The Effect of Month of Birth on Multiple Sclerosis: A Case-Control Study in Northeast Iran

Mohammad Sarmadi [1,2], Mohsen Ramezani Nezhad [3,4], Farhan Asgari Hasanluyi[5], Fereshteh Najafi[6], Ali Tamaddon[7], Sajjad Rahimi [1,2]

Abstract

Background: Multiple sclerosis (MS) is an autoimmune and multi-factorial (e.g. environmental, genetic) disease. We conducted a case-control study of month and season of birth (MOB and SOB) and multiple sclerosis (MS) risk in the east of Iran.

Methods: The MS patients registered in Mashhad and Torbat Heydariyeh MS Society until 20 March 2018 was compared with the MOB and SOB in the healthy population during 1988 to 2018. Case group was matched for age, sex and place of residence with the control group. Differences in the distributions of MOB and SOB between the patients and the control groups were assessed using the chi-square test.

Results: There were 2,160 MS patients in case group and 2,245 in control group. There was a significant relationship between MOB ans SOB with the risk of MS ($P<0.05$). Analysis showed a significant ($p<0.01$) peak in the MOB during Mar-Apr (OR=1.60), May-Jun (OR=1.30) and Aug-Sep (OR=2.42).

Conclusion: The findings show a relationship between MOB and SOB as risk factor for MS in Northeast Iran. Further studies are needed to confirm this result.

Keyword: Multiple sclerosis, Month of Birth, seasonality, case-control, Iran

Acta Neurol Taiwan 2022;31:7-14

INTRODUCTION

MS is a chronic inflammatory disease of the central nervous system, which, based on the results of epidemiological studies, is related to interactions between environmental parameters and genetic factors, but the

From the Department of [1]Department of Environmental Health, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran; [2]Health Sciences Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran; [3]Student of Emergency Nurse, School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran; [4]Department of Medical Emergency, School of nursing and midwifery, Bam University of Medical Sciences, Bam, Iran; [5]Student Research Committee, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran; [6]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [7]Iranian Social Security Organization, Kohgiluyeh and Boyer-Ahmad Province Health Administration, Yasuj, Iran

Received June 1, 2021. Revised June 30, 2021.
Accepted July 5, 2021.

Correspondence to: Mohammad Sarmadi. Department of Environmental Health, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
Email: msarmadi2@gmail.com

main reason behind this disease is unknown yet[1,2]. In recent decades, the etiological effects of MS have been studied and various theories have been presented[3,4]. There have been studies on the association between environmental factors and geographical conditions with MS prevalence[5,6]. Various environmental factors, including infectious agents (especially Epstein–Barr virus and helminthes), exposure to chemicals, smoking and socioeconomic factors, can be effective in development of MS[7-9]. Furthermore, urbanization, industrialization, modernization and consequently, lifestyle factors such as reduced activity, unhealthy diet and obesity are among the most important factors in the incidence of MS[10-12]. Therefore, considering environmental factors associated with the month and season of years, variables such as birth time can be effective in development of MS[13]. Several studies have been carried out on this parameter with different results[14,15]. Most studies have been conducted in the northern hemisphere, suggesting the highest incidence of disease in the spring-born persons and the lowest level in the autumn-born persons[15,16]. Due to limited studies on the MOB in Iran, This study was conducted to determine the effect of MOB on MS risk in the eastern part of Iran.

METHODS

This case-control study was conducted in Mashhad metropolitan and Torbat Heydariyeh city, East of Iran (fig. 1), with a population of about 3,615,000 people. The data of the MS Society of Mashhad and Torbat Heydariyeh were collected from January 1988 until March 20, 2018. The study was designed based on the

