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Epidemiology of Multiple Sclerosis In Turkey, East Mediterranean, and Near East Area

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ABSTRACT

Today, Multiple Sclerosis (MS) is one of the leading non-traumatic causes of permanent neurological disability in young and middle-aged populations. A 2020 statistical survey figures show that it affects 2.8 million people worldwide. This figure corresponds to an average of 1/3000 people, which figure is likely to rise further. Globally, the median estimated prevalence of MS is approximately 36 per 100,000 according to international data, with 2.9 million people living with MS in the World in 2023. Regionally, the estimated median prevalence of MS is highest in Europe and the Americas. Regional differences in incidence generally run parallel to prevalence. A median prevalence and incidence were reported for the Eastern Mediterranean area and Middle East but in the last decades, this has tended to change. Also, the incidence has increased in Mediterranean islands, but not all. Its prevalence increased from 40 per 100,000 to 100 per 100,000 in Turkey while in Greece, Cyprus, Basra Gulf, and the Middle East in general, a similarly increasing trend was observed in recent years. The highest prevalence rates were reported in Iran (148.06 per 100,000) and higher incidence rates were estimated at 6.88 per 100,000 population in Kuwait. The same increase can be seen in some parts of Russia and Western Asia. In fact, the increasing trend in incidence can be seen even in the Far East, in China and Japan, where the prevalence and incidence were originally low.

The gender distribution of MS in the region has also tending to change in recent years, with more females having MS. Of the various risk factors cited for multiple sclerosis, especially migration seems to be an important risk factor for the region, although there are some exceptions.

Introduction

Today, Multiple Sclerosis (MS) is known to be one of the most important non-traumatic neurological diseases causing disability, mostly in young and middle-aged adults. 2020 statistical survey figures show 2.8 million people with MS; this figure has increased to 2.9 million in 2023, which corresponds to an average of 1/3000 people¹. This number is likely to rise further, as adequate data collection facilities in some countries improve. This increase in numbers is especially true for the region and will be discussed further in this article.

The prevalence of multiple sclerosis (usually expressed as the estimated number of people with MS in a given population or cases per 100,000 population at any given time) not only varies considerably worldwide¹ but also appears to be changing and increasing in recent decades. It is generally classically reported to be highest in Northern European populations and is significantly more common in temperate regions than in more equatorial regions. Globally, the median estimated prevalence of MS is approximately 36 per 100,000 according to the 2020 Multiple Sclerosis International Federation (MSIF) Atlas, and by 2023 now there are 2.9 million people living with MS in the World, and this figure is increasing every day².

Several factors are likely to contribute to this increase, including better and better diagnostic methods around the World and quicker diagnosis within each country, longer lives of people with MS, improved treatment/support, and general global population growth, as well as the emergence of better census methods globally. However, it is now accepted that the risk of developing MS may also have increased slightly over the years due to other -possibly environmental- factors and that there is a real increase in the incidence of the disease, especially in women³. It is stated that the prevalence and incidence are increasing all over the World. Research also highlights the many barriers and inequalities that people with MS face in accessing diagnosis, treatment, and care.

Regionally, the estimated median prevalence of MS is highest in Europe and the Americas (133 and 112 per 100,000, respectively), according to the International MS Federation's latest atlas study and it varies significantly between regions and countries. Lately, an increasing prevalence of

MS is observed in the Americas, as well as in the Middle East and North Africa region, the Russian Federation, Canada, Australia, and several European countries (Denmark, Germany, Poland, United Kingdom)². Only 14% (11/81) of countries submitting data to the International MS Federation study reported stable or decreasing prevalence³. Increasingly, the prevalence in Japan, which was reported to be low originally, is also reported to increased from 6.9 per 100.00 in 2003 to 23.3 in 2021 over years^{4,5,6}. It was reported to increase from 0.86 per 100,000 in 1986 to 5.2 in 20137 in China. So, it should be noted that there is also an increasing trend in eastern countries, especially among women.

In the Eastern Mediterranean Region and Middle-Near East Region, there is an increasing trend, and this will be discussed in this article.

