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Associations of serum 25(OH) vitamin D levels with clinical and radiological outcomes in multiple sclerosis, a systematic review and meta-analysis

Elena H. Martínez-Lapiscina[a,f], Rattanaporn Mahatanan[b,f], Chih-Hong Lee[c], Prangthip Charoenpong[d,f], Jia-Pei Hong[e,f,*]

[a] Center of Neuroimmunology and Department of Neurology, Hospital Clinic of Barcelona, Institute d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), University of Barcelona, Spain
[b] Department of Internal Medicine, Redington Fairview General Hospital, Skowhegan, ME, USA
[c] Departments of Neurology, Chang Gung Memorial Hospital Linkao Medical Center and Chang Gung University, College of Medicine, Taoyuan, Taiwan
[d] Department of Internal Medicine, Division of Pulmonary and Critical Care, Louisiana State University, Shreveport, Louisiana, USA
[e] Departments of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital Linkao Medical Center and Chang Gung University, College of Medicine, Taoyuan, Taiwan
[f] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

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ABSTRACT

Background: Vitamin D supplementation is recommended for patients with multiple sclerosis (MS). However, a recent meta-analysis based on low-quality trials suggested no evidence of supplementation benefit. A systematic review and meta-analysis of high-quality observational cohort studies should provide us further evidences.
Methods: MEDLINE, EMBASE, and WEB-of-SCIENCE databases were systematically searched to identify eligible studies published before October 2018. Prospective cohort studies assessing the associations of serum 25(OH)D levels with MS relapses, radiological inflammatory lesions, or changes in expanded disability status scale in adults (≥18 years) with MS were included. Pooled RRs were calculated using fixed-effect or random-effects model depending on heterogeneity.
Results: Thirteen studies and 3498 patients were included. Each 25 nmol/L increase in serum 25(OH)D levels was associated with a reduction in (1) clinical relapse rate [RR = 0.90; 95% confidence interval (CI) = 0.83–0.99], (2) gadolinium-enhancing lesions (RR = 0.69; 95% CI = 0.60–0.79), (3) new/enlarging T2 lesions (RR = 0.86; 95% CI = 0.77–0.95), and (4) new active lesions (RR = 0.81; 95% CI = 0.74–0.89) in the magnetic resonance imaging(MRI).
Conclusions: Serum 25(OH)D levels are associated with a modest decrease in relapse rate and radiological inflammatory activities in patients with MS. The association with disability worsening remains inconclusive.

1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system. Although the cause of MS remains unknown, both genetic and environmental factors have been implicated in the development and severity of the MS course [1]. Among odifiable environmental factors, sunlight exposure has been hypothesized as a protective factor in the attempt to explain geographic variations in MS prevalence and changes in risk pattern among migrants [2]. The main mechanism underlying protective effect of sunlight exposure is likely immunomodulatory effects of vitamin D [2,3].

Following evidence from observational studies suggesting a lesser severe MS course among subjects with adequate serum vitamin D levels [4,5], most neurologists have adopted the recommendation of prescribing vitamin D supplementation as an add-on therapy. Nevertheless, the Cochrane systematic review and meta-analysis recently published in 2018 found that current evidence for vitamin D supplementation for MS patients was inconclusive. Authors highlighted the low-quality of randomized controlled trials (RCT) they cited [6]. Most of the trials did not have appropriate sample size and length of follow-up, caveats that might be overcome in ongoing trials [7,8]. In the meantime, well designed and conducted systematic review and meta-analysis from high-quality observational studies may ameliorate the uncertainty and help the clinical decision-making about vitamin D supplementation for

* Corresponding author at: Departments of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Tao-Yuan County, No.5, Fuxing St., Guishan Dist., Taoyuan City 333, Taiwan.
E-mail address: jhong@hsph.harvard.edu (J.-P. Hong).

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patients with MS.

The objective of this systematic review and meta-analysis is to address the association between serum 25-Hydroxyvitamin D [25(OH)D] levels and disease outcomes in patients with clinically isolated syndrome (CIS) or MS by analyzing high-quality prospective cohort studies.

