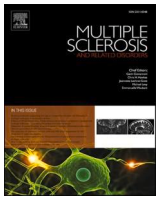
Multiple Sclerosis and Related Disorders 102 (2025) 106634

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

A systematic review and meta-analysis on gene-environment interaction effects on the associations of vitamin D and sun exposure with multiple sclerosis risk

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ARTICLE INFO

Keywords:
Gene-environment interaction
Vitamin D
Sun exposure
Multiple sclerosis

ABSTRACT

Background: Multiple sclerosis (MS) is a complex neurological disease influenced by genetic and environmental factors, including low vitamin D and sun exposure. However, whether these interact with genetic loci is unclear. This systematic review and meta-analysis evaluated gene-environment interaction (GxE) studies on vitamin D and sun exposure in MS risk.

Methods: We searched relevant databases including Medline, Embase, CINAHL, and Web of Science from conception until 8 June 2024. We included observational studies assessing GxE related to vitamin D and/or sun exposure with MS risk. Environmental and genetic exposure and other relevant data were extracted and additive interaction statistics including four-level interactions, synergy index (SI), relative excess risk due to interaction (RERI), and attributable proportion due to interaction (AP) were meta-analysed for comparable studies. All included studies were assessed for quality and risk of bias using recommended checklists.

Results: We included 11 studies (10,857 cases;11,842 controls), of which three examined gene-vitamin D, four gene-sun, and four both gene-vitamin D and gene-sun interactions. Studies used varied measures to assess vitamin D status, most commonly serum 25(OH)D levels, while sun exposure was primarily based on self-reported data. *HLA-DRB1×15:01* variant was the most common genotype evaluated. Consistently, the joint effects of either low vitamin D or low sun exposure with the *HLA-DRB1×15:01* risk variant were stronger than any individual factor.

Under stringent inclusion criteria, our meta-analysis focused on assessing additive interactions between low sun exposure and *HLA-DRB1×15:01* with MS risk. We observed that carriers of both risk factors had a five-fold higher MS risk than those exhibiting neither factor (aOR=5.17;(95 %CI=4.39–6.17), SI=1.49, RERI=1.42, AP=0.28). No publication bias: heterogeneity was moderate.

Conclusions: Nearly half of MS risk was super-additive for low sun and *HLA-DRB1×15:01* interactions and GxE was also evident for low vitamin D and MS risk genes, underscoring the importance of gene-environment interplay in MS risk prediction.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AP, Attributable Proportion (due to interaction); EIMS, Epidemiological Investigation of Multiple Sclerosis; GC, Group-specific Component; GEMS, Genes and Environment in Multiple Sclerosis; GxE, gene-environment interaction; HLA, Human Leukocyte Antigen; LBS, Light brown skin; MS, multiple sclerosis; RERI, Relative Excess Risk due to Interaction; SI, Synergy index; SNPs, single-nucleotide polymorphisms; UVR, ultraviolet radiation; VDR, Vitamin D Receptor; VDRE, vitamin D response element.

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https://doi.org/10.1016/j.msard.2025.106634
Received 29 May 2025; Received in revised form 13 July 2025; Accepted 21 July 2025
Available online 21 July 2025

1. Introduction

Multiple sclerosis (MS) is a complex immune system-associated neurodegenerative disorder of the central nervous system, the aetiology of which comprises a mixture of environmental, lifestyle, and genetic elements (HL et al., 2005). Of the environmental factors, low vitamin D levels and low sun exposure status are well-established risk factors for MS onset (Balasooriya et al., 2024); (McKay et al., 2017). In addition, the International MS Genetic Consortium (IMSGC) studies identified approximately 200 genetic variants (single-nucleotide polymorphisms (SNPs)) associated with MS risk (De Jager et al., 2019). Of these, the *HLA-DRB1×15:01* risk variant, located in the human leukocyte antigen (HLA) locus, has been identified as the most consistent genetic risk factor for MS: Recent meta-analysis showed that carriers of *HLA-DRB1×15:01* have up to three-fold increased risk of MS compared to non-carriers (Xiao et al., 2015). In addition, other genetic risk variants have been implicated in MS, including a number of genes relevant to vitamin D metabolism, synthesis, transport, and signalling (Gauzzi, 2018).

These factors do not act on MS independently (Hunter, 2005), however. Emerging evidence suggests a dynamic interaction between genetic and environmental (GxE) factors in MS risk (Shraim et al., 2022). Interaction refers to the situation where the effect of one exposure on a certain outcome is different across strata of another exposure, the presence and direction can be defined on additive or multiplicative scale (VanderWeele and Knol, 2014). Interaction on an additive scale means that the combined effect of two exposures is greater than the sum of the individual effects of the two exposures, whereas in multiplicative interaction, the combined effects is greater than the product of their individual effects (VanderWeele and Knol, 2014). Assuming a functional interaction, whereby aetiological risk factors have a synergy of effects on health outcomes, additive interactions are more plausible (Knol et al., 2011).

In the context here, however, of GxE, the aetiological interpretation and thus the additive scale is more appropriate and will be the focus of the meta-analysis elements of this work. The most commonly utilised additive interaction statistics includes the synergy index (SI), relative excess risk due to interaction (RERI), and attributable proportion (AP) due to interaction (Vander et al., 2014). Of these, the SI has been described as a preferable method since, unlike the other statistics, its values do not vary across strata of model covariates (Skrondal, 2003).

In their study, van der Mei and colleagues (van der Mei et al., 2014) described the rationale for assessing GxE in neuroepidemiology studies, and the considerations for articles thereof. Estimating only the individual contributions of environmental or genetic factors without considering potential interaction between them will incorrectly estimate the total associations with outcomes, as well as the proportions of disease risk such as the population-attributable risk (Hunter, 2005).

By providing aggregated statistics of the joint effects of each of the environmental and genetic MS risk factors assessed in our review, the findings may provide mechanistic insights on the GxE dynamics in MS and may inform potential public health translation, particularly for risk stratification and prevention strategies.

Systematic review and meta-analysis of GxE dynamics in MS focusing on other MS risk factors such as Epstein-Barr virus (EBV) infection has been conducted previously (Xiao et al., 2015). However, the interaction between MS-associated genetic risk variants and low vitamin D and/or sun exposure as a predictor of MS risk has not been systematically reviewed before.

We hypothesised that individuals carrying MS risk genotypes such as *HLA-DRB1×15:01* positive and/or and risk variant/allele would experience a disproportionately increased risk of MS in the presence of low vitamin D status and/or sun exposure, consistent with additive or multiplicative interaction models.

Therefore, this review systematically evaluated relevant literature of observational studies of GxE of vitamin D and/or sun exposure vs MS risk and applied meta-analysis to comparable studies to estimate pooled statistics of their additive interaction effects.

2. Methods

2.1. Search strategy

We searched Medline (Ovid), Embase, CINAHL (complete), and Web of Science (Core Collection) from conception until 8 June 2024. Search terms included the exposures of interest (sun exposure, vitamin D), the outcome (MS risk), relevant genetic cofactors (MS risk variants as identified by IMSGC, particularly in the *HLA* loci, and genetic factors relevant to vitamin D/sun (e.g., *VDR, GC, CYP24A1, CYP27B1, DHCR7, MC1R*). Definitions of alternative genetic-related terminologies are provided in **Supplementary Table 1a**. To be included, studies must have assessed statistical interaction, either additive or multiplicative, between vitamin D and/or sun and genetic risk variants. The full search strategy used for each database is presented in the **Supplementary Table 1b**

This systematic review was conducted according to the PRISMA statement (**Supplementary Table 2**), and the protocol was registered in PROSPERO (CRD42024559544).

