A Systematic Review of Risk Factors for Onset of Autoimmune Diseases

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Introduction

Autoimmune diseases represent a family of about 100 illnesses that share a common pathogenesis: an immune-mediated attack on the body's own organs(1, 2). Collectively, autoimmune disorders affect five to nine percent of the population(3, 4).They are caused by a failure of the immune system to differentiate between exogenous substances and the body's own tolerated endogenous molecules, leading to a immunological assault on these self-antigens and ultimately systematic(5) or specific organ disease(6). These chronic conditions often require life-long treatments and bear significant risk of mortality(7, 8). It is therefore urgent and important to develop early prevention and control of autoimmune disorders.

The precise aetiology of autoimmune disorders is currently unknown. It is believed that complex interactions between genetic, environmental (e.g., infectious agents) and lifestyle factors may contribute to the aetiology of these diverse disorders. Concordance rates of 20–30% in monozygotic twins emphasise that environmental components interacting with the host genetic factors are important to our understanding of autoimmunity(9). Reports of co-occurence of autoimmune disorders within one same individual point towards shared pathophysiological pathways(10). Yet, because of the variety of autoimmune disorders and because any single autoimmune disease is relatively rare, risk factors for the development of autoimmunity have seldomly been compared across individual conditions and it remains unknown whether autoimmune disorders share a common aetiology(11) .

We have designed this study to systematically review and assess possible risk factors for five among the most common and most studied autoimmune diseases, and to assess commonalities and differences across conditions. With that, we aimed to improve our understanding of autoimmune disease aetiology and support the development of effective prevention strategies or more targeted therapies.

Methods

The systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) Guidelines(12). The protocol outlined prior to this study was registered in the PROSPERO database.

Autoimmune diseases of interest

To represent the diverse spectrum of autoimmunity, we selected five conditions among the most common and most studied autoimmune diseases. These are: Rheumatoid Arthritis, Multiple Sclerosis, Diabetes Type 1, Psoriasis, and Systemic Lupus Erythematosus.

Search strategy

We defined a search strategy based on a set of keywords, synonyms and carefully selected exclusion terms to best identify studies reporting on autoimmune disease risk factors (**appendix**). We searched MEDLine and Embase for studies published between 01/01/2000 and 30/04/2022 using the pre-defined search strategy and conducted secondary referencing by manually reviewing reference lists of key articles. Citation checks and deduplication of results were conducted by Endnote X9 software(13).

Study selection

Studies were included if they reported risk factor(s) for the development of at least one of the autoimmune disorders of interest in humans, and provided estimates of 'hazard ratio', 'odds ratio', 'risk ratio' or 'relative risk' with the corresponding 95% confidence interval (CI), or data necessary to calculate these. Study designs were restricted to primary epidemiological observational study designs (i.e., cohort and case-control studies) and clinical trials. To minimise the risk of small-study effects, we further restricted studies to cohort sizes with at least 500 participants developing the outcome of interest. We placed no restrictions on study setting, participant characteristics, or geographic regions, but included only articles written in English. Where several articles reported on one same study, we included the most recent analysis of the data.

Data extraction

Two researchers (PS and LV) screened all abstracts identified in the initial search and excluded studies in violation of the inclusion criteria using the reference managing website Rayyan(29). Full-text articles were reviewed in duplicate and, in cases of disagreement, consensus was achieved through referral to a third reviewer (NC). An electronic data abstraction form was used to record patient and study characteristics, including study design, geographical location, data collection period, cohort size, mean age, methods of case identification and diagnostic criteria, number of events, and summary statistics were also extracted. When the summary statistic was not provided, we calculated rate ratios from the number of events and person-years at risk. Conversely, if the total number of events was missing, we estimated it using the summary statistic and its confidence interval. Where available, gender stratified incidence data and trends over time were also recorded.

Risk of bias assessment

Observational, non-randomized, studies were evaluated using the Newcastle Ottawa quality assessment scale -tool (14), whereas randomized controlled trials were assessed using the Robins-I tool (15)respectively.

Statistical analysis

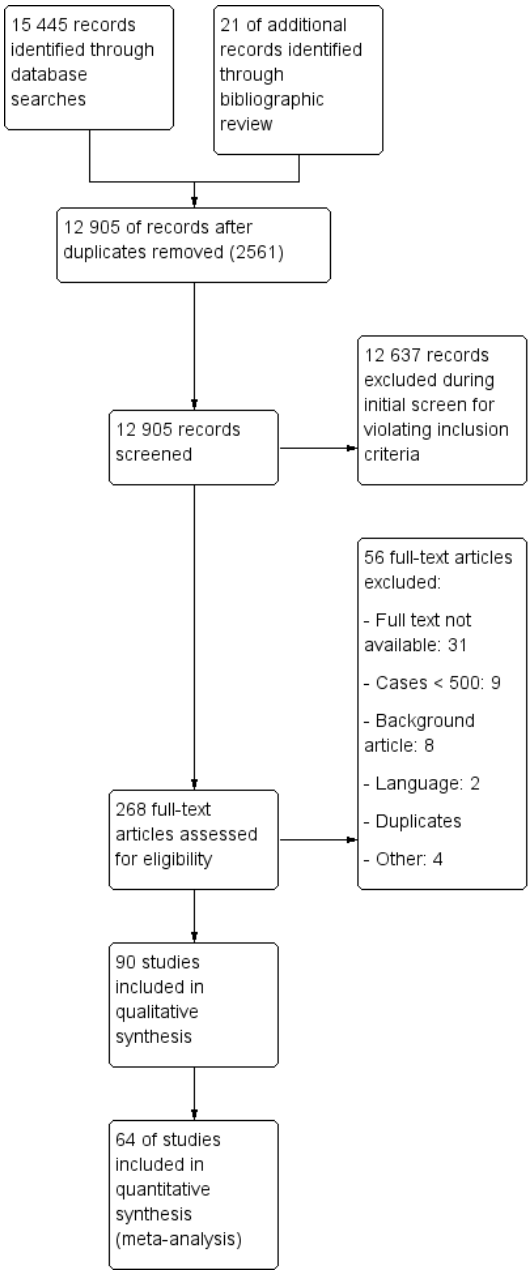
Each risk factor-disease association was examined separately. When at least two studies provided data on the same risk factor and autoimmune disease, we performed a meta-analysis of compatible studies and derived pooled estimates. For other identified and significant risk factors we completed a descriptive synthesis.

Where studies provided both crude and adjusted estimates, preference was given to estimates that were adjusted for known risk factors. Given the rareness of the studied outcome, we considered different risk estimates as rate ratios and calculated pooled estimates and 95% confidence intervals using the inverse variance weighted random effects meta-analysis. We characterized heterogeneity with the I^2 statistic. To illustrate the potential for publication bias and small study effects, funnel plots were drawn to present the effect estimates (horizontal axes) against the standard error (vertical axes) and were interpreted visually (**appendix**). (16) (16)All analyses were completed using Review Manager Software (RevMan, version 5.4, Cochrane Collaboration, Copenhagen, Denmark)

Results

Using our described search strategy, we identified 15 445 articles, of which 268 were eligible for full-text review. Of those, 64 articles met the criteria to be included in the quantitative synthesis. Five studies used the same dataset, the Nurses Health Study 2(17-21), and three used the original Nurses Health Study(17-19). Two studies used the Epidemiological Investigation of Multiple Sclerosis (EIMS) study (22, 23). 33 articles described the risk factor smoking. 11 and 10 studies were documented for mononucleosis and season of birth respectively. Next was Body Mass Index with 7 reports. Periodontitis, deletion of the LCE3C–LCE3B genes and major depression each had seven, six and three studies respectively. The I^2 statistic for heterogeneity varied between low and very high, was highest for season of birth (97%), lowest for smoking and psoriasis (0%), yet remained below 50% for the following risk factor associations: former smoking and both rheumatoid arthritis and psoriasis, overweight, periodontitis and psoriasis, LCE3C-LCE3B deletion and self-reported mononucleosis. All other associations had and I^2-value above 50%.

Figure 1: Study selection PRISMA flow chart



Study characteristics

A detailed summary of the included articles is included in the appendix.

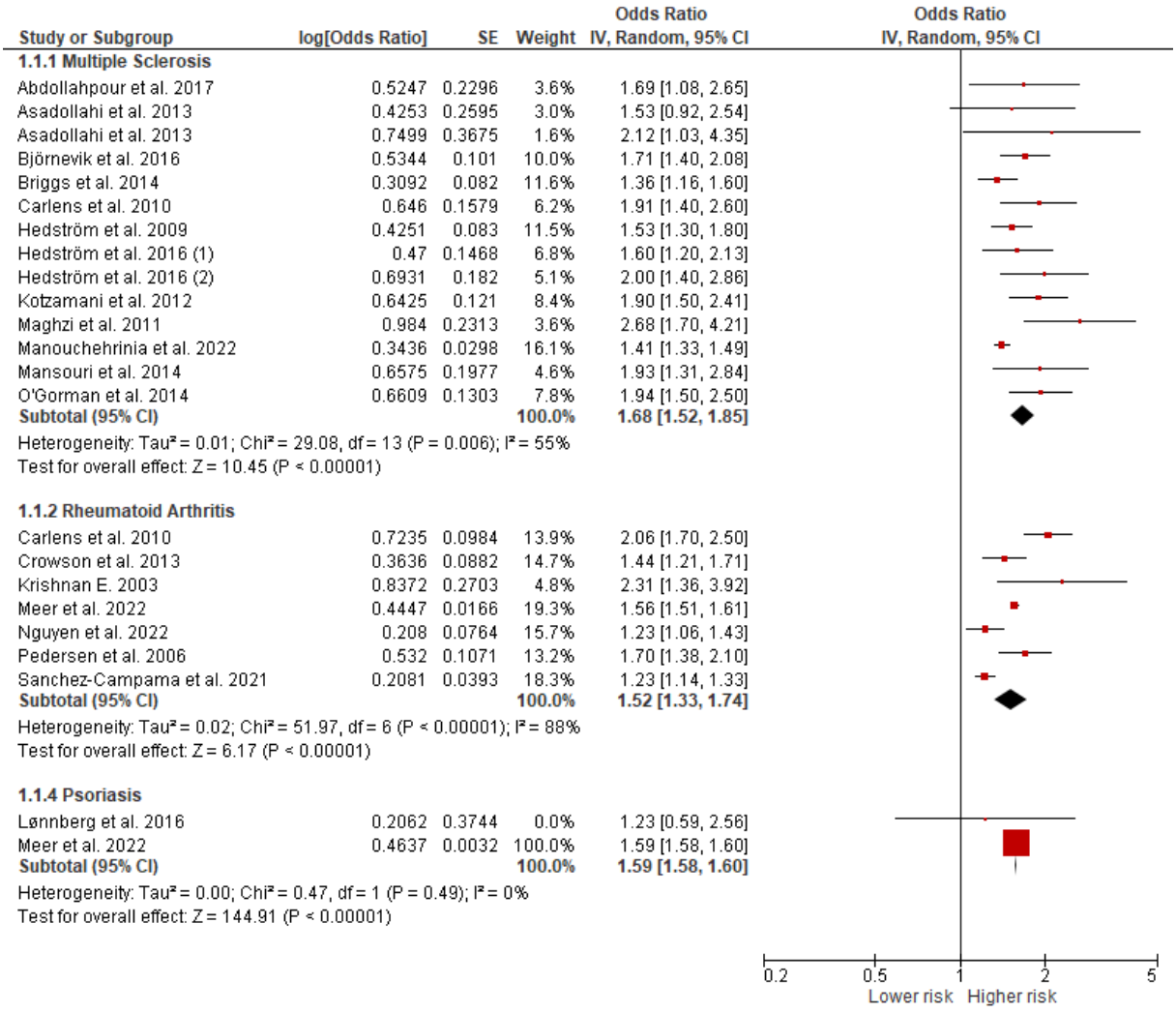
Bias assessment

Visual inspection showed an asymmetrical distribution of studies for ever smoking and multiple sclerosis, obesity and serological diagnosis of mononucleosis (**appendix**). Using the Newcastle Ottawa Scale, 29 studies were considered were considered to be high quality. 30 studies showed high risk of bias and 2 showed very high risk of bias. Three studies could not be assessed because of alternative study methodology.

