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Vitamin D status and the risk of multiple sclerosis: A systematic review and meta-analysis

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HIGHLIGHTS

- Vitamin D plays an important role in the development of multiple sclerosis (MS).
- Our study involves 1007 MS cases making the latest meta-analysis ever conducted.
- MS patients had lower mean levels of 25(OH)D than healthy controls.
- No obvious publication biases were observed in Funnel plots.

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ABSTRACT

To estimate the associations between vitamin D status and multiple sclerosis (MS). We searched electronic databases of the human literature in PubMed, EMBASE and the Cochrane Library up to February, 2014 using the following keywords: 'vitamin D' or '25(OH)D' and 'status' or 'deficiency' or 'insufficiency' and 'multiple sclerosis'. A systematic review and meta-analysis were conducted on observational studies that reported the association between blood vitamin D levels and MS. Eleven studies met the inclusion criteria. 1007 patients and 829 controls were included. Results of our meta-analysis show that MS patients had lower mean levels of 25-hydroxyvitamin D [25(OH)D] than healthy controls (weighted mean difference[MD], −14.52, 95% confidence interval [CI], −23.83 to −5.22). There were statistically significant heterogeneity ($P < 0.00001$; $I^2 = 92\%$). The significant heterogeneity may be due to the differences in ethnicity, country, season of blood sampling and age of the participants studied. To sum up, low vitamin D levels are associated with an increased risk of MS.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with a predilection for white matter within the brain, spinal cord and optic nerves, where both genetic and environmental factors are involved in its pathogenesis [6]. Despite the high prevalence of MS and the significant degree of disability experienced by people with MS, the nature of the environmental factors remains largely unclear.

Recently, emerging data suggest that vitamin D may play an important role in the progression of the development of MS [2]. It is well established that the vitamin D endocrine system plays a critical role in calcium homeostasis and bone health [4]. However, in recent decades, the broad range of physiological actions of vitamin D has been increasingly recognized. In addition to its role in proliferation, differentiation and immunomodulation, there is mounting evidence to support an intricate role of vitamin D in brain development and function in health and disease [7,8]. Optimal balance, muscle strength, and innate immunity require sufficient vitamin D levels, and its deficiency is correlated with increasing risk for a range of adverse health outcomes including cardiovascular diseases, stroke, infectious disease and cancer [11,36]. Increasing evidence has shown that individuals with MS have lower levels of 25-hydroxyvitamin (25[OH]D) relative to healthy controls and vitamin D deficiency has been proposed to be linked to MS through multiple mechanisms [23]. There is an increasing interest in a range of actions of vitamin D and low vitamin D status play an important role in the development or pathogenesis of MS [26,30].

The objective of this systematic review was to quantify precisely the nature and magnitude of the associations between vitamin D status and risk of MS using a meta-analytic approach. Our

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meta-analysis systematically combines evidence on all relevant long-term prospective studies conducted in general populations to date, which involves 1007 MS cases making this the latest meta-analysis of prospective associations ever conducted.

2. Methods

We followed the guidelines for meta-analysis of observational studies in epidemiology (MOOSE) [33].

2.1. Data sources

Our electronic literature searches targeted studies on vitamin D status and MS. We searched the human literature in PubMed, EMBASE and the Cochrane Library up to February 2014 for articles on levels of circulating 25-hydroxyvitamin D [25(OH)D] levels and the risk of MS. The following keywords were used in the search: 'vitamin D' or '25(OH)D' and 'status' or 'deficiency' or 'insufficiency'. Relevant studies were further sought manually in the reference lists of primary papers and reviews.

2.2. Study selection

Full length articles of studies evaluating vitamin D status and MS were scrutinized and subsequently selected if they fulfilled the following inclusion criteria: (a) study design was observational study; (b) study population was MS without pre-existing chronic disease; (c) contained relevant data to calculate the effect size; (d) met the predefined methodological quality assessment criteria for non-randomized observational studies (Box 1) [7]. Studies were excluded: (a) if they were reviews, case reports, letters or comments; (b) vitamin D levels were measured using non-blood biological samples such as amniotic fluid or urine; (c) vitamin D level that was measured was the active metabolite 1.25 dihydroxyvitamin D [1,25$(OH)_2$D] only; (d) incomplete or conflicting result data.

