Systematic Literature Review on Epidemiology of Multiple Sclerosis-A Global Prospect

By

Vrinda Mathur

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2015-2017

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

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that Ms. Vrinda Mathur of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone internship training at Evalueserve SEZ Pvt. Ltd, Gurgaon from 06 February, 2017 to 05 May, 2017.

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

The Internship is in fulfillment of the course requirements.

I wish him all success in all his future endeavors.

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Dean, Academics and Student Affairs
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To whomsoever it may concern

Dear Vrinda Mathur,

We wish to inform you that your release is effective close of working hours on 5 May, 2017.

We confirm that you have worked with Evalueserve from 6 February, 2017 to 5 May, 2017. At the time of relieving you were working as Intern in the Life Sciences and Healthcare department and have successfully completed your project on Epidemiology of Multiple Sclerosis.

During your Internship with us we found that your moral conduct was good.

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled**A Systematic Literature Review on Epidemiology of Multiple Sclerosis: A Global Prospect**and submitted by **Vrinda Mathur,** Enrollment No. **IIHMR – U/02/2015 – 17/0053** under the supervision of**Mr. Rahul Sharma, Assistant Professor, The IIHMR University, Jaipur** for award ofMBA **in Pharmaceutical Management** of the University carried out during the period from **February 6, 2017 to May 5, 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.

Vrinda

Signature

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 Literature Review on Epidemiology of Multiple Sclerosis - A Global Prospect**.

Signature

Abstract

Background: Multiple sclerosis (MS) is a chronic neurologic disorder that affects the central nervous system (CNS) which is characterized by an abnormal immune response. It involves damage to conduction of nerve signals down the axon, and is caused due to chronic inflammation and demyelination of neurons.MS typically begins in early adulthood, with the onset of disease at around 28 years of age. It is also said that women are two times more affected with MS than men. MS is a rare disease affecting more than 2.1 to 2.5 million persons worldwide . The prevalence estimates for MS varies worldwide. The prevalence of MS in the Arabic countries varies from 2 to 48 per 100,000 population. The prevalence increases with higher latitude and close to the equator, it is low. The Quality of life of patients with MS has declined because of the worsening symptoms like cognitive impairment, bladder dysfunction, bowel dysfunction, sleep problems, and sexual dysfunction.

Objective: The aim of this study is to conduct a systematic review of literature so as to determine the epidemiology of Multiple Sclerosis (MS) in all the countries of the world except US, Europe (UK, Spain, France, Germany and Italy), China and Japan. The study also aims to find the geographic and demographic factors in determining the distribution of MS.

Methodology: A comprehensive secondary literature search was performed on PubMed to identify information on the epidemiology of the disease, in the above mentioned geographies. The keywords used for conducting the search were “Epidemiology”, “Incidence”, “Preponderance”, “Prevalence”, “Occurrence”, “Distribution”, “Risk”, “Mortality”, “Survival”, “Frequency”, “Multiple Sclerosis”, “Disseminating Disease”, and mesh terms. Studies which are freely available on the Internet in English and which were published in 2012 and afterwards were included. Research papers or articles focusing on areas other than ones defined in scope and articles whose focus is not on epidemiology were excluded.

Results: The incidence rate of MS in Norway ranged from 5.2 to 10.1 per 100,000 inhabitants of Hordaland County to Nordland County of Norway whereas the prevalence rate ranged from 211.4 to 182.4 per 100,000 populations. In Sweden, there were 307 MS cases in the Gothenburg incidence cohort which was followed up till 2010 and the

prevalent cases during 1931 – 1985 were 28,027 cases out which 25,556 were born in Sweden. In Manitoba – The Province of Canada, the incidence rate of MS ranged from 12.01 to 12.08 per 100,000 populations. The peak incidence occurred in ages 35-44 years and is reported to be 3 times higher in females than males. The mortality also increased over a period of time to 10,370 deaths from 1975 – 2009. In Australia, the prevalence of MS in 100,000 populations is 95.7 and the number of prevalent cases in Tasmania on January 1, 2009 was 265 cases.

Conclusion: In conclusion, the epidemiological rates of MS are the highest in Norway, Sweden and Canada worldwide and females are reported to be affected with MS more than males. Also, the spread of MS is defined by the climate of the geography. Temperate climates are more prone to development of MS than tropical climates. White people of the Northern European descent are also more prone to MS than people belonging to Asian, African or Native American descent.

Acknowledgement

The satisfaction and euphoria that accompany the successful completion of the project would be incomplete without the mention of the people who made it possible. I would hereby like to express my profound sense of gratitude **to Ms. Sheetal Ranganathan, Vice President, Life Sciences and Healthcare**, for giving me the opportunity to carry out my dissertation at **Evalueserve SEZ Pvt. Ltd**. under her experienced and highly qualified team members.

I would also like to express my deep sense of gratitude to **Ms. Sugandh Sharma, Group Manager, Life Sciences and Healthcare – 03**. I am greatly indebted to her for providing her valuable guidance at all stages of the internship, her advice, constructive suggestions, positive and supportive attitude and continuous encouragement, without which it would have not been possible to complete the project.

I owe a debt of gratitude to **Dr. Nehul Saxena, Research Lead, Life Sciences and Healthcare – 03** for her continuous guidance and patience, motivation, and immense knowledge at all stages of the internship that paved way for better understanding of the fundamentals. I would also thank her for the never ending enthusiasm she gave in this project which lead me to walk a path full of optimism and success each day.

I am also thankful to **Mr.Chirag S Shah, Senior Business Analyst, Life Sciences and Healthcare – 03** for helping me settle down and to get aligned with the work environment and for also to find time for my project and impart knowledge necessary for its completion instead of his busy schedule and workload.

I duly acknowledge the help, direct or indirect of the whole department and members of the organization for providing all the facilities for training and completion of my project. The knowledge gained herein and the practical experiences learnt will be invaluable in the end.

I would also like to thank my project **guide Mr. Rahul Sharma, Assistant Professor, The IIHMR University, Jaipur**, for his help, cooperation and wholehearted encouragement. His assistance enabled me, to overcome many obstacles during my project study.

Last but not the least, I must express my sage sense of gratitude to my parents and brother and my colleague **Iha Srivastava** for providing me with unfailing support and continuous encouragement throughout. This accomplishment would not have been possible without them.

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Abbreviations

Abbreviation	Full Form
MS	Multiple Sclerosis
US	United States
UK	United Kingdom
CNS	Central Nervous System
EDSS	Expanded Disability Status Scale
MRI	Magnetic Resonance Imaging
CSF	Cerebro-spinal fluid
QOL	Quality of Life
RRMS	Relapsing-remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
CIS	Clinically Isolated Syndrome
APC	Antigen Presenting Cell
TCA's	Tricyclic Antidepressants
FDA	Food and Drug Administration
PICOS	Population, Intervention, Comparators, Outcomes, Study Design
SLR	Systematic Literature Review
CASP	Critical Appraisal Skills Programme
DET	Data Extraction Table

Chapter 1: Introduction and Scope of Dissertation

Multiple sclerosis (MS) is a chronic neurologic disorder that affects the central nervous system (CNS) which is characterized by an abnormal immune response. It involves damage to conduction of nerve signals down the axon, and is caused due to chronic inflammation and demyelination of neurons **[1].**

It is one of the most common disease of the (CNS) and it affects almost all ages in many part of the world. It is said to occur the most in young people and people living in the northern latitude **[2]**.

MS typically begins in early adulthood, with the onset of disease at around 28 years of age. It is also said that women are two times more affected with MS than men. The highest incidence of MS is found in Caucasians and the lowest is found in Japanese **[1]**.

