------------|--------------------------|----------------------------|-------|---------------------------------|------------------------------------------|-------------------|-----------|----------------------------------|-----------------|-----------------------------|----------------|---------------------------------|------------------|-----------------------------|----------------|
| [13] 1999-2018 | Cross-sectional/ Iranian MS Society registry system | Tehran, Iran | McDonald | Questionnaire | 2506/1945 | 28.49 ± 8.79 | 13.2 | 148 | 35°44'N | Nobody | Middle East | NR | 9 |
| [13] 1999-2018 | Cross-sectional/ Iranian MS Society registry system | Tehran, Iran | McDonald | Questionnaire | 220|1391 | NR | 15.8 | 148 | 35°44'N | All | Middle East | NR | 9 |
| [14] 2004-2018 | Cross-sectional/ Neurology clinic | Shiraz, Iran | McDonald | Medical records | 48/871 | M: 26.4 ± 9.7 | 5.5 | 63.4 | 29.59°N | NR | Middle East | NR | 5 |
| [15] 2015-2017 | Cross-sectional/ Single-center Hospital | Abu Dhabi, UAE | McDonald | Questionnaire | 24/88 | 28.9 ± 10.7 | 24.5 | 7 | 24°28'N | Nobody | Middle East | 1.6 | 5 |
| [16] 2015-2018 | Cross-sectional/ National registry | Saudi Arabia | McDonald | Questionnaire | 315/2465 | 26.8±8.98 | 12.8 | 41 | 23.88°N |NR | Middle East | 1.9 | 5 |
| [7] 1960-2016 | Cross-sectional/ Danish MS Registry | Denmark | Allinson/Miller, Poser and/or McDonald | Medical records | 1122/1005 | NR | 6.2 | 282 | 56° 00 N | NR | Europe | 1.9 | 6 |
| [8] 1994-2014 | Cross-sectional/ Danish MS Registry | Denmark | Poser and McDonald | Medical records | 531/7402 | NR | 7.2 | 282 | 56° 00 N | NR | Europe | 2.1 | 7 |
| [17] 1989-2016 | Cross-sectional/ Iranian MS Society registry system | Tehran, Iran | McDonald | Questionnaire | 2260/1806 | 28.03 ± 8.69 | 12.52 | 116 | 35°44'N | 8.18 | Middle East | 2.80 | 8 |
| [18] 1999-2017 | Cross-sectional/ Iranian MS Society registry system | Tehran, Iran | Before 2001= Poser | Questionnaire | 288/1907 | 15.87 ± 2.28 | 14.9 | 148.06 | 35°44'N | All | Middle East | 3.05 | 8 |
|                            | After 2001= McDonald |                             |                             |                             |                             |                             |                             |                             |                             |                             |                             |                             |                             |                             |                             |
| [19] 2017-2018 | Cross-sectional/ Ardabil MS Registry | Ardabil, Iran | McDonald | Medical records | 85/611 | NR | 14 | 59.37 | 38°15'N | NR | Middle East | 2.7 | 6 |
| [20] 2002-2015 | Cross-sectional/ academic institution | Cleveland, Ohio, USA | McDonald | Medical records | 19/60 | NR | 32 | 288 | 41°30'N | All | North America | NR | 5 |
| [21] 2009-2017 | Cross-sectional/ three major neurology departments (either clinics or wards) | Malaysia | McDonald | Medical records | 6/123 | NR | 4.9 | 3 | 2°30'N | NR | Southeast Asia | NR | 7 |
| [22] 2005-2015 | Cross-sectional/ Iranian MS Society registry system | Tehran, Iran | McDonald | Questionnaire | 50/300 | NR | 16.7 | 115.94 | 35°44'N | All | Middle East | NR | 7 |
| [23] 1991-2017 | Cross-sectional/ | Tehran, Iran | Before 2001= | Questionnaire | 2547/ | NR | 12.8 | 148.06 | 35°44'N | NR | Middle | NR | 6 |
| Year       | Design          | Country                  | Method                        | Study Details          | Gender | Age | Latitude | Country | Region | Size | References |
|-----------|-----------------|--------------------------|-------------------------------|------------------------|--------|-----|----------|---------|--------|------|------------|
| 1990-2015 | Cross-sectional | Tehran, Iran             | Poser (up to 2001)           | Questionnaire          | NR     | 12.8| 35°44'N | Nobody  | Middle East | 242/1647 | [24] |
| 2003-2011 | Cross-sectional | Isfahan, Iran            | Medical records               |                        | NR     | 58.7| 32°39'N | Nobody  | Middle East | 22/221  | [30] |
| 2013-2014 | Cross-sectional | Tehran, Iran             | McDonald or Poser             | Questionnaire          | NR     | 14.1| 35°44'N | NR      | Middle East | 174/1234 | [26] |
| 2010-2014 | Cross-sectional | Abu Dhabi, UAE           | McDonald                      | Questionnaire          | NR     | 12.4| 24°28'N | NR      | Middle East | 32/257   | [27] |
| 2016      | Cross-sectional | Argentina                | McDonald, Poser               | Questionnaire          | NR     | 25  | 34°00'S | South America | 97/1333 | [25] |
| 2013      | Cross-sectional | Hamadan, Iran            | McDonald                      | Questionnaire          | NR     | 61  | 34°52'N | NR      | Middle East | 103/1202 | [29] |
| 2003-2011 | Cross-sectional | Isfahan, Iran            | Medical records               |                        | NR     | 15  | 50°30'N | NR      | Europe    | 650/4315 | [30] |
| 2013-2014 | Cross-sectional | Mazandaran, Iran         | McDonald                      | Questionnaire          | NR     | 57  | 30°12'N | NR      | Middle East | 33/152   | [32] |
| 1990-2011 | Cross-sectional | Rio de Janeiro, Brazil   | McDonald                      | Questionnaire          | NR     | 15  | 22° 55' S | South America | 40/653 | [33] |
| 2011      | Cross-sectional | Isfahan, Iran            | McDonald                      | Questionnaire          | NR     | 11  | 32°39'N | NR      | Middle East | 430/3911 | [34] |
