Systematic Literature Review of Epidemiology of Multiple Sclerosis: A Global Perspective

By

Iha Srivastava

Dissertation submitted for the partial fulfillment of the

MBA Hospital and Health Management

Academic year, 2015-2017

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INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

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This is to certify that **Dr. Iha Srivastava** student of MBA Hospital and Health Management from The IIHMR University, Jaipur has undergone internship training at **Life Sciences and Healthcare, Evalueserve SEZ Pvt. Ltd., Gurgaon**, from **February 6, 2017 to May 5, 2017**.

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish her all success in all his future endeavors.

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Dean, Academics and Student Affairs
The IIHMR University, Jaipur

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Authorised Signatory

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "**A Systematic Literature Review of Epidemiology of Multiple Sclerosis: A Global Perspective**" and submitted by **Dr. Iha Srivastava** Enrollment No **IIHMR-U/20/2015-17/0288** under the supervision of **Dr. D. K. Mangal** for award of **MBA in Hospital and Health Management** of the University carried out during the period from **February 06, 2017 to May 06, 2017** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Iha

Signature

IIHMR UNIVERSITY

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that all ethical issues have been considered while collecting data for my dissertation titled **"A Systematic Review of Literature of Epidemiology of Multiple Sclerosis: A Global Perspective"**.

Iha

IHA SRIVASTAVA

Abstract

Objective: The aim of this study is to conduct a systematic review of literature to determine the epidemiological spectrum of MS in the major geographies of the world including US, Europe (UK, Spain, France, Germany and Italy), China and Japan, to get an insight about the geographic and demographic trend in the distribution of MS.

Methodology: A comprehensive literature search was performed from the time period February, 2017 to May, 2017 on PubMed. The keywords used for search were "Epidemiology", "Incidence", "Preponderance", "Prevalence", "Occurrence", "Distribution", "Risk", "Mortality", "Survival", "Frequency", "Multiple Sclerosis", "Disseminating Disease", and mesh terms. The inclusion criteria for the study was all the freely available full text articles, published in English from 2012 onwards for the given specific geographies such as US, Europe(Italy, Spain, Germany, France, and UK), China and Japan. Research paper or studies beyond the defined scope and whose focus was not on epidemiology were excluded.

Results: A total of 1886 studies were initially identified on PubMed, 13 studies meeting the inclusion criteria. Majority of studies were conducted to study the epidemiology of MS in the regions of Italy, US, France and Spain. Prevalence estimates were reported in commonly in studies. The prevalence of MS in US was estimated at 145.7 to 150.2 per 100,000 while that in Italy was 99.4–188.9 per 100,000. The incidence of MS cases was higher in females 6.7/100,000 than in males was 2.7/100,000. The prevalence was also more in females 224.2 per 100,000 and in males was 71.6 per 100,000. A similar trend was seen in other studied geography as well. The A geographic trend was seen in the distribution of MS cases.

Discussion and Conclusion: There is an increase in the incidence and prevalence estimates of MS over a period of time. The epidemiological rates of MS are the highest in Italy, US and Spain. Females are reported to be afflicted with MS more than males. There is a geographic trend seen in the distribution of MS, showing a high distribution in the northern hemisphere (such as in US, European countries) and low distribution in areas near to the equator (China Japan).

Acknowledgement

This report represents not only my work at the keyboard, but it is a product of cooperation and support from people around. After arigorous period of three months, now I am writing this note of thanks as afinal touch on my dissertation. It has been a period of intense learning for me, not only in the scientific arena, but also on a personal level. I would like to reflect on the people who have supported, guided and helped me so much throughout.

Prima facea, I am grateful to the God for giving me good health and well being.

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I would also like to thank my guide **Dr. D. K. Mangal, Dean (Research),The IIHMR University, Jaipur**, for his help, cooperation and wholehearted encouragement.

I take this opportunity to thank my colleague, **Vrinda Mathur**, for always being a support and strength during this duration and helping me to complete the dissertation.

The acknowledgement would not be complete without expressing my profound gratitude to my parents, sister and spouse for being my pillars of strength, who have always encouraged and helped me at every stage of my personal and academic life, and longed to see this achievement come true.

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Abbreviations

MS	Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
PPMS	Primary progressive Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
PRMS	Progressive-Relapsing Multiple Sclerosis
CIS	Clinically Isolated Syndrome
WHO	World Health Organization
QoL	Quality of Life
DALY	Disabiliy Affected life Years
EDSS	Expanded Disability Status Score
CNS	Central nervous System
BBB	Blood Brain Barrier
NICE	National Institute for Health and Clinical Excellence
MRI	Magnetic Resonance Imaging
CSF	Cerebrospinal Fluid
DMT	Disease Modifying Thearpy
PRISMA	Preffered Reporting Items for Systematic Reviews and Meta-analysis
MRR	Mortality Rate Ratio
SMR	Standardized Mortality rate
CMR	Crude Mortality rate
CASP	Critical Skills Appraosal Programme
DET	Data Extraction Table

Chapter 1: Introduction and Scope of Dissertation

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, which is characterized by inflammation, demyelination and axonal degeneration **[1]**.The term multiple sclerosis is derived from the stiff plaques (sclerosis) which are visible at several different places of the nervous system (multiple). MS was described for the first time in the history by Augustus d'Esté in his diary (1794- 1848) **[2]**. Dr. Walter Moxon first recognized the disease in the year 1873 in England. Later it was discovered in the United States (US), by Dr. Edward Seguin in 1878 **[3]**. The first medical description of MS is linked with Charcot's name (1825-1893) **[4]**.

MS is a rare disease affecting more than 2.1 to 2.5 million persons worldwide **[5]**. US and Europe have approximately 400,000 and 350,000-405,000 patients affected by this disease, respectively **[5]**. The onset of MS occurs early in adulthood (around 28 years of age). The females are afflicted two times more than males with MS. The incidence of disease is high in Caucasians and lowest in Japanese **[6]**.

MS is rare and its epidemiology is not very well documented in India. It is more common in north, settled mostly by Indo-Europeans, than in south inhabited pre-dominantly by Tamils and Dravidians **[7]**.

Close to the equator the prevalence of MS is low and it increases with the increase in latitude **[6]**. Ethnicity also influences the prevalence of MS **[6]**. Higher prevalence of MS in Northern Europe, North America, Australia and New Zealand **[8]** suggests that MS may have been carried around the world by the European colonists.

There are four clinical subtypes of MS: a) relapsing-remitting (RRMS), b) the secondary progressive (SPMS), c) the primary progressive (PPMS) and d) the progressive-relapsing (PRMS) **[9]**.In RRMS, relapses or exacerbations occurs, which worsen the neurological function and after each relapse, a partial or complete recovery takes place called as remission. It is the most common clinical course.RRMS may progresses to SPMS, where the disease has transformed into progressive phase with more prominent damage and loss of the axons. PRMS is associated with steady worsening neurologic function from the beginning with occasional relapses.In PPMS, neurological function worsenswithout any

relapse. In addition to the clinical sub-types described above,the first episode of neurological symptoms continuing for at least 24 hours is referred to as the clinically isolated syndrome" (CIS) **[10-11]**.

MS is characterized by many signs and symptoms. The most common symptoms are numbness or tingling in face, body or extremities, weakness and vision problems, dizziness, spasticity, bladder dysfunction or constipation caused by bowel problems. Weakness, spasticity, loss of balance or sensory deficit may result in difficulty in walking. Symptoms of cerebellar damage, such as ataxia or intention tremor, are also associated with MS.

MS is a progressive disease with unknown etiology and no definitive treatment. However, symptomatic cure is given to alleviate its symptoms.

According World Health Organization (WHO), health is a state of complete physical, mental, and social well-being, not merely the absence of disease. The assessment of the social, emotional and physical well-being over a period of time as the disease progresses would give measurement of quality of life (QoL) in a person. Fatigue, depression, cognitive impairment, bladder dysfunction, bowel dysfunction, sleep problems, and sexual dysfunction have a negative impact on the quality of life (QoL) in individuals affected by MS **[12]**.

MS is a crippling disease and QoL in terms of disability of an affected individual is measured as disability affected life years (DALYs). John F. Kurtzke developed Expanded Disability Status Scale (EDSS) score to define the level of disability of patients. This is a ten point scale from zero to ten. The highest score, EDSS 10.0 indicates death caused by MS **[13]**.