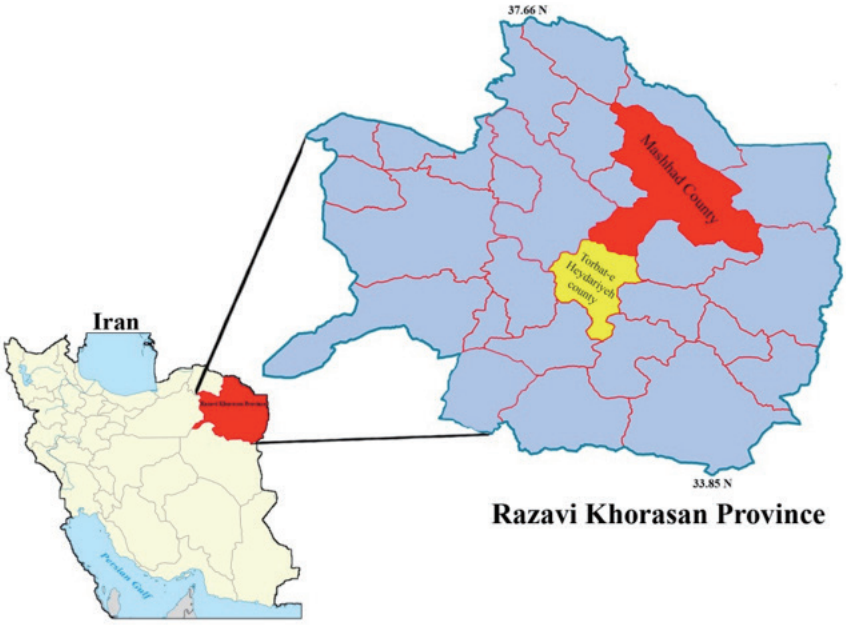

Figure 1. Study location.

For each patient, we consider a code to protect the privacy of individuals. For each MS case, one control was randomly selected from inpatients without major neurological deficits, matched by age, sex, and residential area. After that, the month of birth (MOB) of MS patients was compared to the control group. To investigate the relationship between MS disease and MOB (or SOB), odds' ratio (OR) for each month (or season) compared to other months (or season) and Chi-square test was used. The seasons were grouped as follows: spring (21March–20June), summer (21June–20September), autumn (21September–20December), and winter (21December–20March) based on Iran climate. Statistical analysis was carried out using STATA 14 software. Figure 2 was drawn by Graph pad prism 6 software. This study was approved by the Iran National Committee for Ethics in biomedical Research and Torbat Heydariyeh University of medical sciences (IR.THUMS.REC.1398.045 and IR.THUMS.REC.1395.47).

Table1. Demographic data for case and control groups

		Case=2160	Control:2245	Total : 4405
gender	**Male**	477 (22.1%)	542 (24.1%)	1019
	Female	1683 (77.9%)	1703 (75.9%)	3386
City	**Torbat**	135 (6.2%)	148 (6.6%)	283
	Mashhad	2025 (93.7%)	2097 (93.4%)	4122
Mean age (SD)	**Total**	36.39 (9.41)	37.51 (12.84)	-

Table 2. Odds' ratio distribution by month of birth

Month	Case(n=2160)	Control(n=2245)	OR	P*	95% CI
Farvardin (21Mar-21Apr)	290	198	1.60	<0.001	1.32 – 1.94
Ordiehesht (21Apr-21May)	192	193	1.03	0.73	0.84- 1.27
Khordad (21May-21Jun)	200	163	1.30	0.01	1.05 – 1.61
Tir (21Jun-21Jul)	186	179	1.08	0.44	0.87 – 1.34
Mordad (21Jul-21Aug)	155	191	0.83	0.1	0.66 – 1.03
Shahrivar (21Aug-21Sep)	419	203	2.42	0.0001	2.02 – 2.89
Mehr (21Sep-21Oct)	85	192	0.43	0.0001	0.33 – 0.57
Aban (21Oct-21Nov)	104	182	0.57	0.0001	0.44 – 0.73
Azar (21Nov-21Dec)	121	180	0.68	0.001	0.53 – 0.86
Day (21Dec-21Jan)	135	202	0.67	0.001	0..53 – 0.84
Bahman (21Jan-21Feb)	162	178	0.94	0.59	0.75 – 1.17
Esfand (21Feb-21Mar)	111	184	0.60	0.0001	0.47 – 0.77

*significance in 95% confidence level

Table 3. Odds' ratio distribution by season of birth

Season	Case(n=2160)	Control(n=2245)	OR	P*	95% CI
Spring	682	554	1.40	0.0001	1.23 – 1.60
Summer	760	573	1.58	0.0001	1.39 – 1.80
Fall	310	554	0.51	0.0001	0.43 – 0.59
Winter	408	564	0.69	0.0001	0.60 – 0.80

*significance in 95% confidence level

STROBE checklist[17,18]. In summary, the diagnosis of MS was confirmed by neurologists using MRI images and McDonald diagnostic criteria[19]. Those who could not specify their date of birth or the necessary information were excluded. The details of study are briefly given in Table 1. Study including date of birth, place of birth and gender of patients and control group were gathered.