2.2. Inclusion and exclusion criteria

We included all observational studies that reported GxE analyses where vitamin D and/or sun were the primary exposures evaluated against MS risk and/or MS case status, regardless of the significance level of the interaction metrics. Articles were limited to English-language studies conducted in humans and published in peer-reviewed journals. There were no limitations as to publication date or to the age of study participants. Letters, case reports, reviews, comments, book chapters, and conference abstracts were excluded.

2.3. Study selection

The Covidence systematic review management tool was used to facilitate screening the search results and for the study selection. After the removal of duplicates, titles and abstracts were screened by two independent researchers (MWM and LXU) and disagreements were resolved by a third researcher (SSY), as necessary. Full texts of each article were then reviewed and assessed for final inclusion in the study. Thereupon, data extraction and quality assessment were conducted by MWM. The reference lists and citations of included studies were also screened for potential inclusion in the systematic review (Fig. 1).

2.4. Data extraction

Data extraction format was adopted from Johanna Briggs Institute (JBI) and implemented using Covidence. Data were extracted from relevant articles into spreadsheets separately for gene-vitamin D and gene-sun exposure interactions (**Supplementary Spreadsheet File 1**). Extracted data included relevant study characteristics such as author(s), country, study year, study design, sample size (cases/controls), vitamin D measure used, sun exposure measure(s) used, genotype(s), and allele assessed in GxE (**Supplementary Tables 3 and 4**). Other parameters extracted included SNP allelic variants, the mode of genotype measurement, method(s) of vitamin D and/or sun measurement, the genotype-outcome measures of association, primary exposure-outcome associations, GxE findings, and GxE statistics (as reported or calculated from available data; Tables 1 **and** 2). Where available, we extracted data on genotype distributions and classified them as homozygous risk, heterozygous, or homozygous non-risk. Where reported in the primary studies included in our review, we prioritised dominant models (risk allele carriers vs non-carriers: for example, *HLA-DRB1×15:01* positive vs. *HLA-DRB1×15:01* negative, CC/AC compared

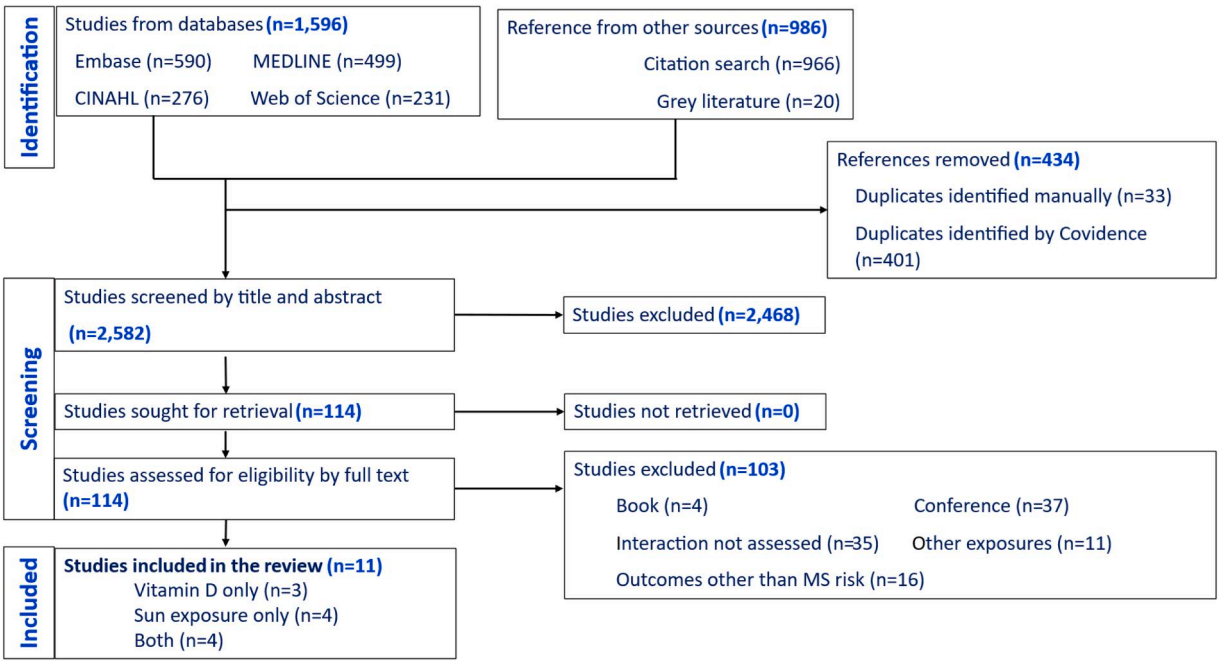

Fig. 1. PRISMA flowchart showing the searched documents screening and inclusion procedure. A. Sun exposure and *HlA-DRB1×15* interaction based on common (fixed) effects model. B. Sun exposure and *HlA-DRB1×15* interaction based on random effect model.

to AA, GG compared to AA), given their common use in GxE literature.

All exposure-outcome associations were reported as OR with 95 %CI and p-values.

2.5. Study quality and risk of bias assessments

We used the STREGA (Strengthening the Reporting of Genetic Association Studies) checklist (Little et al., 2009) to assess studies' quality.

The studies were assessed for risk of bias using the JBI critical appraisal checklist for case-control studies (Institute. JB, 2020) which consists of 10 items, each scored as **1** "**yes**" if the study fulfilled the criterion and **0** "**no**" if it did not. The total score was then converted into a percentage to provide a summary rating of risk of bias for each study: >80 % positive responses indicate low risk of bias, 60–80 % indicate moderate risk, and <60 % indicate high risk.

2.6. Statistical analyses

Data from the included studies were grouped by primary exposure (vitamin D and sun) and then by genes (type and/or genotype). In the studies included here, both multiplicative and additive interactions were extracted, as reported. However, from the data provided, additive interaction statistics were estimated.

For each GxE combination, four-level additive interaction measures of association (environmental$^-$/genetic$^-$, environmental$^-$/genetic$^+$, environmental$^+$/genetic$^-$, environmental$^{+/}$genetic$^+$) were either extracted from the article or estimated from the available data. From these, additive interaction statistics were then estimated:

(1) SI: the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without interaction. Mathematically, $SI = \frac{OR_{G+E+}-1}{(OR_{G+E-}-1)+(OR_{G-E+}-1)}$ where, SI=1 denotes no interaction or exactly additivity; SI>1 means positive interaction or more than additivity; SI<1 means negative interaction or less than additivity.

(2) RERI: the excess risk due to interaction relative to the risk without exposure, and calculated as: $RERI = OR_{G+E+} - OR_{G+E-} - OR_{G-E+} + 1$ where, $G+$ represents presence of genetic factor, G- is absence of genetic factor, $E+$ is presence of environmental factor, and E- refers to absence of environmental factor. OR=odds ratio. RERI=0 means no interaction or exactly additivity; >0 positive interaction or more than additivity; <0 negative interaction or less than additivity.

(3) AP: refers to the attributable proportion of disease that is due to interaction among individuals with both genetic and environmental exposures. It is calculated as $AP = \frac{RERI}{OR_{G+E+}}$ where, AP=0 means no interaction or exactly additivity; >0 positive interaction or more than additivity; <0 negative interaction or less than additivity.