2. Methods

2.1. Data sources and search strategy

This review was conducted using a predefined protocol and in accordance with PRISMA [9] and MOOSE [10] guidelines. Three electronic databases (Ovid MEDLINE, EMBASE, and WEB of SCIENCE) were searched until October 19th, 2018, without length of follow-up and language restrictions. The computer-based searches combined controlled vocabulary and free terms related to [1] vitamin D including different names and metabolites and [2] MS including all phenotypes as well as demyelinating diseases as a general disease ontology. Additionally, we checked the website of National Multiple Sclerosis Society (NMSS) and reference lists of identified articles published in 2017–2018 for potentially relevant studies. We also contacted the authors to ask for additional or English information as needed. Details about terms and strategies for different databases are displayed in Appendix A.

2.2. Eligibility criteria and study selection

Studies were eligible if they were prospective cohort studies and assessed the effect of serum 25(OH)D levels on at least one of the following MS outcomes: relapses, gadolinium-enhancing lesions(GEL), new or enlarging T2 lesions, or disability assessed by expanded disability status scale (EDSS). Study population included adults (≥18 years) with CIS or MS according to the McDonald criteria [11,12]. Pregnant women, adults with pediatric onset MS or familial MS were excluded.

2.3. Data extraction and study quality assessment

Two independent reviewers (EHMLP and JPH or RM and PC) screened the titles and abstracts of all studies initially identified by using Covidence (*Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia*). Any disagreement was resolved through consultation with a third independent reviewer. We used Endnote X7 library (*Clarivate Analytics, USA*) to remove duplicates. Full texts were retrieved from studies that met study criteria. Finally, studies that satisfied all eligibility criteria were included for the final analyses while the others were excluded with specified reasons.

Two reviewers (EHMLP and JPH or RM and PC) independently extracted relevant data using a predesigned form. We extracted the characteristics of each included study, including first author's last name, year of publication, study name, location of study, study population, length of follow-up, serum 25(OH)D levels, relapses rate, GEL, new or enlarging T2 lesions, EDSS, adjusted estimates with 95% confidence interval(CI) and confounding variables.

Two authors (RM and PC or EHMLP and JPH) independently rated the quality of studies, and any disagreement was resolved by a third reviewer's evaluation. The Newcastle-Ottawa Scale (NOS) [13] for cohort studies was used for quality assessment and risk of bias at individual study. The maximum NOS for each study is 9, while studies having less than 5 points are identified as at high risk of bias.

2.4. Data analysis

Exposures were evaluated as continuous [change per 25 nmol/L serum 25(OH)D levels] and categorical [above versus below 50 nmol/L serum 25(OH)D levels] variables.

In order to get a consistent interpretation, units of serum 25(OH)D measurement were converted to nmol/L. For studies using continuous exposures with a definition other than change per 25 nmol/L serum 25(OH)D, we calculated new beta coefficients and standard errors by applying the following formula ($\beta_{25nmol/L} = \beta_{\text{reported unit}}$ x conversion factor; for instance, $\beta_{25nmol/L} = \beta_{50nmo/L}$ x 0.5). For studies reporting categorical exposures, we selected the risk/rate ratio reported for the highest level of serum 25(OH)D compared to the lowest one. Subgroup analysis using estimates without unit transformation were performed as well. Summary of estimates were presented as mean risk differences for continuous outcomes. For dichotomous outcomes, we calculated pooled relative risk and 95% confidence Intervals(CI).

We quantified heterogeneity using I^2 and the I^2 statistic with a value > 50% indicates substantial heterogeneity [14]. The inverse variance-weighted method was used to combine measures using random-effects models to address within and between studies variability if there was evidence for heterogeneity [15]. Otherwise, a fixed effects model was used.

We evaluated publication bias by using funnel plots and Egger regression symmetry tests [16]. Additionally, we defined two *post-hoc* analyses using random-effects meta-regression [17] to evaluate how the effect changed according to disease duration and length of follow-up. We specified at least two years as the optimal length of follow-up because it is the length of follow-up for most randomized clinical trials adopted. Sensitivity analyses were performed to investigate the effect of a single study on the overall risk estimated by removing one study in each turn. Results are displayed as forest plots showing relative risk and the corresponding 95% CI for each individual study and the pooled result. A qualitative synthesis was performed for studies that could not be quantitatively synthetized. All tests were two-tailed and a p-value ≤.05 was considered statistically significant. Statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX).