Smoking risk for autoimmune diseases

Fifteen studies described smoking as a risk factor for multiple sclerosis(22-36), nine studies did so for rheumatoid arthritis(18, 28, 34, 37-42), and eleven for psoriasis(17, 38, 43-51). No relevant studies were found on smoking as a risk factor for systemic lupus erythematosus or type 1 diabetes. A meta-analysis was made for ever smoking, current smoking, former smoking and passive smoking, showing an increased risk for multiple sclerosis, rheumatoid arthritis, and psoriasis for all smoking categories. Pooled odds ratio for ever smoking were 1.68 [1.52 – 1.85], 1.52 [1.33, 1.74], and 1.59 [1.58-1.60] for multiple sclerosis, rheumatoid arthritis, and psoriasis, respectively (**figure 2**). Risk for incident autoimmune disease was generally highest for current smoking than for passive or former smoking (**appendix**).

Figure 2: Forest plot for risk of ever smoking, compared to never smokers, for incident multiple sclerosis, rheumatoid arthritis and psoriasis, respectively.

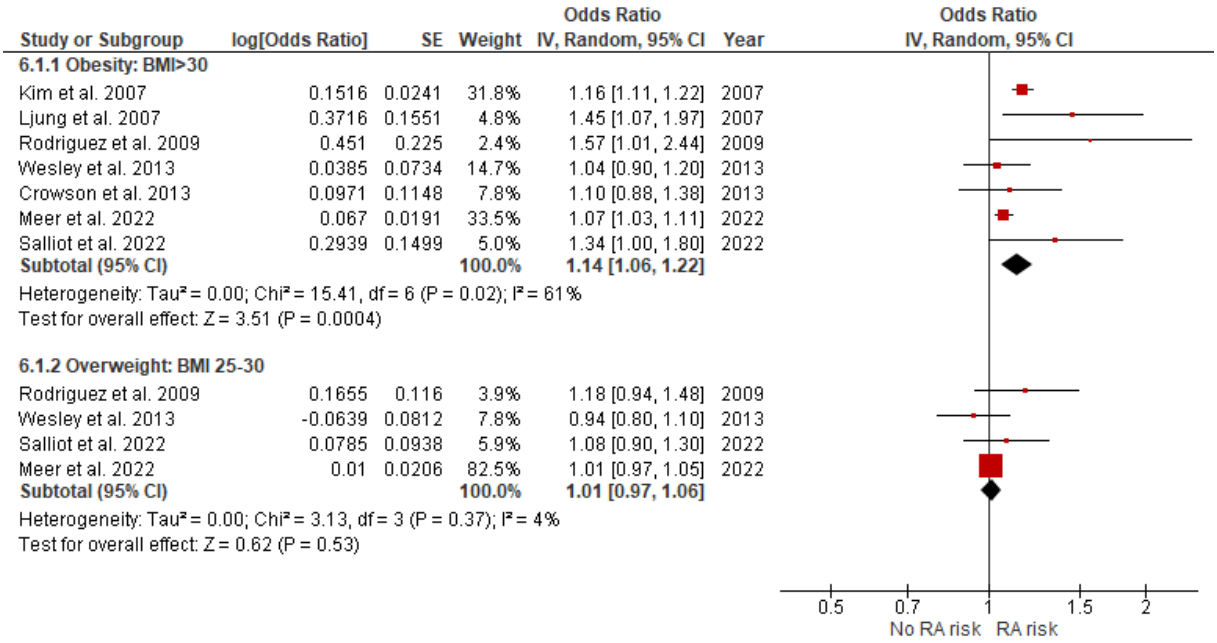


Footnotes
(1) Odds ratio for smoking less than 10 cigarettes a day
(2) Odds ratio for smoking more then 10 cigarettes a day

Overweight and obesity

We found seven(34, 38, 41, 52-55) and four studies(38, 41, 54, 55) concerning rheumatoid arthritis investigating obesity (BMI >30) and excess weight (BMI 25-30). respectively. Pooled OR for obesity was 1.14 [1.06-1.22] (**figure 3**) and 1.01 [0.97-1.06] for a BMI between 25 and 30. For psoriasis, one study found and association with obesity (BMI>30) (OR: 1.27 [1.25–1.30])(38). Another showed an increased risk for metabolically unhealthy overweight and obese individuals (Hazard ratios of 1.29 and 1.33 respectively)(52). A third study demonstrated an increased risk (OR: 1.49 [1.19–1.86])for one unit increase in z-score of BMI for females at the age of 13 years(56). Five studies showed a relationship between MS and different measures of weight (self-reported body size, body size during stages in childhood, BMI intervals, one-unit increase in body size and one standard deviation in childhood BMI)(57-61). One study showed an association between diabetes type 1 and obesity in men over 35 (HR: 1.19)(62).

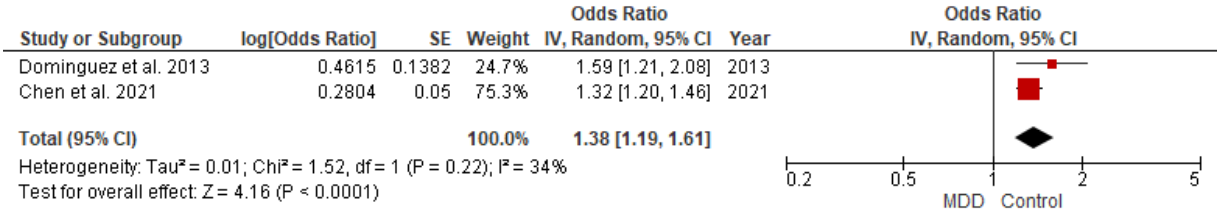
Figure 3: Risk of incident rheumatoid arthritis in obese and overweight individuals, compared to individuals with a normal BMI (18,5-25).



Depression

Two cohort studies were found showing a significantly increased risk of psoriasis in patients with major depressive disorder (MDD)(21, 63). Pooled OR was 1.38 [1.19-1.61] (**figure 4**). Diagnosis of MDD was determined by either anti-depressant use, Mental Health Index (MHI) score > 52 or registration in database. No other studies were found.

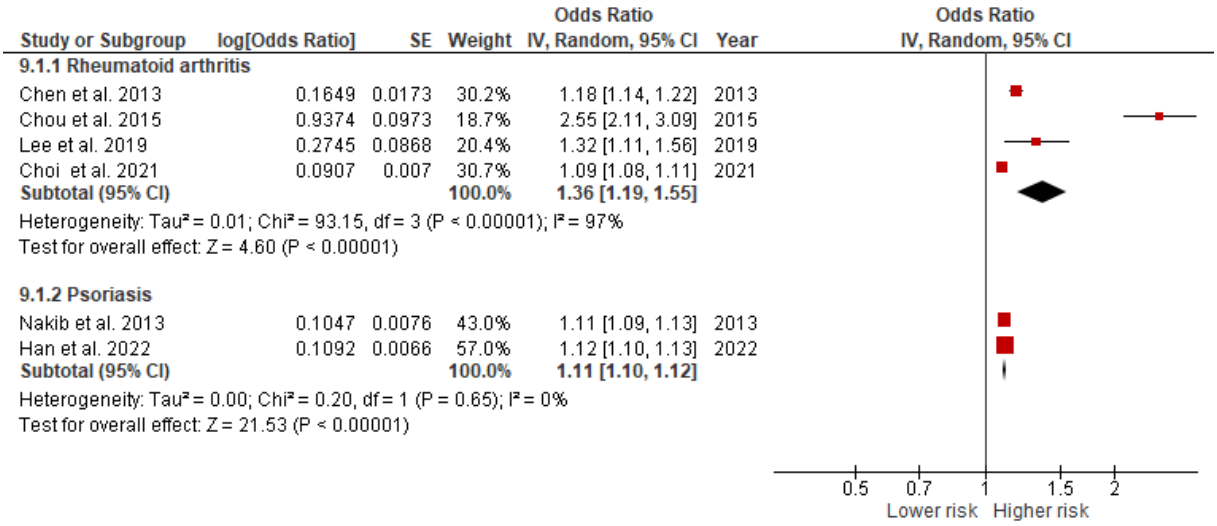
Figure 4: Risk of psoriasis in patients with major depressive disorder.



Periodontitis

A total of four and two studies were included for meta-analysis for risk of rheumatoid arthritis(64-67) and psoriasis(20, 67, 68), respectively. A pooled OR of 1.36 [1.19-1.55] suggest an association between rheumatoid arthritis and periodontitis (**figure 6**). A small, but significant increase in psoriasis risk with an OR of 1.11 [1.10-1.12] (**figure 6**) was observed. No articles were found regarding other autoimmune diseases.

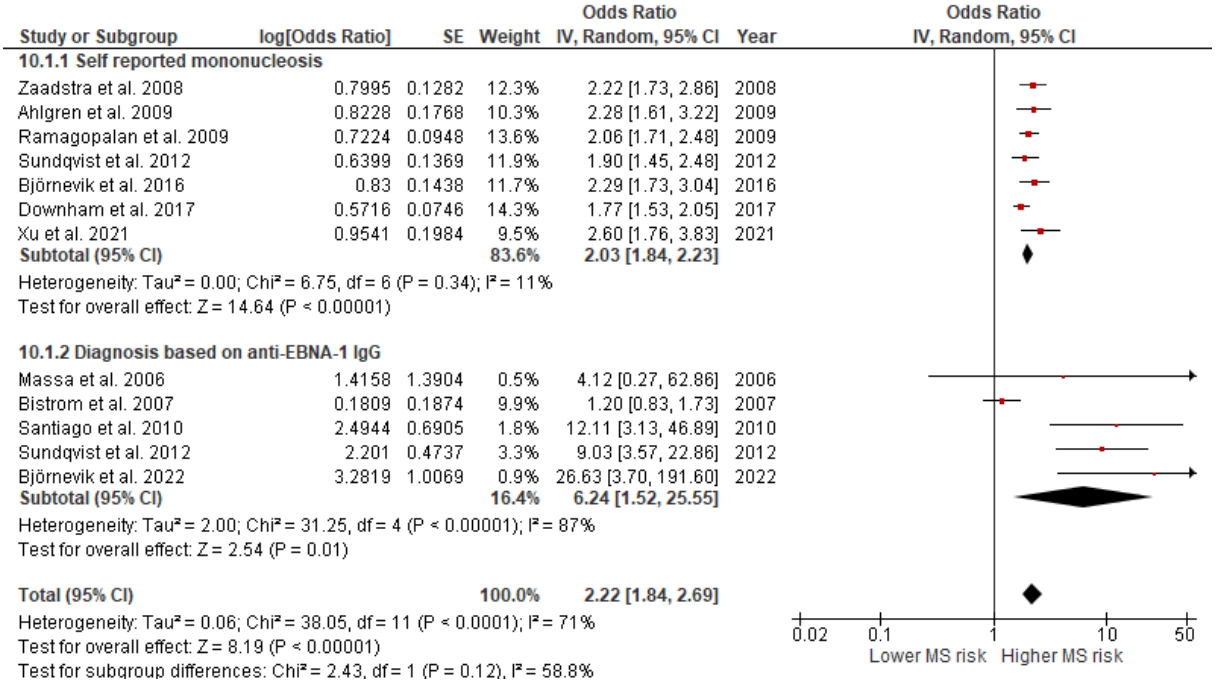
Figure 6: Risk of incident rheumatoid arthritis and psoriasis in individuals with periodontitis.



