Multiple Sclerosis and Related Disorders 49 (2021) 102760

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Self-reported use of vitamin D supplements is associated with higher physical quality of life scores in multiple sclerosis

Steve Simpson-Yap [a,b,*], Pia Jelinek [a,c], Tracey Weiland [a], Nupur Nag [a], Sandra Neate [a], George Jelinek [a]

[a] Neuroepidemiology Unit, Melbourne School of Population & Global Health, The University of Melbourne, Melbourne, Australia
[b] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
[c] Sir Charles Gairdner Hospital, Nedlands, Australia

ARTICLE INFO

Keywords:
Multiple sclerosis
Epidemiology
Vitamin D
Quality of life

ABSTRACT

Background: Sun exposure and vitamin D, including intake and serum levels, have been associated with reduced risk of MS onset and less progression and may affect quality of life (QoL). We investigated the prospective relationship of these factors with QoL from baseline to 2.5 years' follow-up, in an international cohort of people with MS.

Methods: Data derive from the HOLISM international cohort. Sun exposure and vitamin D supplement use were queried at both timepoints. QoL was assessed by MSQOL-54, estimating physical and mental health QoL composite scores. Characteristics of QoL were assessed by linear regression, adjusted for age, sex, socioeconomic status, treated comorbidity number, MS type, disability, clinically significant fatigue, prescription antidepressant medication use, and ongoing relapse symptoms, and baseline QoL score, as appropriate, estimating adjusted coefficients (aβ).

Results: At 2.5-year review, QoL scores were higher among those reporting taking vitamin D supplements (physical: aβ=3.58, 95%CI=1.35-5.80; mental: aβ=3.08, 95%CI=0.72-5.44), particularly average daily dose over 5,000IU/d. Baseline-reported vitamin D supplementation was associated with greater increase in physical (aβ=1.02, 95%CI=0.22-1.81), but not mental QoL (aβ=0.11, 95%CI=-1.00-1.23). Sun exposure was cross-sectionally associated with higher QoL scores at follow-up but was not associated with change in QoL.

Conclusions: Self-reported vitamin D supplement use was cross-sectionally associated with higher physical and mental QoL, but prospectively only with increased physical QoL.

1. Background

Multiple sclerosis (MS) is a progressive demyelinating condition of the central nervous system. Symptoms include motor, sensory and cognitive dysfunction, all of which have a significant impact on quality of life (QoL). QoL is difficult to measure compared to more objective parameters like disability. A commonly used and validated tool for assessing QoL in people with MS is the MSQOL-54, a 54-question instrument which combines the SF-36 (Ware et al., 1993) with 18 MS-specific questions (Vickrey et al., 1995). From the MSQOL-54, two composite scores – physical health (P-QoL) and mental health (M-QoL) – can be derived, each comprising several subdomains.

Clinical characteristics like disability, fatigue, and number of comorbidities have been associated with reduced QoL (Marrie and Horwitz, 2010; Naci et al., 2010; Nourbakhsh et al., 2016; Ochoa-Morales et al., 2019). A growing dimension of research concerns the role of modifiable lifestyle factors. Our group has examined characteristics of QoL in participants from the Health Outcomes and Lifestyle In a Sample of people with Multiple sclerosis (HOLISM) cohort (Jelinek et al., 2016; Jelinek et al., 2013; Jelinek et al., 2015; Leong et al., 2018; Marck et al., 2014; O'Kearney et al., 2019). We previously showed that latitude, self-reported vitamin D supplement use, and higher sun exposure were associated with higher P-QoL and M-QoL. Of these, only self-reported vitamin D supplement use was independently associated after adjustment. Participants reporting consuming >5,000IU/d vitamin D had over 8% higher P-QoL and M-QoL scores compared to those not reporting vitamin D supplement use (Jelinek et al., 2015). However, as a cross-sectional study, causal directionality cannot be inferred. For this,

* Corresponding author at: Neuroepidemiology Unit, Melbourne School of Population & Global Health, The University of Melbourne, Carlton, VIC, Australia.
E-mail address: steve.simpsonyap@unimelb.edu.au (S. Simpson-Yap).

https://doi.org/10.1016/j.msard.2021.102760
Received 9 May 2020; Received in revised form 25 September 2020; Accepted 8 January 2021
Available online 16 January 2021
2211-0348/© 2021 Elsevier B.V. All rights reserved.

prospective analyses must be undertaken. Sun exposure and vitamin D levels have been prospectively associated with reducing the risk of onset and progression of MS (Ascherio et al., 2010), and there is a well-described relationship between latitude and the prevalence and incidence of MS (Alonso and Hernan, 2008; Simpson et al., 2019) and with age of onset (Tao et al., 2016). The prospective relationship of these factors with QoL has been less studied, however. Therefore, we here aimed to replicate our previous cross-sectional findings and to undertake a prospective analysis of the relationship of latitude, self-reported vitamin D supplement use, and sun exposure with QoL over 2.5 years in a sample of people with MS. Our *a priori* hypotheses were that lower latitude, self-reported vitamin D supplement use, and higher sun exposure would be cross-sectionally associated with higher QoL scores at follow-up, and baseline measures would predict lack of worsening in QoL scores, both composites and subdomains.

2. Methods

2.1. Participants and data collection

Participants were enrolled in the HOLISM study for which methodology has been described previously (Hadgkiss et al., 2013; Weiland et al., 2018a). Participants were recruited via online platforms, and SurveyMonkey® was used to provide respondents with a participant information sheet and questionnaire. Inclusion criteria required participants be at least 18yo and self-reporting a physician diagnosis of MS. The University of Melbourne Health Sciences Human Ethics Sub-Committee provided ethical approval (HESC 1545102); all participants provided informed consent.

2.2. Exposures & covariates

Participants completed questionnaires at baseline and 2.5-year timepoints. A range of demographic, lifestyle, and clinical parameters was measured (Hadgkiss et al., 2013; Weiland et al., 2018). Education (none, primary, secondary, trade school, university, graduate school), employment (full and part-time employment, student, stay-at-home carer, unemployed, retired), marital status (single, married, de facto, separated, divorced, widowed), and numbers of persons in the immediate social support network were queried at each review. Perceived relative socioeconomic status (PRSES) was queried at follow-up, asking participants to rate their income relative to their peers, specifically, "If you compare yourself to others in your country, and imagine the poorest people on the first step and the richest people on the ninth step, where would you place yourself today?", options ranging from poorest to richest (Howe et al., 2011). This value reported at 2.5-year review was assumed to be the same at baseline review to allow its inclusion in multivariable models for QoL change analyses. Body mass index (BMI) was calculated from participant-reported height (metres) and weight (kilograms) using the function, weight/height^2. Disability was assessed using the Patient-Determined Disease Steps (PDDS) scale (Hohol et al., 1995), from which the disease duration-adjusted Patient-derived Multiple Sclerosis Severity Score (P-MSSS) was calculated (Kister et al., 2013). Fatigue was assessed using the Fatigue Severity Scale (FSS), clinically significant fatigue defined as mean FSS>5.0 (Krupp et al., 1989). Depression risk was assessed using the Patient Health Questionnaire-2 (PHQ-2), a score>2 indicating depression risk (Kroenke et al., 2003). Doctor-diagnosed relapse numbers in the preceding 12 and 60 months were queried, the latter expressed as an annualised rate. In addition to relapse rate in the preceding intervals, participants were queried as to whether they were experiencing ongoing symptoms from a relapse in the preceding 30 days. This was accounted for in all models since ongoing relapse symptoms can impact on the reporting of QoL scores and other clinical measures. MS type and number of treated comorbidities using the Self-administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003) were queried at baseline. In addition, prescription medication use, including immunomodulatory, antidepressant, and anxiolytic-sedative medications, was queried at each timepoint.

Vitamin D-containing supplement use was queried at each timepoint, as well as frequency and dose; those reporting not taking vitamin D supplements were assigned frequency and dose of 0. From this, average daily dose per week was estimated by multiplying frequency and dose and dividing by 7; again, those not taking vitamin D supplements were assigned an average daily dose of 0. At both baseline and follow-up, participants were asked about their frequency per week of adequate sun exposure, specifically "In the last 12 months, about how often have you got adequate sun exposure (10-15 minutes of sunlight on a day with UV index of 7 (more or less if the UV index is lower or higher))?", and whether they sought sun exposure to increase their vitamin D levels, specifically "Do you intentionally get sun exposure to raise your vitamin D level?". At follow-up, participants were asked about their typical frequency and duration per week of sun exposure in summer and winter. Participants were also queried as to the amount of clothing they wore and how much of their skin was covered or exposed, in summer and in winter, as well as their frequency of sunscreen use, using measures in the Ausimmune Study (Lucas et al., 2011). Frequency and duration in the sun were used to estimate average daily duration of sun exposure per week in each season, multiplying frequency times duration. Erythemally weighted ambient UVR at participant residence (latitude/longitude) was derived from TOMS satellite data (NASA, 2006). Average daily sun exposure was multiplied against the ambient UVR in each season to estimate summer and winter UV loads. That is, in summer and winter, the self-reported hours per day in the sun were multiplied against the seasonal ambient UVR available at the latitude/longitude of participant residence. Participant skin colour was queried at 2.5-year review: participants self-reporting their skin colour using six options ranging from very light to dark.

