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systematic review (Pages: 14267-14278)

Association between the month of birth and Multiple Sclerosis; a meta-analysis

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Abstract

Background

Knowledge regarding true birth-month effect on Multiple Sclerosis (MS) risk has important effect on the adoption of preventive strategies. In this meta-analysis we assessed the Association between month of birth and MS, during 2000-2020**.**

Methods: In this systematic review, an extensive search was performed on the scientific databases including PubMed, SCOPUS and Web of Science. They were electronically searched using detailed search strategy to December 2020. Reviewing and extracting the data were done by two independent authors. I² statistics were used to assess the heterogeneity in the included studies. Depending amount of heterogeneity random or fix effect model was used to estimate the pooled OR.

Results: In the initial search we enrolled 93 records according to search strategy. However, 15 articles, with 181602 total subjects, were finally included in the Meta-analysis. According to results from pooled meta-analysis the excess risk of MS by birth months observed in April and June was 1.03 (1.00 – 1.06), and 1.02 (1.00 – 1.05), respectively; while the lower risks of MS by birth months were attributed to January and November the expected MS birth odds ratio of which has been 0.98 (0.96 – 0.99), and 0.96 (0.93 – 1.01), respectively.

Conclusion: Our meta-analysis showed that Month of birth has a significant effect on subsequent MS risk. This can be due to the amount of ultraviolet light exposure in the third trimester of pregnancy. Increased vitamin D intake from supplements under conditions of limited exposure to sunlight can be effective in preventing MS.

Key Words: Meta-analysis, Month of birth, Multiple sclerosis, Seasonality

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INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) and two-thirds of the patients are women of childbearing age (1). These patients have a clinically isolated syndrome (CIS) defined by a distinct first neurological event with demyelination involved the optic nerve, cerebellum, brainstem, cerebrum or spinal cord (2).

The precise etiology of MS is unknown, although epidemiological studies reported that both genetic and environmental factors are important (3). The risk factors of MS are female gender, smoking, nonexclusive breast feeding, high Epstein-Barr virus antibody levels, having had infectious mononucleosis (4).

The Vitamin D deficiency is one of the environmental factors affecting MS development. Vitamin D is absorbed by the skin when it is exposed to ultraviolet (UV) or sunlight. The vitamin D insufficiency levels during pregnancy affect the immune status of the fetus and the MS risk (5). Likewise, the gene-environment interactions can be the cause of the development of MS (6).

Some studies showed that 'month of birth' affected on the risk of MS. Born in the winter reduced MS risk of neonates (7-9) and in those born in the spring there was an increased MS risk (8, 10, 11), although these results were not consistant. Interestingly, in studies that conducted in northern hemisphere, MS birth was lower in autumn (12), while in southern hemisphere the risk of MS was higher in autumn (November–December), and the risk has fallen in the spring (May–June) (13). Hence, time of born within a year may affect the risk of MS later in life.

Abundant studies have been done for assessing the association between the month of birth and risk of MS, the pooled findings have shown inconsistencies due to differences in statistical methods, sample sizes, and ethnic groups. Besides, they have reported different months to be significantly influential on the risk of MS. Therefore, in this meta-analysis we assessed the effect of birth month on MS based on studies that reported observed vs. expected odds ratio by month, during 2000-2020.

MATERIALS AND METHODS

Data Sources

This meta-analysis is conducted to estimate the association between month of birth and MS. We utilized PRISMA statement as a guide to enhance quality reporting of the review (14). Relevant studies that published in major international electronic bibliographic databases of PubMed, Scopus and Web of Science were systematically searched to October 2020. In addition, hand searches were also performed in order to identify additional relevant studies.

Search strategy

MeSH heading approach was used to perform the search strategy, identifying additional terms in the title, keywords, affiliations (scleroses; birth; birthed; births; months; month; sclerosis; multiple; MS and multiple scleroses). All off title and next abstracts were checked to find out articles with the most relevance. In the next step, the full texts of related articles were assessed to decide upon the articles to be included in meta-analysis. In the final step, cross-referring was done for increasing search sensitivity.

