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Environmental risk factors of multiple sclerosis in the Middle East and North Africa region: A systematic review

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Keywords
Multiple Sclerosis; Risk Factors; Environment; Middle East; North Africa

Abstract

Background: The environmental factors play a major role as risk factors of multiple sclerosis (MS). This study aimed at gathering environmental risk factors of MS in the Middle East and North Africa (MENA).

Methods: We used MEDLINE and EMBASE databases by a systematic review method. Out of a total of 123 studies, 16 studies met the eligibility criteria.

Results: Totally, 47 risk factors were assessed as follows: six studies found sunlight exposure as a protective factor with the odds ratio (OR) ranging from 0.06 to 0.57. Six studies evaluated smoking as a risk factor with the OR ranging from 1.69 in all patients to 6.48 in female patients. Four studies supported measles infection as a risk factor with the OR ranging from 1.60 to 3.77, and in 3 studies, stressful events had a significant association with the OR of 1.80, 1.90, and 32.57.

Conclusion: Among 47 assessed risk factors, sunlight exposure, cigarette smoking, measles infection, Epstein-Barr virus (EBV) infection, and stressful events had a significant association with MS.

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Introduction

Multiple sclerosis (MS), as a leading cause of a long-term disabling neurological disease in young adults,[1] is a chronic inflammatory disease of the central nervous system (CNS) with unclear cause and is believed to occur due to a combination of environmental and genetic causes.[2,3]

Based on a number of recent studies, the incidence of MS is rising worldwide.[1,4] This disease is more prevalent in Northern America (140 cases per 100000 population) and less common in Sub-Saharan Africa (2.1 cases per 100000 population).[4] Moreover, MS has an overall prevalence of 51.52/100000 and the female/male ratio of 2.03 in the Middle East and

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North Africa (MENA) region.[5] It has been acknowledged that both genetic and environmental factors play a major role as risk factors of the disease, although the etiology of MS has not been fully understood.[6] The well-known mentioned risk factors are low sunlight exposure, Epstein-Barr virus (EBV), and smoking.[2,7] These risk factors were mostly studied in Caucasian population rather than in the MENA population.[5,8] Since MS has significant social and economic effects on the health system in many countries, detection of the possible risk factors is necessary to conceivably prevent the disease.[1] According to the rising trend of MS prevalence and incidence in the MENA region,[5] it is very important to detect the possible risk factors and their association with the prevalence of the disease.

To the best of authors' knowledge, there is no comprehensive study on MS risk factors in the MENA region; therefore, the present study aimed at gathering the environmental risk factors mentioned in studies conducted in the MENA region performing a systematic review study.

Materials and Methods

Search strategy: To determine a clear and focused question addressing the environmental risk factors of MS in the MENA region, a systematic literature search of appropriate databases and interfaces such as MEDLINE and EMBASE was performed using the keywords of multiple sclerosis, environmental, risk factor, MENA sub regions (Middle EAST and North Africa), and each country name in the MENA region covering the period from January 1, 1950 to April 25, 2019.

The present study used database-appropriate syntax to optimize searching and evaluating the initial results. Moreover, this study conducted a manual hand-searching of the reference lists of the selected primary articles and related reviews to determine additional studies.[9]

Screening and eligibility criteria: This study used computer databases to find data and statistics on MS environmental risk factors by merely addressing human population studies written in English. The observational studies including case-control and cohort studies were reviewed and analyzed to specify MS risk factors in the selected articles.

The titles and abstracts of all the studies identified by the databases were reviewed. Potentially eligible studies were read in full text and recovered to check if they could satisfy the following inclusion criteria in this systematic review:[10] being a population-based study and involving human samples of patients with MS living in the MENA region,[4] covering data on the environmental risk factors of MS in the target countries,[11] and documenting MS according to the global diagnostic criteria such as the McDonald,[12] Poser,[13] or Schumacher criteria that were used at the study period.[14]

Two experts reviewed the eligible articles independently. If there was any disagreement between the two reviewers, a third expert reviewer would make the final decision in this respect. Review articles, editorials, and letters as well as articles about genetic risk factors were excluded.

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart was established to demonstrate the method of study selection (Figure 1). The classification of the MENA countries in this study was based on the Global Burden of Disease (GBD) classification including 21 countries.[4]

Data extraction and quality assessment: Quality assessment of each eligible article is summarized in the table 1. Repeated publications on the identical data were excluded. The following information was included in a form template by an expert reviewer: first author, year of study, study method, study region, risk factors mentioned in the study, and the sample size of the study.

The extracted information from each individual study was summarized in the respective tables.[15] The study first extracted the measures of effect [e.g., odds ratio (OR), relative risk (RR), confidence interval (CI), and hazard ratio (HR)] and the number of cases and controls from each eligible study and then summarized them in tables 2-5.

Results

As it is shown in figure 1, we reached to 28 articles after the removal of identical and irrelevant studies. Out of the 28 remaining articles, 12 studies were excluded due to incompatibility with the eligibility criteria. One of the mentioned 12 articles was removed because it was about Iranian immigrants in Canada;[16] hence, it was not considered as a study addressing the MENA region. Two studies were removed because they were only about MS demographic risk factors (month of birth).[17,18] Nine of the mentioned studies did not contain sufficient data such as OR, adjusted OR (AOR), and RR to be included in the study.[19,20]

The remaining 16 eligible articles were all written in English and all of them were case-control studies, ranged in sample size from 68 cases with 140 controls to 1217 cases with 787 controls.[21,22]