These additive interaction measures along with confidence intervals and p-values were estimated based on the delta method using the multistate models R package considering the covariance independent assumption (Mathur and VanderWeele, 2018). Unlike conventional meta-analytic approaches, the delta method allows estimating the confidence intervals for interaction effects by calculating standard errors while accounting for the influence of covariates.

A meta-analysis was done for two or more studies of comparable study design employing similar exposure, outcome, and genotype assessment methods (Tables 3 &4). If two or more studies had sample overlaps, only one, prioritised based on data completeness and recency of the study was included in the meta-analysis. Due to the small number of studies included and similar study design applied in these studies, fixed-effect models were employed to estimate pooled GxE statistics, and Forest plots were used to graphically depict study statistics and pooled effects. Additionally, to account for the heterogeneity related to population and measurement differences, we applied random-effects models.

The level of heterogeneity between the studies was assessed using the I^2 statistic, with values of 25 %, 50 %, and 75 % indicating low, moderate, and high heterogeneity, respectively. Publication bias was visually assessed using Funnel plot and quantitatively tested by Egger's regression test.

R (version 4.4.1) was used for all analyses.

Table 1
Summary of the measurement methods of the vitamin D status and genetic risk factors and their GxE findings of the included studies.

Study	Study Year	Genotype used for GxE	Genotype variant/ allele	SNP numbers for genotype	Genotyping method used	Vitamin D measurement/proxy used	Vitamin D GxE findings as reported in each article
Vitamin D measured via serum 25(OH)D							
Hedström (EIMS) (Hedström et al., 2020)	2009–2011	*HLA-DRB1×15:01*	HLA*IMP:02	rs3135388	Illumina exome chip, with extra high-density markers in the HLA region	25(OH)D measured using chemiluminescent immunoassay, 25(OH)*D* < 50nmol/L indicate low vitamin D levels.	Significant positive interaction observed between low 25(OH)D levels and *HLA-DRB1×15:01* risk genotype (AP=0.2, 95 % CI=0.01–0.4).
Bäärnhielm (Bäärnhielm et al., 2012)	2005–2015	*HLA-DRB1×15*	Not reported	Not reported	Sequence-specific primers and OLERUP SSP™ HLA kits	25(OH)D measured using chemiluminescent immunoassay, 25(OH)*D* < 50nmol/L indicate low vitamin D levels.	No additive interaction was observed between low 25(OH)D levels and *HLA-DRB1×15:01* risk genotype (AP=−0.1 (−0.1–0.4)).
Orton (Orton et al., 2008)	2005	*HLA-DRB1×15:01*	Not reported	Not reported	*HLA-DRB1×15:01* genotyped by using a low-resolution panel of allele-specific PCR primers	Mean 25(OH)D levels measured by radioimmunoassay	Although not significant, *HLA-DRB1×15:01* and lower 25(OH)D concentration was associated with increased risk of MS (no interaction statistics reported).
van der Mei (van der Mei et al., 2016)	2003–2006	*HLA-DRB1×15:01*	GG compared to AA	rs9271366	SNPline method (Biosciences, Hoddesdon Herts, UK)	Liquid chromatography-tandem mass spectrometry was used to measure 25(OH)D 25(OH)*D* < 50nmol/L indicate low vitamin D levels.	Some evidence of an additive interaction between *HLA-DRB1×15:01* and low 25(OH)D levels: (OR=7.71, 95 %CI= 2.59–22.94) and synergy index 2.74 but these were not significant ($p = 0.14$).
Langer-Gould (Langer-Gould et al., 2018)	2011–2014	*GC*	A-allele rs7041 and T allele for rs4588	rs7041 and rs4588	Illumina's Human Omni Express Exome	Liquid chromatography, tandem mass spectrometry measured 25(OH)D 25(OH)*D* < 50nmol/L indicate low vitamin D levels.	A multiplicative interaction, between higher 25(OH)D levels and carrying at least one copy of the C allele at rs7041 (aOR=0.41,95 % CI=0.23–0.76; $p = 0.016$) among whites was observed but not in rs4588 genotype.
Other measures							
Simon (Simon et al., 2010)	1996–1999	*VDR*	FokI ff (TT) compared to FF(CC)	rs10735810	Using the TaqMan assay on the ABI PRISM 7900HT Sequence Detection System	Intake of 400 IU/day of vitamin D prior to date of onset symptom of MS	A significant additive interaction between vitamin D intake and the *VDR* FokI polymorphism ($p_{interaction}$=0.04).
Urbaneja (Urbaneja et al., 2020)	2019	*HLA-DRB1×15:01*	Not specified	Not reported	Using a low- and high-resolution allele-specific PCR amplification method	Pale: (white skin, always burns, tans sometimes/never) and light brown skin (LBS): sometimes/rarely burns and always tans based on the Fitzpatrick skin type classification (skin tone interpreted as a stable proxy of vitamin D)	Those people with LBS plus presence of *HLA-DRB1×15:01* had 2.5-fold more risk than people with LBS alone. The percentage of MS patients among individuals who had LBS as the only risk factor was 33 % but when LBS plus the presence of *HLA-DRB1×15:01*, it was 56.0 %. MS risk was significantly increased when LBS, smoker and presence of *HLA-DRB1×15:01* combined (83.3 %) ($p < 0.001$).

Abbreviations: EIMS=Epidemiological Investigation of Multiple Sclerosis; GC=group specific component; GxE=gene-environment interaction; HLA= human leukocyte antigen; HLA*IMP:02=Multi-Population Classical HLA Type Imputation; LBS=light brown skin; VDR=vitamin D receptor; 25(OH)*D* = 5-hydroxy vitamin D.

3. Results

3.1. Study characteristics and data harmonisation

In this review, we included a total of 11 eligible studies, of which three (Urbaneja et al., 2020; Simon et al., 2010; Orton et al., 2008) examined gene-vitamin D, four (Dickinson et al., 2009; Dwyer et al., 2008; Nasr et al., 2024; Hedström et al., 2021) gene-sun, and four (Bäärnhielm et al., 2012; Hedström et al., 2020; Langer-Gould et al., 2018; van der Mei et al., 2016) both gene-vitamin D and gene-sun interactions. The included studies differed in their modelling approaches: however, where feasible, we adopted the genetic model reported by the primary study. When models were specified, we prioritised the dominant models risk allele carriers vs non-carriers: for example, *HLA-DRB1×15:01* positive vs. *HLA-DRB1×15:01* negative (as presented in most of the included studies), CC/AC compared to AA, GG compared to AA), given their common use in GxE literature (**Supplementary Tables 3 and 4).** For interaction analyses we prioritised the additive ((SI, RERI, AP) model for its relevance to public health interpretation but also assessed consistency of interaction effects under dominant and recessive codings where applicable.

Most vitamin D studies assessed serum 25(OH)D levels, a majority (5/7) of these assessing dichotomous serum 25(OH)D (<50 vs ≥50nmol/L). Of the vitamin D studies, most were of general population participants case-control studies, while the study by Orton and colleagues compared monozygotic and dizygotic twin pairs discordant for MS (Orton et al., 2008).

For sun exposure ($n = 8$), the measures used were more varied; only

Table 2
Summary of the measurement methods of the sun exposure and genetic risk factors and their GxE findings of the included studies.