3. Results

3.1. Study identification and selection

We identified 11,996 relevant articles. After removing duplicates, we screened titles and abstracts for 6896 articles and selected 143 articles for evaluation of their full texts. Of those, 13 studies [18–30] met our eligibility criteria and were included in the review. Three articles were not included in the quantitative synthesis [28–30]. We did not calculate the pooled estimates from Loken-Amsrud et al., which used odds ratios while other studies computed either risk or rate ratios [29]. Fig. 1 displays the flow-diagram of literature search.

3.2. Features of included studies

The 13 prospective cohort studies [18–30] reported results from 3498 patients. Study population included adults with average age of 38.5 years (interquartile range [IQR] = 35.2–40.7) and disease duration of 4.85 years (IQR = 1.5–7.8), mostly females (70.2% [IQR = 67–73%]) and White Caucasians (≈90%). All subjects were diagnosed as CIS or relapsing-remitting MS(RRMS) and mostly were treated with disease modifying drugs and followed over 2 years (IQR = 1.25–4.65). Most studies evaluated associations between serum 25(OH)D levels as a continuous exposure with different outcomes. The relapse rate is the most frequently reported endpoint. Table 1 shows the summary of study population and findings of the studies.

3.3. Serum 25(OH)D levels and relapses

Eight [18,20–23,25–27] studies assessed the association between continuous serum 25(OH)D levels and rate of a new relapse. The population of the included studies were similar in terms of gender