In the year 1873 MS was recognized in England by Dr. Walter Moxon and in the year 1878 by Dr. Edward Seguin in the United States **[2]**.

For the first time in history MS was described in Augustus d'Esté's diary (1794- 1848) **[3]** and the first medical description 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]**. The prevalence estimates for MS varies worldwide. The prevalence of MS in the Arabic countries varies from 2 to 48 per 100,000 population **[6].** In India, MS is considered to be rare. It is more common in north, which was settled mostly by Indo-Europeans, than in south where Tamils and Dravidians settled **[7]**. Thus, the geographic variation of MS can be well recognized from above. Prevalence increases with higher latitude and close to the equator, it is low **[8]**.

MS is categorized into four subtypes: Relapsing-Remitting MS, Secondary – Progressive MS, Primary – Progressive MS and Primary- Relapsing MS.

MS is characterized by varied clinical presentation. The most common symptoms are numbness or tingling of the face, the body or extremities, weakness and vision problems, along with dizziness, spasticity, bladder dysfunction or constipation caused by bowel problems. Another characteristic symptom is difficulty in walking due to weakness,

spasticity, loss of balance or sensory deficit causing disability. Symptoms of cerebellar damage, such as ataxia or intention tremor, are also typical for MS.

The Expanded disability status scale (EDSS) measures the progression of the disease. This scare measures between 0 to 10. On a scale of 10, a rating of 0 will indicate a normal neurologic exam whereas a rate of 7.0 on the scale will indicate a patient who is not able to walk without aid and is mostly confined to a wheelchair. The rating of 7 is characterized by disability **[1].**

MS can be diagnosed by significant magnetic resonance imaging (MRI) results. The cerebro-spinal fluid (CSF) also typically shows an increase in IgG synthesis, oligoclonal banding and increase number of myelin basic proteins which can be used as a useful diagnostic test for MS **[1].**

According to Multiple Sclerosis International Federation, the impact on quality of life (QoL) of patients suffering from multiple sclerosis is negative. The disease substantially affects the physical functioning and social functioning of the patient. The QoL of patients with MS has declined because of the worsening symptoms like cognitive impairment, bladder dysfunction, bowel dysfunction, sleep problems, and sexual dysfunction.

The economic burden of the disease is significant. It is described by the direct and the indirect costs involved in the treatment of the disease. The direct costs involves all costs of the treatment spent at the health care system, which includes inpatient hospital care, nursing homes, rehabilitation hospitals, outpatient hospital services, physician services, prescription drugs, diagnostic testing, and medical supplies as well. The total direct costs accounts for about 26% to 87% of the total costs involved and it ranges from 5,600 US International dollars in Canada to 37,000 US international dollars in Sweden. The prevalence-weighted average is 24,000 US international dollars **[9].** The indirect costs accounts for 13% to 74% of the total MS costs **[9]**.

MS is a progressive disease with unknown etiology, no definitive treatment available, however symptomatic treatment is given to alleviate the symptoms. Disease modifying agents are used in the symptomatic treatment of the disease.

There are no comprehensive studies present that give worldwide estimates for the epidemiology of multiple sclerosis. The aim of this study is to conduct a systematic review of literature so as to determine the epidemiology of MS in all the countries of the world except US, Europe (UK, Spain, France, Germany and Italy), China and Japan. This will give an opportunity to the future researchers to understand the market for the disease around the world.

Chapter 2: Review of Literature

2.1 Disease definition

According to a study by Mark H. et al (2009), MS is a chronic neurological auto-immune condition of the CNS that affects the neuronal activity of the brain and spinal cord. It is characterized by the damage of nerve impulse transmission down the axon, and is caused due to chronic inflammation and demyelination of neurons. The demyelination of neurons is characterized by unusual lesions which damages the protective coat (myelin) of nerve fibers which further inhibits the transmission of electrical impulses within the brain and to the spinal cord **[1]**. Gregory F. et al, (2011) suggested that plaques or lesions caused due to inflammatory demyelination within the CNS are the major pathological indication for MS **[10].** These lesions or plaques have been traditionally classified based on the temporal progression of the disease or on the inflammatory destruction. Accordingly the plaques or lesions are classified into acute, chronic active and chronic silent lesions and are thought to occur continuously during the disease progression **[10].**

MS is associated with various clinical signs and symptoms which are increased weakness, imbalance or difficulty in coordination, spasticity, fatigue, bladder or bowel difficulties, vision loss, altered sensory perception, cognitive impairment, and neuropathic pain **[1].**

2.2 Clinical Subtypes

MS is sub-divided into 4 clinical sub-types **[11] (Table 1).**

Table 1 : Types of MS

S.No	Type	Disease Course
1.	Relapsing-Remitting Multiple Sclerosis (RRMS)	• It is the most common type of disease course of MS and accounts for 85% cases. • It is characterized by discrete attacks called as relapses that continue over a period of days and are then followed by partial recovery or complete recovery periods (called remissions). The neurological functions does not worsens during the period between relapses and remissions.
2.	Secondary Progressive Multiple Sclerosis (SPMS)	• It is characterized by progression of initial relapses, followed by gradual deterioration of neurological functioning but it is not associated with acute attacks.
3.	Primary Progressive Multiple Sclerosis (PPMS)	• PPMS involves continuous and steady worsening of the neurological functioning of the brain and spinal cord after the onset of the disease. It has no episodes of relapses and remissions ever.
4	Progressive Relapsing Multiple Sclerosis (PRMS)	• It is characterized by steady worsening of the neurological functioning of the brain and spinal cord after the onset of disease and this worsened functioning is also superimposed with frequent episodes of acute attacks.
5.	Clinically Isolated Syndrome (CIS)	• It is characterized by an initial episode of neurological symptoms of MS that lasts at least for 24 hours and is caused by demyelination and inflammation of neurons.
6.	Benign MS	• It is a form of condition in which a person develops MS for several years but does not develop disability.

2.3 Etiology

The cause of MS is still unknown. According to study by Mark J. et al, (2013) MS occurs due to complex interactions between genetic and environmental factors. This interaction leads to abnormal immune response which results in damage to the myelin sheath, axons, neurons and also oligodendrocytes. The environmental risk factors for MS include exposure to infectious agents as well as sunlight exposure or vitamin D deficiency before age of 15 years **[11].** Many recent studies mention an infectious etiology in children and adolescents with MS. Human herpes virus type 6 (HHV-6), Epstein Barr virus (EBV), and *mycoplasma pneumoniae* are possibly involved in triggering MS. According to the study the pathogens may have peptides with direct sequence homologies with the components of myelin sheath. The genetic factor which influences MS susceptibility the most is the HLA-DRB1*1501 haplotype. It increases the risk of developing MS by 2 to 4 fold and is present in 20% to 30% of the healthy people **[12].**

2.4 Pathophysiology

The pathological activity of MS can be divided into two phases:

The early phase is characterized by inflammation of the central nervous system, which is caused by the infiltration of activated T cells, B cells and macrophages. These activated T cells, macrophages and the antibodies secreted by the B cells (differentiated into plasma cells) further attack selected neurons leading to demyelination. Th1 and Th17 cells (that secrete interleukin-17 and recognize Th1) enters the CNS while the infiltration takes place.

