

# Multiple sclerosis prevalence study

## The comparison of 3 coastal cities, located in the black sea and mediterranean regions of Turkey

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### Abstract

The prevalence of multiple sclerosis (MS) has significantly increased all over the world. Recent studies have shown that Turkey has quite a high prevalence. The aim of this study is to estimate prevalence in the Mediterranean and Black Sea regions of Turkey and to compare the results.

This study was designed as a door to door survey in 3 cities. One is located in the Mediterranean region (South), 2 are located in the Black Sea region (North). A previous validated form was used for screening in the field. The patients were examined first in the field, then in the regional health facility. McDonald criteria were used for the diagnosis.

In total, 26 patients were diagnosed with MS. The prevalence was found to be 18.6/100,000 in Artvin (Black Sea region), 55.5/100,000 in Ordu, (Black Sea region), 52.00/100,000 in Gazipaşa (Mediterranean region). The female/male ratio was 2.25.

This study is the first prevalence study which was conducted in the Mediterranean City (South) of Turkey. The prevalence rate was found to be higher than expected in the Mediterranean city of Gazipaşa. The results showed that the prevalence varies from region to region. Latitude difference was not observed.

**Abbreviations:** EDSS= Expanded Disability Status Scale, GDP= gross domestic product, MRI= magnetic resonance imaging, MS= multiple sclerosis, RRMS= relapsing remitting multiple sclerosis, SPMS= secondary progressive multiple sclerosis.

**Keywords:** door-to-door survey, epidemiology, multiple sclerosis, prevalence, Turkey

### 1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammatory demyelinating and secondary axonal degeneration.<sup>[1]</sup> It is estimated that more than 2 million people live with MS worldwide.<sup>[2]</sup>

Epidemiologic studies about the distribution of MS in a range of populations could help uncover new environmental and racial clues about this disease.

The incidence and prevalence of MS vary in different geographical areas and populations. However, the exact prevalence and geographical distribution of MS still remains uncertain.<sup>[3–6]</sup> Previously, Turkey was considered to have a low

prevalence of MS.<sup>[7]</sup> Recent studies from Turkey (Istanbul, Kandıra, Geyve, Erbaa, Kars, Karabük, and Akçakoca) suggest prevalence of 41.1 to 101.4 per 100,000 population.<sup>[8–11]</sup> These recently conducted studies highlight that Turkey now has a high prevalence rate. MS prevalence in Turkey is shown in supplementary file table, <http://links.lww.com/MD/C570>. The 6 studies were carried out in northern regions of Turkey. There is no prevalence study in the southern region. The location of cities which were studied is shown in supplementary file figure, <http://links.lww.com/MD/C571>. The 3 cities were also chosen due to having a homogenous Turkish population and low migration rate.

The purpose of the study was to evaluate and compare the prevalence rate of 2 regions which have a high latitude difference.

### 2. Materials and methods

This study was carried out as a descriptive, cross-sectional and door-to-door study. The study was approved by the Local Ethics Committee of the Dr Lütfi Kırdar Kartal Training and Research Hospital. Permission was also granted by the local administration of Artvin, Gazipaşa and Ordu. Approval Numbers: (B.10.0. ISM.4.08.03.00-20-4036) (B.100ISM.4520400/730-08.2929)

#### 2.1. The Characteristics of the cities

**2.1.1. Gazipaşa.** Gazipaşa is a coastal city by the Mediterranean Sea which is located between 36.17° north latitude and 32.18° east longitude. It is located 180 km away from Antalya. Gazipaşa has a typically Mediterranean climate; in summer it is hot and dry and in winter it is mild and rainy. Based on the 2012 population census, the population of Gazipaşa was 22,332. The migration rate to and from Gazipaşa is low. Although it is a Mediterranean city, the shoreline does not allow for touristic activities because of its geographical features. The population of the city is stemmed from

Editor: Bernhard Schaller.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:42(e12856)