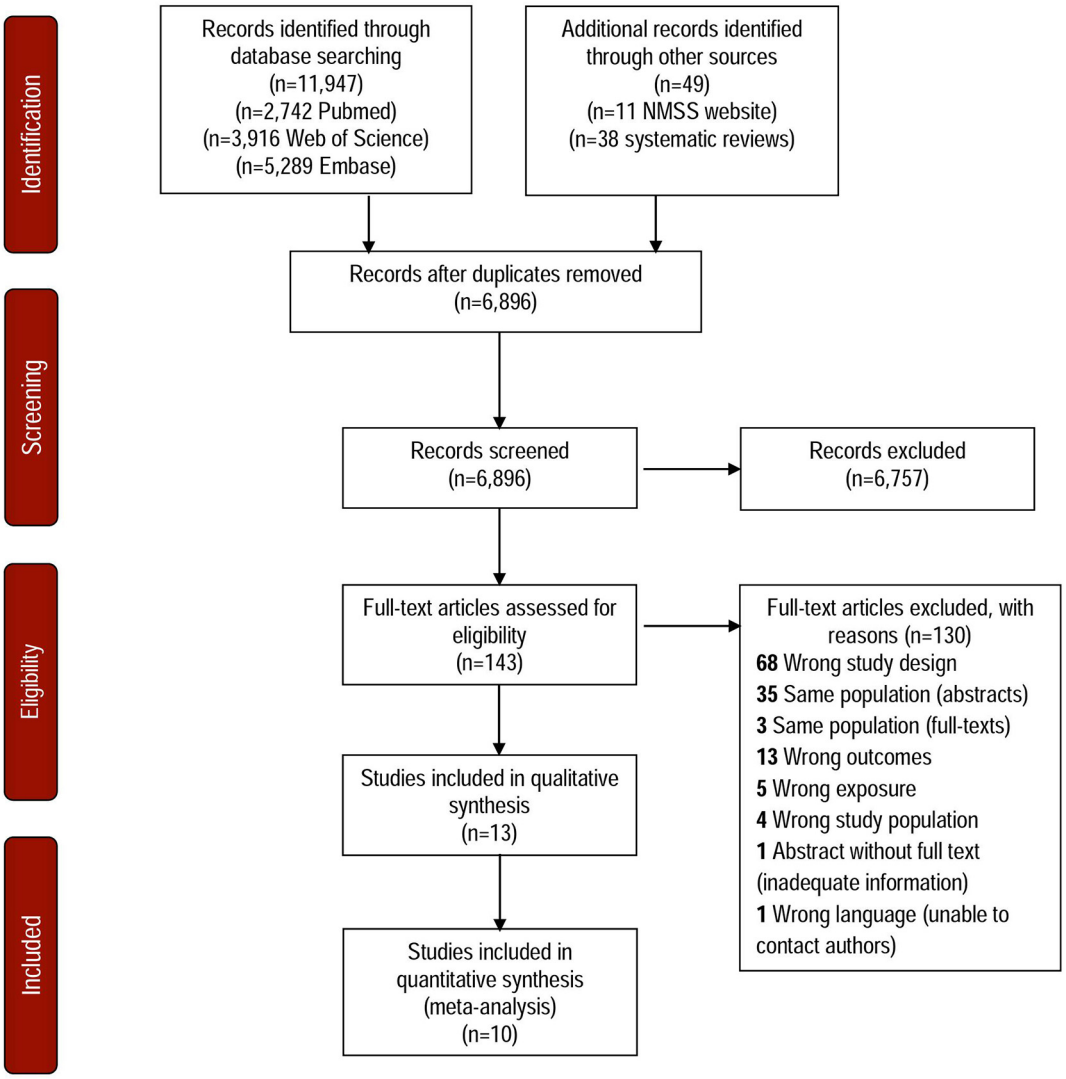

Fig. 1. Flow-diagram of literature search in the meta-analysis.

distribution, age and disease duration. However, there were geographic differences which may be a marker of different genetic background, a variable that was not considered in our study and may at least partially explained the significant statistical heterogeneity across the studies (I^2 = 52%, 95% CI = 0–78; *p*-value = .044), which justified the use of random-effects models. We found the relapse rate decreased by 10% (IQR = 1–17%) per 25 nmol/L increase in serum 25(OH)D levels (Fig. 2A). The effect neither significantly changed with each year of disease duration (RR = 0.98, 95% CI = 0.94–1.01; *p*-value = .188), nor was significantly different in those with follow-up ≥2 years compared to those with shorter follow-up (RR = 1.01, 95% CI = 0.93–1.11; p-value = .714). We did not have enough studies to test publication bias. Three studies addressed the association using serum 25(OH)D levels as categorical exposures [24,25,28]. We pooled two of them with the same cut-off value (50 nmol/L) and used below 50 nmol/L as the reference. A protective association between vitamin D and relapses was found (RR = 0.47, 95% CI = 0.19–1.17, *p*-value of 0.105) [24,25]. The other study used serum 25(OH)D levels above 100 nmol/L as reference also obtained a protective effect of serum 25(OH)D levels in relapses [28].

3.4. Serum 25(OH)D levels and radiological inflammatory activities

Eight studies assessed the association between serum 25(OH)D levels and radiological inflammatory activities measured as: [1] GEL (*n* = 6) [19–21,23,29,30]; [2] new/enlarging T2 lesions (*n* = 4) [21,23,29,30]; [3] new active lesions(either a GEL or a new/enlarging T2 lesion)(*n* = 3) [18,22,29]. The pooled effect estimates were only obtained from studies using serum 25(OH)D levels as a continuous exposure.

We found the rate of GEL decreased by 31% (95% CI = 21–40%) per 25 nmol/L increase in serum 25(OH)D levels using fixed-effect models (I^2 = 21%; *p*-value = .282) [19–21,23] (Fig. 2B). Effect size did not significantly change with each year of disease duration (RR = 0.97, 95% CI = 0.80–1.17; p-value = .565). We could not analyze publication bias due to small sample size. Finally, each 25 nmol/L increase in serum 25(OH)D was associated with a 14% (95% CI = 5–23%) lower rate of new or enlarging T2 lesions [21,23] (Fig. 2C), and 19% (95% CI = 11–26%) decrease in new active lesions [18,22] (Fig. 2D). The pooled effect estimates were calculated using the fixed-effect model as well (I^2 = 0% for both models). The features of the included populations in these studies were similar with a more homogeneous geographic origin (North America and Europe) as compared to the more diverse geographic distributions in the pooled studies for relapses.

3.5. Serum 25(OH)D levels and disabilities

Four articles interrogated relationship between serum 25(OH)D and disability worsening based on change in EDSS score [18,20–22].. All

Table 1
Study population and summary findings of the studies assessing association between serum 25(OH) D levels and MS.