Following the early phase, the transition into the later phase with gradual progression of the disease is characterized by widespread axonal loss and neurodegeneration. The disease course varies between different patients the signs and symptoms depend on the affected area of the central nervous system **[13].**

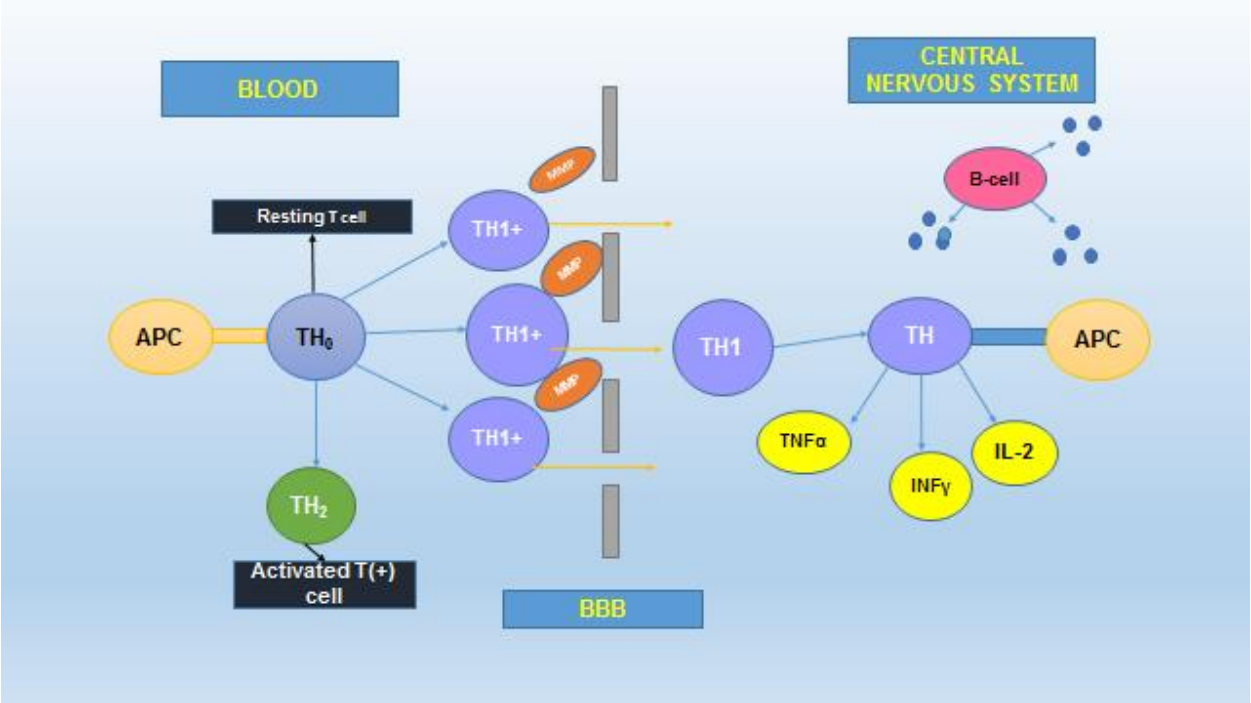

Figure 1: Pathology of MS

Undifferentiated T – cells (TH_o) within the blood periphery are activated by antigen presenting cells (APC's). These activated T cells then undergo proliferation producing increased number of pro-inflammatory T – helper type 1 (TH_1) cells. The activated T- cells then penetrate into the blood – brain barrier with the help of Matrix metalloprotease (MMP). Once in the central nervous system after penetrating through the Blood brain barrier (BBB), the T- cells are again reactivated by APC's causing secretion of pro-inflammatory cytokines which induces central nervous system inflammation by activation of macrophages, other T cells and B cells. The macrophages and T cell then attacks the myelin sheath via cytotoxic mediators that comprise of tumor necrosis factor (TNF)–α, oxygen radicals, and nitric oxide. Also the B-cells secrete demyelinating antibodies after differentiation into plasma cells **[13].**

2.5 Clinical Presentation

According to the National Multiple sclerosis Society the disease is characterized by a first attack of symptoms or a neurological episode called as CIS. The initial symptoms may be mild and not all symptoms affects all patients. The second attack of these symptoms would

be then characterized as RRMS [**14**]. The early signs .and symptoms of MS are described in **Table 2 [15]:**

Table 2: Early signs and symptoms of MS

S.NO	SYMPTOMS	DETAILS
1.	Fatigue	Fatigue is the most common and debilitating symptom of MS and also causes significant disability in patients and the disease progresses.
2.	Numbness and Tingling sensations.	Numbness of face, arms, body and other extremities like arms and legs or loss of sensation may occur.
3.	Spasticity	Muscle spasms and stiffness particularly in the legs is an initial symptom in nearly all MS patients
4.	Weakness	Weakness in MS can result due to demyelination of nerves that stimulates the muscles.
5.	Vision Problems	Patients may initially experience 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.
6.	Dizziness and Vertigo	Patients may have difficulty in walking and keeping their balance and have sensations of spinning surroundings (vertigo).
7.	Bowel and bladder problems	Constipation and urinary retention as well as bowel and bladder incontinence is usually seen as early symptoms in patients with MS.
8.	Pain	Most patients with MS have pain syndromes which includes facial pains, powerful spasms and cramps and also stiffened joints.
9.	Sexual Dysfunction	It involves erectile dysfunction in men and problems in vaginal lubrication in women.
10.	Cognitive Changes	Cognitive problems such as problems in concentrating, reasoning and problem solving and also in the memory.
11.	Depression	The most common symptom is depression, which could be because of emotional changes due to MS or due to stress which is resulted from disability.

The other less common symptoms are described in **Table 3**.

Table 3: Less common symptoms

S.NO	SYMPTOMS	DETAILS
1.	Speech and Swallowing Problems	Many patients have trouble in chewing or swallowing food and also some patients have slurred speech and loss of volume.
2.	Tremors	Tremors can occur in various parts of the body due to damaged areas along the nerve pathways which are responsible for the coordination of movements.
3.	Seizures	Seizures which are abnormal electrical discharges in an injured or a scarred area of the brain are usually reported in 2- 5% of patients with MS.
4.	Pruritus	Pruritus (itching) is an abnormal sensation comprising of sensations of pins and needles.

2.6 Diagnosis

MRI is the significant test to detect lesions or plaques and the changing neurological functioning of the central nervous system. Neurologists use serial MRI's to diagnose and to monitor the worsening of the symptoms **[1].**

Gadolinium enhancement is used to detect BBB penetration and lesions which are characterized by active inflammation. The dark zones also called as **black holes** may appear within the plaques or lesions after axonal loss. A spinal tap is used to evaluate CSF and diagnose the diseases and this diagnostic test can confirm MS and its prognosis. The CSF from an MS patient-typically shows an increase in IgG synthesis, oligoclonal banding and increase number of myelin basic proteins.

