

**DISSERTATION PROJECT
ON
A SYSTEMATIC LITERATURE REVIEW ON
EPIDEMIOLOGY OF MULTIPLE SCLEROSIS –
A GLOBAL PROSPECT**

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CONTENTS

- ❖ Introduction
- ❖ Scope of Dissertation
- ❖ Disease Definition
- ❖ Methodology
- ❖ Results
- ❖ Conclusion

INTRODUCTION

- ❖ 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.

SCOPE OF DISSERTATION

- ❖ 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.
- ❖ The study will give an opportunity to the future researchers to understand the market for the disease around the world.

DISEASE DEFINITION

- ❖ 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.
- ❖ MS occurs due to complex interactions between genetic and environmental factors.
- ❖ MS is categorized into four subtypes: Relapsing-Remitting MS, Secondary – Progressive MS, Primary – Progressive MS and Primary- Relapsing MS.

METHODOLOGY

Objectives :

- ❖ 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

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.

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 – 2017

RESEARCH PROCEDURE ADOPTED

STEP 1 : PREPARATION OF SEARCH STRATEGY

S.No.	Concept	Search string
1	Multiple Sclerosis	“MULTIPLE SCLEROSIS” OR “DISSEMINATING DISEASE”
2	Epidemiology	EPIDEMIOLOG* OR INCIDENCE* OR PREPONDANCE* OR PREVALENCE* 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

- ✓ **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.

STEP IV : FULL TEXT ARTICLE BASED SCREENING

- ✓ 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

STEP V : CRITICAL APPRAISAL OF 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.

STEP VI: DATA EXTRACTION

- ✓ This step involved the 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

RESULTS

In performing this study, the following mentioned PRISMA (Preferred Reporting Items for systematic reviews and Meta analyses) was followed

Identification

Records identified through
database searching
(n = 1886)



Screening

Records after duplicates removed
(n = 1886)



Records screened
(n = 1078)

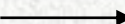
Records excluded
(n = 820)



Eligibility

Full-text articles
assessed for eligibility
(n = 258)

Full-text articles
excluded, with reasons
(n = 242)