First author (year) Study name	Location	Study population	Follow-up (mean)	Exposure	Outcome	Adjusted estimates (95% CI)	Adjusted covariates
Ascherio (2014)[18] BENEFIT	Europe Canada Israel	464 (70.5% ♀); age 31.3 (7.5) median (IQR); 98.5% C 100% CIS (66% treated) Disease duration NN	5 y	50-nmol/L increase in serum 25(OH)D	Relapse New active lesions EDSS	RR = 0.73 (0.46 to 1.16) (rate) RR = 0.61 (0.44 to 0.83) (rate) Beta = −0.16 (−0.37 to 0.04)	Age, sex, treatment, T2 lesion, type of onset, time of follow-up
Munger (2014)[19] BENEFIT	Europe Canada Israel	464 (70.5% ♀); age 31.3 (7.5) median (IQR); 98.5% C 100% CIS (66% treated) Disease duration NN	5 y	50-nmol/L increase in serum 25(OH)D Serum 25(OH)D ≥ 50-nmol/L vs. below (ref low)	Gadolinium-enhancing lesion	RR = 0.43 (0.28 to 0.66) (risk) RR = 0.61 (0.44 to 0.83) (risk)	Age, sex, treatment and interaction of treatment*25(OH) level
Rotstein (2015)[20] CLIMB	US (MA)	247 (69% ♀); age 39.1 (NA) median (IQR); 93.5% C 100% RRMS (all treated) Disease duration 4.0 (NA) median (IQR)	4.3 y	25-nmol/L increase in serum 25(OH)D	Relapse Gadolinium-enhancing lesion EDSS	HR = 0.85 (0.65 to 1.10) HR = 0.58 (0.39 to 0.85) HR = 1.10 (0.86 to 1.41)	Age, sex and disease duration. All treated with same first-line therapy (IFN or GA).
Mowry (2012)[21] EPIC	US (CA)	469 (70% ♀); age 42 (10) median (IQR); 5% H (C: NA) 81% RRMS 19% CIS (64% treated) Disease duration 5 (0–25) median (IQR)	5 y	25-nmol/L increase in serum 25(OH)D	Relapse Gadolinium-enhancing lesion New T2 lesion EDSS	IRR = 0.94 (0.86 to 1.02) IRR = 0.68 (0.53 to 0.87) IRR = 0.85 (0.76 to 0.95) Beta = −0.047 (−0.091 to −0.003)	Age, sex, ethnicity, smoking, treatment
Fitzgerald (2015) [22] BEYOND	Europe Israel Canada US Australia Argentina Brazil	1453 (70% ♀); age 35.9 (NA) median (IQR); 91.1% C 100% RRMS (all treated) Disease duration 4.7 (NA) median (IQR)	2 y	50-nmol/L increase in serum 25(OH)D	Relapse New active lesion EDSS	RR = 1.01 (0.84 to 1.21) (rate) RR = 0.69 (0.55 to 0.86) (rate) RR = 0.77 (0.56 to 1.06) (rate)	Age, sex, treatment, region of residence, disease duration (baseline EDSS for progression).
Mowry (2016)[23] STAyCIS	Canada US	65 (72% ♀); age 34.6 (NA) median (IQR); 90.7% C 100% CIS (0% treated) Disease duration NN	1 y	25-nmol/L increase in serum 25(OH)D (not de-seasonized)	Relapse Gadolinium-enhancing lesion New T2 lesion	HR = 0.92 (0.63 to 1.35) IRR = 0.95 (0.65 to 1.37) IRR = 0.89 (0.69 to 1.14)	Age. According to authors: race, BMI, disability, treatment (atorvastatin versus placebo) or season did not influence results.
Scott (2013)[24] NA	US (PA)	118 (59% ♀); age 46.8 (NA) median (IQR); C:AA 82:18% 100% RRMS (100% treated) Disease duration 15.1 (NA) median (IQR)	1 y	Serum 25(OH)D ≥ 50-nmol/L vs. below (ref low) (not de-seasoned; mostly measured in winter)	Relapse	CIR = 0.26 (0.10 to 0.68)	None. According to authors: race did not influence results.
Stewart (2012)[25] STMLS	Australia	178 (71.9% ♀); age 47.4 (11.4) median (IQR); C: NA 81% RRMS (72.5% treated) Disease duration 10 (5–19) median (IQR)	2.2 y	10-nmol/L increase in serum 25(OH)D (de-seasonized?) Serum 25(OH)D ≥ 50-nmol/L vs. below (ref low) (de-seasonized?)	Relapse	HR = 0.85 (0.79 to 0.93) HR = 0.68 (0.48 to 0.97)	Age, BMI, tobacco, disease duration, progression to secondary progressive MS, exacerbations two-year prior inclusion, stratified on sex and EDSS (time-varying)
Simpson (2018)[26] AusLong	Australia	145 (78.6% ♀); age 37.7 (9.6) median (IQR); C: NA	5 y	10-nmol/L increase in serum 25(OH)D (de-seasonized?)	Relapse	HR = 0.99 (0.93 to 1.05)	Age, sex, treatment, stratified on study site.

