## Review

# Influence of mountain climate on multiple sclerosis

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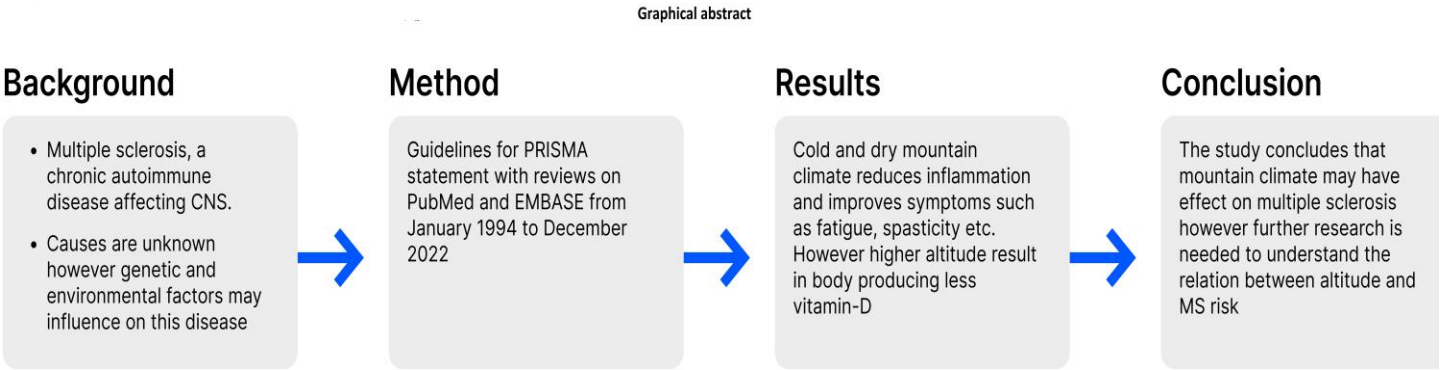
**Abstract**
**Objective:** Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system. Although the exact cause of multiple sclerosis is unknown, it is believed to be a combination of genetic and environmental factors. One of the environmental factors is climate, including the influence of the mountain climate on this disease.
We aimed to analyze current evidence on influence of mountain climate on multiple sclerosis.
**Methods:** We followed the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Reviewers systematically searched Scopus, PubMed and EMBASE for peer-reviewed publications in English from January 1994 to December 2022 reporting MS and influence of mountain climate. The outcome was change in MS incidence rate according to geographical region.
**Results:** The mountainous climate is characterized by high- altitude, low humidity and extreme temperatures, which can have both positive and negative effects on multiple sclerosis. On the one hand, a cold and dry mountain climate can be beneficial for people with multiple sclerosis, as it can reduce inflammation and improve symptoms such as fatigue, cognitive impairment, and spasticity. In addition, high altitude may have a protective effect on multiple sclerosis, as it is associated with a lower incidence rate. On the other hand, mountain climates can also have a negative impact on multiple sclerosis, especially in terms of vitamin D deficiency. Sun exposure is the main source of vitamin D, and people living at higher altitudes get less sunlight due to the thinner atmosphere, resulting in the body producing less vitamin D.
**Conclusion:** Thus, the influence of mountain climate on multiple sclerosis is complex and depends on many factors. Further research is needed to better understand the relationship between altitude and MS risk.




Key words: multiple sclerosis, influence, mountain climate, high altitude, impact, effects
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**Introduction**

Multiple sclerosis (MS) is an autoimmune, inflammatory and neurodegenerative disease of the central nervous system (CNS) (1). Inflammation, demyelination and degeneration of axons are the main pathological mechanisms that cause clinical manifestations. Among diseases of the central nervous system, MS is the most common cause of permanent disability in young people aged of 20 to 40 years (2). The growing arsenal of MS-modifying drugs makes it possible to reduce disability (3) and increase the survival rate of people with MS (4). Consequently, there is an ongoing, urgent need for high-quality epidemiological studies around the world to improve understanding of disease risk and to meet patient needs.

According to a number of studies, MS is registered more often among the population living in northern latitudes, where the climate is colder and less sunny (5).