The economic burden of the disease includes the direct as well as indirect costs. Direct costs include inpatient and outpatient care, cost of drugs, diagnostics, surgical interventions, nursing care, social services, and the travel costs. Indirect costs are losses of production due to short- or long-term sickness related absence from work, disability pension, early old-age pension due to health problems, permanent losses due to premature

death, and sometimes time spent by next of kin to care for the patient. Intangible costs are the humanitarian losses due to pain, anxiety, and suffering **[14]**.

The total all-cause health care costs associated with MS in the US ranges from $8,528 to $52,244 per patient per year **[15]**. Approximately, 26% to 87% of the total costs associated with MS accounts for the direct cost. The indirect costs associated with MS is around 13% to 74% of the total cost **[16]**.According to NHS, UK the cost for hospitalization alone was 43 million £ in 2012-2013 **[17]**.

There are no comprehensive studies present that give worldwide estimates for the epidemiology of MS. The aim of this study is to conduct a systematic review of literature to determine the epidemiological spectrum of MS in the major geographies of the world including US, Europe (UK, Spain, France, Germany and Italy), China and Japan.This will give an insight about the geographic and demographic trend in the distribution of MS across the selected geographies. This would enable to gauge resource utilization for the management of MS and costs associated with the disease, as well as forecasting the health care planning and screening purposes. Moreover, the comparison of epidemiology data across different geography would give insights to fathom the contribution of etiological factors like environmental and genetic factors in MS.

Chapter 2: Review of Literature

2. Review of Literature

2.1 Disease Definition

Multiple sclerosis (MS) is an autoimmune condition of the central nervous system. It is a neurological disease that involves the central nervous system (CNS). MS is characterized by inflammation and demyelination of neurons leading to the impairment of nerve transmission down the axon **[18]**. According to a study by Ringoldet.al., 2006, the name of the disease originates from the fact that demyelination results in the formation of multiple patches of hard, scarred tissue called plaques (sclerosis).

2.2 Disease Characteristics

The average age for onset for MS is 30 years, in adults (ranging 20-50 years) and the preponderance of disease is 3.2 folds more in females as compared to males **[19]**.

2.3 Etiology and Pathogenesis

The etiology of MS is unidentified, but it is likely that numerous factors act in recital to initiate or perpetuate this chronic neurological disorder. According to a study by Laplaud DA et.al. it has been hypothesized that MS results when an environmental agent or event (e.g., viral or bacterial infection, exposure to chemicals, lack of sun exposure) acts in concert with genetic predisposition to immune dysfunction **(Figure 2.1) [20-22]**.

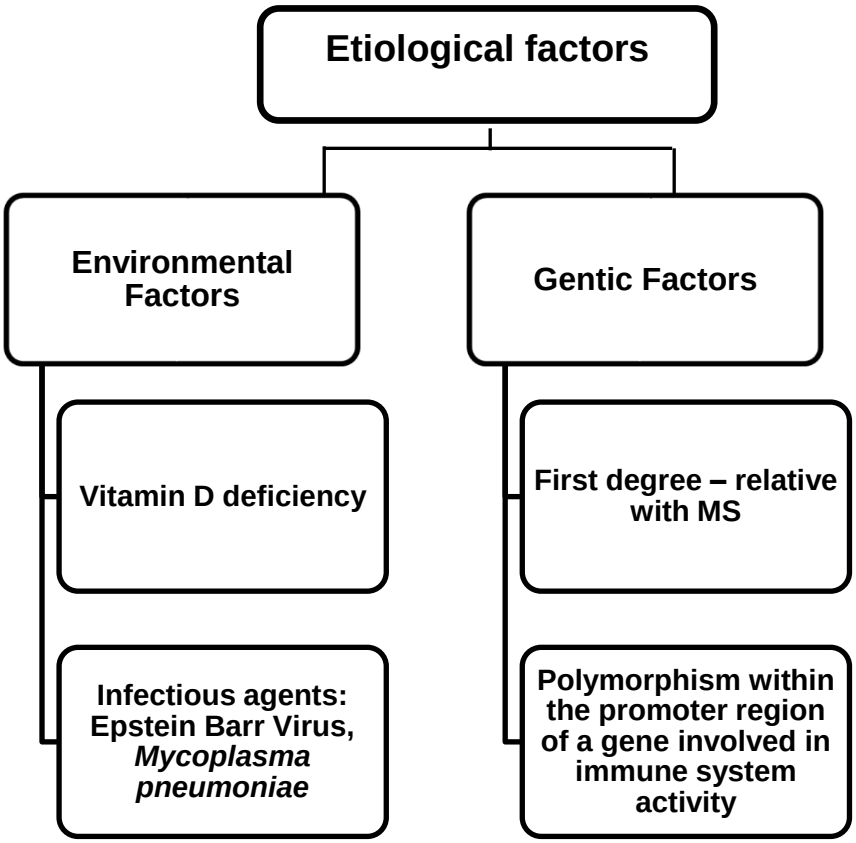


Figure 2.1: Etiological factors for MS

Pathogenesis:

The extensive demyelination and axonal deterioration related to MS within the central nervous system (CNS), clinically manifest as increased neurological deficit. Inflammation occurring adjacent to the lateral ventricles within the corpus callossum, subcortical white matter, optic nerves, and brainstem and throughout the CNS, causeshindrance in the transmission of the action potentials through the axons (Compston and Coles 2008). This result in the clinical features associated with MS [23-24].