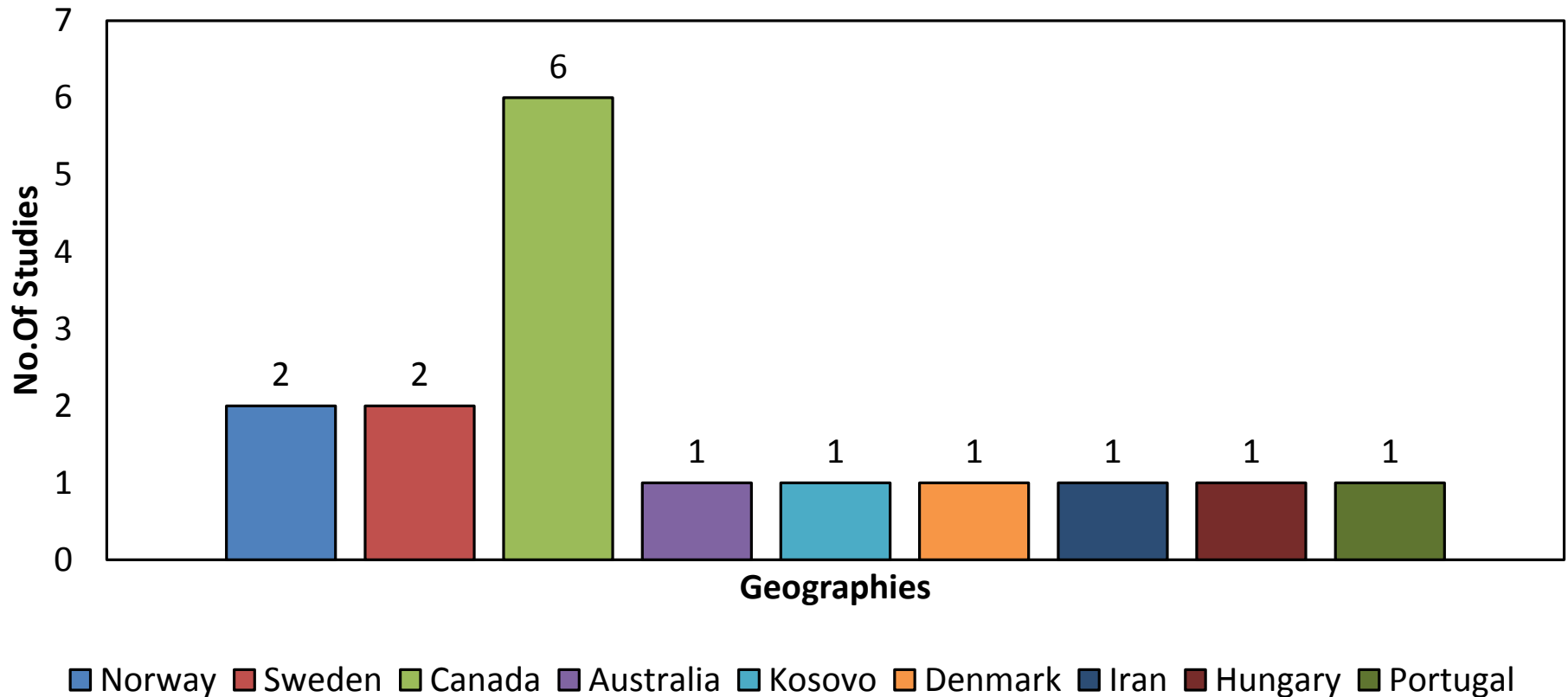


Included

Studies included in
qualitative synthesis
(n = 16)

STUDY DISTRIBUTION GEOGRAPHY WISE

The SLR included relevant articles which were found from the following geographies after applying the inclusion and exclusion criteria:



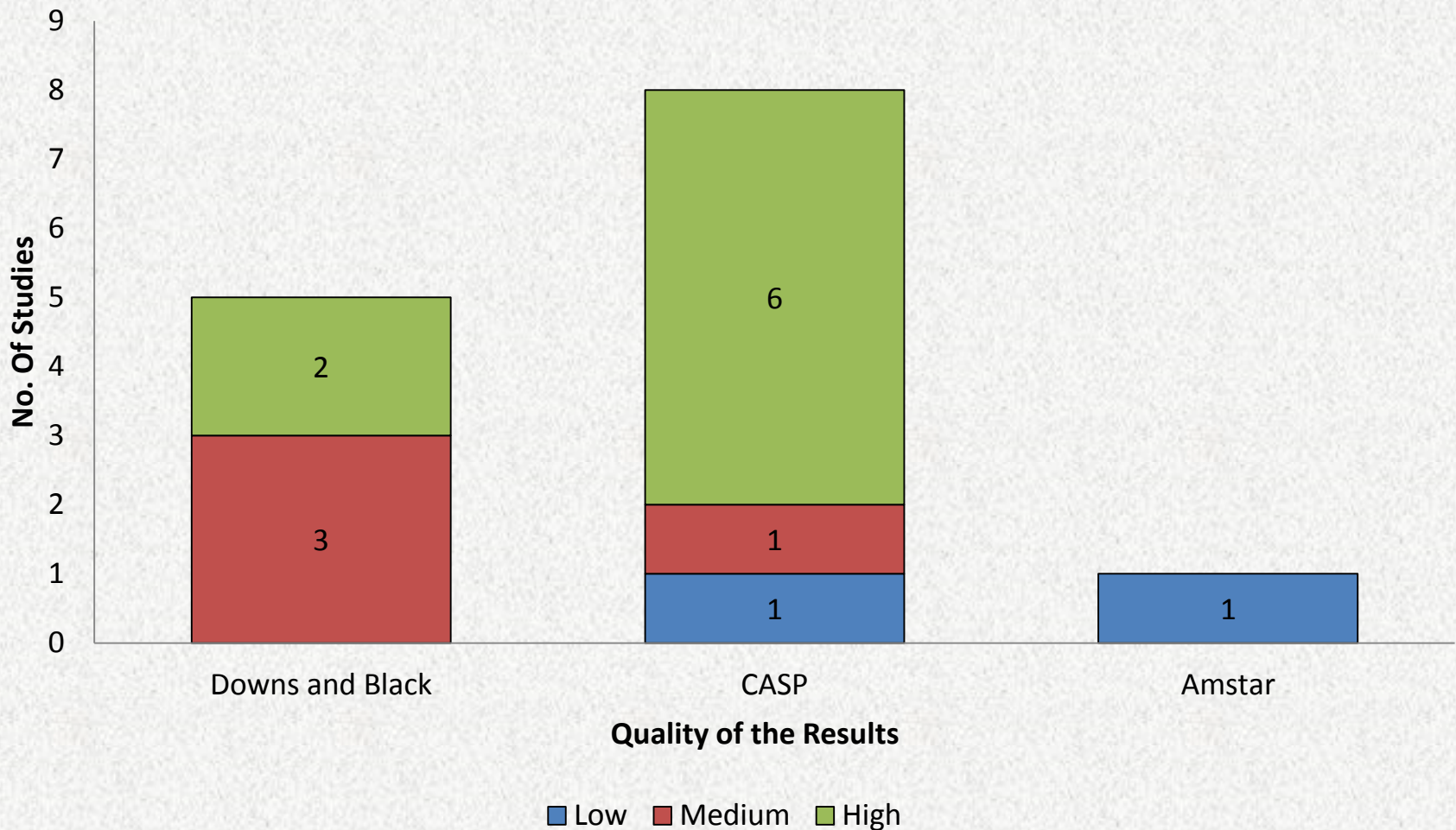
Number of Studies by Country



Country	No. of Studies
Norway	2
Sweden	2
Canada	6
Australia	1
Kosovo	1
Denmark	1
Iran	1
Hungary	1
Portugal	1

QUALITY ASSESSMENT

The following graph shows the combined results of the quality of the sixteen studies included in the review:



KEY FINDINGS

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Norway	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.
	Benaminsen, 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 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.

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Sweden	Skoog, B. et al (2012)	The Population of Gothenburg, N = 4,00,000 who were the residents of Gothenburg during 1950-1964	Poser's diagnostic Criteria	• 307 incident cases of MS in the Gothenburg incident cohort followed up till 2010. • N = 9 deaths were observed till 2010 with the underlying cause of death as RRMS.
	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.

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Canada	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.
	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 2011), N = 5,797	The validations for MS were : Individuals with greater than or equal to 3 hospital, physician, or prescription claims for MS	• 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 from 1.68 to 149.3 per 1,000 persons in MS population • The median survival time from the birth was 75.9 years.

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Canada	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.
	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 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.	-	• 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.

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Canada	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
	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.