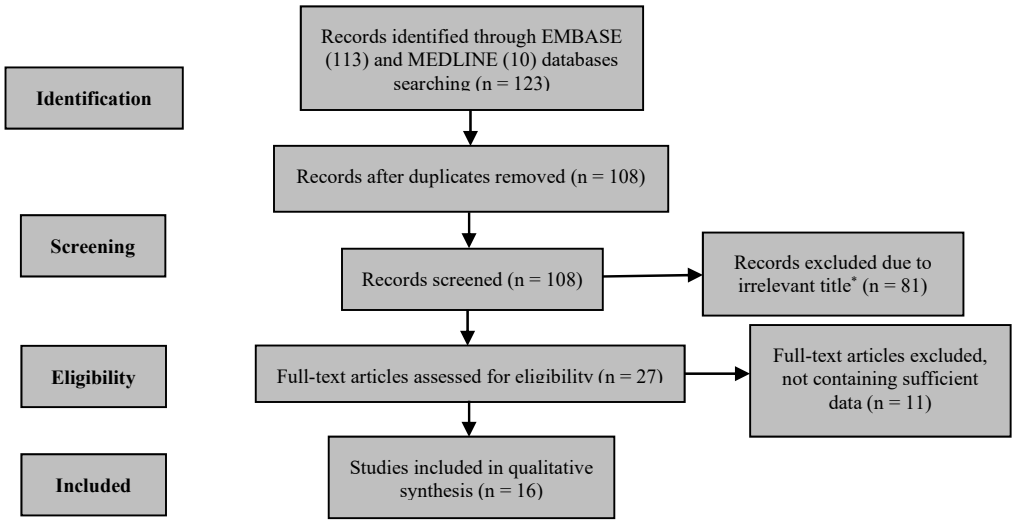

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram
*Studies with a title that was not about assessment of environmental risk factors

Among these 16 articles, five articles were hospital-based studies[21,23-26] and the rest were population-based studies. Among these five studies, all recruited the cases and controls from the same hospital, with the exception of one study which recruited controls from Kuwaiti community living in Kuwait.[25] Totally, the eligible articles assessed 47 environmental factors such as socioeconomic status (SES), dietary lifestyle, infancy diet, smoking status, alcohol use, drug abuse, comorbidity, viral infections, past surgical history, vaccination, fetal problems, head trauma, body size, sunlight exposure, toxin exposure, animal exposure, and stressful events. We summarized the results of the mentioned 16 articles in tables 2-5.

Dietary habit and food consumption: Table 2 indicates the possible association between different dietary habits and MS development. The significant results are as follows: Al Wutayd et al. found that consumption of dairy products (OR = 1.42, 95% CI: 1.04-1.96) and fast foods (AOR = 2.05, 95% CI: 1.03-4.08) more than five times per week increased the risk of MS development; meanwhile, drinking coffee daily (AOR = 0.46, 95% CI: 0.31-0.68) and eating more than five servings of fruit weekly (AOR = 0.25, 95% CI: 0.16-0.38) lowered the risk of MS development.[24] Fish consumption for more than once weekly (AOR = 0.20, 95% CI: 0.05-0.77)[23] and seafood consumption 2-3 times per week (OR = 0.09, 95% CI: 0.04-0.23)[27] decreased the risk of MS development in Halawani et al.[23] and Eftekharian et al.[27] studies, respectively. Shivappa et al. found that pro inflammatory diets [the diets with higher score of dietary inflammatory index (DII)] were considered as pro-inflammatory diets;[21] such as western-type diet, which is high in refined grains, simple carbohydrates, red meats, and high-fat dairy products.[28] These diets can potentially increase the inflammatory markers of the body such as C-reactive protein (CRP), interleukin-6 (IL-6), and homocysteine,[29] and were strongly associated with MS development (AOR = 1.66, 95% CI: 1.19-2.31).[21] In Abbasi et al. study, dairy (AOR = 0.49, 95% CI: 0.33-0.74) and calcium supplements (AOR = 0.44, 95% CI: 0.27-0.71) were revealed as protective factors. In addition, interestingly, this study found that breastfeeding the infants (AOR = 2.90, 95% CI: 1.49-5.65) increased the MS development in infants in the future.[30]

Tobacco and waterpipe smoking, alcohol use, and drug abuse: Table 3 provides the summary of the association of tobacco and waterpipe smoking, alcohol use, and drug abuse with MS. Six of the studies found smoking as a risk factor of the disease with the OR ranging from 1.69 in both male and female patients to 6.48 in female patients.[22,23,27,31-33] Abdollahpour et al. study not only considered smoking as a risk factor but also concluded that being a tobacco smoker (AOR = 1.69, 95% CI: 1.24-2.31), waterpipe smoker (AOR = 1.71, 95% CI: 1.36-2.31), and a passive smoker (AOR = 1.85, 95% CI: 1.48-2.32) had a significant clear dose-response association with MS both for duration of exposure and the amount of smoking.[31] In Roudbari et al. study, smoking increased the risk of developing secondary progressive MS (SPMS) in patients with MS (OR = 2.43, 95% CI: 1.28-4.60).[33]

Table 1. Quality assessment

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Quality score
Abdollahpour et al.[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	9/10
Abbasi et al.[30]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	8/9
Abdollahpour et al.[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
Shivappa et al.[21]	Yes	Yes	No	yes	Yes	Yes	Yes	No	NA	Yes	8/9
Eftekharian et al.[27]	Yes	Yes	Yes	No	Yes	NA	Yes	Yes	NA	Yes	7/8
Rejali et al.[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	9/9
Alonso et al.[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	9/9
Al-Shammri et al.[25]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	NA	7/9
Al-Afasy et al.[37]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	NA	Yes	7/9
Al Wutayd et al.[24]	Yes	Yes	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	8/9
Halawani et al.[23]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/10
Mansouri et al.[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
Abdollahpour et al.[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
Maghzi et al.[38]	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	NA	Yes	8/8
Roudbari et al.[33]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	7/10
Mouhieddine et al.[36]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No	Yes	8/9