Mononucleosis

Diagnosis of mononucleosis was detected as a risk factor in eleven publications, all concerning multiple sclerosis(19, 26, 69-77). In seven studies, the diagnosis was self-reported and in five articles antibody serology (anti-EBNA1-IgG) was determined. When combining self-reported and serological diagnosis, meta-analysis showed an increase in MS risk, OR 2.22 [1.84-2.68]. Self-reported diagnosis and antibody status demonstrated ORs of 2.03 [1.84-2.23] and 6.24 [1.52-25.55] respectively (figure 7).

Figure 7: Risk of incident multiple sclerosis in patients diagnosed with mononucleosis, with subgroups for self-reported and serological diagnosis.

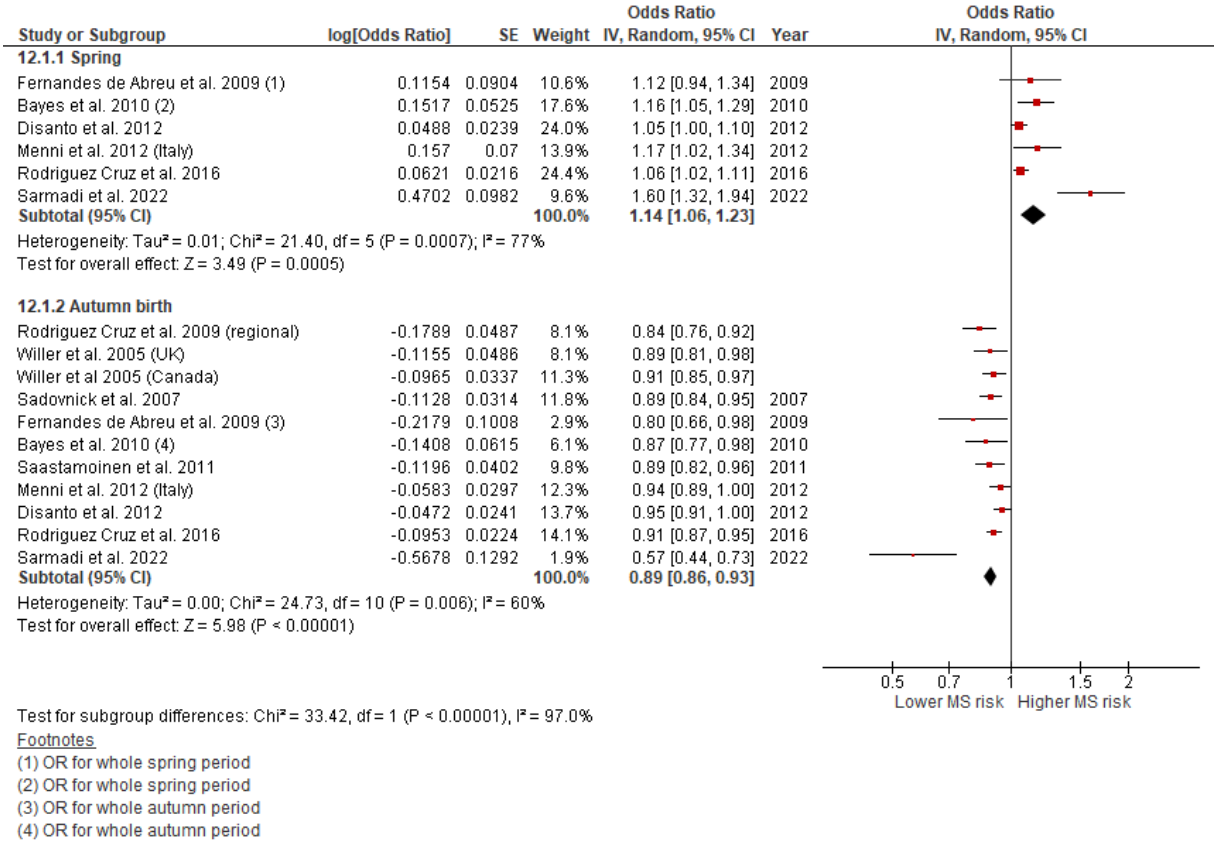


Time of birth

Nine studies(78-86) described the relationship between multiple sclerosis onset and birth in April and/or November months. Three articles mentioned ORs for all seasons. Two of these three publications also showed ORs for birth months(85, 86). April and November months were used as a surrogate for spring and autumn as a means to synthesize this data, when seasonal data were not available.

Six studies showed that persons born in spring displayed a slightly elevated risk of multiple sclerosis, as shown by an OR of 1.14 [1.04-1.26]. Autumn birth, documented in all 10 studies, showed a protective effect for MS: OR 0.89 [0.86-0.93].

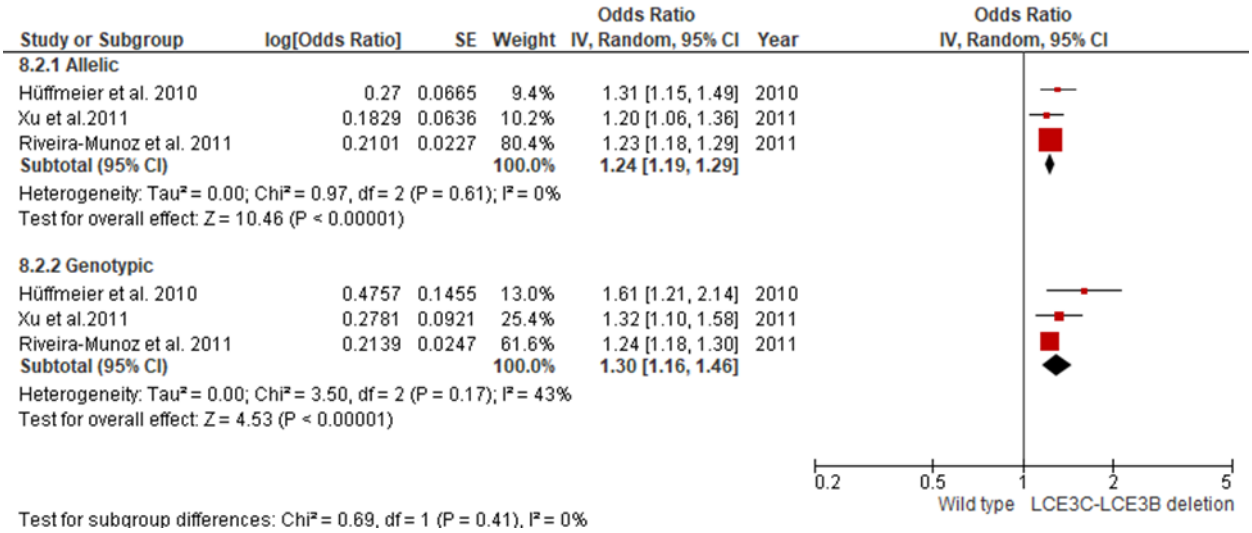
Figure 8: Risk of incident multiple sclerosis in individuals born in spring or autumn months, compared to all other months. Fernandes de Abreu et al. and Bayes et al. were the only studies that provided odds ratios for the whole spring and autumn season.



Genetic factors

Three articles studying the LCE3C–LCE3B gene deletion and only psoriasis were included(87-89). Meta-analysis concluded that the presence of the allele with this deletion was significantly associated with a higher risk of psoriasis with an OR of 1.24 [1.19-1.29]. Similarly, pooled OR for the LCE3C–LCE3B-del/ LCE3C–LCE3B-del genotype, was 1.30 [1.16-1.46] (**figure 5**).

Figure 5: Risk of incident psoriasis in individuals with a LCE3C–LCE3B deletion, either allelic or genotypic (del/del).



Other risk factors

Five and six records were found for alcohol use and vitamin D respectively. Alcohol use was found to be associated with multiple sclerosis, rheumatoid arthritis and psoriasis. Higher vitamin D levels were found to have a protective effect on multiple sclerosis. Meta-analysis for both risk factors was not achieved due to the non-standardized exposure to these risk factors. Articles about breastfeeding, oral contraceptives, allergic diseases, vaccinations, c-section, parental behaviour, and particulate matter 2.5 exposure respectively, all had multiple studies, but no risk factor had more than one study for any autoimmune disease. Therefore, meta-analysis was not possible.

Discussion

This systematic review and meta-analysis quantified the relationship between a multitude of risk factors and onset of five autoimmune diseases. We found that smoking was strongly associated with an increased risk for multiple sclerosis, rheumatoid arthritis and psoriasis. These findings are similar to other meta-analyses. Handel et al. (90) identified a very similar risk ratio of 1.48 [1.35–1.63]. Our results for rheumatoid arthritis are in line with a meta-analysis of Di Guiseppe et al.(91) describing and risk ratio ranging from 1.26 [1.14 -1.39] (among individuals smoking 1 to 10 pack-years) to 1.94 [1.65-2.27] (smoking over 20 pack-years). For psoriasis, a meta-analysis by Armstrong et al. (92) described a slightly higher pooled odds ratio of 1,78 [1,52–2,06] and 1,62 [1,33–1,99] for current and former smoking respectively. Likewise, our review demonstrated that periodontitis correlated with onset of rheumatoid arthritis and psoriasis. Qiao et al. (93) publicised a comparable odds ratio of 1.70 [0.75-3.85] for rheumatoid arthritis. The association with psoriasis was also discovered in a meta-analysis (94)(odds ratio of 2.87 [1.75–4.69]). Surprisingly, relatively few studies were included that described risk factors for systemic lupus erythematosus or diabetes type 1.

Smoking was the most described risk factor and appears to have, at least partially, a common pathogenic mechanism for multiple autoimmune diseases. Cigarette smoking is known to induce a systemic proinflammatory state by increasing oxidative stress and modulating the innate and adaptive immunity(95). Consequently induced damage to pulmonary tissues leads to exposure of intracellular molecules, ultimately resulting in autoreactivity in genetically predisposed individuals (96). For pathogenesis of multiple sclerosis, effector T-cells mature in long tissue and migrate to and attack the central nervous system(97). Smoking also promotes citrullination of endogenous protein into an unfamiliar molecule, subsequently leading to the production of anti-citrullinated protein antibodies (ACPA's) that are well known diagnostic antibodies in rheumatoid arthritis(95). Like multiple sclerosis, a predisposition is thought to exist through variants in the HLA-genes, that may present as an epitope for ACPA's and other auto-antibodies (98). Interestingly, studies included in this review that also reported auto-antibodies, all showed higher effect sizes in ACPA- or RF-positive cases(18, 34, 39), furthermore supporting this theory. For psoriasis smoking disrupts communication between skin-resident autoimmune cells induces a self-sustaining cycle of inflammation that is easily triggered by environmental factors, drugs, infections, sunlight … Again cutaneous T memory cells, directed at antigens in the skin, also play a role in the pathophysiology of psoriasis(99).

Periodontitis was found to be a risk factor for both rheumatoid arthritis and psoriasis. Porphyromonas gingivalis, a common anaerobic periodontal bacterium, produces an enzyme, peptidyl arginine deiminase, with the capability of citrullination of peptides. It is thought that this pathogen is the major factor for rheumatoid arthritis onset, by producing anti-citrullinated protein antibodies (100)). A common pathway between psoriasis and periodontitis, is thought to be the excessive immune response, leading to chronic inflammatory process that is associated with autoimmune diseases in predisposed individuals (101).