RESULTS

The total samples comprised of 2160 MS patients and 2245 control subjects. The mean age of patients and controls was 36.39±9.41 and 37.50±12.84 years, respectively. All of the populations were Persian. A summary of the demographic detailed for the case and control groups are showed in Table1.

The odds ratio distribution of MOB for cases and controls are showed in table 2 and Figure 2; also for SOB in table 3 and Figure 2.

The results showed a statistically significant difference between the case and control group in all months except April-March, Jun-July, July-August and January-February (P>0.05). Also, there was a significant difference between the case and control group in different seasons (P<0.01). The spring and summer have odds' ratio greater than 1, but for the autumn and winter, odds' ratio were recorded less than 1.

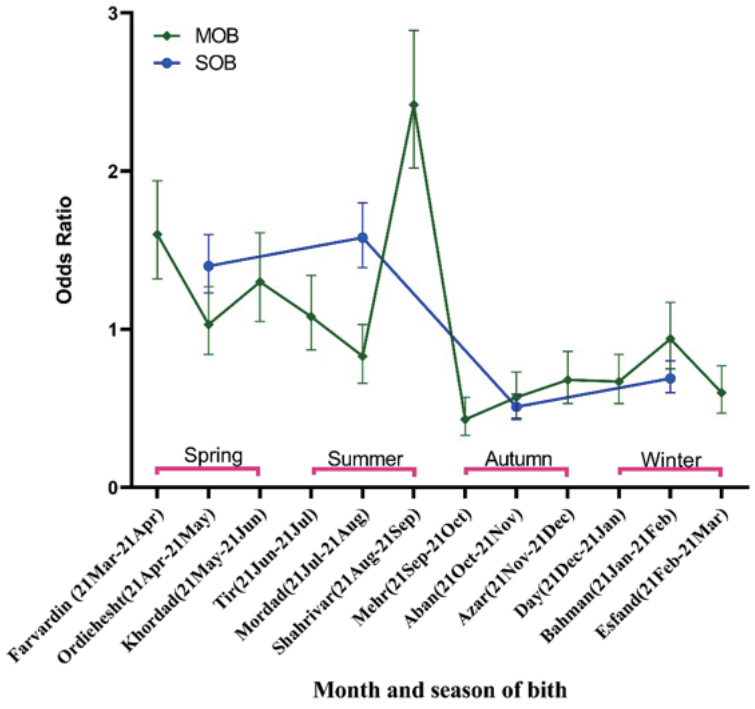

Figure 2. Odds' ratio distribution with 95% CI by month and season of birth

DISCUSSION

Given the unknown etiology of MS and the increased growth of the disease in Iran 20, the aim of this study was to assess the risk of MS in one of the biggest provinces in the east of Iran (Mashhad and Torbat Heydariyeh Cities). Iran is located in a low-risk region of MS, but in some areas, especially Isfahan and Tehran, the prevalence report very high[21]. Some regions in northest Iran also report high prevalence of MS but in small-scale region[19]. Mashhad reported the lowest prevalence of moderate to severe vitamin D deficiency among both women and men[22]. Many studies have been carried out in different regions of the world on two challenging parameters of the season and month of birth, as factors contributing to the development and progression of MS[16,23,24]. We found that most of the births (67%) in the case group occurred in the spring and summer, 21 March-21 September. The spring and summer have odds' ratio >1, which consider a risk factor for MS, but for the autumn and winter, odds' ratio were recorded < 1, which consider a protective factor. This shows that a number of cultural and social factors have affected the birth pattern in different regions. In previeus studies reported that Iranian womens had low level of D vitamin serum. The previous studies represents that vitamin D levels are generally low in Iranian society, especially in women[25,26]. The relationship between vitamin D and the incidence of diseases and sunlight exposure has been explored in studies[27-32]. Iranian female have less exposure to the sunlight due to their culture and lifestyle such as Hijab, which can lead to vitamin D deficiency and, consequently, increased risk of diseases[33,34].