Received: 9 April 2018 / Accepted: 21 September 2018

<http://dx.doi.org/10.1097/MD.00000000000012856>

the Karakeçili branch of Oğuz (Turks). The population of this town consists of homogenous Turks. The income source of the population is glasshouse agriculture of vegetables and fruit. Agricultural workers admit that they use a high number of pesticides while cultivating their crops. The mean gross domestic product (GDP) per capita in Gazipaşa was US\$ 13,626 in 2012.<sup>[12]</sup>

**2.1.2. Artvin.** Artvin is located between 41.10° North latitude and 41.49° east longitude. It has a typically Black Sea climate. The temperature is generally mild during the summer while the winter months bring snow and rain. Based on the 2012 population census, the population was 25,771 and it is homogeneously Turkish. There is no immigration occurring into the city but there is a huge number of out-migration to big cities. There are no industrial plants that could harm the environment. The mean GDP per capita in Artvin was US\$ 9982 in 2012.<sup>[13]</sup>

**2.1.3. Ordu.** Ordu is located in the Black Sea region, which is on 40° north latitude and 37° east longitude. Summers are cool, while the winters are mild with rain and snow at the higher regions. According to the 2012 census, the population of the city centre was 147,913. The homogenous Turkish population is routed in the Çepni Branch of Oğuz. The income sources of the population are agriculture and beekeeping. There is also a hydroelectric plant that produces about 200 million kW-h per year. The mean GDP per capita in Ordu was US\$ 13,626 in 2012.<sup>[14]</sup>

Age distributions of cities and general Turkish populations are shown in Figure 1.

## 2.2. Screening forms

Validated screening forms previously prepared and used in our study conducted at Maltepe, Istanbul in 2002, were used.<sup>[8]</sup> The questionnaire consists of 2 sections containing 26 questions. Section 1, assessed knowledge on MS, while section 2 covered MS symptoms. The questions enquired about current and past symptoms including motor and sensory dysfunction, walking ability, sphincter control, sleep, balance disturbances, ataxia, depression, increased fatigability, and memory disturbances. Surveyors were given practical training. The interviewers were briefed on the procedure including which doors to knock on, what to do if no one is home, interventions method and how to ask the questions and fill the form in.

## 2.3. Establishment of the neuroepidemiological field teams and the study procedure

Four teams consisting of 6 persons (a neurology assistant, a nurse, and 4 surveyors) were put together to collect reliable and precise information together with an initial diagnosis. The team received a 2 day theoretical and practical training by the neurologist and public health specialist. The team visits took place between 08:30 am and 04:00 pm on both weekdays and the weekend. The Gazipaşa study was made between April and May 2012, Artvin study was made on May to June 2012 and Ordu study was made between November- December 2012. All doors were knocked on and residents were interviewed. If children and the elderly could not answer the questions, a family member was interviewed in their place. If no one was home, the teams moved on to the next address. The same home was revisited the following days. The field study lasted around 6 weeks for each city.

## 2.4. The field study

**Phase 1:** For the adults and children who were able to cooperate, the questions were asked directly and the questionnaires were

filled in. For those who could not cooperate, the questions were asked to the people accompanying them. If a person answered affirmatively to 1 or more of the questions in the section about MS symptoms, the neurology assistant in the team examined the persons.

**Phase 2:** The patients who had been provisionally diagnosed with demyelinating disease, MS, optic neuritis or paraplegia during the field visits by the field teams were called to the hospital to be examined by an experienced neurologist. Those unable to come were visited and examined in their homes.

## 2.5. Informed consent

Verbal consent was obtained from all individuals during the screening survey. Adequate time was given to participants to consider participation.

## 2.6. Sample size calculation

**2.6.1. Gazipaşa.** The population of Gazipaşa was 22,332. We calculated the sample size with a confidence level of 99% and an error margin of 0.01%. Totally, 13,451 of the targeted population were screened. Every 2 of 3 houses were visited in each street.