Mononucleosis infection appeared to be the risk factor with the greatest effect size with an odds ratio of 2.22 [1.84-2.68]. This supports the hypothesis that there is an important relationship between Epstein-Barr Virus (EBV) infection and pathogenesis of multiple sclerosis, latent infection of the B lymphocytes. Interestingly, there was a discrepancy between self-reported diagnosis and anti-EBNA-1 seropositivity, with odds ratios of 2.03 [1.84-2.23] and 6.24 [1.52-25.55]. This suggests an underdiagnosis of EBV-infections based on clinical symptoms. Epidemiological studies have found seroprevalence of EBV-antibodies over 90% in adult populations (102), further supporting the idea of underdiagnosis. One of our included studies (71) compared EBV seroconversion with persistent

seronegativity and even found a higher hazard ratio of 32.4 [4.3-245.3], hinting at a possible pivotal role of EBV-infection in development of multiple sclerosis.

Furthermore, timing of birth demonstrated a small but robust effect on multiple sclerosis risk. Lower maternal vitamin D levels in winter months due to low UV exposure is suggested as an explanation for higher risk for individuals born in spring(103).

Finally, the question as to whether some of the observed associations might be confounded by socioeconomic status must be considered. Risk factors, such as obesity, depression and smoking are known to be associated with lower socioeconomic status (104, 105), and autoimmune diseases have been described to be associated with socioeconomic inequality(105). Socioeconomic inequality might in turn be associated with inferior nutritional status, more difficult access to healthcare, behavioural factors (e.g. substance abuse), or higher exposure to infections.(106-108) In this review, only a handful of selected studies controlled for socio-economic status, and a minority of studies for smoking. Generally, for more accurate estimation of risk factors related to socioeconomic status, more research should be performed with adjusting for these possible confounders.

A major strength of this systematic review is the multitude of risk factors studied across several autoimmune diseases, allowing us to study commonalities and differences between autoimmune diseases with unprecedented granularity. A key limitation of this meta-analysis is that we had no individual patient data, the use of which would have provided greater detail about the effects of individual risk factors on autoimmune disease. For this same reason, it was not possible to investigate combined outcomes of autoimmune diseases co-occuring within individuals. A further limitation was that the studies varied in several respects, including differences in study design, study populations (e.g., only women), risk factors and disease diagnosis (e.g., self-reported versus specialist diagnosis), and it is possible that methodological differences might have confounded observed results. Finally, the restriction on studies with at least 500 cases, set to minimise the risk of small-study effects, might have resulted in some relevant studies being missed and might have led to a disproportionate number of retrospective studies, since these studies are easier to execute in larger sample sizes compared to other studies. Recall bias may therefore be present in some of the studies relying on self-reported risk factors.

In total we described eight risk factor that had multiple studies concerning the relationship between said risk factor and at least one autoimmune disease. From the initial 268 included studies, only 64 articles were ultimately used. Many excluded reports described risk factors that were not replicated elsewhere or had incompatible outcome measurements. This shows that many more risk factors require further investigation. Most risk factors that were discovered, are preventable (e.g., smoking, periodontitis, obesity…) and should be considered more strongly in public health strategies. Furthermore, more research should be conducted regarding the pathophysiology between risk factor and onset of autoimmune disease, as this could lead to more targeted therapy. Also, many studies were not comparable due to differences in measurement of exposure. For future research use of more standardized measure of exposure could lead to stronger systematic reviews.

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Appendix

Study characteristics

Table is provided on the next page.

Author	Title	Cases	Controls	Study type	Location	NOS
Abdollahpour et al. 2017	Waterpipe smoking associated with multiple sclerosis: A population-based incident case–control study	547	1057	Case-control	Iran	9
Ahlgren et al. 2009	A population-based case-control study on viral infections and vaccinations and subsequent multiple sclerosis risk	509	2067	Case-control	Sweden	4
Al-Mutairi et al. 2010	Comorbidities associated with psoriasis: an experience from the Middle East	372	371	Case-control	Kuwait	4
Armesto et al. 2012	Psoriasis and type 2 diabetes risk among psoriatic patients in a Spanish population.	661	661	Case-control	Spain	5
Armstrong et al. 2011	Psoriasis and hypertension severity: results from a case–control study	835	2418	Case-control	USA	6
Asadollahi et al. 2013	Cigarette smoking and associated risk of multiple sclerosis in the Iranian population	662	394	Case-control	Iran	6
Bayes et al. 2010	Timing of birth and risk of multiple sclerosis in the Scottish Population	1309	6,198,352	Case-control	Scotland	7
Bistrom et al. 2007	Epstein-Barr virus infection after adolescence and human herpesvirus 6A as risk factors for multiple sclerosis	670	670	Case-control	Sweden	6
Bjørnevik et al. 2016	Level of education and multiple sclerosis risk after adjustment for known risk factors: The EnvIMS study	953	1717	Case-control	Norway	7
Bjørnevik et al. 2022	Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis	801	1566	Case-control	USA	5

Bo et al. 2008	Smokers report more psoriasis, but not atopic dermatitis or hand eczema: results from a Norwegian population survey among adults.	10320	/	Cohort	Norway	6
Briggs et al. 2014	Smoking and Risk of Multiple Sclerosis Evidence of Modification by NAT1 Variants	Kaiser study:1958 Swedish study:1957	Kaiser study:1967 Swedish study:1966	Case-control	USA | Sweden	8
Carlens et al. 2010	Smoking, Use of Moist Snuff, and Risk of Chronic Inflammatory Diseases	277,777		Cohort	Sweden	6
Chen et al. 2021	Major depressive disorder increased risk of psoriasis: A propensity scorematched cohort study	64,486		Cohort	Taiwan	9
Choi et al. 2021	Periodontitis as a Risk Factor for Rheumatoid Arthritis: a Matched-Cohort Study	345,753	345,753	Cohort	Korea	7
Chou et al. 2015	Rheumatoid Arthritis Risk Associated with Periodontitis Exposure: A Nationwide, Population-Based Cohort Study	628,628	168,842	Cohort	Taiwan	9
Crowson et al. 2013	Contribution of Obesity to the Rise in Incidence of Rheumatoid Arthritis	813	813	Case-control	USA	8
Disanto et al. 2012	Month of birth, vitamin D and risk of immune mediated disease: a case control study.	115,172 (MS: 26,994, RA: 39,666, SLE: 4,046, CD: 20,574 and UC: 23,892)	General population	Case-control	England and Scotland	4
Dominguez et al. 2013	Depression and the risk of psoriasis in US women	NHS 2: 86,880		Cohort	USA	6

Downham et al. 2017	Season of infectious mononucleosis as a risk factor for multiple sclerosis: a UK primary care case-control study	9,247	55,033	Case-control	Australia	5
Fernandes De Abreu et al. 2009	Season of birth and not vitamin D receptor promoter polymorphisms is a risk factor for multiple sclerosis	583	9,163,065 (French birth between 1975-1986)	Case-control	France	4
Gerdes et al. 2010	Smoking and alcohol intake in severely affected patients with psoriasis in Germany.	509	2295	Cohort	Germany	6
Goto et al. 2021	Late-onset development of psoriasis in Japan: a population-based cohort study	Cohort: 487,835 Cases: 2793		Cohort	Japan	7
Han et al. 2022	Smoking and Periodontitis Can Play a Synergistic Role in the Development of Psoriasis: A Nationwide Cohort Study	Cohort: 9,718,591 Cases: 207,059		Cohort	Korea	7
Hedström et al. 2009	Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis.	902	1855	Case-control	Sweden	7
Hedström et al. 2013	Smoking and multiple sclerosis susceptibility	7,883	9,264	Case-control	Sweden	7
Hedström et al. 2014	Interaction between passive smoking and two HLA genes with regard to multiple sclerosis risk	EIMS study: 736 KNPC study: 575	EIMS study: 1195 KNPC: 373	Case-control	Sweden (EIMS) and USA (KNPC)	EIMS: 6 KNPC: 7
Hedström et al. 2016	Smoking is a major preventable risk factor for multiple sclerosis	2455	5336	Case-control	Sweden	7
Hüffmeier et al. 2010	Replication of LCE3C-LCE3B CNV as a risk factor for psoriasis and analysis of	1,354	937	Case-control, based on genotyping three	Germany, Netherlands	/

	interaction with other genetic risk factors			SNPs of the LCE3C-LCE3B gene		
Kotzamani et al. 2012	Rising incidence of multiple sclerosis in females associated with urbanization	657	593	Case-control	Greece	4
Krishnan E.	Smoking, gender and rheumatoid arthritis-epidemiological clues to etiology. Results from the behavioral risk factor surveillance system	644	1509	Case-control	USA	5
Lee et al. 2019	Correlation between diabetes mellitus and periodontitis in Taiwan: A nationwide cohort study	15170	63598	Cohort	Taiwan	9
Li et al. 2012	Smoking and risk of incident psoriasis among women and men in the United States: a combined analysis	Cohort: 185,836: NHS: 66,241 NHS 2: 95,531 HPFS: 24,064 Cases: 2410 pts		Cohort	USA	8
Liu et al. 2019	Impact and Timing of Smoking Cessation on Reducing Risk of Rheumatoid Arthritis Among Women in the Nurses' Health Studies	NHS 1: 117,182 NHS 2: 113,550 Cases: 1,528		Cohort	USA	8
Ljung et al. 2016	Abdominal obesity, gender and the risk of rheumatoid arthritis – a nested case–control study. Arthritis Res Ther. 2016;18:277	557	1671	Nested case-control	Sweden	9
Lønnberg et al.	Smoking and risk for psoriasis: a population-based twin study	34,781		Twin study		7
Maghzi et al. 2011	Cigarette Smoking and the Risk of Multiple Sclerosis: A Sibling Case-Control Study in Isfahan, Iran	516	1090	Case-control	Iran	3