These findings are somewhat matching with the previous studies' results[24,35-37]. According to the previous studies, the association between MS and the birth month is related to the latitude and hemisphere in which the individual is born. For example, in the northern hemisphere, MS cases have been frequently observed in the spring months, and fewer cases are observed in the fall months[14,16,23,35,38,39]. However, in the southern hemisphere, people born in the winter months are at higher risk of developing MS,5 which agrees with the findings of our

study. Our findings revealed an approximate sinusoidal pattern between the MOB and the chance of MS, which had the highest significant correlation in Aug-Sep (OR = 2.42, 95% CI = 2.02 – 2.89, P <0.01).

Considering that the birth peak in the population studied was in February and the sinusoidal pattern of MS was proportional to the birth pattern of the whole study, it seems that in Iran, like other countries with similar latitude, most cases of MS are seen in several months of the spring and summer seasons. A possible reason for this result is maternal exposure to sunlight and consequent vitamin D production[13,40]. The first and second trimesters of the mothers whose children were born through spring and summer had been in the cold seasons (Sutumn and Sinter) that it can lead to vitamin D deficiency during first and second trimesters. Regarding to the importance of these trimesters for the formation and health of the fetus, it can cause future problems[3,5,41]. As well some studies showed a correlation between an increased risk of MS with decreased sun exposure of pregnant mothers and children[5,42,43]. Recent study by Karin Hedström et al. has shown that exposure to sunlight, both directly and indirectly, can increase the risk of developing MS[44]. Also, these findings support the assumption that the hot climate and the ample sun exposure have a protective effect on the risk of developing MS.

In addition, those who spend their first and second trimester in autumn and winter are heavily influenced by various infectious and environmental factors. In these seasons, the attack rates of infectious agents such as measles, rubella, and influenza, have been increased to mothers and increased the risk of developing abnormally tissue and hormone in the fetus, which may lead to an increase in the risk of MS in children[5,45-47]. In addition to many environmental factors that can endanger the health of the fetus during pregnancy, the infections that happened during childhood can also affect the development of MS in different societies[48-50], which require extensive future studies.

In the present study, we had some limitations that have a large number of potential confounding factors in season and month of birth such as, education, smoking, vitamin supplements, genetics, nutritional patterns, living standards and health-care facilities in Iran[24]. On the other hand, a large case-control study and good quality recording of MS data in the MS Society of Khorasan are the strengths of this study.

CONCLUSION

As a general conclusion, this study provides evidence of a seasonal influence of month of birth on multiple sclerosis incidences. Sun exposure and vitamin D may be considered as key factors in the development of MS. Furthermore, the effect of pregnancy time on the probability of developing MS was evident in this region, but further research in this area is needed in another region of Iran.

FUNDING

The authors would like to thank the Student Research Committee of Torbat Heydariyeh University of Medical Sciences for their financial support (under grant No. SRC-98-174) for performing this research.

DATA AVAILABILITY

Data cannot be shared for ethical/privacy reasons. The data underlying this article cannot be shared publicly due to privacy of individuals that participated in the study.

REFERENCES

1. Araki Y, Kinoshita M, Motoyama R, et al. Month of birth in multiple sclerosis with and without longitudinally extensive spinal cord lesions: a study of a Japanese national survey. Journal of the neurological sciences. 2013; 330: 67-70.
2. Kazemi Moghadam V, Dickerson AS, Shahedi F, Bazrafshan E, Seyedhasani SN and Sarmadi M. Association of the global distribution of multiple sclerosis with ultraviolet radiation and air pollution: an ecological study based on GBD data. Environmental Science and Pollution Research. 2021; 28: 17802-11.
3. Givon U, Zeilig G, Dolev M and Achiron A. The month of birth and the incidence of multiple sclerosis in the Israeli population. Neuroepidemiology. 2012; 38: 64-8.