2.3. Outcome

Our primary outcome of interest was QoL, measured by MSQOL-54 (Vickrey et al., 1995), from which composite scores for P-QoL and M-QoL were derived. Physical health, health perceptions, energy, role limitations due to physical problems, pain, sexual function, social function, and health distress were combined to estimate the P-QoL composite score (Vickrey et al., 1995). Health distress, overall quality of life, emotional wellbeing, role limitations due to emotional problems, and cognitive function were combined to estimate the M-QoL composite score (Vickrey et al., 1995). Persons missing some number of questions within subdomains were imputed with the mean of the non-missing questions comprising that subdomain (Jelinek et al., 2016). All scores were scaled out of 100%.

2.4. Statistical analyses

Cross-sectional characteristics of QoL composite scores at follow-up were assessed by linear regression since QoL composite scores were continuous scores out of 100%. Due to marked heteroskedasticity, M-QoL was transformed by a theta coefficient identified by Box-Cox regression and the transformed M-QoL evaluated by linear regression; however, all coefficients are back-transformed at the mean of model covariates. All models were adjusted for whether participants were experiencing ongoing symptoms from a recent relapse. Models were further adjusted for age, sex, MS type, P-MSSS, clinically significant fatigue, baseline treated comorbidity number, PRSES, and antidepressant medication use. For all analyses, QoL scores were the dependent variables and primary predictors (latitude, sun exposure and sun-related parameters, and vitamin D supplement use) were the independent variables, along with other model covariates.

Annualised change in QoL composite and subdomain scores were estimated as the difference in score between baseline and 2.5-year

reviews, divided by the intervening duration. Baseline predictors of annualised QoL change were evaluated by linear regression, adjusted for whether participants were experiencing ongoing symptoms from a recent relapse at baseline and/or follow-up and for baseline QoL score. Models were further adjusted for age, sex, MS type, baseline P-MSSS, baseline clinically significant fatigue, baseline treated comorbidity number, PRSES, and baseline antidepressant medication use.

Where baseline covariates were associated with change in total composite scores, the relationships with subdomains of that composite score were evaluated.

Note that for analyses of duration of vitamin D supplement use, these are constrained to those who reported using vitamin D supplements.

All analyses were conducted in STATA/SE 15.0 (StataCorp, College Park, USA).

3. Results

3.1. Sample characteristics

The analysis sample comprised 1,401 participants who participated at both timepoints (Table 1). 1,155 (82.4%) provided data for P-QoL and 1,316 (93.9%) for M-QoL composite scores. The average P-QoL at baseline was 63.36 (IQR: 45.53-80.13), essentially unchanged at follow-up (median=64.36; IQR: 45.27-81.80). The median M-QoL at baseline was 76.10; IQR: 57.95-85.43, essentially unchanged at follow-up (median=76.13; IQR: 55.36-86.96). Subdomains were largely unchanged between baseline and 2.5-year review; only physical health subdomain significantly decreased and health distress significantly increased.

At both timepoints, the cohort predominantly resided at latitudes over 34°, and 80% reported taking vitamin D supplements. Participants significantly increased sun exposure between baseline and 2.5-year review, changing from infrequent sun exposure to 3-4 and 5-6 times per week. The proportions seeking sun exposure to increase their vitamin D were constant at 64.6%, while the proportion taking immunomodulatory medication decreased slightly. The median P-MSSS decreased by 0.4 but other clinical characteristics did not materially differ.

Comparing participants with and without QoL composite scores to allow assessment of bias (Supplemental Table 1), those with data were significantly more likely to be using vitamin D supplements and taking immunomodulatory medications. A greater proportion of those with P-QoL data were male, smaller proportions had comorbidities, secondary-progressive MS (SPMS), or primary progressive MS (PPMS), and the median P-MSSS was 1.2 points lower. For M-QoL, none of the covariates consistently differed between those with and without data. No P-QoL subdomains significantly differed between those with and without M-QoL data. Of the M-QoL subdomains, only overall QoL subdomain was higher among those with P-QoL data; other scores did not differ.

3.2. Cross-sectional characteristics of P-QoL and M-QoL at follow-up

P-QoL and M-QoL were significantly higher among participants of higher education, who were employed, of higher PRSES, and with larger social support networks; and lower among participants with progressive MS types, greater disability, clinically significant fatigue, depression risk, or taking antidepressant or anxiolytic/sedative medications (Supplemental Table 2). On adjustment for age, sex, MS type, P-MSSS, clinically significant fatigue, baseline treated comorbidity number, PRSES, and antidepressant medication use, only the associations of PRSES, support network size, comorbidity number, MS type, disability, fatigue, depression risk, and antidepressant and anxiolytic medication use persisted, while employment and disease duration persisted for P-QoL and education for M-QoL.

Neither QoL composite score significantly varied by latitude, though on adjustment those living at latitudes over 42° had significantly lower physical QoL (Table 2). Compared to those from the southern

Table 1
Cohort characteristics at baseline & 2.5-yr follow-up.

	Baseline[a](n=1,401)	2.5-yr (n=1,401)
Latitude of residence		
≤34°	292 (20.9%)	292 (20.8%)
>34-42°	566 (40.5%)	569 (40.6%)
≥42°	540 (38.6%)	540 (38.5%)
(Missing)	(3 (0.2%))	(0 (0%))
Taking a vitamin D supplement?		
No	271 (19.3%)	271 (19.3%)
Yes	1,130 (80.7%)	1,130 (80.7%)
How often per week in preceding 12 months have you got adequate sun exposure at follow-up?		
Never/<once	392 (31.8%)	298 (25.4%)
1-2 times	368 (29.9%)	320 (27.2%)
3-4 times	258 (20.9%)	306 (26.0%)[‡]
5-6 times	133 (10.8%)	169 (14.4%)[‡]
Every day	81 (6.6%)	82 (7.0%)
(Missing)	(169 (12.1%))	((226 (16.1%))[‡]
Do you try to get sun exposure to increase vitamin D levels?		
No	405 (30.5%)	458 (35.5%)
Yes	921 (69.5%)	834 (64.6%)
	(75 (5.4%))	(109 (7.8%))
Sex		
Male	241 (17.3%)	
Female	1,152 (82.7%)	
(Missing)	(8 (0.6%))	
Level of education completed		
Up to secondary school	292 (21.0%)	232 (16.8%)
Vocational school	203 (14.6%)	222 (16.1%)[†]
Bachelor's degree	533 (38.3%)	521 (37.7%)
Post-graduate study	364 (26.2%)	406 (29.4%)[†]
(Missing)	(9 (0.6%))	(20 (1.4%))[†]
Smoke tobacco?		
Never	707 (52.7%)	677 (50.9%)
Ex-smoker	520 (38.8%)	551 (41.4%)
Current smoker	114 (8.5%)	102 (7.7%)
(Missing)	(60 (4.3%))	(71 (5.1%))
MS-related characteristics		
Type of MS at completion of survey		
Benign/RRMS	939 (68.0%)	
SPMS	144 (10.4%)	
PPMS	100 (7.2%)	
PRMS	18 (1.3%)	
Unsure/other	181 (13.1%)	
(Missing)	(19 (1.4%))	
Treated comorbidity number		
0	516 (36.8%)	
1	392 (28.0%)	
2	270 (19.3%)	
≥3	223 (15.9%)	
Taking any of the 11 specified immunomodulatory medications?[b]		
No	747 (53.3%)	812 (58.0%)
Yes	654 (46.7%)	589 (42.0%)[†]
	Mean (SD; range)	
Annualised change in MSQOL-54 physical health composite score		0.2 (5.1; -21.6-23.3)
Annualised change in MSQOL-54 mental health composite score		0.1 (6.7; -30.7-35.7)
Age	45.9 (10.5; 17.0-79.0)	48.5[‡] (10.5; 20.1-81.5)
BMI	25.2 (5.9; 15.4-57.7)	25.4 (6.0; 14.4-64.1)
	Median (IQR)	
P-MSSS	2.1 (0.6-4.8)	1.7[‡] (0.5-4.6)
Disease duration since symptom onset, years	11.4 (5.4-20.2)	13.9[‡] (8.0-22.9)

(continued on next page)

Table 1 (*continued*)

	Baseline[a](n=1,401)	2.5-yr (n=1,401)
Doctor-diagnosed relapse rate in previous 5 years	0.4 (0-0.8)	0.2[‡] (0-0.6)
FSS	4.7 (3.0-6.0)	4.7 (2.9-6.0)
MSQOL-54 physical health composite score	63.36 (45.53-80.13)	64.36 (45.27-81.80)
MSQOL-54 mental health composite score	76.10 (57.95-85.43)	76.13 (55.36-86.96)

Differences between categorical variables assessed by multinomial logistic regression. Differences between normally distributed continuous terms assessed by two-tailed t-test. Differences between non-normally distributed continuous terms assessed by Kruskal-Wallis rank test.