Study	Study Year	Genotype used for GxE	Genotype variant/allele	SNP numbers for the genotype	Sun exposure measurement used (mostly self-reported unless otherwise specified)	Sun exposure GxE findings as reported in each study
Hedström (GEMS) (Hedström et al., 2020)	2009–2011	*HLA-DRB1×15:01*	HLA*IMP:02	rs3135388	Low winter sun exposure dichotomised into high (a couple of hours per week or a couple of hours per day) or low (less frequent sun exposure)	*HLA-DRB1×15:01* interacted with low winter sun exposure (Ap=0.30; 95 %CI=0.03, 0.50).
		HLA-DRB1×15:01	HLA*IMP:02	rs3135388	Low summer sun exposure dichotomised into high (a couple of hours per week or a couple of hours per day) or low (less frequent sun exposure)	*HLA-DRB1×15:01* interacted with low summer sun exposure (AP=0.3; 95 %CI=0.01, 0.70).
		HLA-DRB1×15:01	HLA*IMP:02	rs3135388	Low overall sun exposure dichotomised into high (a couple of hours per week or a couple of hours per day) or low (less frequent sun exposure)	Generally, low sun exposure was synergistically correlated with *HLA-DRB1×15:01* genotype to increase MS risk (AP=0.3;95 % CI=0.14, 0.60)
Hedström (EIMS) (Hedström et al., 2020)	2005–2015	*HLA-DRB1×15:01*	HLA*IMP:02	rs3135388	UVR exposure based on three questions regarding sun exposure (frequency of sunbathing, travelling to a sunnier country and frequency of use of sunbeds) where a sun exposure index created, acquiring a value between 3 (the lowest exposure) and 12 (the highest exposure)	*HLA-DRB1×15:01* interacted with low UVR exposure regarding MS risk (AP=0.20, 95 %CI=0.10, 0.40)[a].
Bäärnhielm (Bäärnhielm et al., 2012)	2005–2010	*HLA-DRB1×15*	Not reported	Not reported	Low (UVR index≤6) UVR exposure based on frequency of exposure to sunny weather, visits to sunny countries, and use of sunbed on a four-point scale where 3-the lowest exposure and 12-the highest exposure	There was no significant interaction between *HLA-DRB1×15:01* and low UVR exposure (AP=0.01;95 % CI=0.30, 0.30).
Dickinson et.al (Dickinson et al., 2009)	2003–2006	*VDR*	Cdx-2 (GG)	rs11574010	Low (≤2hr/day) winter sun exposure based on time spent in sun during weekends and holidays	There was significant interaction between *VDR* Cdx-2 genotype of GG homozygotes (compared to AA) and low winter sun exposure for those cases reporting low winter sun exposure (≤2 h) in winter during childhood (OR=2.88;95 %CI=1.06–7.82; $p = 0.04$).
		VDR	Fok1	rs10735810	Low (≤2hr/day) winter sun exposure based on time spent in sun during weekends and holidays	The authors reported that *VDR* Fok1 polymorphisms were not associated with MS risk after stratification by any of the sun exposure measures (data not shown).
		VDR	Taq1	rs731236	Low (≤2hr/day) winter sun exposure based on time spent in sun during weekends and holidays	*VDR* Taq1 polymorphisms were not associated with MS risk after stratification by any of the sun exposure measures.
Dwyer (Dwyer et al., 2008)	2003–2006	*MC1R* (One of the RHC variants)	Asp294HisArg151CysArg160Trp	rs3135005	Lower summer sun exposure <2 hrs a day (self-reported)	There was significant interaction b/n lower summer sun exposure and presence of *MC1R* variant to reduce MS risk (OR=5.88; 95 % CI=1.06–33.33; $p = 0.02$).
Nasr (Nasr et al., 2024)	2011–2017	*HLA-DRB1×15, HLA-A*02, CD28, CD86, NFkB1*	Not reported	rs6435203: *CD28,* rs9282641: *CD86,* rs9282641: *NFkB1.* Not reported for others.	Low (<30 min) time spent outdoors in summer as per parent/guardian report	There were not any additive/ multiplicative significant interactions between time spent outdoors and the genetic risk variants.
van der Mei (van der Mei et al., 2016)	2003–2006	*HLA-DRB1×15:01*	GG vs AA	rs9271366	Silicone skin casts were used to objectively measure cumulative past sun exposure (scaled 1 to 6), representing	There was no evidence of an additive interaction between *HLA-DRB1×15:01* and low

(*continued on next page*)

Table 2 (*continued*)

Study	Study Year	Genotype used for GxE	Genotype variant/allele	SNP numbers for the genotype	Sun exposure measurement used (mostly self-reported unless otherwise specified)	Sun exposure GxE findings as reported in each study
					minimal to severe actinic skin damage	actinic damage synergy index=0.98 (p = 0.96).
Hedström (Hedström et al., 2020)	2021	*HLA-DRB1×15:01*	Not reported	rs3135388	Frequency of sunbathing, travelling to a sunnier country and use of sunbeds (based on a four-point scale where 3-the lowest exposure and 12-the highest exposure)	Additive interactions occurred between *HLA-DRB1×15:01* and low sun exposure (AP= 0.2;95 % CI=0.1, 0.3)[a] in Relapsing-onset MS and (AP= 0.4;95 %CI=0.3, 0.6)[a] in Progressive-onset MS.
Langer-Gould (Langer-Gould et al., 2018)	2011–2014	*GC*	CC/AC compared to AA	rs7041 and rs4588	Cumulative lifetime UVR calculated for each participant by combining latitude of residence and usual time outdoors taken from a detailed residency calendar with ambient UVR levels obtained from satellite-derived ground level estimates.	No significant interaction of cumulative UVR and the either *GC* SNP in models that included all participants but higher lifetime UVR exposure was associated with a significantly lower risk of MS in blacks and Hispanics who carried at least one copy of the C allele at rs7041 (30.0 % and 77.2 % respectively) but not in those homozygous for the A allele.

Abbreviations: EIMS=Epidemiological Investigation of Multiple Sclerosis; GC=group specific component; GEMS=Genes and Environment in Multiple Sclerosis; GxE=gene-environment interaction; HLA= human leukocyte antigen; HLA*IMP:02=Multi-Population Classical HLA Type Imputation; MC1R=melanocortin 1 receptor; RHC=red hair colour; UVR=ultraviolet radiation exposure. [a]=The odds ratio reported in single decimal place in the source article.

Table 3
Individual and joint associations of the genetic (HLA risk genes) and environment (low vitamin D) risk factors on MS risk- findings from the included studies.

Study	Study year	Gene/ Genotype	Allele/SNP	Vitamin D measure	[a]OR (95 %CI) gene–MS	Vitamin D-MS	Gene*Vitamin D-MS
Hedström (EIMS) (Hedström et al., 2020)	2020	*HLA-DRB1×15*	rs3135388	25(OH)D	**4.4 (3.4, 5.7)**	**1.4 (1.1, 1.8)**	**6.2 (4.5, 8.6)**
Bäärnhielm (Bäärnhielm et al., 2012)	2012	*HLA-DRB1×15*	Not reported	25(OH)D	3.8 (3, 6.5)	1.6 (1.2, 2.1)	5.1 (3.7, 7.1)
van der Mei (van der Mei et al., 2016)	2016	*HLA-DRB1×15*	GG/AA	25(OH)D	2.68 (1.70, 4.22)	1.77 (0.83, 3.79)	7.71 (2.59, 22.94)
Orton (Orton et al., 2008)	2008	*HLA-DRB1×15*	Not reported	25(OH)D	1.63 (1.10, 2.40)	1.0 (0.5, 2.1)	1.5 (0.7, 3.21)
Simon (Simon et al., 2010)	2009	*VDR*	Fok1 (TT)	Self-reported pre-MS onset vitamin D intake, dichotomised at 400IU/day	0.93 (0.78, 1.09)	Not reported	0.21 (0.06, 0.78)

[a] OR represent presence of genetic factor only, low vitamin D only, and when both genetic factor low vitamin D exists for MS risk. The ORs were adjusted for age, sex, and residence in each study. The change in ORs were negligeable when the models were further adjusted for variables such as smoking, BMI, and others.

