Original Article

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Environmental Factors: Possible Reasons for Higher Incidence and Prevalence of Multiple Sclerosis in High-Income Countries

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Abstract

Background: Multiple sclerosis (MS) has had a remarkable increase in prevalence during recent years. This study was conducted to evaluate the correlation between prevalence and incidence of MS with the income level and lifestyle condition of countries with considering the effect of latitude. **Subjects and Methods:** This is an ecological study with secondary data obtained from several sources such as MS International Federation for MS variables data, and World Bank is a reliable source for economic variables. The latitude is also added in all models as an important effective factor. The bivariate correlation and linear regression were used to analyze of data. **Results:** The prevalence of MS in 2013 (54.06/100,000) increased by 9% in comparison to that in 2008 (49.96/100,000). According to fully adjusted analysis, there were significant positive correlations between income level with the incidence and prevalence of MS in reported 2008 and 2013 ($P < 0.05$) throughout the world. Our results revealed that the mean MS prevalence estimates in northern hemisphere, especially in North of America and Europe were different with those in the southern hemisphere. **Conclusion:** MS is more prevalent in high-income countries and the prevalence in developing countries is increasing by economically growth. It seems that environmental factors related to economic determinants are associated with increased incidence and prevalence of MS, further, geographic location continues to influence risk for MS, but these associations require more studies.

Keywords: Ecological study, incidence, multiple sclerosis, prevalence, socioeconomic status

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system that in most cases causes progressive disability. In general, MS onset occurs in the third and fourth decades of life[1] and is more prevalent among women.[2] Based on the results of meta-regression analyses, the incidence and prevalence of MS have increased since 1965.[3] The MS International Federation (MSIF) has reported that, globally, there were about 2.5 million MS patients in 2013.[4] Migration studies and geographical gradients indicate that environmental exposures and pathophysiological causes have a significant influence on MS risk. In fact, complex interactions between MS-related environmental and pathophysiologic as well as genetic factors may contribute to explaining the different distribution.

In recent years, there has been a general increase in MS prevalence for North America and Europe which in large part can be explained by declines in mortality which, at

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least partly, may be explained by changes in lifestyle or environmental exposures.[5] Urbanization,[6] air pollution,[7] and economic development[8] have been pointed out as possible factors contributing to this. Although there are many questions about the effect of socioeconomic statues (SES) on the prevalence and incidence of MS, it has been reported that MS is more prevalent in countries with higher SES.[9] Complex geographical and socioeconomic patterns for MS have been proposed. In the 2008 and 2013 Atlas of MS, the prevalence of MS was greater in countries with higher latitude and income, although the value of prevalence and incidence vary between these countries, and some regions such as the Middle East do not follow this pattern.[10-13] In addition, there is some evidence of an effect of absolute and relative income in national, social, and personal levels on the health situations of people which may influence the incidence and prevalence of diseases.[14] Therefore, it is valuable to study the association between income and prevalence and incidence of MS on a global level, considering the effect of latitude. Furthermore, investigating the economic situation of countries and its relation to prevalence and incidence of MS can be useful for understanding the underlying factors affecting this disease. Finally, the aim of this study was to evaluate the association between MS prevalence and incidence, with the income level of countries considering the effect of latitude and lifestyle.

Subjects and Methods

Data collection

This is an ecological study based on the information reported by the World Health Organization and MSIF in 2008 and 2013.[15,16] The prevalence and incidence of MS (MS variables) were extracted. The income levels of countries were acquired from the World Bank database.[17] The data on smoking were extracted from the Global health observatory (GHO) for tobacco smoking,[18] and in case of obesity and physical activity, the data were obtained from noncommunicable diseases risk factor collaboration[19] and GHO for prevalence of insufficient physical activity,[20] respectively.

The income level of countries was calculated using the Gross National Income and the World Bank Atlas's method.[21] The total income of a country was divided with its population in a specific year to estimate the income per capita (US$) that shows the average income of a citizen in the country of interest. In the present study, we modified the World Bank's classification by merging the low-income and lower-middle income countries into one class (L and LMI), due to the limited number of low-income countries. Therefore, instead of four classifications, three classes of income levels were considered. The classifications of countries were performed based on the information from 2008 and 2013. Countries with incomplete data on income, prevalence, and incidence were considered missing data.