INCIDENCE:

Incidence refers to the number of new cases diagnosed in a given period (usually a year). The number of new cases per 100,000 population per year can indicate changes in the risk of a disease within a population and indicate whether the frequency of a disease is increasing in a population. It is not affected by changes in survival. MS varies greatly depending on age. Although it is most common in young adults (20-40 years of age), the disease can be seen in individuals of all ages. The estimated global incidence of MS is, on average, 2.1 per 100,000 people per year².

Regional differences in incidence generally run parallel to prevalence; The highest reported incidence is in Europe and America. Iran and Kuwait have reported/estimated incidences around 6.8 per 100,000. MS studies done in similar populations over time have shown increasing incidence. At least part of the increase in incidence can be attributed to increased public awareness, better healthcare, earlier and more effective diagnostic opportunities (such as magnetic resonance imaging), more MS specialists, and changing diagnostic criteria³.

The most significant change in the epidemiology and severity of MS is that, while the overall incidence has increased, the course of the disease has become less severe, especially over the past 25 years since the introduction of disease-modifying therapies (DMTs)⁸. The prevalence of MS appears to have increased over

time. In addition, the course of the disease has changed, the time until disability in patients with relapses (RRMS) has been prolonged, and survival has increased. The transition period to the secondary progressive form (SPMS) has also been prolonged and the proportion of patients developing this type of disease has also decreased. The reason for these changes is probably earlier detection and diagnosis, more patients diagnosed with benign MS, earlier and more effective use of disease-modifying treatments, i.e., better disease management, improvements in life expectancy and data quality/accuracy, and lifestyle changes. It is also partly due to changes in the natural course of the disease. Trends in the MS incidence rate over time are less clear. There is probably a global increase in incidence, but although it is stated that the data and information regarding this increase are not as reliable as the prevalence, there is a certain increase. The difference between regions is less clear.

The most detailed compilation study on this subject was published in 2022 and studies by country were reviewed. In some countries, an increasing incidence has been reported, while in some studies, a decreasing incidence has been reported in certain regions of some countries for specific periods. For example, while an increasing incidence is encountered in Sicily, Italy, a decreasing incidence is reported in the Catania department in the south of Sicily. Apart from this, an increase is reported in many regions of Italy and a decreasing incidence is reported in some parts. Increasing incidence in most of Europe and a decreasing incidence trend in the United Kingdom was reported. The incidence generally increases in the Eastern Mediterranean and the Middle East, as an increasing trend is also observed in Oceania and the Western Pacific. While this study is the largest review to date, the populations on which the included studies were based represent only a small fraction (~3%) of the global population, with more than half from Italy, Norway, and Canada.

However, as general information, studies summarized in this review show an increase of incidence over time, although it is not possible to detect a global incidence increase pattern⁹.

In summary, the most important changes in the understanding of demographic epidemiology of MS in the World in recent years are; (1) an

increase in the prevalence, predominantly due to longer survival; (2) probably an increase in incidence generally all over the World, although some regional decrease areas are also present; (3) an incidence especially predominant in women, changing the male to female sex ratios of MS; (4) a general more careful use or not use of the classical latitudinal gradient notion all over the globe in general¹⁰.

The primary purpose of disease surveillance and epidemiology is to help in measuring health status, dealing with disease prevention, predicting, detecting, and minimizing harm by determining the rate in a particular society; This will be discussed for one region in this article.

Epidemiology of the Region, Epidemiology of MS In Different Populations

Classical knowledge is that in general, MS prevalence is significantly associated with latitude, especially in populations of European descent, with an increasing prevalence in the northern latitudes of Europe and North America and in the southern parts of Australia and New Zealand.

However, there are notable exceptions to this general rule in the region. Sicilians and Sardinians have significantly higher rates of MS than other Italians^{11,12}. Likewise, it has been reported that the rates in the Turkish Republic of Northern Cyprus and Southern Cyprus are higher than in Turkey and Greece^{13,14}. However, the same situation is not observed on all islands in the Mediterranean. The prevalence of MS in Malta was found to be 4.2/100,000 in 1978, and this low rate still continues (13.2/100,000)^{15,16}. This situation may be related to the fact that the ethnic structure of the Maltese is different from that of other Europeans¹⁷. On the islands of Sicily and Sardinia, which are part of Italy, the prevalence is high. On Sicily the prevalence of MS is 120.2/100.0011, while on the island of Sardinia it is 149.7/100.00 in the northwestern region, 143.9/100,000 in the central part and 210.4/100,000 in the southwest region¹² although many environmental characteristics are the same. On the other hand, the prevalence was found to be 8.1/100,000 in the neighboring island of Corsica, which is French territory on the north. The result of many studies could only suggest, only nutritional differences (processed