Abbreviations: 25(OH)*D* = 5-hydroxy vitamin D; EIMS=Epidemiological Investigation of Multiple Sclerosis; HLA= human leukocyte antigen; OR=odds ratio; CI=confidence interval; MS=multiple sclerosis; SNP=single nucleotide polymorphism; VDR=vitamin D receptor.

four studies used the same approach, this being questionnaire-based durations of time in sun, although the cut-off point defining low sun varied. Three studies (Hedström et al., 2021; Bäärnhielm et al., 2012; Hedström et al., 2020) utilising the GEMS and/or EIMS case-control studies assessed sun exposure based on three questions regarding sun exposure (Table 2). The Tasmanian case-control study used silicone skin cast scores (right hand) as an objective measure of cumulative sun exposure (van der Mei et al., 2016).

Genetic risk factors assessed included *HLA-DRB1×15:01*, vitamin D receptor (*VDR*), the group-specific component (GC) encoding vitamin D-binding protein (also sometimes called D binding protein (DBP) but we will use the GC term), and melanocortin 1 receptor (*MC1R*), involved in skin colour. When a study reports only *HLA-DRB1×15* status as positive vs negative, this is typically based on carrier status (presence of at least one *HLA-DRB1×15* allele). Positive *HLA-DRB1×15* was considered either heterozygous or homozygous for the risk allele and negative for no copies of the *HLA-DRB1×15* risk allele.

Some of the included studies (Simon et al., 2010); (Dickinson et al., 2009); (Dwyer et al., 2008) (Langer-Gould et al., 2018) explicitly stated that they assessed Hardy-Weinberg equilibrium (HWE) and reported no significant deviation from equilibrium. For example, the Dickinson et.al (Dickinson et al., 2009) study reported that all Melanocortin 1 receptor (MC1R) SNPs and the *HLA-DRB1×15* marker, rs3135005, did not violate the HWE test using the default of p = 0.001. However, the remaining studies (Urbaneja et al., 2020); (Orton et al., 2008); (Nasr et al., 2024; Hedström et al., 2020); (van der Mei et al., 2016) didn't report whether they assessed the HWE test. These studies reported *HLA-DRB1×15* status using a binary classification (positive vs negative) based on the presence of at least one risk allele (i.e., a dominant allele model). As these studies did not report full genotype distributions (homozygous vs heterozygous vs non-carrier), formal HWE testing could not be performed on their data thus didn't report the HWE test results.

Other study design and methodological characteristics of the studies assessing gene-vitamin D status are shown in **Supplementary Table 3**, while those for gene-sun exposure interaction studies are shown in **Supplementary Table 4**. The detailed information on the genetic variants and the measurements of environmental factors assessed in these interactions are shown in Tables 1 **and** 2.

3.2. Studies' quality and risk of bias

Across the 11 studies included in our review, the median score for the

Table 4
Individual and joint effects of the genetic (HLA risk genes) and environment (low sun exposure) on MS risk-onset based on the included studies.

Study	Study year	Gene locus	Genotype/allele/SNP	Sun exposure	[a]OR (95 %CI)		
					Gene-MS risk	Sun- MS risk	Gene*sun-MS risk
[b]Hedström (GEMS) (Hedström et al., 2020)	2020	*HLA-DRB1×15:01*	rs3135388	Low sun	3.5 (3.2, 3.9)	1.1 (0.9, 1.4)	5.1 (3.7, 6.9)
Bäärnhielm (Bäärnhielm et al., 2012)	2012	*HLA-DRB1×15:01*	Not reported	Low sun	4.1 (3.1, 5.4)	1.5 (1.2, 1.9)	4.6 (3.5, 6.0)
Hedström (Hedström et al., 2021)	2021	*HLA-DRB1×15:01*	rs3135388	Low sun	3.4 (3.1, 3.7)	1.4 (1.3, 1.6)	4.8 (4.1, 5.4)
Dickinson (Dickinson et al., 2009)	2009	*VDR*	Cdx-2-GG (rs11574010)	Low winter sun	1.08 (0.59, 1.95)	Not reported	2.88 (1.06, 7.82)
Dwyer (Dwyer et al., 2008)	2008	*MCR1*	Not reported	Higher summer sun	1.96 (1.06, 3.64)	0.17 (0.03, 0.94)	1.52 (0.85, 2.72)
[b]Hedström (EIMS) (Hedström et al., 2020)	2020	*HLA-DRB1×15:01*	rs3135388	Low UVR	3.7 (3.1, 4.5)	1.4 (1.2, 1.6)	5.3 (4.2, 6.6)
[b]van der Mei (van der Mei et al., 2016)	2016	*HLA-DRB1×15:01*	GG	Low actinic damage	3.46 (1.97, 6.09)	2.00 (1.04, 3.83)	4.38 (2.16, 8.89)
Langer-Gould (Langer-Gould et al., 2018)	2018	*GC*	CC/AC	Low lifetime UVR	Not reported	Not reported	0.06 (0.01, 0.29)
Nasr (Nasr et al., 2024)	2023	*HLA-DRB1×15*	Not reported	Low actinic damage	1.9 (0.4, 9.1)	6.7 (2.8, 33.3)	6.6 (2.7, 15.8)

[a] Adjusted odds ratios represent the presence of genetic factor only, low sun exposure only, and when both genetic factor and low sun exposure exists for MS risk. [a]OR represent presence of genetic factor only, low vitamin D only, and when both genetic factor low vitamin D exists for MS risk. The ORs were adjusted for age, sex, and residence in each study. The change in ORs were negligeable when the models were further adjusted for variables such as smoking, BMI, and others. [b]Studies included in the meta-analysis.

Abbreviations: GEMS=genetic and environmental studied on MS; EIMS=epidemiological investigation on MS; OR=odds ratio; CI=confidence interval; MS=multiple sclerosis; RHC=red hair colour; SNP=single nucleotide polymorphism; VDR=vitamin D receptor; UVR=ultraviolet radiation.

items assessed using the STREGA checklists was 20 (range: 18–22), indicating that the studies were of high quality (Xiao et al., 2015) (**Supplementary Table 5**).

Based on the JBI checklist, we found that all included studies, except for Urbaneja et al. (2019), scored ≥80 %, indicating a generally low risk of bias (**Supplementary Table 6**). The study by Urbaneja et al. (2019) scored 70 % and was classified as having a "moderate risk of bias." One potential reason for this rating relates to possible selection or information bias. Specifically, while 103 out of 149 cases (69.1 %) reported being smokers at MS onset or within ten years prior, only 51 out of 147 controls (34.7 %) did so. This disparity could suggest that the controls might have been selected from a population with lower smoking prevalence or that cases were more likely than controls to recall or report past smoking.

Additionally, we noted a potential for measurement bias, as vitamin D levels were measured after MS diagnosis in some of the included studies (Hedström et al., 2021; Bäärnhielm et al., 2012; Hedström et al., 2020), raising the risk of reverse causality. We noted this in the discussion as a limitation. Concerning the confounders control, we reviewed that all the studies have identified and controlled the potential confounders (at least for age, sex, and study site) and we have noted this in the footnote of Tables 3 **and** 4 in the main manuscript.