Q1: Was the sample representative of the target population?
Q2: Were study participants recruited in an appropriate way?
Q3: Was the sample size adequate?
Q4: Were the study subjects and setting described in detail?
Q5: Is the data analysis conducted with sufficient coverage of the identified sample?
Q6: Were objective standard criteria used for measurement of the condition?
Q7: Was the condition measured reliably?
Q8: Was there an appropriate statistical analysis?
Q9: Are all important confounding factors/subgroups/differences identified and accounted for?
Q10: Were subpopulations identified using objective criteria?
NMO-IgG: Neuromyelitis optica immunoglobulin G; NA: Not available

Table 2. Dietary habit and food consumption

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Fish	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	0.20	0.05-0.77	**< 0.050**
Dairy products	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.42	-	1.04-1.96	**0.030**
Milk	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	0.40	0.13-1.21	-
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	_	0.59	-	0.014
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.32	-	0.92-1.91	0.140
Yogurt	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.35	-	0.001
Cheese	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.70	-	0.120
Conserved food	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.04	0.02-0.10	**< 0.001**
Fast food	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	2.05	1.03-4.08	**0.042**
Fruit	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	0.25	0.16-0.38	**< 0.001**
Coffee	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	0.46	0.31-0.68	**< 0.001**
Vegetable	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.57	-	0.42-0.79	**0.001**
Date	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.94	-	0.68-1.29	0.690
Red meat	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.97	-	0.60-1.57	0.900
DII diet score[*]	Shivappa et al.[21]	Iran	2011-2012	Hospital-based[##] (single center)	68	140	-	1.66	1.19-2.31	**0.003**
Dairy consumption										
Daily	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.49	0.33-0.74	**0.001**
2-3 times/week	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.50	-	1.06-2.49	-
4-7 times/week	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.10	-	0.72-1.60	-
Seafood consumption								-		-
2-3 times/week	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.09	-	0.04-0.23	-
1-2 times/week	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.25	-	0.04-0.34	-
1-2 times/month	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.31	-	0.04-0.52	-
2-3 times/year	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.42	-	0.07-0.54	-

Table 2. Dietary habit and food consumption (continue)

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Supplements										
Vitamin D	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	0.30	-	0.09-1.15	-
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.62	0.36-1.06	0.082
Calcium	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.44	0.27-0.71	**0.001**
Infancy diet							-			
Breast feeding	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	2.90	1.49-5.65	**0.002**
Dried milk	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.78	0.47-1.28	0.321
Cow milk	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.82	0.34-1.93	0.642
Goat milk	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.58	0.51-4.95	0.430
Water and sugar	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.15	0.43-3.05	0.780

Significant results are bolded; [*]The higher score shows more pro-inflammatory diet; [#]Adjusted mostly for age and sex; [##]Cases and controls were taken from the same hospital
DII: Dietary inflammatory index; OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval

Table 3. Tobacco and waterpipe smoking, alcohol consumption, and drug abuse

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Cigarette smoking	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	4.16	1.44-11.97	**< 0.050**
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.62	0.36-1.05	0.075
	Eftekharian et al.[27*]	Iran	2013	Population-based	250	250	2.86	-	1.30-6.33	-
	Eftekharian et al.[27**]	Iran	2013	Population-based	250	250	2.08	-	0.81-5.31	-
	Mansouri et al.[22]	Iran	2008-2013	Population-based	1217	787	_	1.93	1.31-2.73	**< 0.001**
	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	1.70	_	0.90-3.40	0.097
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.72	0.90-3.30	-
	Al-Shammri et al.[25]	Kuwait	-	Hospital-based[###] (single center)	195	146	-	1.90	0.80-4.50	0.128
	Roudbari et al.[33***]	Iran	-	Population-based	144	256	2.43	-	1.28-4.60	**0.007**
Female cigarette smoking	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	6.48	1.46-28.78	**0.002**
Tobacco	Abdollahpour et al.[31]	Iran	2013-2015	Population-based	547	1057	-	1.69	1.24-2.31	**< 0.001**
Passive smoking[¥]	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	1.28	-	0.75-2.20	-
	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	1.48	1.14-1.93	**0.004**
	Abdollahpour et al.[31]	Iran	2013-2015	Population-based	547	1057	-	1.85	1.48-2.32	**< 0.001**
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.13	0.71-1.78	0.614
Passive smoking during childhood	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	2.25	-	1.57-3.20	-
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.00	-	0.72-1.39	> 0.999
Ex-smoker[*]	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.32	-	0.84-1.56	0.430
Current smoker	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.16	-	0.77-1.76	0.470
Waterpipe smoking	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	1.69	1.22-2.34	**0.001**
	Abdollahpour et al.[31]	Iran	2013-2015	Population-based	547	1057	-	1.77	1.36-2.31	**< 0.001**
Alcohol	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	1.61	1.11-2.33	**< 0.012**
Drug abuse										
Life time drug abuse	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	2.93	1.83-4.70	**< 0.001**
Drug abuse (opioids)	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	1.00	0.52-1.92	0.998
Drug abuse (cannabis)	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	1.23	0.61-2.46	0.560
Use of OTC antibiotics										
Weekly	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.98	-	0.44-3.96	
1-2 times per month	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.55	-	0.62-3.84	

Table 3. Tobacco and waterpipe smoking, alcohol consumption, and drug abuse (continue)

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Antibacterial soap usage										
1-2 per week	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.18	-	0.08-0.40	-
1-2 per month	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.43	-	0.22-0.82	-
History of OCP usage	Rejali et al.[26]	Iran	2014	Hospital-based[##] (single center)	200	200	-	0.49	0.31-0.77	**0.002**
Duration of OCP usage	Rejali et al.[26]	Iran	2014	Hospital-based[##] (single center)	200	200	-	0.88	0.80-0.96	**0.008**
OCP starting age	Rejali et al.[26]	Iran	2014	Hospital-based[##] (single center)	200	200	-	0.99	0.92-1.05	0.800