In addition, the countries were classified based on the hemisphere (north and south) and latitude (<25: low latitude, 25–50: moderate, and > 50: high) and entered to analyses accordingly.

Statistical analysis

Average (±standard deviation [SD]) and number (percent) were used to describe quantitative data, respectively. As the MS data in 2013 had less missed data, we have used data in 2013 for analyses.

The bivariate analysis was used to evaluate the correlation between MS variables and income levels of countries in 2013. The correlation between income level and latitude in each hemisphere was also analyzed.

Furthermore, we performed regression analyses, which estimated the effect of income level on MS parameters in 2013 with adjusting the effect of countries latitude. Additional regressions were carried out to investigate the association between latitude and income level with MS variables in northern and southern hemispheres.

Results

Most countries with available data (37.5% and 43.0% in 2008 and 2013) had high-income level. The number of low- and lower-middle income (L and LMI) countries had decreased in 2013 (25.0%), compared to 2008 (33.5%).

The average (±SD) MS prevalence in high-income (HI) countries in 2008 and 2013 report was 87.1 (±54.0) and 97.7 (±63.6), respectively. The incidence was 3.1 (±2.2) in 2008 and 4.6 (±3.7) in 2013. The incidence of MS in HI and upper middle income countries was increased during the study years; however, the incidence in L and LMI countries decreased significantly from 1.8 (±1. 7) in 2008 to 0.4 (±0.2) in 2013 ($P < 0.05$) [Table 1].

The average MS variables based on category of the Earth's hemispheres and latitude presented. The MS prevalence (from 5 to 132/100,000) and incidence (from 1.9 to 7/100,000) increased significantly with increasing latitude during the study period.

Figures 1 and 2 demonstrate the changes in incidence and prevalence of MS in 2008 and 2013. Iceland and Canada were ranked to have the highest MS incidence in 2008 and 2013, respectively. The six countries with the highest incidence in 2008 had changed in 2013. However, most of the countries having the lowest incidence were the same in both years. Guatemala was ranked to have the lowest incidence in both years.

In case of prevalence, except for Canada that had the highest value in both years, the other 15 countries with higher prevalence in 2008 had been changed in 2013 which indicates a dramatic change in MS prevalence during these years. Cameroon and Malawi had the lowest prevalence in 2008 and 2013, respectively. The highest prevalence and incidence variation (Δ) were observed in Denmark and Canada (150/100,000 populations and 9.9/100,000

Table 1: The average of multiple sclerosis variables classified by income level and the earth's hemisphere in 2008 and 2013

Year	Categories	Prevalence[a]		Incidence[a]	
		Average±SD	*P*	Average±SD	*P*
2008	L and LM income	13.1±12.6	**	1.8±1.7	**
	UM income	30.2±27.1		2.7±1.9	
	HI	87.1±54.0		4.1±2.3	
	Total	49.7±41.2		3.1±2.2	
2013	L and LM income	5.1±7.2	**	0.4±0.2	**
	UM income	26.1±23.9		3.1±2.7	
	HI	97.7±63.6		5.9±3.3	
	Total	54.4±51.9		4.6±3.7	

**P<0.01, *P<0.05. [a]Per 100,000 populations. L and LM: Low and lower middle, UM: Upper middle, SD: Standard deviation, HI: High income

populations), respectively.

There were positive significant correlations between income level and incidence and prevalence of MS ($P < 0.05$) [Table 2].

In case of lifestyle indicators, the average body mass index (BMI) was correlated with MS prevalence ($P < 0.05$), but there was no for incidence and BMI ($P > 0.05$). The smoking prevalence was only correlated ($P < 0.05$) with MS prevalence, and there was no correlation between cigarette smoking and incidence of MS ($P > 0.05$). By hemisphere classification, the prevalence and incidence of MS correlated with latitude and income level.

The prevalence and incidence and income level in different countries are illustrated in Figure 3.

Linear regression models demonstrated that both prevalence and incidence of MS increased significantly with increasing income level and latitude ($P < 0.05$). Multivariable regression analyses showed that the latitude and income were statistically positive correlated with prevalence of MS [Table 3]. In case of prevalence, adjusted average BMI had a significant association with the incidence of MS [Table 3].