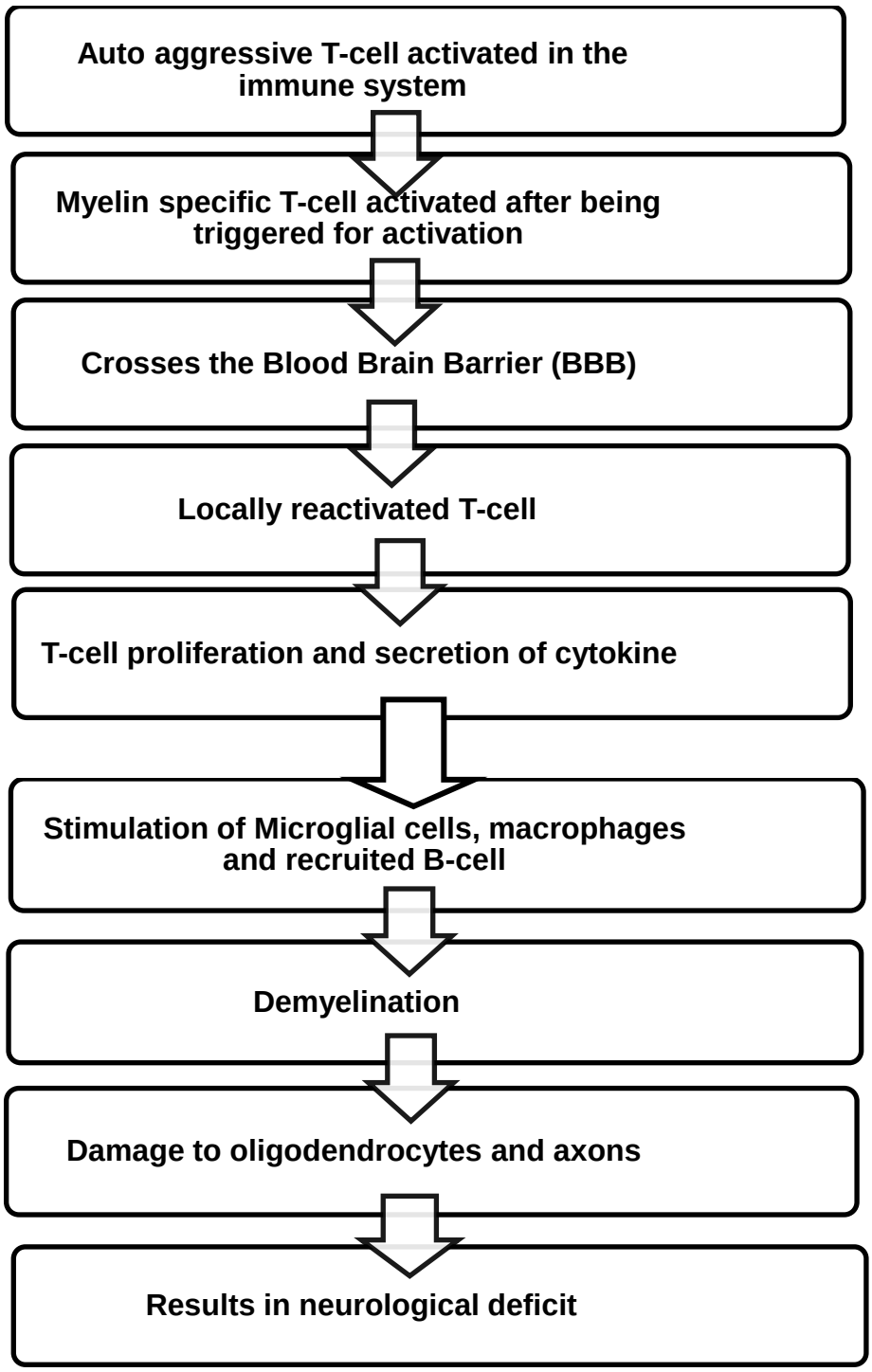
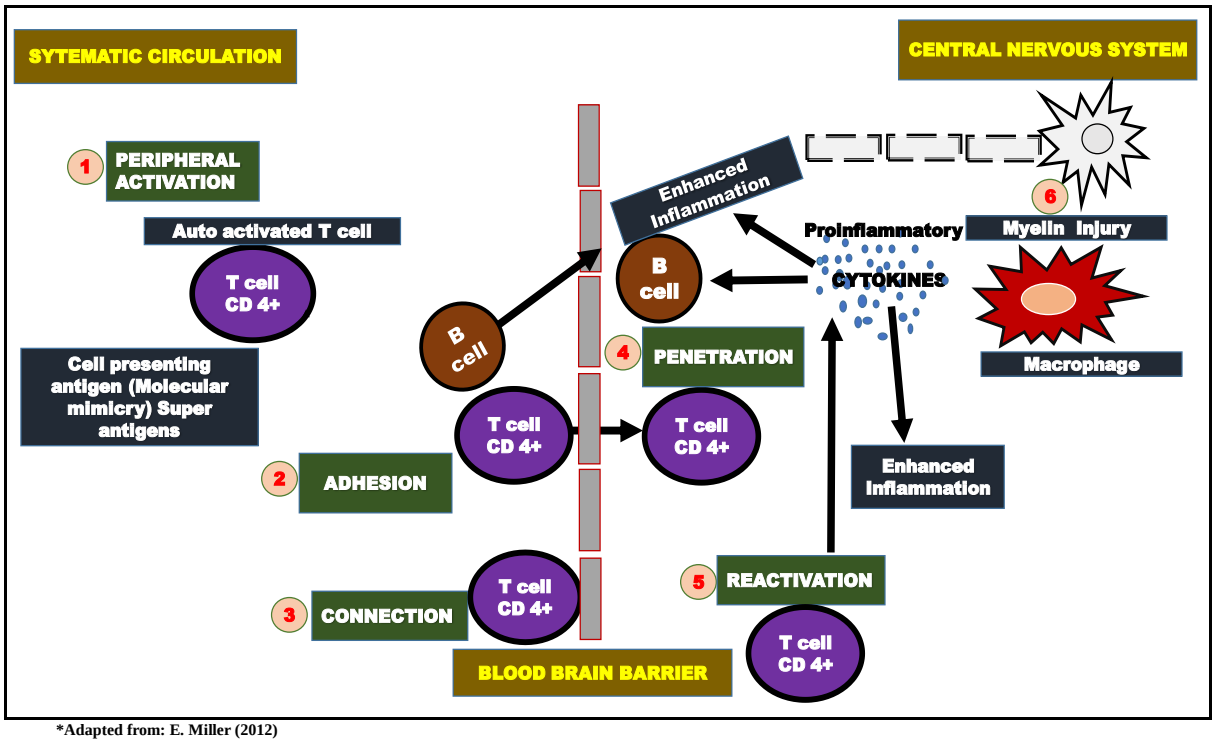


Figure 2.2: Flow chart for pathological mechanism



*Adapted from: E. Miller (2012)

Figure 2.3: Schematic representation of pathological mechanism

2.4 Clinical Subtypes of MS

Four clinical subtypes of have been recognized for MS (Table 2.1) **[25-26]**

Table 2.1: Types of MS

Type	Disease Course
Relapsing/Remitting Multiple Sclerosis (RRMS)	• Most common type • Accounts for approximate 80-85% of cases (National Institute for Health and Clinical Excellence; NICE (2003)) • Characterized by discrete attacks that advance over days to weeks followed by some degree of recovery over weeks to months. In between attacks, the patient has no worsening in neurological function

Type	Disease Course
Secondary Progressive Multiple Sclerosis (SPMS)	• Characterized by initial relapses, followed by gradual neurological deterioration, which progressively worsen • Not associated with acute attacks • 50% of people diagnosed with relapsing remitting MS develop the secondary progressive form within 10 years (NICE, 2003)
Primary Progressive Multiple Sclerosis (PPMS)	• Approximate 10-15% cases • Characterized by steady functional decline from the onset of the disease • No relapses ever
Progressive Relapsing Multiple Sclerosis (PRMS)	• Characterized by steady functional decline from onset of the disease with later superimposed acute attacks • PRMS and PPMS cannot be distinguished during early stages, until the relapses occur

Benign MS is yet another form of disease, in which there is no change in any neurological systems for 15 years or more (Lublin and Reingold 1996). According to a study reported by Weinshenkeret.al. (1995), benign MS has been defined as RRMS, in which EDSS score is less or equal to 3.0 for at least 10 years after the diseaseonset.Sayao et.al. (2007) suggested that, only about 52 % of patients continue toremain benign after 20 years of follow-up after MS diagnosis and about 23 %have progressed to EDSS score ≥ 6 **[27-29]**.

2.5 Clinical Presentation

Clinical signs and symptoms vary among the patients suffering from MS. Fatigue and disturbed sensory, motor, bladder, bowel, sexual, cerebellar, brainstem, optic nerve, and cognitive realms are the protean symptoms of MS. Clinical features may include; fatigue, mobility impairments, weakness, balance impairments, stiffness and spasms, memory and

other cognitive problems, bladder and bowel problems, pain and unpleasant sensations, emotional problems, visual changes, and dizziness (Motl et.al. 2008) **[30]**.

The National Multiple sclerosis Society describes disease by a first attack of symptoms or a neurological episode, which is known as Clinically Isolated Syndrome characterized by initial symptoms, which may be mild and where not all symptoms affects all patients. The second attack of these symptoms would be then characterized as relapsing–remitting multiple sclerosis **[31]**.

The early signs and symptoms are described in the following table 2.2 **[31].**

Table 2.2: Signs and symptoms of MS

SYMPTOMS	DETAILS
Fatigue	• Most common and debilitating symptom of MS • Causes significant disability in patients as the disease progresses
Numbness and Tingling sensations.	Numbness of face, arms, body and other extremities like arms and legs or loss of sensation may occur
Spasticity	Muscle spasms and stiffness particularly in the legs is an initial symptom in nearly all MS patients
Weakness	Weakness in MS can result due to demyelination of nerves that stimulates the muscles
Vision Problems	• Initial onset of blurred or doubled vision, poor contrast or color vision and pain on eye movement • Optic neuritis and inflammation of the nerves in the eye may also be characterized in MS
Dizziness and Vertigo	• Difficulty in walking and keeping balance • Sensations of spinning surroundings (vertigo)
Bowel and bladder problems	• Constipation and urinary retention • Bowel and bladder incontinence
Pain	Facial pain, powerful spasms, cramps and stiff joints.
Sexual Dysfunction	• Erectile dysfunction in men and problems in vaginal lubrication in women
Cognitive Changes	Cognitive problems such as problems in concentrating, reasoning, problem solving and memory loss
Depression	Emotional changes due to MS or due to stress, resulted from disability

Matthews et.al. (1998) conducted a study on 301 people with MS living in Wales, which provided information on the frequency of symptoms (Table 2.3), highlighting the most common symptoms (weakness, sensory symptoms, ataxia, bladder symptoms, and fatigue),

amongst those with MS whilst indicating that not all symptoms may be present throughout the course of the disease **[32]**.