[†] = $p<0.05$ for differences between baseline and 2.5-yr reviews.

[‡] = $p<0.001$ for differences between baseline and 2.5-yr reviews.Abbreviations: BMI = Body mass index; FSS = Fatigue Severity Scale; IQR = Interquartile range; P-MSSS = Patient Determined Multiple Sclerosis Severity Score; PPMS = Primary progressive multiple sclerosis; PRMS = Progressive-relapsing multiple sclerosis; QOL = Quality of Life; RRMS = Relapsing-remitting multiple sclerosis; SD = Standard deviation; SPMS = Secondary progressive multiple sclerosis.

[a] Data is only from baseline participants who also completed 2.5-year data.

[b] Immunomodulatory medications queried include interferon-β-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide, and natalizumab.

hemisphere, participants from the northern hemisphere had 3.6% lower P-QoL scores, persisting on adjustment, while M-QoL was 1.9% lower. Those reporting taking vitamin D supplements had 6.2% higher P-QoL and 6.3% higher M-QoL scores, which attenuated by roughly half on adjustment. Similar results were seen for self-reported frequency and dose of vitamin D supplementation, and average daily supplement dose (the measure combining frequency and dose to realise an average daily dose) above 1,000IU/d was associated with 6-9% higher P-QoL and M-QoL scores, attenuating on adjustment.

Reported "adequate" sun exposure showed no evidence of consistent or dose-dependent associations with QoL scores, and what associations that were present were abrogated on adjustment. Those seeking sun exposure to increase their vitamin D had significantly higher P-QoL and M-QoL, but these associations were no longer present on adjustment. Average sun exposure duration and UV loads in summer and winter showed more consistent associations with both QoL scores, though attenuating on adjustment for P-QoL and essentially abrogated for M-QoL. The amount of skin coverage for summer sun-related attire showed reciprocal associations with QoL scores: those wearing exposing clothes more often had higher QoL scores, while more frequently wearing concealing clothes showed an inverse trend with QoL, though only the positive association of exposing clothes with QoL remained on adjustment. Sun-related attire in winter was not associated with QoL scores. Sunscreen use and skin colour were not associated with QoL scores (data not shown).

3.3. Predictors of change in P-QoL and M-QoL composite scores, baseline to 2.5-year review

The average change in P-QoL composite score was 0.6 (SD=12.8), while the average change in M-QoL composite score was 0.2 (SD=16.9). Neither change in score significantly differed by latitude. Baseline self-reported vitamin D supplement use, particularly higher daily dose (Fig. 1) and average daily dose (Fig. 2), was associated with greater increases in P-QoL, persisting on adjustment. For M-QoL, there were less consistent associations of vitamin D supplement use. Those reporting daily adequate sun exposure at baseline had reduced P-QoL score, though other frequencies of sufficient sun exposure were not associated with either P-QoL or M-QoL change. Seeking sun exposure to increase vitamin D levels was not associated with P-QoL or M-QoL change (Table 3).

3.4. Vitamin D supplement-related predictors of change in P-QoL subdomains, baseline to 2.5-year review

Baseline self-reported vitamin D supplement use, particularly higher dose (both daily and average daily dose) and greater frequency, was associated with significantly higher P-QoL subdomain scores, most consistently for physical health, health perceptions, pain, and sexual function subdomains (Supplemental Tables 3-4).

No baseline parameters significantly predicted M-QoL composite score, so no examination of subdomains was undertaken.

4. Discussion

Through analysing data from a large international sample of people with MS followed over 2.5 years, we found that self-reported vitamin D supplement use, sun exposure, and sun-related attire were cross-sectionally associated with higher P-QoL and M-QoL, in keeping with our baseline results (Jelinek et al., 2015), though the cross-sectional nature of these analyses and the potential for reverse causality precludes causal interpretation. Prospectively, self-reported vitamin D supplement use, specifically intake over 5,000 IU/day, was associated with an increase in P-QoL and M-QoL. Sun exposure measures at baseline were not associated with change in QoL; however, this may reflect a poorer measurement of sun exposure at baseline.

4.1. Vitamin D supplementation

Our findings show self-reported vitamin D supplement use was associated with higher QoL at 2.5-year review, replicating our baseline results (Jelinek et al., 2015), while baseline self-reported vitamin D supplement use was prospectively associated with change in P-QoL and M-QoL scores. The evidence for a role of vitamin D in MS is mixed, with observational studies showing a generally consistent relationship between lower vitamin D levels and increased MS risk and progression (Duan et al., 2014; Martinez-Lapiscina et al., 2020), though randomised controlled trials (RCT) of vitamin D supplement use have generally found no impact on progression (Zheng et al., 2018). Aside from our baseline study (Jelinek et al., 2015), however, there is a comparative paucity of literature on the impact of vitamin D supplement use on QoL. One RCT found that P-QoL improved by 5.4% in people with MS after taking high-dose vitamin D (50,000IU every five days) for three months relative to placebo (Ashtari et al., 2016). Similarly, a study showed people with MS, deficient in vitamin D, improved QoL through supplementation, persisting over 12 months (Beckmann et al., 2020). Conversely, a study comparing 4,370 vs 800 IU/day vitamin D supplement use in 45 people with RRMS found no difference in QoL over a year (Golan et al., 2013). More recently, a study of 149 people with MS, of whom 90% were vitamin D deficient, supplement use led to increased QoL over 12 months (Beckmann et al., 2020). The conflicting results may reflect differences in dose, with higher doses being required to realise a meaningful effect. Additionally, supplement use may only be effective if people are deficient, as found for vitamin D supplement use to reduce infection risk (Martineau et al., 2017).

Amongst the P-QoL subdomains analysed, baseline self-reported vitamin D supplement use was associated with increase in health perceptions, but less with change in social function. This result substantiates our previous results where self-reported vitamin D supplement use was associated with higher health perceptions score (Jelinek et al., 2015). Higher self-reported vitamin D supplement dosage showed a strong dose-dependency. This provides strong evidence that the health perceptions subdomain is significantly improved by vitamin D supplementation. In addition, those participants taking vitamin D supplements at baseline had significant increases in the physical health,

Table 2
Determinants of MSQOL-54 Physical and mental health QoL composite scores at 2.5-yr review, estimating β (95% CI). All determinants measured at 2.5-year review or extrapolated from baseline.