Table 2: The correlation (*r*) between socioeconomic factors and multiple sclerosis variables (per 100,000 populations) in 2013

independent variables	Prevalence[a]	Incidence[a]
Income	0.73**	0.59**
Latitude	0.83**	0.63**
Average BMI	0.37**	0.10

**P<0.01, [a]Per 100,000 populations. BMI: Body mass index

Table 3: Fully adjusted (*B*=unstandardized coefficient) to explain relationship between socioeconomic factors and multiple sclerosis variables (per 100,000 populations)

Variable	Prevalence[a]	Incidence[a]
Income	21.17**	1.07
Latitude	2.01**	0.13**
Average BMI	1.27	0.83*

**P<0.01, *P<0.05. [a]Per 100,000 populations. BMI: Body mass index

Discussion

The prevalence of MS was increased by 9% from 2008 to 2013. Canada had the highest MS prevalence in 2008 and 2013, but several of the 15 countries with the highest prevalence in 2008 had been replaced by other countries in 2013. Changes in MS incidence, mortality, development of health-care facility (diagnosis and treatment), and migration may explain the changes MS prevalence throughout the world.

Our results indicate that the prevalence of MS has increased in developed and high-income countries as compared to other countries. The accumulation of registered patients has been suggested as one reason for the increased prevalence;[22,23] better accessibility to medical and diagnostic facilities is reported as a driver of the high prevalence of MS in countries with HI. For instance, the prevalence of MS in African countries with less accessibility to diagnostic facilities is low; in European countries, a range of prevalence was obtained, ranging from 189/100,000 in Sweden to 22/100,000 in Albania. These variations have also been observed in Americas so that the prevalence in Argentina was six times higher than that in Ecuador.[15] However, in the case of East Asian countries that possess advanced and accessible medical and diagnostic facilities, the prevalence of MS is low.

Another remarkable finding in this study was the significant difference in the prevalence of MS between northern and southern hemispheres and also its rising and declining trends in northern and southern countries, respectively. Most countries with the high prevalence of MS werel ocated at latitudes higher than 50°. The significant relationship between latitude and prevalence of MS in the northern hemisphere was not found in the southern hemisphere. Our results that one unit increase in latitude causes 2.02 increase in prevalence is not consistent with these recent studies and is in accord with the newly published systematic review by GBD 2016 MS Collaborators.[24]

This difference between results of studies may be related to diversity of used database in these studies; however, it should