Table 2.3: Frequency of symptoms

Symptoms	Ever (n (%))	At onset (n (%))
Weakness	268 (89)	66 (22)
Sensory Symptoms	263 (87)	103 (34)
Ataxia	248 (82)	32 (11)
Bladder Symptoms	213 (71)	5 (2)
Fatigue	171 (57)	5 (2)
Cramps	156 (52)	2 (0.6)
Diplopia	155 (51)	25 (8)
Visual symptoms	148 (49)	38 (13)
Bowel Symptoms	126 (44)	0
Dysarthria	110 (37)	2 (0.6)
Vertigo	107 (36)	13 (4.3)
Facial pain	106 (35)	5 (2)
Poor memory	96 (32)	1 (0.3)
Headache	90 (30)	6 (2)
Mental symptoms	68 (23)	1 (0.3)
Deafness	51 (17)	2 (0.6)
Facial weakness	48 (16)	4 (1)
Dysphagia	40 (13)	1 (0.3)

***Data adapted from Matthews (1998)**

2.6 Diagnosis of Multiple sclerosis

MS, being a chronic neurological and autoimmune disease, requires an early and accurate diagnosis for proper and timely management of the patient and the associated symptoms. The diagnosis of MS involves both clinical parameters, such as medical history and neurological examination, and para-clinical measures such as magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination and evoked potential testing.

A new diagnostic criterion for MS was introduced by an International Panel on the Diagnosis of MS in 2001, known as "McDonald Criteria". The most recent revision was made in 2010 by Polman et al. (2011). Common features all these diagnostic criteria are

demonstrating dissemination of lesions in both space and time and to excluding alternative diagnosis. Revised diagnostic criteria allow timely diagnosis of MS **[33]**.

Magnetic Resonance Imaging is considered as significant test in detecting lesions or plaques and the altering neurological function of the central nervous system. Serial MRIs are needed todiagnose and confirm the diagnosis and to keep a check on the worsening of the symptoms.Gdolinium enhancementis used to detect BBB penetration and lesions, which are characterized by active inflammation. The dark zones, which are known as black holes, may appear within the plaques or lesions after loss of axons occurs. An increase inIgG synthesis, oligoclonal banding and number of myelin basic proteins is typically seen in the cerebro-spinalfluid (Mark H. et al, 2009) **[6]**.

2.7 Treatment

No definitive treatment is available for MS. National Institute for Health Clinical Excellence (NICE (2003)) has provided guidelines for the treatment of acute exacerbations and long-term management in MS.

Management of acute exacerbations

Corticosteroids, to be administered during a severe exacerbation or attack of symptoms and depending upon the severity of exacerbation hospitalization may be indicated. Corticosteroids are often administered (intravenous or high dose oral methylprednisolone) for 3-5 days. Rehabilitation service will aim towards the sudden increase in disability.

Long-term management

NICE (2003), guidelines suggest disease modifying therapy (DMT), either interferon beta or glatiramer acetate, in cases of RRMS under the guidance of their neurologist. Other medical treatments such as azathioprine, mitoxantrone, intravenous immunoglobulin, plasma exchange and intermittent methylprednisolone must be prescribed judiciously, only if appropriate **[34].**

According to NICE 2007, **[34]** guidelines, natalizumabis prescribed to rapidly evolving cases of severe RRMS, and NICE 2012, **[35]** recommends fingolimod for those with

highly active RRMS. Rehabilitation services should be provided to manage functional activities and social participation. These services endeavor to maintain the person with MS in their chosen vocational activity, encourage leisure and social interaction, maintain mobility, maintain activities of daily living and help manage symptoms.

Thompson et.al. (2010), suggested a multidisciplinary management, which includes occupational therapy, physiotherapy, pharmacological and surgical treatments of MS to address symptoms such as; spasticity, ataxia, impaired mobility, bladder/bowel and sexual dysfunction, fatigue, cognitive problems, mood disturbance, visual and brainstem symptoms **[36]**.

Chapter 3: Methodology

3. Methodology

3.1 Key research question

The purpose of this study is to explore the epidemiology data of MS in the major geographies like US, Europe (Italy, Spain, Germany, France, and UK), China and Japan.

3.2 Research Design

A comprehensive secondary research was conducted for the articles or studies describing the epidemiology of MS.

It is a descriptive epidemiological study, conducted for three months' time from February 2017 to May 2017.

Table 3.1: Population, Interventions, Comparators, Outcomes, Study Design for SLR

PICOS for SLR	
Population	**Individuals suffering from MS or various clinical sub-types of MS**
Interventions	-
Comparators	-
Outcomes	• **Incidence** • **Prevalence** • **Mortality** • **Frequency** • **Reoccurrence** • **Survival**
Study Design	• **Systematic Reviews and/or meta-analysis** • **Observational studies: prospective or retrospective** • **Registries or disease forums**
Time Frame	**2012 onwards**

3.3 Research procedure adapted

A systematic literature review was conducted to identify information on the epidemiology of the disease, in the above-mentioned geographies.

Step I – Search Strategy Preparation

This step included the following tasks:

- Identification of synonyms of the key concepts-epidemiology and Multiple sclerosis to be searched using PubMed, MeSH terms.
- Preparation of a search strategy using appropriate search operators (Boolean operators, proximity operators and wild card truncations) compatible with PubMed (Table 3.2).

Table 3.2:Search String

S. No.	Concept	Search string
1	Multiple Sclerosis	"MULTIPLE SCLEROSIS" OR "DISSEMINATING DISEASE"
2	Epidemiology	EPIDEMIOL* OR INCIDEN* OR PREPONDERAN* OR PREVALEN* OR OCCURRENCE* OR DISTRIBUTION OR RISK OR MORTALITY OR DEATH* OR DEAD OR SURVIVING OR SURVIVAL OR ALIVE OR LIVING

Step II – Conducting the Search

This step involved conducting keyword-based searches on the following sources using the search strategy prepared in Step I:

- PubMed
- Registries for Multiple sclerosis

The search was conducted to identify the following type of studies:

- Systematic review, meta-analysis, observational studies, real world studies, registries

- General reviews with epidemiological data

Inclusion Criteria

- Articles available in English language
- Full text articles freely available
- Studies published in and after the year 2012
- Articles focusing on epidemiology of the given geographies: US, Europe (Italy, Spain, Germany, France, and UK), China and Japan

Exclusion Criteria

- Research papers or articles focusing on areas other than ones defined in scope
- Articles whose focus is not on epidemiology

Step III – Preliminary Screening

This step involved screening of the citations captured in the searches on the basis of title and abstract and short listing the citations that are potentially relevant for the project. Citations that do not meet the criteria as mentioned in PICOS were excluded.

Step IV – Full Text based Review

This step involved the following:

- Evaluating the citation on the basis of full text to ascertain if it matches the PICOS criteria and exclusion of citations that are non-relevant
- Preparation of a list of relevant results

All results shortlisted after title and abstract based screening were reviewed for full text availability and relevance.

Step V – Critical Appraisal of the relevant results

This step involved the following:

- Identification of the most appropriate tool for quality assessment. The standard tools to be used for quality assessment for example: AMSTAR for systematic

literature reviews, CASP (Critical Skills Appraisal Programme) and Downs and Black for observational studies **[37-39]**

- Conducting the quality assessment and marking the study as low, medium or high quality.

The criteria for ranking studies low, medium and high will be based on the tool used and the final score.

Step VI – Supplementary Searches

This step was conducted to identify epidemiology data from sources other than scientific literature such as grey literature, conferences etc. The step included the following:

- Conducting searches on Google Scholar, national websites, etc.
- Identification of additional sources for the required data such as conferences, rare diseases forums, immune disorders forums etc. and conducting searches on them

Step VII – Data Extraction

This step involved the following:

Development of a Data Extraction Table (DET) template to capture required information from the relevant studies on the areas of interest for Multiple sclerosis. The DET captures the following information:

- Author(s), year of publication
- Publication reference
- Definition of the disease
- Study design
- Study period
- Number of patients/individuals (numerator and denominator)
- Country/geography
- Key estimates of interest (e.g. prevalence, incidence, mortality, frequency, reoccurrence and survival)
- Details of population characteristics (Age, number, ethnicity, country, gender etc.)

Extraction of the data from relevant results in DET.

Chapter 4: Results

4. Results

In performing the study, the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) protocol was followed. The details of which are mentioned below in the Figure 4.1.