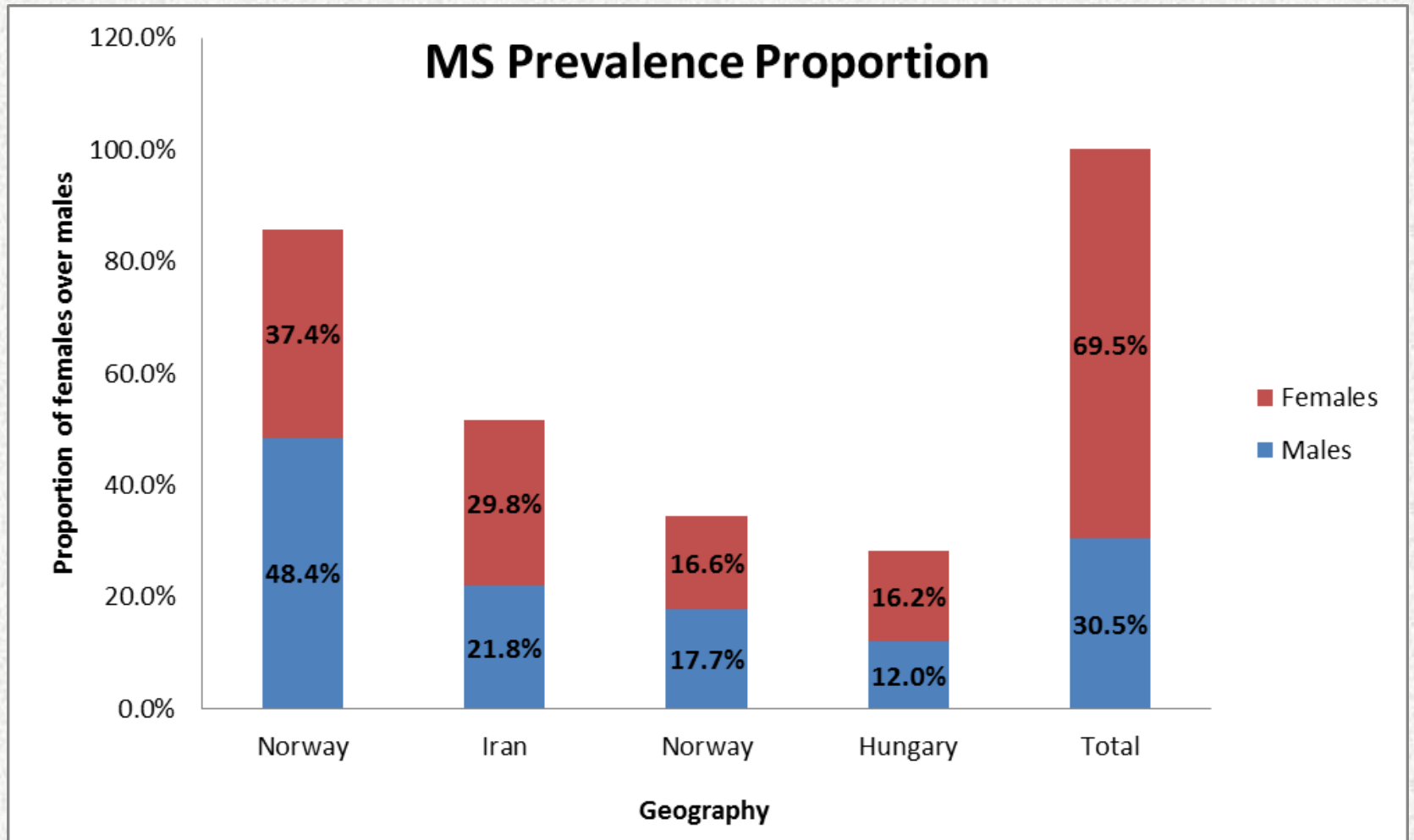
Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Australia	Taylor, B.V. et al (2013)	The population of Australia , N = 2,30,00,000	McDonald's Criteria	• There were 22000 prevalence MS cases with a rate per 100,000 persons: 95.7 • There were 2917 prevalent MS cases in New Zealand 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 Prevalence & Genetics Study (TMSPGS) on census day 1 January 2009 : 265 patients
 Kosovo, Europe	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

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Denmark	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
 Portugal	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.

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Iran	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 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.	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. - The prevalence rate reported by Heydarpour et al (2013) per 100,000 population: 74.28

Geography	Author	Study Population	Diagnostic Technique	Epidemiological Data
 Hungary, Europe	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. • The frequency of Primary Progressive Multiple Sclerosis was reported to be 6.1%.

MS PREVALENCE IN MALES AND FEMALES



CONCLUSION

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



thank
you