Inclusion and exclusion criteria

Papers that reported observed vs. expected MS birth odds ratio by month, original researches in English language, and conducted in 2000-2020 period were considered as eligible for inclusion in current study. Articles with lack of reports about the association between month of birth and MS, and duplicate articles as well as animal studies, case reports, case series, comments, editorials, and reports were excluded.

Data Extraction

Relevant studies were assessed by two independent authors (YV and SK), after that eligible studies were included, tiny disagreements were resolved with more caution by all authors. Data extraction form was used to extract the data. Data extraction form contained the following information: first author, years of publication, population, number of patients, observed vs. expected MS birth odds ratio (OR) and their associated 95% confidence intervals (CI) for each month of winter: December, January, February; spring: March, April, May; summer: June, July, August; and autumn: September, October, November.

Quality assessment

The methodological methods of included studies were assessed by Newcastle-Ottawa Scale (15). Eventually, articles were classified in two groups, high quality studies that gained more than 7 points and low quality studies that gained less than 7 points (Ranged from 1 to 9 points).

Statistical analysis

It was attempted to extract the results regarding the association between month of birth and MS, from the Meta-analyses. We used I^2 statistics to assess the heterogeneity of the included studies. Whenever the heterogeneity was high in studies (I^2 = 25 and more), the random effects model was used (April, May, June, November); while for lower heterogeneity the fixed model was used (I^2= less than 25) (January, February, March, July, August, and September, October, and December). All meta-analyses were performed using Stata software version 12 (Stata Corp, College Station, TX, USA).

RESULTS

In the initial search we enrolled 93 records according to search strategy. We have screened articles by title, abstract and full text, while duplicates were removed; and in final step 15 studies were considered for inclusion in the analysis. Figure 1 shows the diagram of included studies. The 15 analyzed studies offer data from 15 different populations, including 181602 patients with MS. Overall, excess risk of MS by birth months according to observed vs. expected MS birth odds ratio was observed in 9 populations; and in 7 populations, lower risk of MS by birth month was designed (Table 1).