The EDSS measures the progression of the disease. This scare measures between 0 to 10. On a scale of 10, a rating of 0 will indicate a normal neurologic exam whereas a rate of 7.0 on the scale will indicate a patient who is not able to walk without aid and is mostly confined to a wheelchair. The rating of 7 is characterized by disability **[1].**

2.7 Treatment

According to a study by Mark H. et al, (2009) there is currently no cure for MS, but the treatment is limited to management of symptoms, treating exacerbations and also improving the neurological function by a short course of corticosteroids and disease modifying agents. The treatment options for the management of symptoms exhibited by some of the patients are mentioned in the **Table 4.** Given below **[1]**:

Table 4: Symptomatic Treatment of MS

S.NO	SYMPTOM	TREATMENT
1.	Balance and coordination	Meclizine , prochlorperazine, promethazine
2.	Spasticity	Baclofen, botulinium toxin, clonazepam, clonidine, dantrolene, tigabline, tizanidine
3.	Fatigue	Amantadine, Modafinil, fluoxetine, sertraline
4.	Bladder Problems	Desmopressin, oxybutynin, propantheline, tolterodine, amitriptyline, nortriptyline
5.	Bowel Problems	Dicyclomine, laxatives
6.	Pain	Spasticity: Baclofen, botulinium toxin, clonazepam, clonidine, dantrolene, tigabline, tizanidine Neuropathic: carbamazepine, gabapentin, TCA's (tricyclic antidepressants) Acute: Acetaminophen, ibuprofen
7.	Depression	Antidepressants (Duloxetine, selective – serotonin reuptake inhibitors
8.	Sensory	Gabapentin, duloxetine, pregablin, TCA's

According to a study by Ingrid L. et al, (2011) there are 136 ongoing clinical trials which are testing different treatment options for MS which is mentioned on the National MS society webpage. There are currently 8 FDA approved disease modifying agents for relapsing forms of MS. The FDA approved agents includes four drugs of interferon – beta *(*Avonex, Rebif, Betaseron and Extavia*)*,glatiramer acetate (Copaxone), mitoxantrone (Novantrone) and natalizumab (Tysabri). There are many other agents which are immunologically active and are used off label which are nearing study completion and FDA application. The disease modifying agents used for different types of MS are mentioned below in **Table 5 [10]**:

Table 5: Treatment Overview of MS

S.NO	TYPE	TREATMENTS
1.	Non – symptomatic treatment	Interferon beta -1a and 1b, glatiramer acetate, intravenous immunoglobulin
2.	RRMS and SPMS	Interferon beta-1a and 1b, glatiramer acetate, natalizumab, intravenous immunoglobulin, pulse methylprednisolone (for acute relapses For poor responses : mitoxantrone, cyclosphosphamide, mycophenolate, azathioprine, methotrexate, methylprednisolone, intravenous immunoglobulin, cyclosporine
3.	PPMS and PRMS	No specific treatment has been shown to be effective. Ineffective agents: interferon beta, mitoxantrone, rituximab

.

Chapter 3: Methodology

3.1 Key research question

The purpose of this study is to explore the epidemiology of MS world-wide except US, Europe (Italy, Spain, Germany, France, and UK), China and Japan.

3.2 Objective

The aim of this study is to conduct a systematic review of literature so as to determine the epidemiology of Multiple Sclerosis (MS) in all the countries of the world except US, Europe (UK, Spain, France, Germany and Italy), China and Japan. The study also aims to find the geographic and demographic factors in determining the distribution of MS

3.3 Research Design

A systematic literature review was conducted for the articles or studies (systematic reviews/ observational studies/ registries) describing the epidemiology of MS.

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

Table 6: Population, Interventions, Comparators, Outcomes, Study Design for SLR

PICOS for SLR	
Population	**Individuals suffering from MS or various clinical sub-types of MS**
Interventions	**N/A**
Comparators	**N/A**
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 and onwards till April 2017**

3.4 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 MS to be searched using PubMed, MeSH terms.
- Preparation of a search strategy [Figure 2] using appropriate search operators (Boolean operators, proximity operators and wild card truncations) compatible with pubmed.

Figure 2: Search Strategy

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 MS

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

- The articles or studies available in English language
- Full text articles which are available free of cost on the internet
- Studies published in and after the year 2012

- Articles focusing on epidemiology of world-wide except 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 shortlisting 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 Article based Review

This step involves the review of full text articles available free of cost on the internet and includes the following steps:

- 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) for observational studies and Downs and Black for other observational studies..
- 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 – 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 MS. 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

In performing this study, the below mentioned PRISMA (Preferred Reporting Items for systematic reviews and Meta analyses) **[Figure 3]** protocol was followed.

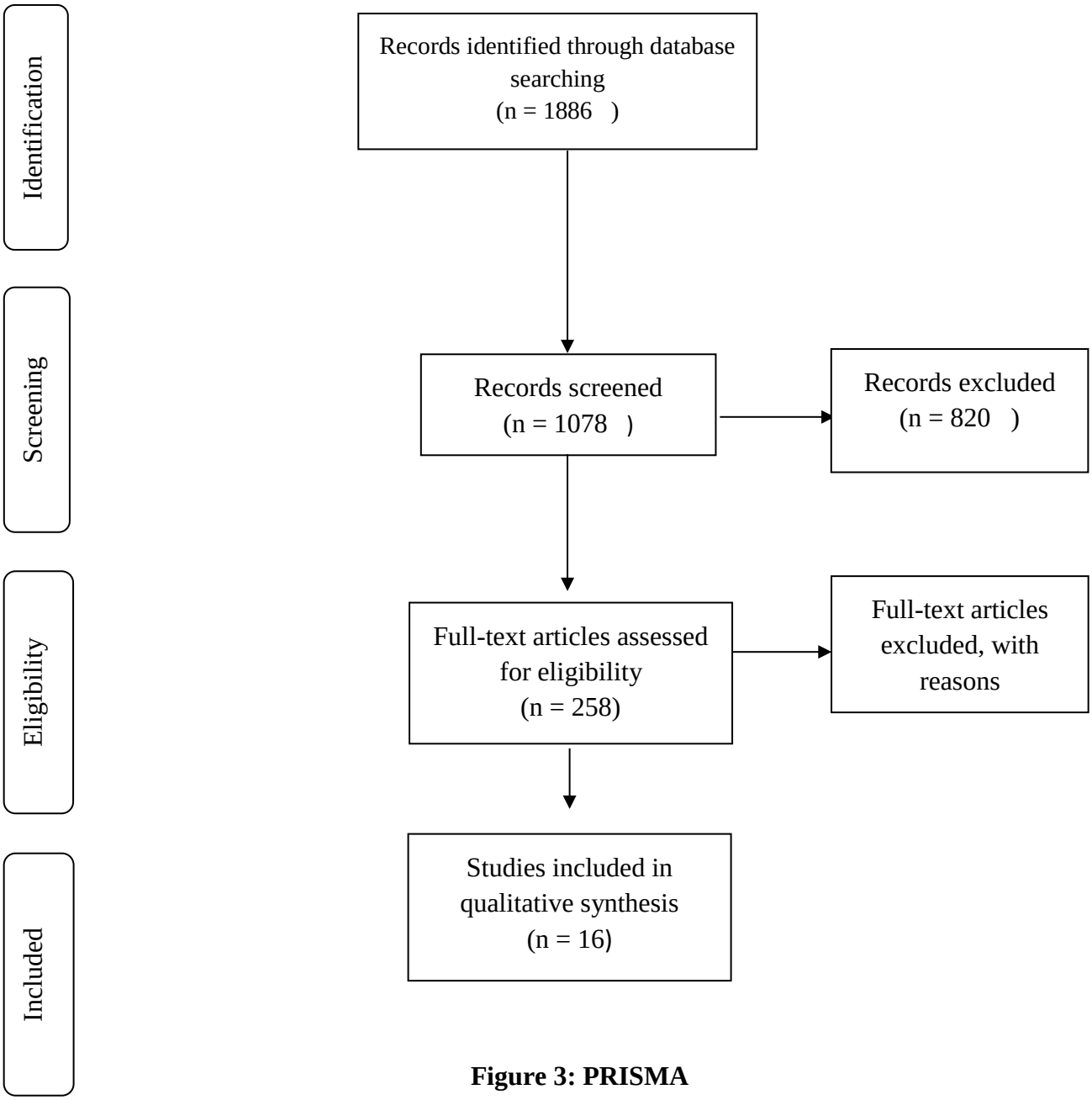

Figure 3: PRISMA

The SLR included relevant articles which were found from the following geographies after applying the inclusion and exclusion criteria. The **Figure. 4** show the number of studies in the respective geographies.