4. Moghaddam VK, Dickerson AS, Bazrafshan E, et al. Socioeconomic determinants of global distribution of multiple sclerosis: an ecological investigation based on Global Burden of Disease data. BMC Neurology. 2021; 21: 145.
5. Staples J, Ponsonby A-L and Lim L. Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. Bmj. 2010; 340: c1640.
6. van der Mei IA, Ponsonby A-L, Blizzard L and Dwyer T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. Neuroepidemiology. 2001; 20: 168-74.
7. Alonso A, Cook SD, Maghzi A-H and Divani AA. A case–control study of risk factors for multiple sclerosis in Iran. Multiple Sclerosis Journal. 2011; 17: 550-5.
8. McAlpine D and Compston A. McAlpine's multiple sclerosis. Elsevier Health Sciences, 2005.
9. Sarmadi M, Bidel Z, Najafi F, et al. Copper concentration in multiple sclerosis: a systematic review and meta-analysis. Multiple Sclerosis and Related Disorders. 2020; 45: 102426.
10. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. The Lancet Neurology. 2004; 3: 709-18.
11. Ebers GC. Environmental factors and multiple sclerosis. The Lancet Neurology. 2008; 7: 268-77.
12. Dehghani R, Yunesian M, Sahraian MA, Gilasi HR and Moghaddam VK. The evaluation of multiple sclerosis dispersal in Iran and its association with urbanization, life style and industry. Iranian journal of public health. 2015; 44: 830.
13. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ and Ebers GC. Timing of birth and risk of multiple sclerosis: population based study. Bmj. 2005; 330: 120.
14. Dobson R, Giovannoni G and Ramagopalan S. The month of birth effect in multiple sclerosis: systematic review, meta-analysis and effect of latitude. J Neurol Neurosurg Psychiatry. 2013; 84: 427-32.
15. Torkildsen Ø, Grytten N, Aarseth J, Myhr KM and Kampman M. Month of birth as a risk factor for multiple sclerosis: an update. Acta Neurologica Scandinavica. 2012; 126: 58-62.
16. Fragoso YD, Adoni T, Almeida SMGd, et al. Multiple sclerosis in South America: month of birth in different latitudes does not seem to interfere with the prevalence or progression of the disease. Arquivos de neuro-psiquiatria. 2013; 71: 573-9.
17. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. International Journal of Surgery. 2014; 12: 1500-24.
18. Von Elm E, Egger M, Altman DG, Pocock SJ, Gøtzsche PC and Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. British Medical Journal. 2007; 335: 806-8.
19. Moghaddam VK, Sarmadi M, Tatari M, Najafi F, Esmaeili A and Hadei M. Epidemiology of Multiple Sclerosis in Torbat-e Heydarieh (Northeast of Iran) during 1982-2016. Multiple sclerosis and related disorders. 2018; 24: 184-9.
20. Sarmadi M, Saravani H, Azizi O, et al. Temporal trends of incidence and prevalence of multiple sclerosis in Razavi Khorasan Province, Northeast Iran. Neurological Sciences. 2021.
21. Pakdel M, Karin Hedström A, Bidkhori M, et al. Do socioeconomic factors affect the prevalence of multiple sclerosis in Iran? Acta Neurologica Scandinavica. 2019; 140: 328-35.
22. Heshmat R, Mohammad K, Majdzadeh SR, et al. Vitamin D Deficiency in Iran: A Multi-center Study among Different Urban Areas. Iranian Journal of Public Health. 1970; 37: 8.
23. Disanto G, Chaplin G, Morahan JM, et al. Month of birth, vitamin D and risk of immune-mediated disease: a case control study. BMC medicine. 2012; 10: 69.
24. Akhtar S, Alroughani R, Al-Shammari A, Al-Abkal J and Ayad Y. Month of birth and risk of multiple sclerosis in Kuwait: A population-based registry study. Multiple Sclerosis Journal. 2015; 21: 147-54.
25. Vatandost S, Jahani M, Afshari A, Amiri MR, Heidarimoghadam R and Mohammadi Y. Prevalence of vitamin D deficiency in Iran: A systematic review and meta-analysis. Nutrition and Health. 2018; 24: 269-78.