Studies were selected in a two stage process. Two reviewers (SRD and ZL) independently scrutinized the electronic literature searches and obtained full-length articles of all citations that met the predefined selection criteria. Final inclusion or exclusion decisions were then made after we read these articles. In cases of duplicate publications, we selected the most complete version. We resolved any disagreements through consensus or arbitration by a third reviewer (SB). We identified 694 articles and after screening the abstracts, we read 37 papers. Eleven primary studies met the inclusion criteria (details see Fig. 1).

We evaluated the methodological quality of each study based on the study design, selection of participants, comparability of groups, definition of outcomes, ascertainment of outcomes and sample size, using the assessment criteria for non-randomized observational studies adapted from Duckitt and Harrington [9]. We excluded any study with a score of zero in any of the 6 items or a total score <7 out of 10 maximal points. Quality scores of all included studies are summarized in Table 1.

2.3. Tabulation and integration

The following information was extracted from the study reports: the first author's last name, year of publication, country of origin, study design, sample size, gender, season of blood sampling, assay method, mean age, scores of Expanded Disability Status Scale (EDSS), adjusted odds ratio and the potential confounding variables in the adjustments. Two authors extracted the data independently and in duplicate. Discrepancies were resolved through discussion to achieve a consensus.

Box 1: Quality assessment of observational studies (total 10 points).*

1. Selection of participants (1/0)
Cohort studies (1/0)
Selected cohort was representative of the general population (population-based studies) or target catchment population (hospital-based studies) (1)
Cohort was a selected unrepresentative group (0)
Case control studies (1/0)
Cases and controls drawn from the same population (1)
Cases and controls drawn from different sources or the selection of groups (0)

2. Comparability of groups (2/0)
No significant differences between the groups reported in terms of age, plurality, smoking, history of preterm birth, pre-eclampsia or gestational diabetes, pre-existing medical conditions were explicitly reported, or these differences were adjusted for (2)
Differences between groups were not examined (1)
Groups differed and no adjustment results provided (0)

3. Definition of outcomes (2/0)
Definition of outcomes
Referenced or standard definition (2)
Explicit non-standard definition (1)
Unspecified or unacceptable definition (0)

4. Ascertainment of outcomes (2/0)
How the diagnosis was made
Prospectively diagnosed or review of notes/hospital discharge records (2)
Retrospective chart review or database coding (1)
Process not described (0)

5. Sample size (1/0)
≥200 participants in a cohort study; ≥50 participants in either group (case/control) (1)
100 ≤ participants < 200 in a cohort; 25 ≤ participants < 50 in either group (case/control) (0.5)
Participants <100 or total number of events <10 in a cohort; participants <25 in either group (case/control) (0)

6. Study design (2/0)
Prospective cohort or nested case-control within a prospective cohort (2)
Cross-sectional, case-control or retrospective cohort (1)
Not described or poorly designed (0)

Exclusion: score zero in any item (1–6) or a total score <7 out of 10 maximal points

*A score based quality assessment criteria for non-randomized observational studies adapted from Duckitt and Harrington [9].

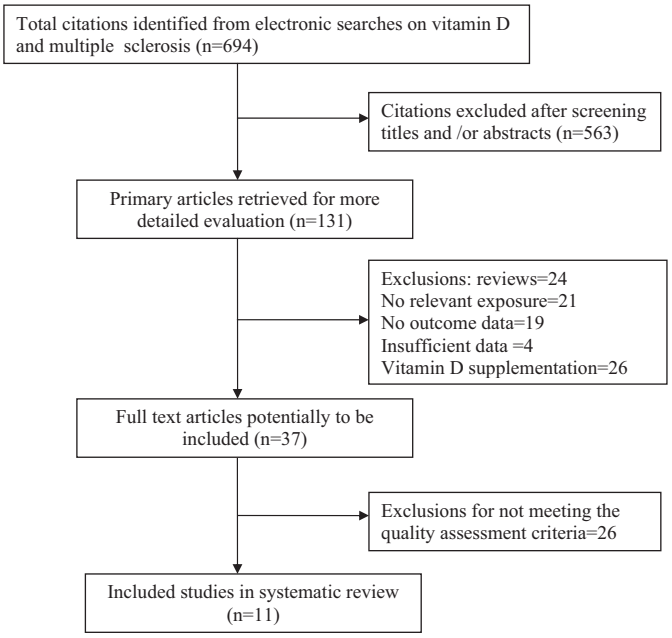

Fig. 1. Flow chart of study selection process in a systematic review.