	P-QoL composite score			Mental health QoL composite score		
	n (%)	Model 1[a]	Model 2[b]	n (%)	Model 1[a]	Model 2[b]
Latitude of residence						
≤34°						
>34-42°	247 (21.4%)	0.00 [Reference]	0.00 [Reference]	275 (20.9%)	0.00 [Reference]	0.00 [Reference]
≥42°	468 (40.5%)	-0.49 (-3.78, 2.81)	-0.30 (-2.41, 1.82)	535 (40.7%)	0.70 (-1.84, 3.25)	0.66 (-1.50, 2.81)
Trend:	440 (38.1%)	-2.26 (-5.60, 1.07)	**-2.25 (-4.42, -0.09)**	506 (38.5%)	-1.45 (-4.04, 1.15)	-1.51 (-3.74, 0.71)
		p=0.15	***p=0.025***		*p=0.17*	*p=0.10*
Hemisphere						
Southern						
Northern	471 (40.8%)	0.00 [Reference]	0.00 [Reference]	555 (42.2%)	0.00 [Reference]	0.00 [Reference]
	684 (59.2%)	**-3.63 (-6.13, -1.13)**	**-3.21 (-4.84, -1.57)**	761 (57.8%)	-1.91 (-3.83, 0.01)	**-1.75 (-3.41, -0.10)**
		p=0.004	***p<0.001***		*p=0.052*	***p=0.038***
Taking a vitamin D supplement at follow-up?						
No	186 (16.1%)	0.00 [Reference]	0.00 [Reference]	206 (15.7%)	0.00 [Reference]	0.00 [Reference]
Yes	969 (83.9%)	**6.15 (2.81, 9.49)**	**3.58 (1.35, 5.80)**	1,110 (84.4%)	**6.28 (3.52, 9.03)**	**3.08 (0.72, 5.44)**
		p<0.001	***p=0.002***		***p<0.001***	***p=0.011***
Vitamin D supplement dose, IU/d						
None	186 (16.4%)	0.00 [Reference]	0.00 [Reference]	206 (16.0%)	0.00 [Reference]	0.00 [Reference]
<2000	125 (11.0%)	1.54 (-3.26, 6.33)	1.51 (-1.62, 4.65)	139 (10.8%)	2.44 (-1.49, 6.38)	0.10 (-3.22, 3.43)
2,000-5,000	193 (17.0%)	4.07 (-0.19, 8.33)	**3.18 (0.36, 6.00)**	226 (17.5%)	**6.42 (3.03, 9.81)**	**4.56 (1.70, 7.43)**
≥5,000	632 (55.6%)	**7.97 (4.50, 11.44)**	**4.01 (1.68, 6.33)**	720 (55.8%)	**7.20 (4.36, 10.05)**	**3.12 (0.68, 5.56)**
Trend:		***p<0.001***	***p<0.001***		***p<0.001***	***p=0.004***
Frequency of vitamin D supplement usage						
Never	186 (16.5%)	0.00 [Reference]	0.00 [Reference]	206 (16.1%)	0.00 [Reference]	0.00 [Reference]
≤3/week	163 (14.5%)	**8.64 (4.19, 13.09)**	**3.69 (0.74, 6.64)**	189 (14.8%)	**5.31 (1.73, 8.89)**	1.03 (-2.07, 4.12)
4-6/week	144 (12.8%)	**9.00 (4.37, 13.62)**	**4.02 (0.96, 7.08)**	160 (12.5%)	**7.07 (3.37, 10.78)**	3.05 (-0.14, 6.25)
Daily	633 (56.2%)	**4.95 (1.48, 8.41)**	**3.41 (1.08, 5.75)**	723 (56.6%)	**6.42 (3.56, 9.28)**	**3.48 (1.02, 5.94)**
Trend:		*p=0.15*	***p=0.032***		***p<0.001***	***p=0.002***
Average daily Vitamin D supplement dose, IU/d						
None	193 (17.3%)	0.00 [Reference]	0.00 [Reference]	216 (17.0%)	0.00 [Reference]	0.00 [Reference]
>0-1,000	147 (13.2%)	2.98 (-1.56, 7.53)	1.85 (-1.14, 4.83)	162 (12.8%)	3.43 (-0.30, 7.15)	0.48 (-2.68, 3.65)
>1,000-3,000	200 (17.9%)	**8.17 (3.97, 12.36)**	**4.14 (1.37, 6.90)**	232 (18.3%)	**7.96 (4.64, 11.29)**	**4.34 (1.51, 7.17)**
>3,000-5,000	330 (29.5%)	**5.80 (2.03, 9.57)**	**3.44 (0.92, 5.97)**	375 (29.6%)	**5.87 (2.81, 8.94)**	2.32 (-0.31, 4.95)
>5,000-500,000	248 (22.2%)	**8.35 (4.37, 12.34)**	**3.76 (1.10, 6.42)**	283 (22.3%)	**8.86 (5.69, 12.04)**	**4.74 (2.01, 7.47)**
Trend:		***p<0.001***	***p=0.006***		***p<0.001***	***p=0.001***
Duration taking vitamin D supplement usage (years)[c]						
<2	182 (18.8%)	0.00 [Reference]	0.00 [Reference]	200 (18.0%)	0.00 [Reference]	0.00 [Reference]
2 - <3	213 (22.0%)	3.65 (-0.51, 7.81)	0.99 (-1.70, 3.68)	238 (21.5%)	2.88 (-0.33, 6.09)	1.49 (-1.26, 4.24)
3 - <5	340 (35.1%)	**5.28 (1.50, 9.06)**	**3.25 (0.79, 5.71)**	384 (34.6%)	**3.54 (0.62, 6.46)**	1.94 (-0.56, 4.44)
≥5	234 (24.2%)	2.81 (-1.27, 6.89)	2.47 (-0.24, 5.17)	287 (25.9%)	**3.21 (0.12, 6.29)**	2.53 (-0.16, 5.22)
Trend:		*p=0.13*	***p=0.020***		***p=0.045***	*p=0.064*
How often per week in preceding 12 months have you got adequate sun exposure at follow-up?						
Never	250 (24.6%)	0.00 [Reference]	0.00 [Reference]	296 (25.6%)	0.00 [Reference]	0.00 [Reference]
1-2 times	289 (28.4%)	3.31 (-0.22, 6.83)	1.37 (-0.94, 3.69)	314 (27.2%)	2.15 (-0.63, 4.93)	1.36 (-1.00, 3.72)
3-4 times	264 (25.9%)	**7.99 (4.39, 11.59)**	1.44 (-0.96, 3.83)	300 (26.0%)	**4.69 (1.93, 7.45)**	1.81 (-0.58, 4.20)
5-6 times	143 (14.1%)	**7.77 (3.49, 12.05)**	1.15 (-1.69, 3.99)	163 (14.1%)	**5.20 (1.96, 8.45)**	1.22 (-1.64, 4.07)
Every day	72 (7.1%)	-0.02 (-5.48, 5.43)	-1.74 (-5.36, 1.89)	82 (7.1%)	-3.49 (-8.00, 1.02)	-2.88 (-6.68, 0.92)
Trend:		***p=0.006***	*p=0.83*		*p=0.17*	*p=0.71*
Do you try to get sun exposure to increase vitamin D levels?						
No	392 (35.2%)	0.00 [Reference]	0.00 [Reference]	488 (35.3%)	0.00 [Reference]	0.00 [Reference]
Yes	722 (64.85)	**4.99 (2.38, 7.59)**	1.46 (-0.25, 3.17)	822 (64.7%)	**3.01 (0.71, 5.31)**	0.92 (-0.80, 2.64)
		p<0.001	*p=0.094*		***p=0.010***	*p=0.29*
Average duration per week in sun in SUMMER, minutes						
0-60	211 (18.9%)	0.00 [Reference]	0.00 [Reference]	251 (19.8%)	0.00 [Reference]	0.00 [Reference]
>60-120	218 (19.6%)	**5.82 (1.85, 9.79)**	0.55 (-2.07, 3.17)	254 (20.1%)	2.76 (-0.39, 5.90)	-0.08 (-2.72, 2.57)
>120-240	274 (24.6%)	**7.92 (4.15, 11.69)**	1.50 (-1.02, 4.01)	300 (23.7%)	**5.61 (2.63, 8.59)**	2.43 (-0.10, 4.95)
>240-360	140 (12.6%)	**11.04 (6.55, 15.53)**	1.83 (-1.16, 4.81)	152 (12.0%)	**5.33 (1.80, 8.88)**	1.30 (-1.74, 4.34)
>360 - 630	271 (24.3%)	**10.45 (6.68, 14.23)**	2.13 (-0.41, 4.67)	309 (24.4%)	**5.80 (2.85, 8.76)**	1.58 (-0.97, 4.12)
Trend:		***p<0.001***	*p=0.062*		***p<0.001***	*p=0.13*
Average UV load per week in SUMMER, kJ/m^2						
0-302.1	264 (23.8%)	0.00 [Reference]	0.00 [Reference]	308 (24.4%)	0.00 [Reference]	0.00 [Reference]
>302.1-612.5	274 (24.7%)	**4.75 (1.21, 8.28)**	1.95 (-0.37, 4.27)	318 (25.2%)	2.33 (-0.47, 5.13)	0.83 (-1.51, 3.18)
>612.5-1-194.8	284 (25.6%)	**9.90 (6.40, 13.40)**	**3.19 (0.83, 5.55)**	313 (24.8%)	**6.16 (3.42, 8.91)**	**3.18 (0.81, 5.55)**
>1,194.8-4,110.8	288 (26.0%)	**10.47 (6.98, 13.96)**	**3.00 (0.65, 5.35)**	232 (25.6%)	**4.80 (2.05, 7.55)**	1.26 (-1.12, 3.65)
Trend:		***p<0.001***	***p=0.008***		***p<0.001***	*p=0.12*
Average duration per week in sun in WINTER, minutes						
0	231 (21.1%)	0.00 [Reference]	0.00 [Reference]	265 (21.4%)	0.00 [Reference]	0.00 [Reference]
>0-45	222 (20.2%)	2.16 (-1.74, 6.07)	2.10 (-0.44, 4.64)	251 (20.2%)	1.38 (-1.70, 4.45)	2.08 (-0.51, 4.67)
>45-90	201 (18.3%)	**6.07 (2.06, 10.08)**	2.21 (-0.42, 4.82)	227 (18.3%)	2.84 -0.28, 5.97)	1.03 (-1.68, 3.74)
>90-180	201 (18.3%)	**4.56 (0.55, 8.56)**	**3.25 (0.64, 5.86)**	224 (18.1%)	2.30 (-0.84, 5.45)	2.43 (-0.24, 5.09)
>180-630	242 (22.1%)	**5.31 (1.49, 9.13)**	**2.92 (0.42, 5.43)**	274 (22.1%)	**3.53 (0.56, 6.50)**	**3.20 (0.66, 5.74)**
Trend:		***p=0.003***	***p=0.017***		***p=0.018***	***p=0.020***

(*continued on next page*)

Table 2 (*continued*)