26. Hovsepian S, Amini M, Aminorroaya A, Amini P and Iraj B. Prevalence of vitamin D deficiency among adult population of Isfahan City, Iran. J Health Popul Nutr. 2011; 29: 149-55.
27. Delbandi A-A, Torab M, Abdollahi E, et al. Vitamin D deficiency as a risk factor for endometriosis in Iranian women. Journal of Reproductive Immunology. 2021; 143: 103266.
28. Saki F, Dabbaghmanesh MH, Omrani GR and Bakhshayeshkaram M. Vitamin D deficiency and its associated risk factors in children and adolescents in southern Iran. Public Health Nutrition. 2015; 20: 1851-6.
29. Joukar F, Naghipour M, Hassanipour S, Fakhrieh Asl S, Pourshams A and Mansour-Ghanaei F. Vitamin D deficiency associated with reproductive factors in northern Iranian women: The PERSIAN Guilan Cohort Study (PGCS). Clinical Nutrition ESPEN. 2020; 38: 271-6.
30. Rasouli E, Sadeghi N, Parsi A, Hashemi SJ, Nayebi M and Shayesteh A. Relationship Between Vitamin D Deficiency and Disease Activity in Patients with Inflammatory Bowel Disease in Ahvaz, Iran. Clin Exp Gastroenterol. 2020; 13: 419-25.
31. Orjuela-Grimm M, Carreño SB, Liu X, et al. Sunlight exposure in infancy decreases risk of sporadic retinoblastoma, extent of intraocular disease. Cancer Reports. n/a: e1409.
32. Ostkamp P, Salmen A, Pignolet B, et al. Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity. Proceedings of the National Academy of Sciences. 2021; 118: e2018457118.
33. Maghzi AH, Ghazavi H, Ahsan M, et al. Increasing female preponderance of multiple sclerosis in Isfahan, Iran: a population-based study. Mult Scler. 2010; 16: 359-61.
34. Johnson PA and Johnson JC. Shedding light on maternal sunlight exposure during pregnancy and considerations for public health policy. Health Science Inquiry. 2020; 11: 112-8.
35. Saastamoinen K-P, Auvinen M-K and Tienari PJ. Month of birth is associated with multiple sclerosis but not with HLA-DR15 in Finland. Multiple Sclerosis Journal. 2012; 18: 563-8.
36. Ramagopalan S, Link J, Byrnes J, et al. HLA-DRB1 and month of birth in multiple sclerosis. Neurology. 2009; 73: 2107-11.
37. Tremlett HL and Devonshire VA. Does the season or month of birth influence disease progression in multiple sclerosis? Neuroepidemiology. 2006; 26: 195-8.
38. Grytten N, Torkildsen Ø, Aarseth JH, et al. Month of birth as a latitude-dependent risk factor for multiple sclerosis in Norway. Multiple Sclerosis Journal. 2013; 19: 1028-34.
39. Tremlett H, Van Der Mei IA, Pittas F, et al. Monthly ambient sunlight, infections and relapse rates in multiple sclerosis. Neuroepidemiology. 2008; 31: 271-9.
40. Rostami M, Tehrani FR, Simbar M, et al. Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial. The Journal of Clinical Endocrinology & Metabolism. 2018; 103: 2936-48.
41. Munger KL, Åivo J, Hongell K, Soilu-Hänninen M, Surcel H-M and Ascherio A. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the Finnish maternity cohort. JAMA neurology. 2016; 73: 515-9.
42. van der Mei IA, Ponsonby A-L, Dwyer T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. Bmj. 2003; 327: 316.
43. Kampman M, Wilsgaard T and Mellgren S. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. Journal of neurology. 2007; 254: 471-7.
44. Hedström AK, Olsson T, Kockum I, Hillert J and Alfredsson L. Low sun exposure increases multiple sclerosis risk both directly and indirectly. Journal of Neurology. 2020; 267: 1045-52.
45. Wagner CL, Taylor SN, Johnson DD and Hollis BW. The role of vitamin D in pregnancy and lactation: emerging concepts. Women's Health. 2012; 8: 323-40.
46. Choi R, Kim S, Yoo H, et al. High prevalence of vitamin D deficiency in pregnant Korean women: the first trimester and the winter season as risk factors for vitamin D deficiency. Nutrients. 2015; 7: 3427-48.
47. Marques AH, O'Connor TG, Roth C, Susser E and Bjørke-Monsen A-L. The influence of maternal prenatal and early childhood nutrition and maternal

prenatal stress on offspring immune system development and neurodevelopmental disorders. Frontiers in neuroscience. 2013; 7: 120.
48. Langley K, Rice F and Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva pediatrica. 2005; 57: 359-71.
49. Chałubiński M and Kowalski ML. Life Time Prevention of Chronic Airway Diseases. Prevention of Chronic Diseases and Age-Related Disability. Springer, 2019, p. 83-90.
50. Zheng T, Zhang J, Sommer K, et al. Effects of environmental exposures on fetal and childhood growth trajectories. Annals of global health. 2016; 82: 41-99.