For example, in Northern Europe, Canada, and the Scandinavian countries, the number of MS cases is between 100 and 300 per 100, 000 population, while in subtropical and equatorial regions such as Africa, Asia, and South America, the incidence is much lower, at less than 5 cases per 100.000 population. This is due to the fact that in more northern regions, the population is more likely to experience vitamin D deficiency, which may be associated with the occurrence of MS (6). In addition, genetic factors and the environment can also influence the occurrence of the disease (7).

In the data of the Multiple Sclerosis Atlas published in 2013 and 2020, female patients make up the majority – 74%, while men - 26%, however, men have a more unfavorable, progressive form of the disease (8, 9). In Scandinavian countries such as Sweden and Finland, gender differences are even more pronounced, where the ratio of women to men reaches 4 to 1.

According to the World Health Organization (WHO), the number of MS cases has been increasing in many countries over the past decade. If in 2013, according to WHO estimates, there were about 2.3 million people suffering from MS in the world, then in 2020 this number increased to 2.8 million (10). However, it should be noted that the increase in the number of MS cases is largely due to improved diagnosis and registration of the disease in various countries, as well as an increase in the life expectancy of the MS population (11).

We aimed to analyze current evidence on influence of mountain climate on multiple sclerosis.

**Methods**

We conducted a literature review and reported results according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA).

**Search strategy**

Search terms had to combine information with main terms, i.e. multiple sclerosis, influence, mountain climate, high altitude, impact, effects. For each of main terms, PubMed and EMBASE were searched using both free text and MeSH and EMTREE terms. The PubMed search was synthetically organized in this way: (Influence of mountain climate) AND (Multiple sclerosis) OR (High altitude) AND (MS) OR (Multiple sclerosis). Similarly, the EMBASE search was synthetically organized in this way: (Effects of mountain climate) AND (MS) OR (Impact of high altitude) AND (Multiple sclerosis). PubMed and EMBASE were searched covering the period between January 1st 1997 and December 31st, 2022, majority had to be from January 1st 2018 to December 31st 2022 looking for record in English and with an abstract. To be eligible and be evaluated in full texts, records had to be referred to primary research and to report, in titles and abstracts, information on influence of mountain climate on multiple sclerosis. Authors were instructed to select records if they: a) referred to MS; b) were primary research articles; c) mentioned influence of high altitude, geographical location and climate; d) mentioned prevalence of MS.

**Prevalence of MS at various altitudes**

The correlation between the incidence of MS and geographical latitude was shown in early studies by Kurtzke J. F. (2000) (12). MS is known to occur more frequently in high latitudes, mainly in Europe, North America, and Scandinavia (13). However, in recent decades, the understanding of the epidemiology of MS has changed significantly. Currently, scientists believe that the geographical distribution of MS is associated with a complex interaction of both genetic, environmental and immunological factors. This may explain the relatively low frequency of MS in Asia and Africa, despite the fact that they are located in the same latitude range as Europe (14).

In general, Europe is one of the regions with a high prevalence of MS - 133/100 000 (15). However, there are geographical differences in the prevalence of MS within Europe as well.

For example, high prevalence rates of MS have been reported in Northern Europe, such as Finland, Sweden and Norway, where the number of cases per 100,000 population reaches 100-150. At the same time, in Southern Europe, for example, in Spain and Italy, the prevalence of MS is much lower and amounts to about 30-50 cases per 100,000 population (16).

As for mountain Kyrgyzstan, the last data on prevalence of MS was studied almost 40 years ago (1981), and it was 5,2 /100000 population (3,2 – among Kyrgyz ethnicity, and 10,8 among non-indigenous) (17).

**Features of the mountain climate**

Mountain climate usually differs from those of lower-lying areas because they are cooler and wetter, with more precipitation and temperature variations throughout the day. High-altitude climates can also be characterized by low pressure, higher ultraviolet radiation, and less oxygen in the air (18).