	P-QoL composite score			Mental health QoL composite score		
	n (%)	Model 1[a]	Model 2[b]	n (%)	Model 1[a]	Model 2[b]
Average UV load per week in WINTER, kJ/m^2						
0-15.9	264 (24.2%)	0.00 [Reference]	0.00 [Reference]	303 (24.5%)	0.00 [Reference]	0.00 [Reference]
>15.0-93.4	275 (25.2%)	1.51 (-2.08, 5.09)	0.63 (-1.69, 2.94)	313 (25.3%)	2.42 (-0.37, 5.21)	**2.48 (0.12, 4.84)**
>93.4-256.6	284 (26.0%)	**4.20 (0.65, 7.76)**	2.08 (-0.23, 4.38)	313 (25.3%)	2.06 (-0.74, 4.85)	1.47 (-0.92, 3.85)
>256.6-2,604.0	270 (24.7%)	**5.01 (1.41, 8.61)**	**3.35 (0.99, 5.70)**	308 (24.9%)	**3.76 (0.99, 6.54)**	**3.78 (1.41, 6.15)**
Trend:		***p=0.002***	***p=0.002***		***p=0.014***	***p=0.007***
How often using sunscreen on majority of exposure skin in WINTER?						
Never	900 (82.7%)	0.00 [Reference]	0.00 [Reference]	1,022 (82.9%)	0.00 [Reference]	0.00 [Reference]
Sometimes	123 (11.3%)	**5.60 (1.62, 9.59)**	1.44 (-1.16, 4.05)	141 (11.4%)	0.61 (-2.45, 3.66)	-1.93 (-4.61, 0.74)
Often	29 (2.7%)	0.79 (-7.04, 8.62)	-1.34 (-6.42, 3.75)	33 (2.7%)	-3.54 (-9.88, 2.80)	-4.16 (-9.55, 1.23)
Always	36 (3.3%)	-1.07 (-8.12, 5.98)	-1.37 (-5.91, 3.17)	37 (3.0%)	-2.09 (-7.97, 3.79)	-2.64 (-7.61, 2.33)
Trend:		*p=0.35*	*p=0.84*		*p=0.39*	***p=0.042***
How often wearing clothes that cover much of skin (e.g., long sleeved shirts, long pants) in SUMMER?						
Never	451 (40.4%)	0.00 [Reference]	0.00 [Reference]	495 (39.1%)	0.00 [Reference]	0.00 [Reference]
Sometimes	496 (44.4%)	0.16 (-2.53, 2.85)	-0.73 (-2.45, 1.00)	558 (44.1%)	-1.57 (-3.66, 0.53)	-1.43 (-3.22, 0.36)
Often	132 (11.8%)	-3.56 (-7.66, 0.54)	-1.96 (-4.65, 0.73)	165 (13.0%)	-2.03 (-5.11, 1.06)	-0.79 (-3.42, 1.84)
Always	37 (3.3%)	**-8.77 (-15.85, -1.68)**	**-4.87 (-9.55, -0.19)**	48 (3.8%)	-4.92 (-10.32, 0.48)	-2.44 (-7.02, 2.14)
Trend:		***p=0.021***	***p=0.031***		***p=0.033***	*p=0.19*
How often wearing clothes that expose much of skin (e.g., shorts & t-shirt or swimwear) in SUMMER?						
Never	94 (8.4%)	0.00 [Reference]	0.00 [Reference]	123 (9.7%)	0.00 [Reference]	0.00 [Reference]
Sometimes	370 (33.2%)	**13.00 (8.33, 17.67)**	**3.88 (0.72, 7.04)**	427 (33.8%)	**5.74 (2.03, 9.45)**	2.52 (-0.62, 5.66)
Often	411 (36.9%)	**17.18 (12.55, 21.81)**	**5.77 (2.62, 8.92)**	454 (35.9%)	**8.03 (4.36, 11.70)**	**4.03 (0.90, 7.16)**
Always	240 (21.5%)	**11.98 (7.06, 16.89)**	**5.60 (2.28, 8.92)**	260 (20.6%)	**6.87 (2.95, 10.79)**	**5.29 (1.98, 8.59)**
Trend:		***p<0.001***	***p=0.001***		***p=0.001***	***p<0.001***
How often wearing clothes that cover much of skin (e.g., long sleeved shirts, long pants) in WINTER?						
Never	63 (5.8%)	0.00 [Reference]	0.00 [Reference]	71 (5.7%)	0.00 [Reference]	0.00 [Reference]
Sometimes	136 (12.5%)	1.03 (-5.30, 7.37)	-2.76 (-6.84, 1.32)	147 (11.9%)	-1.48 (-6.43, 3.48)	-3.91 (-8.03, 0.21)
Often	273 (25.1%)	2.42 (-3.39, 8.23)	-2.40 (-6.16, 1.36)	311 (25.1%)	0.64 (-3.83, 5.11)	-1.46 (-5.16, 2.24)
Always	618 (56.7%)	1.28 (-4.21, 6.78)	**-3.76 (-7.31, -0.22)**	710 (57.3%)	-0.30 (-4.54, 3.94)	-2.32 (-5.81, 1.17)
Trend:		*p=0.84*	***p=0.034***		*p=0.88*	*p=0.69*
How often wearing clothes that expose much of skin (e.g., shorts & t-shirt or swimwear) in WINTER?						
Never	759 (70.1%)	0.00 [Reference]	0.00 [Reference]	865 (70.7%)	0.00 [Reference]	0.00 [Reference]
Sometimes	225 (20.8%)	**3.44 (0.29, 6.58)**	1.71 (-0.36, 3.77)	252 (20.6%)	1.74 (-0.67, 4.15)	1.15 (-0.93, 3.22)
Often	59 (5.5%)	-1.56 (-7.15, 4.03)	0.16 (-3.53, 3.85)	62 (5.1%)	-1.66 (-6.25, 2.94)	-0.67 (-4.59, 3.24)
Always	40 (3.7%)	-1.15 (-7.86, 5.56)	-0.83 (-5.11, 3.46)	45 (3.7%)	0.67 (-4.52, 5.86)	1.34 (-2.96, 5.63)
Trend:		*p=0.73*	*p=0.71*		*p=0.70*	*p=0.50*

Analyses by linear regression, estimating β (95% CI).

[a] Model 1 adjusted for whether participants have ongoing symptoms from a recent relapse.

[b] Model 2 further adjusted for age, sex, PRSES, treated comorbidity number, MS type, P-MSSS, clinically significant fatigue, and prescription antidepressant medication.

[c] Note: duration of vitamin D supplement use analyses constrained to those reporting using vitamin D supplements.

pain, energy, and sexual function subdomains, albeit of mixed dose-dependency. The health perceptions subdomain assesses health perceptions and beliefs overall and compared to others. The physical health subdomain assesses the extent to which participant's health inhibited their being able to do various activities like walking distances, walking up stairs, and bathing/dressing. The pain subdomain assesses the level of pain experienced and how it affects lifestyle. The energy subdomain assesses fatigue, energy, and well-restedness. The sexual function domain assesses the physiological capacity for sexual activity and the degree of satisfaction reached thereby. Although self-reported vitamin D supplement use did not impact change in other subdomains like social function and health distress, taken together, these results show evidence of a causal relationship with most aspects of physical QoL. Nonetheless, it is necessary for other studies to be undertaken on this topic to more conclusively define this relationship.

4.2. Sun exposure and sun-related behaviours

We found no consistent association between sun exposure and QoL. Sun exposure was assessed in differing ways in this study. At baseline, participants were queried on the frequency of 'adequate' sun exposure, relative to their local UV index, and whether they sought out increased sun exposure to raise their vitamin D levels. Neither was an efficient mode of assessing sun exposure, however, since they are not easily quantified or interpreted. Given these difficulties, we were unable to meaningfully assess the relationship of sun exposure with prospective change in QoL.

However, our measure of sun exposure queried at follow-up allowed better analysis, albeit only cross-sectionally. In deriving the average minutes per week through the synthesis of frequency (days/week) and duration (minutes/day), we found strong and dose-dependent associations of summer and winter sun exposure with P-QoL and M-QoL, though attenuated on adjustment. By cross-linking these average weekly durations in each season with ambient UVR available by TOMS satellite (NASA, 2006) for each participants' latitude/longitude of residence, we see more dose-dependent positive associations with QoL, robust to adjustment. Since we did not have these measures at baseline, however, we were unable to evaluate the relationship of these sun exposure measures with change in QoL.