meat production method) as the cause of this difference¹². The island of Cyprus will be discussed later but the last reported prevalence rates are likewise high, 198/100,000 in the South and 90/100,000 in the North^{13,14}. Mild forms of MS are generally seen on the island of Crete, which consists of individuals with a common genetic origin¹⁸. The prevalence studies conducted over time in Turkey are summarized in Table 1.

Table 1: Change in prevalence over the years

Year	City or Region	Prevalence found
2003	Edirne ²⁰	33.9/100,000
2005	İstanbul (Jewish community) ²¹	111/100,000
2006	İstanbul Maltepe ²²	101.4/100,000
2011	İstanbul Kandıra ²³	61/100,000
	Geyve	41/100,000
	Erbaa	53/100,000
2011	Central Black Sea (Ordu, Amasya, Tokat, Sinop, Çorum) average ²⁴	43.2/100,000
2012	Northern Caucasian (Kars) ²⁵	68.97/100,000
2013	Gazipaşa ²⁶	52/100,000
	Artvin	18.6/100,000
2018	Artvin (Karadeniz) ²⁷	18.6/100,000
	Ordu (Karadeniz)	55.5/100,000
	Gazipaşa (Akdeniz)	52.100,000
2021	Geyve ²⁸	49.6/100,000
	Kandıra	48.5/100,000
2023	Afyonkarahisar	105/100,000

The prevalences of individual cities in the Central Black Sea Study, conducted in 2011, with an average of 43.2/100,000 are presented in Table 2.²⁴

Table- 2: Prevalences by Province in the Central Black Sea Study (2011)²⁴

Province	Prevalence
Sinop	60/100,000
Ordu	38.4/100,000
Samsun	46.5/100,000
Tokat	43.7/100,000
Çorum	38.8/100,000
Amasya	37/100,000

The prevalence does not vary greatly between regions in the country - with a few exceptions. However, one can see that it is increasing gradually over the years. In a control prevalence study conducted in Geyve and Kandıra as of 2021, an age-standardized prevalence of 49.6/100,000 in Geyve and 48.5/100,000 in Kandıra was found²⁸. Most recently, in a study that ended in 2023, among the people residing in Afyon Provincial Center; an analysis was conducted by selecting a sample using the stratified sampling method, taking into account demographic factors such as income level, gender, and age, by Türk Börü et al. In this study, the prevalence of MS was found to be 105/100,000 (high) in Afyon city center. While the prevalence is high in those with medium and high economic income, no patients were detected in those with low economic income (data not yet published). In the light of all these studies and data, it is generally accepted that the average prevalence of MS in Turkey is between 41-101/100,000 as of today²⁹.

Checking on the countries around Turkey, a similar increasing trend is seen. In Northern Greece, the prevalence, which was 10.1/100,000 in 1984, reached 119.61/100,000 in 2006 in 23 years. While the average annual incidence rate

was recorded as 2.71/100,000 in the period between 1984-1989, it was observed to increase to 10.73/100,000 in the five-year period between 2002-2006. In other words, there is an upward trend in this region³⁰. The average prevalence was found to be 197.8/100,000 in the 2017-2019 period.³¹ Coming to Cyprus, in 1991 the prevalence of MS among Greek Cypriots using the Poser criteria was found to be 44.5 per 100,000 in several regions of Southern Cyprus³². Later in 1995, with the United Nations bi-communal project, the prevalence of MS was found to be 42/100,000 in Greek Cypriots (in the South) and 40/100,000 in Turkish Cypriots (in the North)³³. Later, a fourteen-year study in Southern Cyprus was concluded in 2016, and the final prevalence rate in Greek Cypriots was found to be 198/100,000¹³. In the Turkish Republic of Northern Cyprus, the most recent prevalence estimate is 90/100,000¹⁴. Here, there is an increase well above the world average in both regions. In Bulgaria, which is also a country of the region, the prevalence of MS was found to be approximately 44/100,000³⁴, and in Moldova it was reported as 20.9/100,000 (25.7 in women, 15.8 in men)³⁵. This figure was later modified to 37 per 100,000 and the estimated prevalence for Belarus was reported to be 40 per 100,000 and 47 per 100,000 people for Romania³⁶. The prevalence was estimated to be 27/100,000 in 2007 and 30.99/100,000 in 2010 for Bosnia-Herzegovina where the annual incidence rate was reported to be 1.6 per 100,000.^{37,38} A report from Croatia gives an overall MS prevalence rate of 143.8 per 100,000 population in 2018⁹. In Kosovo, the prevalence of MS was reported to be 19.6 patients per 100,000 inhabitants and the incidence rate was 0.95 per 100,000⁴⁰.