| 2009-2011 | Cohort         | Germany                  | McDonald                      | Questionnaire          | NR     | 210 | 51.51°N | All      | Europe    | 17/122   | [35] |
| 1977-2012 | Cohort         | Saskatchewan             | Allison and                   | Questionnaire          | NR     | 32.7| 52° 10'N | NR      | North     | 49/150   | [36] |
| Registry                                      | Country                        | Methodology                        | Sample Size | Mean ± SD | Age  | Latitude | Examination Method | Follow-Up Period | Region |
|----------------------------------------------|--------------------------------|------------------------------------|-------------|-----------|------|----------|-------------------|-----------------|--------|
| Saskatchewan, Canada                         |                                | Cross-sectional                     | 884         |           |      |          |                   |                 |        |
| Kuwait                                       | Kuwait                         | McDonald Medical records            | 98/736      | NR        | 13.32| 20° 30’ N|                   |                 | Middle East     | 7      |
| New York, USA                                | New York Medical clinics       | McDonald Questionnaire              | 196/758     | 36.2 ± 8.5| 25.9 | 42° 53’ N|                   |                 | North America   | 8      |
| Kermanshah, Iran                            | Kermanshah Medical records    | McDonald Medical records            | 16/448      | NR        | 3.1  | 34° 23’ N|                   |                 | Middle East     | 6      |
| Qom, Iran                                    | Qom Medical records            | Poser and McDonald Medical records and Questionnaire | 64/572 | NR | 11.2 | 38° 40’ N |                   |                 | Middle East     | 7      |
| East Azerbaijan, Iran                        | East Azerbaijan Medical records | McDonald Medical records            | 71/1000     | NR        | 7.1  | 37° 20’ N|                   |                 | Middle East     | 6      |
| Canada                                       | McDonald Medical records       | McDonald Questionnaire              | 10/63       | NR        | 16   | 60° 00’ N|                   |                 | All North America | 6      |
| Isfahan, Iran                                | Isfahan Medical records        | McDonald Questionnaire              | 119/593     | 29.2 ± 9  | 20.1 | 32° 39’ N|                   |                 | Middle East     | 3.76   |
| Tehran, Iran                                 | Tehran Medical records         | McDonald and Poser Questionnaire    | 773/846     | NR | 9.5  | 32° 00’ N |                   |                 | Middle East     | 6      |
| Mazandaran, Iran                             | Mazandaran Medical records     | McDonald Questionnaire              | 184/2871    | NR | 6.4  | 32° 00’ N |                   |                 | Europe           | 6      |
| Lebanon                                      | Lebanese Medical records       | McDonald Medical records            | 10/202      | NR | 5    | 33° 00’ N|                   |                 | Nobody Middle East | 5      |
| Mazandaran, Iran                             | Mazandaran Medical records     | McDonald Questionnaire              | 7/101       | NR | 7    | 36° 30’ N|                   |                 | Middle East     | 5      |
| Isfahan, Iran                                | Isfahan Medical records        | McDonald Questionnaire              | 206/1718    | NR | 12.2 | 32° 30’ N|                   |                 | Middle East     | 7      |
| Hungary                                      | Hungarian Medical records      | McDonald Medical records            | 33/1500     | NR | 2.2  | 47° 00’ N|                   |                 | Europe           | 2.6    |
| Gorski kotar, Klorje, neighboring regions of the Republics of Croatia and Slovenia, respectively | Poser's Medical records        | McDonald Medical records            | 25/87       | NR | 28.7 | 45° 15’ N|                   |                 | Europe           | 7      |
| Year(s) | Study Type | Country | City/Region | Instrument | ID Range | Latitude | Longitude | Region |
|---------|------------|---------|-------------|------------|-----------|----------|-----------|--------|
| 2004-2005 | Cross-sectional/ Isfahan MS Society registry system | Isfahan, Iran | McDonald | Questionnaire and medical records | 161/1391 | NR | 11.6 | 35.5 | Middle East | NR | 7 |
| 1987-2003 | Cohort/ National MS Centre and Neuromodology department of the University | Belgium | Poser | Medical records | 9/40 | NR | 18.4 | 68 | All Europe | NR | 6 |
| 1972-1997 | Cohort/ University Clinic | London, Ontario, Canada | Poser | Questionnaire and medical records | 208/1044 | NR | 19.9 | 160 | North America | 1.8 | 5 |
| 1973-1992 | Cross-sectional/ National Institute of Neurology and Neurosurgery | Mexico | Poser | Medical records | 9/272 | NR | 3.3 | 1.6 | Central America | NR | 6 |
| 1974-1983 | Cross-sectional, Multi-center Hospital | London, Ontario, Canada | Schumacher | Medical records and Questionnaire | 39/229 | NR | 17 | 88 | North America | NR | 7 |
| 1964-1979 | Cross-sectional/ Both national registry and central hospitals | Jalanjarvi District of Vaasa, Finland | Schumacher | Questionnaire | 15/51 | 33.7 ± 8.7 | 29.4 | 101 | Europe | NR | 6 |

*Repetitive studies have provided the data for both pediatric-onset and adult-onset MS
¶ The information of latitude was gathered from this website: [https://www.mapsofworld.com/](https://www.mapsofworld.com/)
NR: not reported