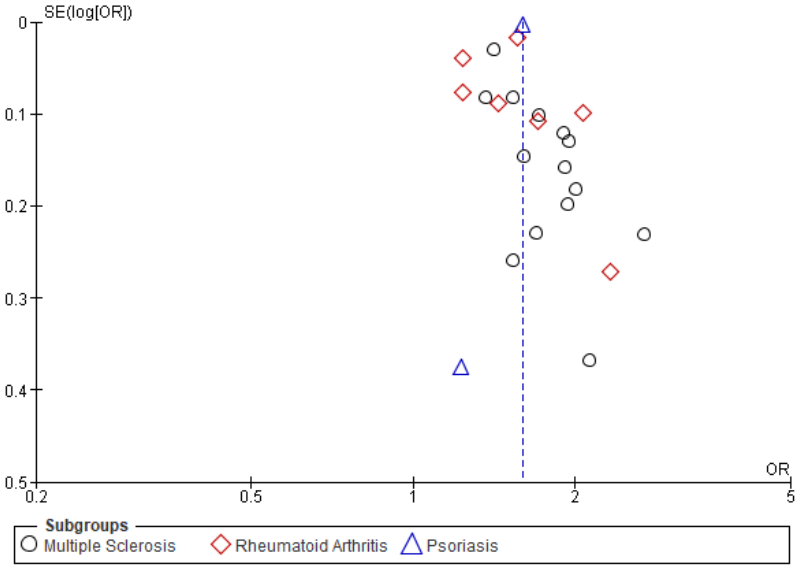
Mansouri et al. 2014	Risk factors for increased multiple sclerosis susceptibility in the Iranian population	1403	883	Case-control	Iran	8
Manouchehrinia et al. 2022	Smoking Attributable Risk in Multiple Sclerosis	9419	9419	Case-control	Sweden	5
Massa et al. 2007	Plasma titers of antibodies against Epstein-Barr virus BZLF1 and risk of multiple sclerosis	Not available	NHS: 32,826 NHS 2: 29,613	Case-control	USA	4
Meer et al. 2022	Risk Factors for Diagnosis of Psoriatic Arthritis, Psoriasis, Rheumatoid Arthritis, and Ankylosing Spondylitis: A Set of Parallel Case-control Studies	Psoriasis: 111,375 Rheumatoid arthritis: 28,341	Psoriasis: 1,113,345 Rheumatoid arthritis: 283,226	Case-control	USA	6
Menni et al. 2012	Short and Long Term Variation in Ultraviolet Radiation and Multiple Sclerosis	Italy: 2,737 USA: 56,020 Denmark: 15,900	General population	Case-control	Italy, USA and Denmark	3
Nakib et al. 2013	Periodontal disease and risk of psoriasis among nurses in the United States	Cohort: 70,020		Cohort	USA	6
Naldi et al. 2005	Cigarette smoking, bodymass index, and stressful life events as risk factors for psoriasis: results from an Italian case–control study.	550	690	Case-Control	Italy	5
Nguyen et al. 2022	Association between passive smoking in childhood and adulthood, and rheumatoid arthritis: Results from the french e3n-epic cohort study	Cases: 698 Cohort: 79 806		Cohort study	France	8
O'Gorman et al. 2014	Smoking increases the risk of multiple sclerosis in Queensland, Australia.	560	480	Case-control	Australia	7
Pedersen et al. 2006	Environmental risk factors differ between rheumatoid arthritis with	515	769	Case-control	Denmark	5

	and without auto-antibodies against cyclic citrullinated peptides					
Ramagopalan et al. 2009	Association of infectious mononucleosis with multiple sclerosis. A population-based study	14362	7671	Case-control	Canada	5
Riveira-Munoz et al. 2011	Meta-analysis confirms the LCE3C_LCE3B deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with HLA-Cw6	9389	9477	Meta-analysis after receiving individual patient data	Global	/
Rodriguez et al. 2009	Rheumatoid arthritis in UK primary care: incidence and prior morbidity.	579	4234	Case-control	Spain	8
Rodriguez Cruz et al. 2016	Time- and Region-Specific Season of Birth Effects in Multiple Sclerosis in the United Kingdom	31,806	61,734,728	Case-control	United Kingdom	6
Saastamoinen et al. 2012	Month of birth is associated with multiple sclerosis but not with HLA-DR15 in Finland.	8,359	7,014,435	Case-control	Finland	5
Sadovnik et al. 2007	A timing-of-birth effect on multiple sclerosis clinical phenotype	21,062	13,783	Case-control	Canada	4
Salliot et al. 2022	Anthropometric Measures and Risk of Rheumatoid Arthritis in the French E3N Cohort Study	Cohort: 98,995 Cases: 698		Cohort	France	8
Sanchez-Campama et al. 2021	The Association Between Smoking and the Development of Rheumatoid Arthritis: A Population-Based Case–Control Study	13,920	69,535	Case-control	Spain	8
Santiago et al. 2010	Relation between Epstein-Barr virus and multiple sclerosis: analytic study of scientific production	502	585	Combination of multiple case-control data	Multiple	/

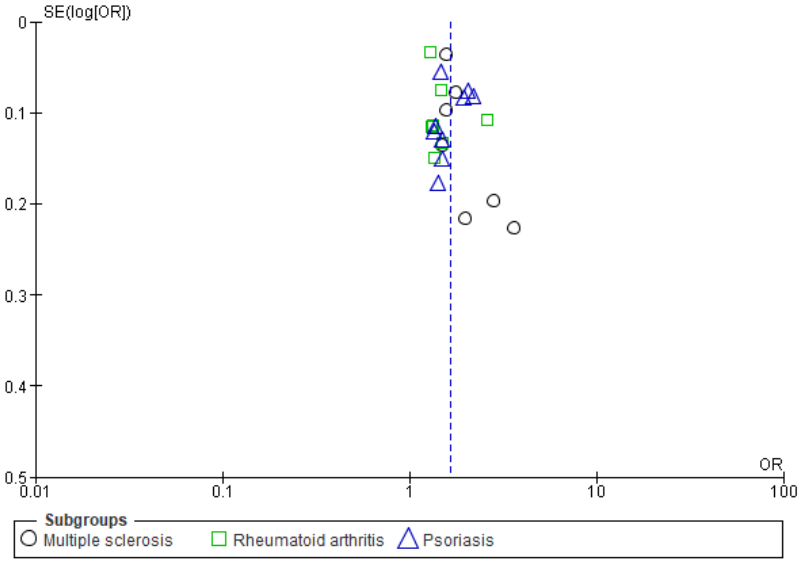
Sarmadi et al. 2022	The Effect of Month of Birth on Multiple Sclerosis: A Case-Control Study in Northeast Iran	2,160	2,245	Case-control	Iran	4
Shapiro et al. 2012	Psoriasis and cardiovascular risk factors: A case-control study on inpatients comparing psoriasis to dermatitis	1079	1079	Case-control	Israel	6
Sundqvist et al. 2012	Epstein-barr virus and multiple sclerosis: Interaction with HLA.	678	1490	Case-control	Sweden	7
Wesley et al. 2013	Association Between Body Mass Index and Anti–Citrullinated Protein Antibody–Positive and Anti–Citrullinated Protein Antibody–Negative Rheumatoid Arthritis: Results From a Population-Based Case–Control Study	2748	3444	Case-control	Sweden	7
Willer et al. 2005	Timing of birth and risk of multiple sclerosis: population based study	42 045	General population	Case-control	Canada, Great Britain, Denmark and Sweden	5
Xu et al. 2012	Deletion of LCE3C and LCE3B genes is associated with psoriasis in a northern Chinese population	970	1064	Case-control	China	6
Xu et al. 2021	Association of Infectious Mononucleosis in Childhood and Adolescence With Risk for a Subsequent Multiple Sclerosis Diagnosis Among Siblings	Cohort: 2 492 980 Cases: 5867		Cohort	Sweden	8
Zaadstra et al. 2008	Selective association of multiple sclerosis with infectious mononucleosis	2877	2673	Case-control	Netherlands	8