4.3. Latitude

There are well-recognised latitudinal variations in MS frequency (Simpson et al., 2019) and age of onset (Tao et al., 2016). We previously reported worse health outcomes in people with MS with increasing latitude (Jelinek et al., 2015). In our baseline sample, latitude was not significantly associated with P-QOL or M-QoL (Jelinek et al., 2015). In this analysis, though trends to a lower P-QoL and M-QoL were seen, these were not indicative of a true association. Only latitude above 42° and northern hemisphere were associated, suggesting participants living in northern USA, Canada, and Europe have lower QoL. Australia, comprising roughly one third of participants at follow-up, had a broad

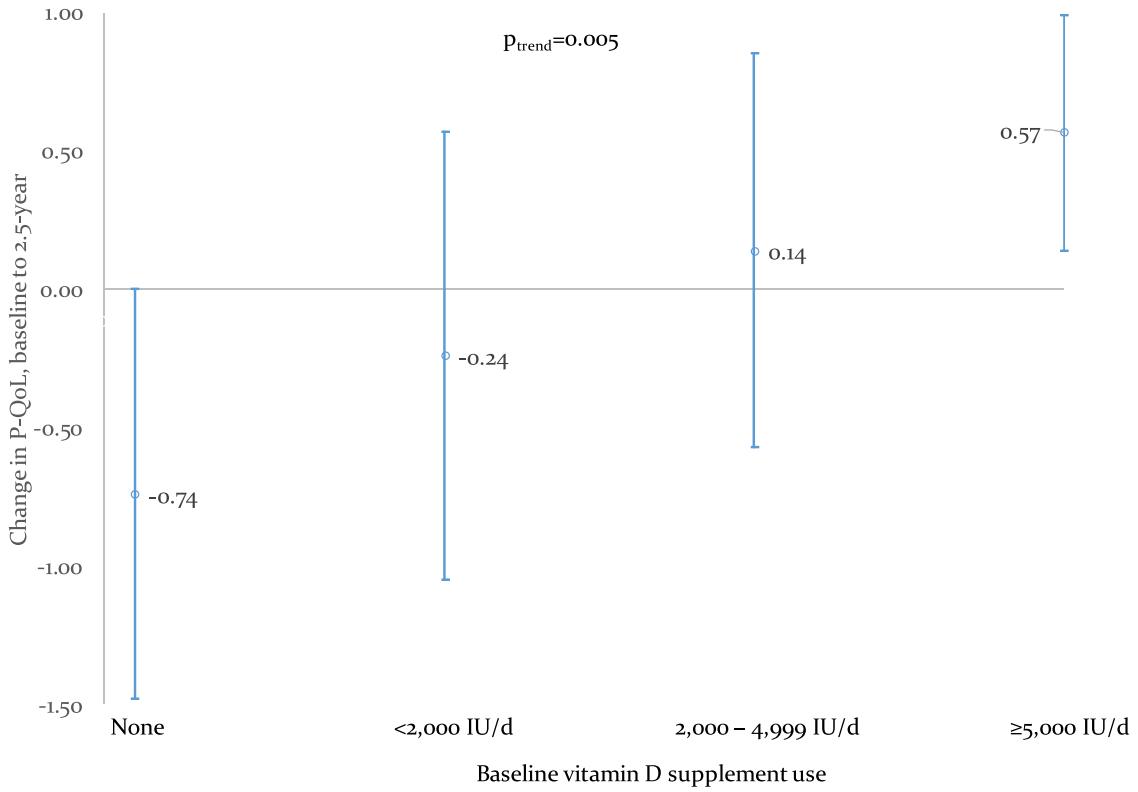

Fig. 1. Baseline vitamin D supplement dose vs subsequent change in P-QoL composite score. Adjusted for whether participants have ongoing symptoms from a recent relapse age, sex, PRSES, treated comorbidity number, MS type, P-MSSS, clinically significant fatigue, and prescription antidepressant medication.

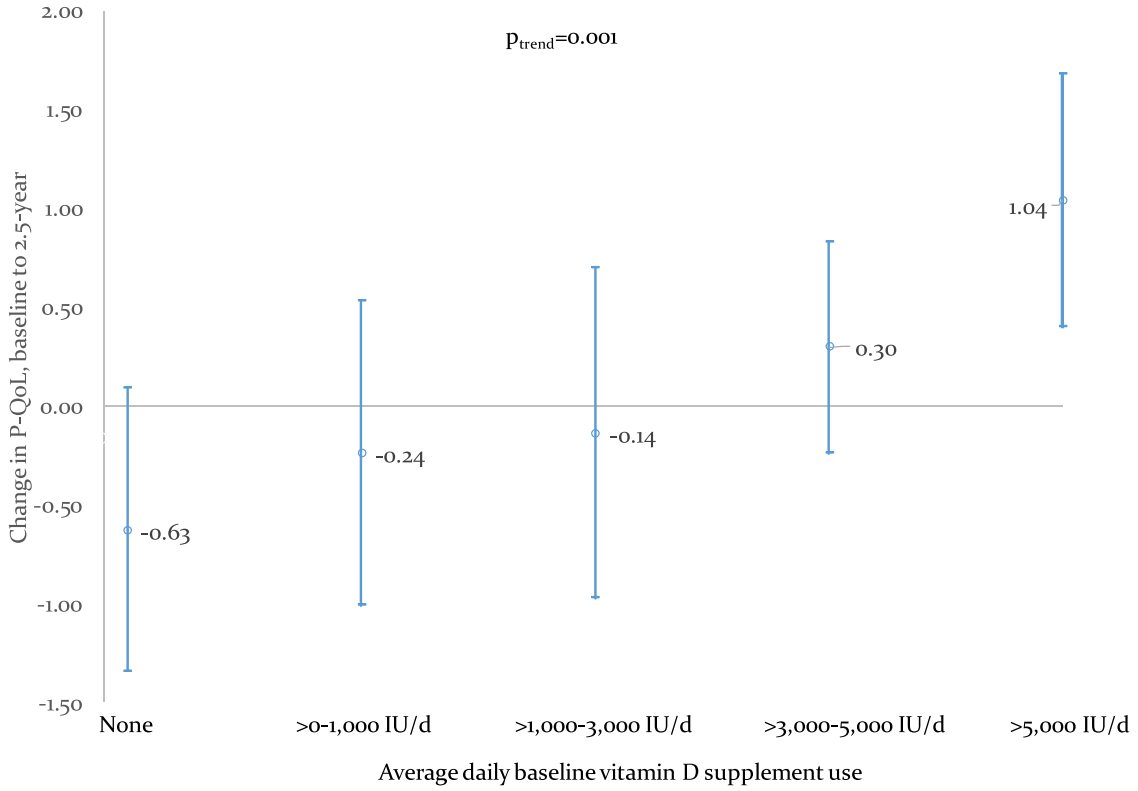

Fig. 2. Baseline average daily vitamin D supplement dose vs subsequent change in P-QoL composite score. Adjusted for whether participants have ongoing symptoms from a recent relapse age, sex, PRSES, treated comorbidity number, MS type, P-MSSS, clinically significant fatigue, and prescription antidepressant medication.

Table 3
Baseline predictors of change in MSQOL-54 physical and e mental health QoL composite scores between baseline and 2.5-yr reviews, estimating β (95% CI).