PRISMA

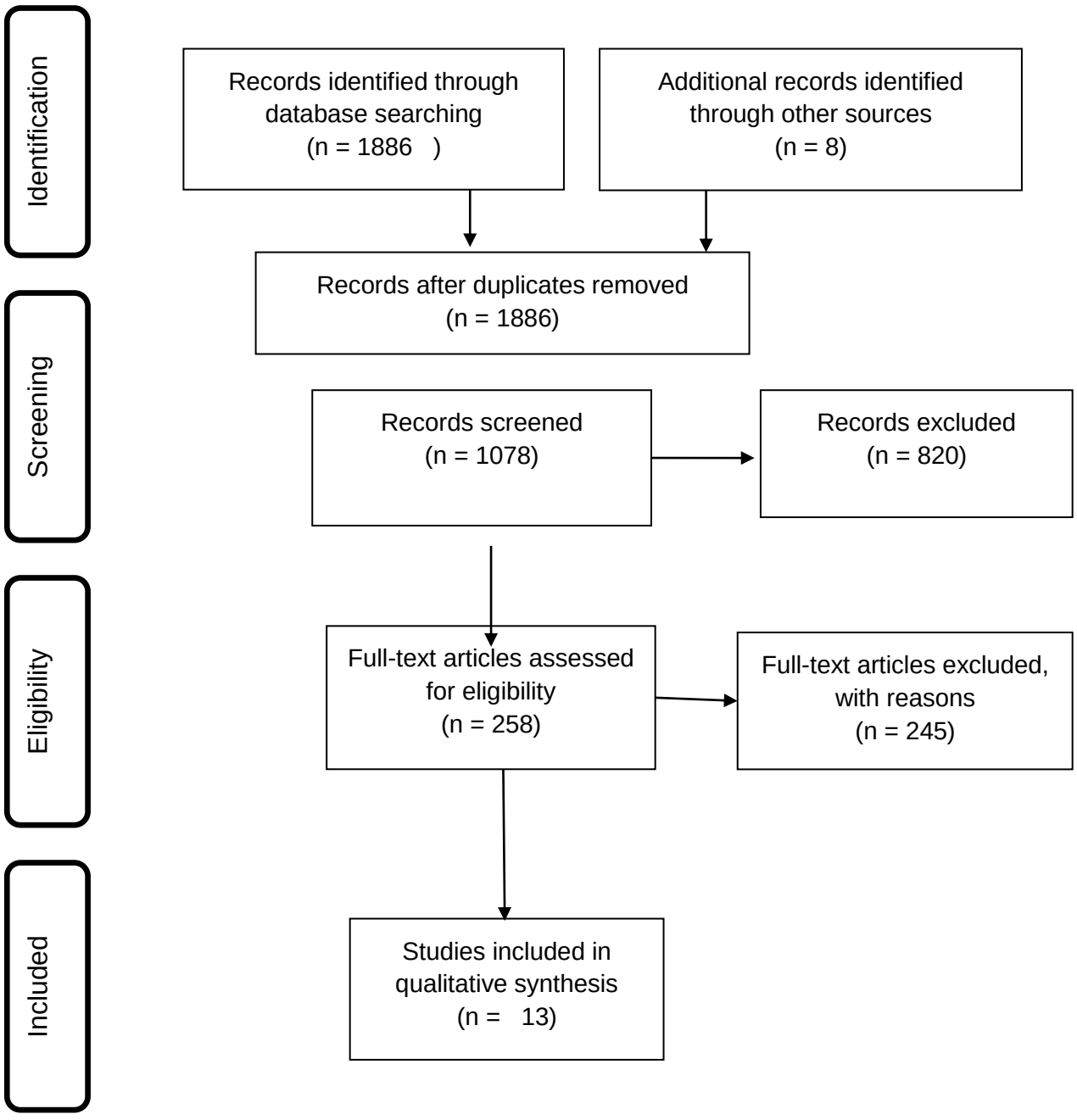


Figure 4.1:PRISMA

The search on epidemiology of MS analysis included studies from countries such as US, UK, Spain, France, Germany, Italy, China and Japan, from the year 2012 onwards. The data reveals that the US and Italy are the widely-studied regions, followed by France, Spain, UK and China (as shown in Figure 4.1).

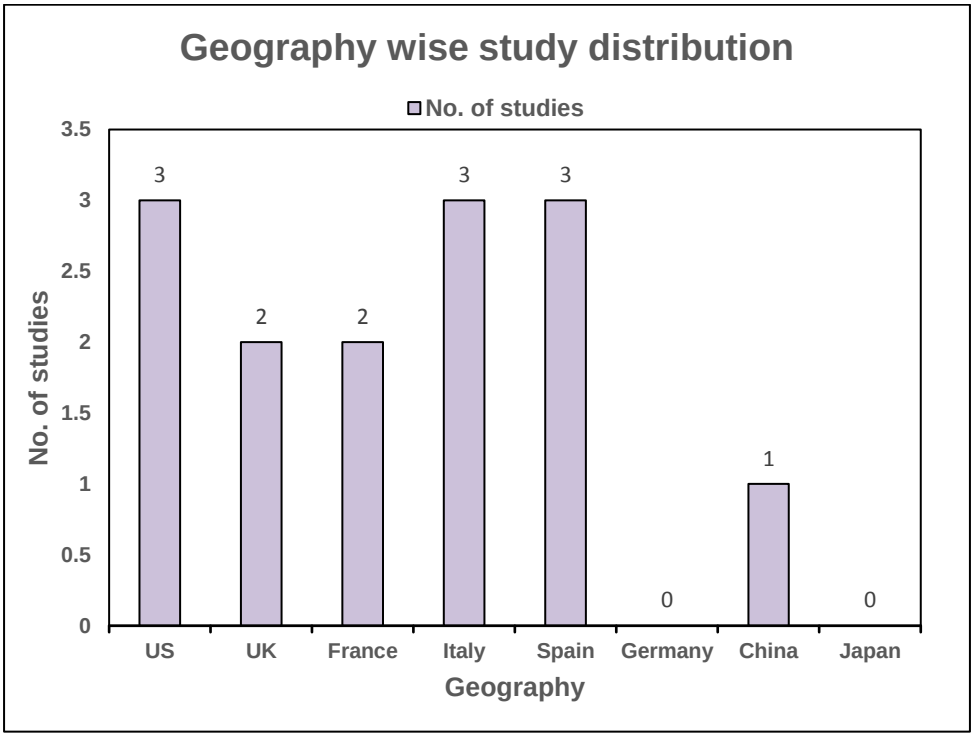


Figure4.2: Geography wise study distribution

Quality of the studies to be reviewed was assessed using quality assessment tools depending upon the study design. Two independent reviewers' critical appraisal tools to assess the methodological quality of each study. The quality scores were categorized as low, medium and high (Table 4.1).

Table 4.1: Quality Checklists and Scores

Quality checklist	Study design	Score	Quality
Amstar	Systematic literature reviews	1-4	Low
		5-7	Medium

Quality checklist	Study design	Score	Quality
		8-11	High
CASP	Observational studies	1-6	Low
		7-9	Medium
		>9	High
Downs and Black	Observational studies	1-8	Low
		9-16	Medium
		>17	High

The quality was assessed using the above-mentioned checklist. The thirteen studies included in the systematic literature review were assessed and the quality was reported using the critical appraisal tools. Quality scores of the studies are presented in Table 4.2

Table 4.2: Study Design and Quality

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
1	**Iglesias, M.B. (2015) [40]**	Epidemiological study of multiple sclerosis in La Rioja	Spain	October 1, 2001-September 30, 2011	Retrospective study	CASP	High
2	**Jick, S.S. (2015) [41]**	Epidemiology of multiple sclerosis: results from a large observational study in the UK	UK	January 1, 2001-December 31, 2006 Data update : 2012	Population-based observational study	CASP	High
3	**Leray, E. (2015) [42]**	Excess Mortality in Patients with Multiple Sclerosis Starts at 20 Years from Clinical Onset: Data from a Large-Scale French Observational Study	France	1940-2009	Multicenter Observational Study	CASP	High
4	**Izquierdo, G. (2015) [43]**	Long-term epidemiology of multiple sclerosis in the Northern Seville District	Spain	January 1, 1991 to December 31, 2011	Longitudinal study	CASP	Medium
5	**Manouchehrinia, A. (2015) [44]**	Mortality in multiple sclerosis: meta-analysis of standardized mortality ratios	-	1949–2012	-	AMSTAR	Medium
6	**Capkun, G. (2015) [45]**	Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: An observational study using the US	US	July 1, 2006-June 30, 2011	Administrative claims database analysis	CASP	High