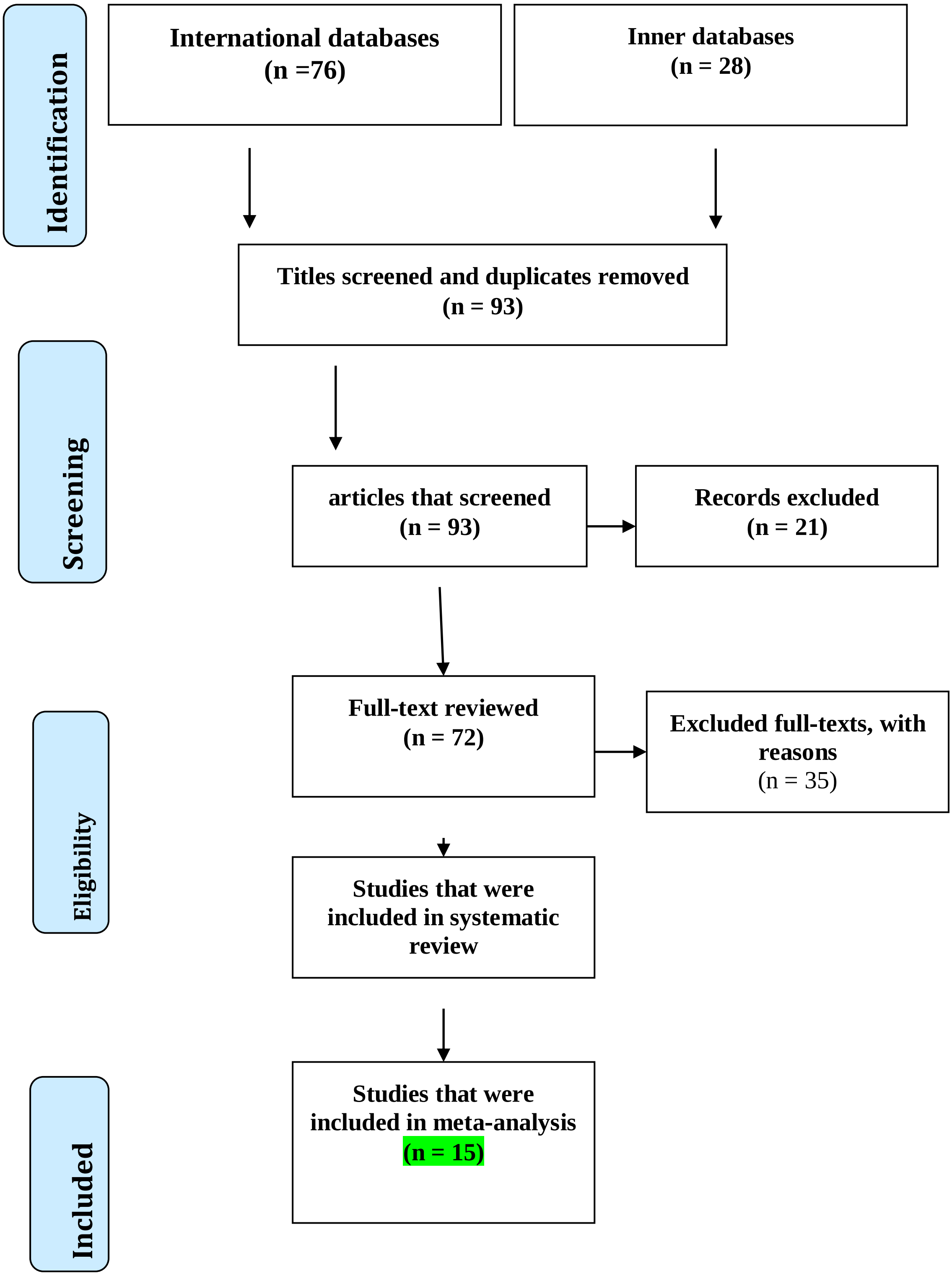


Figure-1: flow chart of included studies

Table-1: characteristics of included studies and critical appraisal, n=181602

(Ref.) First Authors, and year	Population	patients	Excess risk of MS (Months)	lower risk of MS (Months)	Score, Quality	
(16)Dobrakowski P, 2017	Poland	2574	-	-	8	High
(17)Saastamoinen KP,2012	Finland	8359	Oct	-	8	High
(8)Menni C, 2012	Italy	2737	Apr, Oct	-	9	High
(8)Menni C, 2012	Denmark	15900	-	Nov	8	High
(8)Menni C, 2012	White Americans	50650	Jun, Jul	Feb, Oct	9	High
(8)Menni C, 2012	African Americans	5370	Oct, Jul	-	9	High
(18)Rodríguez Cruz PM, 2016	United Kingdom	21138	-	Nov	8	High
(10)Balbuena LD, 2016	Wales	3557	Apr	-	9	High
(7)Salzer J, 2012	Sweden	9361	Jun	Jan, Dec	8	High
(11)Disanto G, 2012	England	15492	Apr, May	Oct, Nov	8	High
(19)Akhtar S, 2015	Kuwait	1035	Nov, Dec	May	9	High
(20)Willer CJ, 2004	Sweden and Denmark	17874	-	Nov	8	High
(9)Grytten N, 2012	Norwegian	6649	Apr, May	Feb	8	High
(21)Eliasdottir O, 2018	Sweden and Iceland	12020	-	-	8	High
(22)Walleczek NK, 2018	Austria	7886	-	-	8	High

The pooled observed vs. expected MS birth odds ratio for 12 months is shown in table 2. According to results from pooled meta-analysis the excess risk of MS by birth months was observed for April and June, while the lower risks of MS by birth months were attributed to January and November (Table2).

The Forrest plot for excess risk month is shown in figure 2. The observed vs. expected MS birth odds ratio for April and June was 1.03 (1.00 – 1.06) and 1.02 (1.00 – 1.05), respectively. The significance heterogeneity was observed for the two investigated months. The Frost plot of lower risk months is shown in figure 3. The observed vs. expected MS birth odds ratio for January and November was 0.98 (0.96 – 0.99) and 0.96 (0.93 – 1.01), respectively. A significant heterogeneity was observed in studies that reported OR for November, but no evidence of heterogeneity was found for January.