		Change in physical QoL composite score			Change in mental health QoL composite score	
		Model 1[a]	Model 2[b]		Model 1[a]	Model 2[b]
Latitude of residence						
≤34°	212 (20.6%)	0.00 [Reference]	0.00 [Reference]	260 (20.8%)	0.00 [Reference]	0.00 [Reference]
>34-42°	422 (41.1%)	-0.59 (-1.39, 0.21)	-0.75 (-1.54, 0.04)	513 (40.9%)	-0.05 (-0.97, 0.87)	-0.03 (-1.13, 1.08)
≥42°	393 (38.3%)	-0.48 (-1.29, 0.33)	-0.77 (-1.58, 0.04)	480 (38.3%)	-0.30 (-1.23, 0.63)	-0.11 (-1.25, 1.03)
Trend:		*p=0.34*	*p=0.11*		*p=0.49*	*p=0.87*
Hemisphere						
Southern	411 (40.0%)	0.00 [Reference]	0.00 [Reference]	530 (42.3%)	0.00 [Reference]	0.00 [Reference]
Northern	616 (60.0%)	0.14 (-0.47, 0.75)	-0.17 (-0.79, 0.45)	723 (57.7%)	0.12 (-0.57, 0.82)	0.22 (-0.63, 1.07)
		p=0.65	*p=0.59*		*p=0.73*	*p=0.62*
Taking a vitamin D supplement at baseline?						
No	177 (17.2%)	0.00 [Reference]	0.00 [Reference]	206 (16.4%)	0.00 [Reference]	0.00 [Reference]
Yes	850 (82.8%)	**0.89 (0.10, 1.68)**	**1.02 (0.22, 1.81)**	1,047 (83.6%)	0.43 (-0.50, 1.35)	0.11 (-1.00, 1.23)
		p=0.027	***p=0.012***		*p=0.37*	*p=0.84*
Vitamin D supplement dose at baseline, IU/d						
None	177 (17.6%)	0.00 [Reference]	0.00 [Reference]	206 (16.8%)	0.00 [Reference]	0.00 [Reference]
<2000	137 (13.6%)	0.29 (-0.79, 1.37)	0.44 (-0.64, 1.51)	172 (14.0%)	-0.657 (-1.92, 0.58)	-0.86 (-2.38, 0.65)
2,000-5,000	184 (18.3%)	0.69 (-0.31, 1.69)	0.90 (-0.12, 1.91)	234 (19.1%)	0.97 (-0.19, 2.12)	0.92 (-0.50, 2.33)
≥5,000	510 (50.6%)	**1.15 (0.31, 1.98)**	**1.25 (0.41, 2.09)**	615 (50.1%)	0.53 (-0.45, 1.52)	0.09 (-1.09, 1.27)
Trend:		***p=0.003***	***p=0.003***		*p=0.081*	*p=0.59*
Frequency of vitamin D supplement usage at baseline						
Never	177 (17.5%)	0.00 [Reference]	0.00 [Reference]	206 (16.7%)	0.00 [Reference]	0.00 [Reference]
≤3/week	92 (9.1%	1.15 (-0.08, 2.38)	**1.38 (0.17, 2.59)**	115 (9.3%)	-0.21 (-1.62, 1.20)	-0.67 (-2.34, 1.00)
4-6/week	52 (5.1%)	0.59 (-0.92, 2.09)	0.79 (-0.72, 2.31)	63 (5.1%)	0.73 (-1.01, 2.47)	0.58 (-1.56, 2.72)
Daily	691 (68.3%)	**0.88 (0.07, 1.69)**	**0.99 (0.17, 1.80)**	850 (68.9%)	0.46 (-0.49, 1.40)	0.18 (-0.96, 1.31)
Trend:		*p=0.083*	*p=0.091*		*p=0.23*	*p=0.55*
Average daily Vitamin D supplement dose at baseline, IU/d						
None	191 (19.0%)	0.00 [Reference]	0.00 [Reference]	225 (18.3%)	0.00 [Reference]	0.00 [Reference]
>0-1,000	149 (14.8%)	0.20 (-0.84, 1.23)	0.33 (-0.70, 1.36)	187 (15.2%)	-0.76 (-1.95, 0.43)	-1.02 (-2.47, 0.42)
>1,000-3,000	137 (13.6%)	0.29 (-0.78, 1.35)	0.53 (-0.55, 1.62)	182 (14.8%)	0.76 (-0.44, 1.97)	0.60 (-0.89, 2.09)
>3,000-5,000	308 (30.6%)	**0.91 (0.03, 1.79)**	0.88 (-0.00, 1.75)	375 (30.5%	-0.05 (1.07, 0.97)	-0.60 (-1.83, 0.62)
>5,000-500,000	223 (22.1%)	**1.35 (0.41, 2.30)**	**1.65 (0.71, 2.60)**	260 (21.2%)	**1.15 (0.04, 2.25)**	0.97 (-0.34, 2.29)
Trend:		***p=0.001***	***p=0.001***		***p=0.031***	*p=0.22*
How often per week in preceding 12 months have you got adequate sun exposure at baseline?						
Never/<once	292 (30.9%)	0.00 [Reference]	0.00 [Reference]	365 (31.9%)	0.00 [Reference]	0.00 [Reference]
1-2 times	287 (30.4%)	0.00 (-0.79, 0.79)	0.05 (-0.73, 0.83)	343 (29.9%)	-0.13 (-1.04, 0.78)	-0.10 (-1.19, 0.99)
3-4 times	198 (21.0%)	0.12 (-0.76, 0.99)	0.15 (-0.73, 1.03)	242 (21.1%)	0.41 (-0.60, 1.42)	0.02 (-1.20, 1.23)
5-6 times	104 (11.0%)	0.00 (-1.08, 1.08)	-0.31 (-1.40, 0.79)	122 (10.7%)	-0.17 (-1.44, 1.09)	-0.65 (-2.19, 0.89)
Every day	63 (6.7%)	**-1.43 (-2.75, -0.12)**	**-1.37 (-2.66, -0.08)**	74 (6.5%)	-0.99 (-2.53, 0.55)	-1.04 (-2.81, 0.73)
Trend:		*p=0.21*	*p=0.13*		*p=0.86*	*p=0.24*
Do you try to get sun exposure to increase vitamin D levels?						
No	299 (29.6%)	0.00 [Reference]	0.00 [Reference]	370 (30.0%)	0.00 [Reference]	0.00 [Reference]
Yes	713 (70.5%)	0.37 (-0.28, 1.02) *p=0.26*	0.20 (-0.45, 0.85)	862 (70.0%)	0.26 (-0.49, 1.00)	0.02 (-0.88, 0.91)
			p=0.55		*p=0.50*	*p=0.97*

Analyses by linear regression, estimating β (95% CI).
[a] Model 1 adjusted for whether participants have ongoing symptoms from a recent relapse. Model 2 further adjusted for age, sex, PRSES, treated comorbidity number, MS type, P-MSSS, clinically significant fatigue, and prescription antidepressant medication

latitudinal range (19-43°), but no gradient suggestive of a true association was evident.

4.4. Limitations

Our results were based on self-reported data. As previously discussed, our measures of sun exposure at baseline were not sufficient for the purpose and although we did use more standard methods (Lucas et al., 2011) to measure sun exposure at follow-up, this precluded prospective analyses of this important parameter. Regardless, objective measures such as serum vitamin D concentrations and polysulphone badges to measure sun exposure would help substantiate these results. Data from future timepoints will also allow comparison of sun exposure measurements and further analysis of vitamin D supplement use and its association with change in QoL.

Another limitation is our utilisation of socioeconomic status at the 2.5-year review for prospective analyses, extrapolating this measure at follow-up to baseline. This assumes that socioeconomic status would be relatively constant over this timeframe, which is a not unreasonable assumption but is a limitation. In addition, our extrapolation of baseline-measured comorbidity number forward for the 2.5-year cross-sectional analyses is a limitation. However, we only assessed treated comorbidity number at this timepoint.

Another limitation is that our cohort had limited change in QoL between the two timepoints, physical and mental QoL only increasing by 0.6 and 0.2, respectively. This limits our ability to demonstrate large measures of association, with high-dose vitamin D supplement use only associated with 1-2 points higher QoL. That said, the consistency between these prospective analyses, as well as our current and previous (Jelinek et al., 2015) cross-sectional analyses, suggests that there may be a true association at play. It would be useful to substantiate these findings in a sample where QoL shows greater change which would allow greater demonstration of heterogeneity of this change between exposure groups.

4.5. Generalisability

Our cohort is generally comparable to other samples of people with

MS, for both demographic and clinical characteristics. That said, it does suffer from healthy participant bias as is typical for epidemiological studies, and particularly a bias towards some of the behaviours advocated for in the Overcoming Multiple Sclerosis (OMS) program (Jelinek, 2016), whose adherents comprise a meaingful proportion of the cohort. However, while supplement use and sun exposure are elements of the OMS program, these are well-recognised behaviours of interest among people with MS given the epidemiological evidence indicating a potential role for them in MS, so we do not believe this bias is a marked hindrance to the present work. The sample was recruited online and so there is a potential to a bias towards recruiting those who are more technologically adept and of higher SES. However, internet access is an increasingly common feature of most countries, particularly those with high prevalence of MS, so we do not believe this is a limitation.

5. Conclusion

QoL in this international population of people with MS was relatively stable over a 2.5-year period. Self-reported vitamin D supplement use was a predictor of improved QoL, adding weight to current hypotheses about MS pathogenesis and progression. Were these results substantiated in other longitudinal studies, particularly those using objective measures of serum vitamin D, and thence by randomised clinical trials, vitamin D supplementation would be an inexpensive and safe intervention that could improve QoL in people with MS.

Ethics approval and consent to participate

The Health Sciences Human Ethics Sub-Committee at The University of Melbourne provided ethical approval for the study (Ethics ID: 1545102). Participants were asked to read the participant information and to consent before entering the survey.

Availability of data and material

Data may not be shared due to the conditions approved by our institutional ethics committee, in that all data are stored as re-identifiable information at The University of Melbourne in the form of password-protected computer databases, and only the listed investigators have access to the data. All data have been reported on a group basis, summarising the group findings rather than individual findings so personal information cannot be identified. Therefore, we can supply aggregate group data on request. Readers may contact Dr Steve Simpson-Yap.

Author statement

Conceptualisation: GAJ, TW, SSY; Methodology: SSY; Software: N/A; Validation: SSY; Formal analysis: SSY; Investigation: SSY; Resources: GAJ, TW, SN, SSY; Data Curation: SSY; Writing - original draft: SSY; Writing - review & editing: SSY, PJ, TW, NN, SN, GAJ; Visualisation: SSY; Supervision: SN; Project Administration: GAJ, TW, SN, NN, SSY; Funding acquisition: GAJ, TW, SN.

Funding

The study was funded by Wal Pisciotta and anonymous philanthropic funders, for which we are thankful.

Declaration of Competing Interest

GJ receives royalties for his books, *Overcoming Multiple Sclerosis* and *Recovering from Multiple Sclerosis*. GJ and SN received remuneration for conducting lifestyle educational workshops for people with MS.

Acknowledgements

We thank all the participants in the HOLISM study for participating in the study and Wal Pisciotta and other anonymous philanthropic funders for supporting this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.102760.