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
		Department of Defense administrative claims database					
7	**Nicoletti, A. (2013) [46]**	Multiple Sclerosis in the Mount Etna region: possible role of volcanogenic trace elements	Italy	Prevalence day: December 31, 2009 Incidence: 1980 to 2008	-	CASP	Medium
8	**Tsai, C.P. (2013) [47]**	Multiple sclerosis incidence associated with the soil lead and arsenic concentrations in Taiwan	Taiwan, Republic of China	1997-2008	National Health Insurance Database study	Downs and black	Medium
9	**Dilokthornsakul, P. (2016)[48]**	Multiple sclerosis prevalence in the United States commercially insured population	US	2008-2012	Retrospective analysis	CASP	High
10	**Bargagli, A.M. (2016) [49]**	Prevalence of multiple sclerosis in the Lazio region, Italy: use of an algorithm based on health information systems	Italy	January 1, 2006-December 31, 2011	Health information system	Downs and black	Medium
11	**Bezzini, D. (2016) [50]**	Prevalence of Multiple Sclerosis in Tuscany (Central Italy): A Study Based on Validated Administrative Data	Italy	-	-	CASP	High
12	**Yaouanq, J. (2015) [51]**	Register-based incidence of multiple sclerosis in Brittany (north-western France), 2000-2001	France	2001-2007	Registry	Downs and black	Medium
13	**Massa,J. (2013) [52]**	Caffeine and alcohol intakes have no association with risk of multiple sclerosis in a	US	1990-1994	Cohort study	CASP	High

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
		prospective study of women					

The following graph **(Figure 4.3)** shows the combined results of the quality of the thirteen studies included in the review:

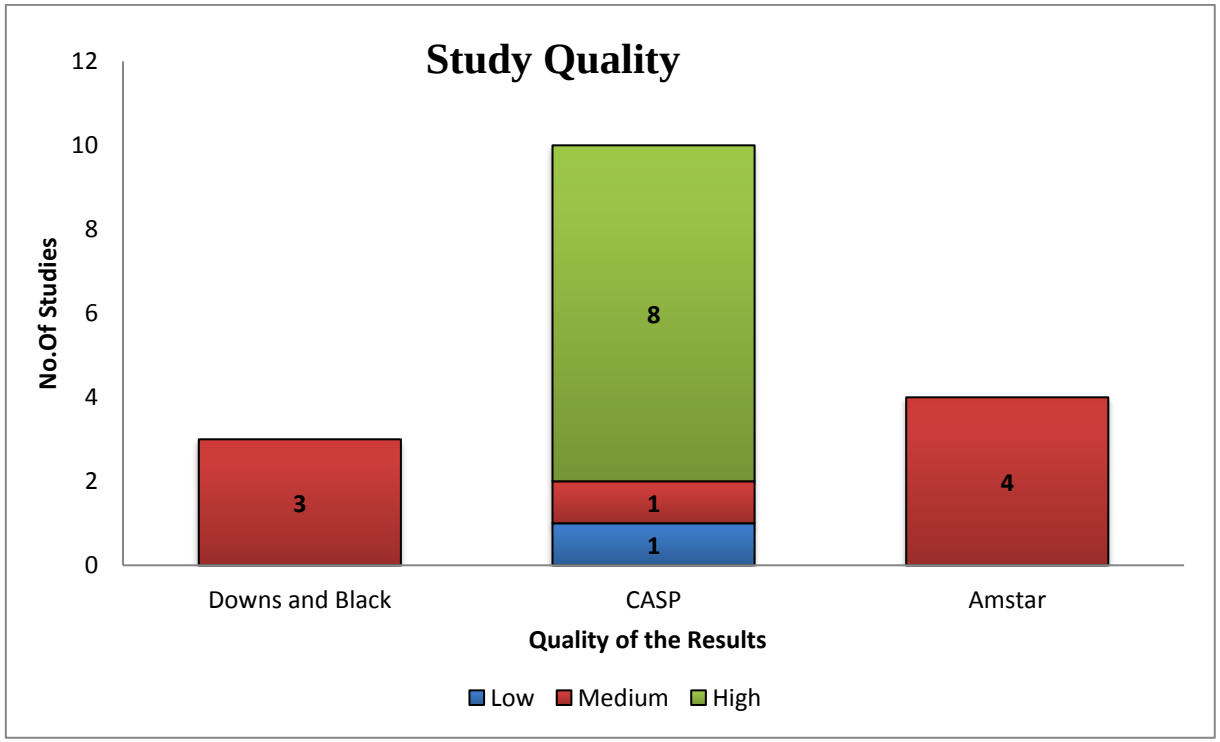


Figure 4.3: Quality score for studies

The key findings from various available studies are given in the Table 4.3. The studies described more about the prevalence estimates of the various regions of the country than the incidence or mortality/survival data. The cases or the study population was ascertained from sources such as MS registries or administrative databases and the hospital and clinic records. Poser's or McDonald's criteria was frequently used to defineddiagnosticcriteria for the MS cases and the diagnosis was established based on review of medical records and assessment by neurologist or health professionals, however the inclusion and exclusion criteria does not seem to be consistent in the studies. , there were two diagnostic criteria's which were used for the case ascertainment of MS. McDonald's criteria of MS facilitates the diagnosis with the first demyelinating attack and then significantly increases the sensitivity of diagnosing MS. The McDonald's criteria of MS state that at least 2 or 3 MRI's should fulfill the diagnostic needs.

The Poser's criteria classified a patient under MS only when the patient has the following:

- Attack: Occurrence of a symptom of neurological dysfunction for more than 24 hours
- Clinical evidence: Neurological dysfunction demonstrable by neurological examination
- Para clinical evidence: Demonstration by any test of the existence of a non-clinical lesion in the CNS

The studies on mortality and survival are analysed using the Kaplan-Meyer survival analysis curve.

Table 4.3: Key Insights Findings

S.No.	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data

S.No.	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
1	UK	**Jick, S.S. et.al. (2015)**	• 1,713 MS incident cases • Data collected from: The UK's Clinical Practice Research Data link (CPRD)	McDonald's Criteria (2005) records	• The number prevalent cases for MS from 1993-2006 were 109; 46 prevalent cases identified from 1993'-2000 and 63 from 2001-2006 • The mortality rate was during 13,573 person-years of follow up, with mean age at death being 56.9 years • The number of deaths was more among females being 79 than in males being 36 • The number of alive MS cases were 1,598 from 1993-2006, with mean age of survival being 41.1 years • The survival rate in females was 1,181 and in males was 417
2	France	**Leray, E. et.al. (2015)**	Recruitment of 27,603 MS cases from 15 centers who were members of European Database for Multiple Sclerosis (EDMUS)	Poser's or McDonald's criteria depending on the period of diagnosis	• 1,569 (5.7%) MS patients died, with a mortality rate of 3.7 (3.55–3.92) per 1000 patient-year • 685 (43.7%) males died with a death rate of 5.53 (5.13–5.96) per 1000 patient-year • 884 (56.3%) females died with a death rate of 2.98 (2.79–3.18) per 1000 patient-year • The number of alive MS cases was reported to be 26,034 and female to male ratio was 2.5:1
3	US	**Capkun, G. et.al. (2015)**	An MS cohort of 15,684 was selected fromUS Department of Defence (DoD) Military health system database	-	Mortality rate was 10.8 per 1000 patient years

S.No.	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
4	Italy	**Nicoletti, A. et.al. (2013)**	• Inhabitants at Western flank of Mount Etna were 56,216 • Data was collected from: ○ Neurological hospitals of Catania ○ MS centers in the province of Messina • Inhabitants at Eastern flank of Mount Etna were 47,229 • Data was collected from: ○ Neurological hospitals of Catania ○ MS centers in the province of Messina	Poser's Criteria	• 51 incident MS cases in Western flank communities • The incidence was higher in females with incidence rate of 4.7/100,000 (95%CI 3.3–6.4) or 38 MS cases while the rate in males was 1.7/100,000 (95% CI 0.9–2.9) or 13 MS cases • 53 prevalent MS cases in Western flank communities • The prevalence was higher in females with prevalence rate of 137.3/100,000 (95% CI 99.4–188.9) or 40 MS cases while the rate in males was 48.0/100,000 (95% CI 26.7–84.4) or 13 MS cases • 59 incident MS cases in Eastern flank communities • The incidence was higher in females with incidence rate of 6.7/100,000 (95%CI 4.8–9.1) or 41 MS cases while the rate in males was 2.7/100,000 (95% CI 1.6–4.2) or 19 MS cases • 65 prevalent MS cases in Eastern flank communities • The prevalence was higher in females with prevalence rate of 230.3/100,000 (95% CI 170.5–305.3) or 45 MS cases while the rate in males was 72.2/100,000 (95% CI 45.3–113.7) or 20 MS cases
5	Taiwan, Republic of China	**Tsai, C.P. et.al. (2013)**	The population data obtained from the year 2000 census in Taiwan was 790,621	Poser's Criteria	• 1240 incident MS cases were reported • The incidence in females was 950 case while in males was 290 with a female to male ratio of 3.3:1
6	US	**Dilokthornsakul, P. et.al. (2016)**	Commercially insured population of US during 2008-2012 was 9,611,353	-	• The prevalence of MS during 2008-2012 ranges from 145.7 - 150.2 • The prevalence of MS in 2012 was 149.2 (95% CI: 147.6–150.9) • The prevalence in females was 224.2/100,000 individuals (95% CI: 221.4–227.1) and in males was 71.6/100,000 individuals (95% CI 70.0–73.2) • The female to male prevalence ratio was estimated to be 3.13 (95% CI 3.10–3.16)