**2.6.2. Artvin.** The population was 25,771. We calculated the sample size with a confidence level of 99% and an error margin of 0.01%. Totally, 16,116 of the targeted population were screened. Every 2 of 3 houses were visited in each street.

**2.6.3. Ordu.** The population of the city centre was 147,913. We calculated the sample size with a confidence level of 95% and an error margin of 0.5%. Totally, 28,800 of the targeted population were screened. Every fifth house was visited in each street.

**2.6.4. Diagnosis.** At the completion of the screening, all participants suspected to have MS were examined by the neurologist. Previous laboratory results and magnetic resonance imaging (MRI) images were re-examined. All findings were recorded, any further investigation including immunological screening and MRI was carried out a nearby hospital. McDonald diagnostic criteria for the diagnosis of MS was used.<sup>[15]</sup> The Kurtzke's Expanded Disability Status Scale (EDSS) was used to evaluate the status of neurological disability.<sup>[16]</sup>

## 2.7. Statistical methods

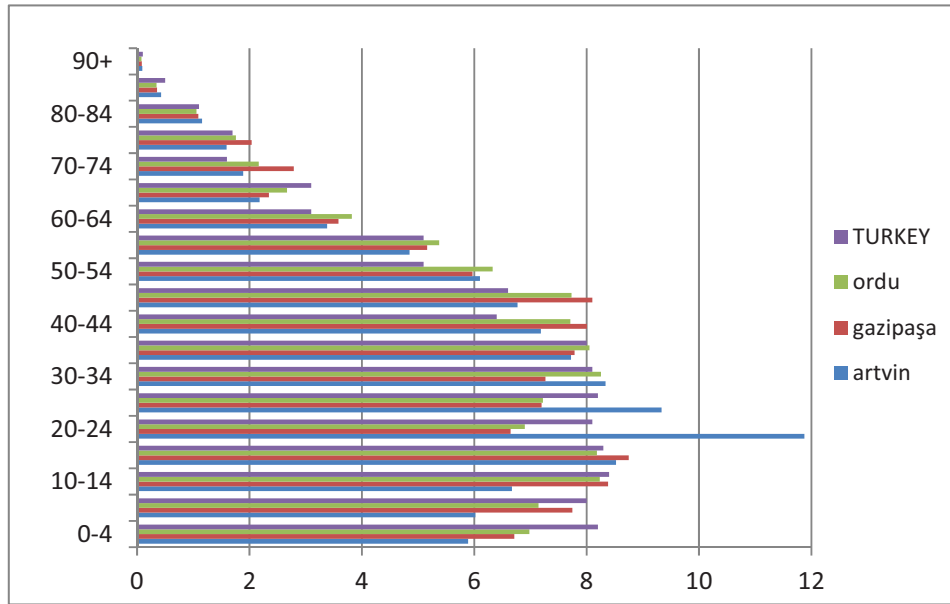
The SPSS 11.5 (version 11.5, SPSS Inc., Chicago, IL) was used for the calculation of frequency distributions and percentages. All the data used in analyses had normal distribution, thus we used parametric methods. The Minitab-16, statistics software (version 16, SPSS Inc.), was used for calculating the Poisson confidence intervals.

## 3. Results

### 3.1. Gazipaşa

In total, 13,451 people were visited. Practically no one (37 persons) refused to participate. Preliminarily, 11 patients were suspected with MS, 7 patients were diagnosed with clinically definitive MS according to the McDonald Criteria 2010. Others were diagnosed with primary lateral sclerosis, dementia and migraine. The female-male ratio was found to be 1.3. A total of 6 patients had relapsing-remitting multiple sclerosis (RRMS) and