Significant results are bolded; [*]Taking 5 cigarette per day; [**]Taking 3-5 cigarette per day; [***]The study evaluated smoking as a risk factor for developing secondary progressive multiple sclerosis (SPMS); [¥]Ever being exposed to passive smoking; [#]Adjusted mostly for age and sex; [##]Cases and controls were recruited from the same hospital; [###]Controls were recruited from Kuwaiti community living in Kuwait

OTC: Over the counter; OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval; OCP: Oral contraceptive pill

Table 4. Medical history

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
History of comorbidity[*]	Al-Shammri et al.[25]	Kuwait	-	Hospital-based[###] (single center)	195	146	-	2.40	1.30-4.70	**< 0.0010**
Autoimmune disease history										
1 autoimmune disease history	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	0.97	0.71-1.32	0.8550
More than 1 autoimmune disease history	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	0.88	0.38-2.03	0.7630
Allergy history	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	1.06	-	0.73-1.89	-
	Mansouri et al.[22]	Iran	2008-2013	Population-based	1217	787	-	1.92	1.55-2.47	**< 0.0010**
Type 1 DM	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	0.39	0.08-1.86	0.2360
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	0.67	0.34-1.31	0.2350
DM	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.11	0.01-0.99	**0.0490**
CVDs	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.54	0.08-3.69	0.5300
SLE	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.19	-	0.02-1.69	0.2200
RA	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	0.73	0.39-1.39	0.3400
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.94	-	0.48-1.86	0.8600
Thyroid disorder	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.55	-	0.30-0.99	**0.0400**
Thyroiditis	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.95	0.44-2.05	0.8860
Hypothyroidism	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	1.08	0.75-1.56	0.6580
Hyperthyroidism	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	0.72	0.37-1.39	0.3250
Crohn's disease	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	6.64	0.59-74.12	0.1240
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.00	-	0.06-16.06	> 0.9999
UC	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	6.64	0.59-74.12	0.1240
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.41	-	0.68-2.93	0.3600
Psoriasis	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	2.15	0.61-7.52	0.2300
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.77	-	0.51-6.10	0.3610
Kidney disease	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	1.02	0.61-1.71	0.9300
Migraine	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	1.24	0.90-1.71	0.1940
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	3.50	1.61-7.59	**0.0020**
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.91	-	0.56-1.49	0.7100
HTN	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.89	0.31-2.53	0.8280
	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	0.10	-	0.04-0.04	0.0010

Table 4. Medical history (continue)

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Psychiatric disorder										
Stress and anxiety disorder	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	3.82	-	2.60-5.50	-
Depression	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	3.30	-	2.30-4.80	-
OCD	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.93	-	1.34-2.80	-
Negative thoughts	Eftekharian et al.[27δ]	Iran	2013	Population-based	250	250	4.83	-	3.03-7.71	-
	Eftekharian et al.[27**]	Iran	2013	Population-based	250	250	1.74	-	1.08-2.80	-
Viral infection history										
Measles infection	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	3.75	1.45-9.70	**< 0.0500**
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.60	1.05-2.45	**0.0290**
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.12	0.66-1.90	-
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	3.77	2.05-6.96	**< 0.0010**
Chickenpox	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	1.25	-	0.73-2.15	-
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.28	0.88-1.87	0.1900
	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.43	-	1.02-2.00	-
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.15	0.78-1.69	-
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.90	-	0.65-1.24	0.5700
Rubella	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.47	0.85-2.55	0.1660
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.61	0.81-3.28	-
Measles and rubella	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	1.70	-	1.20-2.40	-
Hepatitis	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.65	0.10-4.18	-
Mumps	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.85	1.22-2.78	**0.0030**
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.52	0.93-2.49	-
EBV										
Anti-VCA titer	Mouhieddine et al.[36]	Lebanon	2012-2014	Population-based	249	230	1.02	-	1.01-1.03	**0.0020**
Anti-EBNA-1 titer	Mouhieddine et al.[36]	Lebanon	2012-2014	Population-based	249	230	1.14	-	1.10-1.19	**< 0.0001**
Past surgical history										
History of tonsillectomy	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	0.86	-	0.40-1.85	-
	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	0.30	-	0.10-0.90	**0.0290**
	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.65	0.32-1.34	-
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	1.25	-	0.81-1.94	0.3700
Appendectomy	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	2.32	0.89-6.05	-
	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.72	-	0.43-1.19	0.2500

Table 4. Medical history (continue)

Risk factor	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
General anesthesia	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	0.60	-	0.30-1.00	**0.0410**
Vaccination										
Childhood vaccination complete[€]	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.53	0.28-1.00	**0.0500**
Adulthood vaccination[€€]	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	4.57	1.14-18.41	**0.0320**
Varicella vaccine	Mansouri et al.[22]	Iran	2008-2013	Population-based	1217	787	-	1.34	1.02-1.83	**0.0400**
Head trauma										
Head trauma in adulthood	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.49	0.59-3.74	0.3950
History of head trauma	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	1.27	0.94-1.70	0.1160
	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	-	2.60	1.20-5.50	**0.0140**
Cumulative head trauma	Abdollahpour et al.[34]	Iran	2013-2015	Population-based	547	1057	-	1.02	0.90-1.16	0.7700
Childhood head trauma	Abbasi et al.[30€€€]	Iran	2013-2014	Population-based	660	421	-	8.21	1.56-43.06	**0.0130**
	Eftekharian et al.[27ε]	Iran	2013	Population-based	250	250	1.86	-	1.20-2.87	-
	Eftekharian et al.[27εε]	Iran	2013	Population-based	250	250	2.11	-	1.38-4.41	-
Body size										
Large body size[εεε]	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	8.97	1.03-77.98	**< 0.0500**
BMI > 30 kg/m^2	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.92	-	0.62-1.37	0.6700
BMI (25-29.99 kg/m^2)	Al Wutayd et al.[24]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	0.75	-	0.52-1.09	0.1300
Obstetrics and gynecology										
Born in singleton pregnancy	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.94	0.08-11.68	0.9590
Number of pregnancy	Rejali et al.[26]	Iran	2014	Hospital-based[##] (single center)	200	200	-	0.58	0.46-0.74	**< 0.0010**
Born by vaginal delivery	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421		0.80	0.41-1.58	0.5200
Born by cesarean section	Maghzi et al.[38]	Iran	-	Population-based	449	900	2.51		1.43-4.41	**0.0010**
Age of menarche	Rejali et al.[26]	Iran	2014	Hospital-based[##]	200	200	-	0.78	0.67-0.89	**0.0010**
Fetal problems							-			
Post maturity	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.60	0.11-3.34	0.5610
Prematurity	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	4.99	1.34-18.68	**0.0170**
Low birth weight	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.63	0.17-2.38	0.4900