S.No.	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
7	Spain	**Iglesias, M.B. et.al. (2015)**	Population data published by Spain's National Statistics Institute as of 1 October 2011 was 322,955	Poser's or McDonald's criteria	• 107 incident cases were identified with an incidence rate of 3.5 (2.8'-4.2)/100,000 • 210 prevalent cases were identified with a prevalence rate of 65 (56-74)/100,000 • Number of deaths reported was 11
8	Europe (UK and Spain)	**Manouchehrinia, A. et. al. (2015)**	• Qualitative synthesis included 12 articles focusing on epidemiology • The total study population in the 12 articles was 27,928 • The study population in Lalmohamed et.al. (UK) paper was 1270 • The study population in Manouchehrinia et.al. (UK) paper was 923 • The study population in Zarranz et.al. (Spain) paper was 1,283	-	• Combined mortality in MS patients from the 12 studies was 6628, with pooled standardized mortality rate (SMR) of 3.06 and 2.56 in females and males respectively • Lalmohamed et.al. paper reported mortality in 69 MS patients with SMR of 3.94 and 2.96 in females and males respectively • Manouchehrinia et.al. paper reported mortality in 80 MS patients with SMR of 1.80 and 2.41 in females and males respectively • Zarranz et.al. paper reported mortality in 89 MS patients with SMR of 2.73 and 3.26 in females and males respectively
9	Spain	**Izquierdo, G. et. al. (2015)**	163,324 population data as per the official census of 2001	Poser's criteria	• The incidence rate was reported to be 4.6/100,000 • 156 prevalent cases were identified, with a prevalence rate 90.2/100,000 • The prevalence in females was found to be 111 cases with prevalence rate of 127.6/100,000 • The prevalence in males was found to be 45 cases with prevalence rate of 54.2/100,000
10		**Bargagli, A.M. (2016)**	The population of Lazio region was		• 7,377 prevalent MS cases were reported, with a crude prevalence of 130.5 per 100,000

S.No.	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
	Italy		5,500,022	-	• The prevalence in females was found to be 4950 MS cases with crude prevalence rate of 167.9/100,000 • The prevalence in males was found to be 2427 MS cases with crude prevalence rate of 89.7/100,000
11	Italy	**Bezzini, D. (2016)**	The Tuscany region population was 3,667,780		• Prevalent cases reported were 6,890, with a crude prevalence of 187.9/100,000 • The prevalence in females was found to be 4,738 with crude prevalence rate of 248.3/100,000 • The prevalence in males was found to be 2,152 MS cases with crude prevalence rate of 122.3/100,000
12	France	**Yaouanq, J. (2015) [51]**	Population of Brittany as per census 1999 was 2907,178	McDonald's criteria (2010) or Poser's criteria	• The incident MS cases with definite/probable MS were 249, with crude incidence rate of 4.28/100,000 • The incident cases of MS in females was estimated to be 186 and in males as 63, with a gender ratio of 2.95 • The estimated prevalence was 128-171/100,000
13	US	**Massa,J. (2013)[52]**	Nurses' Health Study (NHS) (1980to 2004): 92,275 Nurses' Health Study II (NHSII) (1991 to 2005): 95,051	Treating Neurologists	• The frequency of MS cases in NHS cohort was 93 and in NHS II cohort was 189

US: Among the three reviewed studies, one gives an estimate for the prevalence and the other emphases on the frequency and mortality among the MS patients. The prevalence estimates per 100,000 ranged from 145.7 -150.2 from 2008 to 2012**,** showing not much variation as the prevalence rate for the year 2012 was 149.2 per 100,000. The prevalence in females was 224.2 per 100,000 individuals (95% CI 221.4–227.1) and in males were 71.6 per 100,000 individuals (95% CI 70.0–73.2). The MS prevalence in females was 3.13 (95% CI 3.10–3.16) folds than in males [**48]**. In an MS cohort of 15,684 patients, from 2006 to 2011, the mortality rate was estimated at 10.8, with mortality rate ratio (MRR) of 2.9 (95%CI 2.7–3.2) for all-causemortality andwashighestamongindividualsaged18–29 years (MRR, 95%CI 8.8,3.7–21.0)**[45]**. The frequency of MS cases was reported in study comprising of registered female nurses as 93 and 189, during the period from 1980 to 2004 and 1991 to 2005 respectively. These cases were defined as definite or probable MS cases, out of the incident MS cases **[52]**.

UK: Jick, S.S. et.al., studied the epidemiology of MS across the UK.The incident MS cases present in the 2012 data update were 1713. Out of these 1260 (73.6%) MS cases were females and 453 (26.4) were males. Prevalent cases identified from 1993-2006 were 109. A total of 115 MS patients died during the follow up period accounting to about 24 (49.0%) cases of RRMS, 10 (20.4) cases of PPMS, 10 (20.4) cases of SPMS. Among the deceased MS patients, the mean age at death was 56.9 years while the mean age at first MS diagnosis in patients who died was 51.4 years. Mortality rate in females was 79(68.7%) and in males were36 (31.3%). The survival rate was 1598 from 1993 to 2012, with 631 (78.7%) cases of RRMS, 108 (13.5%) cases of PPMS, 49 (6.1%) cases of SPMS. The alive MS female cases were 1181 (73.9%) and males were 417 (26.1%)**[41]**. A systematic review of epidemiological studies examining comorbidities in people with MS, conducted for European countries, pointed out that in UK deaths occurred in 69 MS cases out of 1270 MS patients in the year from 2001 to 2008 and 80 deceased cases out of 923 MS patients from 1994 to 2012. Cause specific Standardized Mortality Rate (SMR) was studied to identify the impact of gender on MS mortality. Overall SMR from 2001 to 2008 was 3.51 (95% CI 2.63 to 4.69) and varied to 1.99 (95% CI 1.70 to 2.33) from 1994 to 2012 in UK in two different studies**[44]**.

France:A population-based register for patients presenting a putative incidentMS (PIMS), identified249 MS cases (incidence) with definite/probable MS. The cases identified in males and females were 186 and 63, with asex ratio of 2.95 and crude annual incidence of 4.28 per100,000 inhabitants (6.22 for women, 2.23 for men). Mean age at onset of MS in these patients was 33.9 ± 0.7 years. Incidence in different types of MS was reported as 34 (13.6%) cases of PPMS, 174 (69.9%) cases of RRMS and 41(16.5%) of CIS-MS. 11 MS cases were reported as deceased out of 235 patients after a follow up of 5 years**[51]**.

A large-scale multicenter study of mortality in MS in Francefrom 1940 to 2009 was conducted on 27,603 MS patients. The mortality rate was 1569 (5.7%) and death rate 3.7 (3.55–3.92) per 1000 patient-year. Deaths occurred in 884women and 685 men, gave a sex ratio of 1.3. The median agein deceased MS patients was estimated at 56 years and the median disease durationwas 20 years**[42]**.

Spain: Iglesias, M.B. et.al.,**[40]**analysed, the prevalence of MS in La Rioja (Spain), using various variables such as age and sex; type of progression, initial form of the disease, EDSS and number of relapses; disease-modifying treatment and reasons for treatment withdrawal; personal and family history of cancer; and incidence and mortality.The incident MS cases were 107 during the study period, that reaches out to 3.5cases/100,000 (95% CI 2.8-4.2) residents per year. Prevalent MS cases were 210, amounts to 65 patients/100,000 population (95% CI, 56-74). The prevalence rate in different clinical subtypes of MS were 142 (67.6%) in RRRMS, 40(19%) in SPMS, 19 (9%) in PPMS and 9 (4.3%) in PRMS. 11 MS cases were found to be deceased. Over a period of 20 years, from 1991 to 2011, in the Northern Seville District of Spain, incidence of MS was 4.6 (95% CI 4.1–5.1) per 100,000 per year. A significant increase of MS incidence was seen in women from 4.3 (95% CI 3.6–4.9) (1991–2000) to 8.8 (95% CI 7.84–9.69) (2001–2010), while in men, there was not much difference noted as the incidence ranged from 2.5 [95% CI 2.0–2.9] (1991–2000) to 2.8 [95% CI 2.3–3.4] (2001–2010). During this study period, confirmed diagnosis of MS was established in 156 patients. The MS prevalence was 90.2 (95% CI 75.6–104.8) per 100,000; 127.6 (95% CI 103.5–151.8) per 100,000 in women and 54.2 (95% CI 38.0–70.4) per 100,000 in men.