3.3. Gene-environment interactions findings reported

3.3.1. Gene-vitamin D interactions

Seven studies reported evidence of gene-vitamin D interactions for MS risk. The Swedish study (Hedström et al., 2020) showed a significant positive interaction between *HLA-DRB1×15* and low vitamin D levels with lower MS risk (AP=0.2, 95 %CI=0.01–0.40). The Tasmanian case-control study (van der Mei et al., 2016) also showed a trend toward additive interactions between *HLA-DRB1×15:01* and low 25(OH) D levels, but these were not significant ($p = 0.14$).

Some studies also assessed GxE for other genetic variants and vitamin D. For instance, Simon and colleagues (Simon et al., 2010) reported a significant multiplicative interaction between self-reported pre-onset vitamin D dietary intake and the *VDR* FokI polymorphism (Table 1).

3.3.2. Gene-sun exposure interactions

A total of eight studies that assessed gene-sun exposure interactions with MS risk were included in this review. Most studies reported positive additive interaction between *HLA-DRB1×15:01* genotype and low sun exposure vs MS risk. For instance, Hedström and colleagues demonstrated potent and significant positive additive interaction between *HLA-DRB1×15:01* genotype and low sun exposure vs MS risk (AP=0.30; 95 %CI=0.14–0.60) (Hedström et al., 2020).

Some studies evaluated vitamin D-associated genes such as *VDR* and *MC1R*, showing that they interacted with sun exposure in their associations with MS risk. For example, Dickinson and colleagues demonstrated a significant synergistic association between a *VDR* gene polymorphism (Cdx-2 SNP) and low winter sun exposure during childhood (aOR=2.88; 95 %CI=1.06–7.82; $p = 0.04$) (Table 2).

3.4. Individual and joint effects of risk genotypes and low vitamin D on MS risk

Three studies (Bäärnhielm et al., 2012); (Hedström et al., 2020); (van der Mei et al., 2016), all assessing *HLA-DRB1×15* and 25(OH)D, provided complete reports on the odds ratios for the associations between these risk factors and MS risk with comparable gene-environment measurements and study design. Overall, increased odds ratios for MS risk were observed when both *HLA-DRB1×15* positive and low 25(OH)D were present compared to either factor alone or to neither factor being present (Table 3).

Due to sample overlap between the Bäärnhielm et al. (Bäärnhielm et al., 2012) and Hedström et al. (Hedström et al., 2020) (EIMS) studies, the Hedström study which had the most complete data, and the van der Mei et.al (van der Mei et al., 2016) were candidate studies for meta-analysis. Pooling the interaction statistics only from these two studies limits the statistical power to detect a true interaction effect, if one exists. Moreover, these studies differed substantially in sample size: the Hedström et al. (Hedström et al., 2020) included 7069 cases and 6632 controls, whereas the van der Mei (van der Mei et al., 2016) comprised just 282 cases and 558 controls. As a result, any pooled additive interaction estimate would be heavily weighted toward the Hedström et al. (Hedström et al., 2020) study, potentially skewing the

findings. Consequently, we didn't conduct a meta-analysis for the vitamin D and *HLA-DRB1×15* interactions.

3.5. Individual and joint effects of MS risk genotypes and low sun exposure on MS

Four studies (Hedström et al., 2021; Bäärnhielm et al., 2012; Hedström et al., 2020); (van der Mei et al., 2016) out of eight (Table 4), all evaluating GxE between *HLA-DRB1×15* risk variant and sun exposure status, provided complete reports of the odds ratios for the individual and combined associations of *HLA-DRB1×15:01* positive and low sun with MS risk. Consistently, an increased odds ratios for MS risk were observed when both *HLA-DRB1×15* positive and sun exposure were present, compared to neither factor.

Due to sample overlap between the Bäärnhielm et al. (Bäärnhielm et al., 2012) and Hedström et.al (Hedström et al., 2020) (EIMS) studies, we excluded the less complete Bäärnhielm et al. study and thus our meta-analysis was limited to three studies (Bäärnhielm et al., 2012); (Hedström et al., 2020); (van der Mei et al., 2016). Individuals with low sun exposure and with *HLA-DRB1×15:01* risk genotype had a stronger association with MS risk compared to those with none of these (aOR=5.17, 95 %CI=4.17–6.17). All three statistics showed a significant additive interaction between *HLA-DRB1×15:01* positivity and low sun exposure (S = 1.49; 95 %CI=1.28–1.69; AP=0.28; 95 % CI=0.20–0.35; RERI=1.42; 95 %CI=1.04–1.81) (Fig. 2A). In the random-effects model, these results didn't change materially (Fig. 2B).

3.6. Publication bias and heterogeneity

As shown in the funnel plot and tested using the Eggers test **(Supplementary Figure 2**), there was no evident publication bias for the association between *HLA-DRB1×15:01* and low sun exposure with MS risk (p = 0.96).

The heterogeneity levels were low for low sun exposure and *HLA-DRB1×15:01*(I^2=0.0 %, p = 0.38) (Figure 2).

4. Discussion

We reviewed 11 studies on gene-environment interactions of vitamin D and sun exposures and genetic risk loci in MS risk. This review showed positive interactions between MS risk genes, primarily *HLA-DRB1×15* risk variant, and environment MS risk factors including low vitamin D and/or sun exposure. The genetic and environmental risk factors appear to work jointly to affect MS, suggesting the importance of considering both when developing strategies for MS prevention or screening.

One key observation from this review is the diversity in exposure assessment. The vitamin D exposure was measured in various ways, both direct (serum 25(OH)D) and indirect (dietary intake, skin tone). Similarly, sun exposure was measured in a variety of ways, all self-reported, including the direct (frequency/duration of time in sun, including deriving total UV load from ambient UV data) and indirect (sunbathing, travelling to a sunnier country and use of sunbeds). This heterogeneity reflects not only the complexity of capturing environmental exposures and the evolving methodologies in the field but also makes direct comparisons between studies and pooling average estimates more challenging, suggesting the need to have a standardised exposure measurement methods that enable reasonable comparison between studies and help quantitively aggregate the GxE studies in MS involving 25(OH) D levels and sun exposure.

Another point of review was related to the timing of 25(OH)D levels measurement, being measured after MS onset. Thus, the included studies demonstrated only association of 25(OH)D levels with MS risk, without being able to confirm causal inference. However, some studies such as Hedström et al. (Hedström et al., 2020), have reported that the findings remained similar when they restricted the analysis to the participants with disease onset within the past year. Moving forward, well-designed prospective studies assessing vitamin D status before the onset of MS and monitoring the effects of vitamin D supplementation over time could provide more definitive insights into the causal relationship and potential therapeutic implications.

Concerning the genetic loci, *HLA-DRB1×15:01* was the most consistently replicated MS variant identified in the studies included in our review. Although we included other gene loci such as the VDR, MC1R, and CD58 loci, and others, there were insufficient studies exist to conduct a meta-analysis involving these gene loci and MS risk.

Due to the aforementioned heterogeneities in the exposure measurements, we were able to quantitatively synthesise the GxE effects on MS risk for the *HLA-DRB1*15:01 risk variant and sun exposure but not vitamin D status.