The Russian Federation is located on a land area of more than 17,000,000 km² and there are large variations between regions. This is explained in relation to both environmental conditions and also the ethnic groups in the region. Prevalence values in the country put the country in the medium-high group. While prevalences such as 30-50/100.00 are reported in the European parts of the country, these rates rise to 50-100/100.00 in some parts. While there is a moderate prevalence in the regions where Turkic groups close to Europe live, it is low in the North Caucasus and Ural regions. The MS prevalence rate is reported to be 2-3 times higher among the people of Russian origin living in the area

than the indigenous peoples of the Caucasus. However, the incidence has started to increase significantly in all these regions in recent years, in all the ethnic groups. Although it is understood that in the Asian part, especially in remote Siberian regions, it is lower in local populations and higher in later settled Russian-origin populations; the incidence is increasing including the Far Asian part⁴¹. The prevalence was found to be 5.2/100,000 in Kyrgyzstan, which is located in a mountainous area at an altitude of 500-3000 m above sea level⁴². This rate is 3.2 for Kyrgyz of ethnic Asian origin and 10.8/100,000 for the native population of European (Germanic) origin. Now, this rate is lower than the rates of similar ethnic populations in Europe. It is understood that an environmental factor also plays some role here. The information given from Uzbekistan shows a prevalence of 1.1/100,000 and an average incidence of 1.1/100,000 between 2015 and 2017, and an incidence of 1.8/100,000 in Tashkent city and Bukhara province⁴³. A prevalence of 12/100,000 is reported in Azerbaijan⁴⁴. Reported prevalence values for Iran have increased every year, and rates such as 98.06 and 148.06/100,000 have started to be reported in recent years. The incidence values reported in Iran in various years are between 4-6/100,000. In the most recent studies, the incidence was found to be 6.7 per 100,000 (10.5 in women, 3.0 in men) and it was determined that it tended to increase most in the 20-39 age range⁴⁵. In some regions, it continued to increase⁴⁶.

It is mentioned in some studies that Parsis are more commonly affected than other ethnic groups in South Asia¹⁹. Rates such as 85.05 in Kuwait, 39/100,000 in Jordan, and 54.77/100,000 in the United Arab Emirates were reported⁴⁷. In Saudi Arabia, which was previously reported to have a lower prevalence compared to the neighboring countries, a prevalence rate of 61.95/100,000 was reported in recent evaluations⁴⁸. In Oman, a prevalence of 15.9/100,000 was last reported as of 2021, and the incidence was reported to have increased from 1 in 2015 to 1.18 per 100,000 cases in 2018⁴⁹. As of 2018, the prevalence of MS in Lebanon was determined as 62.91 per 100,000, and the incidence was determined as 8.36 per 100,000 cases⁵⁰. It was found to be 51.92 per 100,000 in the Western bank of Palestine. The incidence has also varied between 1.96 and 6.08 over the years⁵¹. A prevalence of 11.73/100,000

was reported in Iraq, and the incidence, which was 0.5 in 2005, became 1.5 in 2017⁵². The increase is obvious in most countries. The prevalence rate in the Qatari population was found to be 64.6/100,000 which was higher than other Persian Gulf countries. In Kuwait, 31/100,000 and Dubai 55/100,000 was reported^{53,54,55}. Different ethnic groups are known to populate Sudan, including tribal communities who were displaced during the civil war; and a study that was published in 2009 suggests that the few MS patients were largely from northern tribes where hybrid Arab- African races dominated. The prevalence and incidence are accepted to be low⁵⁶.