Significant results are bolded; [*]Presence of any chronic medical illnesses; [#]Adjusted mostly for age and sex; [##]Cases and controls were recruited from the same hospital; [###]Controls were recruited from Kuwaiti community living in Kuwait; [δ]Negative thoughts often; [δδ]Negative thoughts sometimes; [€]Complete vaccination according to the Iran Ministry of Health's immunization program; [€€]Vaccination after 18 years old and this vaccination must be 1 month prior to diagnosis; [€€€]Head trauma during childhood that needs at least 24-hour admission in emergency department in hospital; [ε]History of head trauma during childhood for once; [εε]History of head trauma during childhood for few times; [εεε]Based on a figure rating scale

OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval; DM: Diabetes mellitus; CVD: Collagen vascular disease; SLE: Systemic lupus erythematous; RA: Rheumatoid arthritis; UC: Ulcerative colitis; HTN: Hypertension; OCD: Obsessive compulsive disorder; EBV: Epstein-Barr virus; VCA: Viral capsid antigen; EBNA-1: Epstein-Barr nuclear antigen 1; BMI: Body mass index

Table 5. Exposure and event

Risk factors	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
Sunlight exposure										
Sunlight exposure	Halawani et al.[23]	Saudi Arabia	2017-2018	Hospital-based[##] (single center)	80	160	-	0.06	0.00-0.65	**< 0.0500**
	Abdollahpour et al.[35]	Iran	2013-2015	Population-based	547	1057	-	0.22	0.12-0.40	**< 0.0010**
	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.09	0.02-0.38	**< 0.0010**
	Mansouri et al.[22]	Iran	2008-2013	Population-based	1217	787	-	0.23	0.15-0.31	**< 0.0010**
	Alonso et al.[32*]	Iran	2007-2010	Population-based	394	394	-	0.62	0.53-0.73	**< 0.0001**
	Alonso et al.[32**]	Iran	2007-2010	Population-based	394	394	-	0.34	0.19-0.60	**0.0002**
	Al Wutayd et al.[24***]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	0.57	0.38-0.85	**< 0.0010**
	Al Wutayd et al.[24¥]	Saudi Arabia	-	Hospital-based[##] (multi center)	307	307	-	0.48	0.30-0.76	**< 0.0010**
Sunscreen	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	2.44	1.26-4.72	**0.0080**
Low sun exposure[¥¥]	Al-Shammri et al.[25]	Kuwait	-	Hospital-based[###] (single center)	195	146	-	5.30	2.70-10.50	**< 0.0010**
Fully shrouded outdoor dressing	Al-Shammri et al.[25]	Kuwait	-	Hospital-based[###] (single center)	195	146	-	2.20	1.00-5.00	**0.0650**
Sun exposure in childhood										
2 hours per day	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.51	-	0.22-1.17	-
2-6 hours per day	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.44	-	0.20-0.98	-
6-8 hours per day	Eftekharian et al.[27]	Iran	2013	Population-based	250	250	0.66	-	0.30-1.46	-
Toxin exposure								-		
Exposure to solvents[€]	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	2.10	-	1.10-3.80	**0.0200**
Toxic fumes from oil wells	Al-Afasy et al.[37]	Kuwait	2010-2012	Population-based	101	202	12.50	-	1.60-95.70	**0.0150**
Toxin	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.90	0.34-2.41	0.8350
Heavy metal	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.85	0.23-3.23	0.8150
Mercury lead	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.77	0.14-4.26	0.7660
Microwave exposure[€€]	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	3.55	2.24-5.63	**< 0.0010**
Animal exposure										
Animal ownership (cat)	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.67	0.35-1.31	-
Dog	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.57	0.30-1.06	-
Bird	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.11	0.73-1.68	-
Sheep	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.70	0.32-1.54	-
Goat	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.97	0.36-2.59	-
Cow	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.64	0.30-1.40	-
Pet exposure	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	1.48	0.88-2.47	0.1370
Amount of pets										

Table 5. Exposure and event (continue)

Risk factors	Study	Country of study	Study period	Study setting	Case number	Control number	OR	AOR[#]	95% CI	P
1	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	1.27	0.83-1.94	-
2	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.55	0.27-1.14	-
3+	Alonso et al.[32]	Iran	2007-2010	Population-based	394	394	-	0.56	0.23-1.36	-
Stressful events[€€€]	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	32.57	17.21-61.64	**< 0.0010**
	Eftekharian et al.[27δ]	Iran	2013	Population-based	250	250	1.90	-	1.30-2.70	-
	Al-Afasy et al.[37δδ]	Kuwait	2010-2012	Population-based	101	202	-	1.80	1.10-3.50	**0.0220**
Childhood hospital admission[δδδ]	Abbasi et al.[30]	Iran	2013-2014	Population-based	660	421	-	0.74	0.08-6.52	0.7840