## Age distribution (%) graphic of males



## Age distribution (%) graphic of females

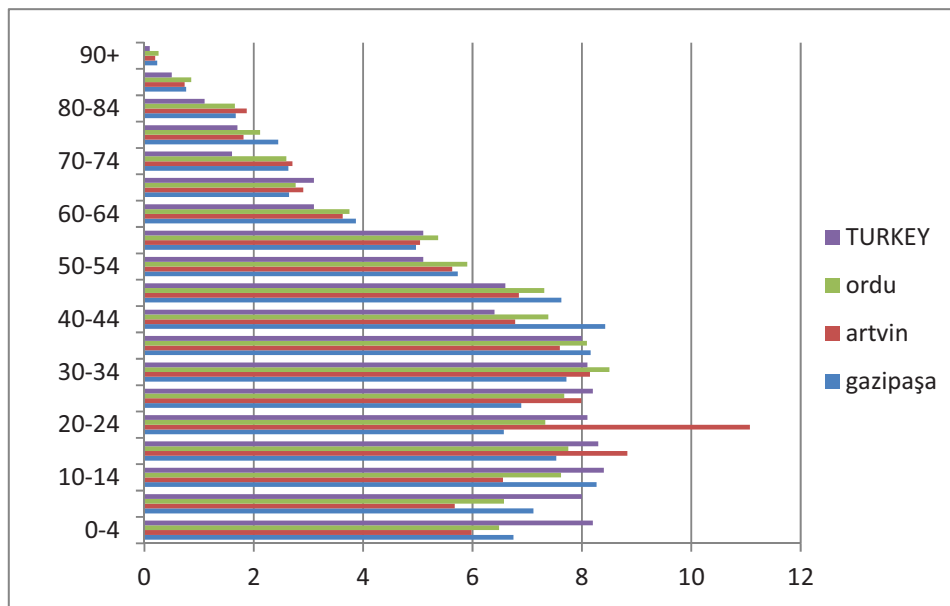


Figure 1. Age distributions of cities and general Turkish populations.

1 patient had secondary progressive multiple sclerosis (SPMS). The average age of the patients was  $39.7 \pm 9.9$ . The mean onset age of the disease was  $31.6 \pm 10.4$ . The mean EDSS of the patients was found to be  $4.0 \pm 1.5$ . Also, the mean duration of the disease was  $8.1 \pm 4.6$  years. The MS prevalence was found to be 52.0 per 100,000 of the total population. It was found to be 46.8/100,000 after age standardization.

### 3.2. Artvin

A total of 16,116 people were screened. Practically no one (51 persons) refused to participate. 9 people who were suspected of

having MS were later neurologically examined and radiological and laboratory findings were checked by our team. 3 patients were diagnosed with clinically definitive MS. Others were diagnosed with optic neuritis, cervical radiculopathy, panic disorder and essential tremor. All MS patients were diagnosed before the study, all were female, but 1 of them was RRMS and 1 was SPMS. The mean age of the patients was  $42.7 \pm 2.3$  and the mean age of MS onset was found to be  $25.7 \pm 10.7$ . The mean EDSS of the patients was  $3.2 \pm 2.2$ . The average duration of the disease was  $17 \pm 9.6$  years. The prevalence of MS was 18.6 per 100,000 in Artvin and it was 17.1/100,000 after age standardization.

### 3.3. Ordu

We intended to cover about one-fifth (28800) of the total population (147,913). Practically no one (94 persons) refused to participate. 21 people who were suspected as having MS, were neurologically examined and their laboratory and radiological findings were also checked. 16 patients who were diagnosed with clinically definitive MS were also diagnosed with MS before the screening. Others were diagnosed with systemic lupus erythematosus, Parkinson's disease, muscular dystrophy and radiologically isolated syndrome. Out of all the clinically definitive MS patients, 10 were female and 6 were male. Female to male ratio was 1.6. In addition, 12 patients were RRMS and 4 were SPMS. The mean age of the patients was  $41.1 \pm 11$ . The average age at the onset of the disease was found as  $34.6 \pm 12.7$  and the mean duration of the disease was found as  $6.81 \pm 5.6$  years. Also, the mean EDSS was found to be  $2.8 \pm 1.6$ .