The increasing trend in the incidence and prevalence of MS in the region is partly due to the increase in MS worldwide, but also due to genetic susceptibility, an increase in public awareness, environmental factors, nutrition, increases in diagnostic and treatment opportunities, and the change in socioeconomic life. There are large differences in absolute increases between countries.

AGE FACTOR:

Basically, the disease occurs most frequently in the third to fourth decades of life, but the age of incidence varies from post-pubertal teens to people in their 50s. Rare cases occur in infants or patients in their 60s, but extreme caution should be exercised in these cases to exclude alternative processes. It is generally known as a disease of young adults. In other words, "MS usually occurs at a very productive stage in people's lives when they are planning their families and building their careers, and therefore it can have a significant impact on affected individuals, families, and society"³. The average peak of clinical onset occurs in the early twenties in women and in the late twenties in men. In Turkey, the average age of onset was determined to be 41.8 ± 12.0 years in the 2006 Maltepe study²², and the average age was found to be 35.1 ± 10.2 years in the Northeast study²⁵. In Kuwait, the age of onset was reported to be 26.87 years in 2014⁵⁵. In the latest large survey-based study conducted in Turkey, the average age of participants was 37, and the average age at diagnosis was 28 years²⁹. For Turkey, taking the average of all studies, the average age of diagnosis is 32, and it is a little later in men.

Although MS is usually accepted as a disease of young adults and is infrequent in children, it doesn't just affect adults. About 2-10% of all the patients are those below 18; this is also true for this region⁵⁷. In the pediatric Turkish cohort, predominantly the RRMS form of the disease is reported, brainstem, cerebellar, Acute Disseminated Encephalomyelitis-like symptoms, facial paralysis and seizures are common, onset with sensory symptoms is less common than it is in adulthood, vitamin D deficiency and subclinical visual evoked potential abnormalities are frequent, the time between attacks is longer in the beginning and disability accumulates more quickly with early onset⁵⁸.

GENDER DISTRIBUTION:

Women are more likely to get this disease. The approximate global female-male ratio is 2-3:1. These rates were reported as 69%-31% in the atlas of the International MS Federation¹. There are significant variations between countries. The rate is even higher in some regions. While in some countries the ratio of women to men is as high as 4:1, in many countries it increases in favor of women³. Again, according to the latest data from the International Federation, the number of women with MS is more than three times higher than men in the Western Pacific and Southeast Asia regions. Although the female-male ratio is 2:1 in the Eastern Mediterranean Region, this ratio has increased 3 or even 4 times in a few countries in this region. These include Egypt, Iran, Palestinian Authority, and Sudan². The increase in the male-female ratio in favor of women continues in many countries around the world. In Greece, in the 14-year period between 1999 and 2012, hospital admissions for female MS patients were higher than for males, and the 25-44 age group increased more than other age groups⁵⁹.

Although the female-to-male ratio is similar in various studies in Turkey, there are also regional differences. For example, in the study conducted in Maltepe, Istanbul, the ratio was found to be 1.5:1²². In the Black Sea-Mediterranean study, the ratio (women to men) was reported as 2.25:1²⁶ while the Central Black Sea study found it to be 2.4:1²⁴ and in the North East study, the female-male ratio was found to be 4:1²⁵. In the 1999 natural history study, one of the oldest detailed studies performed in Turkey, this ratio was found to be 1.8:1⁶⁰. Although it has not been researched in detail, it can be said that the