Significant results are bolded; [*]Sunlight exposure more than 1 hours per day; [**]Sunlight exposure more than 2.5 hours per day; [***]High level of sunlight exposure during primary school; [¥]High level of sunlight exposure during university; [¥¥]Less than 15 minutes per day; [€]Paints and pesticides; [€€]Using microwave less than 3 times a week; [€€€]Such as death of a parent or sibling or child, divorce of parents, getting married, divorced, unplanned pregnancy/abortion, major personal injury or illness, being ousted from work, retirement, major change in living conditions, major change in financial state,… 1 month prior to diagnosis; [δ]Developing a sudden shock upon hearing bad news; [δδ]Being in Kuwait during Iraqi invasion in 1990; [δδδ]Hospital admission for at least 24 hours during childhood; [#]Adjusted mostly for age and sex; [##]Cases and controls were recruited from the same hospital; [###]Controls were recruited from Kuwaiti community living in Kuwait
OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval

However, only Alonso et al. found smoking as a risk factor for female patients (OR = 6.48, 95% CI: 1.46-28.78) and not for male patients (OR = 0.72, 95% CI: 0.31-1.68).[32] In contrast, three studies did not support smoking as a risk factor of MS.[25,30,34] According to Abdollahpour et al. study, there was a significant association between MS and alcohol consumption (AOR = 1.61, 95% CI: 1.11-2.31) and lifetime drug abuse (AOR = 2.93, 95% CI: 1.83-4.70).[35]

Medical history: Table 4 summarizes the possible association between medical histories and MS. According to Al-Shammri et al. study, the presence of any chronic medical illness (AOR = 2.40, 95% CI: 1.30-4.70) might increase the chance of MS development.[25] Mansouri et al. study supported allergy history (AOR = 1.92, 95% CI: 1.55-2.47) as a risk factor of the disease;[22] however, Halawani et al. study did not support the presence of any significant association between allergy history and MS development.[23] Abbasi et al. study revealed that the presence of diabetes mellitus (DM) (AOR = 0.11, 95% CI: 0.01-0.99) might decrease the risk of MS.[30] Al Wutayd et al. study supported thyroid disorder (OR = 0.55, 95% CI: 0.30-0.99) as a protective factor of the disease.[24] However, the other two studies revealed that there was not any significant association between MS and thyroid diseases such as hypothyroidism, hyperthyroidism, and thyroiditis.[30,34] Migraine headache was evaluated in three studies, only one of which reported it as a risk factor (OR = 3.50, 95% CI: 1.61-7.59).[30] The other two studies did not find any significant association between MS and migraine headache.[24,34] Eftekharian et al. study revealed that being depressed (OR = 3.30, 95% CI: 2.30-4.80), having obsessive-compulsive disorder (OCD) (OR = 1.93, 95% CI: 1.34-2.80), often (OR = 4.83, 95% CI: 3.03-7.71) and sometimes (OR = 1.74, 95% CI: 1.08-2.80) experiencing negative thoughts, and having anxiety disorder (OR = 3.82, 95% CI: 2.60-5.50) were all significantly associated with MS.[27] In four studies, measles infection was significantly associated with MS (OR range: 1.60-3.77 and OR mean = 2.70).[23,24,27,30] In Eftekharian et al. study, childhood history of measles and rubella was revealed as a risk factor of MS (OR = 1.70, 95% CI: 1.20-2.40). In addition, there was a significant association between a history of chickenpox infection and MS (OR = 1.43, 95% CI: 1.02-2.00).[27]

Abbasi et al. study supported a significant association between mumps infection and MS (OR = 1.85, 95% CI: 1.22-2.78).[30] Meanwhile, Alonso et al. study indicated that there was not any significant association between measles infection and MS.[32] Mouhieddine et al. study evaluated the relation of anti-EBV antibody titers with environmental risk factors. This study showed a significant association between higher titer of anti-viral capsid antigen (anti-VCA) titer (OR = 1.02, 95% CI: 1.01-1.03) and anti-Epstein-Barr nuclear antigen (anti-EBNA)-1 titer (OR = 1.14, 95% CI: 1.10-1.19) with MS; furthermore, according to this study, smoking along with positive anti-VCA (OR = 1.39, 95% CI: 1.07-1.81) and anti-EBNA-1 (OR = 1.40, 95% CI: 1.07-1.83) had significant association with MS.[36] The past surgical history section in table 4 examines the association between tonsillectomy and MS;[23,24,32,37] however, only Al-Afasy et al. study reported that there was a significant association in this regard (OR = 0.30, 95% CI: 0.10-0.90).[37] In addition, two studies addressed appendectomy and did not indicate any significant association in this respect.[24,32] According to Al-Afasy et al. study, general anesthesia (OR = 0.60, 95% CI: 0.30-1.00) may decrease the risk of MS.

Abbasi et al. study revealed that complete vaccination during childhood that was performed by immunization program launched by Iranian Ministry of Health (AOR = 0.53, 95% CI: 0.28-1.00) decreased the risk of MS. However, vaccination after 18 years old (AOR = 4.57, 95% CI: 1.14-18.41) increased the chance of MS development.[30] Three studies considered the history of head trauma as a risk factor.[27,30,37] The AOR was 2.6 in Al-Afasy et al. study;[37] however, it must be mentioned that Abbasi et al.[30] and Eftekharian et al.[27] studies only supported the history of head trauma in childhood as a risk factor with the AOR of 8.21 and OR of 1.86, respectively. Abdollahpour et al. study reported that head trauma was not significantly associated with MS development.[34] In Halawani et al. study from western region of Saudi Arabia, a large body size was significantly associated with MS (AOR = 8.97, 95% CI: 1.03-77.98),[23] while another study from Saudi Arabia did not report its significant association with MS.[24] According to Rejali et al. study, a higher number of pregnancies (AOR = 0.58, 95% CI: 0.46-0.74) and a higher menarche age (AOR = 0.78, 95% CI: 0.67-0.89) decreased the risk of MS significantly.[26] In addition, Maghzi et al. study reported that being born by cesarean section was significantly associated with MS in female population (OR = 2.69, 95% CI: 1.30-5.58), while no significant association

was observed in male population (OR = 2.25, 95% CI: 0.90-5.63).[38] Abbasi et al. study revealed that premature birth (AOR = 4.99, 95% CI: 1.34-18.68) might increase the risk of developing MS.