(*continued on next page*)

Table 1 (*continued*)

First author (year) Study name	Location	Study population	Follow-up (mean)	Exposure	Outcome	Adjusted estimates (95% CI)	Adjusted covariates
		100% CIS (50.3% treated) Disease duration NN					
Wang (2018)[27] NA	China	109 (53.2% ♀); age 38 (33–46) median (IQR); 100% Asian 100% RRMS (17.4% treated) Disease duration 6 (4–10) median (IQR)	1 y (median)	2.5-nmol/L increase in serum 25(OH)D (not de-seasonized)	Relapse	HR = 0.99 (0.84 to 0.95)	None. According to authors: age, sex, EDSS, use of IFN and season did not influence results.
Runia (2010)[28] Rotterdam Study	The Netherlands	73 (77% ♀); age 39.4 (9.1) median (IQR); 100% C 100% RRMS (82% treated) Disease duration 5.2 (4.1) median (IQR)	1.7 y	Serum 25[OH]D < 50 nmol/L vs. ≥100 nmol/L (ref high) Serum 25[OH]D 50–100 nmol/L vs. ≥100 nmol/L (ref high)	Relapse	IRR = 1.9 (1.1 to 3.2) [low] IRR = 1.4 (0.8 to 2.2) [intermediate]	Age, sex, exacerbations two-year prior inclusion, EDSS, treatment, infection
Loken-Amsrud[29] (2012) OFAMS	Norway	88 (65% ♀); age 39 (19–58) median (range); 100% C 100% RRMS (all treated) Disease duration 3 (0−23) median (range)	1.5 y	10-nmol/L increase in serum 25(OH)D (de-seasonized?)	Gadolinium-enhancing lesion New T2 lesion New active lesion	OR = 1.055 (0.939 to 1.185) OR = 1.028 (0.920 to 1.149) OR = 1.023 (0.921 to 1.136)	Age, sex.
Ferre (2018)[30] NA	Italy	89 (74% ♀); age 29.6 (NA) median (IQR); C: NA 100% RRMS (all treated) Disease duration 9.7 (NA) median (IQR)	2 y	Serum 25[OH]D ≥ 100 nmol/L vs. < 50 nmol/L (ref low)	Gadolinium-enhancing lesion New T2 lesion	IRR = 0.16 (0.01 to 1.61) IRR = 0.12 (0.01 to 0.99)	Exacerbations two-year prior inclusion and baseline lesion counts

De-seasoned vitamin D unless otherwise stated. Abbreviations: RRMS: Relapsing Remitting Multiple Sclerosis; CIS: Clinically Isolated Syndrome; C: Caucasian; H: Hispanic; AA: African-American; IQR: Interquartile range; 25(OH)D: 25-Hidroxy-Vitamin D; ref.: reference; EDSS: Expanded Disability Status Scale; RR: Risk or Rate Ratio; HR: Hazard Ratio; IRR: Incidence Rate Ratio; CIR: Cumulative Incidence Rate; OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; NN: Not Needed; NA: Not Applicable; IFN: interferón; GA: glatiramer acetate; Studies: BENEFIT: Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment; CLIMB: Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital; EPIC: Expression/genomics, Proteomics, Imaging, and Clinical; BEYOND: Betaferon Efficacy Yielding Outcomes of a New Dose; OFAMS: Placebo-controlled trial of W-3 fatty acids in MS; STAyCIS; Atorvastatin (Lipitor) Therapy in Patients With Clinically Isolated Syndrome at Risk for Multiple Sclerosis; STMLS: Southern Tasmanian Multiple Sclerosis Longitudinal Study; AusLong: Ausimmune longitudinal study.