Mountain climate can have a diverse impact not only on the dynamics of multiple sclerosis, but also on the course of other neurological diseases. For example, people who suffer from migraine may experience worsening symptoms in mountainous environments, especially due to changes in atmospheric pressure and oxygen. This can cause headache, nausea, and vomiting, as well as other migraine-related symptoms (19). There is evidence for the impact of mountain climates on the course of Parkinson's disease, although research in this area is still mixed. For example, a 2018 meta-analysis showed that people living in mountainous regions have a lower risk of developing Parkinson's disease than those living in low-lying areas, but this relationship has not been confirmed in further studies (20). At the same time, for some people, the mountain climate can be beneficial. For example, mountain air is considered beneficial for people with asthma, as the air is cleaner and drier, which helps to reduce lung inflammation. In each case, many factors must be taken into account, such as the specific disease, climatic conditions, geographical location, and many others, in order to more accurately assess the impact of the mountain climate on a particular disease.

The mountain climate can have both positive and negative effects on the course of multiple sclerosis, and its impact today is difficult to assess unambiguously (21). A follow-up study from 2007 showed that in most MS patients, there is a link between climate conditions, geographical location and the prevalence of MS (22).

**Negative impact of mountainous terrain on MS patients**

There are studies that indicate that residents of mountainous regions have a higher risk of MS compared to residents of low-lying areas. A number of such studies were conducted in Switzerland where it was found that residents of mountainous regions of Switzerland had a higher risk of MS than residents of low-lying areas. In particular, it was found that the frequency of MS was 30% higher in residents, living at an altitude of more than 800 meters above sea level, compared with residents of low-mountain areas. The authors suggested that this might be due to lower vitamin D levels in mountain dwellers caused by limited access to sunlight in mountain environments, exposure to magnetic fields and other factors related to the high-altitude environment, as well as a higher incidence of infections that may play a role in the development of MS (23, 24).

However, in a study conducted in Italy by Puthenparampil et al. (25), no such connection was found. According to the authors, genetic or other environmental factors in the Italian highlands do not have the same impact on the incidence of MS as in Switzerland (25).

In 2017, Hedström et al. (26) analyzed data of more than 21 000 MS patients and more than 68 000 healthy control groups living in different regions of Sweden. Analysis of the data obtained showed that residents of high-mountain areas had a higher frequency of MS than residents of low-mountain areas. However, authors note that other factors such as socio-economic status and genetic factors may influence this outcome, and caution that further observations are needed to confirm the relationship between high-altitude life and multiple sclerosis risk (26).

In addition, purulent climate can also worsen the course of MS. This is due to the fact that climatic conditions can contribute to the development of stress, which can lead to exacerbations of the disease (27).

The mountain climate, in turn, is characterized by lower atmospheric pressure, lower oxygen concentrations, and more ultraviolet rays, which was confirmed in a study conducted in 2005 in China. Scientists have suggested that low atmospheric pressure at altitude and lower oxygen concentrations may lead to lower blood oxygen levels and worse MS symptoms, such as fatigue, weakness, motor neuron dysfunction, and other neurological manifestations.

Excess UV rays can also have a negative impact on the health status of people with MS, as they can cause inflammatory processes and damage to myelin in the nervous system (28).

All of these factors can have a negative impact on the human immune system and increase the risk of MS. However, there is evidence that some patients may feel better in dry climates and high temperatures (29).

**Favorable effects of the mountain climate on the course of MS**

There is also evidence that people living in mountainous regions may be more susceptible to severe MS, possibly due to higher levels of UV rays, increased immune system activity, and higher altitude, which may increase the risk of developing other health problems (30).

Moreover, a number of publications indicate that the climatic conditions of the highlands can prevent the occurrence of MS. For example, in a study conducted among residents of the Andean Mountain range in South America suffering from MS and living in different regions of the country, it was found that the population living at altitudes above 3000 meters had significantly fewer cases of MS than the population living at lower altitudes. The authors suggested that this might be due to lower infection rates and higher sun exposure at altitude, which may have a protective effect against MS (31). In a study that examined the prevalence of MS in Chile, it was found that residents of high-altitude areas had a lower incidence of MS than residents of low-altitude areas. It has been suggested that this may be due to the fact that the level of ultraviolet radiation is higher at altitude, which leads to higher levels of vitamin D in the body (32).

In a number of studies also conducted in South America, it was shown that local residents living at an altitude of more than 4,000 meters have a lower risk of MS than the population living at lower altitudes. The authors attributed this tendency to the fact that high-altitude residents have a better adaptation to low levels of oxygen in the air, which helps them to use oxygen in their tissues more efficiently. In addition, the presence of other risk factors, such as smoking or environmental pollution, can also increase the likelihood of MS, even in residents of high-altitude regions (33).