The number of MS cases varied in the different clinical subtypes of MS being 115 (73.7%) of RRMS, 17 (10.9) of PPMS and 24 (15.4) of SPMS**[43]**. In a systematic review conducted on European countries, reported 89 deaths in 1283 MS patients during 1987 to 2011. The CMR reported was 5.41 (95% CI 4.29 to 6.54) in 16,422 person years. The author studied cause specific SMR and reported overall SMR at 2.78 (95% CI 2.20 to 3.35), and it was more in males 3.26 (95% CI 2.27 to 4.24) than in females 2.73 (95% CI 1.94 to 3.51)**[44]**.

Italy: Italy is one of the most studied regions of the Europe. In a study conducted in the Mount Etna region to evaluate the possible association between Multiple Sclerosis and exposure to volcanogenic trace elements, estimated that prevalence in population of the eastern flank137.6/100,000 compared to the 94.3/100,000 in population of the western one. Out of 53 prevalent cases in the western flank, 13 (48.0/100,000 (95% CI 26.7–84.4)) were males and 40 {137.3/100,000 (95% CI 99.4–188.9)) were females. While, in the eastern flank community out of 65 prevalent MS cases, 20 MS cases(72.2/100,000 (95% CI 45.3–113.7)) were males and 45 MS cases (230.3/100,000 (95% CI 170.5–305.3)) were females. In addition, the incidence cases were high in Eastern flank to be 59 MS cases, 4.6/100,000 (95% CI 3.1–5.9), compared with the western population to be 51 MS cases, 3.2/100,000 (95% CI 2.4–4.2) with a relative risk of 1.41 (95% CI 0.97–2.05). Incidence risks increased over the time in both populations reaching a peak of 6.4/100,000 in the eastern flank and of 4.4/100.000 in the western flank during 2000–2009. The female to male incidence ratio was 2.5 **[46]**.

The prevalent MS cases identified in central Italy region were 7377 during 2006 to 2011, with peak prevalence at 35-44 years and 45-54 years in both males and females. Crude prevalence rate was 130.5/100,000 (95 % CI 127.5-133.5): 89.7/100,000 for males and 167.9/100,000 for females and overallstandardized prevalence rate was 119.6/100,000 (95 % CI 116.8-122.4). The study estimated significant differences in MS prevalence within the region, with estimates ranging from 96.3 (95 % CI 86.4-107.3) for Latina to 169.6 (95 % CI 147.6-194.9) for Rieti**[50]**. The MS prevalence in Tuscany (central Italy) was 6,890 cases (4,738

females and 2,152 males) with a prevalence rate of 187.9 per 100,000 in 2011. The prevalent cases were found in the age range of 16-64 years **[49]**.

China: In an attempt to the association of soil heavy metal factors and the MS incidence in Taiwan,1240 new MS cases were reported from the National Health Insurance Research Database and were verified with serious disabling disease certificates in 1997 to 2008. The age at diagnosis was 25 to 44 years, and female to male ratio of incident MS cases was 3.3**[47]**.

Chapter 5: Discussion

5. Discussion

The study gives a broad picture of epidemiological range of MS in the major geographies of the world including US, Europe (UK, Spain, France, Germany and Italy), China and Japan, from the articles/studies published from 2012 onwards. The studies included in the review have been critically appraised for the study quality using an objective measure and a predetermined set of criteria. The aim of the study was to comprehensively catalogue the geographic and demographic variations in the prevalence, incidence, and survival mortality in patients with MS, to identify the regions under represented. The data reveals that the US and Italy are the widely-studied regions, followed by France, Spain, UK and China.

Much of the literature has focused on specificregions or individual cities within a given country like in Italy the focus was on central region and similarly in France. The studies catering to US gives insights about the epidemiology data for MS from the administrative database, commercial insured population and in females from the cohort of registered nurses, while for most of the studies from European country case ascertainment was through the national statistics databases or MS registries.

MS affects more than 2.1 to 2.5 million persons worldwide **[5]**. The prevalence rate was highest for Italy followed by US and then other European countries and China. The incidence cases of MS in Spain estimated from 2001 to 2011 in a study was 3.5 per 100,000 while from 1991 to 2011, incidence per 100,000 ranged from 4.1 to 5.1. similarly, in Italy, the incidence rate rose from 3.6 to 4.2 per 100,000 in 2009. The peak age at diagnosis of MS was 25 to 44 years. The incidence of MS in females was higher than in males, and also a few geographies reported more cases in females than others within Europe. In Italy, within two regions of Mt. Etna the incidence of MS in females ranged from 4.7 to 6.7 per 100,000 while in Spain it was 4.3 to 8.8. Comparatively the incidence rate ws lesser in males ranging from 1.7 to 2.7 per 100,000 in Italy and 2.5 to 2.8 per 100,000 in Spain. It was observed that a very minor change in the incidence rate was seen in males in Spain from 1991 to 2011, while a huge increase was seen in females (4.3 to 8.8: almost double). Thus, the incidence estimates reveal that there

is an increase in the cases of MS across all the geographies and this is more in females. The prevalence also reflects a similar increase in rate. Highest prevalence was seen in Italy 187.9 per 100,000, followed by that in US 145.7 to 150.2 per 100,000 and the lowest in Spain 56 to 74 per 100,000. The mortality due to MS ranged from 2.8 in France to 3.8 per 1000 person-years in Wales. Also, the highest mortality rate was estimated in US 10.8 per 1000 person-years.The mortality and survival analysis reveals that SMR in UK in females was 2.96 and in males was 3.94, while in Spain it was more in females 3.26 than in maes 2.73 reflecting better prognosis, how so ever heterogeneity in the data was found.Though, the distribution pattern is not uniform, still it implicates the role of latitude and equator in the spread of MS. These studies also reported changes in the sex ratio of MS over time and in various regions. The female to male ratio increased to 3.13 in US reflecting an increasingincidence of the disease in women.

Case ascertainment varied greatly across the studies, showing an inconsistency in the available resources. A country like US, European nations where the entire health care is funded provides administrative health care databases, which are regularly updated and maintained.

This review has a few limitations. The data search was restricted to few specific geography like the US, Europe (UK, Spain, Germany, Italy, and France), China and Japan. In addition, the study included only the freely available articles published in English from 2012 onwards and limited time period available to conclude the study.Strengths of the study is the comprehensive evaluation of study quality, and the independent data abstraction by two reviewers.

The key findings from the study can be summarized as follows:

- There is an increase in the incidence and prevalence estimates of MS over a period of time
- There is a geographic trend seen in the distribution of MS, showing a high distribution in the northern hemisphere (such as in US, European countries) and low distribution in areas near to the equator (China Japan)
- Females were afflicted more than the males with MS

Chapter 6: Conclusion

6. Conclusion

The study reports the epidemiology data estimates of MS across different geographies. Based on the results it can be concluded the MS cases have increased over time across all the studied geographies. There is an increase in the incident MS cases in females. Future researchers can pay attention to the variation in MS in different ethnicities, in addition to widely studied geography wise distribution, as this can help in evaluation of the attributable risks ofpotential etiological factors for MS like the genetic factors.

Ethical Considerations

Institutional (IIHMR University, Jaipur) ethical committee and Life Science and Healthcare Department, Evalueserve SEZ clearance was obtained prior to the initiation of the study. This may not be factually correct information ICMR Ethics committee does not approve dissertation proposals. The study is an original piece of research work, performed as per the appropriate prevailing professional standards. Care was taken to ensure that there is no infringement of any copyrights or violation of any other rights of any third parties. If some text matter or data has been copied or adapted from other articles, the sources have been cited.

Ethical Approval

The approval from the Committee for Ethics and Review of Research, IIHMR University, Jaipur and Life Sciences and Healthcare Department, Evalueserve SEZ.

Dissemination of the Results

The results to be presented to the concerned panel at the IIHMR University, Jaipur, as a partial fulfillment of the requirements for qualifying for the degree of MBA in Hospital and Health Management.

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