The trend of MS birth by month was shown in figure 4. According to the line trend more people with MS were born in May and fewer were born in November.

Table-2: meta-analysis of observed patients with multiple sclerosis compared with the expected patients, by month

	Observed/expected MS births (95% CI)	Heterogeneity	
		I-squared (%)	P-value
January	0.98 (0.96 – 0.99)	16.6	0.273
February	0.99 (0.97 – 1.01)	0.0	0.519
March	0.99 (0.97 – 1.01)	14.1	0.299
April	1.03 (1.00 – 1.06)	53.1	0.010
May	1.05 (0.98 – 1.04)	53.3	0.010
June	1.02 (1.00 – 1.05)	53.2	0.010
July	1.01 (0.99 – 1.03)	8.8	0.358
August	1.01 (0.99 – 1.03)	0.0	0.868
September	0.99 (0.97 – 1.01)	0.0	0.847
October	0.98 (0.96 – 1.00)	0.0	0.503
November	0.96 (0.93 – 1.01)	62.1	0.001
December	1.00 (0.98 – 1.03)	42.0	0.049

CI: Confidence Interval 95%

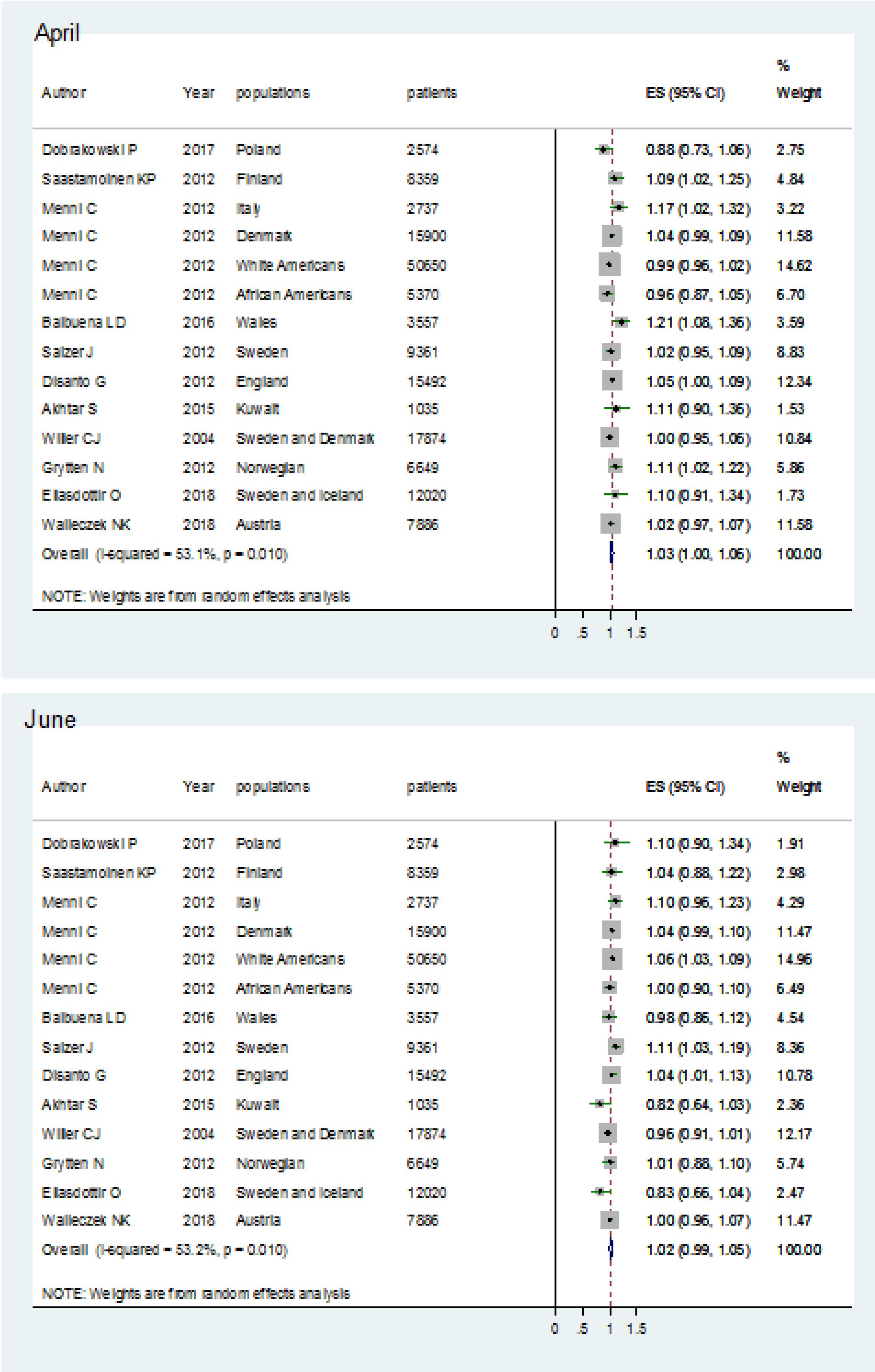
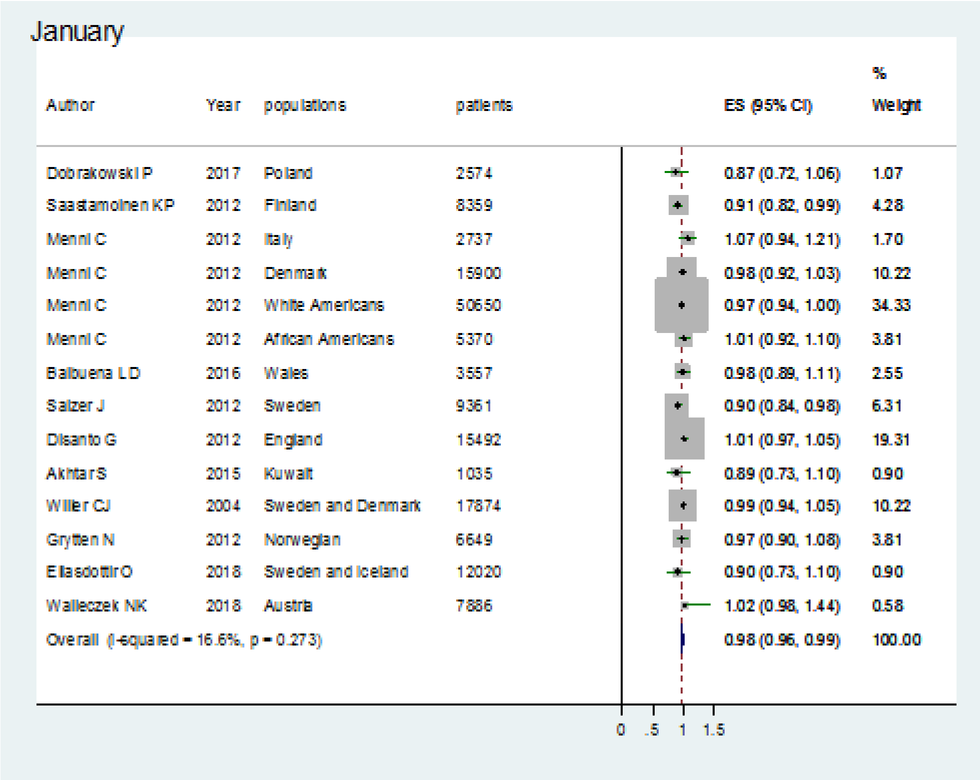


Figure-2: Lower risks of MS by months according to observed vs. expected MS birth odds ratio (April) (June), MS: Multiple Sclerosis