Another studies, indicates that the mountain climate can help to reduce inflammatory processes in MS. For example, lower oxygen levels in mountainous regions can stimulate the production of erythropoietin, which in turn can have an anti-inflammatory effect (34). In addition, mountain regions may be less polluted than cities and other urbanized areas, which may help to reduce the environment that causes inflammation.

The low risk of developing MS in high-altitude regions may also be related to the fact that high-altitude climates are characterized by a lower level of oxygen pressure than in low-altitude regions, which in turn can lead to changes in the body's immune system. For example, the level of cytokines, inflammatory proteins that play an important role in the development of MS, can be reduced under low oxygen conditions (35).

In addition, the mountain climate can affect the level of physical activity, the quality of sleep and the presence of stress in people living in this region. Some evidence suggests that increasing the level of physical activity and reducing stress can reduce the risk of MS and improve the course of the disease (6).

**Conclusion**

There is the lower prevalence of MS in high altitudes. The influence of mountain climate on multiple sclerosis is complex and depends on many factors. Research on the impact of mountain climate on multiple sclerosis is still limited and controversial. However, it should be noted that the scientific understanding of the impact of mountain climate on MS still requires additional study. In fact, individual factors, such as the severity of the disease and the general health of the patient, can also influence how the body reacts to the mountain climate. Further research is needed to better understand the relationship between altitude and MS risk.

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**References**

1.Rodríguez Murúa S , Farez MS , Francisco J Quintana FJ. The immune response in multiple sclerosis. Rev Pathol 2022; 17: 121-39. doi: 10.1146/annurev-pathol-052920-040318

2.Jusupova AT, Kadyrova BB, Dzhaparalieva NT, Kulov BB. Analysis of the risk factors and the prevalence of multiple sclerosis (literature review). Vestnik KRSU 2022; 22: 121-6.

3.Washington F, Langdon D. Factors affecting adherence to disease-modifying therapies in multiple sclerosis: systematic review. J Neurol 2022; 269: 1861-72. doi: 10.1007/s00415-021-10850-w