Funnel plots

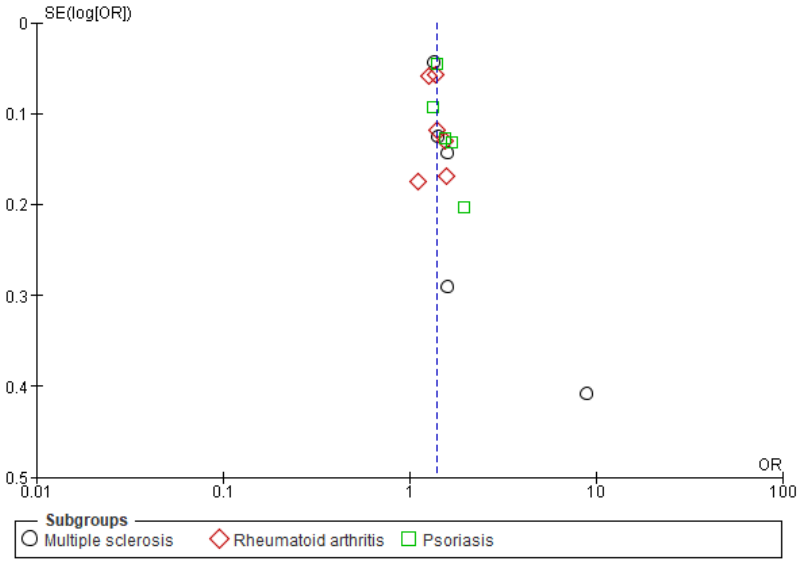
1) Ever smoking



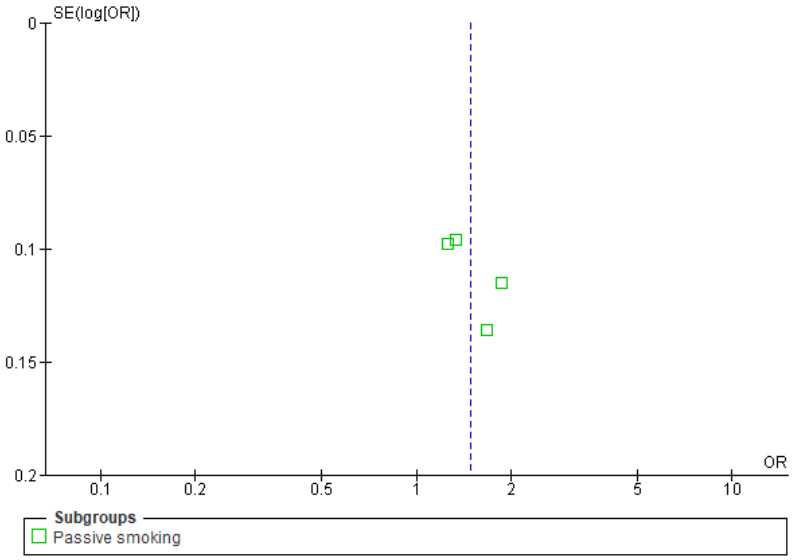
2) Current smoking



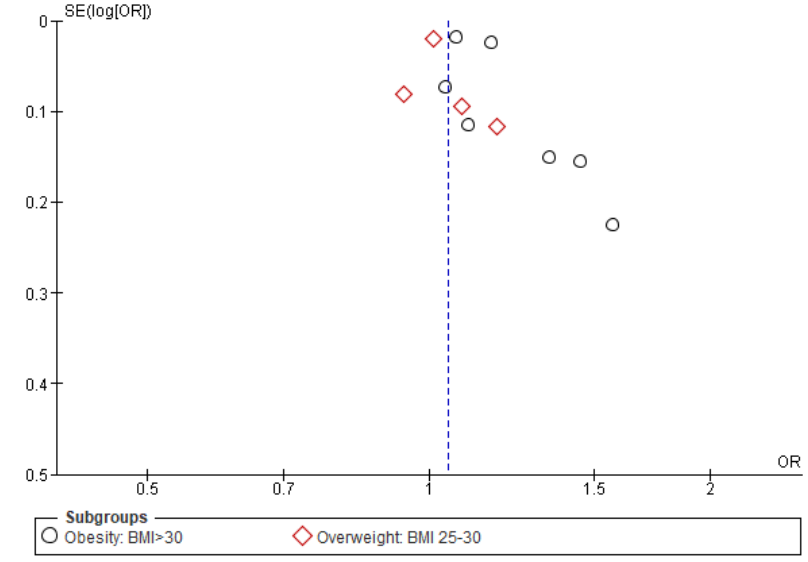
3) Former smoking



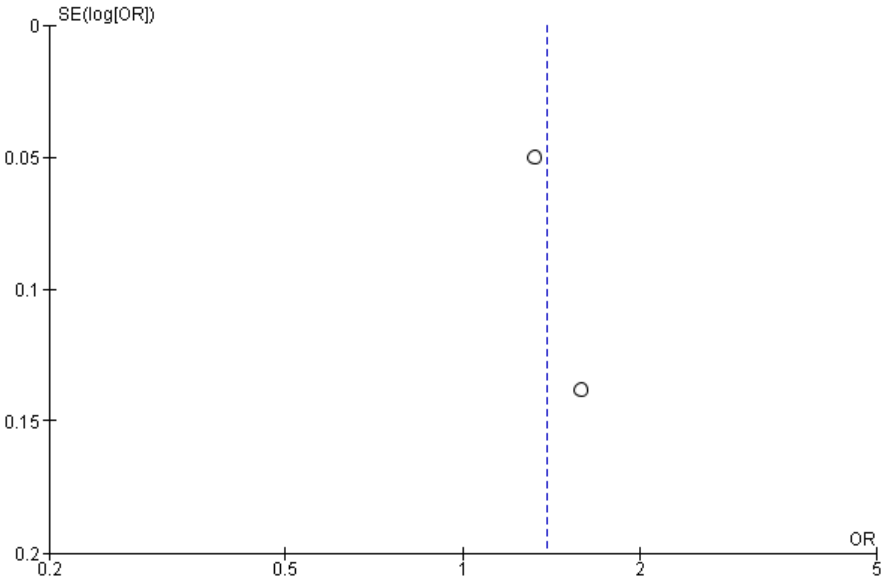
4) Passive smoking



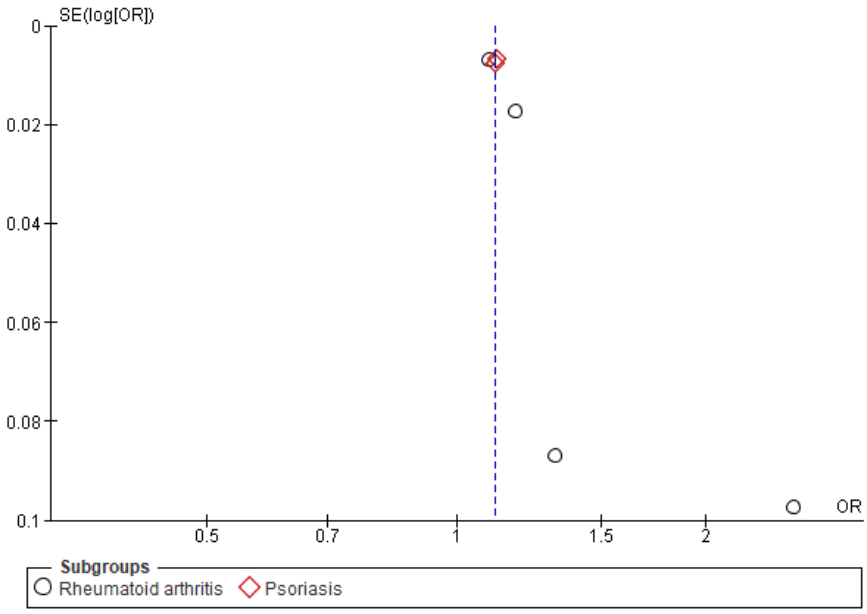
5) Obesity and overweight



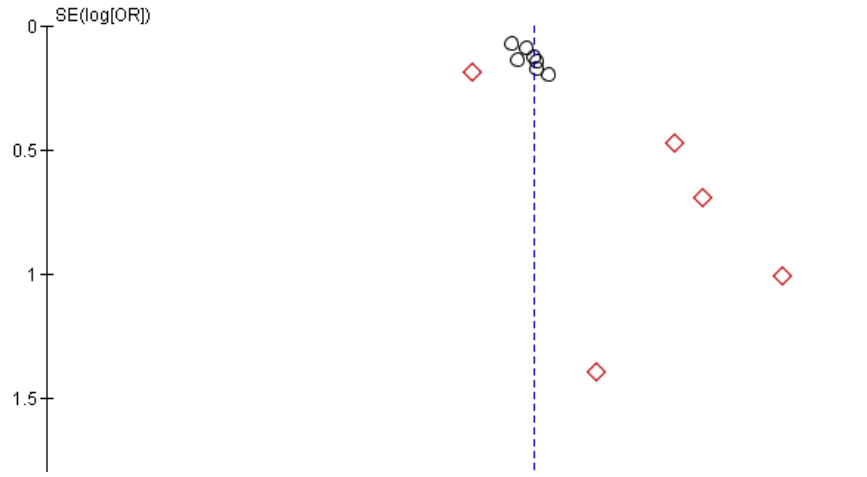
6) Depression



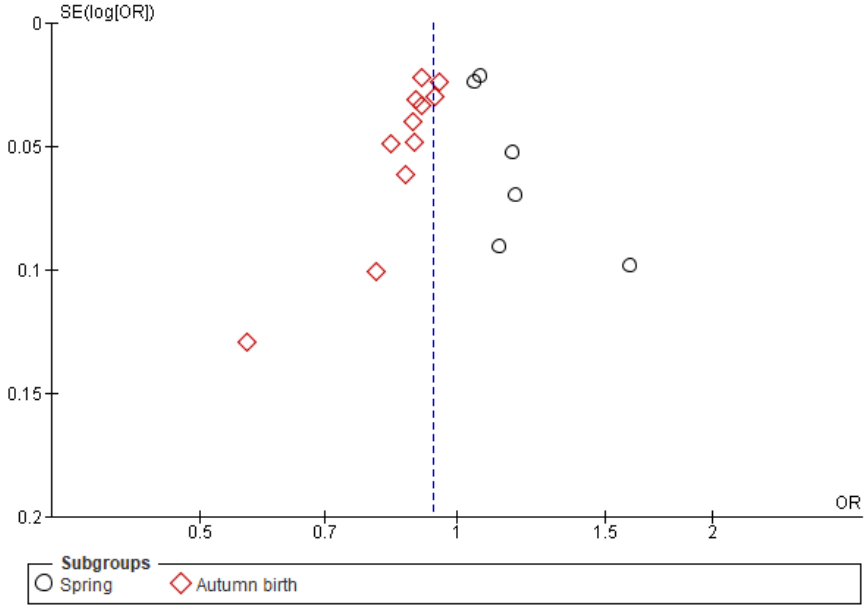
7) Periodontitis



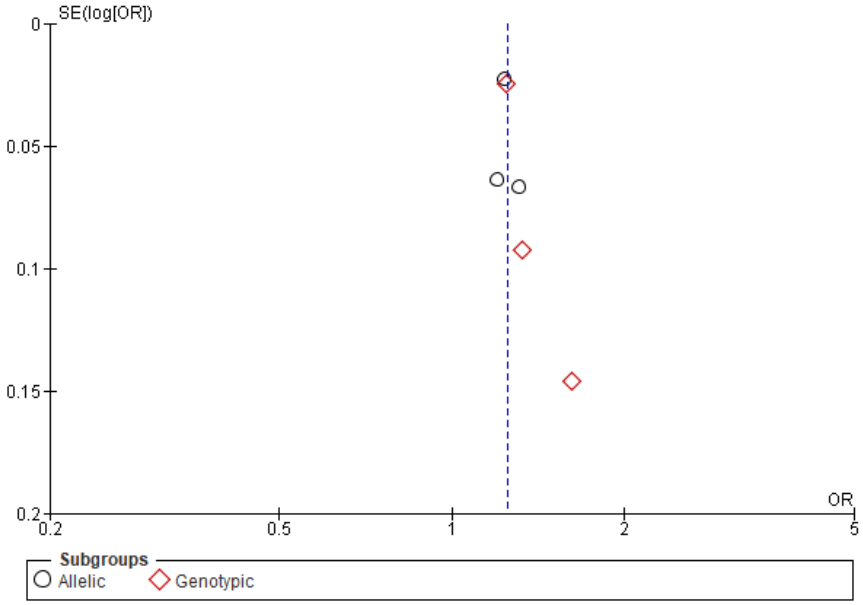
8) Mononucleosis



9) Time of birth



10) LCE3C-LCE3B deletion



Search strategies:

1) Embase:

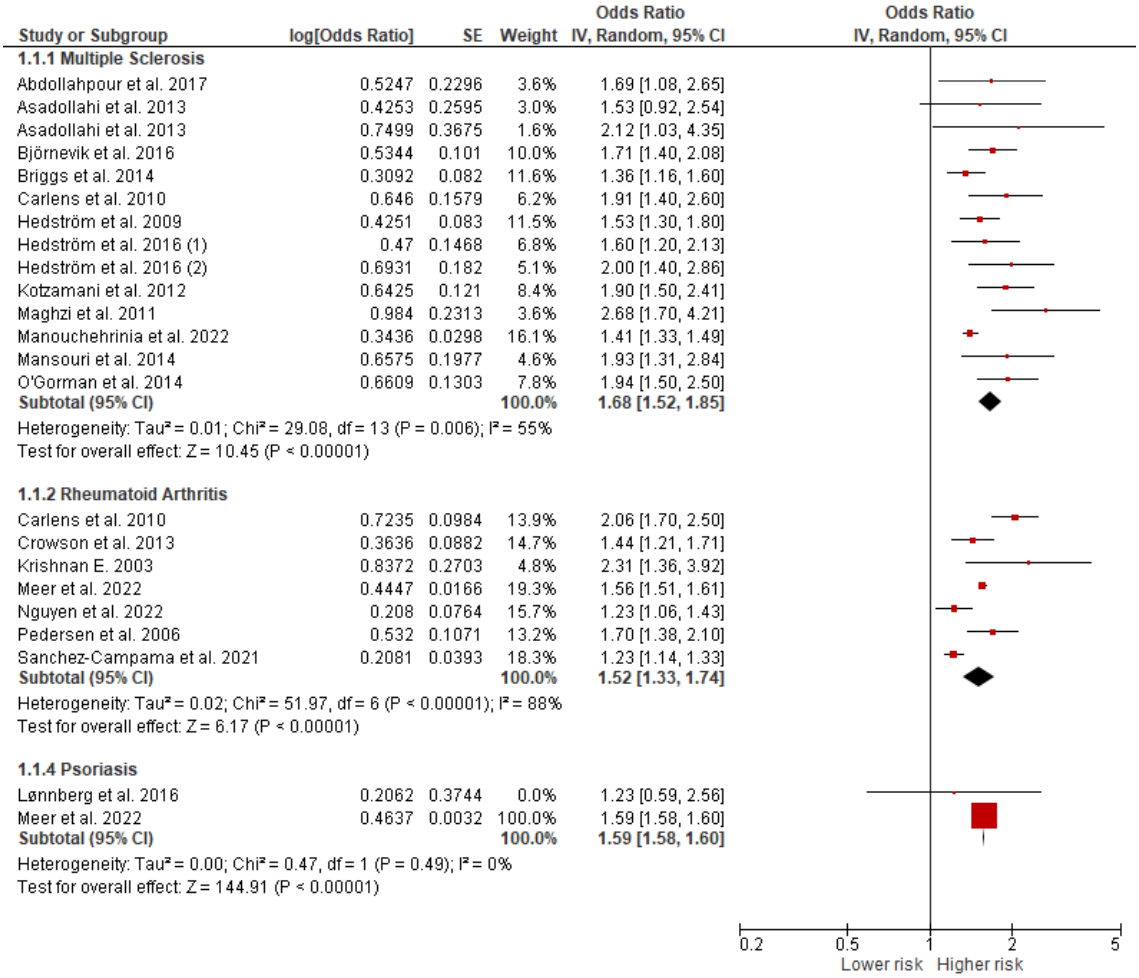
('psoriasis'/exp OR 'psoriasis':ti,ab OR 'psoria*':ti,ab OR 'psoriases':ti,ab OR 'pustulosis palmaris et plantaris':ti,ab OR 'palmoplantaris pustulosis':ti,ab OR 'arthritis, rheumatoid'/exp OR 'rheumatoid arthritis':ti,ab OR 'rheumatoid polyarthritis':ti,ab OR 'arthritis deformans':ti,ab OR 'arthrosis deformans':ti,ab OR 'chronic articular rheumatism':ti,ab OR 'chronic polyarthritis':ti,ab OR 'rheumarthritis':ti,ab OR 'rheumatic arthritis':ti,ab OR 'rheumatic polyarthritis':ti,ab OR 'juvenile idiopathic arthritis':ti,ab OR 'multiple sclerosis'/exp OR 'multiple scleros*':ti,ab OR 'insular sclerosis':ti,ab OR 'disseminated sclerosis':ti,ab OR 'sclerosis multiplex':ti,ab OR 'ms*':ti,ab OR 'lupus erythematosus, systemic'/exp OR 'lupus':ti,ab OR 'sle':ti,ab OR 'diabetes mellitus, type 1'/exp OR 'iddm':ti,ab OR 'dmi':ti,ab OR 'dm1':ti,ab OR 'diabetes type 1':ti,ab OR 'diabetes type i':ti,ab OR 'dm type 1':ti,ab OR 'dm type i':ti,ab OR 't1dm':ti,ab OR 'tidm':ti,ab OR 'autoimmune diabetes':ti,ab OR 'ketosis-prone diabetes mellitus':ti,ab OR (diabetes:ti,ab AND ('type 1':ti,ab OR 'insulin dependent':ti,ab OR 'insulin-dependent':ti,ab OR 'juvenile':ti,ab))) NOT ('cardiovascular':ti OR 'encephalopathy':ti OR 'atrial fibrillation':ti OR 'misdiagnosis':ti OR 'covid-19':ti OR 'cytokine':ti OR 'polymorphism*':ti OR 'fracture':ti OR 'differential diagnosis':ti OR 'retinopathy':ti OR 'nephropathy':ti OR 'neuropathy':ti OR 'bone mineral density':ti OR 'cancer':ti OR 'thromboembolism':ti OR 'quality of life':ti OR 'management':ti OR 'hypoglycaemia':ti OR 'rna':ti OR 'dna':ti) AND 'risk factor':ti,ab