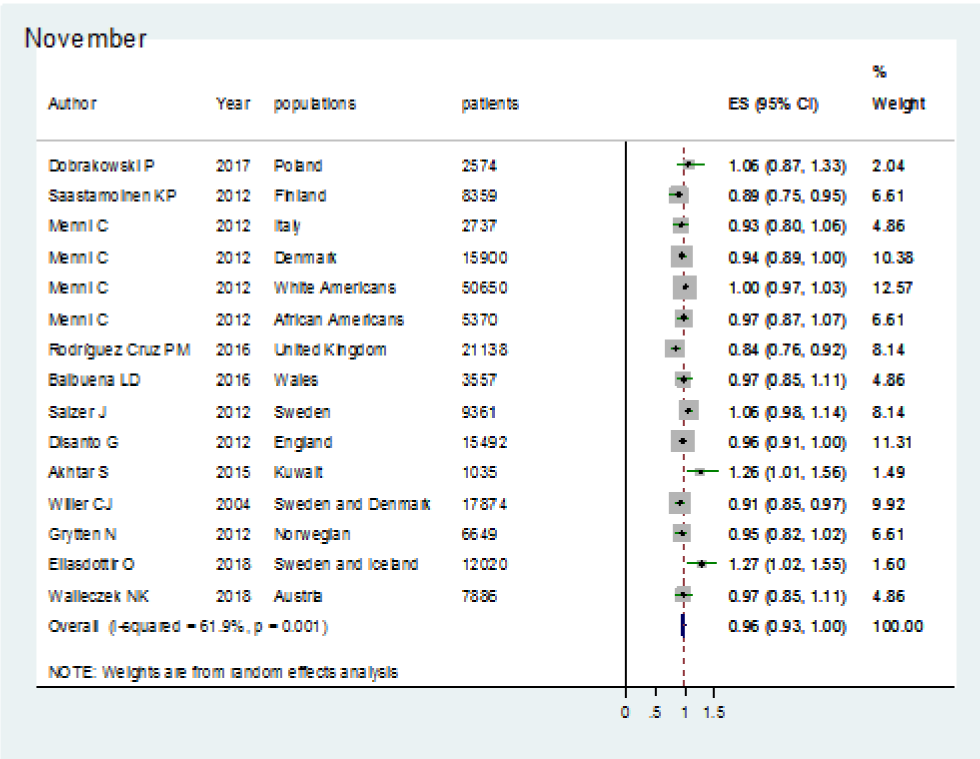


Figure-3: Lower risks of MS by months according to observed vs expected MS birth odds ratio (January) (November), MS: Multiple Sclerosis

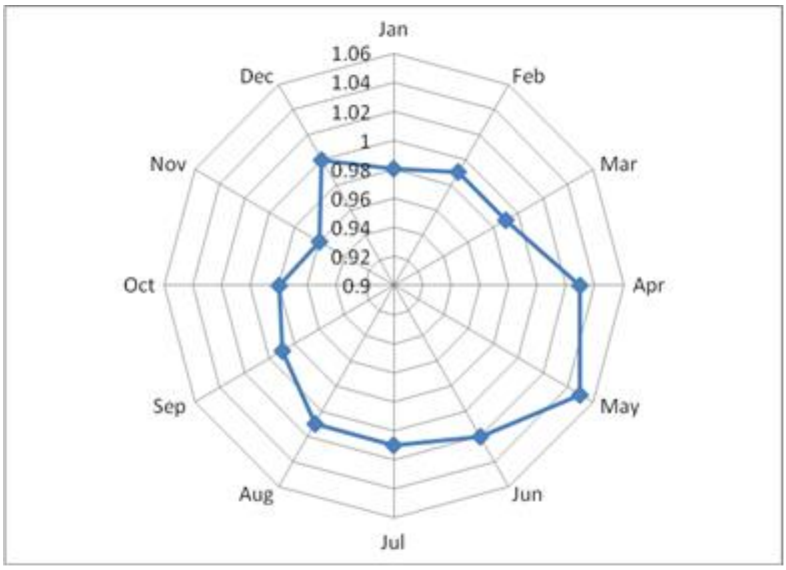


Figure-4: Pooled results of observed/expected births in patients with MS

Discussion

This meta-analysis was conducted to assess the effect of birth month on MS. Knowledge regarding true birth-month effect on MS risk can have important influence on the adoption of preventive strategies. Therefore, in this Meta-analysis we evaluated the association between month of birth and MS risk in 10 individual studies. It was revealed that the excess risk of MS by birth months was observed for April and June, and the lower risk of MS by birth months was found to be in January and November.