Exposure and event: The possible association of exposure and events with MS is summarized in table 5. In six studies, sunlight exposure was considered as a protective factor with the OR ranging from 0.06 to 0.57 with the mean of 0.32.[22-24,30,32,35] Furthermore, Al-Shammri et al.[25] and Abbasi et al.[30] studies revealed that the use of sunscreen (AOR = 2.44, 95% CI: 1.26-4.72) and less exposure to sunlight (AOR = 5.30, 95% CI: 2.70-10.50) increased the risk of MS (AOR = 5.30, 95% CI: 2.70-10.50), respectively. In contrast to the mentioned findings, Eftekharian et al. study revealed that there was no significant association between MS and sunlight exposure during childhood, with the exception of 2-6 hours of sunlight exposure per day (OR = 0.44, 95% CI: 0.20-0.98).[27] In Al-Afasy et al. study, the exposure to paints and pesticide (OR = 2.10, 95% CI: 1.10-3.80) and toxic fumes from oil wells (OR = 12.50, 95% CI: 1.60-95.70) was significantly associated with the risk of developing MS.[37] Moreover, Abbasi et al. study revealed that microwave exposure (AOR = 3.55, 95% CI: 2.24-5.63) was significantly associated with MS. There are two studies that addressed the association between animal exposure and MS and revealed no significant association in this regard.[30,32] In three studies, stressful events were found to have a key role in development of MS with the OR of 1.90, 32.57, and 1.80, respectively.[27,30,37]

Discussion

The present study has summarized the major environmental risk factors associated with MS in the MENA region following a systematic review. Evaluated risk factors were mostly about MS disease onset except for one (cigarette smoking in Roudbari et al.[33] study) which was about relapse-remitting MS (RRMS) progression to SPMS. According to the results, majority of the evaluated risk factors were milk consumption, smoking status, migraine, measles infection, chickenpox infection, tonsillectomy, sunlight exposure, and stressful events. Therefore, the current study focused on these risk factors in particular.

The present study holds neutral perception towards the association between MS and dairy products and milk consumption as various results were extracted from three studies that evaluated the mentioned two factors.[23,24,30]

According to an umbrella review of systematic reviews and meta-analyses addressing the association of environmental risk factors with MS, smoking had a strong association with the onset of MS.[2] However, our results in this study revealed that only six of the studies reported the significant association of smoking with MS, while three of the studies did not support a significant association in this regard. The studies with a larger sample size tended to support smoking as a risk factor;[22,31] however, surprisingly one of the studies with a relatively large sample size did not find a significant association between smoking and MS. The mentioned study pointed that the mentioned finding could be attributed to the higher number of female patients with less tendency to smoking as compared with male patients.[30] It appears that smoking in susceptible individuals carrying certain genes increases the risk of MS development.[39,40] Although the exact etiology of smoking effect on MS is indefinite, it is pointed that a sustained exposure to cigarette smoking can increase pro-inflammatory mediators that can lead to autoimmune diseases.[41] Nicotine may increase blood-brain barrier (BBB) permeability; hence, it may increase the infiltration of immune cells into CNS.[42] Overall, in line with findings of previous studies, our results mostly confirm smoking as a risk factor for MS.[2,43,44] The possible reason for the mentioned controversial findings may be the genetic diversity of the study populations. For example, the presence of human leukocyte antigen-DRB1*15:01 (HLA-DRB*15:01) and the absence of HLA-A*02:01 in Swedish population make smokers 10 times more likely to develop MS.[45]

Among three studies addressing the migraine-MS association, only one study revealed a robust association.[30] However, the researchers of the mentioned study noted that migraine could be a symptom of MS caused by plaques in the midbrain area.[46] Contrary to our results, a meta-analysis study indicated that patients with MS were twice more likely to have migraine without aura headache, though the causal relationship between migraine and MS was unclear.[47] In several studies, migraine often occurs prior to MS; hence, migraine may be considered as a possible risk factor of MS.[48-50] According to a recent study, migraine also increases rates of MS relapse.[51] All of these studies suggest the possible association between MS and migraine.

Over many years of conducting studies aimed at determining the association between measles

infection and MS, the results of some studies have indicated a significant association,[52] while several studies have not supported a significant association in this regard.[2,53] Two of the measles infection complications, namely acute disseminated encephalomyelitis (ADEM) and subacute sclerosing panencephalitis (SSPE), are about demyelination of CNS, which may suggest that measles infection with demyelinating lesions can develop MS.[54] Another study showed an increased level of anti-measles antibody in serum and cerebrospinal fluid (CSF) of patients diagnosed with MS over time.[55] However, according to a Swedish cohort study, no effect was observed on MS incidence after mass measles, mumps, and rubella (MMR) vaccination in Swedish population. The mentioned finding indicated the fact that the decreased incidence of measles infection did not change the incidence of MS; hence, this finding may discredit the association between MS and measles infection.[56] Interestingly, measles infection at older ages was more common among patients with MS as compared to healthy individuals.[57] The mentioned finding suggests that a mature immune system response against measles infection antigen can subsequently lead to MS development.[24] According to our result, all four studies, with the exception of one study, suggested a strong association between MS and measles infection.