References

Alonso, A., Hernan, M.A., 2008. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 71 (2), 129–135.
Ascherio, A., Munger, K.L., Simon, K.C., 2010. Vitamin D and multiple sclerosis. Lancet Neurol. 9 (6), 599–612.
Ashtari, F., Toghianifar, N., Zarkesh-Esfahani, S.H., Mansourian, M., 2016. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Neurol. Res. 38 (10), 888–892.
Beckmann, Y., Ture, S., Duman, S.U., 2020. Vitamin D deficiency and its association with fatigue and quality of life in multiple sclerosis patients. EPMA J. 11 (1), 65–72.
Duan, S., Lv, Z., Fan, X., Wang, L., Han, F., Wang, H., Bi, S., 2014. Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis. Neurosci. Lett. 570, 108–113.
Golan, D., Halhal, B., Glass-Marmor, L., Staun-Ram, E., Rozenberg, O., Lavi, I., Dishon, S., Barak, M., Ish-Shalom, S., Miller, A., 2013. Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and immunomodulatory properties. BMC Neurol. 13 (1), 60.
Hadgkiss, E.J., Jelinek, G.A., Weiland, T.J., Pereira, N.G., Marck, C.H., van der Meer, D. M., 2013. Methodology of an international study of people with multiple sclerosis recruited through web 2.0 platforms: demographics, lifestyle, and disease characteristics. Neurol. Res. Int. 2013, 580596.
Hohol, M.J., Orav, E.J., Weiner, H.L., 1995. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. Neurology 45 (2), 251–255.
Howe, L.D., Hargreaves, J.R., Ploubidis, G.B., De Stavola, B.L., Huttly, S.R., 2011. Subjective measures of socio-economic position and the wealth index: a comparative analysis. Health Policy Plan. 26 (3), 223–232.
Jelinek, G.A., 2016. Overcoming Multiple Sclerosis: the Evidence-Based 7 Step Recovery Program, 2nd ed. Allen & Unwin, Crows Nest.
Jelinek, G.A., De Livera, A.M., Marck, C.H., Brown, C.R., Neate, S.L., Taylor, K.L., Weiland, T.J., 2016. Lifestyle, medication and socio-demographic determinants of mental and physical health-related quality of life in people with multiple sclerosis. BMC Neurol. 16 (1), 235.
Jelinek, G.A., Hadgkiss, E.J., Weiland, T.J., Pereira, N.G., Marck, C.H., van der Meer, D. M., 2013. Association of fish consumption and Omega 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. Int. J. Neurosci. 123 (11), 792–800.
Jelinek, G.A., Marck, C.H., Weiland, T.J., Pereira, N., van der Meer, D.M., Hadgkiss, E.J., 2015. Latitude, sun exposure and vitamin D supplementation: associations with quality of life and disease outcomes in a large international cohort of people with multiple sclerosis. BMC Neurol. 15, 132.
Kister, I., Chamot, E., Salter, A.R., Cutter, G.R., Bacon, T.E., Herbert, J., 2013. Disability in multiple sclerosis: a reference for patients and clinicians. Neurology 80 (11), 1018–1024.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2003. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med. Care 41 (11), 1284–1292.
Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46 (10), 1121–1123.
Leong, T.I., Weiland, T.J., Jelinek, G.A., Simpson, S., Brown, C.R., Neate, S.L., Taylor, K. L., O'Kearney, E., Milanzi, E., De Livera, A.M., 2018. Longitudinal associations of the healthy lifestyle index score with quality of life in people with multiple sclerosis: a prospective cohort study. Front. Neurol. 9, 874.
Lucas, R.M., Ponsonby, A.L., Dear, K., Valery, P.C., Pender, M.P., Taylor, B.V., Kilpatrick, T.J., Dwyer, T., Coulthard, A., Chapman, C., van der Mei, I., Williams, D., McMichael, A.J., 2011. Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology 76 (6), 540–548.
Marck, C.H., Hadgkiss, E.J., Weiland, T.J., van der Meer, D.M., Pereira, N.G., Jelinek, G. A., 2014. Physical activity and associated levels of disability and quality of life in people with multiple sclerosis: a large international survey. BMC Neurol. 14, 143.
Marrie, R.A., Horwitz, R.I., 2010. Emerging effects of comorbidities on multiple sclerosis. Lancet Neurol. 9 (8), 820–828.
Martineau, A.R., Jolliffe, D.A., Hooper, R.L., Greenberg, L., Aloia, J.F., Bergman, P., Dubnov-Raz, G., Esposito, S., Ganmaa, D., Ginde, A.A., Goodall, E.C., Grant, C.C., Griffiths, C.J., Janssens, W., Laaksi, I., Manaseki-Holland, S., Mauger, D., Murdoch, D.R., Neale, R., Rees, J.R., Simpson Jr., S., Stelmach, I., Kumar, G.T., Urashima, M., Camargo Jr., C.A., 2017. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 356, i6583.

Martinez-Lapiscina, E.H., Mahatanan, R., Lee, C.H., Charoenpong, P., Hong, J.P., 2020. Associations of serum 25(OH) vitamin D levels with clinical and radiological outcomes in multiple sclerosis, a systematic review and meta-analysis. J. Neurol. Sci. 411, 116668.

Naci, H., Fleurence, R., Birt, J., Duhig, A., 2010. The impact of increasing neurological disability of multiple sclerosis on health utilities: a systematic review of the literature. J. Med. Econ. 13 (1), 78–89.

NASA, 2006. Total Ozone Mapping Spectrometer: May 23, 2006. NASA. Available at: http://iridl.ldeo.columbia.edu/SOURCES/.NASA/.GSFC/.TOMS/.EPTOMS/.monthly/.

Nourbakhsh, B., Julian, L., Waubant, E., 2016. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Eur. J. Neurol. 23 (9), 1482–1486.

O'Kearney, E.L., Brown, C.R., Jelinek, G.A., Neate, S.L., Taylor, K.T., Bevens, W., De Livera, A.M., Simpson Jr., S., Weiland, T.J., 2019. Mastery is associated with greater physical and mental health-related quality of life in two international cohorts of people with multiple sclerosis. Mult. Scler. Related Disord. 38, 101481.

Ochoa-Morales, A., Hernández-Mojica, T., Paz-Rodríguez, F., Jara-Prado, A., Trujillo-De, Los, Santos, Z., Sánchez-Guzmán, M.A., Guerrero-Camacho, J.L., Corona-Vázquez, T., Flores, J., Camacho-Molina, A., Rivas-Alonso, V., Dávila-Ortiz de Montellano, D.J., 2019. Quality of life in patients with multiple sclerosis and its association with depressive symptoms and physical disability. Mult. Scler. Related Disord. 36, 101386.

Sangha, O., Stucki, G., Liang, M.H., Fossel, A.H., Katz, J.N., 2003. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 49 (2), 156–163.

Simpson Jr., S., Wang, W., Otahal, P., Blizzard, L., van der Mei, I.A.F., Taylor, B.V., 2019. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J. Neurol. Neurosurg. Psychiatry.

Tao, C., Simpson Jr., S., van der Mei, I., Blizzard, L., Havrdova, E., Horakova, D., Shaygannejad, V., Lugaresi, A., Izquierdo, G., Trojano, M., Duquette, P., Girard, M., Grand'Maison, F., Grammond, P., Alroughani, R., Terzi, M., Oreja-Guevara, C., Sajedi, S.A., Iuliano, G., Sola, P., Lechner-Scott, J., Pesch, V.V., Pucci, E., Bergamaschi, R., Barnett, M., Ramo, C., Singhal, B., D, L.A.S., Slee, M., Verheul, F., Fernandez Bolanos, R., Amato, M.P., Cristiano, E., Granella, F., Hodgkinson, S., Fiol, M., Gray, O., McCombe, P., Saladino, M.L., Sanchez Menoyo, J.L., Shuey, N., Vucic, S., Shaw, C., Deri, N., Arruda, W.O., Butzkueven, H., Spelman, T., Taylor, B. V., 2016. Higher latitude is significantly associated with an earlier age of disease onset in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 87 (12), 1343–1349.

Vickrey, B.G., Hays, R.D., Harooni, R., Myers, L.W., Ellison, G.W., 1995. A health-related quality of life measure for multiple sclerosis. Quality of life research: an international journal of quality of life aspects of treatment. Care Rehabil. 4 (3), 187–206.

Ware, J., Snow, K., Kosinsky, M., Gandek, B., 1993. SF-36 Health Survey: Manual and Interpretation Guide. The Health Institute, New England Medical Center, Boston.

Weiland, T.J., De Livera, A.M., Brown, C.R., Jelinek, G.A., Aitken, Z., Simpson Jr., S.L., Neate, S.L., Taylor, K.T., O'Kearney, E., Bevens, W., Marck, C.H., 2018. Health Outcomes and Lifestyle In a Sample of People with Multiple Sclerosis (HOLISM): longitudinal and Validation cohorts. Front. Neurol. Under review.

Zheng, C., He, L., Liu, L., Zhu, J., Jin, T., 2018. The efficacy of vitamin D in multiple sclerosis: a meta-analysis. Mult. Scler. Related Disord. 23, 56–61.