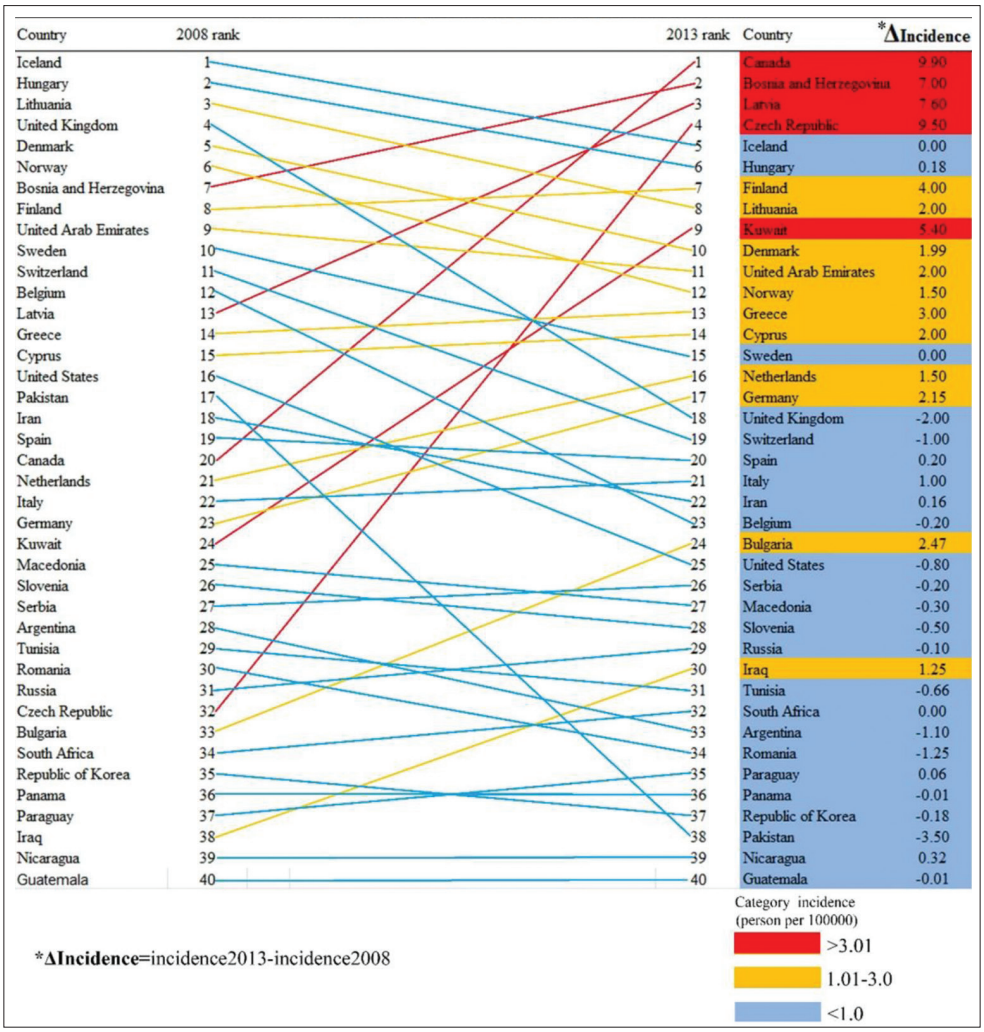

Figure 1: The changes in incidence of multiple sclerosis (per 100,000 populations) in 2008 and 2013

be noted that most of the countries included in this study were from the northern hemisphere that are mainly developed and have HI. Thus, the explanation of this issue parallelly has the same explanation for the difference prevalence among high-income and low-income countries.[25,26]

Both MS prevalence and incidence increased with increasing income [Tables 2 and 3]. The increase in prevalence can be related by change in lifestyle and environmental conditions. Environmental factors such as air pollution and urbanization (which is related to obesity and Vitamin D deficiency) could explain the high prevalence of MS in countries with higher income.[7,27] Studies investigating the relationship between MS and air pollution or urbanization have shown that a complex combination of urbanization-related factors can be associated with the increase in MS prevalence.[6,28]

In countries with higher income and better health services, genetically and physically susceptible people grow and reach older ages. In contrast, in countries with lower income and less development where health services are weak, most susceptible people decease at younger ages, and mainly genetically and physically stronger people reach older ages.[29,30]

Therefore, the population of high-income countries consist of a combination of susceptible and nonsusceptible people, among them susceptible people are at risk for chronic diseases such as MS, while low-income countries mainly consist of nonsusceptible populations with a lower risk of MS. This can be easily noticed in the Atlases of Chronic Diseases.[31,32] In addition, to confirm this hypothesis, we can point to the Middle Eastern countries that have experienced dramatic developments in the health sector during recent decades. Most of the countries with substantial health development such as Iran, Kuwait, Jordan, and Qatar are those with a significant increase in MS prevalence.[33] Besides, the exposures to the population in lower income countries are very different than in HI countries. More infections and animal exposures at an early age occur in lower income countries which may protect against MS (Kurtzke PMSA theory).[34]

From an ecological point of view, we believe that there is a landscape mosaic for MS formed by the social and economic situation of countries. In this landscape, developing countries are located in the middle stages of this trend; while developed countries are at the peak and maturity stages of this evolution,