Only one of the five studies addressing the history of chickenpox in the present systematic review study indicated a significant association between MS and chickenpox.[27] According to a cross-sectional study conducted in 2013 about varicella zoster virus (VZV) participation in MS relapses in Mexican population, a transient presence of VZV during the relapse phase of MS and a decrease of VZV during the remission phase proposed the possible role of VZV in the pathogenesis of MS.[58] A molecular mimicry between VZV antigens and neuronal cells is suggested. The mentioned molecular mimicry can cause autoimmune cross-reaction against neuronal cells of the CNS in this recent study;[59] however, our study did not support a significant association in this respect, as only one of the five studies investigating the history of chickenpox supported the presence of a significant association.[27]

According to a recent systematic review and meta-analysis study, the history of tonsillectomy under the age of 20 years can increase the risk of MS.[60] This finding may support the theory that removal of tonsils as one of the immune system organs can facilitate invasion of the upper respiratory tract infections that may trigger MS development.[60] Meanwhile, the results of the current study indicated that one study supported the history of tonsillectomy as a protective factor of MS,[37] and the other three studies did not find a significant association in this respect.[23,24,32] Therefore, the reviewers of the present study hold a neutral perspective in this regard.

Based on the findings of recent studies, obesity is considered as one of the MS risk factors;[43,61] however, the results of the current study revealed diverse results. For instance, two studies conducted in Saudi Arabia can be mentioned in this respect.[23,24] Two variables of large body size[23] and a high amount of fast food consumption[24] that can lead to obesity supported obesity as a risk factor for MS; however, one of these studies did not find a significant association between high body mass index (BMI) and MS development.[24] Contrary to the mentioned finding, another study reviewing case-control studies from Sweden and America revealed that BMI ≥ 27 kg/m^2 in individuals with susceptible genotypes (presence of HLA-DRB1*15 and absence of HLA-A*02), as compared with individuals not carrying the susceptible genotype, made them much more likely to develop MS.[62] It can be concluded that genotype might be a confounding factor resulting in different observations in various studies.

Almost all of the studies addressing sunlight exposure in the present study found it as a protective factor of MS. Sunlight exposure is considered as one of the major protective factors not only in our eligible studies conducted in the MENA region but also in most of the worldwide studies.[63] Many studies have already pointed that sunlight exposure can decrease MS development both independent from vitamin D[64] and by increasing the amount of cholecalciferol (vitamin D_3)[65] which modulates the immune system.

Our results supported stressful events as a risk factor of MS since all three studies evaluating stressful events revealed a strong association between MS and stress.[27,30,37] On the other hand, a cohort study conducted in 2014 in Danish population revealed that there was a little causal association between MS development and major stressful life events such as child death, divorce, and spouse death.[66] Furthermore, an American cohort study did not support a significant association between stressful events (e.g., history

of physical and sexual abuse) and development of MS.[67] However, a nationwide cohort study focusing on bereaved parents in Denmark suggested that losing a child younger than 18 years old as a stressful event increased the risk of MS development in mournful parents.[68]

In agreement with findings of the present study, a systematic review study conducted in 2011 indicated that stress could affect MS onset and its clinical course.[69] However, our overall knowledge suggests that stress, instead of being MS etiological cause, is a triggering factor that leads to relapse attacks.[67]

The following section presents the risk factors that are significantly associated with MS according to the results provided by multiple studies; however, they are not discussed in the current study due to either lack of data addressing them in the studies conducted in the MENA region or even non-consideration of them as risk factors of MS based on our results. These risk factors are EBV and vitamin D deficiency. EBV is considered as one of the prominent MS risk factors;[43,70] however, unfortunately we only found one study about EBV that contained OR and 95% CI on MENA region with our search strategy.[36] This study indicates a significant association between higher anti-VCA, anti-EBNA-1 titers and MS development and also supports presence of smoking history along with positive mentioned EBV-related antibodies in individual's serum as an amplifier for increased risk of MS.[36] However, there is still studies in MENA region that provide results showing significant association between higher anti-EBV antibody titers and MS without providing measures of effect such as OR and 95% CI.[71,72] Based on a recent study investigating the findings from meta-analyses and Mendelian randomization studies, it can be concluded that a lower level of serum vitamin D is significantly associated with an increased risk of MS development.[43] However, our findings about vitamin D supplementation, which is considered as a potential protective factor for MS and can lead to a higher level of vitamin D, are not significantly associated with a lower risk of MS.[23,30] Similarly, there is not strong evidence supporting vitamin D supplementation as a protective factor for MS based on the findings of previous studies.[2,73]

The present study had some limitations. Firstly, some of the covered studies had a small sample size.[21,23,25,33] Secondly, the number of studies conducted in the MENA region, as compared with the European and American counterparts, was rather few, which made it more difficult to make precise conclusion.

One of the major possible reasons for different observed results in the MENA region, as compared to the findings of studies conducted in different parts of the world, is the ethnic and genetic diversity within different geographical regions. Since certain genotypes along with environmental risk factors make subjects prone to developing MS. Another explanation for the reported controversial findings might be the geographical differences. For instance, in a study about Iranian immigrants in British Colombia in Canada, the rate of standardized MS prevalence among Iranians living in Canada was three times higher than the rate of MS prevalence among Iranian population in Iran.[16] Other possible reasons can be differences in the methodological designs of the studies as well as the smaller sample size in some of the covered studies.

Conclusion

The review of 47 environmental risk factors in this study indicated that sunlight exposure, cigarette smoking, measles infection, EBV infection, and stressful events had a significant association with MS in the MENA region. Further studies are required to shed more light on the findings presented in this review study.

Conflict of Interests

The authors declare no conflict of interest in this study.

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