One female patient was diagnosed with systemic lupus erythematosus by her rheumatologist a year ago. Two male patients had Parkinson's disease and 1 male patient was diagnosed with muscular dystrophy. A female patient who had headaches had normal neurological findings. The brain MRI was performed in the local hospital and demyelinating lesions were found. She was diagnosed with radiologically isolated syndrome by our team. The prevalence of MS was found to be 55.5 per 100,000. After age standardization, it was found to be 52.0/100,000.

### 3.4. Summation

In the 3 areas where we conducted our survey, 26 patients were diagnosed with clinically definite MS. The mean age of the patients was  $40.3 \pm 10$  years. 18 of these patients were female and 8 were male. The female/male ratio was 2.25. The clinical course of the disease was RRMS in 19 and SPMS in 7 cases. The mean onset of the disease was  $31.6 \pm 12$  years. The mean duration of the disease was  $8.7 \pm 6.3$  years. The mean EDSS of the patients was  $3.2 \pm 1.7$ . No patients had a family history of MS.

All patients had cranial MRI, which supported the diagnosis. The cerebrospinal fluid (CSF) analyzed was examined in 12 patients and oligoclonal band was positive for 7 of them. Visual-evoked potentials had been undertaken on 9 of the patients, and only 4 patients had prolonged p100 latency. The demographical and clinical characteristics of the patients are shown in Table 1. The initial symptoms of the patients are shown in Table 2.

## 4. Discussion

This study estimated the prevalence rate of 2 cities in the Black Sea region and 1 coastal city in the Mediterranean region. Until

**Table 1**

**Demographical and clinical characteristics of the patients.**

Mean Age (years)	40.3 ± 10
Female/Male	2.25
RRMS/SPMS	19/7
Disease onset (mean, years)	31.6 ± 12
Disease duration (mean, years)	8.7 ± 6.3
EDSS (mean)	3.2 ± 1.7
OCB (+/-)	7/5
VEP (+/-)	4/5

EDSS = Expanded Disability State Scale; multiple sclerosis; OCB = oligoclonal band; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive; VEP = visual evoked potential.

**Table 2**

**Initial symptoms of the clinically definite MS patients; number of the patients.**

	Ordu	Artvin	Gazipaşa	Total
Pyramidal	2	1	3	6
Cerebellar	1			1
Brainstem	5	1		6
Sensory	3	1	2	6
Visual	5		2	7
Autonomic				
Mental				

now, there has been no estimated prevalence of MS in the Mediterranean region of Turkey. The results are surprising. The prevalence in Artvin was found to be 18.6/100,000 and the prevalence in Ordu was found to be 55.5/100,000. The 2 are located on the Black Sea Coast. The prevalence of Gazipaşa was 52.0/100,000, which is located on the Mediterranean coast.

In the Black Sea region, 2 cities, Artvin and Ordu have similar geographical and climatic characteristics. However, Ordu has an almost 3 times higher prevalence of MS than Artvin. Gazipaşa and Ordu have almost the same prevalence rate, despite 1 being in the Black Sea region and 1 in the Mediterranean region. This shows a discrepancy as the 2 areas have different climatic characteristics. This discrepancy cannot be explained by geographical, climatic, racial or methodological differences as the study was conducted by the same team, using the same methods and within the same Turkish population. While our previous studies showed that the prevalence of MS in Istanbul was 101.4/100,000, Geyve, a neighboring city at the same latitude, showed a prevalence of 41.1/100,000.<sup>[8,9]</sup> This demonstrates a similar discrepancy to that of Ordu and Artvin.