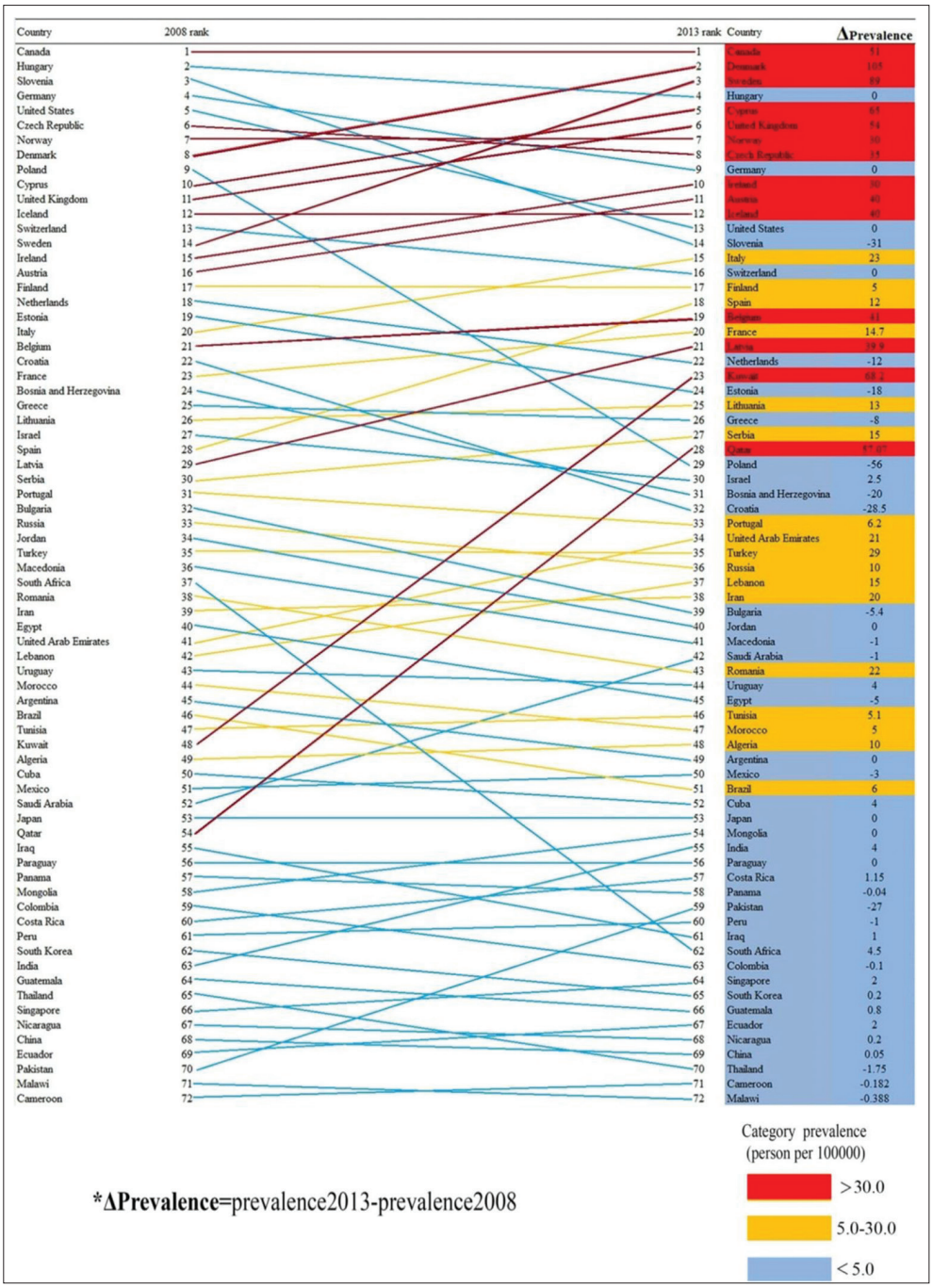

Figure 2: The changes in prevalence of multiple sclerosis (per 100,000 populations) in 2008 and 2013

it is roughly accepted in national scale.[29]

In addition to the relationship of income level with the prevalence and incidence of MS, Figure 1 shows an irregular pattern in the incidence of MS. The six countries with the highest incidence in 2008 were replaced by other countries in 2013. Explaining the reason behind this change is difficult. Outcomes of economic development, such as urbanization, increased prevalence of tobacco smoking, obesity, and decreased physical activity, were addressed as lifestyle factors influencing (29, 30) the prevalence and incidence of MS.[29]

Although this study was conducted on a global scale, the information for many countries was unavailable or missing. In addition, the quality of information for some of the included countries may be suboptimal. We cannot rule out that some of the difference in ranks of countries between 2008 and 2013 may be due to biases in data collection and implementation of registry programs. Such information was not available in our study. Neither did we have the opportunity to take into consideration the different diagnostic criteria for MS used in different countries.