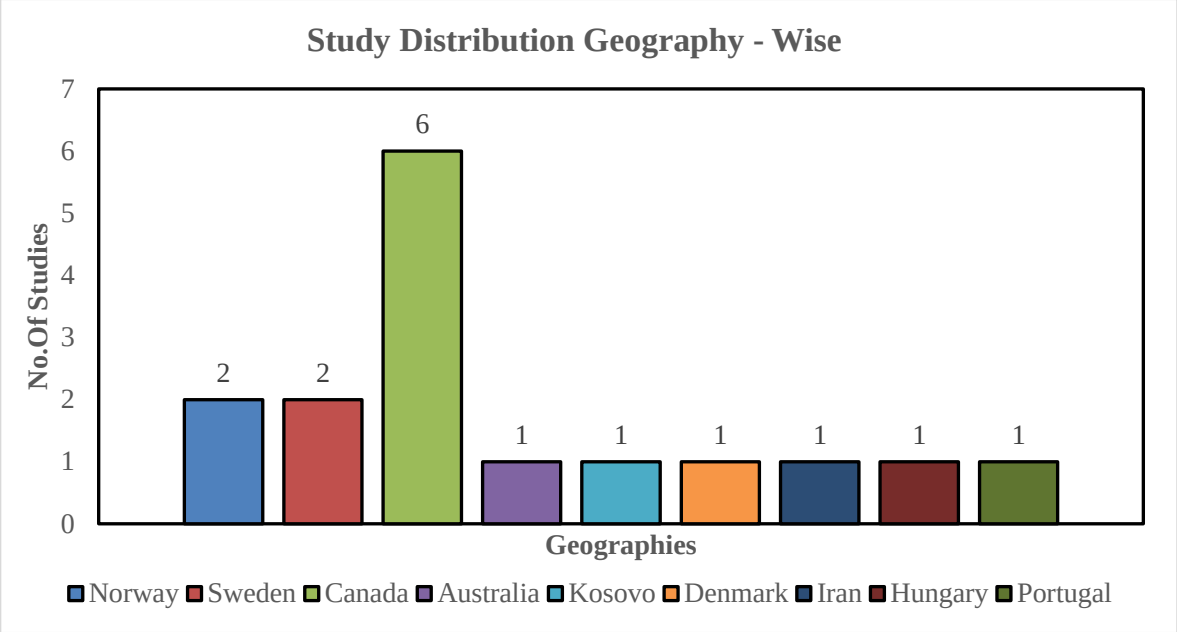

Figure 4: Study Distribution Geography –Wise

Figure 5: Number of Studies Country Wise

The quality of the studies which were reviewed were assessed using quality assessment tools depending upon the research design of the study. Two independent reviewers used critical appraisal tools to assess the study quality of each result. The quality scores were categorized as low, medium and high. (**Table 7**)

Table 7: Critical Appraisal

Quality Checklist	**Study Design**	**Score**	**Quality**
Amstar [16]	Systematic Literature Review	• 1-4 • 5-7 • 8-11	• Low • Medium • High
CASP[17]	Observational Studies (Case Control and Cohort Studies)	• 1-4 • 5-7 • 8-11	• Low • Medium • High
Downs and Black [18]	Observational Studies(Data from Registries , Administrative health data)	• 1-8 • 9-16 • 17-27	• Low • Medium • High

The quality was assessed using the above mentioned checklist. The sixteen studies included in the systematic literature review were assessed and the following quality was reported using the critical appraisal tools in **Table 8**

Table 8: Critical Appraisal Results

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
1	**Grytten, N. (2015)**	A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway	Norway	Follow-up for incidence : 60 year (1953 - 2013)	-	Downs and black	Medium
2	**Skoog, B. (2012)**	A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy	Sweden	MS Cohort with disease onset during: 1950-1964 Follow-up till: 2010	Longitudinal study	CASP	High
3	**Torabi, M. (2014)**	Application of three focused cluster detection methods to study geographic variation in the incidence of multiple sclerosis in Manitoba, Canada	Canada	1990-2006	-	Downs and black	Medium
4	**Taylor, B.V. (2013)**	Assessing possible selection bias in a national voluntary MS longitudinal study in Australia	Australia	Census date: 7 March 2006	Longitudinal study	CASP	Medium
5	**Marrie, R.A. (2015)**	Effect of comorbidity on mortality in multiple sclerosis	Canada	April 1, 1984-March 31, 2012	Case Control Study	CASP	Good

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
6	**Zeqiraj, K. (2014)**	Epidemiological characteristics and functional disability of multiple sclerosis patients in Kosovo	Kosovo, Europe	2003-2012	Prospective – Retrospective Study	CASP	Low
7	**Etemadifar, M. (2013)**	Epidemiology of multiple sclerosis in Iran: a systematic review	Iran	2006-2013	Population-based Study	Downs and black	Medium
8	**Green, C. (2013)**	Exploring the implications of small-area variation in the incidence of multiple sclerosis	Canada	1990-2006	Population-based Study	CASP	High
9	**Poulsen, A.H. (2012)**	Mobile phones and multiple sclerosis-a nationwide cohort study in Denmark	Denmark	1987-2004	Review	AMSTAR	-
10	**Scalfari, A. (2013)**	Mortality in patients with multiple sclerosis	-	-	Retrospective cross-sectional epidemiological study	CASP	High
11	**Benjaminsen, E. (2014)**	Multiple sclerosis in the far north--incidence and prevalence in Nordland County, Norway, 1970-2010	Norway	1970-2010	Registry and PAR	Downs and black	High
12	**Warren, S.A. (2016)**	Multiple Sclerosis Mortality Rates in Canada, 1975-2009	Canada	1975-2009	Cross-sectional study	CASP	High
13	**Westerlind, H. (2014)**	New data identify an increasing sex ratio of multiple sclerosis in Sweden	Sweden	-	Registry	CASP	
14	**Zsiros, V. (2014)**	Prevalence of multiple sclerosis in Csongrad County, Hungary	Hungary	1999-2013	Cross-Sectional Study	CASP	Medium

S. No.	Key Author	Study Title	Geography	Study period	Study Design	Checklist	Quality
15	**Kingwell, E. (2012)**	Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada	Canada	August 1, 1980-December 31, 2004	Registry	CASP	-
16	**de Sá, J. (2012)**	Capture-recapture as a potentially useful procedure for assessing prevalence of multiple sclerosis: methodologic exercise using Portuguese data	Portugal , European Union	Data collection period - September 2009 to December 2010 Prevalence Date - 31st December 2009	Population based Study	CASP	High

The following graph **(Figure 5)** shows the combined results of the quality of the sixteen studies included in the review:

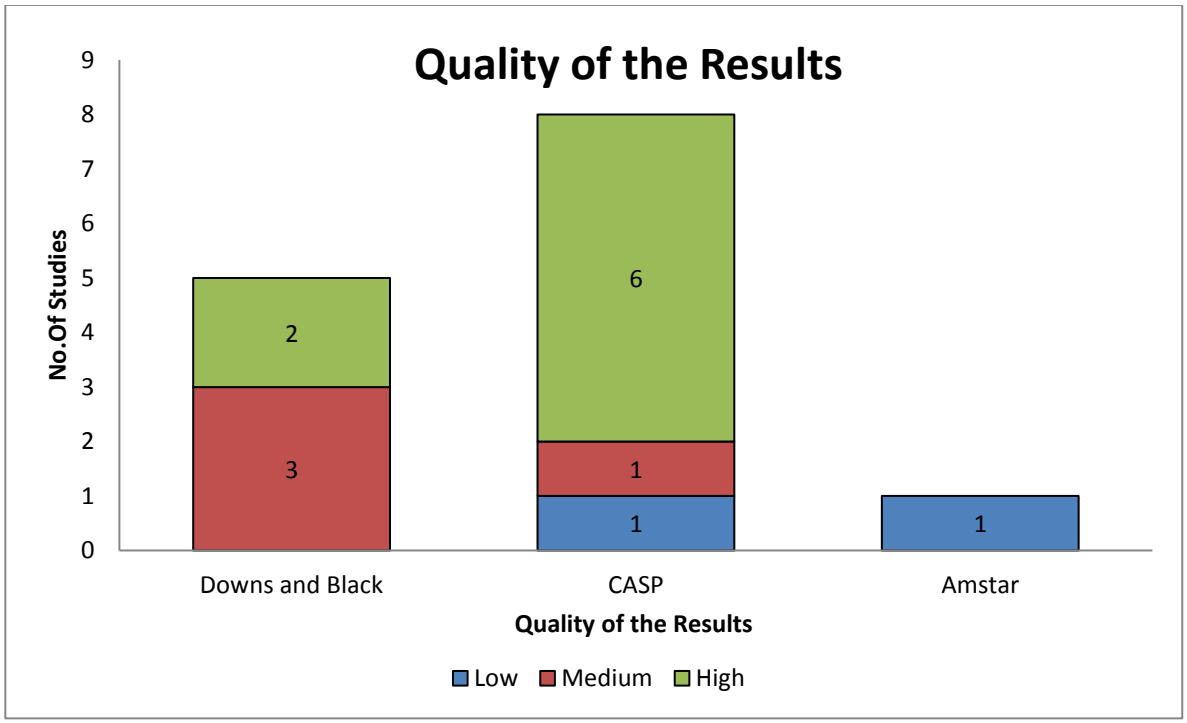

Figure 6: Quality of Results

The epidemiology of MS is presented in the following segment geography – wise:

- **Norway**: The review included 2 studies of Norway discussing about the epidemiology of MS. The incidence and prevalence rate of MS differs in the counties of Norway. The incidence rate in Hordaland County per 100,000 inhabitants was reported to be 5.2 during 2007 – 2013 whereas in Nordland County it was reported to be 10 .1 during 2005 – 2009 The prevalence rate also differed in both the counties i.e. in Hordaland County the crude prevalence was 211.4 per 100,000 inhabitants on January 1, 2013 and in Nordland county it was given to be 182.4 per 100,000 inhabitants on January 1, 2010. The prevalence of MS was also reported to be higher in females than males by both the studies in the two counties mentioned above. The prevalence rate in females per 100,000 inhabitants of Hordaland County was reported to be 270.9 and in males it was given to be 151.8 per 100,000 inhabitants. Similar results were obtained by the study carried out in

Nordland County which states the prevalence of MS to be higher in females i.e. 249.7 than 115.6 per 100,000 inhabitants in males **[19] [20]** . The mortality was also recorded by one study which was carried out in Hordaland County. On January 1, 2013 there were 393 patients who had died with the underlying cause of MS **[19]**.

- **Sweden:** The systematic review included two studies of Sweden discussing about the prevalence and incidence of MS. Skoog, B. et al (2012) reported the incident cases in the Gothenburg city of Sweden. There were 307 MS cases in the Gothenburg incidence cohort which was followed up till 2010. Out of the 307 MS cases, 202 cases were classified as having RRMS and 44 cases as PPMS, 44 under CIS, 8 under possible progressive MS and 9 cases were unidentified. Also, out of the 202 cases classified under RRMS, there were 9 deaths reported till 2010 **[21]**. Westerlind, H. et al (2014) studied the epidemiology of MS on the population taken from the Total Population Register of Sweden and reported the prevalent cases during 1931 – 1985 i.e. 28,027 cases out which 25,556 were born in Sweden. The prevalence and incidence of MS is reported to be higher in females than males i.e. the women MS patients to men MS patients ratio increased from 1931 to 1985 i.e. it is increased from 1.70 to 2.67 **[22]**.

- **Canada**: The incidence, prevalence and mortality of MS was included from six studies from Canada in the review. The average incidence rate of MS per 100,000 population during 1990 – 2006 was reported to be 12.08 **[23]**. Also, Warren, S.A. et al (2016) included the population data from Socio-economic Information Management System (CANSIM) data and the statistics of Canada from 1975-2009 and reported that there were 10,370 deaths due to MS during the mentioned time period. The mortality was also reported to be higher in females than males i.e. 6450 female deaths were recorded as compared to 3920 male deaths **[24]**. Scalfari, A. et al (2013) reported the mortality of MS in the Canadian population in one of its study of his systematic literature review that 1025 deaths were observed from August 1, 1980 to December 31, 2004. The author also reported that the mortality was higher in females than in males i.e. 635 female deaths were recorded as

compared to 390 male deaths **[25] [26]**. The average incidence of the Manitoba – Province of Canada is reported to be 12.1 per 100,000 population and there were 2290 incident MS cases recorded from 1990-2006. Also, the author reported that the peak incidence occurred between ages 35-44 years with 3 times higher in women than men across all ages **[27]**. Marrie, R.A. et al (2015) reported that 433 patients had died with the underlying cause of death as MS during April 1, 1984 to March 31, 2012 and the age specific mortality rates ranged from 1.68 to 149.3 per 1,000 persons in MS population. Also, the median survival time for the population studied was 75.9 years from the birth of the patient **[28].**

- **Iran**: The review included one study which is a systematic literature review by Etemadifar, M. et al (2013) and the estimates of prevalence of MS ranged from 7.69 to 74.28 per 100,000 population. This study also reported the estimates of incidence of MS that ranged from 2.2 to 6.6 per 100,000 population in 2005. The crude prevalence in females was reported to 33.2 per million in 2007.The prevalence estimates were reported to be higher in females than males per 100,000 population i.e. in females it was 113.49 than in males i.e.37.41 **[29].**

- **Australia**: The review included one study which discusses about the prevalence of MS in Australia and Tasmania – A Commonwealth state of Australia. Taylor, B.V. et al (2013) reported that the prevalence of MS in 100,000 populations is 95.7 and the number of prevalent cases in Tasmania on January 1, 2009 was 265 cases **[30].**

- **Denmark**: The review included one study which discusses about the incidence and mortality among MS patients. Paulsen, A.H. et al (2012) reported that there were 406 incident cases in 4,0,63,040 persons – year during 1987 – 2004. Also, the author reported that there were 61 deaths among 4,934 persons – year **[31].**

- **Kosovo, Europe**: The review included one study which focuses on the epidemiology of MS in Kosovo. The incidence rate per 100,000 inhabitants was reported to be 0.95 whereas the prevalence rate per 100,000 inhabitants was

reported to be 19.6 and the mortality rate per 100,000 inhabitants was reported to be 0.14 **[32].**

- **Hungary, Europe**: Zsiros, V. et al (2014) discusses about the epidemiology of MS in the population of Csongrad County. There were 259 newly diagnosed incident cases of MS during 1999 – 2003. The crude prevalence of MS on January 1, 2013 was reported by the author to be 89.8 per 100,000 population. The female prevalence i.e. 128.6 per 100,000 persons was reported to be higher than males i.e. 46.6 per 100,000 people. There were 86 deaths observed due to MS during 1999 – 2013 **[33].**

- **Portugal**: The review included one study of Portugal, European Union which discusses about the prevalence of MS in the population of Lisbon's Northern health area i.e. Odivelas, Benefica, and Pontinha. De Sá, J. et al (2012) reported that the observed prevalence on December 31, 2009 was 41.4 per 100,000 population. Also, the prevalence per 100,000 population in Odivelas is 38.9 and in Benefica is 44.8 and in Pontinha is 45.4. The ascertainment age – adjusted crude prevalence was reported to be 58 per 100,000 populations **[34]**.