4.1. MS risk genotypes and low vitamin D GxE effects on MS risk

This systematic review identified several studies that evaluated the interaction between low vitamin D status and genetic risk factors,

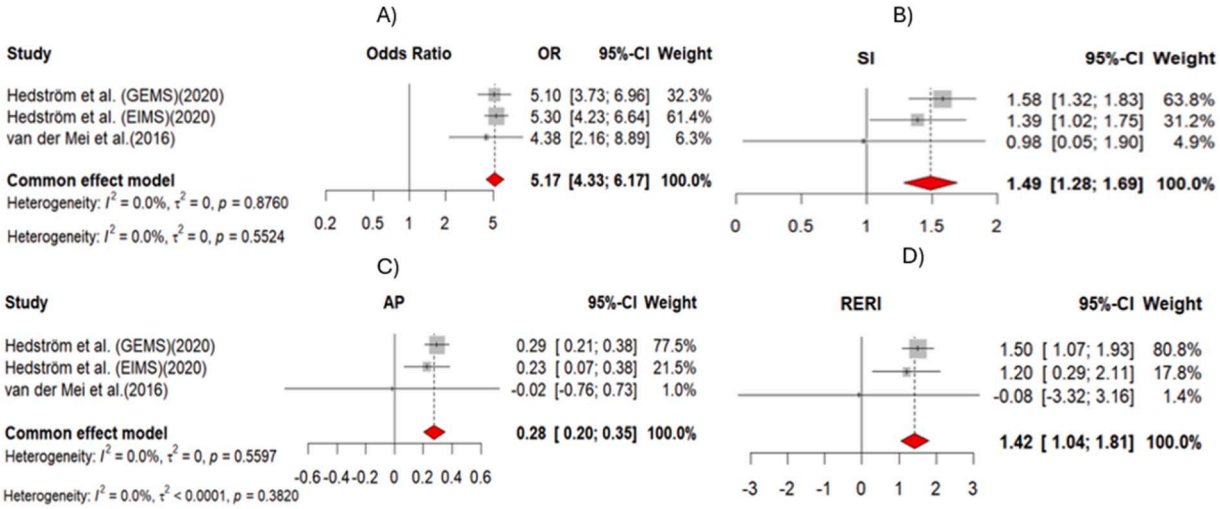

Fig. 2a. Additive interaction measures showing interaction between low sun exposure and *HLA-DRB1×15:01* positivity and MS risk on fixed effects model. **A**) pooled odds ratio (OR)[95 %CI]. **B**) synergy index (SI) [95 %]. **C)** attributable proportion due to interaction (AP) [95 %CI]. **D)** excess risk due to interaction (RERI) [95 %CI] computed to assess the additive interactions. Weights were estimated proportional to the study sample size. Generally, a pooled positive additive interaction was observed between low sun exposure and *HLA-DRB1×15* positive for MS risk across the interaction metrics.

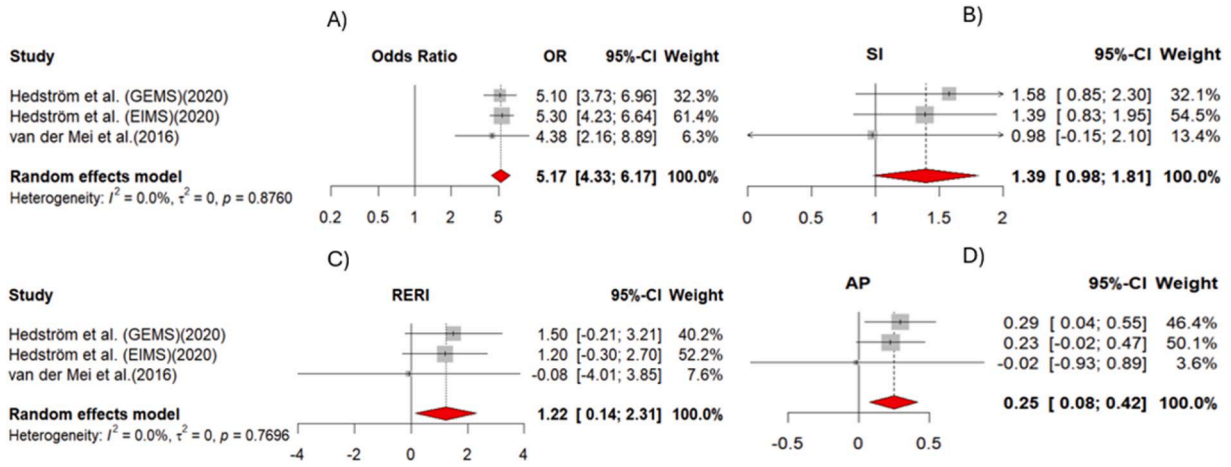

Fig. 2b. Additive interaction measures showing interaction between low sun exposure and *HLA-DRB1×15:01* positivity and MS risk on random effects model. **A**) pooled odds ratio (OR)[95 %CI]. **B**) synergy index (SI) [95 %]. **C)** excess risk due to interaction (RERI) [95 %CI]. **D**) attributable proportion due to interaction (AP) [95 %CI] computed to assess the additive interactions. Weights were estimated proportional to the study sample size. Overall, a pooled positive additive interaction was observed between low sun exposure and *HLA-DRB1×15* positive for MS risk across the interaction metrics.

particularly the *HLA-DRB1×15:01* variant and VDR polymorphisms, in relation to MS risk. Among the most consistent findings, was evidence of a positive additive interaction between low serum 25(OH)D levels and *HLA-DRB1×15:01* genotype. For instance, the Swedish EIMS study (Hedström et al., 2020) reported a significant interaction (AP=0.2 (95 % CI: 0.01–0.4)), suggesting that approximately 20 % of the MS risk among individuals exposed to both low vitamin D and *HLA-DRB1×15:01* positivity is due to the interaction between these factors.

Other studies explored gene-vitamin D interactions beyond *HLA-DRB1×15:01*. For example, Simon et al. (Simon et al., 2010). reported a significant interaction between vitamin D intake and the vitamin D receptor (VDR) FokI polymorphism ($p = 0.04$), suggesting that individuals with specific VDR genotypes may respond differently to vitamin D exposure in terms of MS risk. Additionally, the Langer-Gould et al. (Langer-Gould et al., 2018). study observed a protective multiplicative interaction between higher 25(OH)D levels and the GC rs7041 C allele, but only among white participants. Furthermore, some studies used skin tone as a proxy for vitamin D status, such as the study by Urbaneja et al. (Urbaneja et al., 2020) which found that individuals with light brown skin and *HLA-DRB1×15:01* had a substantially higher MS risk than those with either factor alone.

The GxE findings in our review align with previous studies (Sintzel et al., 2018); (Xiao et al., 2015), indicating that low vitamin D levels combined with *HLA-DRB1×15* risk variant were jointly and positively associated with MS risk.

The biologic mechanism underpinning how the interaction between the two factors contributes an increased risk for MS risk remains unclear. A suggested mechanism involves vitamin D altering *HLA-DR* antigen expression and presentation (Rigby et al., 1990). Evidently, the vitamin D response element (VDRE) in the promoter region of *HLA-DRB1* is highly conserved on *DRB1×15:01* haplotypes, providing a biological and functional explanation for the interactions between this genotype and vitamin D and MS risk (Ramagopalan et al., 2009). Another plausible mechanism is that low vitamin D levels are linked to reduced CD4+/CD8+ *T*-cell counts, leading to immune dysregulation, which in turn increases the likelihood of EBV reactivation (Rasheed and Khan, 2024). This reactivation may enhance the presentation of EBV-derived peptides by antigen-presenting cells expressing the *HLA-DRB1×15:01* allele, potentially triggering pathogenic CD4+ *T*-cell responses involved in MS development

Our review also highlighted that genetic variants in the vitamin D pathway modify the link between circulating vitamin D metabolite levels and MS risk. The most consistently implicated genetic regions associated with vitamin D in MS include those involved in vitamin D metabolism/transport such as *CYP24A1, CYP27B1*, and *GC* (Sawcer et al., 2011). Differential genotypes in these genes affect the transport, synthesis, and catabolism of vitamin D, thereby affecting levels of 25 (OH)D and 1,25$(OH)_2$D (Sawcer et al., 2011). However, we noted that more GxE studies assessing these, and other genetic variants are required so that future meta-analyses can aggregate them and provide more comprehensive evidence.