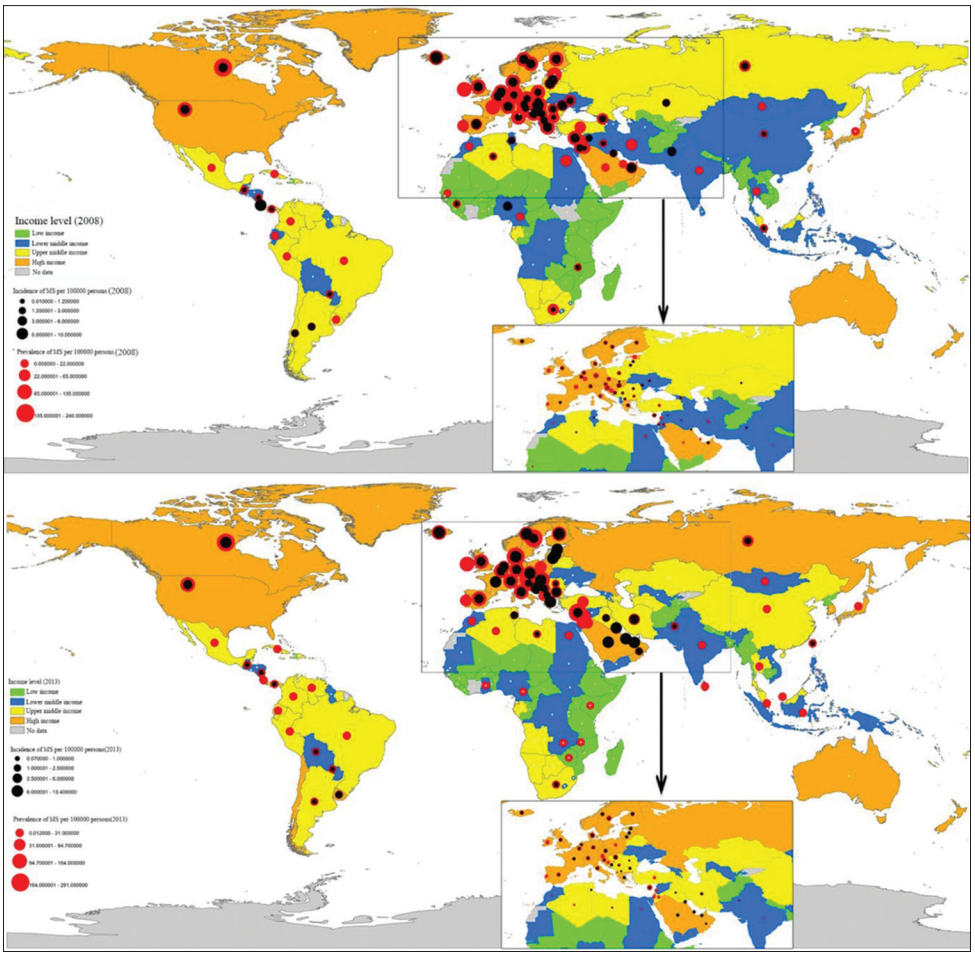

Figure 3: The distribution map of income level, incidence, and prevalence in 2008 and 2013

On the other hand, outcomes of economic development such as urbanization, increased prevalence of tobacco smoking, obesity, and decreased physical activity were addressed as lifestyle factors influencing (29, 30) the prevalence and incidence of MS.

For a better comparison of prevalence or incidence between several regions, the differences in age distribution, race, availability of diagnostic facilities, medical advancements, and presence of screening programs should be considered. Such information was not available in this study.

However, our study provides an overall picture for other researchers to carry out studies at smaller scales. We acknowledge that there has been a set amount of limitations in our study. First, all countries did not have same registry programs which it might cause some over- or underestimates in our results. It also should be noticed that, among countries that had registry programs, patient motivation methods for registering were vary that it was another source of bias. In addition, because of better education and awareness people who are living in developed countries are more inclined to participate in registry programs that is might lead to overestimate in developed countries. On the other hand, data of some cities, or in some cases one city, were addressed as countryside data that they may be differ with actual measures. Readers should be cautious in interpreting the results and interpret the results with consideration of other credible sources.

In addition, it seems that using more recent data of MS and also including other indices related to socioeconomic situation such as human development index or social development index could result in more valuable findings.

Conclusion

Our study illustrates a rise in MS prevalence across the world between 2008 and 2013, more pronounced in developed countries. The majority of developed countries are located in higher latitudes where the ultraviolet exposure and lower natural intake of Vitamin D are significantly less than lower latitudes and areas located near equator. During given years with improvement in economic level and subsequently, lifestyle changes, increasing air pollution and industrial exposures, and improvement of diagnosing facilities, the accumulation of MS cases increased in developing countries. From an ecological aspect, it seems that an ecological sequence based on the social, economic, and welfare situation of countries is occurring.

However, further studies are required for a better understanding of this landscape mosaic.

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Conflicts of interest

There are no conflicts of interest.

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