4.Ostolaza A, Corroza J, Ayuso T. Multiple sclerosis and aging: comorbidity and treatment challenges. Mult Scler Rel Dis ; 50: 102815 Doi: 10.1016/j.msard.2021.102815
5.Simpson S Jr., Wang W, Otahal P, Blizzard L, van der Mei IAF, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J Neurol Neurosurg Psychiatry 2019; 90: 1193-2000.
6.Scazzone C, Agnello L, Bivona G, Lo Sasso B, Ciaccio M. Vitamin D and genetic susceptibility to multiple sclerosis. Biochemistr Gen 2021; 59: 1-30. doi: 10.1007/s10528-020-10010-1
7.Alfredsson L, Olsson T. Lifestyle and environmental factors in multiple sclerosis. Cold Spring Harb Perspect Med 2019; 9: a028944. doi: 10.1101/cshperspect.a028944
8.Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurol 2014; 83: 1022–4. DOI: 10.1212/WNL.0000000000000768
9.Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Multipl Scler 2020; 26: 1816-21. doi: 0.1177/1352458520970841
10.Wallin M, Culpepper W, Campbell J, Nelson LM, Langer-Gould A, Ann Marrie R, et al. The prevalence of MS in the United States – A population-based estimate using health claims data. Neurology 2019; 92: 1029–40. doi: 10.1212/WNL.0000000000007035
11.Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol 2019; 26: 27-40. doi: 10.1111/ene.13819
12.Kurtzke JF. Multiple sclerosis in time and space-geographic clues to cause. J Neurovirol 2000; 6 Suppl 2: S134-40.
13.Lane J, Ng HS, Poyser C, Lucas RM, Tremlett H. Multiple sclerosis incidence: A systematic review of change over time by geographical region. Mult Scler Relat Dis 2022l; 63: 103932. doi: 10.1016/j.msard.2022.103932
14.Cheong WL, Mohan D, Warren N, Reidpath DD. Multiple sclerosis in the Asia Pacific region: A systematic review of a neglected neurological disease. Front Neurol 2018; 9: 1533-41. doi: 10.3389/fneur.2018.00432
15.Multiple Sclerosis International Federation. Atlas of MS 2020: Mapping multiple sclerosis around the world. Available at: URL: https://www.msif.org/wp-content/uploads/2020/12/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf
16.Koutsouraki E, Costa V, Baloyannis, S, Baloyannis I. Epidemiology of multiple sclerosis in Europe: A Review. Intern Rev Psychiatr 2010; 22: 2-13. doi: 10.3109/09540261003589216
17.Toktomushev Ch.T. Clinical forms and features of the course of multiple sclerosis in the conditions of the mountain climate of Kyrgyzstan: Dis. cand. Med. Sci.: (14. 00. 13). - M., 1981.
18.Gottfried M, Pauli H, Futschik A, Akhalkatsi M, Barancok P, Alonso B, et al.. Continent-wide response of mountain vegetation to climate change. Nature Climate Change 2012;2: 111-5. doi: 10.1038/nclimate1329
19.Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007; 68: 343-9. doi: 10.1212/01.wnl.0000252808.97649.21
20.Bellou A, Belbalis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. Parkinson Rel Dis 2016; 23: 1-9. doi: 10.1016/j.parkreldis.2015.12.008
21.Kamm CP, Uitdehaag BM, Polman CH. Multiple sclerosis: current knowledge and future outlook. Eur Neurol 2014; 72: 132-41. DOI: 10.1159/000360528
22.Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol 2004; 3: 709-18. doi: 10.1016/S1474-4422(04)00933-0
23.Beer S, Kesselring J. Multiple sclerosis in the Bern canton (Switzerland). An epidemiologic study. Thieme 1988; 56: 394-401. doi: 10.1055/s-2007-1001802
24.Beer S, Kesselring J. High prevalence of multiple sclerosis in Switzerland. Neuroepidemiol 1994; 13: 14-8. doi: 10.1159/000110353
25.Puthenparampil M, Perini P, Bergamaschi R, Capobianco M, Filippi M, Gallo P. Multiple sclerosis epidemiological trends in Italy highlight the environmental risk factors. J Neurol 2022; 269: 1817-24. doi: 10.1007/s00415-021-10782-5
26.Hedstrom AK, Hillert J, Olsson T, Alfredsson L. Smoking and multiple sclerosis susceptibility. Eur J Epidemiol 2013; 28: 867–74. doi: 10.1007/s10654-013-9853-4 PMID: 24146047
27.Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis. JAMA Neurol 2001; 58: 1081-6. doi: 10.1001/archneur.58.7.1081

28.Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Nat Acad Sci 2007; 104 (Suppl 1): 8655-60. DOI: 10.1073/pnas.0701985104
29.Gorman C, Lucas R, Taylor B. Environmental Risk Factors for Multiple Sclerosis: A Review with a focus on molecular mechanisms. Int J Mol Sci 2012; 13: 11718–52. doi: 10.3390/ijms130911718
30.Pugliatti M, Harbo H, Holmoy T, Kampman MT, Myhr KM, Riise T, Woldson C. Environmental risk factors in multiple sclerosis. Acta Neurol Scandin Suppl 2008; 188: 34-40. doi: 10.1111/j.1600-0404.2008.01029.x
31.Correale J, Farez M, Galtan MI. Environmental factors influencing multiple sclerosis in Latin America. Mult Scler J Exp Transl Clin 2017; 3: 2055217317715049 doi: 10.1177/2055217317715049
32.Skalli A, Haddou EH, Jaoudi R, Razine R, Mpandzou GA, Tibar H, et al. Association of vitamin D status with multiple sclerosis in a case-control study from Morocco. Revue Neurol (Paris) 2018; 174: 150-6. doi: 10.1016/j.neurol.2017.06.030
33.Hernán MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. Brain 2005; 128: 1461-5. doi: 10.1093/brain/awh471
34.Digicaylioglu M, Lipton A. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades. Nature 2001; 412: 641-7. doi: 10.1038/35088074
35.Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. Progr Cardiovasc Dis 2010; 52: 467-84. doi: 10.1016/j.pcad.2010.02.003
36.Motl RW, McAuley E. Physical activity, disability, and quality of life in older adults. Phys Med Rehab Clin North Am 2010; 21: 299-308. doi: 10.1016/j.pmr.2009.12.006