Collectively, findings in this review support a role for GxE involving *HLA-DRB1×15:01* risk variant and genes related to vitamin D pathways in MS pathogenesis, though heterogeneity in vitamin D measurement, genotype methods, and statistical approaches underscores the need for further harmonised and larger prospective studies.

4.2. Joint effects of MS risk genotypes and low sun exposure on MS risk

In this review we showed that low sun exposure positively interacted with the *HLA-DRB1×15:01* risk genotype. Aggregating the four-level interaction terms, an elevated odds ratio (up to five-fold) was observed in the association between a combination of low sun exposure and *HLA-DRB1×15* positivity and an outcome of MS case status. The SI statistic showed that the excess risk of MS due to the joint effect of *HLA-DRB1×15* risk gene and low sun exposure was 1.49-times greater than the sum of their individual effects. Also, the RERI statistic showed that combined effect of these factors on MS risk was 1.42-times greater than what would be expected if their effects were merely additive. Lastly, the AP statistic reflected that the 28 % increased risk of MS in people exposed to both *HLA-DRB1×15* MS risk gene and low sun exposure was due to the interaction between these two factors.

Although the biologic mechanism underlying the augmented effects of the *HLA-DRB1×15* positivity and low sun exposure interactions on MS risk remains unclear, these factors may act on the immune system and potentially via the vitamin D-mediation (Lucas and Ponsonby, 2006).

Direct sunlight or ultraviolet (UV) exposure have been found to have immunological effects independent of those that are vitamin D-related (Hart et al., 2011). These include systemic immune reactions and attenuated systemic autoimmunity via the induction of skin-derived tolerogenic dendritic cells (DCs) and regulatory T-cells (Tregs) (Breuer et al., 2014).

Finally, an important aspect of this work is its implication to the field of health economics. The additive interaction statistics aggregated in our meta-analysis can be used to model the cost-effectiveness of interventions using methods such as the incremental cost-effectiveness

ratios (ICER) (Dakin and Gray, 2018). A systematic review by Welton and colleagues (Dakin and Gray, 2020) highlights the significance of considering additive interactions in economic evaluations and assessing the cost-effectiveness of combined exposures/health strategies.

Therefore, accounting for these interaction effects is crucial when implementing vitamin D- or sun exposure-related interventions, particularly for *HLA-DRB1×15:01*.

4.3. Strengths and limitations

This systematic review and meta-analysis comprehensively reviewed the available studies of gene-environment interactions for vitamin D and sun vs MS risk. We utilised robust interaction metrics based on additive rather than multiplicative interaction since the former is considered to be biologically more plausible (VanderWeele, 2015).

However, there are some noteworthy limitations to consider in our review. Firstly, that the methods of sun exposure measurement were varied across studies, may introduce misclassification bias. Secondly, we observed differences in the timing of sun exposure (sun exposure in childhood, teenage years, adulthood or cumulative exposure), potentially influencing our results. It has been suggested that sun exposure measurement across the lifespan is important (van der Mei et al., 2011). Third, in some studies (Hedström et al., 2021; Bäärnhielm et al., 2012; Hedström et al., 2020), vitamin D was measured after MS diagnosis, which limit the ability to draw causal inference and underscores the need for future GxE prospective cohort or large mendelian randomization studies, where feasible. Nonetheless, other studies (Simon et al., 2010); (Langer-Gould et al., 2018); (van der Mei et al., 2016) measured vitamin D levels close to, or even prior to, MS onset, thereby strengthening the ability to evaluate the causal relationship between low vitamin D levels and/or sun exposure and MS risk. Fourth, we note that the current evidence for gene loci other than the *HLA-BRB1×1501* is insufficient for meta-analysis but of potential interest and thus future reviews may consider including other gene loci (e.g., *VDR, MC1R, CD58*) if sufficient studies exist. Fifth, some of the included studies reported *HLA-DRB1×15*:01 status in a binary format (positive vs negative), rather than providing full genotype distributions (homozygous, heterozygous, non-carriers). This binary classification prevented formal testing for Hardy-Weinberg equilibrium, which relies on complete genotype frequencies. As a result, our ability to evaluate potential population stratification or genotyping error in these studies was limited. This constraint should be considered when interpreting the GxE interaction estimates. Lastly, due to the small number of studies included in the meta-analysis, methods such as funnel plots, Egger's test, and heterogeneity assessments may lack the statistical power to accurately detect publication bias or between-study variability, and their associated results should therefore be interpreted with caution.

4.4. Implications and future directions

This review provides information regarding the potential biological mechanisms underlying MS development and suggests the need to integrate genetic (*HLA-DRB1×15*) and environmental (vitamin D, sun exposure) risk factors in MS risk assessment and prevention strategies. Screening for these factors may help identify high-risk individuals for targeted interventions. Further gene-vitamin D and/or sun exposure interaction studies, considering comprehensive genetic components and employing consistent measurements of vitamin D and sun exposure are recommended in this field.

4.5. Conclusions

In conclusion, this systematic review and meta-analysis, which included all the currently available studies assessing GxE for vitamin D and sun with regard to MS risk, identified substantial joint effects of low vitamin D and *HLA-DRB1×15* and significant positive additive interactions between *HLA-DRB1×15* and low sun exposure vs MS risk. We were unable to quantitatively aggregate additive interactions for low vitamin D and *HLA-DRB1×15* for want of sufficient comparable studies. Additionally, we couldn't conduct a meta-analysis for non-*HLA-DRB1×15* genes for the same reason, but the potential for GxE for such loci, particularly genes involved in vitamin D metabolism/transport/signalling, justifies further investigations. Our results suggest that individuals with joint exposure to low vitamin D and/or sun and *HLA-DRB1×15* risk genotype maybe prioritised in MS prevention/intervention strategies.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to paraphrase statements, locate alternative words, and check spellings and typos. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Role of funding

This work was supported by The University of Melbourne, Australia through a university-funded PhD scholarship awarded to Mehari Merid. The funding body had no role in the design, analysis, interpretation, or writing of this manuscript.

CRediT authorship contribution statement

Mehari Woldemariam Merid: Conceptualization, Data curation, Investigation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Liyang Xu:** Methodology, Software, Formal analysis, Visualization, Writing – review & editing. **Yuan Zhou:** Methodology, Visualization, Validation, Writing – review & editing. **Ingrid van der Mei:** Methodology, Validation, Visualization, Writing – review & editing. **Daniel J. Park:** Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing. **Steve Simpson-Yap:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

Yuan Zhou is supported by a grant from the Australian Medical Research Future Fund (2024,516) and a Centre of Research Excellent grant from the Australian National Health & Medical Research Council (2035,302). None of the other authors have any relevant conflicts of interest.

Acknowledgements

We gratefully acknowledge the library personnel at The University of Melbourne who assisted us in selecting appropriate databases and applying effective searching techniques to locate relevant articles for our review. We also extend our thanks to Professor Anne-Louise Ponsonby for her guidance, comments, and scientific consultations for this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106634.

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