2) Medline:

(("Psoriasis"[Mesh] OR "Psoriasis"[tiab] OR "Psoria*" [tiab] OR "Psoriases" [tiab] OR "Pustulosis Palmaris et Plantaris" [tiab] OR "Palmoplantaris Pustulosis" [tiab]) OR ("Arthritis, Rheumatoid"[Mesh:NoExp] OR "rheumatoid Arthritis"[tiab] OR "rheumatoid polyarthritis"[tiab] OR "arthritis deformans"[tiab] OR "arthrosis deformans"[tiab] OR "chronic articular rheumatism"[tiab] OR "chronic polyarthritis"[tiab] OR "rheumarthritis"[tiab] OR "rheumatic arthritis"[tiab] OR "rheumatic polyarthritis"[tiab] OR "rheumatic polyarthritis"[tiab] OR "juvenile idiopathic arthritis"[tiab]) OR ("Multiple Sclerosis"[Mesh] OR "Multiple Scleros*"[tiab] OR "insular sclerosis"[tiab] OR "Disseminated Sclerosis"[tiab] OR "Sclerosis Multiplex"[tiab] OR "MS*"[tiab]) OR ("Lupus Erythematosus, Systemic"[Mesh] OR "Lupus"[tiab] OR "SLE"[tiab]) OR ("Diabetes Mellitus, Type 1"[Mesh] OR "IDDM"[tiab] OR "DM1"[tiab] OR "DMI"[tiab] OR "DM1"[tiab] OR "Diabetes type 1"[tiab] OR "Diabetes type I"[tiab] OR "DM type 1"[tiab] OR "DM type I"[tiab] OR "T1DM"[tiab] OR "TIDM"[tiab] OR "autoimmune diabetes"[tiab] OR "Ketosis-Prone Diabetes Mellitus"[tiab]) OR (diabetes[tiab] AND ("type 1"[tiab] OR "insulin dependent"[tiab] OR "insulin-dependent"[tiab] OR "juvenile"[tiab])) NOT ("cardiovascular"[ti] OR "encephalopathy"[ti] OR "atrial fibrillation"[ti] OR "misdiagnosis"[ti] OR "COVID-19"[ti] OR "cytokine"[ti] OR "polymorphism*"[ti] OR "fracture"[ti] OR "cancer"[ti] OR "differential diagnosis"[ti] OR "retinopathy"[ti] OR "nephropathy"[ti] OR "neuropathy"[ti] OR "bone mineral density"[ti] OR "cancer"[ti] OR "thromboembolism"[ti] OR "quality of life"[ti] OR "hypoglycaemia"[ti] OR "management"[ti] OR "hypoglycaemia"[ti] OR "RNA"[ti] OR "DNA"[ti]) AND (("Risk factor"[Mesh] OR "risk factor"[tiab])

Forest Plots

1) Ever smoking

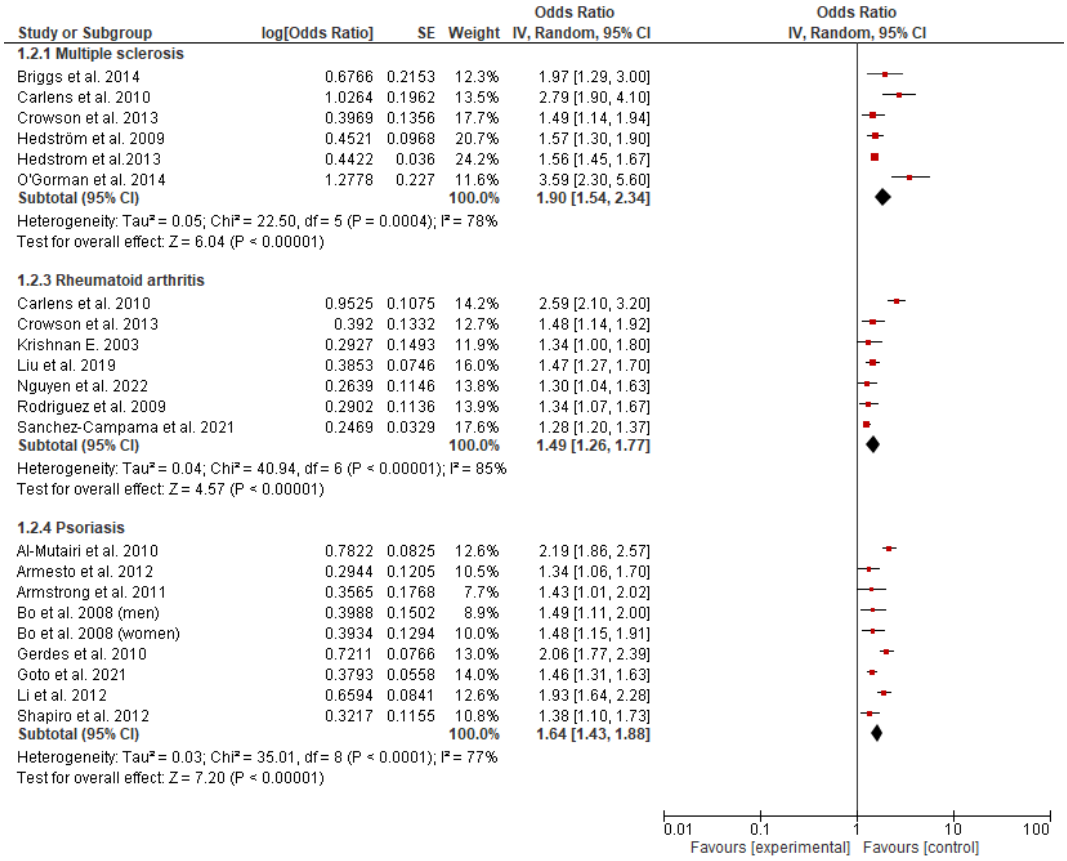


Footnotes

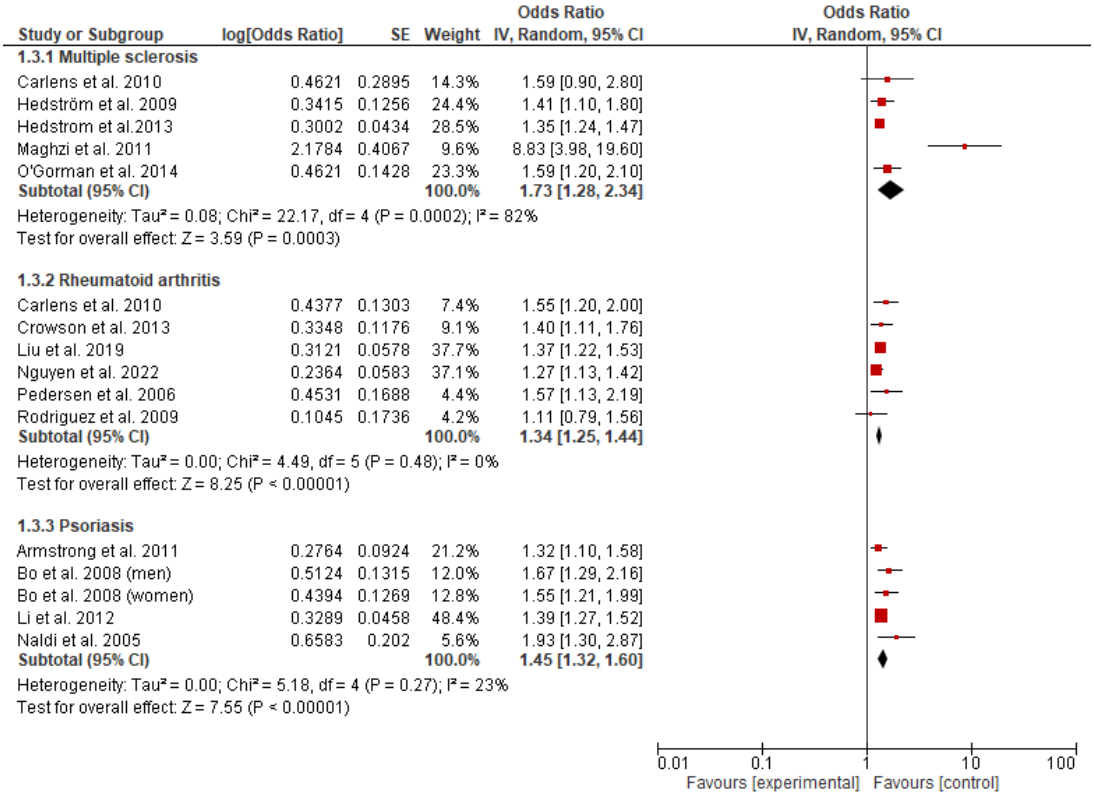
(1) Odds ratio for smoking less than 10 cigarettes a day