Many environmental factors can be considered as contributing factors when discussing the etiology of MS. Previous studies have shown that, in general, the more industrialized a city, the higher the prevalence rate.<sup>[17]</sup> However, despite Ordu being a more highly industrialized city than Gazipaşa, the prevalence rates are very similar. The reason for this may be explained by the pesticides and herbicides used by farmers in their greenhouses or unknown environmental factors may also be the cause. Greenhouse cultivation is very common and it is the main source of income in Gazipaşa. According to farmers' statement, they use extensive pesticides and herbicides senselessly. The lowest prevalence rate was found in Artvin, a city with no industrialization and a generally undisturbed natural environment. Some studies also have shown a correlation between prevalence rates and special types of heavy industry.<sup>[18]</sup> A study in Ordu investigated the concentration of heavy metals in lichen samples known to be indicator plants of pollutants, found there to be high levels of heavy metals. This could be related to industrial, urban pollution.<sup>[19]</sup>

Recent studies have shown that low sun exposure and low vitamin D level associated with a high prevalence of MS.<sup>[20]</sup> Mediterranean regions have a higher level of sun exposure than those in the Black Sea Coast. However, the prevalence rates of Ordu (in the Black Sea region) and Gazipaşa (in the Mediterranean Sea region) are very similar and the prevalence rate of Artvin is much lower than Gazipaşa. Another study, conducted on the Greek Island Crete, showed that the sun exposure rate in a control group is similar to an MS group.<sup>[21]</sup>

Furthermore, some published studies reported an association between latitude and MS with increasing risk of MS from South to North.<sup>[22]</sup> However, this latitude gradient was not observed in some areas of Italy, Northern Europe, and Iran.<sup>[17,22,23]</sup> No latitude difference was observed regarding the prevalence from Southern to Northern Turkey.

Recent studies showed a substantial increase in MS incidence and prevalence in Mediterranean regions and the Middle East. Our previous studies and this study show that Turkey is a region with a high prevalence rate which is similar to figures reported in Western countries in the Middle East countries and Mediterranean countries.<sup>[3,4,17,24]</sup>

In North Eastern Greece, a neighbor of Turkey, the prevalence rate recorded was 111.6/100,000 in 2006.<sup>[25]</sup>

In Middle Eastern countries, limited data is available on the prevalence rate of MS.<sup>[4]</sup> Much of it comes from hospital-based studies. In Iran, Turkey's neighbor, some studies reported that the prevalence rate has increased dramatically. The national MS prevalence rate in Iran was calculated at 54.5/100,000 in 2013.<sup>[17]</sup>

#### 4.1. Limitations of the study

The disadvantage of the cross-sectional study is that some patients are unwilling to discuss their health problem or they may have forgotten any light attacks that they may have had in the past. In addition, while identifying the onset of disease and its' duration, recall bias may have occurred. Despite there were scarcely any immigrants, migration could be a possible bias. Another limitation is that other diseases that mimic MS such as neuromyelitis optica spectrum disorder and neurodegenerative diseases can be misdiagnosed with MS even by experts. Furthermore, sampling technique might be inadequate to project the entire population.

#### 4.2. Strengths of the study

This study was carried out as a door-to-door study, compared to other studies which used administrative records or hospital-based methods. During the screening, there was a neurology assistant in the field in each team at all times. Each diagnosis of MS was confirmed by 2 different neurologists, 1 field neurologist and 1 resident neurologist. This further eliminates any potential for bias.

### 5. Conclusion

In summary, this is the first time that a study has been conducted in a city on the Mediterranean Coast of Turkey. In general, Turkey has a high prevalence rate of MS and this figure varies from region to region as well as in the same region. Second, no significant latitude difference was observed from southern to northern Turkey. Further investigations are needed to confirm these results and our recommendation is to explore especially the southern cities of Turkey where the data is lacking.

### Acknowledgments

We extend our thanks to John Francis Kurtzke† for comments that greatly improved the manuscript and all residents of the neurological clinic of Kartal Dr Lütfi Kırdar Training and Research Hospital who helped us on this project along with local government authorities of Gazipaşa, Artvin and Ordu. We also thank Jessica Wells for editing and proof reading the manuscripts.

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