The key findings from the studies are given below in **Table 9: Key Findings**

Table 9: Key Findings

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
1.	Norway **[19]**	Grytten, N. et al (2015)	The population of Norway living in Hordaland County was N = 490,570 and were followed for 60 years (from 1953-2015)	a) Onset from 1953 : Poser's Criteria b) Onset from 2003 : McDonald's Criteria	• Incidence rate of MS per 100,000 inhabitants: 5.2 during 2007-2013 • The prevalence rate of patients living in Hordaland County on 1 January 2013 per 100,000 inhabitants : 211.4 • The prevalence rate of MS was reported to be higher in females per 100,000 inhabitants i.e. 270.9 than in males i.e. 151.8. • The number of patients who died on 1 January 2013 due to MS: 393 cases.
2.	Sweden **[21]**	Skoog, B. et al (2012)	The Population of Gothenburg, N = 4,00,000 who were	Poser's diagnostic Criteria	• 307 incident cases of MS in the Gothenburg incident cohort followed up till 2010.

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
			the residents of Gothenburg during 1950-1964		• N = 9 deaths were observed till 2010 with the underlying cause of death as RRMS.
3.	Sweden **[22]**	Westerlind, H. et al (2014)	The population of Sweden from the Total Population Register, N = 15,000,000 from 1931–1985	-	• 28,027 MS patients were prevalent and were identified through the registry out of which 25,556 were born in Sweden. • The women MS patients to men MS patients ratio increased from 1931 to 1985 i.e. it is increased from 1.70 to 2.67.
4.	Canada **[23]**	Torabi, M. et al (2014)	The population of Manitoba, N = 1130000 – 1180000 during 1990 and 2006	-	• Average incidence rate of MS per 100,000 populations: 12.08.
5.	Canada **[28]**	Marrie, R.A. et al (2015)	Manitobans with MS from April 1, 1984 (beginning of fiscal year 1984) to March 31, 2012 (end of fiscal year	The validations for MS were : Individuals with greater than or equal to 3 hospital,	• From April 1, 1984 to March 31, 2012, N = 1257 patients died out of which N = 433 had died with MS as Cause of Death (COD) on their death certificates. • The Age specific mortality rates ranged

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
			2011), N = 5,797	physician, or prescription claims for MS	from 1.68 to 149.3 per 1,000 persons in MS population • The median survival time from the birth was 75.9 years.
6.	Canada **[27]**	Green, C. et al (2013)	The population of City of Manitoba, N = 12, 00,000 and the population denominator data from 1990-2006 and was obtained from provincial population register.	A validated case definition by : a) Physician b) Hospital c) Prescription claims	• 2290 incident MS cases from 1990-2006 with average incidence rate per 100,000 persons : 12.1 • The peak incidence occurred between 35-44 years with 3 times higher in women than men across all ages.
7.	Australia **[30]**	Taylor, B.V. et al (2013)	The population of Australia , N = 2,30,00,000	McDonald's Criteria	• There were 22000 prevalence MS cases with a rate per 100,000 persons: 95.7 • There were 2917 prevalent MS cases in New Zealand on the census date of 7th March 2006 with the crude prevalence rate per 100,000 population : 72.4 • The prevalence in the population analyzed in the Tasmanian MS

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
					Prevalence & Genetics Study (TMSPGS) on census day 1 January 2009 : 265 patients
8.	Kosovo, Europe **[32]**	Zeqiraj, K. et al (2014)	The population included , N = 412 MS patients at Clinic of Neurology in Prishtina, Kosovo from 2003-2012	McDonald's Criteria	• The incidence rate of MS: 0.95 per 100,000 inhabitants. • The prevalence rate: 19.6 per 100,000 inhabitants. • The mortality rate : 0.14 per 100,000 inhabitants
9.	Denmark **[31]**	Poulsen, A.H. et al (2012)	The subscription holders accrued 4,0,63,040 years of follow up maximum 18.0 years are, N = 405,971	Poser's Criteria	• 406 incident cases in 4,0,63,040 persons year • Deaths in subscription holder with Multiple Sclerosis in 4934 persons year, n = 61 deaths
10.	Norway **[20]**	Benjaminsen, E. et al (2014)	Population at risk on January 1, 2010 in Nordland county, N = 236271	• Poser Criteria (1983) • McDonald Criteria (2001)	• 497 incident cases in 1970–2009 • Yearly average incidence per 100,000 : 10.1 in the period 2005-2009 • On 1 January, 2010 there are 431

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
					prevalent cases. • The crude prevalence rate per 100,000 persons : 182.4 • Crude prevalence among women per 100,000 persons i.e. 249.7 was higher than men i.e. 115.6 per 100,000 persons.
11.	Iran **[29]**	Etemadifar, M. et al (2013)	• MS cases from 3 articles (relevant from 2012 onwards) focusing on epidemiology were studied. • The study population in Moghtaderi et al (2012), N = 1,3,46,367 from 1996 – 2006. • The study population in	• All three studies used McDonald's Criteria for case assessment.	• Prevalence of MS in 1,3,46,367 in Moghtaderi et al (2012): 7.69 per 100,000 population with N = 206 prevalent cases. • The incidence rate reported by Sharafaddinzadeh et al (2012) per 100,000 population : 2.2 • The prevalence rate reported by Sharafaddinzadeh et al (2012) per 100,000 population: 16.28 with N = 696 prevalent cases. • The incidence rate reported by Heydarpour et al (2013) per 100,000 population: 6.6 in 2005.

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
			Sharafaddinzadeh et al (2012) , N = 4,2,00,000 in 2009 • The study population in Heydarpour et al (2013), N = 1, 4,1,03,853 from 1996-2006.		• The prevalence rate reported by Heydarpour et al (2013) per 100,000 population: 74.28
12.	Canada **[25]**	Scalfari, A. et al (2013)	• The study reviews 16 articles focusing on the mortality analysis and other epidemiological factors of MS(1 is relevant i.e. from 2012 onwards) • The study	-	• Out of the cohort in this study the mortality was, N = 1025 deaths. • The survival time from onset or diagnosis of MS: 47.5 years.

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
			population in Kingwell et al (2012), N = 6917 patients with MS with a follow up of 25 years during August 1, 1980 – December 31, 2004.		
13.	Hungary, Europe **[33]**	Zsiros, V. et al (2014)	The population of Csongrad County as per the latest census by Hungarian Central Statistical Office in 2011, N = 421,827	• Poser Criteria (until 2001) • McDonald Criteria (after 2001)	• The newly diagnosed cases which were incident between 1999-2003, N = 259 cases. • The crude prevalence per 100,000 population: 89.8 with N = 379 prevalent cases on 2013 January 1. • The female prevalence i.e. 128.6 per 100,000 persons was reported to be higher than males i.e. 46.6 per 100,000 people. • The mortality in the period 1999-2013, N = 86 deaths due to MS.