female-male ratio has also increased in favor of women in Turkey. In the most recent large nationwide survey-based study, 71.5% of respondents were women²⁹ (2.5:1 female-to-male ratio). This ratio is 2.48:1 in the USA and 2.35:1 in Sweden⁶¹, while in Bosnia- Herzegovina it was reported to be 1.5:1, in Kosovo it was reported to be 2.3:1^{37,40}. This female-to-male ratio was reported to be 3:1 in Iran⁴⁵ 2:1 in the Western region of Palestine⁵¹ 2.18:1 in Iraq⁵² and 2:1 in Azerbaijan, one of the Turkic republics⁴⁴ while in Uzbekistan it was found to be 1:1.6 (more diagnosed male patients)⁴³. In the Middle East and Persian Gulf, Qatar had a female-male ratio of 1.33:1⁵³, Dubai, United Arab Emirates 2.85:1⁵⁴, Lebanon 1.8:1⁶², and Kuwait, 1.8:1⁶³. An exploratory analysis conducted in different geographical regions around the world also shows a latitudinal trend in increasing sex ratio⁶⁴. Although the exact explanation for the increasing rate of MS in women in recent years all over the world is not known, there is also an underlying epigenetic phenomenon among the proposed mechanisms. Increased adiposity in the general population and higher obesity rates, especially in young women, younger age at menarche, getting pregnant at an older age (pregnancy may protect against the risk of MS), change in menopause, and increased smoking rates in women are thought to be effective^{65,66}.

RISK FACTORS:

The change (increase) in the female:male sex ratio all over the world strongly makes one think of environmental influences on the risk of MS, especially acting at the population level¹⁰. The most emphasized environmental risk factors are; ultraviolet radiation, vitamin D and season of birth, Epstein-Barr virus (EBV) infection, cigarette and tobacco smoking, tobacco product exposure, obesity, microbiome and diet, and later childbirth. Others are migration and migration-related factors, menopause, genetic factors, and parental influence. Of these, migration will be discussed in detail here, since it is of interest and relevant to the region.

Migration: Migration data have often been used to support the view that an environmental factor plays a role in the pathogenesis of MS. Although there are some exceptions, these data show that people who migrate from high-risk areas to low-risk areas after adolescence carry their old high risks with them. The risk of those who migrated during childhood seems to be related to the new

area to which the person migrates. The age factor appears to be quite important in epidemiological studies conducted in populations migrating from countries with low MS prevalence to countries with high MS prevalence. For those who immigrated before the age of 14-15, the prevalence seems to match the country they immigrated to, and for those who immigrated afterward, it seems to match the country they left. However, not all epidemiological studies give the same results, therefore, as a result of migration and immigrant research, genetic and environmental factors are supported to some extent, but a definitive result cannot be obtained⁶⁷.

To exemplify the above statements for the area, immigrants to Israel can be given. Some among Jews who immigrated to Israel, the MS risk of those who were the grandchildren of European immigrants and were born in this country was similar to the local population born in this country, whereas the MS risk in newly immigrated people was similar to the rates in the country they immigrated from^{68,69}. These and other epidemiological studies have highlighted that regional factors are more important than ethnicity, pushing the effect of genetic predisposition into the background. On the other hand, as an opposite example, some studies mention that Parsis are more commonly affected than other ethnic groups in South Asia⁷⁰. The ethnic group defined as "Parsis" is actually followers of the Zoroastrian religion who had migrated from Iran many years or decades ago to various central and frontal Asian countries, and their origins are Iran. It is seen that they show different (mostly higher) prevalence rates than the Asian and Western countries they live in^{71,72,73}. Some have been in these countries for more than a number of centuries and they are less likely to have MS theoretically than they actually do. In two studies on Parsi Zoroastrians in India, the MS disease rate was significantly higher than in other groups in India.⁷³

When we look at the patients in Turkey, migration has not emerged as an important factor in Turkey's reality until today⁷⁴, but this may change in the future, considering the large number of illegal immigrants coming to the country which will not be similar in European countries. The migration effect manifests itself differently in Northern Cyprus. While the prevalence was similar in Northern and Southern

Cyprus in the 1990s (40/100,000 in the North, 42/100,000 in the South), it has been reported that in the past 20 years the prevalence was 90/100,000 in Northern Cyprus and 198/100,000 in the South. Although there is an increase in both sides, migration is considered to be one of the factors that may cause the difference¹⁴, reducing the average figure in the north.

Conclusion

The prevalence of MS is increasing in regions like the World in general; the incidence is also increasing, but at different rates in different countries. As seen, some countries have a quite different rate. Similarly, the female-to-male ratio is increasing too; and in the future migration will be an important subject for further detailed analysis for this region.

Conflicts of Interest Statement

The author has no conflicts of interest to declare.

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