(2) Odds ratio for smoking more then 10 cigarettes a day

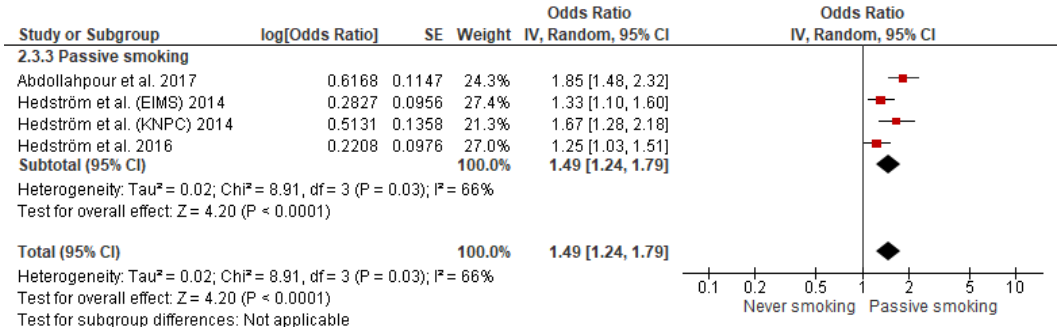
2) Current smoking



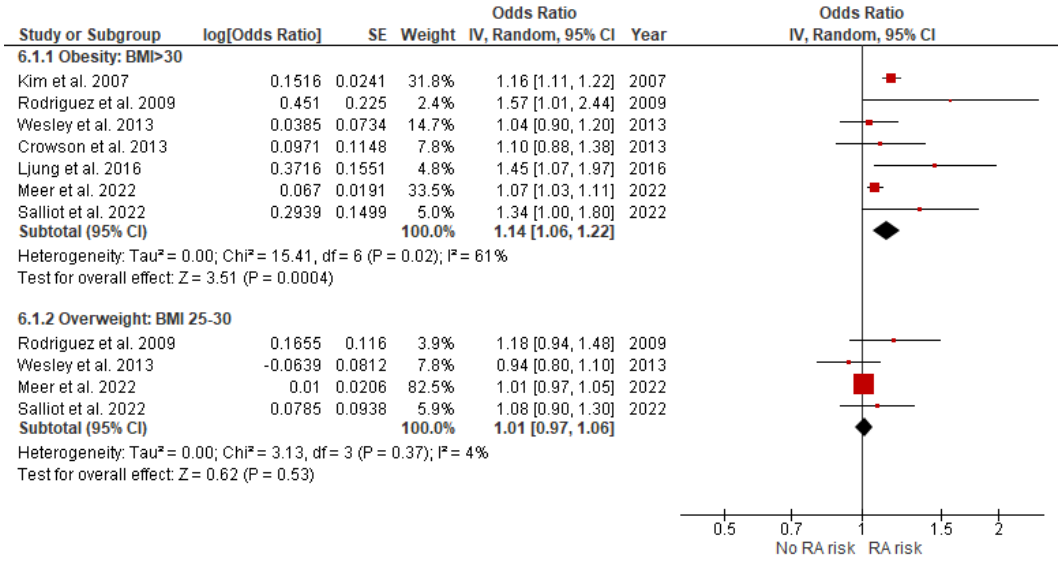
3) Former smoking



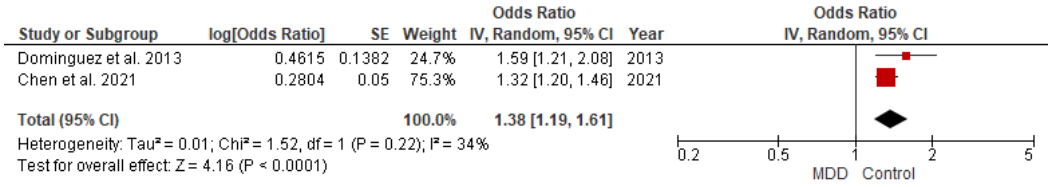
4) Passive smoking and multiple sclerosis risk



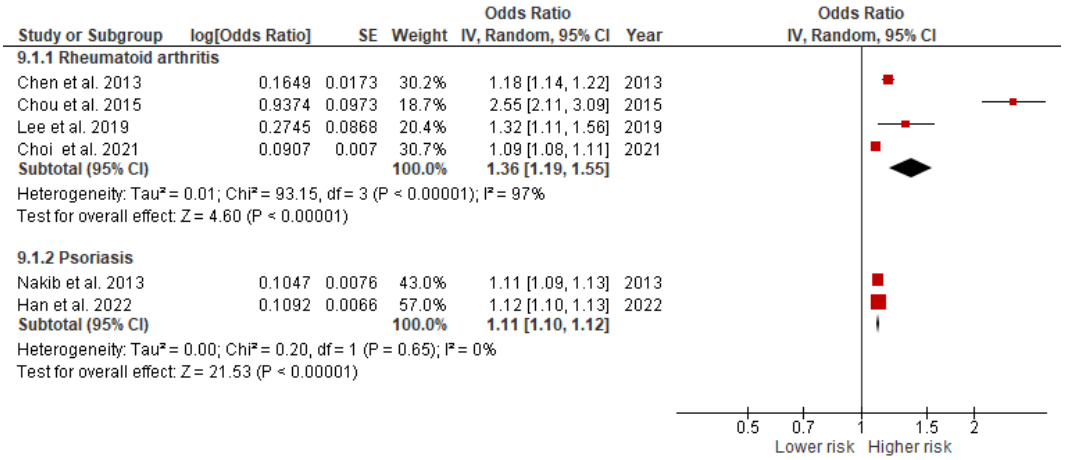
5) Overweight and obesity and rheumatoid arthritis



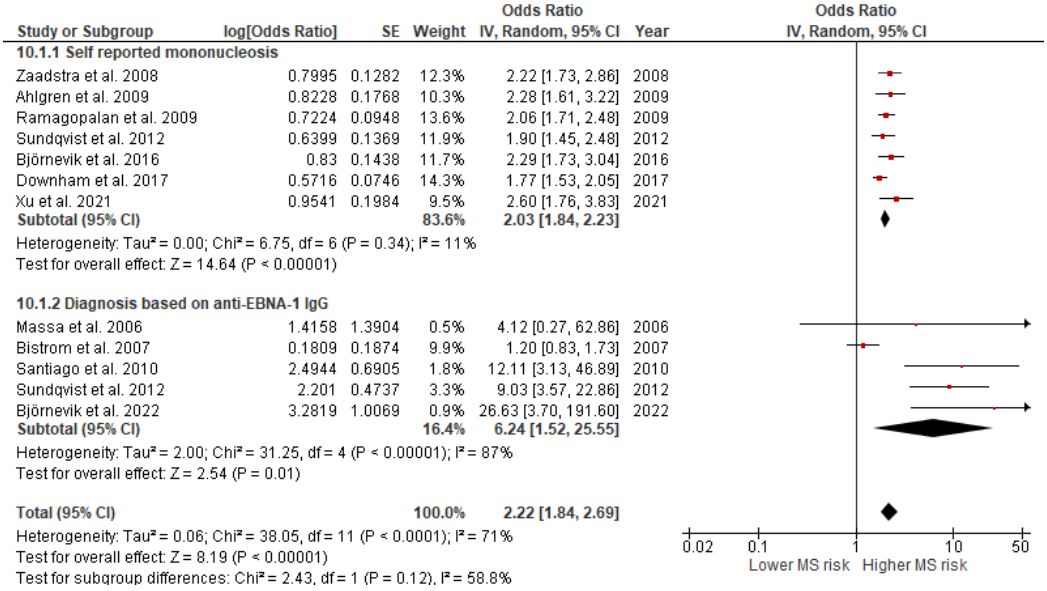
6) Depression and psoriasis



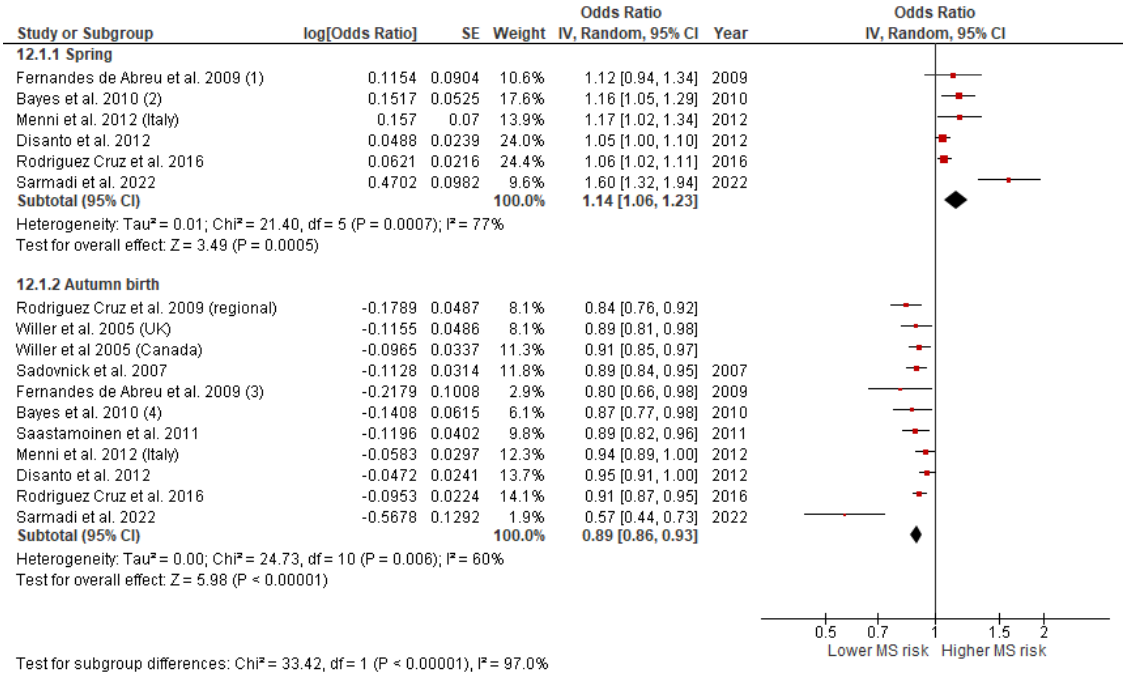
7) Periodontitis



8) Mononucleosis and multiple sclerosis risk



9) Time of birth



Test for subgroup differences: Chi² = 33.42, df = 1 (P < 0.00001), I² = 97.0%

Footnotes

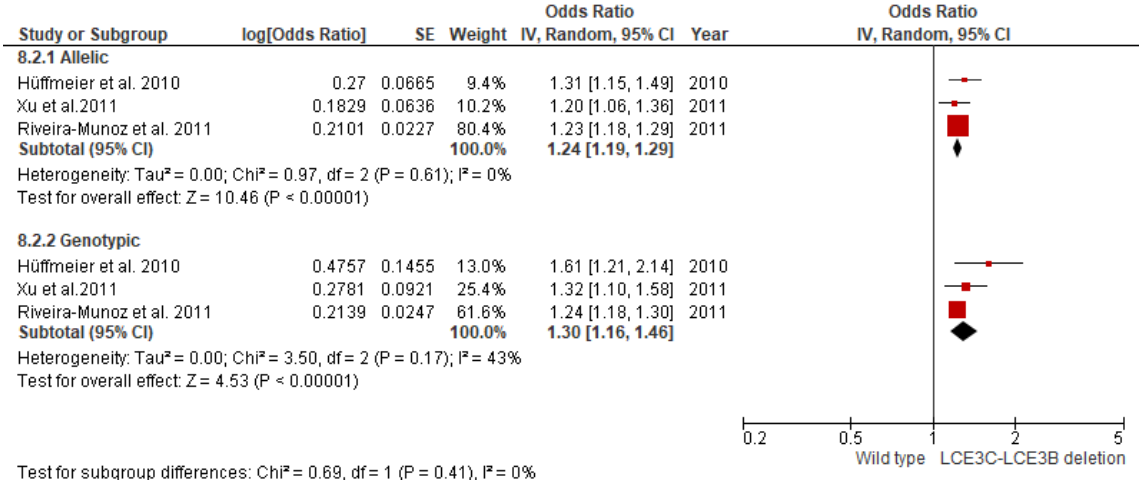
(1) OR for whole spring period

(2) OR for whole spring period

(3) OR for whole autumn period

(4) OR for whole autumn period

10) LCE3C and LCE3B deletion and psoriasis risk



Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%