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
					• The frequency of Primary Progressive Multiple Sclerosis was reported to be 6.1%.
14.	Canada **[24]**	Warren, S.A. et al (2016)	The population at risk estimates were retrieved from Socio-economic Information Management System (CANSIM) data, Statistics Canada from 1975-2009	-	• The mortality in the period 1975-2009, N = 10,370 due to MS • The age standardized mortality rate per 100,000 population : 1.23 in 2006

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
15.	Canada **[26]**	Kingwell, E. et al (2012)	The study population included MS patients in the British Columbia MS database between August 1, 1980 to December 31, 2004, N = 6917.	Poser's Criteria	• The mortality in MS patients between August 1, 1980 to December 31, 2004 was reported to be N = 1,025. • The mortality statistics was reported to be higher in females MS patients than males MS patients i.e. female MS deaths = 635 than male MS deaths = 390. • There were 5,223 patients who survived and the median time for survival from the onset of disease: 47.5 years. • The standardized mortality rate in patients with RRMS, N = 784 cases is 2.87 and in patients with PPMS, N = 236 cases is 2.89.

S.No	Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
16.	Portugal **[34]**	de Sá, J. et al (2012)	The study population included the resident population catchment Lisbon's Northern health area, N = 229,342	McDonald's Criteria 2001	• The observed prevalence on December 31, 2009 is 41.4 per 100,000 population. • The prevalence per 100,000 population in Odivelas is 38.9 and in Benefica is 44.8 and in Pontinha is 45.4 • The ascertainment age – adjusted crude prevalence per 100,000 population: 58.

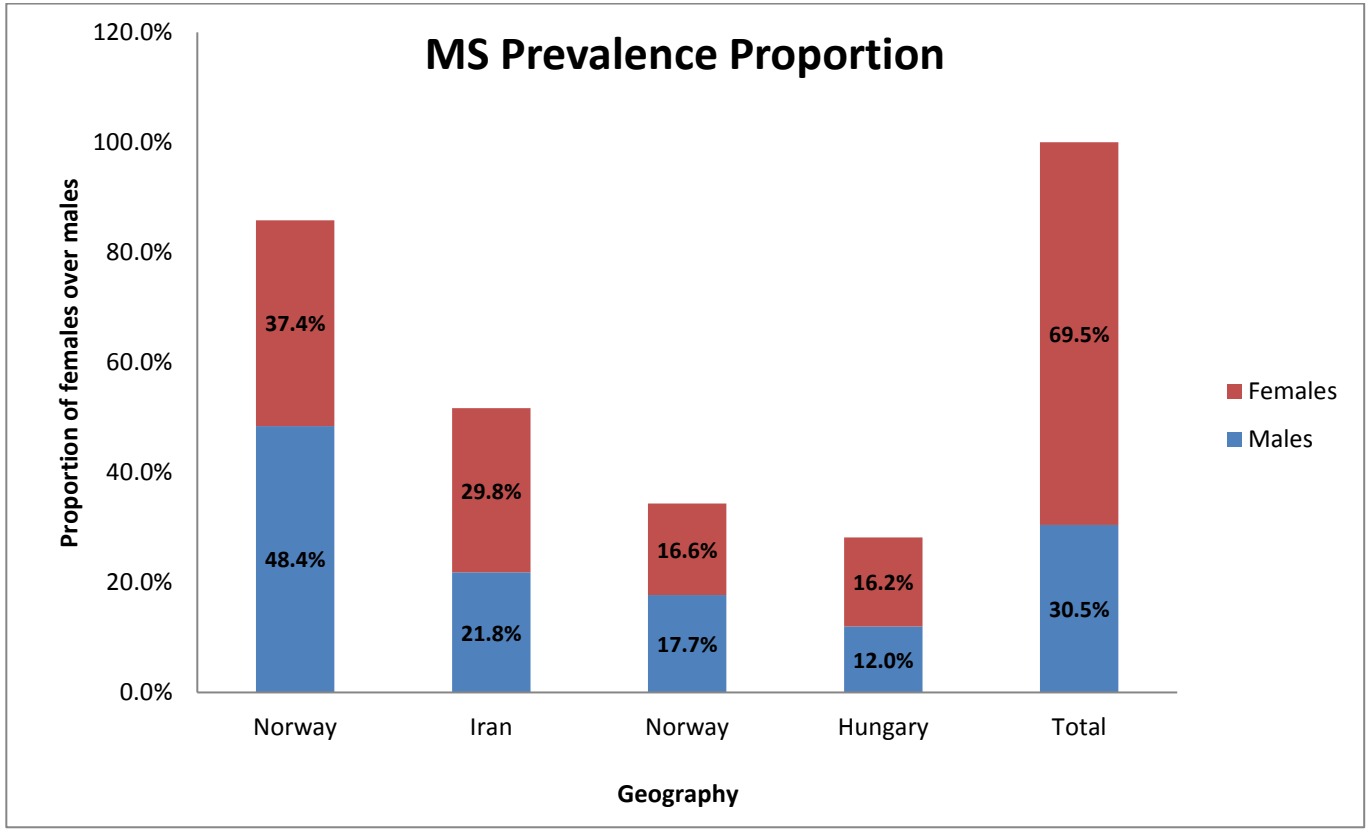

Figure 7: Prevalence of MS in Males and Females

Chapter 5: Discussion

This systematic literature review was conducted for finding the epidemiology of MS world-wide. A comprehensive literature search was performed on PubMed using a search string to find out the incidence, prevalence and mortality of MS. The results included sixteen studies discussing about the same in nine geographies world-wide. The highest numbers of studies were of Canada followed by the Scandinavian countries of Europe and other geographies as well.

The population studied in all the sixteen results was taken from administrative health claims, total population registers and registries of the specific geographies respectively and also the populations of MS centers were observed to furnish the epidemiological spread of MS.

The prevalence, incidence and mortality rates in all geographies increased over a period of time.

The results included the highest number of studies i.e. six studies from Canada. The incidence rate of MS ranged from 12.01 to 12.08 per 100,000 populations in Manitoba. The peak incidence occurred in ages 35-44 years and is reported to be 3 times higher in females than males. The mortality also increased over a period of time to 10,370 deaths from 1975 – 2009.

The incidence, prevalence and mortality rates were also reported to be higher in the Scandinavian countries of Europe. The incidence rate of MS in Norway ranged from 5.2 to 10.1 per 100,000 inhabitants of Hordaland County to Nordland County of Norway whereas the prevalence rate ranged from 211.4 to 182.4 per 100,000 populations. The number of prevalent cases in Sweden also increased to 28,027 cases from 1931 – 1985.

MS is reported to affect females 2 times more than males. All studies included in this review reported higher incidence, prevalence and mortality rates of MS in females than males. The prevalence rate in females per 100,000 inhabitants of Hordaland County was reported to be 270.9 and in males it was given to be 151.8 per 100,000 inhabitants. Also, in Canada the incidence was reported to be 3 times higher in females than males

The mortality statistics was also greater for women than men i.e. the number of female deaths ranged from 635 to 6450 as compared male deaths whose estimates ranged from 392 to 3920 deaths.

Also, 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 climate plays a major role in defining the spread of MS as the people living in Canada, Northern Europe, Australia and New Zealand and other geographies are more affected with MS than people living in the Africa, Asia, and Gulf area.

MS develops more in areas with temperate climates and in White people belonging to the Northern European descent.

The key findings from this study are broadly classified as following:

1. The epidemiology of MS overshadowed in the geographies with temperate climates in the world which included the Scandinavian countries, Canada, United States.
2. The prevalence statistics was found to be higher in females than males in Norway, Iran and Hungary.
3. There were very few studies which reported the incidence, prevalence and mortality rates of MS in geographies with tropical climates of the world.

Chapter 6: Conclusion

In conclusion, the epidemiological rates of MS are the highest in Norway, Sweden and Canada out of the nine geographies worldwide and females are reported to be affected with MS more than males. Also, the spread of MS is defined by the climate of the geography. Temperate climates are more prone to development of MS than tropical climates. White people of the Northern European descent are more prone to MS than people belonging to Asian, African or Native American descent.

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