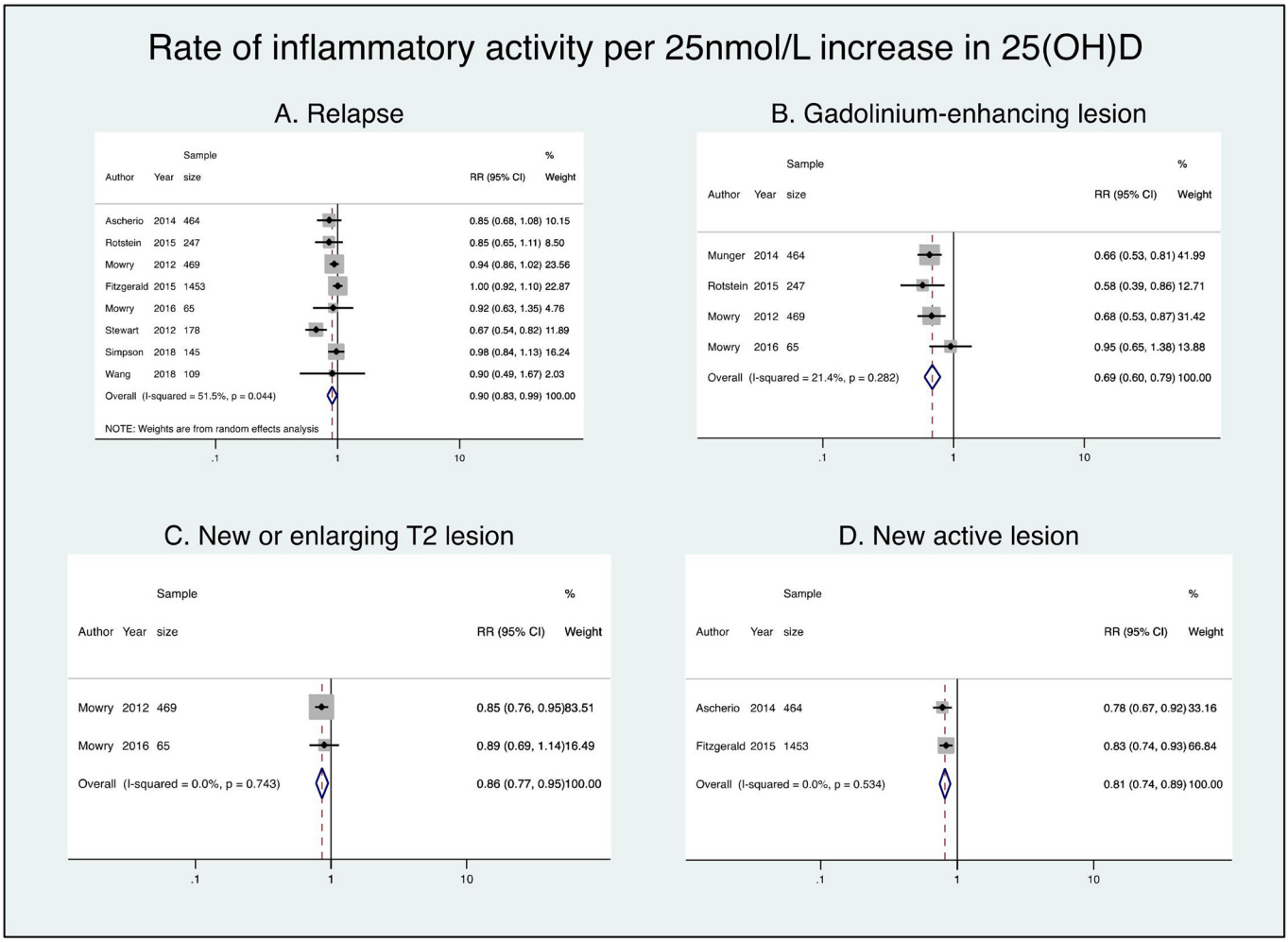

Fig. 2. Rate of new inflammatory activity markers per 25nmol/L increase in serum 25(OH) D levels. Forest plots from quantitative synthesis of the association between serum 25(OH)D levels and rate of new inflammatory activity marker.

studies showed inverse association between serum 25(OH)D levels and disability worsening but only one study reached statistical significance.