Results from many epidemiological studies indicated that seasonal pattern of birth is associated with increased incidence of some diseases. In fact, environmental factors during pregnancy may increase the risk of developing some diseases for fetus in future (23). The effect of seasonal pattern of birth for some disease like schizophrenia and bipolar disorders, celiac disease, suicide and type 1 diabetes have been proven previously (24-27).

Our findings showed an excess of MS among people born in spring, while a decrease in MS births was being reported in autumn. Vitamin D deficiency in pregnancy might disturb the establishment of myelination and can increase odds of MS later in life. Increase in sunlight exposure is relevant to the increase in serum vitamin D concentrations and subsequent decreased risk of MS (28). Effect of gestational vitamin D deficiency on impair brain development of animals has been proved in experimental studies (29). One of the reasons for increased risk of MS among spring births in this study can be related to gestational maternal vitamin D deficiency due to limited exposure to sunlight in the third trimester of pregnancy. Since the specific genome for susceptibility to MS has not, yet, been found, and according to new findings the genetic characteristics do not alone explain the occurrence of MS, therefore, environmental excusers such as UVR can induce MS in subjects that inherit genome of MS especially in females (8).

This study has some limitations: Firstly, lack of ethnic background of sub-populations led us to fail to analyze the subgroups. Secondly, due to lack of information in entered studies we could not adjust confounding effects of seasonally varying factors such as ambient temperature, changes in diet, etc. Thirdly, not including studies from the southern hemisphere due to lack of inclusion criteria can affect generalizability of findings.

Conclusion

Our meta-analysis revealed that Month of birth has a significant effect on subsequent MS risk. This can be due to amount of ultraviolet light exposure in the third trimester of pregnancy. Increased vitamin D intake from supplements under conditions of limited exposure to sunlight can be effective in preventing MS.

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Conflict of interest statement

The authors declare that have no conflict of interest.

REFERENCES

1. Bennett KA. Pregnancy and multiple sclerosis. Clinical obstetrics and gynecology. 2005;48(1):38-47.
2. Okuda D, Mowry E, Beheshtian A, Waubant E, Baranzini S, Goodin D, et al. Incidental MRI anomalies suggestive of multiple sclerosis The radiologically isolated syndrome. Neurology. 2009;72(9):800-5.
3. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. The Lancet Neurology. 2010;9(7):727-39.
4. Poorolajal J, Mazdeh M, Saatchi M, Ghane ET, Biderafsh A, Lotfi B, et al. Multiple sclerosis associated risk factors: a case-control study. Iranian journal of public health. 2015;44(11):1498.
5. van der Mei IA, Ponsonby A-L, Dwyer T, Blizzard L, Taylor BV, Kilpatrick T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. Journal of neurology. 2007;254(5):581.
6. Ramagopalan SV, Hanwell HE, Giovannoni G, Knappskog PM, Nyland HI, Myhr K-M, et al. Vitamin D–Dependent Rickets, HLA-DRB1, and the Risk of Multiple Sclerosis. Archives of neurology. 2010;67(8):1034-5.
7. J. S, A. S, P. S. Season of birth and multiple sclerosis in Sweden. Acta Neurologica Scandinavica. 2010;122(1):70-3.
8. Menni C, Lowell WE, Bentzen J, Bergamaschi R, Martinelli Boneschi F, Martinelli V, et al. Short and Long Term

Variation in Ultraviolet Radiation and Multiple Sclerosis. International Journal of Environmental Research and Public Health. 2012;9(3):685-97.

9. Grytten N, Torkildsen Ø, Aarseth JH, Benjaminsen E, Celius EG, Dahl OP, et al. Month of birth as a latitude-dependent risk factor for multiple sclerosis in Norway. Multiple Sclerosis Journal. 2013;19(8):1028-34.

10. Balbuena LD, Middleton RM, Tuite-Dalton K, Pouliou T, Williams KE, Noble GJ. Sunshine, Sea, and Season of Birth: MS Incidence in Wales. PLOS ONE. 2016;11(5):e0155181.

11. Disanto G, Chaplin G, Morahan JM, Giovannoni G, Hyppönen E, Ebers GC, et al. Month of birth, vitamin D and risk of immune-mediated disease: a case control study. BMC Medicine. 2012;10:69-.

12. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC. Timing of birth and risk of multiple sclerosis: population based study. BMJ. 2005;330(7483):120.

13. Staples J, Ponsonby A-L, Lim L. Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. The BMJ. 2010;340:c1640.

14. Peters JPM, Hooft L, Grolman W, Stegeman I. Reporting Quality of Systematic Reviews and Meta-Analyses of Otorhinolaryngologic Articles Based on the PRISMA Statement. PLOS ONE. 2015;10(8):e0136540.

15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses2009 Septamber 15, 2017. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

16. Dobrakowski P, Bogocz M, Cholewa K, Rajchel M, Kapica-Topczewska K, Wawrzyniak S, et al. Month of birth and level of insolation as risk factors for multiple sclerosis in Poland. PLoS ONE. 2017;12(4):e0175156.

17. Saastamoinen K-P, Auvinen M-K, Tienari PJ. Month of birth is associated with multiple sclerosis but not with HLA-DR15 in Finland. Multiple Sclerosis Journal. 2012;18(5):563-8.

18. Rodríguez Cruz P, Matthews L, Boggild M, et al. Time- and region-specific season of birth effects in multiple sclerosis in the united kingdom. JAMA Neurology. 2016;73(8):954-60.

19. Akhtar S, Alroughani R, Al-Shammari A, Al-Abkal J, Ayad Y. Month of birth and risk of multiple sclerosis in Kuwait: A population-based registry study. Multiple Sclerosis Journal. 2015;21(2):147-54.

20. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC, et al. Timing of birth and risk of multiple sclerosis: population based study. BMJ : British Medical Journal. 2005;330(7483):120-.

21. Eliasdottir O, Hildeman A, Longfils M, Nerman O, Lycke J. A nationwide survey of the influence of month of birth on the risk of developing multiple sclerosis in Sweden and Iceland. Journal of neurology. 2018;265(1):108-14.

22. Walleczek NK, Frommlet F, Bsteh G, Eggers C, Rauschka H, Koppi S, et al. Month-of-birth-effect in multiple sclerosis in Austria. 2018:1352458518810924.

23. Tochigi M, Okazaki Y, Kato N, Sasaki T. What causes seasonality of birth in schizophrenia? Neuroscience research. 2004;48(1):1-11.

24. Torrey EF, Rawlings RR, Ennis JM, Merrill DD, Flores DS. Birth seasonality in bipolar disorder, schizophrenia, schizoaffective disorder and stillbirths. Schizophrenia research. 1996;21(3):141-9.

25. Vaiserman A, Carstensen B, Voitenko V, Tronko M, Kravchenko V,

Khalangot M, et al. Seasonality of birth in children and young adults (0–29 years) with type 1 diabetes in Ukraine. Diabetologia. 2007;50(1):32-5.

26. Lewy H, Meirson H, Laron Z. Seasonality of birth month of children with celiac disease differs from that in the general population and between sexes and is linked to family history and environmental factors. Journal of pediatric gastroenterology and nutrition. 2009;48(2):181-5.

27. Veisani Y, Delpisheh A, Sayehmiri K, Moradi G, Hassanzadeh J. Seasonality and time patterns in attempted suicide in Ilam province of Iran: An appraisal of current data of 2010 -2014. Medical Journal of the Islamic Republic of Iran. 2017;31:11-.

28. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. Jama. 2006;296(23):2832-8.

29. Cui X, McGrath JJ, Burne TH, Mackay-Sim A, Eyles DW. Maternal vitamin D depletion alters neurogenesis in the developing rat brain. International journal of developmental neuroscience. 2007;25(4):227-32.