3.6. Heterogeneity, study quality, assessments of bias, and sensitivity analyses

To explore the source of heterogeneity of the included studies, sensitivity and subgroup analyses were conducted. We pre-specified the subgroup analysis between serum 25(OH)D levels and MS outcomes according to different types of MS (RRMS and progressive MS) and different NOS(> 4 or ≤ 4). However, the subgroup analyses to evaluate sources of heterogeneity were not applicable because no study recruited patients with progressive MS and all studies were ranked with NOS > 4. We carried out a sensitivity analysis excluding one study at a time, showing that no single study substantially affected the pooled estimates(Appendix B, Figs. B.1 and B.2). We repeated analyses using the original estimates without unit transformation of serum 25(OH)D to test the robustness of the pooled estimates and found similar results (Appendix B, Figs. B.3). Additionally, we defined two *post-hoc* analyses using random-effects meta-regression [17] to evaluate how the pooled estimates changed according to disease duration and length of follow-up. The *post-hoc* analyses revealed neither disease duration nor length of follow-up significantly changed the pooled estimates.

Overall, the quality of the included studies was good (median NOS = 9). Detailed information on the assessment of study quality was provided as supplementary materials (Appendix C). Because of the insufficient number of studies, neither Funnel Plot nor Egger Test [16] could be used to assess publication bias.

4. Discussion

4.1. Main results

In this systematic review and meta-analysis, we found that each 25 nmol/L increase in serum 25(OH)D levels is associated an average 10% decrease in new relapses and a 14–31% reduction in the risk of new radiological inflammatory activity in the middle-aged, predominantly White Caucasian population with early relapsing MS. Relationship between serum 25(OH)D levels and disability worsening remains inconclusive.

4.2. Strengths and limitations

This meta-analysis has some strengths. First, population was homogeneous in terms of demographic and baseline MS-related features, which helped interpretation of the results. Second, most of the studies had an appropriate good quality and low risk of bias. These studies consisted of adequate assessment of exposures and blinded assessment of outcomes that are consistent with the standard care of MS patients.

This meta-analysis also has some caveats. First, the low number of studies in each assessment category prevented us from exploring

publication bias. Second, the population in this meta-analysis only consisted of patients with CIS or early MS and the results should not be applied to progressive MS, which has remarkable differences in radiological inflammatory activity and pathology. Similarly, nearly 90% of the study population were White Caucasians, which limited the applicability of results toward other races and ethnicities. Third, the included studies assessing disability worsening, which is the most relevant outcome in MS, were sparse and heterogeneous. Lastly, we evaluated the association between serum 25(OH)D and new radiological inflammatory activities by baseline serum 25(OH)D level under the assumption that serum 25(OH)D levels were stable throughout the entire follow-up of MS course.

4.3. Applicability, implications for clinical health practice and future research

The Cochrane systematic review and meta-analysis concluded that evidence from current RCT had very low quality and provided inconclusive results [6]. Our meta-analysis included high-quality observational prospective cohort studies and supported that vitamin D might have a modest protective effect on MS course. Findings from this meta-analysis support the current recommendation of routine assessment of serum 25(OH)D levels in patients with MS. Nevertheless, this association cannot be translated to modifying serum 25(OH)D levels is beneficial to MS patients since the number of studies are still limited and publication biases cannot be excluded. Future studies should focus on establishing the guideline of adequate serum 25(OH)D levels in MS patients. The effects of serum 25(OH)D levels in progressive MS and non-White patients deserve further investigation as well.

5. Conclusions

This meta-analysis suggests that serum 25(OH)D levels are associated with a modest decrease in relapse rate and radiological inflammatory activities in patients with relapsing MS at early stage. The association with disability worsening remains inconclusive.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.116668.

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